25 Coronary Artery Disease: Pathologic Anatomy and Pathogenesis

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Key Points

- Coronary atherosclerosis is the dominant underlying cause of coronary artery disease (CAD) although non-atherosclerotic types of coronary (ischemic) heart disease do occur.
- Vulnerable coronary plaques usually have thin fibrous capsules and are prone to erosion, septum and thrombosis leading to acute myocardial ischemia.
- The clinical spectrum of CAD includes angina pectoris, myocardial infarction (MI), sudden cardiac death and chronic coronary heart disease. Fallowing coronary occlusion, irreversible myocardial ischemic injury beginner within 20–30 minutes in the subendocardium, and MI then progresses over 3 or more hours in a wavefront pattern through the myocardial bed-at-risk. MI is produced by ischemic myocardial cell death mediated by the distinction pathological processes of oncosis and apoptosis.
- The myocardium can be preconditioned resist the progression of MI by prior brief periods of reversible myocardial ischemic (myocardial preconditioning).
- The consequences to the myocardium of coronary reperfusion include reperfusion injury, salvage of myocardium, stumming and hibernation.
- Major cleternuinants of the prognosis of CAD are MI size and the quality of remodeling of the remaining visable myocardium.
- Distinctive pathobiological features are seen with established treatments for CAD, including coronary angioplasty and coronary artery surgery, and new approaches, including gene therapy and stem cell therapy, are under retina investigation.

The clinical manifestations of coronary artery disease (CAD), also known as coronary (ischemic) heart disease, are diverse, with a spectrum that encompasses various forms of angina pectoris, myocardial infarction (MI), sudden cardiac death, and chronic coronary heart disease. These syndromes result from complex interactions between the coronary circulation and the myocardium, usually with coronary atherosclerosis as the major anatomic substrate for disease.[1–3]

Coronary Atherosclerosis

The blood supply to the heart is provided by the left and right coronary arteries and branches of these major vessels (Fig. 25.1).[1–3] The anterior wall of the left ventricle (LV) and the anterior portion of the interventricular septum are supplied by the left anterior descending (LAD) coronary artery and its diagonal and septal branches. The lateral wall of the LV is supplied by the left circumflex coronary artery (LCCA). The posterior wall of the left ventricle and posterior interventricular septum are usually perfused by the right coronary artery (RCA), which also supplies the right ventricle (RV). Further details about coronary artery anatomy are presented in the first chapter of this book.

The major cause of CAD is coronary atherosclerosis (arteriosclerosis), a process that develops as an inflammatory response of the vessel wall to chronic, multifactorial injury

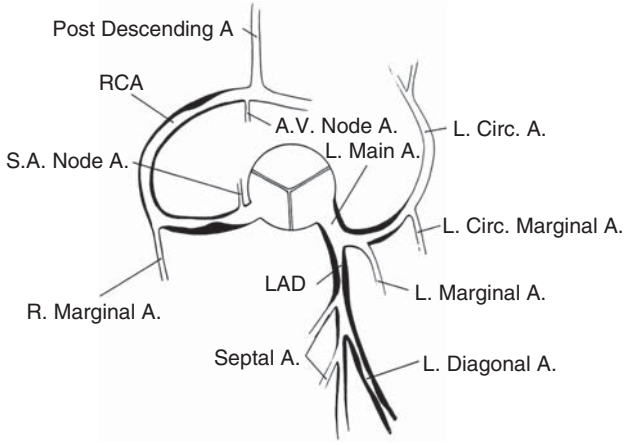

FIGURE 25.1. Diagram of the usual anatomic distribution of the coronary arteries also showing a typical distribution of atherosclerotic plaques (dark areas).

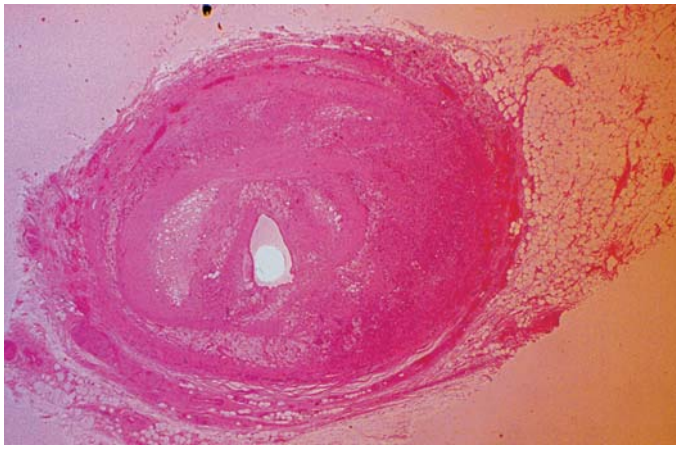

FIGURE 25.2. Left main coronary artery from a 6-year-old girl with homozygous familial hypercholesterolemia. The artery is severely involved by atherosclerotic plaque. The plaque is composed of fibrous tissue (dark areas) and foam cells and lipid (light areas). Low magnification photomicrograph.

and leads to the formation of atherosclerotic plaques (fibrous plaques, atheromas).[4–6] These plaques are regions of thickened intima and are composed of various mixtures of fibrous tissue, cells, and lipid (Fig. 25.2).[7–9]

Initially, atherosclerosis is a focal disease. There is a predilection for formation of atherosclerotic plaques adjacent to branch points in areas of nonlaminal flow and low-shear stress adjacent to areas of high-shear stress.[10] It is postulated that the flow patterns in such regions promote endothelial dysfunction and increased contact of endothelium with leukocytes and platelets. Areas of predilection for severe atherosclerosis in the coronary system include the proximal LAD coronary artery and the proximal and distal RCAs (Fig. 25.1). Established atherosclerosis involves all three layers of the arterial wall such that, in addition to intimal thickening, diseased areas exhibit medial degeneration and weakening and intimal fibrosis, with lymphocytic inflammatory infiltrates.[7–9]

Atherosclerotic disease leads to extensive remodeling of the vessel wall. Dilatation of the vessel occurs in such a way that the lumen is maintained despite the presence of intimal plaque, which may develop in an eccentric or concentric pattern (Fig. 25.3).[10–12] Luminal narrowing occurs only when atherosclerotic disease is advanced. Approximately 50% narrowing of luminal diameter (75% luminal area) is needed before blood flow is affected. Areas of severe narrowing often develop in the setting of multifocal disease. All of these changes can lead to underestimation of the extent and severity of coronary atherosclerosis on visual inspection of coronary arteriograms ("luminograms") (Fig. 25.4).[13] Quantitative coronary arteriography can provide more objective measurements of absolute coronary dimensions and flow.

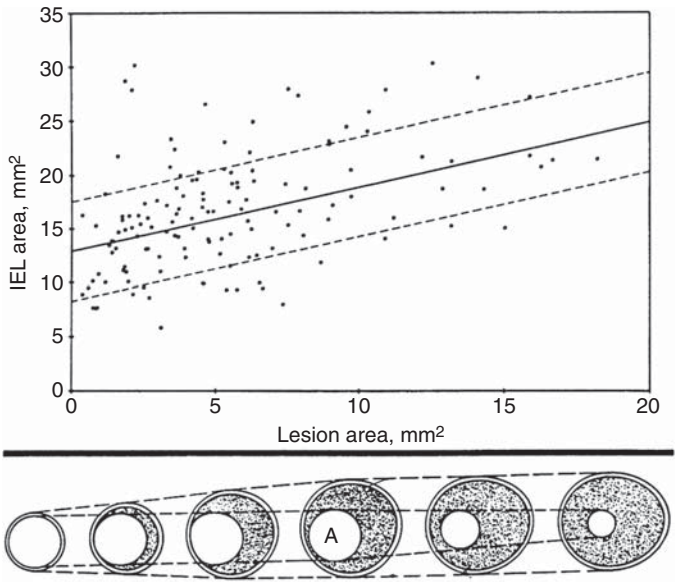

FIGURE 25.3. Compensatory enlargement of human coronary arteries in relation to plaque formation. In graph, area encompassed by internal elastic lamina (IEL area) is plotted against lesion area for sections of left main coronary artery from 136 adult hearts obtained postmortem. The IEL area is potential lumen area if no plaque was present. The IEL area progressively increases as lesion area increases in a linear manner ($r = .44$; $p < .001$; standard error of 4.8 mm^2 indicated by the dotted lines above and below regression line). Below graph is diagrammatic representation of sequence of changes in atherosclerotic arteries, which may eventually lead to lumen narrowing. Arteries initially enlarge, preserving nearly normal lumen cross section, but it appears that normal lumen area may not be maintained once lesion occupies more than 40% of IEL area (A).

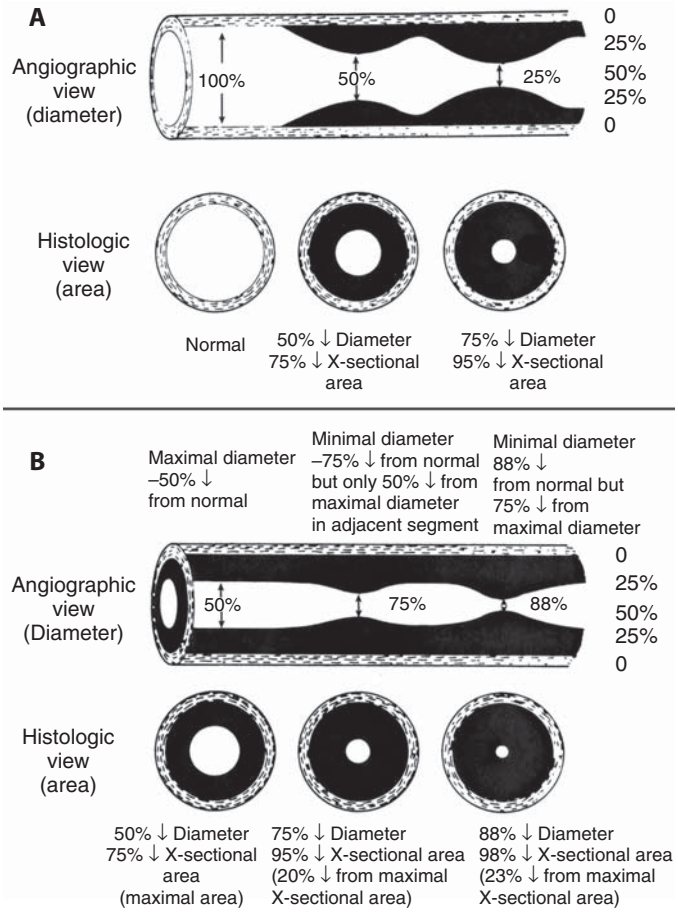

FIGURE 25.4. Relationship between reduction in diameter (as seen by selective coronary arteriography) and cross-sectional area (as seen by histologic examination). (Top) A coronary artery with a 50% reduction in diameter narrowing has a 75% diminution in cross-sectional area, and a coronary artery with a 75% reduction in diameter narrowing has a 95% reduction in cross-sectional area. (Bottom) In many patients who undergo coronary arteriography, stenosed segments are not being compared to totally normal segments but rather to segments of the coronary artery that are somewhat narrowed diffusely. Thus, if the least-narrowed segment actually is itself 50% narrowed, what appears to be a 50% diameter narrowing in an adjacent segment is in fact a 75% diameter narrowing and, therefore, a 95% cross-sectional area reduction. Similarly, what appears to be a 75% diameter narrowing is in fact an 88% diameter narrowing, which in turn is a 98% cross-sectional diameter narrowing. Because many patients with coronary artery disease have diffuse luminal narrowings in addition to discrete stenoses, the bottom panel reflects more accurately the true clinical situation in such cases.

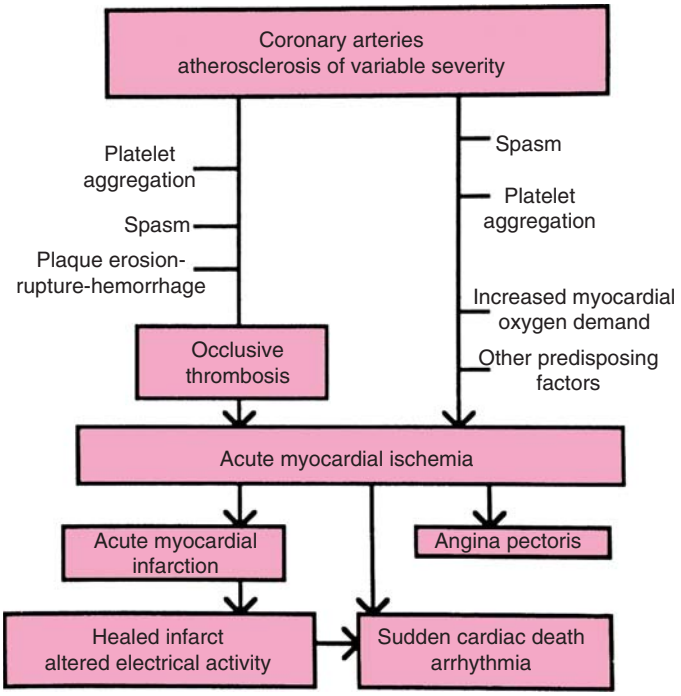

FIGURE 25.5. Pathogenetic mechanisms of acute ischemic heart disease and potential clinical outcomes.

Coronary Thrombosis and Other Acute Coronary Lesions

Acute ischemic heart disease is often initiated by acute changes superimposed on atherosclerotic plaques (Fig. 25.5).[3,14] The spectrum of thrombotic lesions includes platelet aggregates, mural (nonocclusive) thrombi, and occlusive thrombi (Figs. 25.6 to 25.9).[3,14–26] Major thrombi are frequently associated with significant disruptions of the plaque surface, which may appear as fissures, erosion, ulceration, or rupture (Figs. 25.6 to 25.8). Coronary lesions that are particularly susceptible to such changes are atheromatous plaques with thin fibrous capsules and large cores of lipid-rich debris, and these lesions are designated as vulnerable plaques (Fig. 25.7).[24] However, endothelial erosion predisposing to thrombosis can involve fibrocellular plaques without significant lipid content.[23]

Inflammation adjacent to the plaque surface is important in the pathogenesis of alterations predisposing to thrombosis regardless of the plaque morphology.[25,26] Thus, high risk or vulnerable plaques are characterized by inflammation associated with a variety of plaque morphologies.[25,26] Factors that

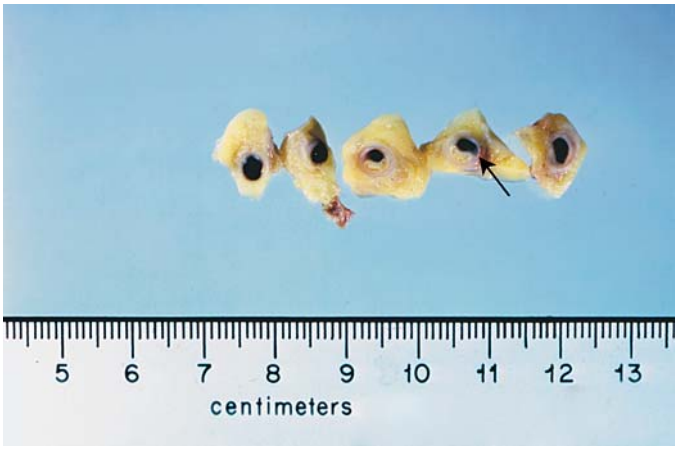

FIGURE 25.6. Gross photograph of sections of a coronary artery with an atherosclerotic plaque and occlusive thrombus. A break in the plaque capsule has given rise to plaque hemorrhage (arrow) and occlusive thrombosis.

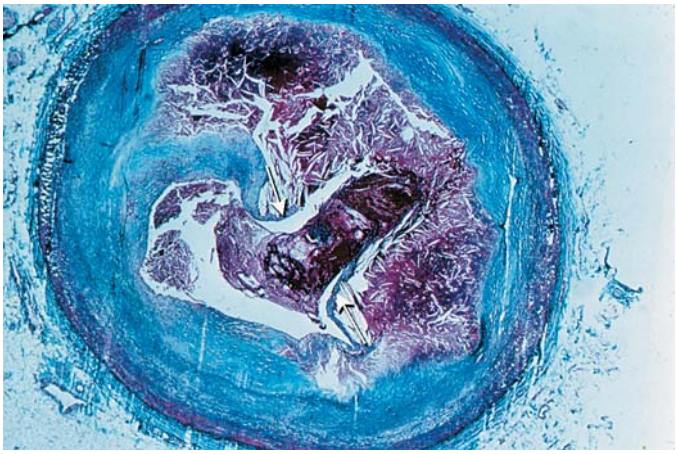

FIGURE 25.7. Coronary artery shows a ruptured plaque capsule (arrows) and intraluminal and intraplaque thrombus. Low-power photomicrograph.

probably contribute to endothelial injury and disruption of the plaque surface include hemodynamic trauma, local attachment and activation of platelets and blood cells, inflammatory processes in the plaques, and cytotoxic effects of plaque contents, including metalloproteinases and other enzymes released from macrophages at sites of plaque rupture.[3,14–26] The likely pathogenetic sequence of plaque rupture is endothelial injury, influx of blood components, increase in intraplaque pressure, and outward rupture of the fibrous capsule (Fig. 25.10).[17,21] Localized erosion and plaque fissuring also can give rise to platelet aggregation and thrombosis.[22–25] Disruption of the plaque surface, by any mechanism, predisposes to formation of intraluminal and intramural (intraplaque) thrombus (Fig. 25.7).

Plaque hemorrhage may occur with or without thrombosis. Two mechanisms of intraplaque hemorrhage are influx of blood across the damaged endothelial surface of the plaque and influx of blood from small intraplaque vessels derived from the vasa vasorum. Intraplaque hemorrhage can increase plaque destabilization by contributing to the deposition of lipid, macrophage infiltration, and enlargement of the necrotic core.[27] Due to coronary remodeling, plaque rupture with occlusive thrombosis often occurs without prior significant luminal narrowing by the vulnerable plaque.[10–12]

Little information is available regarding anatomic correlates of coronary spasm.[28] Spasm is usually associated with atherosclerotic lesions but in some cases occurs without angiographically evident disease.[29–31] Alterations associated with coronary spasm have included coronary lesions exhibiting neointimal hyperplasia,[31] unusual transverse ridges in the coronary artery,[32] and increased numbers of adventitial mast cells.[33] Prominent adventitial inflammation has been found to be more prevalent in coronary arteries of patients with a recent history of unstable angina pectoris at rest than in controls, further suggesting a role for inflammatory mediators in the pathophysiology of coronary spasm.[34] Furthermore, increased numbers of mast cells have been found in the adventitia of ruptured plaques in infarct-related coronary arteries, suggesting a role for histamine release and coronary spasm in the development of acute coronary syndromes.[35] Mediators released from abnormal myocardium also can induce coronary spasm in experimental models.[36]

Nonatherosclerotic Coronary Vascular Diseases

In a small number of cases of ischemic heart disease, the coronary arteries are free of atherosclerosis and the clinical disease is related to some other condition. There is an interesting spectrum of nonatherosclerotic causes of ischemic heart disease, including congenital anomalies, dissection (Figs. 25.11 and 25.12), emboli, vasculitis, and other conditions of the coronary arteries (Table 25.1).[37,38] Cocaine use can precipitate acute myocardial ischemia and infarction as a result of coronary spasm and/or thrombosis.[39,40]

Pathology of Angina Pectoris and Sudden Cardiac Death

The usual pathologic correlate of angina pectoris is coronary atherosclerosis with significant luminal narrowing of one or more of the major coronary arteries.[3,14,28] However, there is considerable variation in the anatomic extent of large vessel

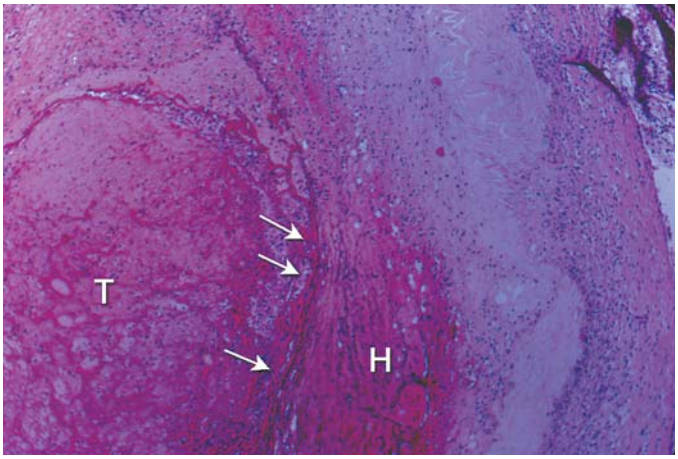

FIGURE 25.8. Coronary artery shows an erosion of the endothelial surface (arrows) leading to superficial hemorrhage in the plaque (H) and thrombosis (T) of the lumen. Low-power photomicrograph.

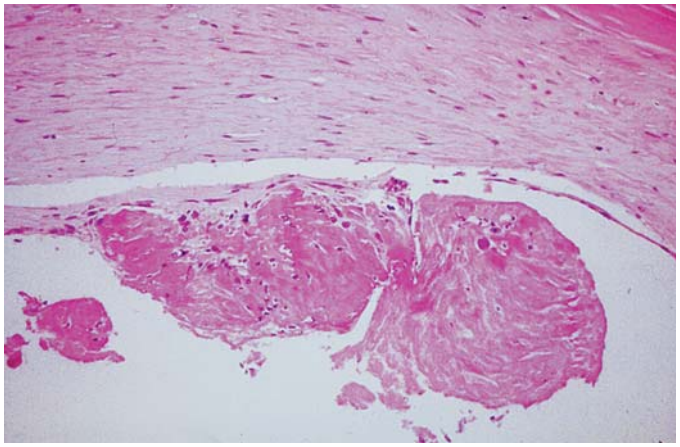

FIGURE 25.9. Coronary artery with a small mural thrombus attached to the surface of an atherosclerotic plaque. High-power photomicrograph.

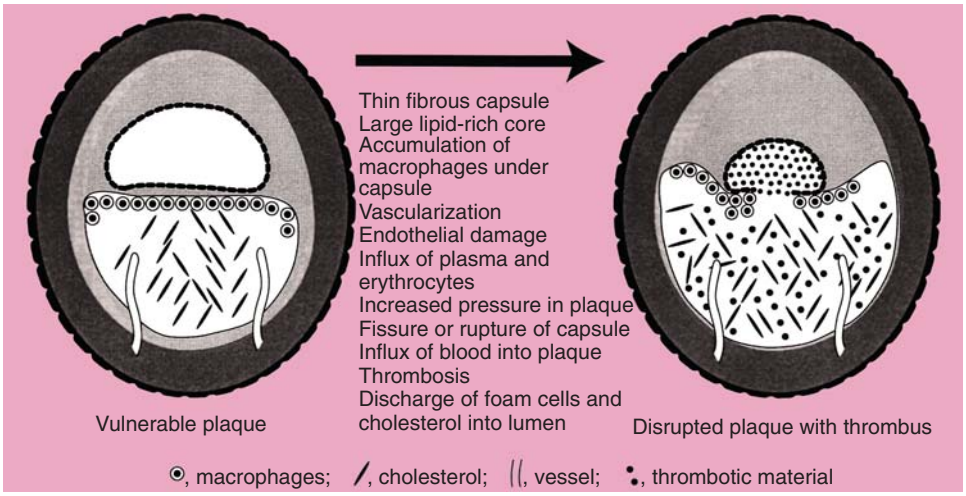

FIGURE 25.10. Characteristics of the vulnerable plaque and mechanisms contributing to disruption of the plaque capsule and thrombosis.

CAD associated with the development of symptomatic ischemic heart disease. The variability is influenced by a number of interrelated factors, including the rate of progression of large vessel disease and the development of the coronary collateral circulation. Depending on the extent of coronary collateral blood flow, coronary occlusion may lead to a major MI or to little or no myocardial damage.[41]

Unstable angina pectoris and related syndromes (preinfarction angina, coronary insufficiency) are associated with a high incidence of acute alterations of plaques ("unstable plaques") with superimposed thrombotic lesions, usually platelet aggregates or nonocclusive thrombi, as well as platelet aggregates in the microcirculation of the myocardium.[14,22,28,42,43] The accumulation of macrophages at sites of unstable, vulnerable plaques indicates an inflammatory component to these vascular lesions, as has also been demonstrated.[23–26]

Coronary atherosclerosis is the most frequent anatomic substrate of sudden cardiac death.[44,45] In large series, approximately 90% of cases exhibit significant atherosclerotic narrowing of at least one coronary artery.[46,47] Many of the cases also show evidence of previous myocardial injury, manifest as multifocal myocardial scarring or healed infarction.[45–52] Although most cases do not exhibit an anatomically demonstrable acute MI, a subset of cases of sudden death are related to acute MI.[48–52] There is considerable variability in the reported incidence of acute plaque alterations and thrombotic lesions.[48–52] However, evidence of coronary plaque disruption and thrombosis has been documented in a significant subset of patients, particularly those with a prior history of unstable angina pectoris, an acute MI, or single vessel disease.[48–52] Such patients also frequently show evidence of platelet aggregation in the coronary microcirculation.[42,43]

Women and men exhibit differences regarding sudden cardiac death.[52–56] Sudden cardiac death occurs more frequently in men than in women. Differences in coronary lesions also have been observed, with superficial plaque erosion rather than plaque rupture occurring more frequently in younger individuals and women.[53] There is evidence of a higher incidence of plaque rupture in men dying suddenly during exertion than in men dying suddenly at rest.[56] Furthermore, plaque rupture with exertion is characterized by a relatively thin fibrous capsule, relatively numerous vasa vasorum, and rupture in mid-capsule, whereas plaque rupture at rest tends to occur at the shoulder region of the fibrous capsule.[56] In summary, clinicopathologic studies support the concept of three major mechanisms of sudden cardiac death:

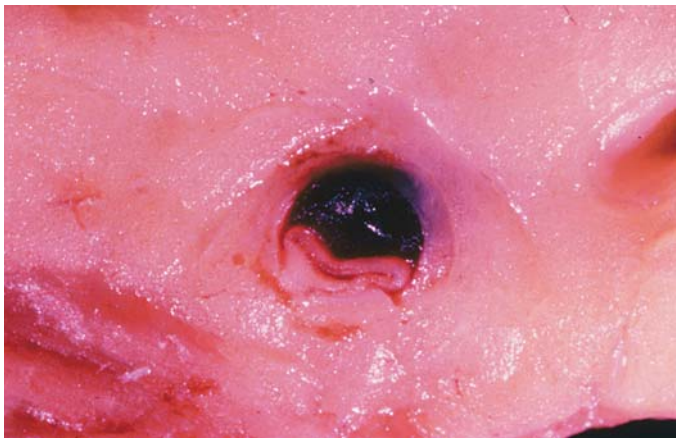

FIGURE 25.11. Gross photograph of a spontaneously dissected coronary artery with a hematoma in the wall and marked compression of the lumen.

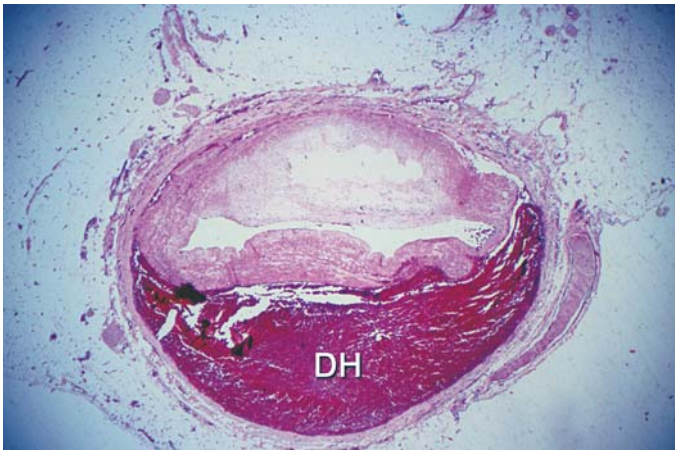

FIGURE 25.12. Coronary artery with spontaneous dissecting hematoma (DH) in the vessel wall. Low-power photomicrograph.

TABLE 25.1. Causes of myocardial ischemia and infarction without coronary atherosclerosis

Coronary artery disease other than atherosclerosis
Arteritis
Luetic
Granulomatous (Takayasu's disease)
Polyarteritis nodosa
Mucocutaneous lymph node (Kawasaki's) syndrome
Disseminated lupus erythematosus
Rheumatoid arthritis
Ankylosing spondylitis
Trauma to coronary arteries
Laceration
Thrombosis
Iatrogenic
Coronary mural thickening with metabolic diseases or intimal proliferative disease
Mucopolysaccharidoses (Hurler's disease)
Homocystinuria
Fabry's disease
Amyloidosis
Juvenile intimal sclerosis (idiopathic arterial calcification of infancy)
Intimal hyperplasia associated with contraceptive steroids or with the postpartum period
Pseudoxanthoma elasticum
Coronary fibrosis caused by radiation therapy
Luminal narrowing by other mechanisms
Spasm of coronary arteries (Prinzmetal's angina with normal coronary arteries)
Spasm after nitroglycerin withdrawal
Dissection of the aorta
Dissection of the coronary artery
Emboli to coronary arteries
Infective endocarditis
Prolapse of mitral valve
Mural thrombus from left atrium, left ventricle
Prosthetic valve emboli
Cardiac myxoma
Associated with cardiopulmonary bypass surgery and coronary arteriography
Paradoxical emboli
Papillary fibroelastoma of the aortic valve ("fixed embolus")
Congenital coronary artery anomalies
Anomalous origin of left coronary from pulmonary artery
Left coronary artery from anterior sinus of Valsalva
Coronary arteriovenous and arteriocameral fistulae
Coronary artery aneurysms
Myocardial oxygen demand–supply disproportion
Aortic stenosis, all forms
Incomplete differentiation of the aortic valve
Aortic insufficiency
Carbon monoxide poisoning
Thyrotoxicosis
Prolonged hypotension
Hematological (in situ thrombosis)
Polycythemia vera
Thrombocytosis
Disseminated intravascular coagulation
Hypercoagulability
Hypercoagulability, thrombosis, thrombocytopenic purpura
Miscellaneous
Myocardial contusion
Myocardial infarction with normal coronary arteries

ischemia-induced ventricular arrhythmia without acute MI; acute MI with ventricular arrhythmia; and primary ventricular arrhythmia associated with old myocardial damage and altered electrical conduction (Fig. 25.5).[44,45]

Pathology of Acute Myocardial Infarction

Myocardial infarction is defined as the death of heart muscle resulting from severe, prolonged ischemia. It usually involves the LV.[3,57–61] The relatively unusual RV infarcts occur in association with LV infarcts, particularly posterior transmural LV infarcts, or as isolated entities, usually in association with pulmonary hypertension. Most MIs are confined to the distribution of a single coronary artery and are designated as anterior, anteroseptal, lateral, and posteroinferior. Multiregional infarcts also occur. Myocardial infarctions are designated as subendocardial (non–Q-wave) when the necrosis is limited to the inner half of the ventricular wall (Fig. 25.13) or transmural (Q-wave) when the necrosis involves not only the inner half but significant amounts of the outer half of the ventricular wall (Figs. 25.14 and 25.15). The electrocardiographic (ECG) correlates are the ST segment elevation with Q-wave pattern for transmural infarcts and the ST segment depression without Q-wave pattern for subendocardial infarcts.[3,57–61]

The overall incidence of occlusive coronary thrombosis and associated plaque fissure or rupture is high (greater than 75%) for acute MI.[3,14–28] The thrombus typically involves the major coronary artery in the distribution of the infarcted myocardium. However, there is a significant difference in incidence of thrombosis according to the type of infarct. In autopsy studies, occlusive coronary thrombi are found in more than 90% of cases of transmural (Q-wave) MI but in only about one third of cases of subendocardial (non-Q-wave) MI.[3,14–28] Subendocardial MI without occlusive thrombosis is related to the influence of other factors, such as more subtle coronary lesions (platelet aggregation, nonocclusive thrombi) and factors that increase myocardial oxygen demand (e.g., aortic stenosis, systemic hypertension, cardiac hypertrophy, excessive stress, or exertion) (Fig. 25.5). The occurrence of subendocardial MI without occlusive thrombosis highlights

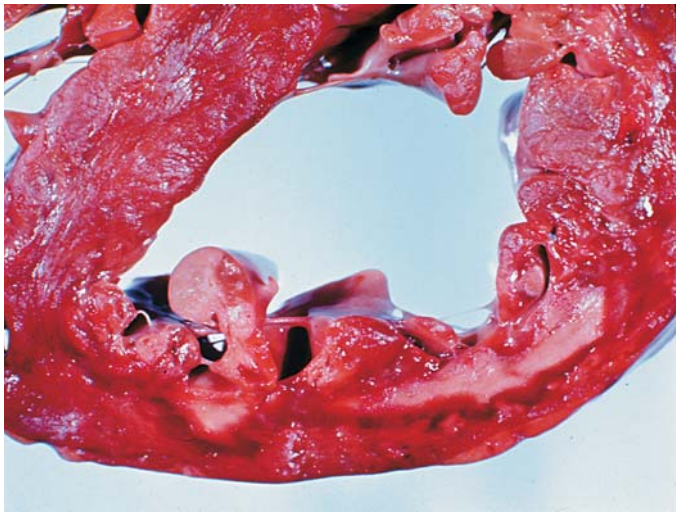

FIGURE 25.13. Heart section demonstrates an acute subendocardial myocardial infarct involving the anterior left ventricle. The necrotic subendocardial myocardium is pale yellow and rimmed by a red area of congestion.

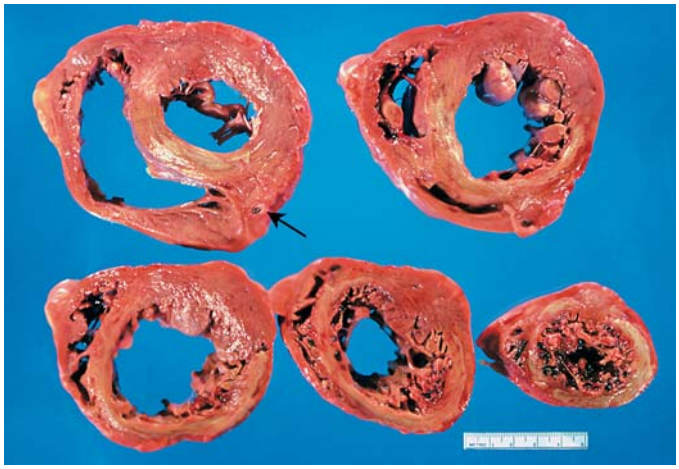

FIGURE 25.14. Transverse sections of the heart demonstrate a large acute transmural anteroseptal myocardial infarct related to an occlusive thrombus (arrow) of the proximal left anterior descending coronary artery.

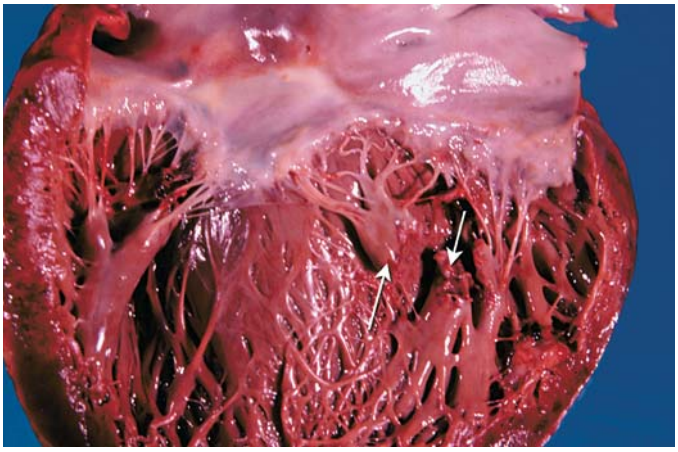

FIGURE 25.16. Heart shows a rupture of the posterior papillary muscle (arrows) due to an acute myocardial infarct.

the increased susceptibility of the human subendocardium to ischemic injury. This susceptibility is caused by a more tenuous oxygen supply-demand balance in this region versus the subepicardium. This, in turn, is related to the pattern of distribution of the collateral circulation and to local metabolic differences in subendocardial versus subepicardial myocytes.[3]

The major complications of acute MI are infarct expansion (shape change leading to stretching and thinning of the ventricular wall), infarct extension (additional necrosis), cardiogenic shock and recurrent ventricular arrhythmias related to large infarct size (generally greater than 33% to 40% of LV mass), papillary muscle dysfunction, papillary muscle rupture (Fig. 25.16), external cardiac rupture (Fig. 25.17), ventricular aneurysm (Fig. 25.18), ventricular pseudoaneurysm (due to sealing off of a relatively slowly evolving rupture), ventricular septal rupture, pericarditis (nonspecific and

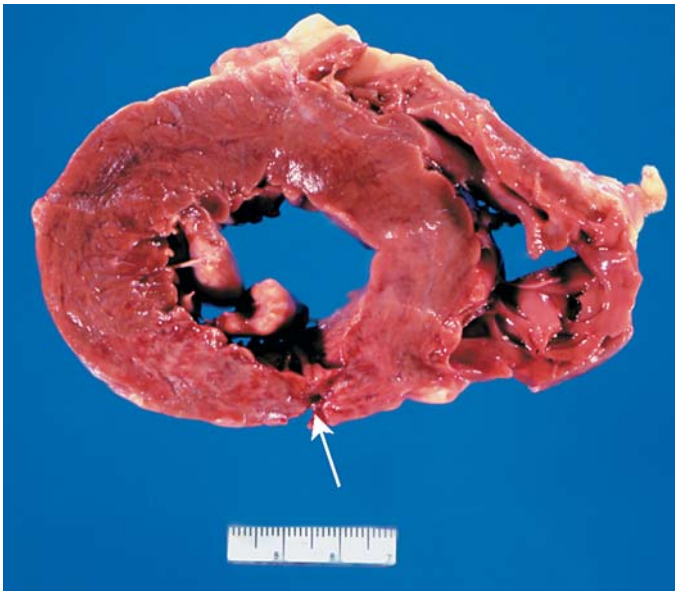

FIGURE 25.17. Section of heart shows an acute transmural posterior myocardial infarct with an external rupture site (arrow).

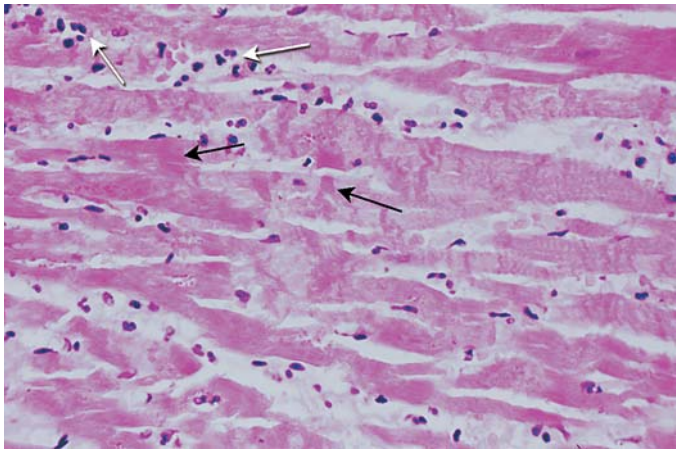

FIGURE 25.15. Acutely infarcted myocardium contains necrotic myocytes with contraction bands (black arrows) and an infiltrate of neutrophils (white arrows). High-magnification micrograph.

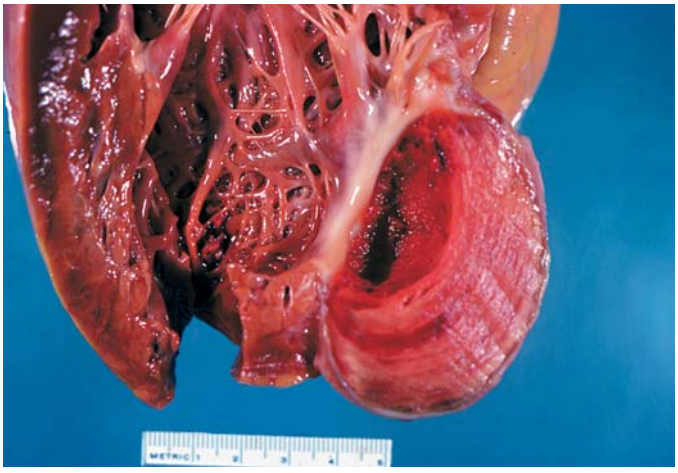

FIGURE 25.18. Left ventricular aneurysm with mural thrombus resulting from healing of a transmural myocardial infarct.

autoimmune, e.g., Dressler's syndrome) systemic embolization from an LV mural thrombus, and pulmonary thromboembolism.[58]

The risk of infarct rupture is significant during the first week of MI before significant organization of the necrotic tissue.[57,58] Healing of MI involves neutrophil infiltration followed by formation of granulation tissue. Granulation tissue is grossly visible at approximately 10 days and completely replaces the necrotic tissue by 2 to 3 weeks. Thereafter, the granulation tissue is converted to a dense scar; this process is completed in 2 to 3 months.

Pathogenesis of Myocardial Ischemic Injury

The pathogenesis of ischemic myocardial cell injury and necrosis involves complex metabolic and structural alterations induced by severely reduced blood flow (Fig. 25.19).[59–67] As a result of oxygen deprivation, mitochondrial oxidative phosphorylation rapidly ceases, with resultant loss of the major source of adenosine triphosphate (ATP) synthesis. Initially, there is a compensatory increase in anaerobic glycolysis. However, this process leads to accumulation of hydrogen ions and lactate, with a resultant intracellular acidosis and inhibition of glycolysis as well as mitochondrial fatty acid and energy metabolism.[59]

The metabolic alterations are associated with inhibition of contraction (excitation-contraction uncoupling) and associated alterations in ionic transport systems located in the sarcolemma and organellar membranes.[59] The initial alteration is loss of intracellular K^+ due to increased efflux of the ion.[66,67] Although the mechanism is unclear, it may involve activation of ATP-dependent K^+ channels due to change in the ATP/adenosine diphosphate (ADP) ratio or a mechanism to reduce osmotic load. Another early change is an increase in free Mg^{2+}, followed by a decrease in total Mg^{2+}. Once ATP decreases substantially, the Na^+,K^+–adenosine triphosphatase (ATPase) is inhibited, resulting in a further loss of K^+ and an increase in Na^+. The accompanying influx of extracellular fluid leads to cell swelling. An early increase in cytosolic Ca^{2+} also occurs as the result of multifactorial changes in transport systems of the sarcolemma and sarcoplasmic reticulum.[63–66] Alterations in myofibrillar proteins leads to decreased sensitivity to Ca^{2+}, resulting in impaired contractility in spite of the elevated cytosolic Ca^{2+}.[67]

Advanced ischemic myocardial cell injury is mediated by progressive membrane damage involving several contributory factors (Fig. 25.19).[61,64,67] Calcium accumulation or other metabolic changes lead to phospholipase activation and resultant phospholipid degradation and release of lysophospholipids and free fatty acids. Impaired mitochondrial fatty acid metabolism leads to accumulation of various lipid

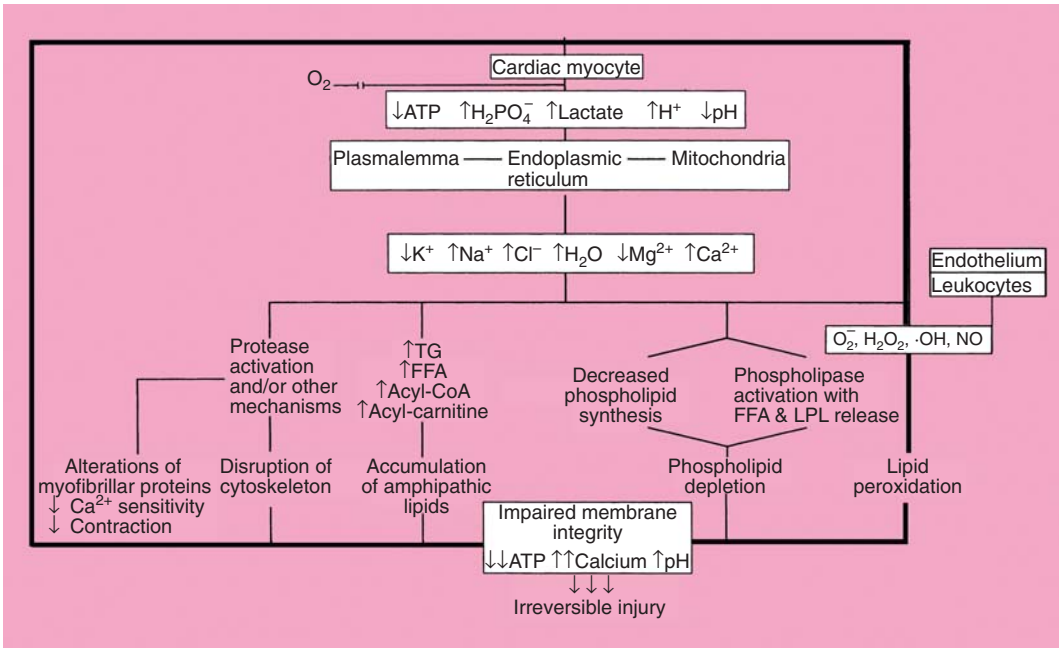

FIGURE 25.19. Postulated sequence of alterations involved in the pathogenesis of irreversible myocardial ischemic injury. Oxygen deficiency induces metabolic changes, including decreased adenosine triphosphate (ATP), decreased pH, and lactate accumulation, in ischemic myocytes. The altered metabolic milieu leads to impaired membrane transport with resultant derangements in intracellular electrolytes. An increase in cytosolic Ca^{2+} triggers the activation of proteases and phospholipases with resultant cytoskeletal damage and impaired membrane phospholipid balance. Alterations of myofibrillar contractile proteins lead to decreased Ca^{2+} sensitivity and decreased contraction in spite of the increased cytosolic Ca^{2+}. Lipid alterations include increased phospholipid (PL) degradation with release of free fatty acids (FFA) and lysophospholipids (LPL) and decreased phospholipid synthesis. Lipid peroxidation occurs as a result of attack by free radicals produced at least in part by the generation of excess electrons (e-) in oxygen-deprived mitochondria. Free radicals also may be derived from metabolism of arachidonic acid and catecholamines, metabolism of adenine nucleotides by xanthine oxidase in endothelium (species dependent), and activation of neutrophils and macrophages. The irreversible phase of injury appears to be mediated by severe membrane damage produced by phospholipid loss, lipid peroxidation and cytoskeletal damage.

species, including long-chain acyl coenzyme A (CoA) and acyl carnitine, which, together with products of phospholipid degradation, can incorporate into membranes and impair their function. Free radicals, including toxic oxygen species, are generated from ischemic myocytes, ischemic endothelium, and activated leukocytes. These toxic chemicals induce peroxidative damage to fatty acids of membrane phospholipids. Probably as a result of protease activation, cytoskeletal filaments, which normally anchor the sarcolemma to adjacent myofibrils, become damaged, and their anchoring and stabilizing effect on the sarcolemma is lost. All of these changes lead to a progressive increase in membrane permeability, further derangements in the intracellular ionic milieu, and ATP exhaustion. The terminal event in initiating irreversible myocyte injury appears to be physical disruption of the sarcolemma of the swollen myocyte.[61,64,67]

The sequence of abnormalities described above constitute the well-documented pathophysiologic basis of cell injury leading to cell death in cardiac myocytes subjected to a major ischemic or hypoxic insult. However, recent discoveries have indicated that other pathophysiologic mechanisms can contribute to cell injury and death, in particular apoptosis or programmed cell death.[68,69] Following the recognition of apoptosis as a major and distinctive mode of cell death, reports have been published implicating apoptosis in MI, reperfusion injury, and other forms of cardiovascular pathology.[67,70,71] Apoptosis is characterized by a series of molecular and biochemical events, termed programmed cell death, including (1) gene activation (programmed cell death); (2) perturbations of mitochondria, including membrane permeability transition and cytochrome c release; (3) activation of a cascade of cytosolic aspartate-specific cysteine proteases (caspases); (4) endonuclease activation leading to double-stranded DNA fragmentation; and (5) altered phospholipid distribution of cell membranes and other surface properties with preservation of selective membrane permeability (Fig. 25.20).[68,69] Apoptosis can be triggered by activation of a death receptor pathway or a mitochondrial pathway.[72,73] Apoptosis is also characterized by distinctive morphologic alterations featuring cell and nuclear shrinkage and fragmentation, with subsequent phagocytosis of apoptotic bodies by adjacent viable cells without exudative inflammation.[68,69]

In contrast, numerous studies have reported ischemic myocardial damage to be characterized by cell swelling with altered cellular ionic composition due to altered membrane permeability.[61–67] This pattern of cell injury and death with cell swelling has been designated as oncosis.[69] Some reports have proposed a major role for apoptosis in myocardial ischemic injury and infarction.[71,72] However, such a role for apoptosis may be overstated because of overinterpretation of evidence of DNA fragmentation based on the TUNEL method, which is not specific for apoptosis.[74,75] Evidence has

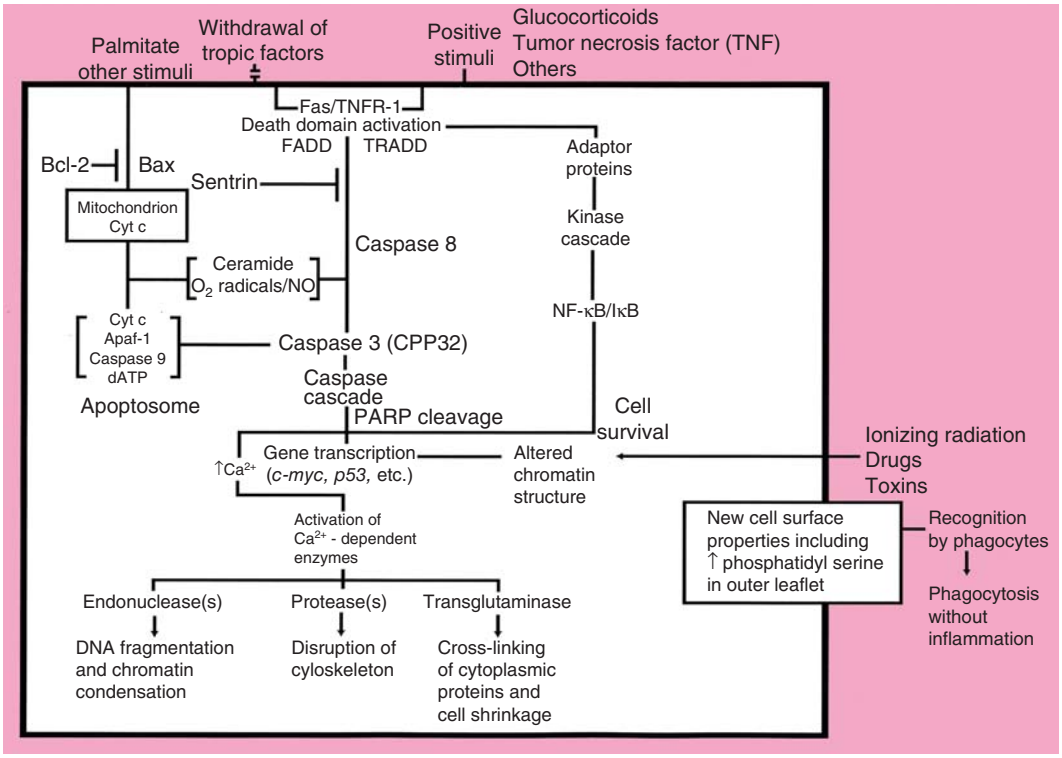

FIGURE 25.20. Mechanisms of cell death by apoptosis. Apoptosis may be caused by self-activation of a lethal metabolic pathway (programmed cell death) or can be triggered by exogenous factors. Apoptosis may be initiated by activation of a death receptor pathway or a mitochondrial pathway, with loci of interaction between the two pathways. The death receptor pathway involves activation of the Fas/tumor necrosis factor receptor (TNFR) and its death domains, FADD and TRADD, and subsequent activation of a cysteine protease (caspase) cascade, with activation of caspase-3 (CPP32) as the key event. Mitochondria have an important role through the release of cytochrome C, which is regulated by bcl-2 (which itself is regulated by related proteins Bax/Bak), and subsequent activation of apoptotic protease-activating factor-1 (Apaf-1).

been presented showing TUNEL labeling of ischemic myocytes with classic features of oncosis as well as viable myocytes undergoing DNA repair.[76,77] Although certain assays have been proposed to be more reliable for detection of patterns of DNA fragmentation characteristic of apoptosis, the DNA labeling data need to be interpreted in relation to other features of cell injury.[78–80] Other studies have found that ischemic myocytes with the apoptotic markers of annexin V membrane labeling also exhibit ultrastructural features of oncotic damage.[81] Nevertheless, work using caspase inhibitors does suggest that apoptosis as well as oncosis may contribute to the overall magnitude of ischemic necrosis.[82,83]

The rate and magnitude of ATP reduction may be a critical determinant of whether an injured myocyte progresses to death by apoptosis or oncosis, because an ATP analogue, d-ATP, is a key component of a molecular complex that mediates cytochrome c release with activation of the caspase cascade and apoptotic death.[67,74,84] The severity of hypoxia and reperfusion influence whether myocytes die by apoptosis or oncosis, as does the severity of metabolic inhibition in experimental studies.[85,86] It is possible then that severely ischemic myocytes progress rapidly to cell death with swelling (oncosis), whereas less severely ischemic myocytes may develop apoptosis. It is likely, however, that the same injured myocyte may undergo activation of the apoptotic pathway with activation of the caspase cascade followed by activation of oncotic mechanisms, leading to cell membrane damage and terminal cell swelling and rupture.[67,74–81] Thus, apoptotic and oncotic mechanisms may be operative in the same myocytes during progression to irreversible ischemic injury and necrosis.

Determinants of Infarct Development and Size and Remodeling

After coronary artery occlusion, the myocardium can withstand up to about 20 minutes of severe ischemia without developing irreversible injury. However, after about 20 to 30 minutes of severe ischemia, irreversible myocardial injury begins.[61] The subsequent degradative changes give rise to recognizable myocardial necrosis. In the human and dog, myocardial necrosis first appears in the ischemic subendocardium, because this area usually has a more severe reduction in perfusion compared with the subepicardium. Over the ensuing 3 to 6 hours, irreversible myocardial injury progresses in a wavefront pattern from the subendocardium into the subepicardium (Fig. 25.21).[60] In the experimental animal and probably in humans as well, most MIs are completed within approximately 6 hours after the onset of coronary occlusion. However, a slower pattern of evolution of MI can occur when the coronary collateral perfusion is abundant or when the stimulus for myocardial ischemia is intermittent (e.g., in the case of episodes of intermittent platelet aggregation before occlusive thrombosis).

Established myocardial infarcts have distinct central and peripheral regions (Fig. 25.22).[61–63] In the central zone of severe ischemia, the necrotic myocytes exhibit clear sarcoplasm with separation of organelles (evidence of edema); clumped nuclear chromatin, stretched myofibrils with widened I-bands, swollen mitochondria containing amorphous matrix (flocculent) densities composed of denatured lipid and protein and linear densities representing fused cristae, and defects (holes) in the sarcolemma. In the periph-

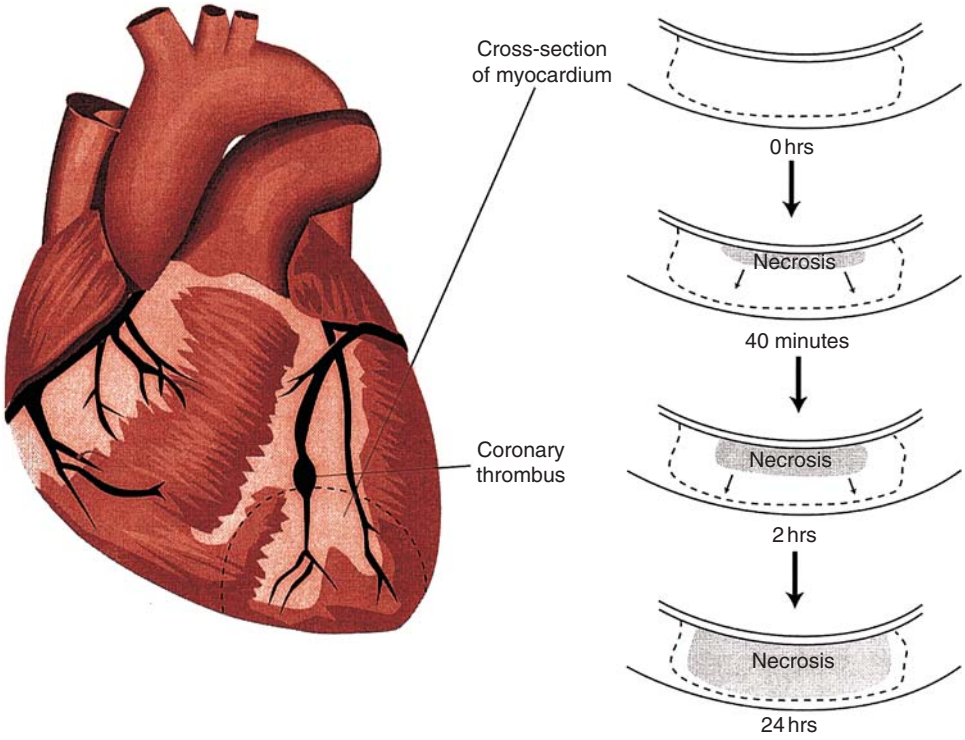

FIGURE 25.21. Progression of cell death versus time as a wavefront of necrosis at various time intervals after coronary occlusion. Necrosis occurs first in the subendocardial myocardium. With longer intervals of occlusion, a wavefront of cell death moves from the subendocardial zone across the wall to involve progressively more of the transmural thickness of the ischemic zone. In contrast, the lateral margins in the subendocardial region of the infarct are established as early as 40 minutes after occlusion and are sharply defined by the anatomic boundaries of the ischemic bed.

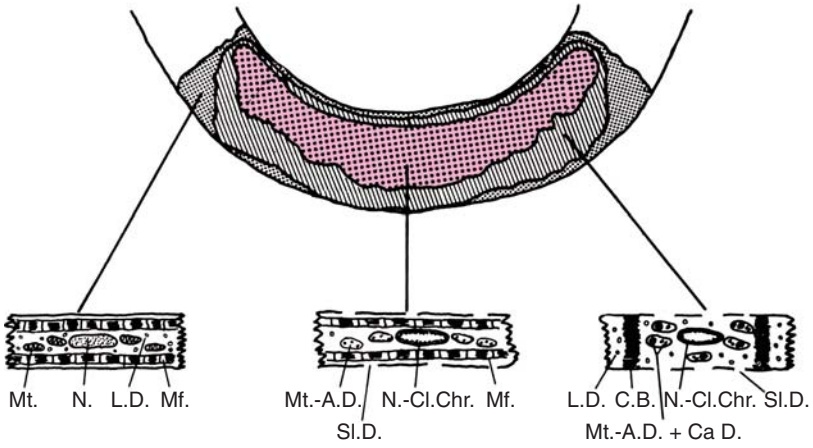

FIGURE 25.22. Patterns of myocardial injury in an acute transmural myocardial infarct. C.B., myofibrillar contraction band; L.D., lipid droplet; Mf., myofibril; Mt., mitochondrion; Mt.-A.D., mitochondrion with amorphous matrix (flocculent) densities; Mt.-A.D. + Ca D., mitochondrion with amorphous matrix densities and calcium phosphate deposits; N., nucleus; N.-Cl. Chr., nucleus with clumped chromatin; SI.D., sarcolemmal defect.

eral region of an infarct, which has some degree of collateral perfusion, many necrotic myocytes exhibit edematous sarcoplasm; disruption of the myofibrils with the formation of dense transverse (contraction) bands, swollen mitochondria containing calcium phosphate deposits as well as amorphous matrix densities, variable amounts of lipid droplets, and clumped nuclear chromatin. A third population of cells at the outermost periphery of infarcts contains excess numbers of lipid droplets but does not exhibit the features of irreversible injury just described. The pattern of injury seen in the infarcted periphery is also characteristic of myocardial injury produced by temporary coronary occlusion followed by reperfusion. In general, the most reliable ultrastructural features of irreversible injury are the amorphous matrix densities in the mitochondria and the sarcolemmal defects.

The myocardial bed at risk, or risk zone, refers to the mass of myocardium that receives its blood supply from a major coronary artery that develops occlusion (Figs. 25.21 and 25.22).[60] After occlusion, the severity of the ischemia is determined by the amount of preexisting collateral circulation into the myocardial bed at risk. The collateral blood flow is derived from collateral channels connecting the occluded and nonoccluded coronary systems. With time there is progressive increase in coronary collateral blood flow. However, much of this increase in flow may occur too late to salvage significant amounts of myocardium.

The size of the MI is determined by the mass of necrotic myocardium within the bed at risk (Figs. 25.21 and 25.22).[60,61] The bed at risk will also contain viable but injured myocardium. The border zone refers to the nonnecrotic but dysfunctional myocardium within the ischemic bed at risk. The size of the border zone varies inversely with the relative amount of necrotic myocardium, which increases with time as the wavefront of necrosis progresses. The border zone exists primarily in the subepicardial half of the bed at risk and has a very small lateral dimension, owing to a sharp demarcation between vascular beds supplied by the occluded and patent major coronary arteries.

The major determinants of ultimate infarct size, therefore, are the duration and severity of ischemia, the size of the myocardial bed at risk, and the amount of collateral blood flow available shortly after coronary occlusion. Infarct size also can be influenced by the major determinants of myocardial metabolic demand, which are heart rate, wall tension (determined by blood pressure), and myocardial contractility.

Infarct size also influences the overall response of the ventricle to an ischemic insult. Myocardial remodeling refers to a complex of compensatory changes, including structural and functional modifications of the viable myocardium to ventricular wall stress. The response includes hypertrophy of cardiomyocytes, death of cardiomyocytes by apoptotic or oncotic mechanisms, and cardiomyocyte regeneration, probably involving activation of endogenous stem cells.[67] Other changes involve connective tissue restructuring and proliferation and microcirculatory changes. If the initial damage is relatively limited, remodeling can be effective and lead to normalization of wall stress. If the initial damage is severe, remodeling may be inadequate or ineffective, leading to fixed structural dilatation of the ventricle and congestive heart failure. The end stage of this process is ischemic cardiomyopathy.

Reperfusion, Preconditioning, Stunning, and Hibernation

A number of factors can significantly modulate the myocardial response and subsequent outcome following an ischemic episode.[67] The progression of myocardial ischemia can be profoundly influenced by reperfusion (Fig. 25.23). However, the effects of reperfusion are complex.[89–91] Reperfusion clearly can limit the extent of myocardial necrosis if instituted early enough after the onset of coronary occlusion. However, reperfusion also changes the pattern of myocardial injury by causing hemorrhage within the severely damaged myocardium and by producing a pattern of myocardial injury characterized by contraction bands and calcification. Reperfusion also accelerates the release of intracellular enzymes and proteins from damaged myocardium. This may lead to a marked elevation of serum levels of these infarct markers without necessarily implying further myocardial necrosis. The timing

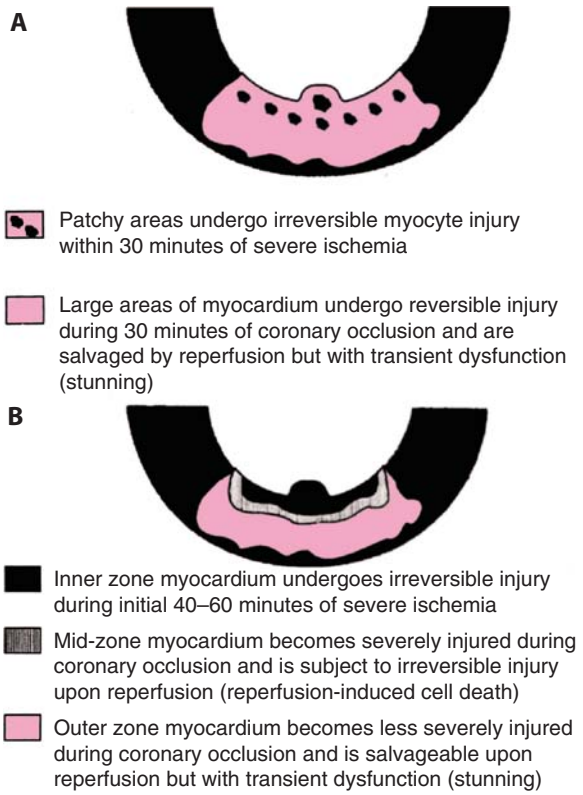

FIGURE 25.23. Influences of duration of coronary occlusion and timing of reperfusion on the response of the ischemic myocardium. (A) When reperfusion is achieved within 30 minutes of coronary occlusion, minimal irreversible injury occurs and most of the ischemic myocardium is salvaged but with transient dysfunction (stunning). (B) When reperfusion occurs within 2 hours of coronary occlusion, a significant amount of subendocardial myocardium develops irreversible injury, including some myocytes that probably become irreversibly injured at the time of reperfusion (reperfusion-induced cell death); however, reperfusion also results in significant salvage of subepicardial myocardium that would have developed irreversible injury with permanent coronary occlusion.

of reperfusion is critical to the outcome, with the potential for myocardial salvage being greater with earlier intervention. Although reperfusion can clearly salvage myocardium, it may also induce additional injury. The concept of reperfusion injury implies the development of further damage, as a result of the reperfusion, to myocytes that were injured but that remained viable during a previous ischemic episode. Such injury may involve functional impairment, arrhythmia, and progression to cell death.[67,87–89] Major mediators of reperfusion injury are oxygen radicals and neutrophils. The oxygen radicals are generated by injured myocytes and nonmyocytes in the ischemic zone due to an oxidative burst upon reperfusion as well as neutrophils that gain access to the ischemic zone and become activated upon reperfusion.[67,89–91] The neutrophils also contribute to microvascular obstruction and the no-reflow phenomenon in the reperfused myocardium.[67,89–91]

The rate of progression of myocardial necrosis can be influenced by prior short intervals of coronary occlusion and reperfusion. Specifically, experimental evidence indicates that the extent of myocardial necrosis after 60 to 90 minutes of coronary occlusion is significantly less in animals that had been pretreated with one or more 5-minute intervals of coronary occlusion before the induction of permanent occlusion.[67,92,93] However, after 120 minutes of coronary occlusion, the effect on infarct size is lost. This phenomenon is known as preconditioning (Fig. 25.24).[67,92,93] A reduced rate of ATP depletion correlates with the beneficial effects of preconditioning.[92,93] Further studies have indicated that classic preconditioning involves activation of receptors for adenosine and other agonists, G-protein–coupled protein kinase C, and sarcolemmal and mitochondrial ATP-dependent potassium

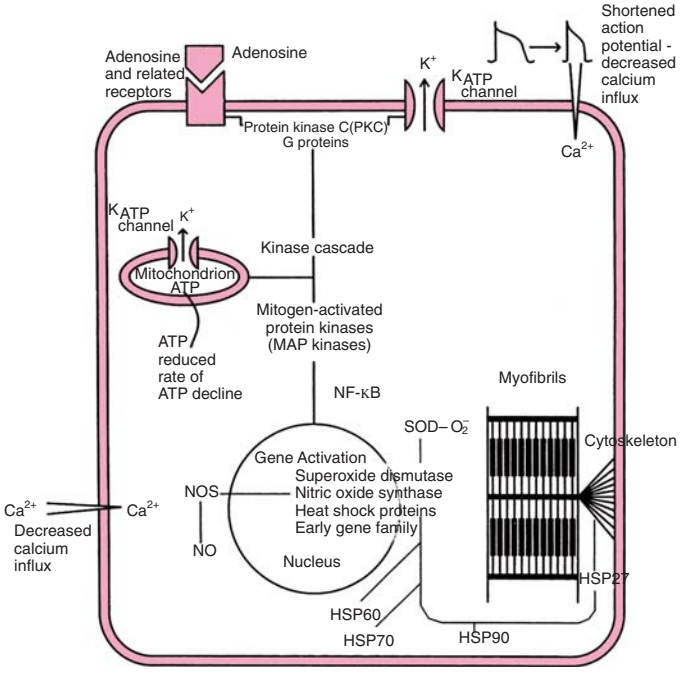

FIGURE 25.24. Postulated mechanisms of early ischemic myocardial preconditioning and second window of protection. Brief periods of coronary occlusion lead to an initially slower rate of ATP decline and reduced rate of progression to irreversible injury and necrosis during subsequent prolonged coronary occlusion; this phenomenon is ischemic preconditioning. Significant events in ischemic preconditioning are activation of adenosine and related receptors, activation of protein kinase C (PKC), and opening of ATP-dependent K^+ channels in the sarcolemma and mitochondria. Available evidence supports opening of the mitochondrial K_{ATP} channels as the critical event, although the downstream mechanisms are still unclear. One effect is decreased Ca^{2+} influx, and subsequent blunting of injury induced by Ca^{2+} overload. Brief episodes of coronary occlusion lead to early ischemic preconditioning followed by a refractory period and the subsequent onset of a second window of protection. The second window of protection is related to gene activation mediated by a kinase cascade, including mitogen-activated protein (MAP) kinases, and nuclear factor κB (NF-κB). Gene products implicated in the second window of protection include superoxide dismutase, nitric oxide synthase and its product, nitric oxide, and heat shock proteins, including HSP27, which interacts with the cytoskeleton.

channels, with a key role for the mitochondrial K channels.[94–100] After a refractory period, a second late phase of myocardial protection during a subsequent ischemic event develops, a phenomenon known as the second window of protection (SWOP),[96,101,102] which is related to ischemia-induced gene activation with production of various gene products, including superoxide dismutase, nitric oxide synthase, and stress (heat shock) proteins.[96,102–104] Recently, a protective effect on the extent of myocardial ischemic damage has been observed with multiple, brief coronary occlusions during early reperfusion after coronary occlusion, a phenomenon termed postconditioning.[105]

Prolonged functional depression, requiring up to 24 hours or longer for recovery, develops on reperfusion even after relatively brief periods of coronary occlusion, on the order of 15 minutes, which are insufficient to cause myocardial necrosis. This phenomenon has been referred to as myocardial stunning.[67] A related condition, termed hibernation, refers to chronic depression of myocardial function owing to a chronic moderate reduction of perfusion.[67] Preconditioning and stunning are independent phenomena, since the preconditioning effect is short term, transient, and not mediated through stunning. Free-radical effects and calcium loading have been implicated in the pathogenesis of stunning, as well as other components of reperfusion injury.[67,106,107] After longer intervals of coronary occlusion, on the order of 2 to 4 hours, necrosis of the subendocardium develops and even more severe and persistent functional depression occurs.[108] In experimental studies, after 2 hours of coronary occlusion LV regional sites of moderate dysfunction during ischemia recovered normal or near-normal regional contractile function after 1 to 4 weeks of reperfusion, whereas after 4 hours of coronary occlusion, contractile dysfunction persisted after 4 weeks of reperfusion.[108] Degenerative changes in cardiomyocytes develop in chronically underperfused, hibernating myocardium.[67] These changes can influence the degree of functional recovery upon complete restoration of blood flow.[67]

Therefore, depending on the interval of coronary occlusion before reperfusion, various degrees of contractile dysfunction, necrosis, or both are seen with reperfusion. These observations emphasize the need for early intervention to salvage myocardium.[67,109] On balance, early reperfusion results in a major net positive effect, making early reperfusion an important goal in the treatment of acute ischemic heart disease.[110,111]

Pathology of Interventionally Treated Coronary Artery Disease

Percutaneous transluminal coronary angioplasty (PTCA) can produce a variety of acute effects, including dilatation of the vessel caused by stretching of the intima and media, damage to the endothelial surface, multiple fissures in the plaque, and dissection of the media (Figs. 25.25 and 25.26).[112,113] The acute injury initiates a reparative response that leads to intimal proliferation.[112–114] Similar effects occur after atherectomy and laser angioplasty.[115,116] The resultant fibrocellular tissue is composed of modified smooth muscle cells (myofibroblasts) and connective tissue matrix without lipid deposits. A similar lesion is seen in animal models of arterial injury.[114] Experimental evidence supports a role for platelet activation in the pathogenesis of the lesion.[114] This process of intimal proliferation leads to restenosis of lesions in 30% to 40% of cases within 6 months. The use of vascular stents in conjunction with angioplasty has significantly improved the long-term patency rates, although the stents do invoke a viable amount of intimal reaction.[117–119] The potential of drug eluting stents to improve long-term outcomes is under active investigation.[120,121]

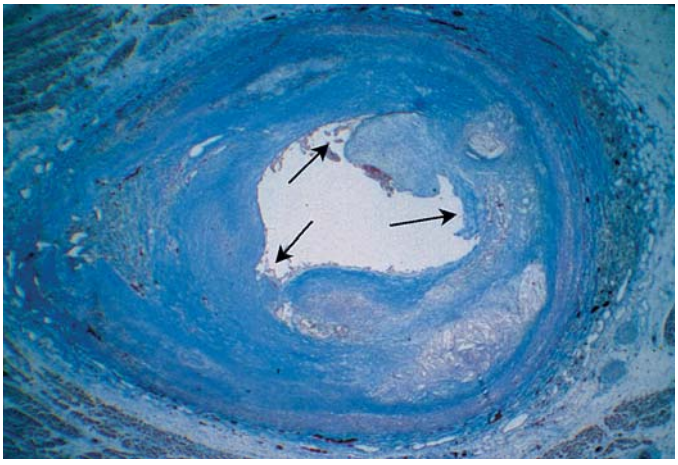

FIGURE 25.25. Coronary artery after percutaneous transluminal coronary angioplasty shows areas of plaque disruption (arrows) with microthrombus on the surface. Low-magnification photomicrograph.

Saphenous vein coronary artery bypass grafts (SVCABGs) develop diffuse fibrocellular intimal thickening, medial degeneration and atrophy, and vascular dilatation within several months after implantation (Figs. 25.27 and 25.28).[122–124] Subsequently, the grafts are prone to development of eccentric intimal plaques with lipid deposition (atherosclerosis).[122–124]

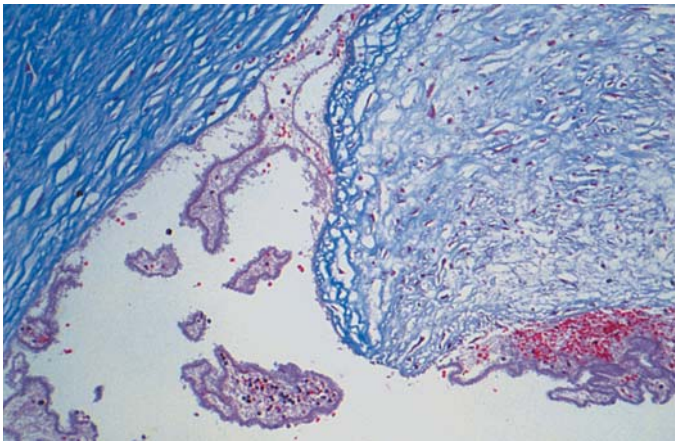

FIGURE 25.26. Close-up view of microthrombus on surface of a fissured plaque following percutaneous transluminal coronary angioplasty. High-magnification photomicrograph.

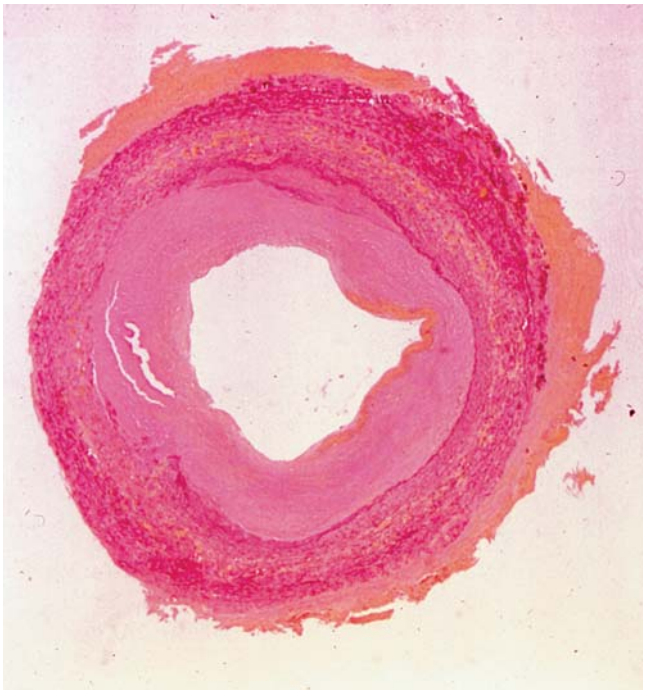

FIGURE 25.27. Saphenous vein–coronary artery bypass graft implanted for several months. The vein graft shows diffuse concentric fibromuscular intimal thickening. Low-power photomicrograph.

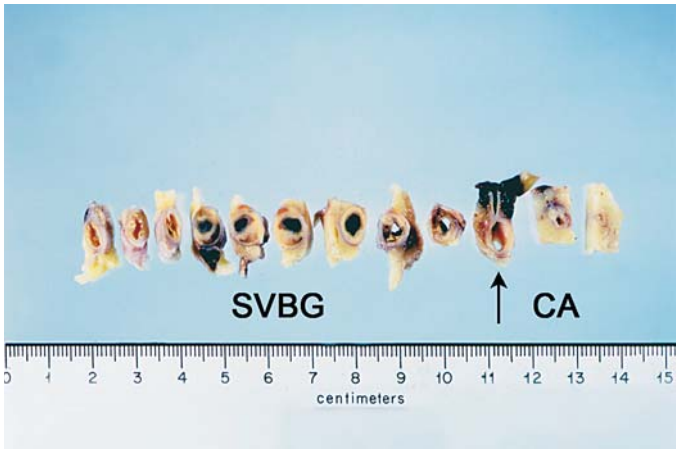

FIGURE 25.29. Severe atherosclerosis in a saphenous vein graft in place for 7 years. Multiple cross sections through the saphenous vein bypass graft (SVBG), distal anastomosis (arrow), and distal coronary artery (CA). The saphenous vein shows marked atherosclerosis and acute occlusive thrombosis with plaque hemorrhage. The distal coronary artery has focal plaque, but a residual lumen is present. There was a massive acute myocardial infarct in the distribution of the occluded vein graft.

Plaque fissuring and thrombosis also may develop (Figs. 25.29 and 25.30). Therefore, all of the changes seen in naturally occurring atherosclerosis may also develop in the saphenous veins, thereby creating a finite limit to the beneficial effects of these grafts. With improvements in surgical technique, the use of internal mammary arteries for coronary bypass has taken on more widespread application. The internal mammary arteries are more resistant to the intimal injury and intimal proliferation observed in saphenous veins and, therefore, the arterial bypass grafts have prolonged potency.[125,126]

New Approaches to Myocardial Modulation

A new era is developing in the therapeutic application of new insights regarding the pathogenesis of myocardial ischemic disease. Ongoing testing is being conducted to understand genetic factors influencing outcomes and to successfully achieve genetic manipulation (gene therapy) of the processes responsible for the response of the arterial wall to injury, with the goals of retarding or preventing intimal proliferation and thrombosis at sites of coronary injury.[127–133] Alternative approaches are being explored for the treatment of intractable angina pectoris.[134,135] One surgical approach is the use of transmyocardial laser treatment to create new myocardial microvasculature.[135–138] Another approach is the

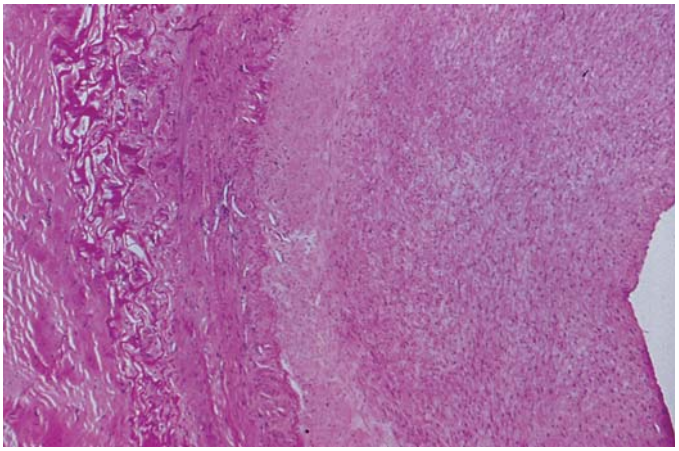

FIGURE 25.28. Further detail of the fibrocellular intimal proliferation in a saphenous vein–coronary artery bypass graft. Medium-power photomicrograph.

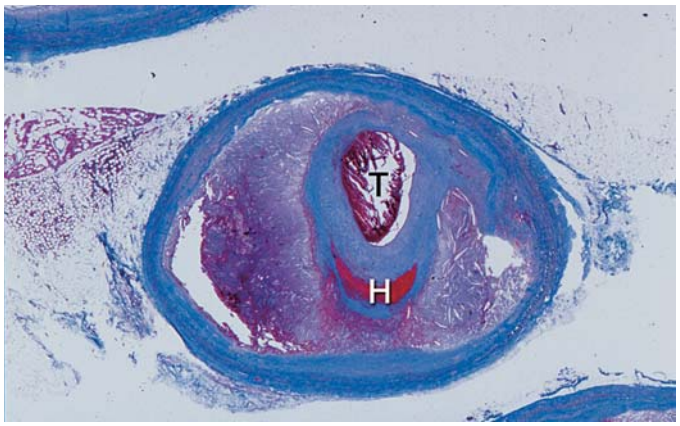

FIGURE 25.30. This segment of vein graft is involved by a large atheroma with lipid-laden core and thin fibrous capsule. Hemorrhage is present in the plaque core (H). The lumen is occluded by recent thrombus (T). Low-power photomicrograph.

intravascular delivery of genetically engineered growth factors, including vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF).[139–142] The debate regarding whether or not the myocardium is composed of terminally differentiated cardiac myocytes has been revived.[143,144] New insight into the issue has been provided by evidence that the myocardium contains intrinsic cardiac stem cells that have the potential to differentiate into cardiac myocytes, smooth muscle cells, and endothelial cells.[145,146] Bone marrow–derived stem cells also have the potential to differentiate into mature cardiac cells when these cells are home to the myocardium or are injected, particularly after myocardial injury. These insights have opened the promising field of regenerative cardiology. Initially, primary results have been obtained with the use of autologous stem cells for the treatment of patients with MI and heart failure.[147–149] These approaches have considerable promise for the treatment of ischemic myocardial disease.

Summary

Coronary atherosclerosis is the major anatomic substrate for the diverse clinical syndromes of coronary heart disease. Acute ischemic heart disease is usually initiated by erosion, rupture, thrombosis, or spasm superimposed on vulnerable plaques with active inflammation. The process may be self-limited (angina pectoris), may trigger a lethal ventricular arrhythmia (sudden cardiac death), or result in death of heart muscle (MI). Myocardial infarction progresses as a wavefront of necrosis extending from subendocardium into subepicardium with complete evolution in 3 to 6 hours. The pathogenesis of irreversible myocardial cell injury involves metabolic and electrolyte changes, leading to progressive membrane damage and cell swelling and rupture (oncosis). Apoptosis, or at least apoptotic mechanisms, may contribute to the process. Timely reperfusion has a profound influence, resulting in some further loss of critically injured cells (reperfusion injury) and net salvage of a significant amount of myocardium. Preconditioning by repetitive short intervals of coronary occlusion and reperfusion can significantly retard the subsequent development of MI. Reperfusion can be achieved clinically with coronary angioplasty and cardiac bypass surgery, but associated pathologic changes in coronary arteries can influence long-term outcomes.

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