- Left-to-right shunts are most common and are typically associated with ASD, VSD, or PDA. These lesions result in chronic right-sided pressure and volume overloads that eventually cause pulmonary hypertension with reversal of flow and right-to-left shunts with cyanosis (Eisenmenger syndrome).
- Right-to-left shunts are most commonly caused by TOF or TGA. These are cyanotic lesions from the outset and are associated with polycythemia, peripheral cyanosis effects, and paradoxical emboli.
- Obstructive lesions include valve stenoses and aortic coarctation; the clinical severity of the lesion depends on the degree of stenosis and the patency of the ductus arteriosus.

ISCHEMIC HEART DISEASE

IHD represents a group of related entities resulting from myocardial ischemia—an imbalance between myocardial supply (perfusion) and cardiac demand for oxygenated blood. Ischemia not only limits tissue oxygenation (and thus ATP generation), but also reduces the availability of nutrients and the removal of metabolic wastes (Chapter 2). Thus, cardiac ischemia is generally less well tolerated than hypoxemia per se, such as may occur with severe anemia, cyanotic heart disease, or advanced lung disease.

In more than 90% of cases, myocardial ischemia results from reduced blood flow due to obstructive atherosclerotic lesions in the epicardial coronary arteries; consequently, IHD is frequently referred to as coronary artery disease (CAD). In most cases, there is a long period (up to decades) of silent, slow progression of coronary lesions before the sudden onset of symptoms. Thus, IHD is often the late manifestation of coronary atherosclerosis that began during childhood or adolescence (Chapter 11).

IHD can declare itself through one or more of the following clinical presentations:

- *Myocardial infarction (MI),* in which ischemia causes frank cardiac necrosis
- *Angina pectoris* (literally "chest pain"), in which ischemia is not severe enough to cause infarction, but the symptoms nevertheless portend infarction risk
- *Chronic IHD* with heart failure
- *Sudden cardiac death (SCD)*

In addition to coronary atherosclerosis, myocardial ischemia can be caused by coronary emboli, myocardial vessel inflammation, or vascular spasm. Moreover, otherwise modest coronary artery occlusions may become consequential in the setting of increased cardiac energy demand (e.g., myocardial hypertrophy or increased heart rate), hypoxemia, or systemic hypotension (e.g., shock). Some conditions can have multiple deleterious effects. Thus, tachycardia increases oxygen demand (because of more contractions per unit time) while decreasing functional supply (by decreasing the relative time spent in diastole, when cardiac perfusion occurs).

Epidemiology

IHD is the single largest cause of mortality worldwide, accounting for over 12% of global deaths; in the industrialized nations, this amounts to over 7.5 million casualties each year. Even in low income countries, advances in the treatment and prevention of infectious diseases, and the increasing adoption of westernized diets is accelerating IHD incidence; it is predicted soon to become the leading cause of mortality there as well.

At the same time, there is cause for optimism; since peaking in the mid-1960s, the overall death rate from IHD has fallen in the United States by over 50%. This remarkable improvement can be attributed to the following:

- *Prevention,* achieved by modifying important risk factors, such as smoking, level of blood cholesterol, and hypertension. Additional risk reduction can occur through weight loss, exercise, and maintaining good glycemic control in diabetic patients.
- *Diagnostic and therapeutic advances,* allowing earlier and more effective treatments. The latter include cholesterol- (and inflammation-) lowering drugs such as statins, thrombolysis for acute coronary occlusions, better medical management after MI, coronary angioplasty and stenting, coronary artery bypass graft (CABG) surgery, and improved therapies for heart failure and arrhythmias using left VADs, implantable defibrillators, and cardiac resynchronization approaches. Even a simple daily prophylactic aspirin can have therapeutic benefit.

Continuing this encouraging trend will be challenging, particularly in view of the increased longevity of "baby boomers" (which will lead to a doubling of individuals older than 65 years of age by 2050), and the "obesity epidemic." New therapeutic advances will depend on understanding the genetic determinants of coronary atherosclerosis and IHD. Thus, the observation that MIs occur in only a fraction of individuals with coronary disease suggests that simple control of atherosclerotic risk factors is only part of the story.

Pathogenesis

The dominant cause of IHD syndromes is insufficient coronary perfusion relative to myocardial demand; in the vast majority of cases, this is due to either of the following:

- *Chronic,* progressive atherosclerotic narrowing of the epicardial coronary arteries
- Variable degrees of superimposed *acute* plaque change, thrombosis, and vasospasm.

The individual elements and their interactions are discussed next.

Chronic Vascular Occlusion

More than 90% of patients with IHD have atherosclerosis involving one or more of the epicardial coronary arteries (Chapter 11). A fixed lesion obstructing greater than 70% of vascular cross-sectional area (so called "critical stenosis") is typically cited as the threshold for symptomatic ischemia precipitated by exercise (characteristically manifesting as exertional angina). With this degree of obstruction, compensatory coronary arterial vasodilation is no longer sufficient to meet even moderate increases in myocardial demand. Obstruction of 90% of the cross-sectional area of the lumen generally leads to inadequate coronary blood flow, even at rest. Slowly developing obstructions induce the formation

of collateral circulation that can mitigate the effects of even high-grade stenoses by allowing alternate channels to perfuse at-risk myocardium. Consequently, rather than just assessing the extent of local vascular stenosis, measurements of coronary flow across the stenosis (flow reserves) provide a better assessment of the consequences of fixed coronary artery occlusions, particularly when multifocal.

Although only a single major coronary epicardial vessel may be affected, two or all three—the left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA)—are often involved simultaneously by obstructive atherosclerosis. Clinically significant plaques can be located anywhere along the course of the vessels, although they tend to predominate within the first several centimeters of the LAD and LCX. Sometimes the major epicardial branches are also involved (i.e., LAD diagonal branches, LCX obtuse marginal branches, or posterior descending branch of the RCA), but atherosclerosis of the intramyocardial (penetrating) branches is rare. Thus, most atherosclerotic stenoses can be accessed by coronary catheterization.

Acute Plaque Change

The risk of an individual developing clinically important IHD depends in part on the number, distribution, structure, and degree of obstruction by atheromatous plaques. However, the varied clinical manifestations of IHD cannot be explained by the anatomic disease burden and fixed stenoses alone. This is particularly true for the so-called acute coronary syndromes, namely when unstable angina, acute MI, and sudden death are caused abruptly by acute plaque changes. These acute coronary syndromes are typically initiated by an unpredictable and sudden conversion of a stable atherosclerotic plaque to an unstable and potentially life-threatening atherothrombotic lesion through rupture, superficial erosion, ulceration, fissuring, or deep hemorrhage (collectively called acute plaque change) (Chapter 11). In most instances, acute plaque changes—typically associated with intralesional inflammation—precipitate the formation of a superimposed thrombus that partially or completely occludes the artery. It remains to be seen whether aggressive anti-inflammatory regimens are a means to reduce such acute coronary events.

Consequences of Myocardial Ischemia

- *Stable angina* results from increases in myocardial oxygen demand that outstrip the ability of coronary arteries with fixed stenoses to increase oxygen delivery; it is usually not associated with plaque disruption.
- *Unstable angina* is caused by acute plaque change that results in thrombosis and/or vasoconstriction, and leads to incomplete or transient reductions in coronary blood flow. In some cases, microinfarcts can occur distal to disrupted plaques due to thromboemboli.
- *MI* is often the result of acute plaque change that induces an abrupt thrombotic occlusion, resulting in myocardial necrosis.
- *Sudden cardiac death* may be caused by regional myocardial ischemia that induces a fatal ventricular arrhythmia. This can result from a fixed stenosis or acute plaque change.

Each of these important syndromes is discussed in detail next, followed by an examination of the important myocardial consequences.

Angina Pectoris

Angina pectoris is characterized by paroxysmal and usually recurrent attacks of substernal or precordial chest discomfort caused by transient (15 seconds to 15 minutes) myocardial ischemia that is insufficient to induce myocyte necrosis. The anginal pain is a consequence of the ischemia-induced release of adenosine, bradykinin, and other molecules that stimulate sympathetic and vagal afferent nerves. Three overlapping patterns of angina pectoris are recognized, caused by varying combinations of decreased perfusion, increased demand, and coronary arterial pathology. Importantly, not all ischemic events are perceived by patients; silent ischemia is particularly common in the geriatric population and in the setting of diabetic neuropathy.

- *Stable (typical) angina* is the most common form of angina; it is caused by an imbalance in coronary perfusion (due to chronic stenosing coronary atherosclerosis) relative to myocardial demand. Stable angina does not occur at rest, but in a given patient can be reliably induced by activities that increase the energy requirements of the heart, including physical activity, emotional excitement, or psychological stress. Angina pectoris is classically described as a crushing or squeezing substernal sensation that can radiate down the left arm or to the left jaw *(referred pain)*. The pain is usually relieved by rest (decreasing demand) or by administering vasodilators, such as nitroglycerin and calcium channel blockers (thereby increasing perfusion).
- *Prinzmetal variant angina* is an uncommon form of episodic myocardial ischemia caused by coronary artery spasm. Although individuals with Prinzmetal variant angina can also have significant coronary atherosclerosis, the anginal attacks are unrelated to physical activity, heart rate, or blood pressure, and can occur at rest. Prinzmetal angina generally responds promptly to vasodilators.
- *Unstable* or *crescendo angina* refers to a pattern of increasingly frequent, prolonged (>20 min), or severe angina, precipitated by progressively lower levels of physical activity or even occurring at rest. Unstable angina is associated with plaque disruption and superimposed thrombosis, distal embolization of the thrombus, and/or vasospasm; it is an important harbinger of MI, potentially portending complete vascular occlusion.

Myocardial Infarction

MI, also commonly referred to as "heart attack," is the death of cardiac muscle due to prolonged ischemia. Roughly 1.5 million individuals in the United States suffer an MI each year, causing approximately 610,000 deaths annually. The major underlying cause of IHD is atherosclerosis; although MIs can occur at virtually any age, 10% of MIs occur in people younger than 40 years of age, and 45% occur in people younger than 65 years of age. Nevertheless, the frequency rises progressively with increasing age and with increasing atherosclerotic risk factors (Chapter 11). Through middle age, male gender increases the relative risk of MI; indeed, women are generally protected against MI during their reproductive years. However, postmenopausal decline in estrogen production is usually associated with accelerated CAD, and IHD is the most common cause of death in older

women. Unfortunately, postmenopausal hormonal replacement therapy has not been shown to be protective, and in fact, in some cases, may be detrimental.

Pathogenesis

Coronary Arterial Occlusion. The following sequence of events likely underlies most MIs (see Chapter 11 for additional details):

- An atheromatous plaque is eroded or suddenly disrupted by endothelial injury, intraplaque hemorrhage, or mechanical forces, exposing subendothelial collagen and necrotic plaque contents to the blood.
- Platelets adhere, aggregate, and are activated, releasing thromboxane A_2, adenosine diphosphate (ADP), and serotonin—causing further platelet aggregation and vasospasm (Chapter 4).
- Activation of coagulation by tissue factor and other mechanisms adds to the growing thrombus.
- Within minutes, the thrombus can evolve to completely occlude the coronary artery lumen.

The evidence for this scenario derives from autopsy studies of patients dying of acute MI, as well as imaging studies demonstrating a high frequency of thrombotic occlusion early after MI; interestingly, comparison to prior angiograms shows that these thrombi are usually at a site that did not previously have a critical (>70%) fixed stenosis. Typically, when angiography is performed within 4 hours of the onset of MI, it demonstrates coronary thrombosis in almost 90% of cases. However, when angiography is performed 12 to 24 hours after onset of symptoms, evidence of thrombosis is seen in only 60% of patients, even without intervention. Thus, at least some occlusions clear spontaneously through lysis of the thrombus or relaxation of spasm. This sequence of events in a typical MI also has therapeutic implications: early thrombolysis and/or angioplasty can be highly successful in limiting the extent of myocardial necrosis.

In approximately 10% of cases, MI occurs in the absence of the typical coronary atherothrombosis. In such situations, other mechanisms may be responsible for the reduced coronary blood flow:

- *Vasospasm* with or without coronary atherosclerosis, perhaps in association with platelet aggregation or due to drug ingestion (e.g., cocaine or ephedrine).
- *Emboli* from the left atrium in association with atrial fibrillation, a left-sided mural thrombus, vegetations of infective endocarditis (IE), intracardiac prosthetic material, or paradoxical emboli from the right side of the heart or the peripheral veins traversing a patent foramen ovale and into the coronary arteries
- *Uncommon causes* of MI without atherothrombosis include disorders of small intramural coronary vessels (e.g., vasculitis), hematologic abnormalities (e.g., sickle cell disease), amyloid deposition in vascular walls, vascular dissection, marked hypertrophy (e.g., due to aortic stenosis), lowered systemic blood pressure (e.g., shock), or inadequate myocardial "protection" during cardiac surgery.

Myocardial Response. Coronary arterial obstruction diminishes blood flow to a region of myocardium, causing ischemia, rapid myocardial dysfunction, and eventually—with prolonged vascular compromise—myocyte death. The anatomic region supplied by that artery is referred to as the area at risk. The outcome depends predominantly on the severity and duration of flow deprivation (Fig. 12.9).

The early biochemical consequence of myocardial ischemia is the cessation of aerobic metabolism within seconds, leading to inadequate production of high-energy phosphates (e.g., creatine phosphate and adenosine triphosphate) and accumulation of potentially noxious metabolites (e.g., lactic acid) (see Fig. 12.9A). Because of the exquisite dependence of myocardial function on oxygen and nutrients, myocardial contractility ceases within a minute or so of the onset of severe ischemia. Such loss of function contributes to decreased systolic function long before myocyte death occurs.

As detailed in Chapter 2, ultrastructural changes (including myofibrillar relaxation, glycogen depletion, cell and mitochondrial swelling) also develop within a few minutes

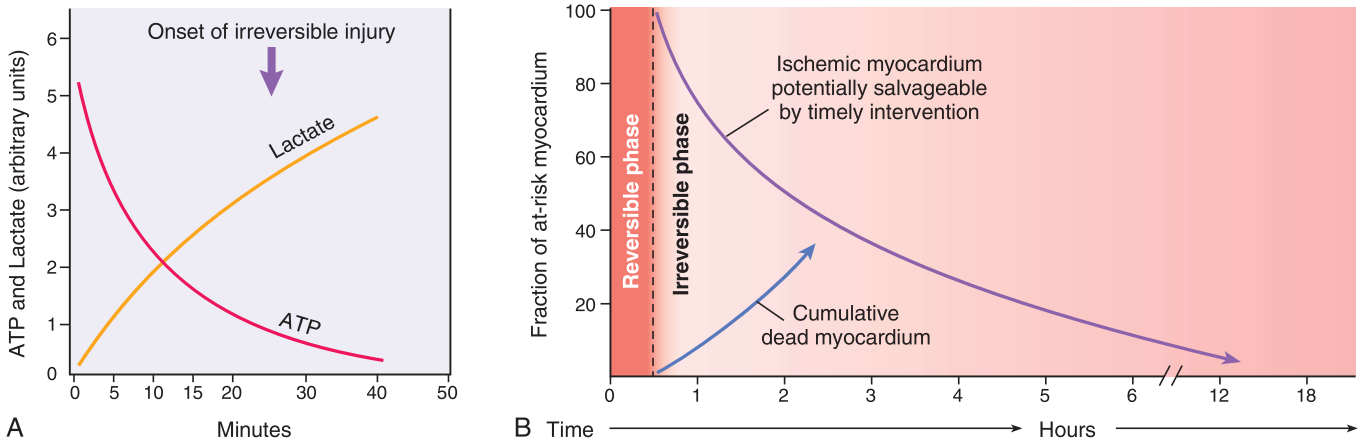

Figure 12.9 Temporal sequence of early biochemical findings and progression of cardiomyocyte necrosis after onset of severe myocardial ischemia. (A) Early changes include loss of adenosine triphosphate (ATP) and accumulation of lactate. (B) For approximately 30 minutes after the onset of even the most severe ischemia, myocardial injury is potentially reversible. Thereafter, progressive loss of viability occurs that becomes complete by 6 to 12 hours. The benefits of reperfusion are greatest when it is achieved early and are progressively lost when reperfusion is delayed. (Originally modified with permission from Antman E: Acute myocardial infarction. In Braunwald E, et al., editors: *Heart Disease: a Textbook of Cardiovascular Medicine*, ed 6, Philadelphia, 2001, WB Saunders, pp 1114–1231.)

of the onset of ischemia. Nevertheless, these early manifestations of ischemic injury are potentially reversible. Indeed, experimental and clinical evidence shows that only severe ischemia (blood flow 10% or less of normal) lasting 20 to 30 minutes or longer leads to irreversible damage (necrosis) of cardiac myocytes. This delay in the onset of permanent myocardial injury provides the rationale for rapid diagnosis in acute MI—to permit early coronary intervention to establish reperfusion and salvage as much "at risk" myocardium as possible.

The earliest detectable feature of myocyte necrosis is disruption of the integrity of the sarcolemmal membrane, allowing intracellular macromolecules to leak out of necrotic cells into the cardiac interstitium and ultimately into the microvasculature and lymphatics. This escape of intracellular myocardial proteins into the circulation forms the basis for blood tests that can sensitively detect irreversible myocyte damage, and are important for managing MI (see later). With prolonged severe ischemia, injury to the microvasculature follows injury to the cardiac myocytes. The temporal progression of these events is summarized in Table 12.4.

Table 12.4 Approximate Time of Onset of Key Events in Ischemic Cardiac Myocytes

Feature	Time
Onset of ATP depletion	Seconds
Loss of contractility	<2 minutes
ATP reduced	
to 50% of normal	10 minutes
to 10% of normal	40 minutes
Irreversible cell injury	20–40 minutes
Microvascular injury	>1 hour

ATP, Adenosine triphosphate.

The progression of ischemic necrosis in the myocardium is summarized in Fig. 12.10. Irreversible injury of ischemic myocytes first occurs in the subendocardial zone. This region is especially susceptible to ischemia because it is the last area to receive blood delivered by the epicardial vessels, and also because it is exposed to relatively high intramural

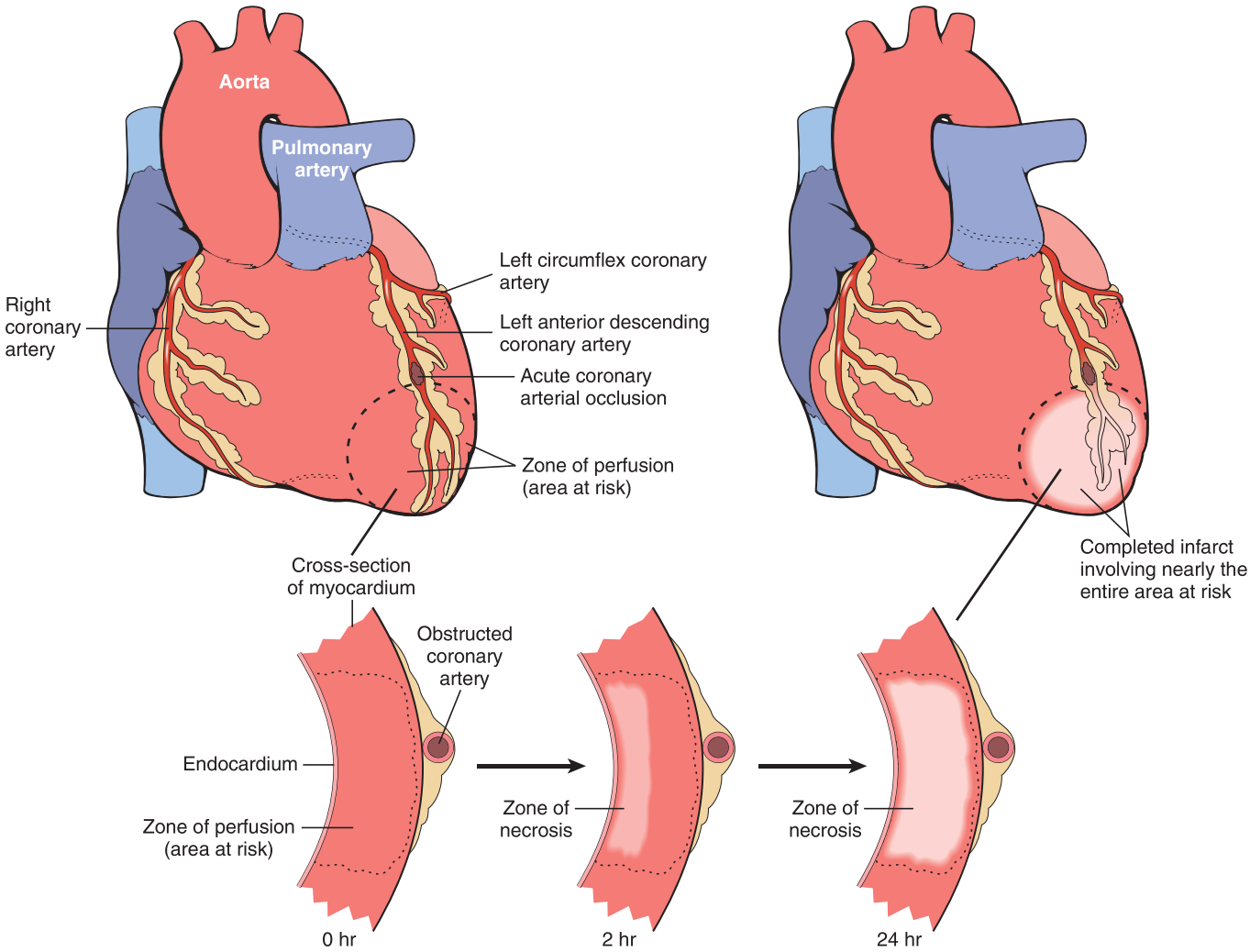

Figure 12.10 Progression of myocardial necrosis after coronary artery occlusion. Necrosis begins in a small zone of the myocardium beneath the endocardial surface in the center of the ischemic zone. The area that depends on the occluded vessel for perfusion is the "at risk" myocardium *(shaded)*. Note that a very narrow zone of myocardium immediately beneath the endocardium is spared from necrosis because oxygen and nutrition can be provided by diffusion from the ventricle.

pressures, which act to impede the inflow of blood. With more prolonged ischemia, a wavefront of cell death moves through other regions of the myocardium, driven by progressive tissue edema and myocardial-derived reactive oxygen species and inflammatory mediators.

The location, size, and specific morphologic features of an acute MI depend on the following:

- The *location, severity, and rate of development of coronary obstructions* due to atherosclerosis and thromboses
- The *size of the vascular bed* perfused by the obstructed vessels
- The *duration* of the occlusion
- The *metabolic and oxygen needs* of the myocardium at risk
- The extent of *vascular collateralization*
- The presence, site, and severity of coronary *arterial spasm*
- *Other factors,* such as heart rate, cardiac rhythm, and blood oxygenation

An infarct usually achieves its full extent within 3 to 6 hours; in the absence of intervention, an infarct caused by occlusion of an epicardial vessel can involve the entire wall thickness (transmural infarct). Clinical intervention within this critical window of time can lessen the size of the infarct within the territory at risk.

Patterns of Infarction. The distribution of myocardial necrosis correlates with the location and cause of the decreased perfusion (Fig. 12.11).

Knowledge of the areas of myocardium perfused by the major coronary arteries allows correlation of specific vascular obstructions with their corresponding areas of MI. Typically, the LAD branch of the left coronary artery supplies most of the apex of the heart, the anterior wall of the left ventricle, and the anterior two-thirds of the ventricular septum. By convention, the coronary artery—either RCA or LCX—that perfuses the posterior third of the septum is called "dominant" (even though the LAD and LCX collectively perfuse the majority of the left ventricular myocardium). In a right dominant circulation (present in approximately 80% of individuals), the RCA supplies the entire right ventricular free wall, the posterobasal wall of the left ventricle, and the posterior third of the ventricular septum, and the LCX generally perfuses only the lateral wall of the left ventricle. Thus, RCA occlusions can potentially lead to left ventricular damage.

Although most hearts have numerous intercoronary anastomoses (collateral circulation), relatively little blood normally courses through these. However, when a coronary artery is progressively narrowed over time, blood flows via the collaterals from the high- to the low-pressure circulation causing the channels to enlarge. Through such progressive dilation and growth of collaterals, stimulated by ischemia, blood flow is provided to areas of myocardium that would otherwise be deprived of adequate perfusion. Indeed, in the setting of extensive collateralization, the normal epicardial perfusion territories may be so expanded that subsequent occlusion leads to infarction in paradoxical distributions.

Transmural infarctions occur when there is occlusion of an epicardial vessel (in the absence of any therapeutic intervention)—the necrosis involves virtually the full thickness of the ventricular wall in the distribution of the affected coronary. This pattern of infarction is usually associated with a combination of chronic coronary atherosclerosis, acute

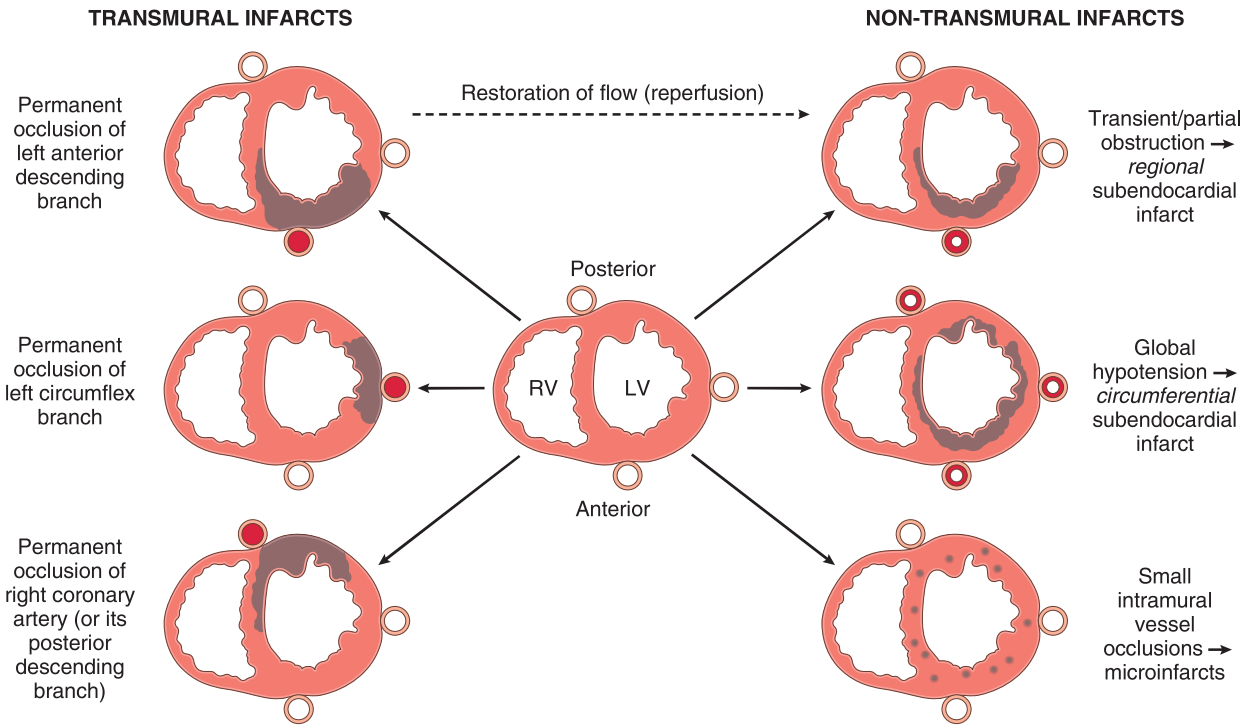

Figure 12.11 Distribution of myocardial ischemic necrosis correlates with the location and nature of decreased perfusion. *Left,* the positions of transmural acute infarcts resulting from occlusions of the major coronary arteries; *top to bottom,* left anterior descending, left circumflex, and right coronary arteries. *Right,* the types of infarcts that result from a partial or transient occlusion, global hypotension, or intramural small vessel occlusions.

plaque change, and superimposed thrombosis (discussed earlier).

Subendocardial (nontransmural) infarctions can occur as a result of a plaque disruption followed by a coronary thrombus that becomes lysed (therapeutically or spontaneously) before myocardial necrosis extends across the full thickness of the wall. Subendocardial infarcts can also result from prolonged, severe reduction in systemic blood pressure, as in shock superimposed on chronic, otherwise noncritical, coronary stenoses. In the subendocardial infarcts that occur as a result of global hypotension, myocardial damage is often circumferential, rather than being limited to the distribution of a single major coronary artery.

Multifocal microinfarction refers to a pattern that is seen when there is pathology involving only smaller intramural vessels. It can occur in the setting of microembolization, vasculitis, or vascular spasm, for example, due to endogenous catecholamines (epinephrine) or drugs (cocaine or ephedrine). Elevated levels of catecholamines also increase heart rate and myocardial contractility, exacerbating ischemia caused by the vasospasm. The outcome of such vasospasm can be sudden cardiac death (usually caused by a fatal arrhythmia) or an ischemic dilated cardiomyopathy (discussed later).

MORPHOLOGY

The temporal evolution of the morphologic changes in acute MI and subsequent healing are summarized in Table 12.5.

Nearly all transmural infarcts involve at least a portion of the left ventricle (comprising the free wall and ventricular septum); they encompass nearly the entire perfusion zone of the occluded coronary artery save for a narrow rim (approximately 0.1 mm) of viable subendocardial myocardium that is preserved by diffusion of oxygen and nutrients from the ventricular lumen.

The frequencies of involvement of each of the three main arterial trunks and the corresponding sites of myocardial lesions resulting in infarction (in the typical right dominant heart) are as follows (left side of Fig. 12.11):

- Left anterior descending coronary artery (40% to 50%): infarcts involving the anterior wall of left ventricle near the apex; the anterior portion of ventricular septum; and the apex circumferentially
- Right coronary artery (30% to 40%): infarcts involving the inferior/posterior wall of the left ventricle; posterior portion of ventricular septum; and the inferior/posterior right ventricular free wall in some cases
- Left circumflex coronary artery (15% to 20%): infarcts involving the lateral wall of the left ventricle except at the apex

Other locations of critical coronary arterial lesions causing infarcts are sometimes encountered, such as the left main coronary artery, the secondary (diagonal) branches of the left anterior descending coronary artery, or the marginal branches of the left circumflex coronary artery. Of MIs caused by a right coronary obstruction, 15% to 30% extend from the posterior free wall of the septal portion of the left ventricle into the adjacent right ventricular wall. Isolated infarction of the right ventricle is unusual (only 1% to 3% of cases), as is infarction of the atria.

The gross and microscopic appearance of an infarct depends on the interval of time between the MI and death. Damaged myocardium undergoes a progressive sequence of morphologic changes involving typical ischemic coagulative necrosis, the predominant mechanism of cell death in MI (although apoptosis

Table 12.5 Evolution of Morphologic Changes in Myocardial Infarction

Time	Gross Features	Light Microscope	Electron Microscope
Reversible Injury			
0–½ hour	None	None	Relaxation of myofibrils; glycogen loss; mitochondrial swelling
Irreversible Injury			
½–4 hours	None	Usually none; variable waviness of fibers at border	Sarcolemmal disruption; mitochondrial amorphous densities
4–12 hours	Dark mottling (occasional)	Early coagulative necrosis; edema; hemorrhage	
12–24 hours	Dark mottling	Ongoing coagulative necrosis; pyknosis of nuclei; myocyte hypereosinophilia; marginal contraction band necrosis; early neutrophilic infiltrate	
1–3 days	Mottling with yellow-tan infarct center	Coagulative necrosis, with loss of nuclei and striations; brisk interstitial infiltrate of neutrophils	
3–7 days	Hyperemic border; central yellow-tan softening	Beginning disintegration of dead myofibers, with dying neutrophils; early phagocytosis of dead cells by macrophages at infarct border	
7–10 days	Maximally yellow-tan and soft, with depressed red-tan margins	Well-developed phagocytosis of dead cells; granulation tissue at margins	
10–14 days	Red-gray depressed infarct borders	Well-established granulation tissue with new blood vessels and collagen deposition	
2–8 weeks	Gray-white scar, progressive from border toward core of infarct	Increased collagen deposition, with decreased cellularity	
>2 months	Scarring complete	Dense collagenous scar	

can also occur); this is followed by stereotypical inflammation and repair that parallels responses to injury in other tissues (Chapter 2).

Early morphologic recognition of acute MI can be difficult, particularly when death occurs within only a few hours of symptom onset. MIs less than 12 hours old are usually not apparent on gross examination alone; however, if the infarct preceded death by at least 2 to 3 hours, it is possible to highlight the area of necrosis by immersion of tissue slices in a solution of **triphenyltetrazolium chloride.** This gross histochemical stain imparts a brick-red color to intact, noninfarcted myocardium with preserved lactate dehydrogenase activity. Because dehydrogenases leak out through the damaged membranes of dead cells, an infarct appears as an unstained pale zone (Fig. 12.12). By 12 to 24 hours after infarction, an MI can usually be identified grossly as a reddish-blue area of discoloration caused by congestion and extravasated blood. By 3 to 7 days, it is rimmed by a hyperemic zone of highly vascularized early wound healing **(granulation tissue).** Thereafter, the infarct becomes progressively more sharply defined, yellow-tan, and soft. Over the succeeding weeks, the injured region evolves to a fibrous scar.

The histopathologic changes also proceed in a fairly predictable sequence (Fig. 12.13). The typical changes of coagulative necrosis become detectable in the first 6 to 12 hours. "Wavy fibers" may

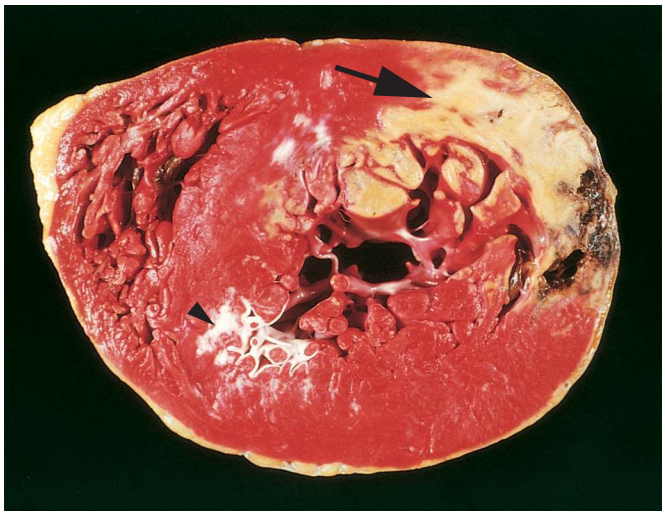

Figure 12.12 Acute myocardial infarct, predominantly of the posterolateral left ventricle, demonstrated histochemically by a lack of staining by triphenyltetrazolium chloride in areas of necrosis *(arrow)*. The staining defect is due to the lactate dehydrogenase leakage that follows cell death. Note the myocardial hemorrhage at one edge of the infarct that was associated with cardiac rupture, and the anterior scar *(arrowhead)*, indicative of an old infarct. The specimen is oriented with the posterior wall at the top.

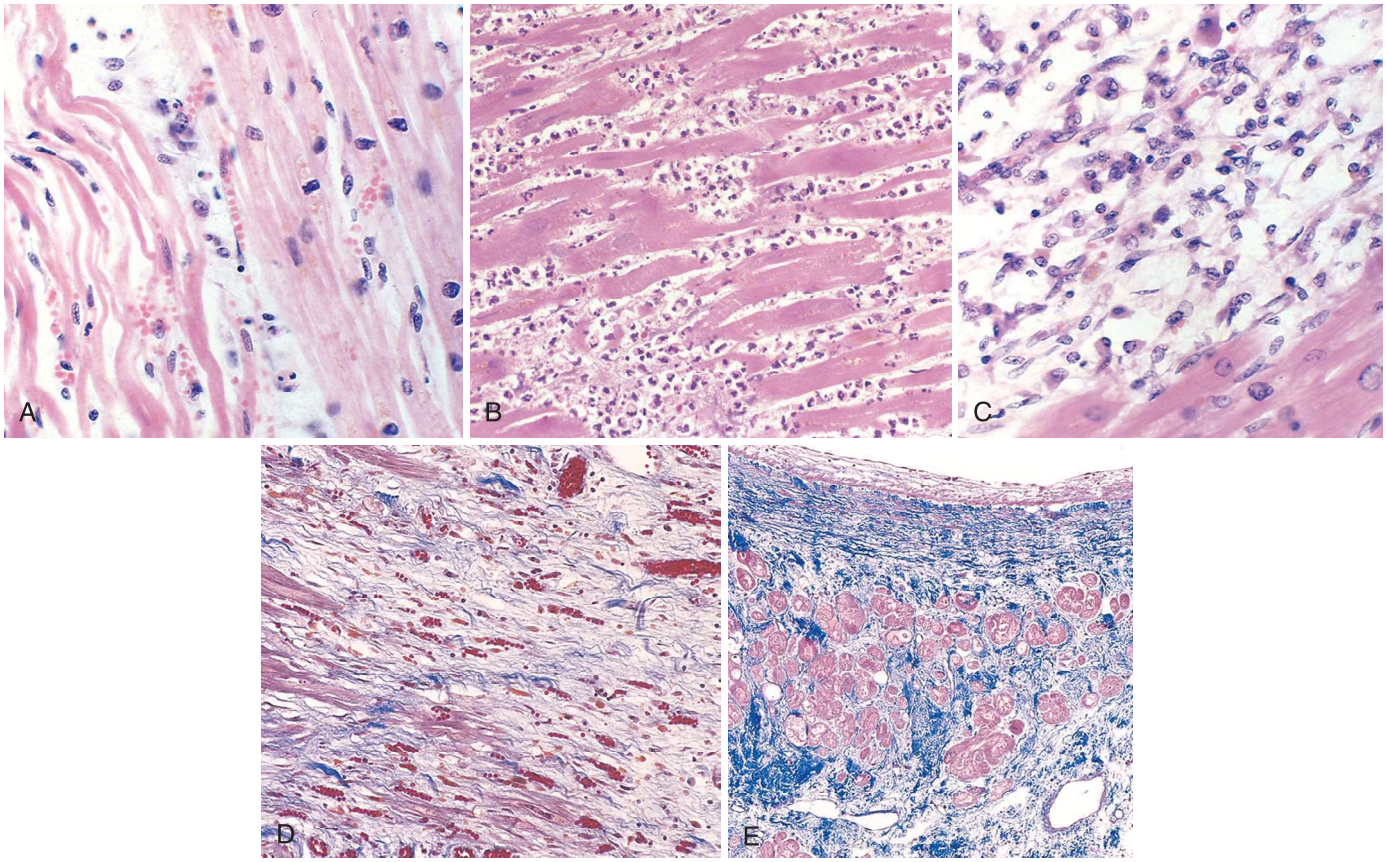

Figure 12.13 Microscopic features of myocardial infarction and its repair. (A) One-day-old infarct showing coagulative necrosis and wavy fibers (elongated and narrow, as compared with adjacent normal fibers at *right*). Widened spaces between the dead fibers contain edema fluid and scattered neutrophils. (B) Dense polymorphonuclear leukocytic infiltrate in an acute myocardial infarction that is 3 to 4 days old. (C) Removal of necrotic myocytes by phagocytosis (approximately 7 to 10 days). (D) Granulation tissue characterized by loose collagen and abundant capillaries. E, Healed myocardial infarct in which the necrotic tissue has been replaced by a dense collagenous scar. The residual cardiac muscle cells show evidence of compensatory hypertrophy. D and E are stained with Masson's trichrome, rendering collagenous connective tissue a deep blue color; note the accumulation of extracellular matrix (density of blue stain) between the early granulation tissue and the subsequent dense scar.

be present at the periphery of the infarct, resulting from the contractions of viable myocardium that cause the stretching and buckling of adjacent, noncontractile dead fibers. An additional sublethal ischemic change may be seen in the margins of infarcts: this so-called **myocyte vacuolization** reflects intracellular accumulations of salt and water within the sarcoplasmic reticulum, and marks myocytes that are viable but poorly contractile.

Necrotic myocardium elicits acute inflammation (typically most prominent 1 to 3 days after MI), followed by a wave of macrophages that remove necrotic myocytes and neutrophil fragments (most pronounced 3 to 7 days after MI). The infarcted zone is progressively replaced by granulation tissue (most prominent 7 to 10 days after MI), which in turn forms the provisional scaffolding on which dense collagenous scar forms; because cardiac myocytes are terminally differentiated cells, no cardiomyocyte proliferation is seen. In most instances, scarring is well advanced by the end of the sixth week, but the efficiency of repair depends on the size of the original lesion and the ability of the host tissues to heal. Healing requires the migration of inflammatory cells and ingrowth of new vessels from the infarct margins. Thus, an MI heals from its borders toward the center, and a large infarct may not heal as fast or as completely as a small one. Moreover, malnutrition, poor vasculature, or exogenous anti-inflammatory steroids can impede effective infarct scarring (Chapter 3). Once an MI is completely healed, it is impossible to distinguish its age: whether present for 8 weeks or 10 years, fibrous scars look the same.

The following discussion considers the changes that result from interventions that can limit infarct size by salvaging myocardium that is not yet necrotic.

Infarct Modification by Reperfusion. The therapeutic goal in acute MI is to salvage the maximal amount of ischemic myocardium; this is accomplished by restoration of tissue perfusion as quickly as possible (hence the adage "time is myocardium"). Such reperfusion is achieved by thrombolysis (dissolution of thrombus by tissue plasminogen activator), angioplasty, or coronary arterial bypass graft. Unfortunately, although preservation of viable (but at-risk) heart can improve both short- and long-term outcomes, reperfusion is not an unalloyed blessing. Indeed, late restoration of blood flow into ischemic tissues can be associated with arrhythmias, and can incite greater local damage than might otherwise have occurred—so-called reperfusion injury.

The effects of reperfusion on myocardial viability and function are summarized in Fig. 12.14. Although the clinical significance of myocardial reperfusion injury is debated, it has been estimated that up to 50% (or more) of the ultimate infarct size can be attributed to its effects. To date, clinical trials to prevent reperfusion injury have not been fruitful, but this remains an active area of investigation. Factors that contribute to reperfusion injury include the following:

- *Mitochondrial dysfunction:* Ischemia alters the mitochondrial membrane permeability, which allows proteins to move into the mitochondria. This leads to swelling and rupture of the outer membrane, releasing mitochondrial contents that promote apoptosis.
- *Myocyte hypercontracture:* During periods of ischemia, the intracellular levels of calcium are increased as a result of impaired calcium cycling and sarcolemmal damage. After reperfusion, the contraction of myofibrils is augmented and uncontrolled, causing cytoskeletal damage and cell death.
- *Free radicals* including superoxide anion (•O2), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), nitric oxide–derived peroxynitrite, and hydroxyl radicals (•OH) are produced within minutes of reperfusion and cause damage to the myocytes by altering membrane proteins and phospholipids.
- *Leukocyte aggregation,* which may occlude the microvasculature and contribute to the "no-reflow" phenomenon. Further, leukocytes elaborate proteases and elastases that cause cell death.
- *Platelet and complement activation* also contribute to microvascular injury. Complement activation is thought to play a role in the no-reflow phenomenon by injuring the endothelium.

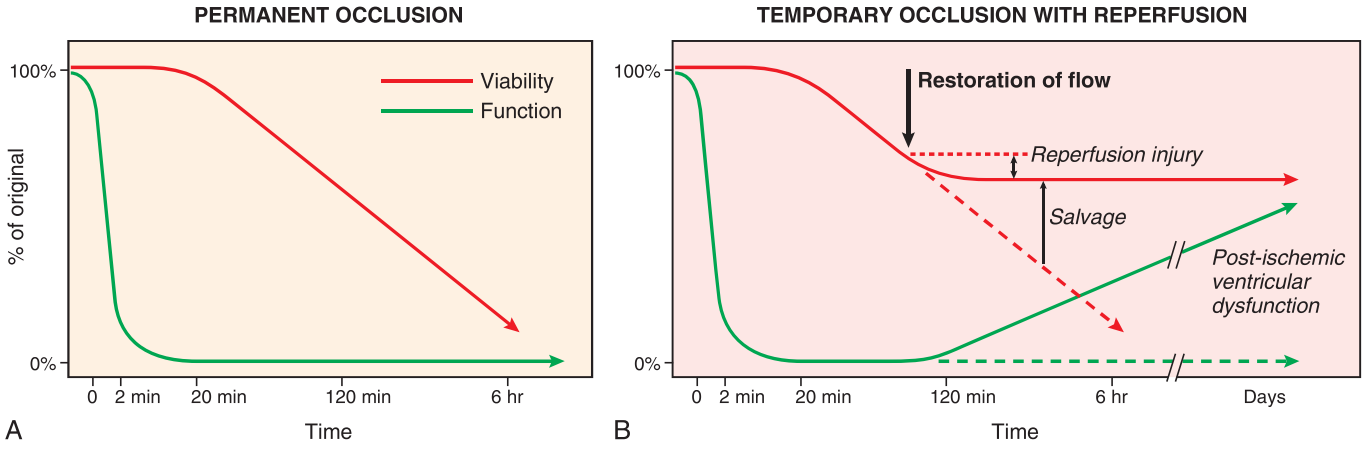

Figure 12.14 Effects of reperfusion on myocardial viability and function. After coronary occlusion, contractile function is lost within 2 minutes, and viability begins to diminish after approximately 20 minutes. If perfusion is not restored (A), then nearly all myocardium in the affected region suffers death. (B) If flow is restored, then some necrosis is prevented, myocardium is salvaged, and at least some function can return. The earlier reperfusion occurs, the greater the degree of salvage. However, the process of reperfusion itself may induce some damage (reperfusion injury), and return of function of salvaged myocardium may be delayed for hours to days (postischemic ventricular dysfunction or stunning).

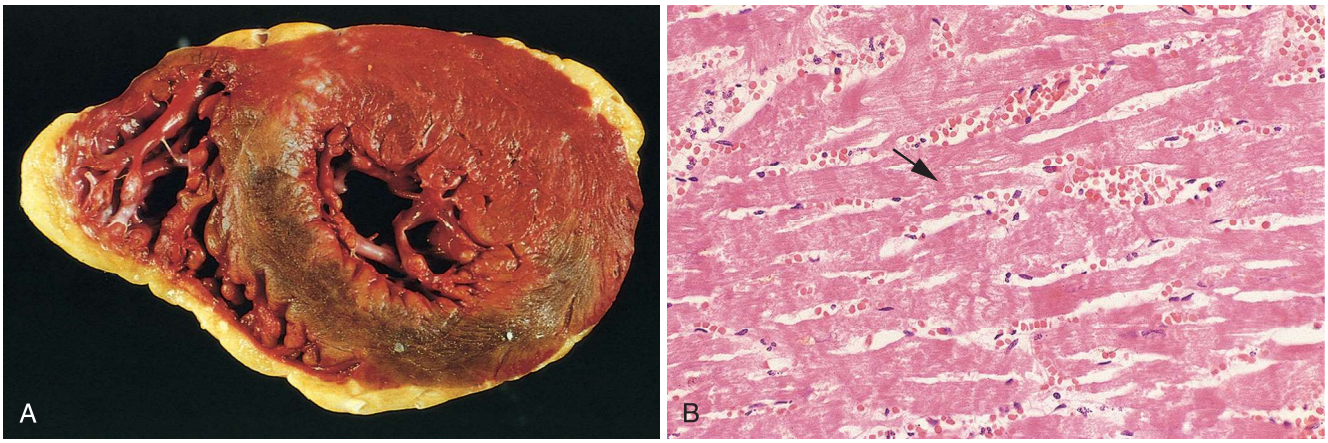

Figure 12.15 Consequences of myocardial ischemia followed by reperfusion. Gross (A) and microscopic (B) appearance of myocardium modified by reperfusion. (A) Large, densely hemorrhagic, anterior wall acute myocardial infarction in a patient with left anterior descending artery thrombus treated with streptokinase, a fibrinolytic agent (slice is stained with triphenyl tetrazolium chloride; see Fig. 12.12). Specimen oriented with posterior wall at top. (B) Myocardial necrosis with hemorrhage and contraction bands, visible as dark bands spanning some myofibers *(arrow)*.

The typical appearance of reperfused myocardium in the setting of an acute MI is shown in Fig. 12.15. Such infarcts typically are hemorrhagic as a consequence of vascular injury and leakiness. Microscopically, irreversibly damaged myocytes after reperfusion develop contraction band necrosis; in this pathologic process, intense eosinophilic bands of hypercontracted sarcomeres are created by an influx of calcium across plasma membranes that heightens actin-myosin interactions. In the absence of ATP, the sarcomeres cannot relax and get stuck in an agonal tetanic state. Thus, although reperfusion can salvage reversibly injured cells, it also alters the morphology of irreversibly injured cells.

The biochemical abnormalities (and their functional consequences) may also persist for days to weeks in reperfused myocytes. Such changes are thought to underlie a phenomenon referred to as stunned myocardium, a state of prolonged contractile dysfunction induced by short-term ischemia that usually recovers after several days. Myocardium that is subjected to chronic, sublethal ischemia can also enter into a state of lowered metabolism and function called hibernation. Subsequent revascularization (e.g., by CABG surgery, angioplasty, or stenting) often restores normal function to such hibernating myocardium.

Clinical Features

MI is diagnosed by clinical symptoms, laboratory tests for the presence of myocardial proteins in the plasma, and characteristic electrocardiographic changes. Patients with MI classically present with prolonged (more than 30 minutes) chest pain described as crushing, stabbing, or squeezing, associated with a rapid, weak pulse. Profuse sweating (diaphoresis), and nausea and vomiting are common and can suggest involvement of the posterior-inferior ventricle with secondary vagal stimulation. Dyspnea due to impaired contractility of the ischemic myocardium and the resultant pulmonary congestion and edema is a frequent symptom. However, in as many as 25% of patients the onset is entirely asymptomatic (e.g., in the setting of diabetic neuropathy), and the disease is discovered only by electrocardiographic changes or laboratory tests that show evidence of myocardial damage (see later).

Owing to the characteristic electrocardiographic changes resulting from myocardial ischemia or necrosis in various distributions, a transmural infarct is sometimes referred to as an ST-elevation myocardial infarct (STEMI) and a subendocardial infarct as a non–ST-elevation infarct (NSTEMI). Depending on the extent and location of the vascular involvement, microinfarctions show nonspecific changes or can even be electrocardiographically silent.

The laboratory evaluation of MI is based on measuring the blood levels of proteins that leak out of irreversibly damaged myocytes; previously, this involved measurement of the MB fraction of creatine kinase (CK-MB). Currently, the most clinically useful biomarkers of myocardial damage are cardiac-specific troponins T and I (cTnT and cTnI), proteins that normally regulate calcium-mediated contraction of cardiac muscle (Fig. 12.16). The diagnosis of myocardial injury is established when blood levels of troponin are elevated above threshold levels; the tempo and magnitude of appearance of these serum markers after MI depends on several factors, including the volume of damaged myocardium, blood flow and lymphatic drainage in the area of the infarct, and the rate of elimination of the marker from the blood. Cardiac troponins begin to rise in 2 to 4 hours and peak at 24 to 48 hours after an acute infarct. With reperfusion, troponin levels may be higher and peak earlier owing to more rapid washout of the marker from the necrotic tissue.

Significant acute elevation in serum troponin can also be seen in other conditions that cause death of cardiac myocytes, such as myocarditis and myocardial trauma. On the other hand, low-level serum troponin elevation ("troponin leak") can occur in a host of other conditions, including congestive heart failure, pulmonary embolus, renal failure, and sepsis. These elevations do not usually follow the same abrupt-injury time course, so serial measurements may be helpful in distinguishing different etiologies.

Recommended initial therapies for acute MI make sense based on the pathophysiologic features discussed earlier and include the following:

- *Oxygen supplementation* to improve blood oxygen saturation for patients with hypoxia or respiratory distress
- *Nitrates* to induce vasodilation and reverse vasospasm

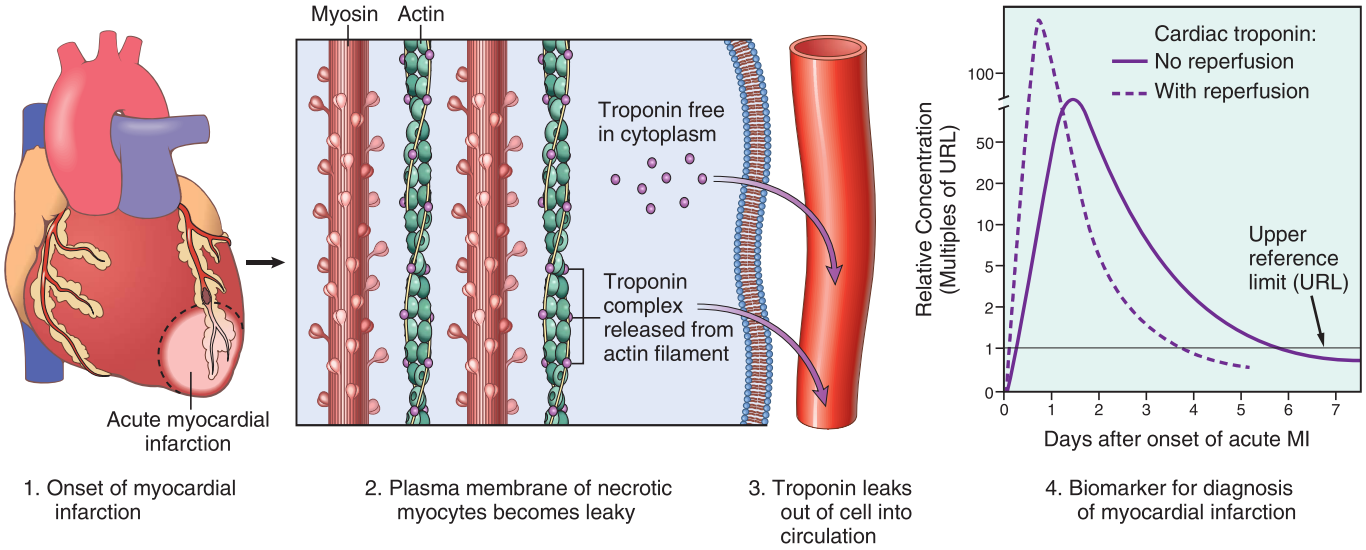

Figure 12.16 Release of myocyte proteins in myocardial infarction. Troponin I or troponin T are now most routinely used as diagnostic biomarkers of myocyte injury.

- *Antiplatelet agents* such as aspirin, ADP receptor inhibitors, and GPIIb/IIIa inhibitors
- *Anticoagulant therapy* with unfractionated heparin, low-molecular-weight heparin, direct thrombin inhibitors, and/or factor Xa inhibitors to prevent coronary artery thrombus propagation
- *Beta blockers* to decrease myocardial oxygen demand and to reduce the risk of arrhythmias, unless contraindicated such as in heart failure
- *Prompt reperfusion* to salvage myocardium, by either fibrinolytic medications or transcatheter interventions
- *Improve myocardial oxygen supply versus demand* by management of other factors, such as anxiety, ischemic pain, abnormal hemodynamics, anemia, and respiratory disorders
- *Early arrhythmia monitoring* and management

Consequences and Complications of Myocardial Infarction

Extraordinary progress has been made in improving patient outcomes after acute MI. The overall in-hospital death rate for MI is approximately 7% to 8%, with STEMI patients experiencing slightly higher mortality (10%) than NSTEMI patients (6%). Unfortunately, mortality for out-of-hospital MIs is substantially worse: one-third of patients who are unfortunate enough to suffer a STEMI at home will die, usually of an arrhythmia within 1 hour of symptom onset and before they can receive medical attention. Such statistics make the rising rate of CAD in countries with limited hospital facilities all the more worrisome.

Nearly three-fourths of patients experience one or more of the following complications after an acute MI (Fig. 12.17):

- *Contractile dysfunction.* In general, MIs affect left ventricular pump function in proportion to the volume of damage. In most cases, there is some degree of left ventricular failure manifested as hypotension, pulmonary congestion, and pulmonary edema. Severe "pump failure" *(cardiogenic shock)* occurs in roughly 10% of patients with transmural MIs and typically is associated with infarcts that damage 40% or more of the left ventricle.
- *Papillary muscle dysfunction.* Although papillary muscles rupture infrequently after MI, they often are dysfunctional and can be poorly contractile as a result of ischemia, leading to postinfarct mitral regurgitation. Much later, papillary muscle fibrosis and shortening, or global ventricular dilation also can cause mitral regurgitation.
- *Right ventricular infarction.* Although isolated right ventricular infarction occurs in only 1% to 3% of MIs, the right ventricle is affected by RCA occlusions leading to posterior septal or left ventricular infarction. In either case, right-sided heart failure is a common outcome, leading to pooling of blood in the venous circulation and systemic hypotension.
- *Myocardial rupture.* Rupture complicates only 1% to 5% of MIs, but is frequently fatal when it occurs. Left ventricular free wall rupture is most common, usually resulting in rapidly fatal hemopericardium and cardiac tamponade (see Fig. 12.17A). Ventricular septal rupture creates a VSD with left-to-right shunting (see Fig. 12.17B), and papillary muscle rupture leads to severe mitral regurgitation (see Fig. 12.17C). Rupture occurs most commonly within 3 to 7 days after infarction—the time in the healing process when lysis of necrotic myocardium is maximal and when much of the infarct has been converted to soft, friable granulation tissue. Risk factors for free wall rupture include age older than 60 years, anterior or lateral wall infarctions, female gender, lack of left ventricular hypertrophy, and first MI (because scarring associated with prior MIs tends to limit the risk for myocardial tearing).
- *Arrhythmias.* MIs lead to myocardial irritability and conduction disturbances that can cause sudden death. Approximately 90% of patients develop some form of rhythm disturbance, with the incidence being higher in STEMIs versus NSTEMIs. MI-associated arrhythmias include heart block of variable degree (including asystole),

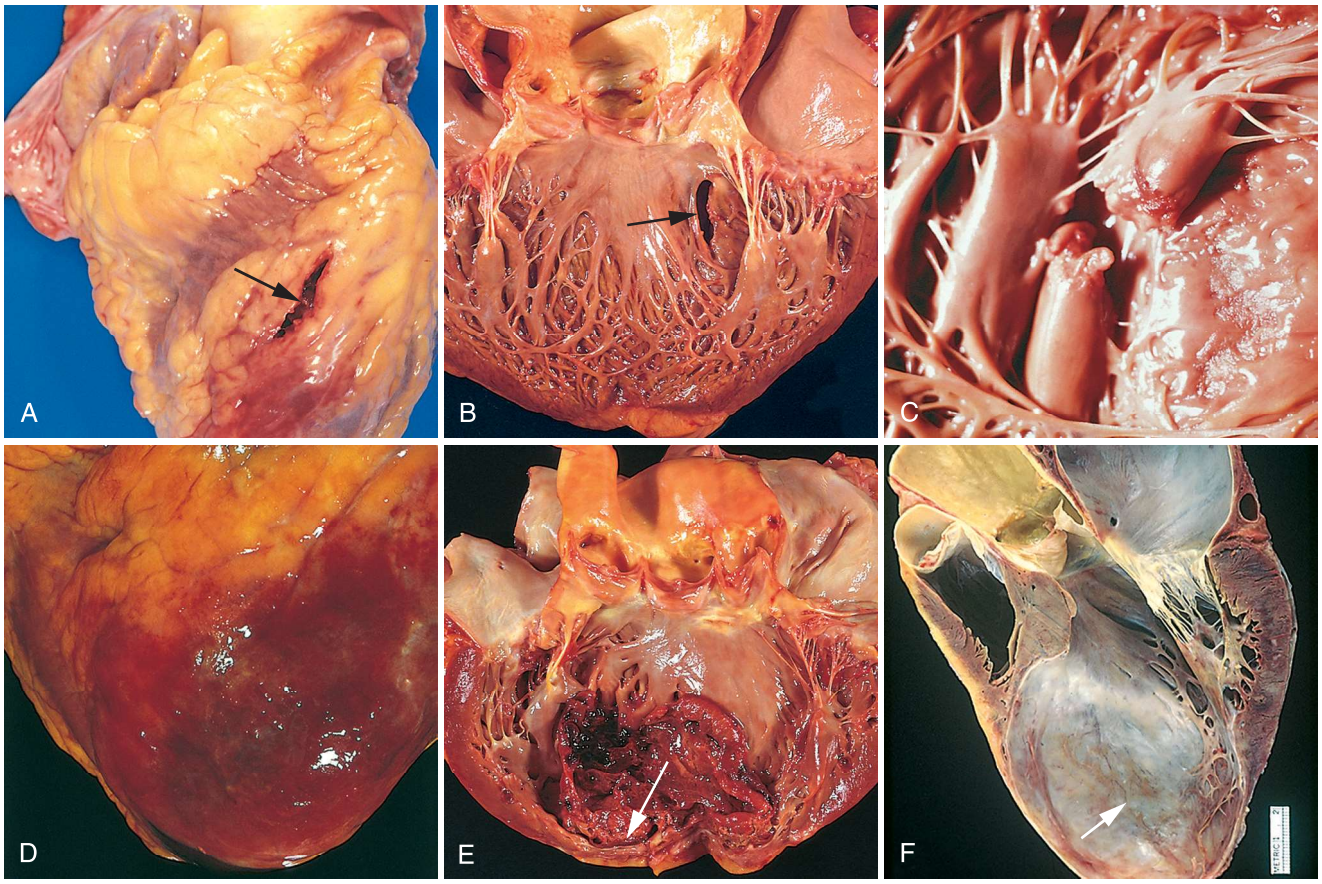

Figure 12.17 Complications of myocardial infarction. (A) Anterior myocardial rupture in an acute infarct *(arrow)*. (B) Rupture of the ventricular septum *(arrow)*. (C) Complete rupture of a necrotic papillary muscle. (D) Fibrinous pericarditis, showing a dark, roughened epicardial surface overlying an acute infarct. E, Early expansion of anteroapical infarct with wall thinning *(arrow)* and mural thrombus. F, Large apical left ventricular aneurysm *(arrow)*. The left ventricle is on the right in this apical four-chamber view of the heart. (A–E, Reproduced with permission from Schoen FJ: *Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles*, Philadelphia, 1989, WB Saunders; F, Courtesy William D. Edwards, MD, Mayo Clinic, Rochester, Minn.)

bradycardia, supraventricular tachyarrhythmias, ventricular premature contractions or ventricular tachycardia, and ventricular fibrillation. The risk for serious arrhythmias (e.g., ventricular fibrillation) is greatest in the first hour and declines thereafter.

- *Pericarditis.* Transmural MIs can elicit a fibrinohemorrhagic pericarditis; this is an epicardial manifestation of the underlying myocardial inflammation (see Fig. 12.17D). Heralded by anterior chest pain and a pericardial friction rub, pericarditis typically appears 2 to 3 days after infarction and then gradually resolves over the next few days. Extensive infarcts or severe pericardial inflammation occasionally can lead to large effusions or can organize to form dense adhesions that eventually manifest as a constrictive lesion. Rarely patients can develop an intense pericarditis weeks after MI *(Dressler syndrome)* due to formation of antibodies against damaged myocardium.
- *Chamber dilation.* Because of the weakening of necrotic muscle, there may be disproportionate stretching, thinning, and dilation of the infarcted region (especially with anteroseptal infarcts).
- *Mural thrombus.* With any infarct, the combination of attenuated myocardial contractility (causing stasis), chamber dilation, and endocardial damage (causing a thrombogenic surface) can foster mural thrombosis (see Fig. 12.17E), potentially leading to left-sided thromboembolism.
- *Ventricular aneurysm.* A late complication, aneurysms of the ventricle most commonly result from a large transmural anteroseptal infarct that heals with the formation of a thinned wall of scar tissue (see Fig. 12.17F). Although ventricular aneurysms frequently give rise to formation of mural thrombi, arrhythmias, and heart failure, they do not rupture.
- *Progressive heart failure.* This is discussed in the Chronic Ischemic Heart Disease section later in this chapter.

The risk of postinfarct complications and the prognosis of the patient depend primarily on the infarct size, location, and fraction of the wall thickness involved (subendocardial or transmural). Thus, large transmural infarcts yield a higher probability of cardiogenic shock, arrhythmias, and late CHF. Patients with anterior transmural infarcts are at greatest risk for free-wall rupture, expansion, mural thrombi, and aneurysm. In contrast, posterior transmural infarcts are more likely to be complicated by conduction blocks, right ventricular involvement, or both; when acute VSDs occur in this area they are more difficult to manage. Moreover, female gender, age older than 70 years, diabetes mellitus and previous MI are poor prognostic factors in patients with ST

elevation myocardial infarcts. With subendocardial infarcts, only rarely do pericarditis, rupture, and aneurysm occur.

In addition to the sequence of repair in the infarcted tissues described earlier, the noninfarcted segments of the ventricle undergo hypertrophy and dilation; collectively, these changes are termed ventricular remodeling. The compensatory hypertrophy of noninfarcted myocardium is initially hemodynamically beneficial. However, this adaptive effect may be overwhelmed by ventricular dilation (with or without ventricular aneurysm) and increased oxygen demand, which can exacerbate ischemia and depress cardiac function. There may also be changes in ventricular shape and stiffening of the ventricle due to scar formation and hypertrophy that further diminish cardiac output. Some of these deleterious effects appear to be reduced by ACE inhibitors, which lessen the ventricular remodeling that can occur after infarction.

Long-term prognosis after MI depends on many factors, the most important of which are the residual left ventricular function and the extent of any vascular obstructions in vessels that perfuse the remaining viable myocardium. The overall total mortality within the first year can be as high as 30%; thereafter, each passing year is associated with an additional 3% to 4% mortality among survivors. Infarct prevention (through control of risk factors) in individuals who have never experienced MI (primary prevention) and prevention of reinfarction in MI survivors (secondary prevention) are important strategies that have received much attention and achieved considerable success.

The relationship of the causes, pathophysiology, and consequences of MI are summarized in Fig. 12.18, including the possible outcomes of chronic IHD and sudden death, discussed later.

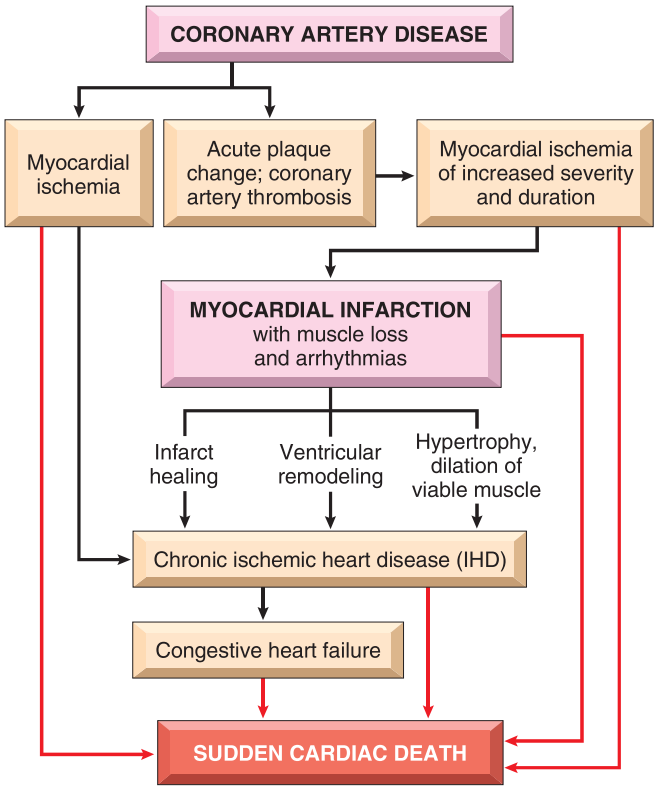

Figure 12.18 Schematic for the causes and outcomes of ischemic heart disease *(IHD)*, showing the interrelationships among coronary artery disease, acute plaque change, myocardial ischemia, myocardial infarction, chronic IHD, congestive heart failure, and sudden cardiac death.

Chronic Ischemic Heart Disease

The designation chronic IHD (often called ischemic cardiomyopathy by clinicians) is used here to describe progressive congestive heart failure as a consequence of accumulated ischemic myocardial damage and/or inadequate compensatory responses. In most instances, there has been a prior MI and sometimes previous coronary arterial interventions and/or bypass surgery. Chronic IHD usually appears postinfarction due to the functional decompensation of hypertrophied noninfarcted myocardium (see earlier discussion of cardiac hypertrophy). However, in other cases severe obstructive CAD may present as chronic congestive heart failure in the absence of prior infarction. Patients with chronic IHD account for almost 50% of cardiac transplant recipients.

MORPHOLOGY

Patients with chronic IHD have cardiomegaly, with left ventricular hypertrophy and dilation. Invariably there is some degree of stenotic coronary atherosclerosis. Discrete scars representing healed infarcts are usually present. The mural endocardium often has patchy fibrous thickenings (due to abnormal wall shear forces), and mural thrombi may be present. Microscopic findings include myocardial hypertrophy, diffuse subendocardial myocyte vacuolization, and interstitial fibrosis.

KEY CONCEPTS

ISCHEMIC HEART DISEASE

- The vast majority of IHD is due to coronary artery atherosclerosis. Vasospasm, vasculitis, or embolism are less common causes.
- Cardiac ischemia results from a mismatch in coronary supply and myocardial demand, and it presents as different, albeit overlapping, syndromes:
  - Angina pectoris is chest pain on exertion due to inadequate perfusion, and is typically due to atherosclerotic disease with greater than 70% fixed stenosis (so-called critical stenosis).
  - Unstable angina results from a small fissure or rupture of atherosclerotic plaque triggering platelet aggregation, vasoconstriction, and formation of a mural thrombus that needs not necessarily be occlusive. Chest pain may occur, even at rest or with minimal exertion.
  - Acute MI typically results from acute thromboses after plaque disruption; most occur in plaques that did not previously exhibit critical stenosis.
  - Chronic IHD is progressive heart failure due to ischemic injury, either from prior infarctions or chronic low-grade ischemia.
- Myocardial ischemia leads to loss of function within 1 to 2 minutes but causes necrosis only after 20 to 30 minutes. MI is diagnosed based on symptoms, electrocardiographic changes, and measurement of serum troponins. Gross and histologic changes of infarction require hours to days to develop.