CHAPTER
17

Alterations in Cardiac Function

Heart disease remains a leading cause of death and disability in the United States and throughout the world. Currently, it is the number one cause of death in the United States. It is also the leading cause of permanent disability in the U.S. labor force and accounts for 19% of Social Security disability payments.[1] By the year 2020, it is projected that cardiovascular disease will, for the first time in human history, be the most common cause of death worldwide.[2]

In an attempt to focus on common heart problems that affect persons in all age groups, this chapter is organized into five sections: disorders of the pericardium, coronary heart disease, myocardial and endocardial diseases, valvular heart disease, and heart disease in infants and children.

DISORDERS OF THE PERICARDIUM

The pericardium is a double-layered serous membrane that isolates the heart from other thoracic structures, maintains its position in the thorax, and prevents it from overfilling. The two layers of the pericardium are separated by a thin layer of serous fluid, which prevents frictional forces from developing as the inner visceral layer, or epicardium, comes in contact with the outer parietal layer of the fibrous pericardium.

The pericardium is subject to many of the same pathologic processes (*e.g.*, congenital disorders, infections, trauma, immune mechanisms, and neoplastic disease) that affect other structures of the body. Pericardial disorders frequently are

KEY CONCEPTS

DISORDERS OF THE PERICARDIUM

- The pericardium isolates the heart from other thoracic structures, maintains its position in the thorax, and prevents it from overfilling.
- The two layers of the pericardium are separated by a thin layer of serous fluid, which prevents frictional forces from developing between the visceral and parietal layers of the pericardium.
- Disorders that produce inflammation of the pericardium interfere with the friction-reducing properties of the pericardial fluid and produce pain.
- Disorders that increase the fluid volume of the pericardial sac interfere with cardiac filling and produce a subsequent reduction in cardiac output.

associated with or result from another disease within the heart or in the surrounding structures.

Pericardial Effusion

Pericardial effusion refers to the accumulation of fluid in the pericardial cavity. Normally, there is about 30 to 50 mL of thin, clear, straw-colored fluid in the pericardial sac. The amount of fluid, the rapidity with which it accumulates, and the elasticity of the pericardium determine the effect the effusion has on cardiac function. Small pericardial effusions may produce no symptoms or abnormal clinical findings. Even a large effusion that develops slowly may cause few or no symptoms, provided the pericardium is able to stretch and avoid compressing the heart. However, a sudden accumulation of even 200 mL may raise intracardiac pressure to levels that seriously limit the venous return to the heart. Symptoms of cardiac compression also may occur with relatively small accumulations of fluid when the pericardium has become thickened by scar tissue or neoplastic infiltrations.

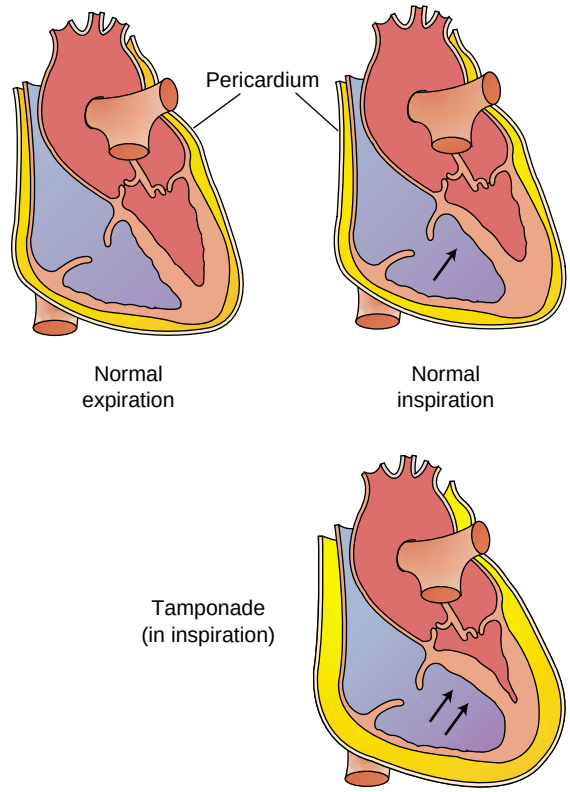
Cardiac tamponade represents an increase in intrapericardial pressure caused by an accumulation of fluid or blood in the pericardial sac. It can occur as the result of conditions such as trauma, cardiac surgery, cancer, uremia, or cardiac rupture caused by myocardial infarction. The seriousness of cardiac tamponade results from impairment in diastolic filling and reduction in stroke volume and cardiac output. The severity of the condition depends on the amount of fluid that is present and the rate at which it accumulated. A rapid accumulation of fluid results in an elevation of central venous pressure, jugular venous distention, a decline in venous return to the heart, a decrease in cardiac output despite an increase in heart rate, a fall in systolic blood pressure, pulsus paradoxus, and signs of circulatory shock.

Pulsus paradoxus, which refers to an exaggeration (>10 mm Hg) of the normal (2 to 4 mm Hg) decrease in systolic blood pressure that occurs during inspiration, is a clinical indicator of cardiac tamponade. The decreased intrathoracic pressure that occurs during inspiration normally accelerates venous flow, increasing right atrial and right ventricular filling. This causes the interventricular septum to bulge to the left, producing a decrease in left ventricular filling, stroke volume output, and systolic blood pressure. In cardiac tamponade, the left ventricle is compressed from within by movement of the interventricular septum and from without by fluid in the pericardium (Fig. 17-1). This produces a marked decrease in left ventricular filling and left ventricular stroke volume output, often within a beat of the beginning of inspiration.

The echocardiogram is a rapid, accurate, and widely used method for evaluating pericardial effusion. Aspiration and laboratory analysis of the pericardial fluid may be used to identify the causative agent. Cardiac catheterization may be used to determine the hemodynamic effects of pericardial effusion and cardiac tamponade. Pericardiocentesis, the removal of fluid from the pericardial sac, may be a lifesaving measure in severe cardiac tamponade.

Pericarditis

Pericarditis represents an inflammatory process of the pericardium.[3] It can result from a number of diverse causes. Most forms of pericarditis occur secondary to other systemic or car-



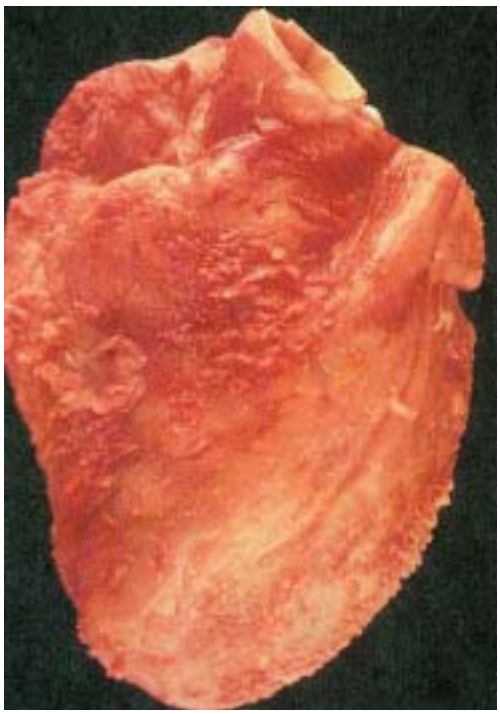
■ **FIGURE 17-1** ■ Effects of respiration and cardiac tamponade on ventricular filling and cardiac output. During inspiration venous flow into the right heart increases, causing the interventricular septum to bulge into the left ventricle. This produces a decrease in left ventricular volume, with a subsequent decrease in stroke volume output. In cardiac tamponade, the fluid in the pericardial sac produces further compression of the left ventricle, causing an exaggeration of the normal inspiratory decrease in stroke volume and systolic blood pressure.

diac disease. Primary pericarditis is unusual and most often of viral origin. Most causes of pericarditis evoke an acute pericarditis. Exceptions are tuberculosis and fungal infections, which often produce chronic reactions.[4]

Acute Pericarditis

Acute pericarditis can be classified according to cause (*e.g.*, infections, trauma, rheumatic fever) or the nature of the exudate (*e.g.*, serous, fibrinous, purulent, hemorrhagic). Like other inflammatory conditions, acute pericarditis often is associated with increased capillary permeability. The capillaries that supply the serous pericardium become permeable, allowing plasma proteins, including fibrinogen, to leave the capillaries and enter the pericardial space. This results in an exudate that varies in type and amount according to the causative agent. Acute pericarditis frequently is associated with a fibrinous (fibrin-containing) exudate, which heals by resolution or progresses to deposition of scar tissue and formation of adhesions between the layers of the serous pericardium (Fig. 17-2). Inflammation also may involve the superficial myocardium and the adjacent pleura.

Viral infection (especially infections with the coxsackieviruses and echoviruses, but also influenza, Epstein-Barr, varicella, hepatitis, mumps, and human immunodeficiency viruses) is one of the most common causes of acute pericarditis. Viral pericarditis is seen more frequently in men than in women. It is commonly preceded by a prodromal phase during which fever, malaise, and other flulike symptoms are present. Often it is preceded by an upper respiratory tract infection. Although the acute symptoms of viral pericarditis usually subside in several weeks, easy fatigability often continues for several months.



■ **FIGURE 17-2** ■ Fibrinous pericarditis. The heart of a patient who died of uremia displays a shaggy, fibrinous exudate covering the visceral pericardium. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 585]. Philadelphia: Lippincott Williams & Wilkins)

In many cases, the condition is self-limited, resolving in 2 to 6 weeks. Rarely, it may persist and produce recurrent subacute or chronic disease.

Other causes of acute pericarditis are rheumatic fever, postpericardiotomy syndrome, post-traumatic pericarditis, metabolic disorders (*e.g.*, uremia, myxedema), and pericarditis associated with connective tissue diseases (*e.g.*, systemic lupus erythematosus, rheumatoid arthritis). With the increased use of open-heart surgery in the treatment of various heart disorders, postpericardiotomy syndrome has become a commonly recognized form of pericarditis. Pericarditis with effusion is a common complication in persons with renal failure, in those with untreated uremia, and in those being treated with hemodialysis. Irradiation may initiate a subacute pericarditis, with an onset usually within the first year of therapy. It is most commonly associated with high doses of radiation delivered to areas near the heart.

The manifestations of acute pericarditis include a triad of chest pain, pericardial friction rub, and serial electrocardiographic (ECG) changes. The clinical findings and other manifestations may vary according to the causative agent. Nearly all persons with acute pericarditis have chest pain. The pain usually is abrupt in onset, occurs in the precordial area, and is described as sharp. It may radiate to the neck, back, abdomen, or side. It typically is worse with deep breathing, coughing, swallowing, and positional changes because of changes in venous return and cardiac filling. A pericardial friction rub results from the rubbing and friction between the inflamed pericardial surfaces. Serial ECGs are useful in differentiating acute pericarditis from myocardial infarction. Treatment of acute pericarditis depends on the cause. When infection is present, antibiotics specific for the causative agent usually are prescribed. Anti-inflammatory drugs such as aspirin and nonsteroidal anti-inflammatory agents (NSAIDs) may be given to minimize the inflammatory response and the accompanying undesirable effects.

Chronic Pericarditis With Effusion

Chronic pericarditis with effusion is characterized by an increase in inflammatory exudate that continues beyond the acute period. In some cases, the exudate persists for several years. The process commonly is associated with other forms of heart disease, such as rheumatic fever, congenital heart lesions, or hypertensive heart disease. Systemic diseases, such as lupus erythematosus, rheumatoid arthritis, and scleroderma also are causes of chronic pericarditis, as are metabolic disturbances associated with acute and chronic renal failure. In most cases of chronic pericarditis, no specific pathogen or cause can be identified. Unlike with acute pericarditis, the signs and symptoms of chronic pericarditis often are minimal, with the condition being detected for the first time on a routine chest x-ray film. As the condition progresses, the fluid may accumulate and compress the adjacent cardiac structures and impair cardiac filling.

Constrictive Pericarditis

In constrictive pericarditis, fibrous scar tissue develops between the visceral and parietal layers of the serous pericardium. In time, the scar tissue contracts and interferes with diastolic filling of the heart, at which point cardiac output and cardiac reserve becomes fixed. Ascites is a prominent early finding and may be accompanied by pedal edema, dyspnea on exertion,

and fatigue. The jugular veins also are distended. Surgical removal of the pericardium may be necessary in persons with severe compromise of cardiac function.

In summary, Disorders of the pericardium include pericardial effusion, acute and chronic pericarditis, and constrictive pericarditis. Pericardial effusion, which refers to the presence of an exudate in the pericardial cavity, can increase intracardiac pressure, compress the heart, and interfere with venous return to the heart. Cardiac tamponade is a life-threatening cardiac compression resulting from excess fluid in the pericardial sac. Acute pericarditis is characterized by chest pain, ECG changes, and a friction rub. Among its causes are infections, uremia, rheumatic fever, connective tissue diseases, and myocardial infarction. In constrictive pericarditis, scar tissue develops between the visceral and parietal layers of the serous pericardium. In time, the scar tissue contracts and interferes with cardiac filling.

CORONARY HEART DISEASE

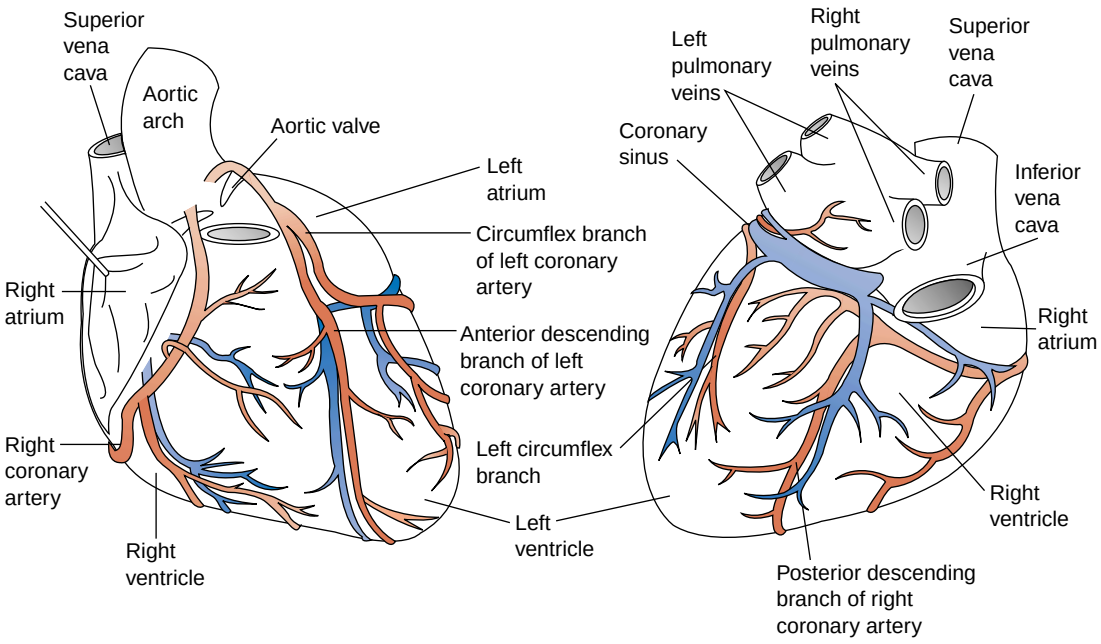
The term *coronary heart disease* (CHD) describes heart disease caused by impaired coronary blood flow. In most cases, CHD is caused by atherosclerosis. Diseases of the coronary arteries can cause angina, myocardial infarction or heart attack, cardiac dysrhythmias, conduction defects, heart failure, and sudden death. Heart attack is the largest killer of American men and women, claiming more than 218,000 lives annually.[1] Each year, 1.5 million Americans have new or recurrent heart attacks, and one third of those die within the first hour, usually as the result of cardiac arrest resulting from ventricular fibrillation.

During the past 50 years, there have been phenomenal advances in understanding the pathogenesis of CHD and in the development of diagnostic techniques and treatment methods for disease. However, declines in morbidity and mortality have failed to keep pace with these scientific advances, probably because many of the outcomes are more dependent on lifestyle factors and age than on scientific advances.

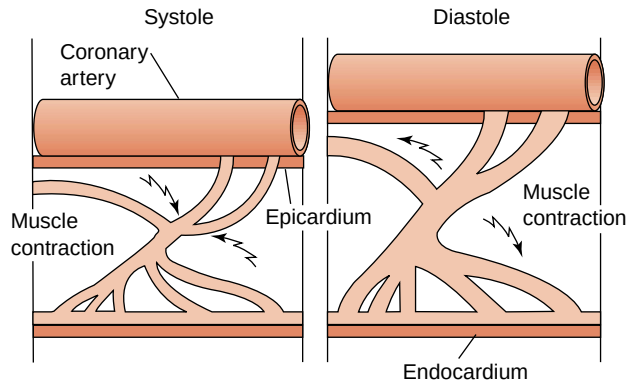
Coronary Circulation

There are two main coronary arteries, the left and the right, which arise from the coronary sinus just above the aortic valve (Fig. 17-3). The left coronary artery extends for approximately 3.5 cm as the *left main coronary artery* and then divides into the *anterior descending* and *circumflex branches*. The left anterior descending artery passes down through the groove between the two ventricles, giving off diagonal branches, which supply the left ventricle, and perforating branches, which supply the anterior portion of the interventricular septum and the anterior papillary muscle of the left ventricle. The circumflex branch of the left coronary artery passes to the left and moves posteriorly in the groove that separates the left atrium and ventricle, giving off branches that supply the left lateral wall of the left ventricle. The *right coronary artery* lies in the right atrioventricular groove, and its branches supply the right ventricle. The sinoatrial node usually is supplied by the right coronary artery. The right coronary artery usually moves to the back of the heart, where it forms the *posterior descending artery*, which supplies the posterior portion of the heart (the interventricular septum, atrioventricular [AV] node, and posterior papillary muscle). In 10% to 20% of persons, the left circumflex, rather than the right coronary artery, moves posteriorly to form the posterior descending artery.

Although there are no connections between the large coronary arteries, there are anastomotic channels that join the small arteries (Fig. 17-4). With gradual occlusion of the larger vessels, the smaller collateral vessels increase in size and provide alternative channels for blood flow.[5] One of the reasons CHD does



■ **FIGURE 17-3** ■ Coronary arteries and some of the coronary sinus veins.



■ **FIGURE 17-5** ■ The compressing effect of the contracting myocardium on intramyocardial blood vessels and subendocardial blood flow during systole and diastole.

not produce symptoms until it is far advanced is that the collateral channels develop at the same time the atherosclerotic changes are occurring.

The openings for the coronary arteries originate in the root of the aorta just outside the aortic valve; thus, the primary factor responsible for perfusion of the coronary arteries is the aortic blood pressure. Changes in aortic pressure produce parallel changes in coronary blood flow.

In addition to generating the aortic pressure that moves blood through the coronary vessels, the contracting heart muscle influences its own blood supply by compressing the intramyocardial and subendocardial blood vessels.[5] The large epicardial coronary arteries lie on the surface of the heart, with the smaller intramyocardial coronary arteries branching off and penetrating the myocardium before merging with a network or plexus of subendocardial vessels that supply the endocardium. During systole, contraction of the cardiac muscle compresses the intramyocardial vessels that feed the subendocardial plexus, and the increased pressure in the ventricle causes further compression of these vessels (Fig. 17-5). As a result, blood flow through the subendocardial vessels occurs mainly during diastole. Thus, there is increased risk of subendocardial ischemia and infarction when diastolic pressure is low, when a rapid heart rate decreases the time spent in diastole, and when an elevation in diastolic intraventricular pressure is sufficient to compress the vessels in the subendocardial plexus.[5,6]

Heart muscle relies primarily on fatty acids and aerobic metabolism to meet its energy needs. Although the heart can engage in anaerobic metabolism, this process relies on the continuous delivery of glucose and results in the formation of large amounts of lactic acid. Blood flow usually is regulated by the need of the cardiac muscle for oxygen. Even under normal resting conditions, the heart extracts and uses 60% to 80% of oxygen in blood flowing through the coronary arteries, compared with the 25% to 30% extracted by skeletal muscle.[5] Because there is little oxygen reserve in the blood, myocardial ischemia develops when the coronary arteries are unable to dilate and increase blood flow during periods of increased activity or stress.

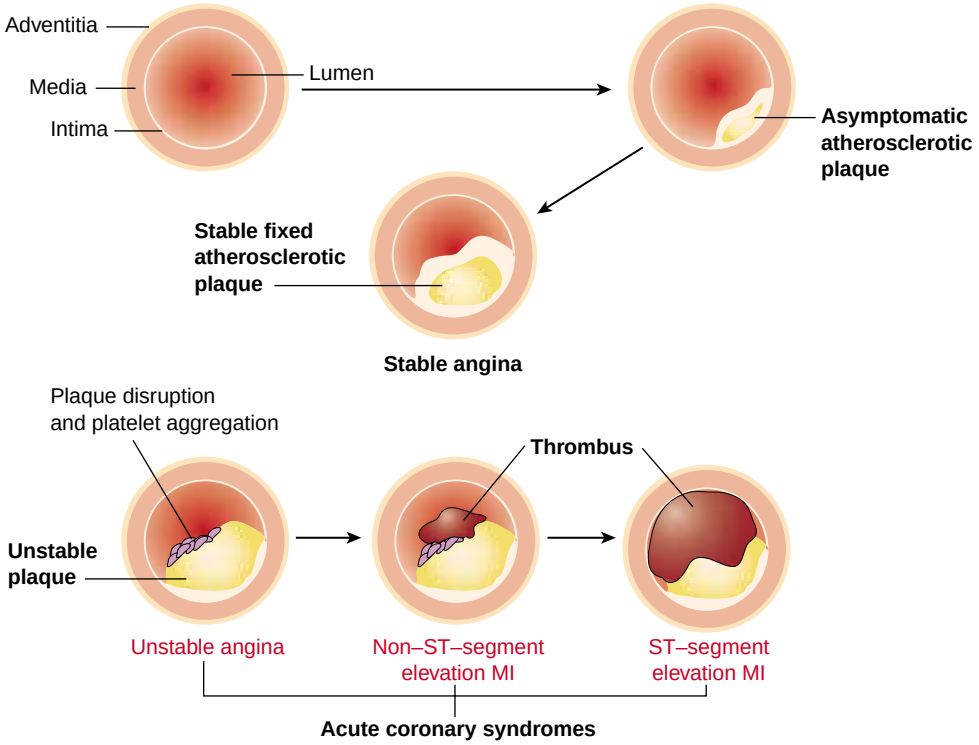
Pathogenesis of Coronary Heart Disease

Atherosclerosis (discussed in Chapter 15) is by far the most common cause of CHD, and atherosclerotic plaque disruption the most frequent cause of myocardial infarction and sudden death. More than 90% of persons with CHD have coronary atherosclerosis.[4] Most, if not all, have one or more lesions causing at least 75% reduction in cross-sectional area, the point at which augmented blood flow provided by compensatory vasodilation no longer is able to keep pace with even moderate increases in metabolic demand.[4]

Atherosclerosis can affect one or all three of the major epicardial coronary arteries and their branches (*i.e.*, one-, two-, or three-vessel disease). Clinically significant lesions may be located anywhere in these vessels but tend to predominate in the first several centimeters of the left anterior descending and left circumflex or the entire length of the right coronary artery.[4] Sometimes the major secondary branches also are involved.

There are two types of atherosclerotic lesions: the *fixed* or *stable plaque*, which obstructs blood flow, and the *unstable* or *vulnerable plaque*, which can rupture and cause platelet adhesion and thrombus formation. The fixed or stable plaque is commonly implicated in chronic ischemic heart disease (stable angina, variant or vasospastic angina, and silent myocardial ischemia) and the unstable plaque in unstable angina and myocardial infarction (Fig. 17-6).

Atherosclerotic plaques are made up of a soft lipid-rich core with a fibrous cap. Plaques with a thin fibrous cap overlying a large lipid core are at greatest risk for rupture. Plaque disruption may occur with or without thrombosis. When the plaque injury is mild, intermittent thrombotic occlusions may occur and cause episodes of anginal pain at rest. More extensive thrombus formation can progress until the coronary artery becomes occluded, leading to myocardial infarction. Platelets play a major role in linking plaque disruption to acute CHD. As a part of the response to plaque disruption, platelets aggregate and release



■ **FIGURE 17-6** ■ Atherosclerotic plaque. Stable fixed atherosclerotic plaque in stable angina and unstable plaque with plaque disruption and platelet aggregation in acute coronary syndromes.

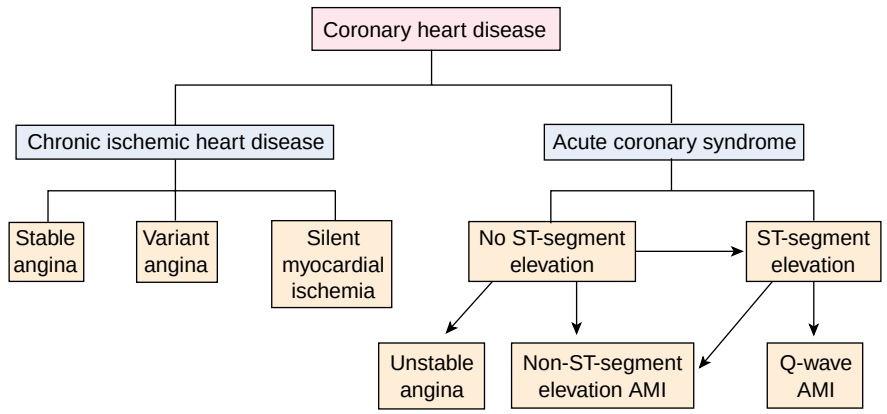
substances that further propagate platelet aggregation, vasoconstriction, and thrombus formation. Because of the role that platelets play in the pathogenesis of CHD, antiplatelet drugs (*e.g.*, low-dose aspirin) are frequently used for preventing heart attack.

There are two types of thrombi formed as a result of plaque disruption: white platelet-containing thrombi and red fibrin-containing thrombi. The thrombi in unstable angina have been characterized as grayish-white and presumably platelet rich.[4] Red thrombi, which develop with vessel occlusion in myocardial infarction, are rich in fibrin and red blood cells superimposed on the platelet component and extended by the stasis of blood flow.

Coronary heart disease is commonly divided into two types of disorders: chronic ischemic heart disease and the acute coronary syndromes (Fig. 17-7). There are three types of chronic ischemic heart disease: chronic stable angina, variant or vasospastic angina, and silent myocardial ischemia. The acute coronary syndromes represent the spectrum of ischemic coronary disease ranging from unstable angina through myocardial infarction.

Chronic Ischemic Heart Disease

The term *ischemia* means "to suppress or withhold blood flow." Limitations in coronary blood flow most commonly are the result of atherosclerosis, with vasospasm and thrombosis as contributing factors. The metabolic demands of the heart are increased with everyday activities such as mental stress, exercise, and exposure to cold. In certain disease states such as thyrotoxicosis, the metabolic demands may be so excessive that the blood flow may be inadequate despite normal coronary arteries. In other situations, such as aortic stenosis, the coronary arteries may not be diseased, but the perfusion pressure may be insufficient to provide adequate blood flow.

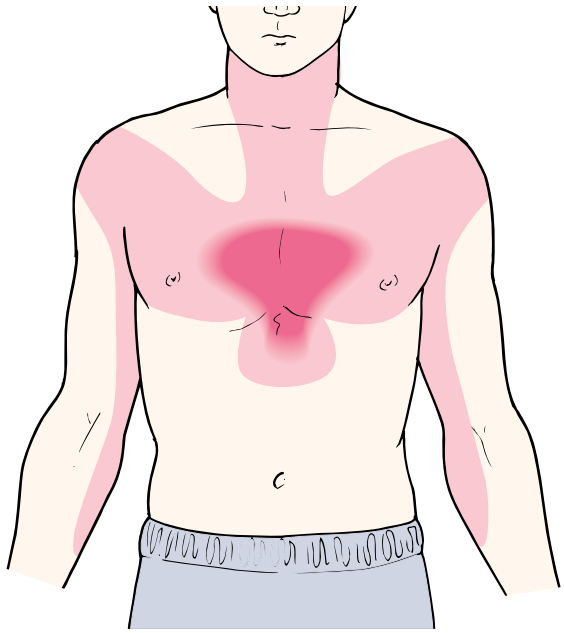


■ **FIGURE 17-7** ■ Types of chronic ischemic heart disease and acute coronary syndromes.

KEY CONCEPTS

ISCHEMIC HEART DISEASE

- The term *ischemic heart disease* refers to disorders in coronary blood flow due to stable or unstable atherosclerotic plaques.
- Stable atherosclerotic plaques produce fixed obstruction of coronary blood flow, with myocardial ischemia occurring during periods of increased metabolic need, such as in stable angina.
- Unstable atherosclerotic plaques tend to fissure or rupture, causing platelet aggregation and potential for thrombus formation with production of a spectrum of acute coronary syndromes of increasing severity, ranging from unstable angina, to non–ST-segment elevation myocardial infarction, to ST-segment elevation myocardial infarction.



■ **FIGURE 17-8** ■ Areas of pain due to angina.

Stable Angina

The term *angina* is derived from a Latin word meaning "to choke." Angina pectoris is characterized by recurring episodes of chest pain or pressure sensation associated with transient myocardial ischemia. Stable angina is the initial manifestation of ischemic heart disease in approximately half of persons with CHD.[7] Although most persons with stable angina have atherosclerotic heart disease; angina does not develop in a considerable number of persons with advanced coronary atherosclerosis. This probably is because of their sedentary lifestyle, the development of adequate collateral circulation, or the inability of these persons to perceive pain. In many instances, myocardial infarction occurs without a history of angina.

Stable angina is usually precipitated by situations that increase the work demands of the heart, such as physical exertion, exposure to cold, and emotional stress. The pain typically is described as a constricting, squeezing, or suffocating sensation. It usually is steady, increasing in intensity only at the onset and end of the attack. The pain of angina commonly is located in the precordial or substernal area of the chest; it is similar to myocardial infarction in that it may radiate to the left shoulder, jaw, arm, or other areas of the chest (Fig. 17-8). In some persons, the arm or shoulder pain may be confused with arthritis; in others, epigastric pain is confused with indigestion. Angina commonly is categorized according to whether it occurs with exercise or during rest, is of new onset, or is of increasing severity.

The diagnosis of stable angina is based on a detailed pain history and the presence of risk factors. Typically, chronic stable angina is provoked by exertion or emotional stress and relieved within minutes by rest or the use of nitroglycerin. A delay of more than 5 to 10 minutes before relief is obtained suggests that the symptoms are not caused by ischemia or that they are caused by severe ischemia.[8] Angina that occurs at rest, is of new onset, or is increasing in intensity or duration denotes an increased risk for myocardial infarction and should be evaluated using the criteria for acute coronary syndromes. Noncoronary causes of chest pain, such as that caused by esophageal or musculoskeletal disorders, are excluded. ECG, echocardiography, exercise stress testing or pharmacologic imaging studies, and coronary angiography may be used to confirm the diagnosis and describe the type of angina (exercise vs. vasospastic).

The treatment goals for stable angina are directed toward prevention of myocardial infarction and symptom reduction.[7] Both nonpharmacologic and pharmacologic treatment methods are used. Nonpharmacologic methods are aimed at symptom control and lifestyle modifications to lower risk factors for coronary disease. They include smoking cessation in persons who smoke, stress reduction, a regular exercise program, limiting dietary intake of cholesterol and saturated fats, weight reduction if obesity is present, and avoidance of cold or other stresses that produce vasoconstriction. Immediate cessation of activity often is sufficient to abort an anginal attack. Sitting down or standing quietly may be preferable to lying down because these positions decrease preload by producing pooling of blood in the lower extremities.

Pharmacologic methods include the use of antiplatelet drugs, β-adrenergic blocking drugs, calcium channel blockers, and/or long-acting nitrates. Sublingual nitroglycerin or nitroglycerin spray may be prescribed for immediate relief of anginal pain. Coronary artery bypass surgery or percutaneous transluminal coronary angioplasty may be indicated in persons with significant coronary artery occlusion (to be discussed).

Variant Angina

The syndrome of variant angina or *Prinzmetal's angina* was first described by the American cardiologist Myron Prinzmetal and associates in 1959.[9] Subsequent evidence indicated variant angina is caused by spasms of the coronary arteries, so the condition is often referred to as *vasospastic angina*.[10] In most instances, the spasms occur in the presence of coronary artery stenosis; however, variant angina has occurred in the absence of visible disease.

Unlike stable angina that occurs with exertion or stress, variant angina usually occurs during rest or with minimal exercise and frequently occurs during sleep. It commonly follows a cyclic or regular pattern of occurrence (*e.g.*, it happens at the same time each day). Dysrhythmias often occur when the pain is severe, and most persons are aware of their presence during an attack. ECG changes are significant if recorded during an attack. Persons with variant angina who have serious dysrhythmias during spontaneous episodes of pain are at a higher risk of sudden death.

Persons with variant angina usually experience response to treatment with calcium antagonists. These agents, along with short- and long-term nitrates, are the mainstay of treatment of variant angina. Because the two drugs act through different mechanisms, their beneficial effects may be additive.

Silent Myocardial Ischemia

Silent myocardial ischemia occurs in the absence of anginal pain. The factors that cause silent myocardial ischemia appear to be the same as those responsible for angina: impaired blood flow from the effects of coronary atherosclerosis or vasospasm. Silent myocardial ischemia affects three populations: persons who are asymptomatic without other evidence of CHD, persons who have had a myocardial infarct and continue to have episodes of silent ischemia, and persons with angina who also have episodes of silent ischemia.[11] The reason for the painless episodes of ischemia is unclear. The episodes may be shorter and involve less myocardial tissue than those producing pain. Another explanation is that persons with silent angina have defects in pain threshold or pain transmission, or autonomic neuropathy with sensory denervation. There is evidence of an increased incidence of silent myocardial ischemia in persons with diabetes mellitus, probably the result of autonomic neuropathy, which is a common complication of diabetes.[12]

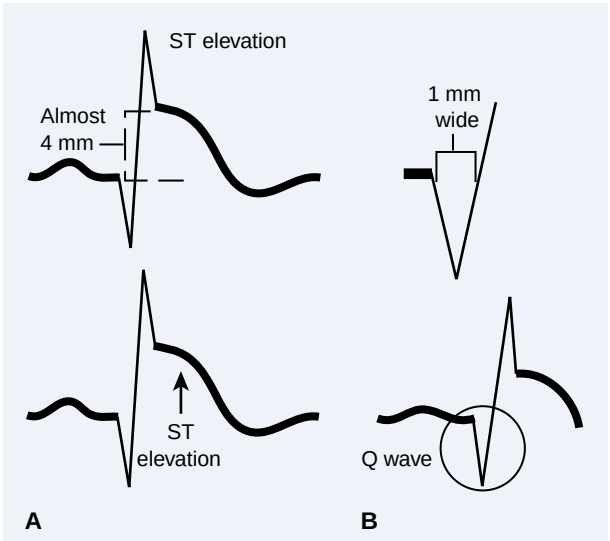
Acute Coronary Syndromes

The term *acute coronary syndromes* (ACS) has recently been accepted to describe the spectrum of acute ischemic heart diseases that include (1) unstable angina, (2) non–ST-segment elevation (non–Q-wave) myocardial infarction, and (3) ST-segment elevation (Q-wave) myocardial infarction[13,14] (Fig. 17-9).

Persons with an ACS are routinely classified as low risk or high risk based on presenting characteristics, ECG variables, serum cardiac markers, and the timing of presentation. Persons with ST-segment elevation on ECG are usually found to have complete coronary occlusion on angiography, and many ultimately have Q-wave myocardial infarction. Persons without ST-segment elevation are those in which coronary occlusion is subtotal or intermittent.

Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction

Unstable angina is characterized by symptoms at rest (usually prolonged, *i.e.*, >20 minutes); new-onset (<2 months) exertional angina; or recent (<2 months) acceleration in angina severity.[15] It is considered to be a clinical syndrome of myocardial ischemia ranging between stable angina and myocardial infarction. Unlike chronic stable angina, which is caused by a fixed obstruction, unstable angina most frequently results from atherosclerotic plaque disruption and repair. Unstable angina and non–ST-segment elevation myocardial infarction are similar conditions but have different severity.[15] They differ primarily in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of serum cardiac markers.



■ **FIGURE 17-9** ■ Illustration of an ECG tracing showing ST-segment elevation (**A**) and Q wave in acute coronary syndromes (**B**).

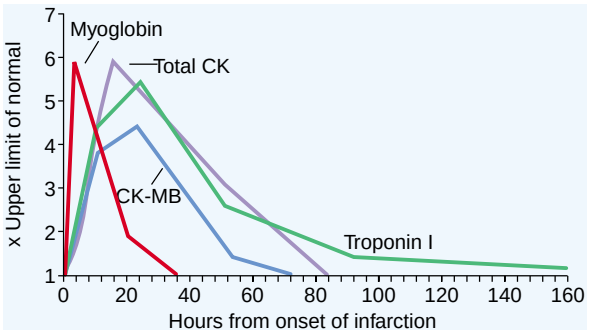
The diagnosis of unstable angina/non–ST-segment elevation myocardial infarction is based on pain severity and presenting symptoms, hemodynamic stability, ECG findings, and serum cardiac markers (see Box 17-1). Persons who have no serum markers for myocardial damage are considered to have unstable angina, whereas those with serum markers are considered to have non–ST-segment elevation myocardial infarction. When chest pain has been unremitting for longer than 20 minutes, the possibility of ST-segment elevation myocardial infarction usually is considered.[13]

ST-Segment Elevation Myocardial Infarction

Acute myocardial infarction (AMI), also known as a heart attack, is characterized by the ischemic death of myocardial tissue associated with atherosclerotic disease of the coronary arteries. Elevation of the ST segment usually indicates acute myocardial injury. When the ST segment is elevated without associated Q waves, it is called a *non–Q-wave infarction*. A non–Q-wave infarction usually represents a small infarct that may evolve into a larger infarct. The area of infarction is determined by the coronary artery that is affected and by its distribution of blood flow. Approximately 30% to 40% of infarcts affect the right coronary artery, 40% to 50% affect the left anterior descending artery, and the remaining 15% to 20% affect the left circumflex artery.[4]

The onset of AMI usually is abrupt, with pain as the significant symptom. The pain typically is severe and crushing, often described as being constricting, suffocating, or like "someone sitting on my chest." It usually is substernal, radiating to the left arm, neck, or jaw, although it may be experienced in other areas of the chest. Unlike that of angina, the pain associated

Serum Cardiac Markers



The relative timing, rate of rise, peak values, and duration of cardiac marker elevation above the upper limit of normal for multiple serum markers following AMI. (Modified from Antman E.M. [1994]. General hospital management. In Julian D.G. & Braunwald E. [Eds.], *Management of acute myocardial infarction* [p. 63]. London: W.B. Saunders Ltd.).

- *Myoglobin* is an oxygen-carrying protein, similar to hemoglobin, that is normally present in cardiac and skeletal muscle. It is a small molecule that is released quickly from infarcted myocardial tissue and becomes elevated within 1 hour after myocardial cell death, with peak levels reached within 4 to 8 hours. Because myoglobin is present in both cardiac and skeletal muscle, it is not cardiac specific.
- *Creatine kinase* (CK), formerly called *creatinine phosphokinase,* is an intracellular enzyme found in muscle cells. Muscles, including cardiac muscle, use adenosine triphosphate (ATP) as their energy source. Creatine, which serves as a storage form of energy in muscle, uses CK to convert ADP to ATP. CK exceeds normal range within 4 to 8 hours of myocardial injury and declines to normal within 2 to 3 days. There are three isoenzymes of CK, with the MB isoenzyme (CK-MB) being highly specific for injury to myocardial tissue.
- *The troponin complex* consists of three subunits (*i.e.,* troponin C, troponin I, and troponin T) that regulate calcium-mediated contractile process in striated muscle. These subunits are released during myocardial infarction. Cardiac muscle forms of both troponin T and troponin I are used in diagnosis of myocardial infarction. Troponin I (and troponin T; not shown) rises more slowly than myoglobin and may be useful for diagnosis of infarction, even up to 3 to 4 days after the event. It is thought that cardiac troponin assays are more capable of detecting episodes of myocardial infarction in which cell damage is below that detected by CK-MB level.

with myocardial infarction is more prolonged and not relieved by rest or nitroglycerin, and narcotics frequently are required. Women often experience atypical ischemic-type chest discomfort, whereas the elderly may report shortness of breath more frequently than chest pain.[16]

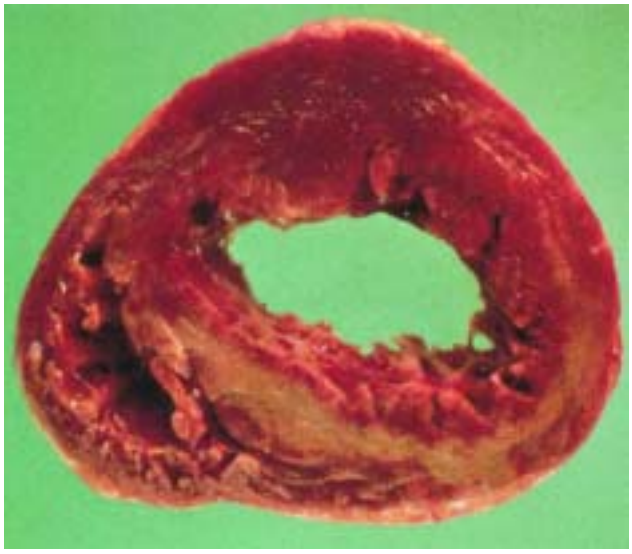
Gastrointestinal complaints are common. There may be a sensation of epigastric distress; nausea and vomiting may occur. Reports of fatigue and weakness, especially of the arms and legs, are common. Pain and sympathetic stimulation combine to give rise to tachycardia, anxiety, restlessness, and feelings of impending doom. The skin often is pale, cool, and moist. The impaired myocardial function may lead to hypotension and shock.

Sudden death from AMI is death that occurs within 1 hour of symptom onset. It usually is attributed to fatal dysrhythmias, which may occur without evidence of infarction. Approximately 30% to 50% of persons with AMI die of ventricular fibrillation within the first few hours after symptoms begin.[16] Early hospitalization after onset of symptoms greatly improves chances of averting sudden death because appropriate resuscitation facilities are immediately available when potentially fatal ventricular dysrhythmias occur.

Pathologic Changes. The extent of the infarct depends on the location and degree of occlusion, amount of heart tissue supplied by the vessel, duration of the occlusion, metabolic needs of the affected tissue, extent of collateral circulation, and other factors such as heart rate, blood pressure, and cardiac rhythm. A myocardial infarct may involve the endocardium, myocardium, epicardium, or a combination of these. *Transmural infarcts* involve the full thickness of the ventricular wall and most commonly occur when there is obstruction of a single artery.[4] *Subendocardial infarcts* involve the inner one third to one half of the ventricular wall and occur more frequently in the presence of severely narrowed but still patent arteries. Most infarcts are transmural, involving the free wall of the left ventricle and often the interventricular septum (Fig. 17-10).

The principal biochemical consequence of AMI is the conversion from aerobic to anaerobic metabolism with inadequate production of energy to sustain normal myocardial function. Although gross tissue changes are not apparent for hours after onset of an AMI, the ischemic area ceases to function within a matter of minutes, and irreversible myocardial cell damage occurs after 20 to 40 minutes of severe ischemia.[4]

The term *reperfusion* refers to re-establishment of blood flow through use of thrombolytic therapy or revascularization procedures. Early reperfusion (within 15 to 20 minutes) after onset of ischemia can prevent necrosis. Reperfusion after a longer interval can salvage some of the myocardial cells that would have died because of longer periods of ischemia. Even though much of the viable myocardium existing at the time of reflow ultimately recovers, critical abnormalities in biochemical function may persist, causing impaired ventricular function. The recovering area of the heart is often referred to as a *stunned myocardium*. Because myocardial function is lost before cell death occurs, a stunned myocardium may not be capable of sustaining life, and persons with large areas of dysfunctional myocardium may require life support until the stunned regions regain their function.[4]



■ **FIGURE 17-10** ■ Acute myocardial infarct. A cross-section of the ventricles of a man who died a few days after the onset of severe chest pain shows a transmural infarct in the posterior and septal regions of the left ventricle. The necrotic myocardium is soft, yellowish, and sharply demarcated. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 558]. Philadelphia: Lippincott Williams & Wilkins)

Myocardial cells that undergo necrosis are gradually replaced with scar tissue. An acute inflammatory response develops in the area of necrosis approximately 2 to 3 days after infarction. Thereafter, macrophages begin removing the necrotic tissue; the damaged area is gradually replaced with an ingrowth of highly vascularized granulation tissue, which gradually becomes less vascular and more fibrous.[4] At approximately 3 to 7 days, the center of the infarcted area is soft and yellow; if rupture of the ventricle, interventricular septum, or valve structures occurs, it usually happens at this time. Replacement of the necrotic myocardial tissue usually is complete by the seventh week. Fibrous scar tissue lacks the contractile, elastic, and conductive properties of normal myocardial cells.

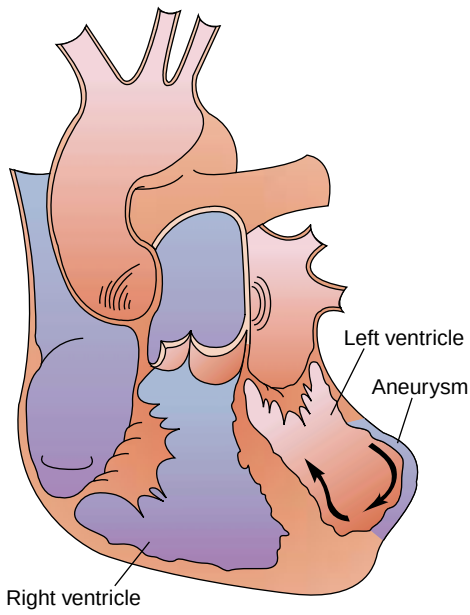
Complications. The size and location of the infarction determine the acute course, clinical complications, and long-term prognosis. Among the early complications of AMI are life-threatening dysrhythmias, sudden death, heart failure, and cardiogenic shock (see Chapter 18). Recurrent infarction may occur in the region of infarction (infarct extension). It may be associated with prolonged or intermittent episodes of chest pain.

Other complications of AMI include pericarditis, development of thromboemboli, rupture of the heart, and formation of ventricular aneurysms. Pericarditis may complicate the course of AMI. It usually appears on the second or third day after infarction. Dressler's syndrome describes the signs and symptoms associated with pericarditis, pleurisy, and pneumonitis: fever, chest pain, dyspnea, and abnormal laboratory test results (*i.e.*, elevated white blood cell count and sedimentation rate) and ECG findings. The symptoms may arise between 1 day and several weeks after infarction and are thought to represent a hypersensitivity response to tissue necrosis. Thromboemboli are a potential complication of AMI, arising as venous thrombi or occasionally as clots from the wall of the ventricle. Immobility and impaired cardiac function contribute to stasis of blood in the venous system. Infrequent, but dreaded, complications of AMI include rupture of the myocardium, the interventricular septum, or a papillary muscle. Complete rupture of the left ventricular wall, which usually occurs 3 to 7 days after AMI when the injured ventricular tissue is soft and weak, usually results in instant death.

An aneurysm is an outpouching of the ventricular wall that develops in 10% to 20% of persons surviving AMI, usually those with anterior Q-wave infarctions.[16] Scar tissue does not have the characteristics of normal myocardial tissue; when a large section of ventricular muscle is replaced by scar tissue, an aneurysm may develop (Fig. 17-11). This section of the myocardium does not contract with the rest of the ventricle during systole. Instead, it diminishes the pumping efficiency of the heart and increases the work of the left ventricle, predisposing the patient to heart failure. Ischemia in the surrounding area predisposes the patient to development of dysrhythmias, and stasis of blood in the aneurysm can lead to thrombus formation. Surgical resection may be performed to improve ventricular function.

Diagnosis and Treatment. Diagnosis of AMI is based on presenting signs and symptoms, ECG charges, and serum cardiac markers. ECG changes may not be present immediately after the onset of symptoms, except as dysrhythmias. The occurrence of dysrhythmias and conduction defects depends on the areas of the heart and conduction pathways that are included in the infarct. Typical ECG changes include ST-segment elevation, prolongation of the Q wave, and inversion of the T wave.

The treatment of ACS depends on the extent of ischemia and/or infarction. Because the specific diagnosis of AMI is often difficult to make at the time of entry into the health care system, the immediate management of all ACS is generally



■ **FIGURE 17-11** ■ Paradoxical movement of a ventricular aneurysm during systole.

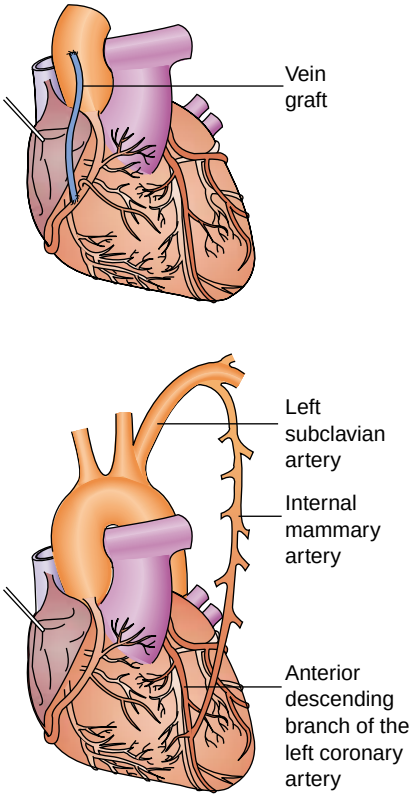
the same. The American College of Cardiology/American Heart Association (ACC/AHA) Task Force guidelines for management of AMI recommend that the initial emergency department management of myocardial infarction include administration of oxygen by nasal prongs; sublingual nitroglycerin; adequate analgesia; and aspirin (160 to 325 mg).[16] ECG monitoring should be instituted, and a 12-lead electrocardiogram should be performed. The severe pain of AMI gives rise to anxiety and recruitment of autonomic nervous system responses, both of which increase the work demands of the heart. Morphine is often given intravenously for pain relief because it has a rapid onset of action and the intravenous route does not elevate serum enzymes. Aspirin is given for its antiplatelet effects.

Immediate reperfusion therapy, using thrombolytic agents or revascularization procedures, is usually indicated for persons with ECG evidence of infarction. The best results occur if treatment is initiated within 60 to 90 minutes of symptom onset.[17] The magnitude of benefit declines after this period, but it is possible that some benefit can be achieved for as long as 12 hours after the onset of pain.

Thrombolytic agents dissolve blood and platelet clots and are used to reduce mortality and limit infarct size. Revascularization interventions include percutaneous transluminal coronary angioplasty (PTCA), coronary stent implantation, and coronary artery bypass surgery. PTCA involves the recanalization of a stenotic vessel using balloon dilatation (Fig. 17-12). The procedure is done under local anesthesia in the cardiac catheterization laboratory and is similar to cardiac catheterization for coronary angiography. Implantation of coronary stents (fenestrated, stainless-steel tubes) reduces the occurrence of restenosis after PTCA. A new approach to the prevention of coronary restenosis after balloon angioplasty and stent placement is the use of localized intracoronary radiation. The procedure, also known as *brachytherapy*, is credited with inhibiting cell proliferation, vascular lesion formation, and prevention of constrictive arterial remodeling. The radiation source can be impregnated into stents, or the radiation can be delivered by a radiation catheter containing a sealed source of radiation (radioactive seeds, wire, or ribbon) that is inserted into the treatment site and then removed.[18]

Coronary artery bypass surgery remains an option for patients who have significant CHD uncontrolled by angioplasty or pharmacologic therapy. In this surgical procedure, revascularization of the myocardium is effected by placing a saphenous vein graft between the aorta and the affected coronary artery distal to the site of occlusion or by using the internal mammary artery as a means of revascularizing the left anterior descending artery or its branches (Fig. 17-13).

Rehabilitation Programs. Rehabilitation programs for persons with ACS incorporate rest, exercise, and risk factor modification. An exercise program is an integral part of a cardiac rehabilitation program. It includes activities such as walking, swimming, and bicycling. These exercises involve changes in muscle length and rhythmic contractions of muscle groups. Most exercise programs are individually designed to meet each person's physical and psychological needs. The goal of the exercise program is to increase the maximal oxygen consumption by the muscle tissues, so that these persons are able to perform more work at a lower heart rate and blood pressure. In addition to



■ **FIGURE 17-13** ■ Coronary artery revascularization. (**Top**) Saphenous vein bypass graft. The vein segment is sutured to the ascending aorta and the right coronary artery at a point distal to the occluding lesion. (**Bottom**) Mammary artery bypass. The mammary artery is anastomosed to the anterior descending left coronary artery, bypassing the obstructing lesion.

exercise, cardiac risk factor modification incorporates strategies for smoking cessation, weight loss, stress reduction, and control of hypertension and diabetes.

In summary, CHD is a disorder of impaired coronary blood flow, usually caused by atherosclerosis. Myocardial ischemia occurs when there is a disparity between coronary blood flow and the metabolic needs of the heart. The *chronic ischemic heart diseases* include stable angina, variant angina, and silent myocardial ischemia. Stable angina is associated with a fixed atherosclerotic obstruction and pain that is precipitated by increased work demands on the heart and relieved by rest. Variant angina results from spasms of the coronary arteries. Silent myocardial ischemia occurs without symptoms. Treatment includes nonpharmacologic methods, such as pacing of activities and avoidance of activities that cause angina, and the use of pharmacologic agents, including aspirin, β-adrenergic blockers, calcium channel blockers, and nitrates.

The acute coronary syndromes result from unstable atherosclerotic plaques with plaque disruption, platelet aggregation, and thrombus formation. They include unstable angina, non–ST-segment elevation AMI, and ST-segment (Q wave) elevation AMI. Unstable angina is an accelerated form of angina in which the pain occurs more frequently, is more severe, and lasts longer than chronic stable angina. AMI refers to the ischemic death of myocardial tissue associated with obstructed blood flow in the coronary arteries. ST-segment elevation and Q wave AMI differ in terms of the extent of myocardial damage. The complications of AMI include potentially fatal dysrhythmias, heart failure and cardiogenic shock, pericarditis, thromboemboli, rupture of cardiac structures, and ventricular aneurysms. Treatment goals focus on the reestablishment of myocardial blood flow through rapid recanalization of the occluded coronary artery, prevention of clot extension through use of aspirin and other antiplatelet and antithrombotic agents, alleviation of pain, and measures such as the administration of oxygen to increase the oxygen saturation of hemoglobin. Thrombolytic agents, PTCA, and coronary artery bypass surgery are measures used to recanalize or bypass the occluded artery.

MYOCARDIAL AND ENDOCARDIAL DISEASE

Myocardial diseases, including myocarditis and the primary cardiomyopathies, are disorders originating in the myocardium, but not from cardiovascular disease. Both myocarditis and the primary cardiomyopathies are causes of sudden death and heart failure.

Myocarditis

The term *myocarditis* is used to describe an inflammation of the heart muscle and conduction system without evidence of myocardial infarction.[19,20] Viruses are the most important cause of myocarditis in North America and Europe.[20] Coxsackieviruses A and B and other enteroviruses probably account for most of the cases. Myocarditis is a frequent pathologic cardiac finding in persons with acquired immunodeficiency syndrome (AIDS), although it is unclear whether it is caused by the human immunodeficiency virus itself or by a secondary infection. Other causes of myocarditis are radiation therapy, hypersensitivity reactions, or exposure to chemical or physical agents that induce acute myocardial necrosis and secondary inflammatory changes. A drug that is increasingly associated with myocarditis is cocaine, probably because of its vasoconstrictor properties.[20]

Myocardial injury attributable to infectious agents is thought to result from necrosis caused by direct invasion of the offending organism, toxic effects of exogenous toxins or endotoxins produced by a systemic pathogen, or destruction of cardiac tissue by immunologic mechanisms initiated by the infectious agent. The immunologic response may be directed at foreign antigens of the infectious agent that share molecular characteristics with those of the host cardiac myocardial cells (*i.e.*, molecular mimicry; see Chapter 10), providing a continuous stimulus for the immune response even after the infectious agent has been cleared from the body.

The *manifestations of myocarditis* vary from an absence of symptoms to profound heart failure or sudden death. When viral myocarditis occurs in children or young adults, it often is asymptomatic. Acute symptomatic myocarditis typically manifests as a flulike syndrome with malaise, low-grade fever, and tachycardia that is more pronounced than would be expected for the level of fever present. There commonly is a history of an upper respiratory tract or gastrointestinal tract infection, followed by a latent period of several days. Cardiac auscultation may reveal an S_3 ventricular gallop rhythm and a transient pericardial or pleurocardial rub. In approximately one half of the cases, myocarditis is transient, and symptoms subside within 1 to 2 months. In other cases, fulminant heart failure and life-threatening dysrhythmias develop, causing sudden death. Still others progress to subacute and chronic disease.

The diagnosis of myocarditis is based on clinical manifestations and ECG changes. Serum creatinine kinase often is elevated. Troponin T or troponin I, or both, may be elevated, providing evidence of myocardial cell damage.[20] Confirmation of active myocarditis requires endomyocardial biopsy.

Treatment measures focus on symptom management and prevention of myocardial damage. Bed rest is necessary, and activity restriction must be maintained until fever and cardiac symptoms subside to decrease the myocardial workload. Activity is gradually increased but kept at a sedentary level for 6 months to 1 year. The use of corticosteroids and immunosuppressant drugs remains a matter of controversy. Although treatment of myocarditis is successful in many persons, some experience congestive heart failure and can expect only a limited life span. For these persons, heart transplantation becomes an alternative.

Cardiomyopathies

The cardiomyopathies are a group of disorders that affect the heart muscle. They can develop as primary or secondary disorders. The primary cardiomyopathies, which are discussed in this chapter, are heart muscle diseases of unknown origin. Secondary cardiomyopathies are conditions in which the car-

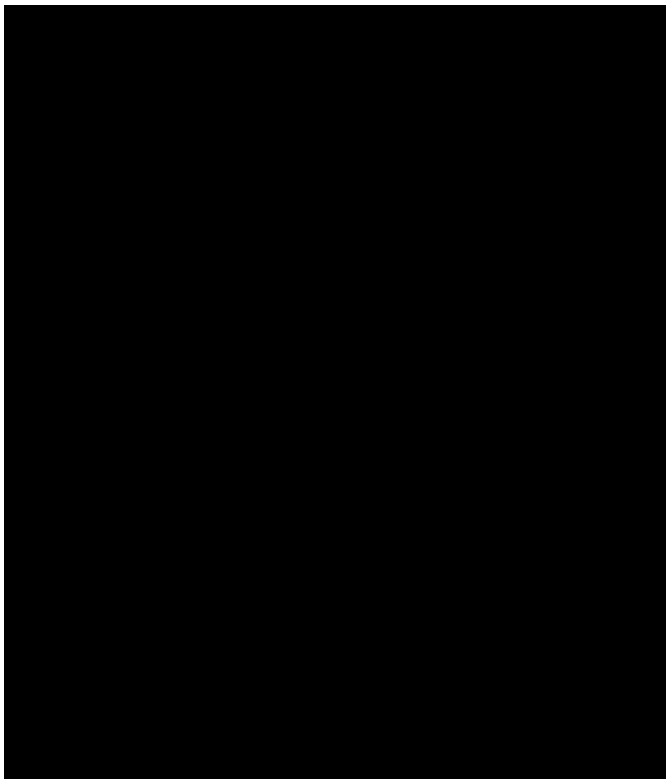
diac abnormality results from another cardiovascular disease, such as myocardial infarction. The onset of the primary cardiomyopathies often is silent, and symptoms do not occur until the disease is well advanced. The diagnosis is suspected when a young, previously healthy, normotensive person experiences cardiomegaly and heart failure.

In 1989, the International Society and Federation of Cardiology and the World Health Organization categorized the primary cardiomyopathies into three groups: dilated, hypertrophic, and restrictive[21] (Fig. 17-14). This classification was enlarged in 1996 to include arrhythmogenic right ventricular cardiomyopathy.[22] Peripartum cardiomyopathy is a disorder of pregnancy.

Dilated Cardiomyopathies

Dilated cardiomyopathies are characterized by progressive cardiac hypertrophy and dilation and impaired pumping ability of one or both ventricles. Although all four chambers of the heart are affected, the ventricles are more dilated than the atria. Because of the wall thinning that accompanies dilation, the thickness of the ventricular wall often is less than would be expected for the amount of hypertrophy present.[23] Mural thrombi are common and may be a source of thromboemboli. The cardiac valves are intrinsically normal. Microscopically, there is evidence of scarring and atrophy of myocardial cells.

Dilated cardiomyopathy may result from a number of different myocardial insults, including infectious myocarditis, alcohol and other toxic agents, metabolic influences, neuromuscular diseases, and immunologic disorders. Genetic influences have been documented in some cases. Often the cause is unknown; these cases are appropriately designated as *idiopathic dilated cardiomyopathy*.



The most common initial manifestations of dilated cardiomyopathy are those related to heart failure. There is a profound reduction in the left ventricular ejection fraction (*i.e.*, ratio of stroke volume to end-diastolic volume) to 40% or less, compared with a normal value of approximately 67%. After symptoms have developed, the course of the disorder is characterized by a worsening of heart failure, development of mural thrombi, and ventricular dysrhythmias. The most striking symptoms of dilated cardiomyopathy are dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, weakness, fatigue, ascites, and peripheral edema. The systolic blood pressure is normal or low, and the peripheral pulses often are of low amplitude. Pulsus alternans, in which the pulse regularly alternates between weaker and stronger volume, may be present. Tachycardia, atrial fibrillation, and complex ventricular dysrhythmias leading to sudden cardiac death are common.

The treatment of dilated cardiomyopathy is directed toward relieving the symptoms of heart failure and reducing the workload of the heart. Digoxin, diuretics, and afterload-reducing drugs are used to improve myocardial contractility and decrease left ventricular filling pressures. Avoiding myocardial depressants, including alcohol, and pacing rest with asymptomatic levels of exercise or activity is imperative. Insertion of an internal cardioverter-defibrillator may be indicated for controlling recurrent ventricular dysrhythmias. In persons with severe heart failure that is refractory to treatment, cardiac transplantation may be considered.

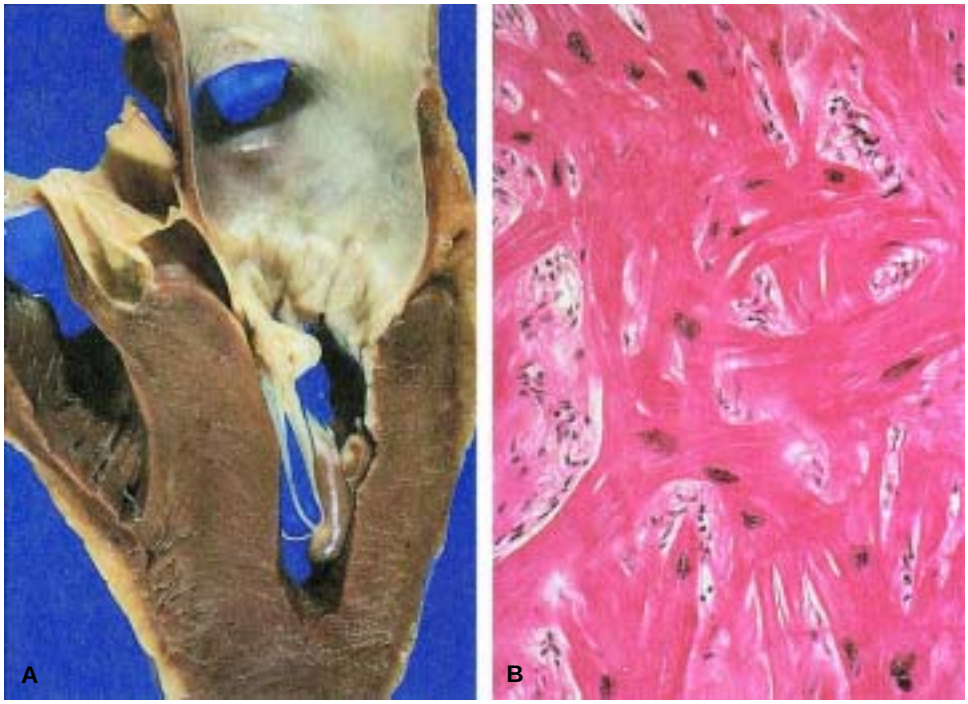
Hypertrophic Cardiomyopathies

Hypertrophic cardiomyopathy is characterized by left, right, or left and right ventricular hypertrophy and abnormal diastolic filling. Although the hypertrophy may be symmetric, the involvement of the ventricular septum often is disproportionate, producing intermittent left ventricular outflow obstruction.[24] Synonyms for this disorder include *idiopathic hypertrophic subaortic stenosis* and *asymmetric septal hypertrophy*.

Symptomatic hypertrophic cardiomyopathy commonly is a disease of young adulthood. The cause of the disorder is unknown, although it often is of familial origin, with the disorder being inherited as an autosomal dominant trait. Molecular studies of the genetic alterations responsible for hypertrophic cardiomyopathy suggest that the disease is caused by mutation in one of four genes encoding the proteins of the cardiac muscle fibers.[24] More than 50 mutations in these proteins have been identified. The prognosis of persons with different myosin mutations varies greatly; some mutations are relatively benign, whereas others are associated with premature death.

A distinctive microscopic finding in hypertrophic cardiomyopathy is myofibril disarray (Fig. 17-15). Instead of the normal parallel arrangement of myofibrils, the myofibrils branch off at random angles, sometimes at right angles to an adjacent fiber with which they connect. Small bundles of fibers may course haphazardly through normally arranged muscle fibers.[4,25] These disordered fibers may produce abnormal movements of the ventricles, with uncoordinated contraction and impaired relaxation. Arrhythmias and premature sudden death are common with this disorder. Study results have shown that 36% of young athletes who die suddenly have probable or definite hypertrophic cardiomyopathy.[1]

The manifestations of hypertrophic cardiomyopathy are variable; for reasons that are unclear, in some persons, the dis-



■ **FIGURE 17-15** ■ Hypertrophic cardiomyopathy. (**A**) The heart has been opened to show striking asymmetric left ventricular hypertrophy. The interventricular septum is thicker than the free wall of the ventricle and impinges on the outflow tract. (**B**) A section of the myocardium shows myocardial fiber disarray characterized by oblique and often perpendicular orientation of adjacent hypertrophic myocytes. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 580]. Philadelphia: Lippincott Williams & Wilkins)

order remains stable for many years, with symptoms gradually increasing as the disease progresses, but others experience sudden cardiac death as first evidence of the disease.[24] Atrial fibrillation is a common precursor to sudden death in those who die of dysrhythmias. Dyspnea is the most common symptom associated with a gradual elevation in left ventricular diastolic pressure resulting from impaired ventricular filling and increased wall stiffness caused by ventricular hypertrophy. Because of the obstruction to outflow from the left ventricle, increasingly greater levels of ventricular pressure are needed to eject blood into the aorta, limiting cardiac output. Chest pain, fatigue, and syncope are common and worsen during exertion.

The treatment of hypertrophic cardiomyopathy includes medical and surgical management. The goal of medical management is to relieve the symptoms by lessening the pressure difference between the left ventricle and the aorta, thereby improving cardiac output. Drugs that block the β-adrenergic receptors may be used in persons with chest pain, dysrhythmias, or dyspnea.[24] These drugs reduce the heart rate and improve myocardial function by allowing more time for ventricular filling and reducing ventricular stiffness. The calcium channel-blocking drug verapamil may be used as an alternative to the β-adrenergic blockers. Increased calcium uptake and increased intracellular calcium content are associated with an increased contractile state, a characteristic finding in patients with hypertrophic cardiomyopathy.

Surgical treatment may be used if severe symptoms persist despite medical treatment. It involves incision of the septum with or without the removal of part of the muscle tissue (*i.e.*, myectomy). It is accompanied by all the risks of open heart surgery. Implantable cardioverter-defibrillators may be used to abort lethal arrhythmias.[24]

Restrictive Cardiomyopathies

Of the three categories of cardiomyopathies, the restrictive type is the least common in Western countries. With this form of cardiomyopathy, ventricular filling is restricted because of excessive rigidity of the ventricular walls, although the contractile properties of the heart remain relatively normal. The condition is endemic in parts of Africa, India, South and Central America, and Asia.[26] Outside the tropics, the most common causes of restrictive cardiomyopathy are endocardial infiltrations such as amyloidosis. Amyloid infiltrations of the heart are common in the elderly. The idiopathic form of the disorder may have a familial origin.

Symptoms of restrictive cardiomyopathy include dyspnea, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, ascites, fatigue, and weakness. The manifestations of restrictive cardiomyopathy resemble those of constrictive pericarditis. In the advanced form of the disease, all the signs of heart failure are present except cardiomegaly.

Arrhythmogenic Right Ventricular Cardiomyopathy

In arrhythmogenic right ventricular cardiomyopathy, the right ventricular myocardium is replaced with a fibrofatty deposit. This condition frequently has a familial predisposition, with an autosomal dominant inheritance pattern. Sudden death caused by arrhythmias is common, particularly in the young.[22]

Peripartum Cardiomyopathy

Peripartum cardiomyopathy refers to left ventricular dysfunction developing during the last month before delivery to 5 months after delivery. The condition is relatively rare, with an estimated incidence of 1 per 3000 to 4000 live birth pregnancies.[27] Risk factors for peripartum cardiomyopathy include advanced maternal age, African-American race, multifetal pregnancies, preeclampsia, and gestational hypertension.[27] The reported mortality rate ranges from 18% to 56%. Survivors may not recover completely and may require heart transplantation.

The cause of peripartum cardiomyopathy is uncertain. A number of causes have been proposed, including myocarditis, an abnormal immune response to pregnancy, maladaptive response to the hemodynamic stresses of pregnancy, or prolonged inhibition of contractions in premature labor.

The signs and symptoms resemble those of dilated cardiomyopathy. Because many women experience dyspnea, fatigue, and pedal edema during the last month of normal pregnancy, the symptoms may be ignored and the diagnosis delayed. The diagnosis is based on echocardiography studies, ECG, and other tests of cardiac function. Treatment methods are similar to those used in dilated cardiomyopathy.

There are two possible outcomes of peripartum cardiomyopathy. In approximately one half of cases, the heart returns to normal within 6 months, and the chances for long-term survival are good. In these women, heart failure returns only during subsequent pregnancies. In the other one half of cases, cardiomegaly persists, the prognosis is poor, and death is probable if another pregnancy occurs. In women with cardiomyopathy associated with documented viral myocarditis, the likelihood of recurrence is low.

Disorders Affecting the Endocardium

Infective Endocarditis

Infective endocarditis is a relatively uncommon, life-threatening infection of the endocardial surface of the heart, including the heart valves. Because bacteria are the most common infecting organisms, the condition may be referred to as *bacterial endocarditis*. Despite important advances in antimicrobial therapy and improved ability to diagnose and treat complications, infective endocarditis continues to produce substantial morbidity and mortality.

Two factors contribute to the development of infective endocarditis: a damaged endocardial surface and a portal of entry by which the organism gains access to the circulatory system. The presence of valvular disease, prosthetic heart valves, or congenital heart defects provides an environment conducive to bacterial growth.[4,28,29] In persons with pre-existing valvular or endocardial defects, simple gum massage or an innocuous oral lesion may afford the pathogenic bacteria access to the bloodstream. Transient bacteremia may emerge in the course of seemingly minor health problems, such as an upper respiratory tract infection, a skin lesion, or a dental procedure.

Although infective endocarditis usually occurs in persons with pre-existing heart lesions, it also can develop in normal hearts of intravenous drug abusers. The mode of infection is a contaminated drug solution or a needle contaminated with skin flora. Intravenous drug abuse is the most common source of right-sided (tricuspid) lesions. Although staphylococcal infections are common, intravenous drug users may be infected with unusual organisms, such as gram-negative bacilli, yeasts, and fungi.

In hospitalized patients, infective endocarditis may arise as a complication of infected intravascular or urinary tract catheters. Infective endocarditis also may complicate prosthetic heart valve replacement. It can develop as an early infection that follows surgery or as a later infection that results from the long-term presence of the prosthesis.

Depending on the duration of the disease, presenting manifestations, and complications, cases of infective endocarditis can be classified as acute, subacute, or chronic.[30] *Acute infective endocarditis* is thought primarily to affect persons with normal hearts and usually is caused by suppurative organisms such as *Staphylococcus aureus* and *Streptococcus pyogenes*. *Subacute endocarditis* is seen most frequently in patients with damaged hearts and usually is caused by less virulent organisms such as *Streptococcus viridans* and *Staphylococcus epidermis*. Certain low-virulence organisms such as *Legionella* and *Brucella* may produce a chronic form of the disease.

Pathophysiology. The pathophysiology of infective endocarditis involves the formation of intracardiac vegetative lesions that have local and distant systemic effects. The vegetative lesion that is characteristic of infective endocarditis consists of a collection of infectious organisms and cellular debris enmeshed in the fibrin strands of clotted blood. The infectious loci continuously release bacteria into the bloodstream and are a source of persistent bacteremia. These lesions may be singular or multiple, may grow to be as large as several centimeters, and usually are found loosely attached to the free edges of the valve surface (Fig. 17-16). As the lesions grow, they cause valve destruction, leading to valvular regurgitation, ring abscesses with heart block, and valve perforation. The loose organization of these lesions permits the organisms and fragments of the lesions to form emboli and travel in the bloodstream. The fragments may lodge in small blood vessels, causing small hemorrhages, abscesses, and infarction of tissue. The bacteremia also can initiate immune responses thought to be responsible for the skin manifestations, arthritis, glomerulonephritis, and other immune disorders associated with the condition.

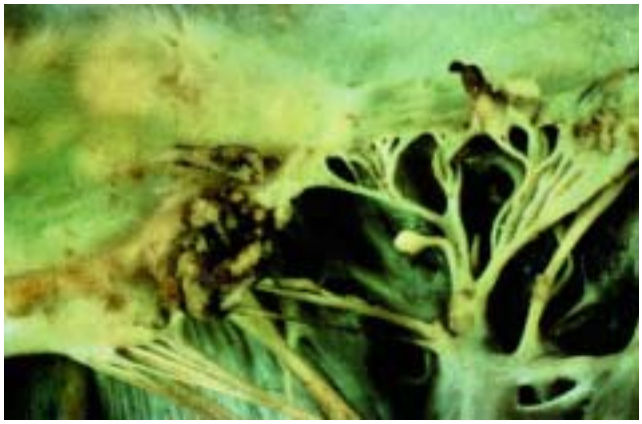


FIGURE 17-16 Bacterial endocarditis. The mitral valve shows destructive vegetations, which have eroded through the free margin of the valve leaflet. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 572]. Philadelphia: Lippincott Williams & Wilkins)

Clinical Course. The clinical course of infective endocarditis is determined by the extent of heart damage, the type of organism involved, site of infection (*i.e.*, right or left side of the heart), and whether embolization from the site of infection occurs. Destruction of infected heart valves is common with certain forms of organisms, such as *S. aureus*. Peripheral embolization can lead to metastatic infections and abscess formation; these are particularly serious when they affect organs such as the brain and kidneys. In right-sided endocarditis, which usually involves the tricuspid valve, septic emboli travel to the lung, causing infarction and lung abscesses.

The signs and symptoms of infective endocarditis include fever and signs of systemic infection, change in the character of an existing heart murmur, and evidence of embolic distribution of the vegetative lesions. In the acute form, the fever usually is spiking and accompanied by chills. In the subacute form, the fever usually is low grade, of gradual onset, and frequently accompanied by other systemic signs of inflammation, such as anorexia, malaise, and lethargy. Small petechial hemorrhages frequently result when emboli lodge in the small vessels of the skin, nail beds, and mucous membranes. Splinter hemorrhages (*i.e.*, dark red lines) under the nails of the fingers and toes are common. Cough, dyspnea, arthralgia or arthritis, diarrhea, and abdominal or flank pain may occur as the result of systemic emboli.

The blood culture is the most definitive diagnostic procedure and is essential in determining treatment. The optimal time to obtain cultures is during a chill, just before a temperature rise. Usually two separate positive cultures are required for diagnosis. The echocardiogram is useful in detecting underlying valvular disease. Transesophageal echocardiography is rapid and noninvasive, and has proved useful for detecting vegetations. Other signs, such as the presence of embolic disease or evidence of immunologic phenomena such as glomerulonephritis or rheumatoid factor, provide useful diagnostic information.

Treatment of infective endocarditis focuses on identifying and eliminating the causative microorganism, minimizing the residual cardiac effects, and treating the pathologic effects of the emboli. Antibiotic therapy is used to eradicate the pathogen. Surgery may be indicated for moderate to severe heart failure, progressive renal failure, significant emboli, dysrhythmias, or left-sided endocarditis. Infected prosthetic valves may need to be replaced.

Of great importance is the prevention of infective endocarditis in persons with prosthetic heart valves, previous bacterial endocarditis, certain congenital heart defects, and other known risk factors.[30] Prevention can be largely accomplished through prophylactic administration of an antibiotic before dental and other procedures that may cause bacteremia.[30]

Rheumatic Heart Disease

Rheumatic fever is an acute, immune-mediated, multisystem inflammatory disease that follows a group A (β-hemolytic) streptococcal (GAS) throat infection. The most serious aspect of rheumatic fever is the development of chronic valvular disorders that produce permanent cardiac dysfunction and sometimes cause fatal heart failure years later. In the United States and other industrialized countries, the incidence of rheumatic fever and the prevalence of rheumatic heart disease has markedly declined during the past 40 to 50 years. This decline has been attributed to the introduction of antimicrobial agents for improved treatment of GAS pharyngitis, increased access to medical care, and improved economic standards, along with better and less crowded housing. Unfortunately, rheumatic fever and rheumatic heart disease continue to be major health problems in many underdeveloped countries, where inadequate health care, poor nutrition, and crowded living conditions still prevail.

Rheumatic fever is primarily a disease of school-aged children. The incidence of acute rheumatic fever peaks between 5 and 15 years of age.[4] The disease usually follows an inciting GAS throat infection by 1 to 4 weeks. Rheumatic fever and its cardiac complications can be prevented by antibiotic treatment of the initial GAS throat infection. Evidence of a streptococcal infection is established through the use of throat cultures, antigen tests, and antibodies to products liberated by the streptococci. Throat cultures taken at the time of the acute infection usually are positive for GAS infection. It takes several days to obtain the results of a throat culture. The development of rapid tests for direct detection of GAS antigens has provided at least a partial solution for this problem. Penicillin (or another antibiotic in penicillin-sensitive patients) is the treatment of choice for GAS.

Pathogenesis. The pathogenesis of rheumatic fever is unclear, and why only a small percentage of persons with uncomplicated streptococcal infections contract rheumatic fever remains unknown. The time frame for development of symptoms in relation to the sore throat and the presence of antibodies to the GAS organism strongly suggest an immunologic origin. Like other immunologic phenomena, rheumatic fever requires an initial sensitizing exposure to the offending streptococcal agent, and the risk of recurrence is high after each subsequent exposure.

Rheumatic fever can manifest as an acute, recurrent, or chronic disorder. The acute stage of rheumatic fever includes a history of an initiating streptococcal infection and subsequent involvement of the connective tissue of the heart, blood vessels, joints, and subcutaneous tissues. Common to all is a lesion called the *Aschoff body*, which is a localized area of tissue necrosis surrounded by immune cells.[4] The *recurrent phase* usually involves extension of the cardiac effects of the disease. The *chronic phase* of rheumatic fever is characterized by permanent deformity of the heart valves and is a common cause of mitral valve stenosis. Chronic rheumatic heart disease usually does not appear until at least 10 years after the initial attack, sometimes decades later.

Clinical Course. Most children with rheumatic fever have a history of sore throat, headache, fever, abdominal pain, nausea, vomiting, swollen glands (usually at the angle of the jaw), and other signs and symptoms of streptococcal infection. Other clinical features associated with an acute episode of rheumatic fever are related to the acute inflammatory process and the structures involved in the disease process. The course of rheumatic fever is characterized by a constellation of disorders that include carditis, migratory polyarthritis of the large joints, erythema marginatum, subcutaneous nodules, and Sydenham's chorea.

Acute rheumatic carditis, which complicates the acute phase of rheumatic fever, may progress to chronic valvular disorders. The carditis can affect the pericardium, myocardium, or endocardium, and all of these layers of the heart usually are involved. Both the pericarditis and myocarditis usually are self-limited manifestations of the acute stage of rheumatic fever.

The involvement of the endocardium and valvular structures produces the permanent and disabling effects of rheumatic fever. Although any of the four valves can be involved, the mitral and aortic valves are affected most often. During the acute inflammatory stage of the disease, the valvular structures become red and swollen; small vegetative lesions develop on the valve leaflets. The acute inflammatory changes gradually proceed to development of fibrous scar tissue, which tends to contract and cause deformity of the valve leaflets and shortening of the chordae tendineae. In some cases, the edges or commissures of the valve leaflets fuse together as healing occurs.

The manifestations of acute rheumatic carditis include a heart murmur in a child without a previous history of rheumatic fever, change in the character of a murmur in a person with a previous history of the disease, cardiomegaly or enlargement of the heart, friction rub or other signs of pericarditis, and congestive heart failure in a child without discernible cause.

Although not a cause of permanent disability, polyarthritis is the most common finding in rheumatic fever. The arthritis involves the larger joints, particularly the knees, ankles, elbows, and wrists, and almost always is migratory, affecting one joint and then moving to another. In untreated cases, the arthritis lasts approximately 4 weeks. A striking feature of rheumatic arthritis is the dramatic response (usually within 48 hours) to salicylates.

Erythema marginatum lesions are maplike, macular areas most commonly seen on the trunk or inner aspects of the upper arm and thigh. Skin lesions are present only in approximately 10% of patients who have rheumatic fever; they are transitory and disappear during the course of the disease. The subcutaneous nodules are 1 to 4 cm in diameter. They are hard, painless, and freely movable and usually overlie the extensor muscles of the wrist, elbow, ankle, and knee joints. Subcutaneous nodules are rare, but when present, they occur most often in persons with carditis.

Chorea (*i.e.*, Sydenham's chorea), sometimes called *St. Vitus' dance,* is the major central nervous system manifestation. It is seen most frequently in girls and is the least common of the clinical manifestations. The choreic movements are spontaneous, rapid, purposeless, jerking movements that interfere with voluntary activities. Facial grimaces are common, and even speech may be affected. The chorea is self-limited, usually running its course within a matter of weeks or months.

Diagnosis and Treatment. The diagnosis of rheumatic fever is based on the Jones criteria, which were initially proposed in 1955 and revised in 1984 and 1992 by a committee of the AHA.[31,32] The criteria group the signs and symptoms of rheumatic fever into major and minor categories. The presence of two major signs (*i.e.*, carditis, polyarthritis, chorea, erythema marginatum, and subcutaneous nodules) or one major and two minor signs (*i.e.*, arthralgia, fever, and prolonged PR interval) accompanied by evidence of a preceding GAS infection indicates a high probability of rheumatic fever. The erythrocyte sedimentation rate, C-reactive protein, and white blood cell count commonly are used to confirm recent infection. Echocardiography/Doppler ultrasound (echo-Doppler) may be used to identify cardiac lesions in persons who do not have typical signs of cardiac involvement during an attack of rheumatic fever.[32]

Treatment of acute rheumatic fever is designed to control the acute inflammatory process and prevent cardiac complications and recurrence of the disease. During the acute phase, antibiotics, anti-inflammatory drugs, and selective restriction of physical activities are prescribed. Penicillin is usually the antibiotic of choice. Salicylates are used to reduce fever and relieve joint pain and swelling. A short course of corticosteroids may be used when the response to salicylates is ineffective. Because of the high risk for recurrence after subsequent GAS throat infections, treatment during the acute phase of the disease is usually followed by secondary prophylaxis using penicillin or an alternative antibiotic.[33] The duration of prophylaxis depends on whether residual valvular disease is present or absent. Usually, prophylaxis is also instituted during dental or other procedures that might provide the GAS with access to the bloodstream.

In summary, myocardial disorders represent a diverse group of disorders of myocardial muscle cells, not related to coronary artery disease. Myocarditis is an acute inflammation of cardiac muscle cells, most often of viral origin. Myocardial injury from myocarditis is thought to result from necrosis caused by direct invasion of the offending organism, toxic effects of exogenous toxins or endotoxins produced by a systemic pathogen, and destruction of cardiac tissue by immunologic mechanisms initiated by the infectious agent. Although the disease usually is benign and self-limited, it can result in sudden death or chronic heart failure, for which heart transplantation may be considered.

The cardiomyopathies represent disorders of the heart muscle. Cardiomyopathies may manifest as primary or secondary disorders such as myocardial infarction. There are four main types of primary cardiomyopathies: dilated cardiomyopathy, in which fibrosis and atrophy of myocardial cells produces progressive dilation and impaired pumping ability of the heart; hypertrophic cardiomyopathy, characterized by myocardial hypertrophy, abnormal diastolic filling, and in many cases intermittent left ventricular outflow obstruction; restrictive cardiomyopathy, in which there is excessive rigidity of the ventricular wall; and arrhythmogenic right ventricular cardiomyopathy. Peripartum cardiomyopathy occurs during pregnancy. The cause of many of the primary cardiomyopathies is unknown. The disease is suspected when cardiomegaly and heart failure develop in a young, previously healthy person.

Infective endocarditis involves the invasion of the endocardium by pathogens that produce vegetative lesions on the endocardial surface. The loose organization of these lesions permits the organisms and fragments of the lesions to be disseminated throughout the systemic circulation. Two predisposing factors contribute to the development of infective endocarditis: a damaged endocardium and a portal of entry through which the organisms gain access to the bloodstream.

Rheumatic fever, which is associated with an antecedent GAS throat infection, is an important cause of heart disease. Its most serious and disabling effects result from involvement of the heart valves. Because there is no single laboratory test, sign, or symptom that is pathognomonic of acute rheumatic fever, the Jones criteria are used to establish the diagnosis during the acute stage of the disease.

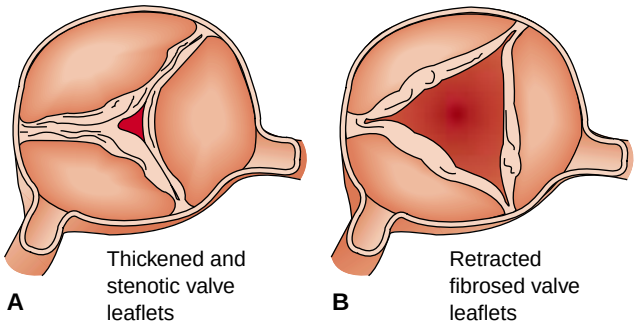
VALVULAR HEART DISEASE

The function of the heart valves is to promote directional flow of blood through the chambers of the heart. Dysfunction of the heart valves can result from a number of disorders, including congenital defects, trauma, ischemic damage, degenerative changes, and inflammation. Although any of the four heart valves can become diseased, the most commonly affected are the mitral and aortic valves. Disorders of the pulmonary and tricuspid valves are uncommon, probably because of the low pressure in the right side of the heart.

Hemodynamic Derangements

The heart valves consist of thin leaflets of tough, flexible, endothelium-covered fibrous tissue firmly attached at the base to the fibrous valve rings (see Chapter 14). Capillaries and smooth muscle are present at the base of the leaflet but do not extend up into the valve. The leaflets of the heart valves may be injured or become the site of an inflammatory process that can deform their line of closure. Healing of the valve leaflets often is associated with increased collagen content and scarring, causing the leaflets to shorten and become stiffer. The edges of the valve leaflets can heal together so that the valve does not open or close properly.

Two types of mechanical disruptions occur with valvular heart disease: narrowing of the valve opening so it does not open properly and distortion of the valve so it does not close properly (Fig. 17-17). *Stenosis* refers to a narrowing of the valve orifice and failure of the valve leaflets to open normally. Blood flow through a normal valve can increase by five to seven times the resting volume; consequently, valvular stenosis must be severe before it causes problems. Significant narrowing of the valve orifice increases the resistance to blood flow through the valve, converting the normally smooth laminar flow to a less efficient turbulent flow. This increases the volume and work of the chamber emptying through the narrowed valve—the left atrium in the case of mitral stenosis and the left ventricle in aortic stenosis. Symptoms usually are noticed first during situations of increased flow, such as exercise. An *incompetent* or *regurgitant valve* permits backward flow to occur when the valve should be closed, with blood flowing back into the left ventricle during diastole when the aortic valve is affected and back into the left atrium during systole when the mitral valve is diseased.



■ **FIGURE 17-17** ■ Disease of the aortic valve as viewed from the aorta. (**A**) Stenosis of the valve opening. (**B**) An incompetent or regurgitant valve that is unable to close completely.

The effect that valvular heart disease has on cardiac function is related to alterations in blood flow across the valve and to the resultant increase in work demands on the heart that the disorder generates. Many valvular heart defects are characterized by heart murmurs resulting from turbulent blood flow through a diseased valve. Disorders in valve flow and heart chamber size for mitral and aortic valve disorders are illustrated in Figure 17-18.

Mitral Valve Disorders

The mitral valve controls the directional flow of blood between the left atrium and the left ventricle. The edges or cusps of the AV valves are thinner than those of the semilunar valves; they are anchored to the papillary muscles by the chordae tendineae. During much of systole, the mitral valve is subjected to the high pressure generated by the left ventricle as it pumps blood into the systemic circulation. During this period of increased pressure, the chordae tendineae prevent the eversion of the valve leaflets into the left atrium.

Mitral Valve Stenosis

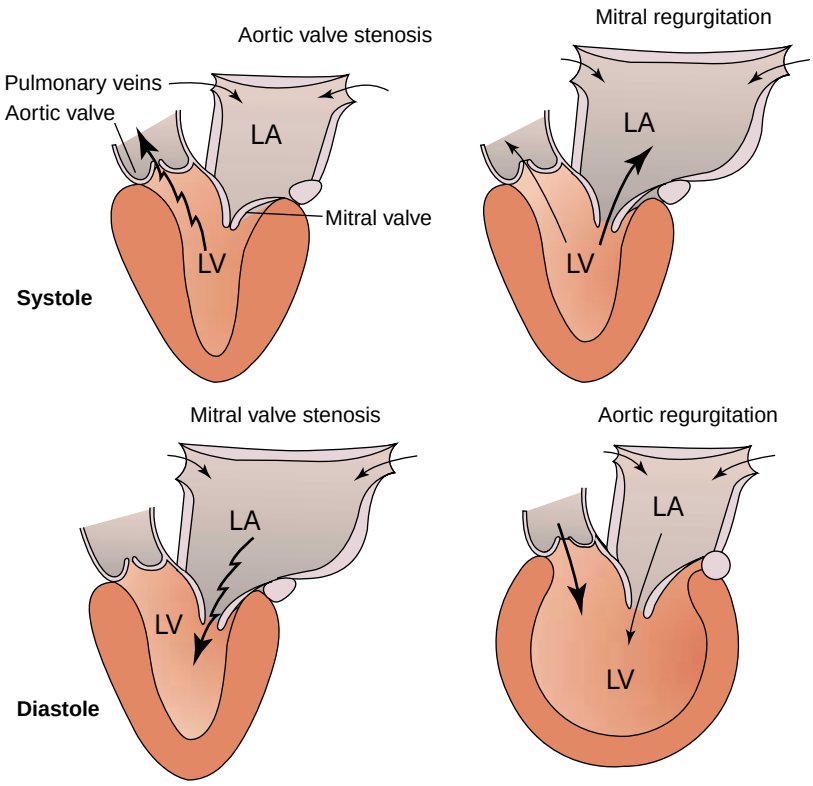
Mitral valve stenosis represents the incomplete opening of the mitral valve during diastole with left atrial distention and impaired filling of the left ventricle. Mitral valve stenosis most commonly is the result of rheumatic fever. Less frequently, the defect is congenital and manifests during infancy or early childhood.[34] Mitral valve stenosis is a continuous, progressive, lifelong disorder, consisting of a slow, stable course in the early years and progressive acceleration in later years. The 10-year survival rate for persons with untreated mitral stenosis is 50% to 60%, depending on symptoms at the time of presentation.[34,35]

Mitral valve stenosis is characterized by fibrous replacement of valvular tissue, along with stiffness and fusion of the valve apparatus (Fig. 17-19). Typically, the mitral cusps fuse at the edges, and involvement of the chordae tendineae causes short-

KEY CONCEPTS

VALVULAR HEART DISEASE

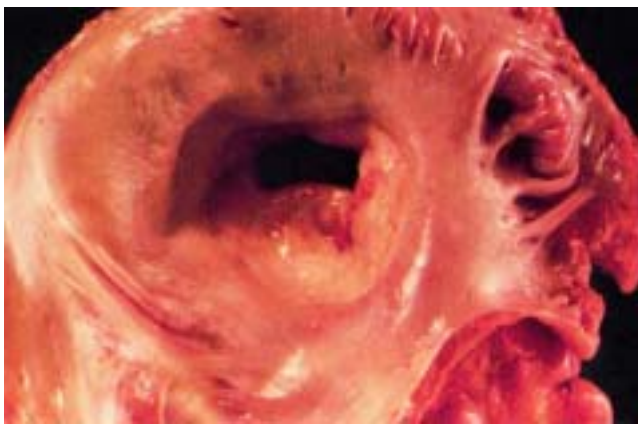
- The heart valves determine the direction of blood flow through the heart chambers.
- Valvular heart defects exert their effects by obstructing flow of blood (stenotic valve disorder) or allowing backward flow of blood (regurgitant valve disorders).
- Stenotic valvular defects produce distention of the heart chamber that empties blood through the diseased valve and impaired filling of the chamber that receives blood that moves through the valve.
- Regurgitant valves allow blood to move back through the valve when it should be closed. This produces distention and places increased work demands on the chamber ejecting blood through the diseased valve.



■ **FIGURE 17-18** ■ Alterations in hemodynamic function that accompany aortic valve stenosis, mitral valve regurgitation, mitral valve stenosis, and aortic valve regurgitation. *Thin arrows* indicate direction of normal flow, and *thick arrows* the direction of abnormal flow.

ening, which pulls the valvular structures more deeply into the ventricles. As the resistance to flow through the valve increases, the left atrium becomes dilated and left atrial pressure rises (see Fig. 17-18). The increased left atrial pressure eventually is transmitted to the pulmonary venous system, causing pulmonary congestion.

The rate of flow across the valve depends on the size of the valve orifice, the driving pressure (*i.e.*, atrial minus ventricular pressure), and the time available for flow during diastole. As the condition progresses, symptoms of decreased cardiac output occur during extreme exertion or other situations that cause tachycardia and thereby reduce diastolic filling time. In the late stages of the disease, an increase in pulmonary vascular resistance leads to the development of pulmonary hypertension; this increases the pressure against which the right heart must pump and eventually leads to right-sided heart failure.



■ **FIGURE 17-19** ■ Chronic rheumatic valvulitis. A view of the mitral valve from the left atrium shows rigid, thickened, and fused leaflets with a narrow orifice, creating the characteristic "fish mouth" appearance of the rheumatic mitral stenosis. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 570]. Philadelphia: Lippincott Williams & Wilkins)

The signs and symptoms of mitral valve stenosis depend on the severity of the obstruction and are related to the elevation in left atrial pressure and pulmonary congestion, decreased cardiac output caused by impaired left ventricular filling, and left atrial enlargement with development of atrial arrhythmias and mural thrombi. The murmur of mitral valve stenosis is heard during diastole when blood is flowing through the constricted valve orifice; it is characteristically a low-pitched, rumbling murmur, best heard at the apex of the heart.

The symptoms are those of pulmonary congestion, including recurrent nocturnal dyspnea and orthopnea. Palpitations, chest pain, weakness, and fatigue are common complaints. Premature atrial beats, paroxysmal atrial tachycardia, and atrial fibrillation may occur as a result of distention of the left atrium. Atrial fibrillation develops in 30% to 40% of persons with symptomatic mitral stenosis.[34] Together, the fibrillation and distention predispose to mural thrombus formation. The risk of arterial embolization, particularly stroke, is significantly increased in persons with atrial fibrillation. Anticoagulation therapy is often used to prevent systemic embolization in persons with atrial fibrillation.

Mitral Valve Regurgitation

Mitral valve regurgitation is characterized by incomplete closure of the mitral valve, with the left ventricular stroke volume being divided between the forward stroke volume that moves

into the aorta and the regurgitant stroke volume that moves back into the left atrium during systole (see Fig. 17-18). Mitral valve regurgitation can result from many processes. Rheumatic heart disease is associated with a rigid and thickened valve that does not open or close completely. In addition to rheumatic disease, mitral regurgitation can occur as the result of papillary muscle dysfunction, stretching of the valve structures caused by dilatation of the left ventricle or valve orifice, or mitral valve prolapse. Acute mitral regurgitation can result from rupture of the chordae tendineae or papillary muscles, most commonly the result of myocardial infarction.

The hemodynamic changes that occur with mitral valve regurgitation occur more slowly, allowing for recruitment of compensatory mechanisms. An increase in left ventricular end-diastolic volume permits an increase in total stroke volume, with restoration of forward flow into the aorta. Augmented preload and reduced or normal afterload (provided by unloading the left ventricle into the left atrium) facilitates left ventricular ejection. At the same time, a gradual increase in left atrial size allows for accommodation of the regurgitant volume at a lower filling pressure.

The increased volume work associated with mitral regurgitation is relatively well tolerated, and many persons with the disorder remain asymptomatic for 10 to 20 years despite severe regurgitation.[34,35] The degree of left ventricular enlargement reflects the severity of regurgitation. As the disorder progresses, left ventricular function becomes impaired, the forward (aortic) stroke volume decreases, and the left atrial pressure increases, with the subsequent development of pulmonary congestion. Mitral regurgitation, like mitral stenosis, predisposes to atrial fibrillation.

Mitral Valve Prolapse

Sometimes referred to as the *floppy mitral valve syndrome*, mitral valve prolapse occurs in 2% to 6% of the population.[36] The disorder is seen more frequently in women than in men and may have a familial basis. Although the cause of the disorder usually is unknown, it has been associated with Marfan's syndrome, osteogenesis imperfecta, and other connective tissue disorders and with cardiac, hematologic, neuroendocrine, metabolic, and psychological disorders.

Pathologic findings in persons with mitral valve prolapse include a myxedematous (mucinous) degeneration of mitral valve leaflets that causes them to become enlarged and floppy so that they prolapse or balloon back into the left atrium during systole (Fig. 17-20).[25] Secondary fibrotic changes reflect the stresses and injury that the ballooning movements impose on the valve. Certain forms of mitral valve prolapse may arise from disorders of the myocardium that result in abnormal movement of the ventricular wall or papillary muscle; this places undue stress on the mitral valve.

Most persons with mitral valve prolapse are asymptomatic, and the disorder is discovered during a routine physical examination. A minority of persons have chest pain mimicking angina, dyspnea, fatigue, anxiety, palpitations, and lightheadedness. Unlike angina, the chest pain often is prolonged, ill defined, and not associated with exercise or exertion. The pain has been attributed to ischemia resulting from traction of the prolapsing valve leaflets. The anxiety, palpitations, and dysrhythmias may result from abnormal autonomic nervous system function that commonly accompanies the disorder. Rare cases of sudden death have been reported for persons with mitral valve prolapse, mainly those with a family history of similar occurrences.

■ **FIGURE 17-20** ■ Mitral valve prolapse. A view of the mitral valve from the left atrium shows redundant and deformed leaflets that billow into the left atrial cavity. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 574]. Philadelphia: Lippincott Williams & Wilkins)

The treatment of mitral valve prolapse focuses on the relief of symptoms and the prevention of complications. Persons with palpitations and mild tachyarrhythmias or increased adrenergic symptoms and those with chest discomfort, anxiety, and fatigue often have response to therapy with the β-adrenergic–blocking drugs. In many cases, the cessation of stimulants such as caffeine, alcohol, and cigarettes may be sufficient to control symptoms. Infective endocarditis is an uncommon complication in persons with a murmur; antibiotic prophylaxis usually is recommended before dental or surgical procedures associated with bacteremia. Persons with severe valve dysfunction may require valve surgery.

Aortic Valve Disorders

The aortic valve is located between the aorta and left ventricle. The aortic valve has three cusps and sometimes is referred to as the *aortic semilunar valve* because its leaflets are crescent or moon shaped (see Chapter 14, Fig. 14-10). The aortic valve has no chordae tendineae. Although their structures are similar, the cusps of the aortic valve are thicker than those of the mitral valve. The middle layer of the aortic valve is thickened near the middle, where the three leaflets meet, ensuring a tight seal. Between the thickened tissue and their free margins, the leaflets are more thin and flimsy.

An important aspect of the aortic valve is the location of the orifices for the two main coronary arteries, which are located behind the valve and at right angles to the direction of blood flow. It is the lateral pressure in the aorta that propels blood into the coronary arteries. During the ejection phase of the cardiac cycle, the lateral pressure is diminished by conversion of potential energy to kinetic energy as blood moves

forward into the aorta. This process is grossly exaggerated in aortic stenosis because of the high flow velocities.

Aortic Valve Stenosis

Aortic stenosis is characterized by increased resistance to ejection of blood from the left ventricle into the aorta (see Fig. 17-18). Because of the increased resistance, the work demands on the left ventricle are increased, and the volume of blood ejected into the systemic circulation is decreased. The most common causes of aortic stenosis are rheumatic fever and congenital valve malformations. Congenital malformations may result in unicuspid, bicuspid, or misshaped valve leaflets. In elderly persons, stenosis may be related to degenerative atherosclerotic changes of the valve leaflets. Approximately 25% of persons older than 65 years and 35% of those older than 70 years of age have echocardiographic evidence of sclerosis, with 2% to 3% having evidence of aortic stenosis.[35]

The progression of aortic stenosis varies widely among individuals. The progression may be more rapid in persons with degenerative calcific disease than in those with congenital or rheumatic disease.[35] The aortic valve must be reduced to approximately one fourth its normal size before critical changes in cardiac function occur.[34] Significant obstruction to aortic outflow causes a decrease in stroke volume, along with a reduction in systolic blood pressure and pulse pressure. Because of the narrowed valve opening, it takes longer for the heart to eject blood; the heart rate often is slow, and the pulse is of low amplitude. There is a soft, absent, or paradoxically split S_2 sound and a harsh systolic ejection murmur that is heard best along the left sternal border.

Persons with aortic stenosis tend to be asymptomatic for many years despite severe obstruction. Eventually, symptoms of angina, syncope, and heart failure develop. Angina occurs in approximately two thirds of persons with advanced aortic stenosis and is similar to that observed in CHD. Syncope (fainting) is most commonly caused by the reduced cerebral circulation that occurs during exertion when the arterial pressure declines consequent to vasodilation in the presence of a fixed cardiac output. Exertional hypotension may cause "graying out" spells or dizziness on exercise.[36] Dyspnea, marked fatigability, peripheral cyanosis, and other signs of low-output heart failure usually are not prominent until late in the course of the disease.

Aortic Valve Regurgitation

Aortic regurgitation is the result of an incompetent aortic valve that allows blood to flow back to the left ventricle during diastole (see Fig. 17-18). As a result, the left ventricle must increase its stroke volume to include blood entering from the lungs as well as that leaking back through the regurgitant valve. This defect may result from conditions that cause scarring of the valve leaflets or from enlargement of the valve orifice to the extent that the valve leaflets no longer meet. Rheumatic fever ranks first on the list of causes of aortic regurgitation; failure of a prosthetic valve is another cause.

Chronic aortic regurgitation, which usually has a gradual onset, represents a condition of combined left ventricular volume and pressure overload. As the valve deformity increases, regurgitant flow into the left ventricle increases, diastolic blood pressure falls, and the left ventricle progressively enlarges. Hemodynamically, the increase in left ventricular volume results in the ejection of a large stroke volume that usually is adequate to maintain the cardiac output until late in the course of the disease. Most persons remain asymptomatic during this compensated phase, which may last decades. The only sign for many years may be soft systolic aortic murmur.

As the disease progresses, signs and symptoms of left ventricular failure begin to appear. These include exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. In aortic regurgitation, failure of aortic valve closure during diastole causes an abnormal drop in diastolic pressure. Because coronary blood flow is greatest during diastole, the drop in diastolic pressure produces a decrease in coronary perfusion. Although angina is rare, it may occur when the heart rate and diastolic pressure fall to low levels. Persons with severe aortic regurgitation often report an uncomfortable awareness of heartbeat, particularly when lying down, and chest discomfort caused by pounding of the heart against the chest wall. Tachycardia, occurring with emotional stress or exertion, may produce palpitations, head pounding, and premature ventricular contractions.

The major physical findings relate to the widening of the arterial pulse pressure. The pulse has a rapid rise and fall, with an elevated systolic pressure and low diastolic pressure caused by the large stroke volume and rapid diastolic runoff of blood back into the left ventricle. Korotkoff sounds may persist to zero, even though intra-arterial pressure rarely falls below 30 mm Hg.[34] The large stroke volume and wide pulse pressure may result in prominent carotid pulsations in the neck, throbbing peripheral pulses, and a left ventricular impulse that causes the chest to move with each beat. The turbulence of flow across the aortic valve during diastole produces a high-pitched or blowing sound.

Diagnosis and Treatment

Valvular defects usually are detected through cardiac auscultation (*i.e.*, heart sounds). Diagnosis is aided by echocardiography and cardiac catheterization. Echocardiography uses ultrasound signals in the range of 2 to 5 million Hz to create an image of the internal structures of the heart because the chest wall, blood, and different heart structures all reflect ultrasound differently. The echocardiogram is useful for determining ventricular dimensions and valve movements, obtaining data on the movement of the left ventricular wall and septum, estimating diastolic and systolic volumes, and viewing the motion of individual segments of the left ventricular wall during systole and diastole. Transesophageal echocardiography is particularly useful in assessing valve function.

The treatment of valvular defects consists of medical management of heart failure and associated problems and surgical intervention to repair or replace the defective valve. Surgical valve repair or replacement depends on the valve that is involved and the extent of deformity. Valvular replacement with a prosthetic device usually is reserved for severe disease. Percutaneous balloon valvuloplasty involves the opening of a stenotic valve by guiding an inflated balloon through the valve orifice. The procedure is done in the cardiac catheterization laboratory and involves the insertion of a balloon catheter into the heart by way of a peripheral blood vessel.

In summary, dysfunction of the heart valves can result from a number of disorders, including congenital defects, trauma, ischemic heart disease, degenerative changes, and inflammation. Rheumatic endocarditis is a common cause. Valvular heart disease produces its effects through disturbances of blood flow. A stenotic valvular defect is one that causes a decrease in blood flow through a valve, resulting in impaired emptying and increased work demands on the heart chamber that empties blood across the diseased valve. A regurgitant valvular defect permits the blood flow to continue when the valve is closed. Valvular heart disorders produce blood flow turbulence and often are detected through cardiac auscultation.

HEART DISEASE IN INFANTS AND CHILDREN

Heart disease in infants and children encompasses both congenital and acquired disorders. About 40,000 infants are born each year with a congenital heart defect, and 25% of these have defects that are severe enough to cause death within the first year if not corrected.[1] Premature infants have a higher incidence of congenital heart defects, most commonly patent ductus arteriosus and atrial septal defects. Advances in diagnostic methods and surgical treatment have greatly increased the long-term survival and outcomes for children born with congenital heart defects. This section of the chapter provides a discussion of the fetal and perinatal circulations; congenital heart disorders, and Kawasaki's disease, an acquired heart disorder of young children.

The major development of the fetal heart occurs between the fourth and seventh weeks of gestation, and during this time, most congenital heart defects arise. The development of the heart may be altered by environmental, genetic, and chromosomal influences. Most congenital heart defects are thought to be multifactorial in origin, resulting from an interaction between a genetic predisposition to develop a heart defect and environmental influences. Infants born to parents with congenital heart defects or with siblings who have congenital heart defects are at higher risk. A number of chromosomal abnormalities are associated with congenital heart disease, most prominently Down syndrome and Turner's syndrome (see Chapter 4). Other intrauterine factors such as maternal diabetes, congenital rubella, maternal alcohol ingestion, and treatment with anticonvulsant drugs are also associated with congenital heart disorders.[37]

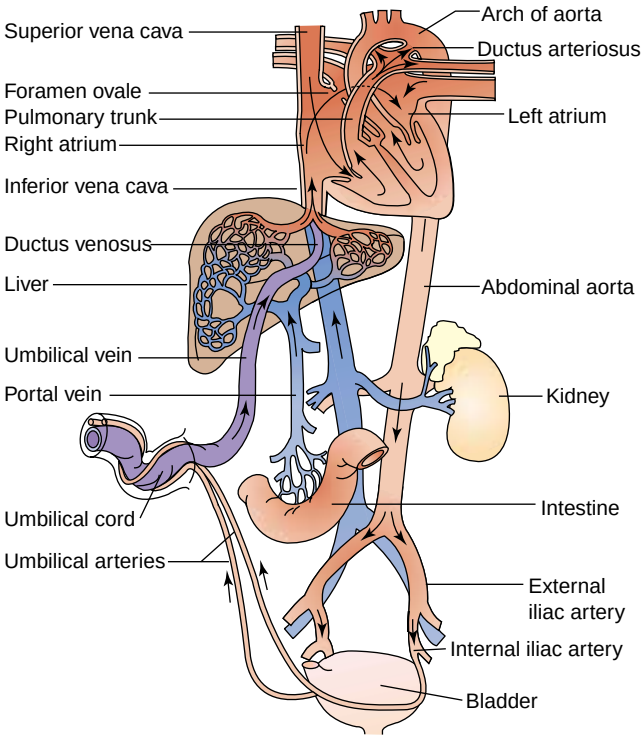
Fetal and Perinatal Circulation

The birth process produces dramatic changes in the circulation. It produces an increased risk of disorders such as patent ductus arteriosus in infants who are born prematurely, and it challenges the circulatory function in infants with congenital heart defects.

The fetal circulation is different anatomically and physiologically from the postnatal circulation. Before birth, oxygenation of blood occurs by way of the placenta, and after birth, it occurs by way of the lungs. The fetus is maintained in a low-oxygen state (PO_2 to 30 to 35 mm Hg and 60% to 70% hemoglobin saturation).[38] To compensate, fetal cardiac output is higher than at any other time (400 to 500 mL/kg/minute).

In the fetus, blood enters the circulation through the umbilical vein and returns to the placenta by way of the two umbilical arteries (Fig. 17-21). A vessel called the *ductus venosum* allows blood from the umbilical vein to bypass the hepatic circulation and pass directly into the inferior vena cava. From the inferior vena cava, blood flows into the right atrium and then is directed through the foramen ovale into the left atrium. Blood then passes into the left ventricle and is ejected into the ascending aorta to perfuse the head and upper extremities. In this way, the best-oxygenated blood from the placenta is used to perfuse the brain. At the same time, venous blood from the head and upper extremities returns to the right side of the heart by way of the superior vena cava, moves into the right ventricle, and is ejected into the pulmonary artery. The pulmonary vascular resistance is very high because the lungs are fluid filled, and the resultant alveolar hypoxia contributes to intense vasoconstriction. Because of the high pulmonary vascular resistance, the blood that is ejected into the pulmonary artery is diverted through the ductus arteriosus into the descending aorta. This blood perfuses the lower extremities and is returned to the placenta by way of the umbilical arteries.

At birth, the infant takes its first breath and switches from placental to pulmonary oxygenation of the blood. The most dramatic alterations in the circulation after birth are the elimination of the low-resistance placental vascular bed and the marked pulmonary vasodilation that is produced by initiation of ventilation. The pressure in the pulmonary circulation and the right side of the heart fall as fetal lung fluid is replaced by



■ **FIGURE 17-21** ■ Fetal circulation.

air and as lung expansion decreases the pressure transmitted to the pulmonary blood vessels. With lung inflation, the alveolar oxygen tension increases, causing reversal of the hypoxemia-induced pulmonary vasoconstriction of the fetal circulation. Cord clamping and removal of the low-resistance placental circulation produce an increase in peripheral vascular resistance and a resultant increase in left ventricular pressure. The accompanying increase in left atrial pressure as compared to right atrial pressure promotes closure of the foramen ovale. Reversal of the fetal hypoxemic state also produces constriction of ductal smooth muscle, contributing to closure of the ductus arteriosus. Closure of the foramen ovale and the ductus arteriosus normally occur within the first day of life, effectively separating the pulmonary and systemic circulations.

The birth process also initiates a sequence of maturational changes in the pulmonary blood vessels and pulmonary vascular resistance. After the initial precipitous fall in pulmonary vascular resistance, a more gradual decrease in pulmonary vascular resistance is related to regression of the medial smooth muscle layer in the pulmonary arteries. During the first 2 to 9 weeks of life, gradual thinning of the medial smooth muscle layer of pulmonary arteries results in further decreases in pulmonary vascular resistance. By the time a healthy, term infant is several weeks old, the pulmonary vascular resistance has fallen to adult levels.

Several factors, including prematurity, alveolar hypoxia, lung disease, and congenital heart defects, may affect postnatal pulmonary vascular development.[37] If an infant is born prematurely, the smooth muscle layers of the pulmonary vasculature may develop incompletely or regress in a shorter period. Much of the development of the smooth muscle layer in the pulmonary arterioles occurs during the latter part of gestation; as a result, infants who are born prematurely have less medial smooth muscle. These infants follow the same pattern of smooth muscle regression, but because less muscle exists, the muscle layer may regress in a shorter period. The pulmonary vascular smooth muscle in premature infants also may be less responsive to hypoxia. For these reasons, a premature infant may demonstrate a larger decrease in pulmonary vascular resistance and a resultant shunting of blood from the aorta through the ductus arteriosus to the pulmonary artery within hours of birth.

Hypoxia during the first days of life may delay or prevent the normal decrease in pulmonary vascular resistance. During this period, the pulmonary arteries remain reactive and can constrict in response to hypoxia, acidosis, hyperinflation of the alveoli, and hypothermia. Alveolar hypoxia is one of the most potent stimuli of pulmonary vasoconstriction and pulmonary hypertension in the neonate.

Congenital Heart Disorders

Congenital heart diseases are commonly classified according to their anatomic defects (atrial septal or ventricular septal defects), the hemodynamic alterations caused by the anatomic defects (left-to-right or right-to-left shunts), and their effect on tissue oxygenation (cyanotic or noncyanotic defects).[39,40]

Shunting and Cyanotic Disorders

Shunting of blood refers to the diverting of blood flow from one system to the other—from the arterial to the venous system (*i.e.*, left-to-right shunt) or from the venous to the arterial system (*i.e.*, right-to-left shunt). The shunting of blood in congenital heart defects is determined by the presence of an abnormal opening between the right and left circulations and the degree of resistance to flow through the opening. The shunting of blood can affect both the oxygen content of the blood and the volume of blood being delivered to the vessels in the pulmonary circulation.

A *right-to-left* shunt results in unoxygenated blood moving from the right side of the heart into the left side of the heart and then being ejected into the systemic circulation. Cyanosis develops when sufficient unoxygenated blood mixes with oxygenated blood in the left side of the heart. Children with right-to-left shunts are considered to have a cyanotic heart defect, whether they have recognizable cyanosis or not. In a *left-to-right* shunt, blood intended for ejection into the systemic circulation is recirculated through the right side of the heart and back through the lungs; this increased volume distends the right side of the heart and pulmonary circulation and increases the workload placed on the right ventricle. Children with left-to-right shunts are considered to have a noncyanotic heart defect, even though they are cyanotic for other reasons, such as low cardiac output.

Congenital heart defects manifest with numerous signs and symptoms. Some defects, such as patent ductus arteriosus and small ventricular septal defects, close spontaneously, and in other, less severe defects, there are no signs and symptoms. The disorder typically is discovered during a routine health examination. Pulmonary congestion, heart failure, and decreased peripheral perfusion are the chief concerns in children with more severe defects. Such defects often cause problems shortly after birth or early in infancy. The child may exhibit cyanosis, respiratory difficulty, and fatigability and is likely to have difficulty with feeding and failure to thrive. A generalized cyanosis that persists longer than 3 hours after birth suggests congenital heart disease.

One technique for evaluating the cyanosis consists of administering 100% oxygen for 10 minutes. If the infant "pinks up," the cyanosis probably was caused by a respiratory problem and not a heart deffect. Because infant cyanosis may appear as a duskiness, it is important to assess the color of the mucous membranes, fingernails, toenails, tongue, and lips.

The manifestations and treatment of heart failure in the infant and young child are similar to those in the adult, but the infant's small size and limited physical reserve makes the manifestations more serious and treatment more difficult (see Chapter 18). The treatment plan usually includes supportive therapy designed to help the infant compensate for the limitations in cardiac reserve and to prevent complications. Surgical intervention often is required for severe defects; it may be done in the early weeks of life or, conditions permitting, delayed until the child is older.

Most children with structural congenital heart disease and those who have had corrective surgery are at risk for the development of infectious endocarditis. These children should receive prophylactic antibiotic therapy during periods of increased risk of bacteremia.

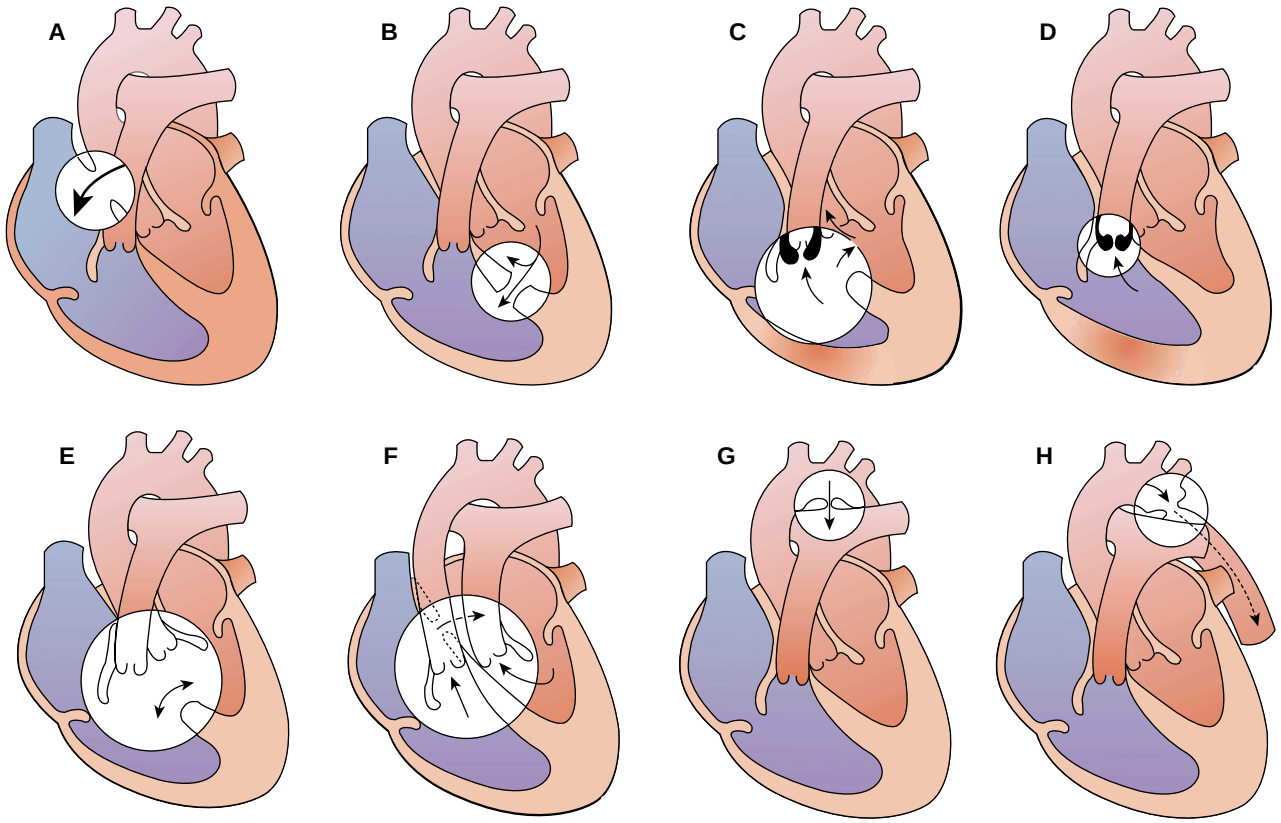
Types of Defects

Congenital heart defects can affect almost any of the cardiac structures or central blood vessels. Defects include communication between heart chambers, interrupted development of the heart chambers or valve structures, malposition of heart

chambers and great vessels, and altered closure of fetal communication channels. The particular defect reflects the embryo's stage of development at the time it occurred. Some congenital heart disorders, such as tetralogy of Fallot, involve several defects. At least 35 types of defects have been identified, the most common being patent ductus arteriosus (6% to 11%), atrial septal defects (8% to 13%), and ventricular septal defects (20% to 25%).[1]

Patent Ductus Arteriosus. Patent ductus arteriosus results from persistence of the fetal ductus beyond the prenatal period. In fetal life, the ductus arteriosus is the vital link by which blood from the right side of the heart bypasses the lungs and enters the systemic circulation (Fig. 17-22G). After birth, this passage no longer is needed, and it usually closes during the first 24 to 72 hours. The physiologic stimulus and mechanisms associated with permanent closure of the ductus are not entirely known, but the fact that infant hypoxia predisposes to a delayed closure suggests that the increase in arterial oxygen levels that occurs immediately after birth plays a role. Additional factors that contribute to closure are a fall in endogenous levels of prostaglandins and adenosine and the release of other vasoactive substances. After constriction, the lumen of the ductus becomes permanently sealed with fibrous tissue within 2 to 3 weeks. Ductal closure may be delayed or prevented in very premature infants, probably as a result of a combination of factors, including decreased medial muscle in the ductus wall, decreased constrictive response to oxygen, and increased circulating levels of vasodilating prostaglandins. Hemodynamically significant patent ductus arteriosus is observed in approximately one half of infants with birth weights of less than 1000 g.[38] Ductal closure also may be delayed in infants with congenital heart defects that produce a decrease in oxygen tension.

As is true of other heart and circulatory defects, patency of the ductus arteriosus may vary; the size of the opening may be small, medium, or large. After the infant's pulmonary vascular resistance falls, the patent ductus arteriosus provides for a continuous runoff of aortic blood into the pulmonary artery, causing a decrease in aortic diastolic and mean arterial pressure and a widening of the pulse pressure. With a large patent ductus, the runoff is continuous, resulting in increased pulmonary blood flow, pulmonary congestion, and increased resistance against which the right side of the heart must pump. Increased pul-



■ **FIGURE 17-22** ■ Congenital heart defects. (**A**) Atrial septal defect. Blood is shunted from left to right. (**B**) Ventricular septal defect. Blood is usually shunted from left to right. (**C**) Tetralogy of Fallot. This involves a ventricular septal defect, dextroposition of the aorta, right ventricular outflow obstruction, and right ventricular hypertrophy. Blood is shunted from right to left. (**D**) Pulmonary stenosis, with decreased pulmonary blood flow and right ventricular hypertrophy. (**E**) Endocardial cushion defects. Blood flows between the chambers of the heart. (**F**) Transposition of the great vessels. The pulmonary artery is attached to the left side of the heart and the aorta to the right side. (**G**) Patent ductus arteriosus. The high-pressure blood of the aorta is shunted back to the pulmonary artery. (**H**) Postductal coarctation of the aorta.

monary venous return and increased work demands may lead to left ventricular failure.

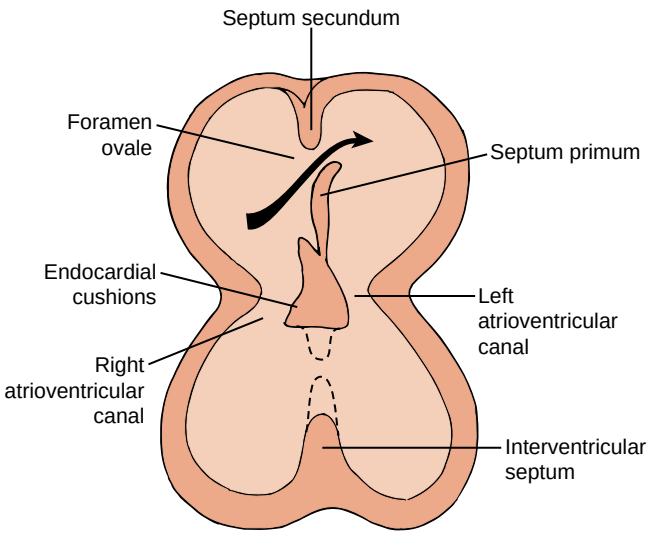
Patent ductus arteriosus can be treated either pharmacologically or surgically. Drugs that inhibit prostaglandin synthesis (*e.g.*, indomethacin), may be used to induce closure of a patent ductus arteriosus.

Atrial Septal Defects. An atrial septal defect is an abnormal opening in the atrial septum that allows communication between the left and right atrium (see Fig. 17-22A). It differs from a patent foramen ovale, which does not usually permit flow unless right atrial pressures are elevated.

Partitioning of the atria takes place during the 4th and 5th weeks of development and occurs in two stages, beginning with the formation of a thin, crescent-shaped membrane called the *septum primum* followed by the development of a second membrane called the *septum secundum*. As the septum secundum develops, it gradually overlaps an opening in the upper part of septum primum, forming an oval opening with a flap-type valve called the foramen ovale (see Fig. 17-23). The foramen ovale, which closes shortly after birth, allows blood from the umbilical vein to pass directly into the left heart, bypassing the lungs.

Atrial septal defects may be single or multiple and vary from a small, asymptomatic opening to a large, symptomatic opening. Most atrial septal defects are small and discovered inadvertently during a routine physical examination.[41] In the case of an isolated septal defect that is large enough to allow shunting, the flow of blood usually is from the left to the right side of the heart because of the more compliant right ventricle and because the pulmonary vascular resistance is lower than the systemic vascular resistance. This produces right ventricular volume overload and increased pulmonary blood flow.

Young children with atrial septal defects are usually asymptomatic but experience symptoms later in life, usually during adolescence when the changes in pulmonary vasculature may reverse the direction flow through the defect and create a right-to-left shunt with development of cyanosis. Adolescents and young adults may experience atrial fibrillation or atrial flutter and palpations because of atrial dilation. Symptomatic defects are usually treated surgically.



■ **FIGURE 17-23** ■ Development of the endocardial cushions, right and left atrioventricular canals, the interventricular septum, and septum primum and septum secundum of the foramen ovale. Note that blood from the right atrium flows through the foramen ovale to the left atrium. *Dotted line* indicates site for development of the membranous intraventricular septum.

Ventricular Septal Defects. A ventricular septal defect is an opening in the ventricular septum that results from an imperfect separation of the ventricles during early fetal development (see Fig. 17-22B). Ventricular septal defects are the most common form of congenital heart defect, accounting for 20% to 25% of congenital heart disorders.[38] Ventricular septal defects may be the only cardiac defect, or they may be one of multiple cardiac anomalies.

The ventricular septum originates from two sources: the interventricular groove of the folded tubular heart that gives rise to the muscular part of the septum, and the endocardial cushions that extend to form the membranous portion of the septum (Fig. 17-23). The upper membranous portion of the septum is the last area to close, and it is here that most defects occur.

Depending on the size of the opening, the signs and symptoms of a ventricular septal defect may range from an asymptomatic murmur to congestive heart failure. If the defect is small, it allows a small shunt and small increases in pulmonary blood flow. These defects produce few symptoms, and approximately one third close spontaneously.[37] With medium-size defects, a larger shunt occurs, producing a larger increase in pulmonary blood flow (*i.e.*, twice as much blood may pass through the pulmonary circulation as through the systemic circulation). The increased pulmonary flow most often occurs under relatively low pressure. Most of the children with such defects are asymptomatic and have a low risk for development of pulmonary vascular disease. Children with large defects often have a severe left-to-right shunt, often complicated by pulmonary hypertension and congestive heart failure.

Most infants with a ventricular septal defect are asymptomatic during early infancy because the higher pulmonary vascular resistance prevents shunting. The infant with a large, uncomplicated ventricular septal defect usually is asymptomatic until pulmonary vascular resistance begins to fall at approximately 4 to 25 weeks of age. After a large shunt develops, the infant breathes rapidly, feeds poorly, and is diaphoretic (*i.e.*, signs of congestive heart failure). Right-to-left shunting produces cyanosis.

The treatment of a ventricular septal defect depends on the size of the defect and accompanying hemodynamic derangements. Children with small or medium-size defects are followed up closely in the hope that the defect will close spontaneously. Prophylactic antibiotic therapy is given during periods of increased risk for bacteremia. Congestive heart failure is treated medically. Surgical intervention is required for infants who do not have a response to medical management.

Endocardial Cushion Defects. The endocardial cushions form the AV canals, the upper part of the ventricular septum, and the lower part of the atrial septum (Fig. 17-23). Endocardial cushion defects are responsible for approximately 5% of all congenital heart defects. As many as 50% of children with Down's syndrome have endocardial cushion defects.[37]

Because the endocardial cushions contribute to multiple aspects of heart development, several variations with this type of defect are possible. The terms most commonly used to categorize endocardial cushion defects are *partial* and *complete AV canal defects*.[37] In partial AV canal defects, the two AV valve rings are complete and separate. In complete canal defect, there is a common AV valve orifice along with defects in both the atrial and ventricular septal tissue. Many variations of these two forms of endocardial cushion defect are possible (see Fig. 17-22E).

The direction and magnitude of a shunt in a child with endocardial cushion defects are determined by the combination of defects and the child's pulmonary and systemic vascular resistance. With complete AV canal defects, congestive heart failure and intercurrent pulmonary infections appear early in infancy. There is left-to-right shunting and transatrial and transventricular mixing of blood. Pulmonary hypertension and increased pulmonary vascular resistance are common. Cyanosis develops with progressive shunting.

The treatment for endocardial cushion defects is determined by the severity of the defect. With an atrial septal defect, surgical repair usually is planned on an elective basis before the child enters school. Palliative or corrective surgery is required in infants with complete AV canal defects who have congestive heart failure and do not experience a response to medical treatment.

Pulmonary Valve Stenosis. Pulmonary valve stenosis may occur as an isolated valvular lesion or in conjunction with more complex defects, such as tetralogy of Fallot. In isolated valvular defects, the pulmonary cusps may be absent or malformed, or they may remain fused at their commissural edges; all three abnormalities often coexist.

Pulmonary valvular defects usually cause some impairment of pulmonary blood flow and increase the workload imposed on the right side of the heart (see Fig. 17-22D). Most children with pulmonic valve stenosis have mild to moderate stenosis that does not increase in severity. These children are largely asymptomatic. Severe defects are manifested by marked impairment of pulmonary blood flow that begins during infancy and is likely to become more severe as the child grows. Cyanosis develops in approximately one third of children younger than 2 years of age.[37] The ductus arteriosus may provide the vital accessory route for perfusing the lungs in infants with severe stenosis. When pulmonary stenosis is extreme, increased pressures in the right side of the heart may delay closure of the foramen ovale.

Treatment measures designed to maintain the patency of the ductus arteriosus may be used as a temporary measure to maintain or increase pulmonary blood flow in infants with severe pulmonary stenosis. Pulmonary valvotomy often is the treatment of choice. Transcatheter balloon valvuloplasty may be used in some infants with moderate degrees of obstruction.[38]

Tetralogy of Fallot. As the name implies, tetralogy of Fallot consists of four associated congenital heart defects: (1) a ventricular septal defect involving the membranous septum and the anterior portion of the muscular septum; (2) dextroposition or shifting to the right of the aorta, so that it overrides the right ventricle and is in communication with the septal defect; (3) obstruction or narrowing of the pulmonary outflow channel, including pulmonic valve stenosis, a decrease in the size of the pulmonary trunk, or both; and (4) hypertrophy of the right ventricle because of the increased work required to pump blood through the obstructed pulmonary channels[38] (see Fig. 17-22C).

Most children with tetralogy of Fallot display some degree of cyanosis, thus the term *blue babies*. The cyanosis develops as the result of decreased pulmonary blood flow and because the right-to-left shunt causes mixing of unoxygenated blood with the oxygenated blood, which is ejected into the peripheral circulation. Hypercyanotic attacks ("tet spells") may occur during the first months of life. These spells typically occur in the morning during crying, feeding, or defecating. These activities increase the infant's oxygen requirements. Crying and defecating may further increase pulmonary vascular resistance, thereby increasing right-to-left shunting and decreasing pulmonary blood flow. With the hypercyanotic spell, the infant becomes acutely cyanotic, hyperpneic, irritable, and diaphoretic. Later in the spell, the infant becomes limp and may lose consciousness. Placing the infant in the knee-chest position increases systemic vascular resistance, which increases pulmonary blood flow and decreases right-to-left shunting. During a hypercyanotic spell, toddlers and older children may spontaneously assume the squatting position, which functions like the knee-chest position to relieve the spell.[37]

Because of the hypoxemia that occurs in these children, palliative surgery designed to increase pulmonary blood flow often is needed during early infancy, with corrective surgery performed at a later age. Palliative surgery involves the creation of a surgical shunt to increase pulmonary blood flow. The most popular procedures use the subclavian artery or prosthetic material to create a shunt between the aorta and pulmonary artery.

Transposition of the Great Vessels. In complete transposition of the great vessels, the aorta originates in the right ventricle, and the pulmonary artery originates in the left ventricle (see Fig. 17-22F). The defect is more common in infants whose mothers have diabetes and in boys. In infants born with this defect, survival depends on communication between the right and left sides of the heart in the form of a patent ductus arteriosus or septal defect. Prostaglandin E_1 may be administered in an effort to maintain the patency of the ductus arteriosus. Balloon atrial septostomy may be done to increase the blood flow between the two sides of the heart. In this procedure, a balloon-tipped catheter is inserted into the heart through the vena cava and then passed through the foramen ovale into the left atrium. The balloon is inflated and brought back through the foramen ovale, enlarging the opening as it goes. Corrective surgery is essential for long-term survival.[38]

Coarctation of the Aorta. Coarctation of the aorta is a localized narrowing of the aorta, proximal (preductal or coarctation of infancy) or distal (postductal) to the ductus. Approximately 98% of coarctations are postductal (see Fig. 17-22H). The anomaly occurs twice as often in males as in females. Coarctation of the aorta may be a feature of Turner's syndrome (see Chapter 4).

The classic sign of coarctation of the aorta is a disparity in pulsations and blood pressures in the arms and legs. The femoral, popliteal, and dorsalis pedis pulsations are weak or delayed compared with the bounding pulses of the arms and carotid vessels. The systolic blood pressure in the legs obtained by the cuff method normally is 10 to 20 mm Hg higher than in

the arms.[38] In coarctation, the pressure is lower and may be difficult to obtain. The differential in blood pressure is common in children older than 1 year of age, approximately 90% of whom have hypertension in the upper extremities greater than the 95th percentile for age (see Chapter 16).

Children with significant coarctation should be treated surgically; the optimal age for surgery is 2 to 4 years. If untreated, most persons with coarctation of the aorta die between 20 and 40 years of age. The common serious complications are related to the hypertensive state. In some centers, balloon valvoplasty has been used for treatment of unoperated coarctation. This method is still being developed, and ongoing clinical trials are needed to determine its long-term effectiveness and possible complications.[38]

Kawasaki's Disease

Kawasaki's disease is an acute febrile disease of young children. First described in Japan in 1967 by Dr. Tomisaku Kawasaki, the disease affects the skin, brain, eyes, joints, liver, lymph nodes, and heart. The disease can produce aneurysmal disease of the coronary arteries and is the most common cause of acquired heart disease in young children. Although first reported in Japanese children, the disease affects children of many races, occurs worldwide, and is increasing in frequency.

Kawasaki's disease is characterized by a vasculitis (*i.e.*, inflammation of the blood vessels) that begins in the small vessels (*i.e.*, arterioles, venules, and capillaries) and progresses to involve some of the larger arteries, such as the coronaries.[42] The cause of Kawasaki's disease is unknown, but it is thought to be of immunologic origin. It has been hypothesized that some unknown antigen, possibly a common infectious agent, triggers the immune response in a genetically predisposed child.

Clinical Course

The course of the disease is triphasic and includes an acute febrile phase that lasts approximately 7 to 14 days; a subacute phase that follows the acute phase and lasts from days 10 through 24; and a convalescent phase that follows the subacute stage and continues until the signs of the acute-phase inflammatory response have subsided and the signs of the illness have disappeared.[42]

The *acute phase* begins with an abrupt onset of fever, followed by bilateral conjunctivitis, usually without exudates; erythema of the oral and pharyngeal mucosa with "strawberry tongue" and dry fissured lips; redness and swelling of the hands and feet; rash of various forms; and enlarged cervical lymph nodes. The fever typically is high, reaching 40°C (104°F) or more, has an erratic spiking pattern, is unresponsive to antibiotics, and persists for 5 or more days.[42] The conjunctivitis begins shortly after the onset of fever, persists throughout the febrile course of the disease, and may last as long as 3 to 5 weeks.

The *subacute phase* begins when fever and other acute signs have subsided and lasts until all signs of the disease have disappeared. The subacute phase is associated with peeling of the skin of the fingertips and ends of the toes, thrombocytosis, the development of coronary aneurysms, and the greatest risk of sudden death. The *convalescent stage* persists from the complete resolution of symptoms until all signs of inflammation have disappeared. This usually takes approximately 8 weeks.

In addition to the major manifestations that occur during the acute stage of the illness, there are several associated, less specific characteristics of the disease, including arthritis, urethritis and pyuria, gastrointestinal manifestations (*e.g.*, diarrhea, abdominal pain), hepatitis, and hydrops of the gallbladder.[42] Arthritis or arthralgia occurs in approximately 30% of children with the disease, characterized by symmetric joint swelling that involves large and small joints. Central nervous system involvement occurs in almost all children and is characterized by pronounced irritability and lability of mood.

Cardiac involvement is the most important manifestation of Kawasaki's disease. Coronary vasculitis develops in between 10% and 40% of children within the first 2 weeks of the illness, manifested by dilatation and aneurysm formation in the coronary arteries, as seen on two-dimensional echocardiography. The manifestations of coronary artery involvement include signs and symptoms of myocardial ischemia or, rarely, overt myocardial infarction or rupture of the aneurysm. Pericarditis, myocarditis, endocarditis, heart failure, and dysrhythmias also may develop.

Diagnosis and Treatment

As with rheumatic fever, the diagnosis of Kawasaki's disease is based on clinical findings because no specific laboratory test for the disease exists. Clinical criteria developed by the Japan Kawasaki Disease Research Committee and subsequently by the AHA are used in establishing a diagnosis of Kawasaki's disease.[43] Chest radiographs, ECG tests, and two-dimensional echocardiography are used to detect coronary artery involvement and follow its progress. Coronary angiography may be used to determine the extent of coronary artery involvement.

Intravenous gamma globulin and aspirin are considered the best therapy for prevention of coronary artery abnormalities in children with Kawasaki's disease.[42] During the acute phase of the illness, aspirin usually is given in larger doses and for its anti-inflammatory and antipyretic effects.[42] After the fever is controlled, the aspirin dose is lowered, and the drug is given for its anti–platelet-aggregating effects.

In summary, congenital heart defects arise during fetal heart development and reflect the stage of development at the time the causative event occurred. Several factors contribute to the development of congenital heart defects, including genetic and chromosomal influences, viruses, and environmental agents such as drugs and radiation. The cause of the defect often is unknown. The defect may produce no effects, or it may markedly affect cardiac function. Congenital heart defects commonly produce shunting of blood from the right to the left side of the heart or from the left to the right side of the heart. Left-to-right shunts typically increase the volume of the right side of the heart and pulmonary circulation, and right-to-left shunts transfer unoxygenated blood from the right side of the heart to the left side, diluting the oxygen content of blood that is being ejected into the systemic circulation and causing cyanosis. The direction and degree of shunt depend on the size of the defect that connects the two sides of the heart and the difference in resistance between the two sides of the circulation. Congenital heart defects often are classified as defects that produce cyanosis and those that produce little or no cyanosis. Depending on the

severity of the defect, congenital heart defects may be treated medically or surgically. Medical and surgical treatment often is indicated in children with severe defects.

Kawasaki's disease is an acute febrile disease of young children that affects the skin, brain, eyes, joints, liver, lymph nodes, and heart. The disease can produce aneurysmal disease of the coronary arteries and is the most common cause of acquired heart disease in young children.

REVIEW QUESTIONS

- Explain the decrease in cardiac output and pulsus paradoxus that occur with cardiac tamponade.
- Describe blood flow in the coronary circulation and relate it to anginal pain that occurs during increased activity and tachycardia.
- Characterize the pathogenesis of atherosclerosis in terms of fixed atherosclerotic lesions, unstable plaque, and thrombosis with obstruction. Explain the role of low-dose aspirin in prevention of CHD.
- Define the term *acute coronary syndromes* and distinguish among chronic stable angina, unstable angina, non–ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction in terms of pathology, symptomatology, ECG changes, and serum cardiac markers.
- Compare the heart changes that occur with dilated, hypertrophic, constrictive cardiomyopathies, and arrhythmogenic right ventricular cardiomyopathy.
- Describe the relation between the infective vegetations associated with infective endocarditis and explain their relationship to the extracardiac manifestations of the disease.
- State the function of the heart valves and relate to alterations in hemodynamic changes (obstruction or regurgitation of blood flow), changes in stroke volume output, and nature of the heart murmur in terms of its occurrence during systole or diastole.
- Describe the anatomic defects and altered patterns of blood flow in children with atrial septal defects, ventricular septal defects, endocardial cushion defects, pulmonary stenosis, tetralogy of Fallot, patent ductus arteriosus, transposition of the great vessels, and coarctation of the aorta.

connection

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