Coronary Artery Disease: Pathological Anatomy and Pathogenesis

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Abstract

Coronary atherosclerosis is the major anatomic substrate for the diverse clinical syndromes of coronary heart disease. Coronary atherosclerosis is a disease that develops as an inflammatory response of the arterial wall to chronic, multifactorial injury. Acute ischemic heart disease is usually initiated by erosion, rupture, thrombosis and/or spasm superimposed on vulnerable atherosclerotic 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, myocardial infarction (MI). MI progresses as a wavefront of necrosis extending from subendocardium into subepicardium with complete evolution in 3–4 h. The pathogenesis of irreversible myocardial cell injury involves metabolic and electrolyte changes, and activation of necroptotic and apopotic mechanisms of cell injury and death. 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. Progress in understanding the pathobiology of myocardial ischemic injury is leading to new therapeutic approaches to combine with established approaches for reperfusion and salvage of myocardium.

Keywords

Coronary atherosclerosis • Vulnerable coronary plaques • Coronary plaque erosion, rupture and thrombosis • Pathology of acute coronary syndromes • Acute myocardial infarction • Pathogenesis of myocardial ischemic injury • Myocardial remodeling • Reperfusion and reperfusion injury • Stunning and hibernation • Preconditioning and postconditioning • Therapeutic interventions • Coronary artery bypass grafts • Coronary stents

Introduction

The clinical manifestations of coronary heart disease (CAD), also known as ischemic heart disease, are diverse, with a spectrum that encompasses various forms of acute coronary syndrome (ACS), including angina pectoris, myocardial infarction (MI), and sudden cardiac death, as well as chronic coronary heart disease. These syndromes result

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J.T. Willerson, D.R. Holmes, Jr. (eds.), *Coronary Artery Disease*, Cardiovascular Medicine,
DOI 10.1007/978-1-4471-2828-1_1,

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 major cause of CAD is coronary atherosclerosis (arteriosclerosis), a process that develops as an inflammatory response of the vessel wall to chronic, multifactorial injury and leads to the formation of atherosclerotic plaques (fibrous plaques, atheromas) in the coronary arteries (Figs. 1.1 and 1.2) [1–3]. These plaques are regions of thickened intima and are composed of various mixtures of fibrous tissue, cells, and lipid [4, 5].

Atherogenesis involves complex interactions between the vessel wall and soluble and formed elements of the blood (Fig. 1.2) [4–8]. Important factors in the initiation and growth of plaques are: (1) endothelial injury or dysfunction; (2) monocyte/macrophage accumulation; (3) influx of T lymphocytes; (4) platelet aggregation and attachment; (5) smooth muscle proliferation; (6) influx of plasma LDL; (7) oxidation of LDL; (8) progressive lipid accumulation in foam cells from uptake of oxidatively modified LDL; (9) apoptotic death of foam cells; (10) extracellular lipid deposition; and (11) hemodynamic influences related to blood pressure and pattern of blood flow.

Inflammation has a major role in the pathogenesis and clinical expression of atherosclerosis to the extent that atherosclerosis is now considered an inflammatory disease [4, 9–11]. Many key features of the inflammatory process have been found to occur in the development of atherosclerotic lesions (Fig. 1.3). Altered endothelial cells in lesion prone areas express a certain profile of adhesion molecules that lead to the recruitment, attachment and transmigration of

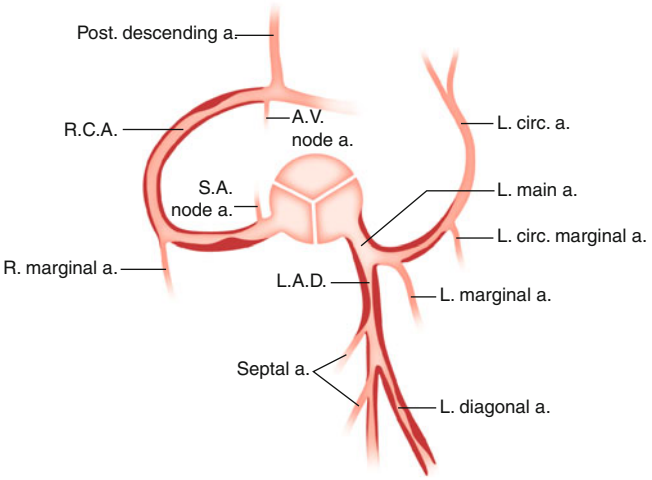

Fig. 1.1 Diagram of the usual anatomic distribution of the coronary arteries also showing a typical distribution of atherosclerotic plaques (*dark areas*). The blood supply to the heart is provided by the left and right coronary arteries and branches of these major vessels. The anterior wall of the left ventricle (*LV*) and the anterior portion of the interventricular septum are supplied by the left anterior descending coronary artery (*LAD*) 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 (From Willerson et al. [1]. Reprinted with permission from Wolters Kluwer)

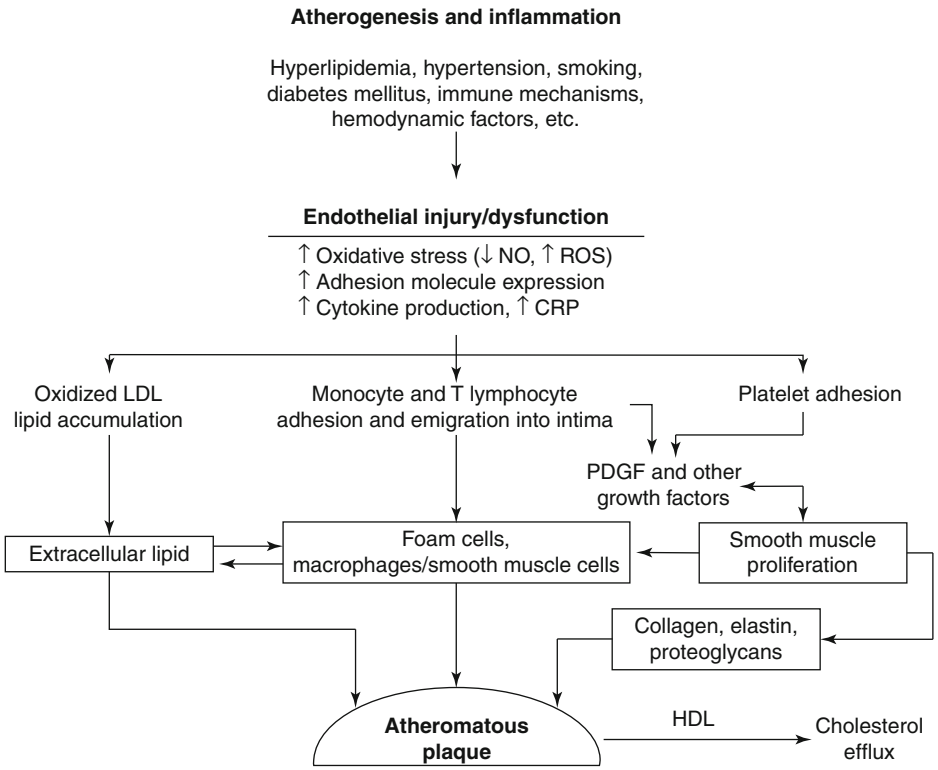

Fig. 1.2 Schematic diagram of postulated sequence of events and cellular interactions in atherogenesis. *CRP* C-reactive protein, *NO* nitric oxide, *ROS* reactive oxygen species, *LDL* low density lipoprotein, *HDL* high density lipoprotein (From Buja and McAllister [4]. Reprinted with permission from Springer)

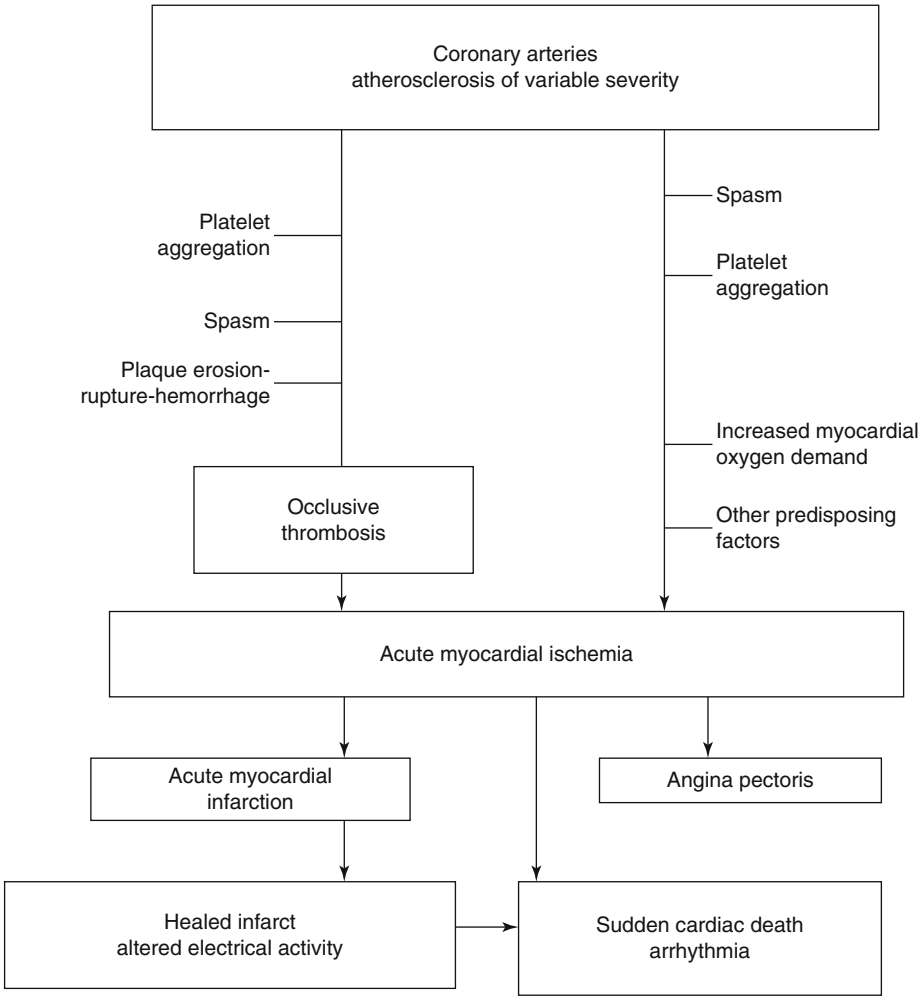

Fig. 1.3 Pathogenetic mechanisms of acute ischemic heart disease and potential clinical outcomes (From Buja and McAllister [3] (Reprinted with permission from Springer)

blood monocytes and T lymphocytes. The local environment within the intima leads to transformation of the leukocytes into activated macrophages and T lymphocytes and promotes the chemical signaling between the two cell types. Cytokines produced by the macrophages create a proinflammatory environment that facilitates the recruitment of more inflammatory cells. The production of other mediators, including platelet derived growth factor (PDGF)-like molecules, leads to the recruitment and proliferation of vascular smooth muscle cells in the lesions. Production of superoxide anion and other reactive oxygen species leads to oxidation of low density lipoprotein (LDL). Subsequently, unregulated uptake of oxidized LDL by macrophages and smooth muscle cells via their scavenger receptors leads to formation of foam cells. As the plaques grow, a central core of necrotic debris and extracellular lipid develops related to apoptotic death of foam cells [8]. Smooth muscle cells lay down the connective tissue matrix comprising the fibrous capsule of the plaque. Macrophages produce collagenases and metalloprotenases that are important in the turnover of the connective tissue matrix [9, 11]. An excess of the degradative enzymes leads to degradation and thinning of the fibrous capsule. Plaques prone to rupture and ruptured plaques exhibit an inflammatory profile characterized by prominent numbers of macrophages and lymphocytes adjacent to the plaque capsule, increased expression of inflammatory mediators, increased local concentration of metalloproteinases, and prominent apoptosis of plaque cells [12, 13]. The inflammatory nature of atherosclerosis is manifest by the correlation of increased blood levels of inflammatory markers, especially high sensitivity C-reactive protein (hs CRP) and the subsequent development of atherosclerotic disease [14].

Initially, atherosclerosis is a focal disease. There is a predilection for formation of atherosclerotic plaques adjacent to branch points in areas of low-velocity flow and low shear stress adjacent to areas of high shear stress [6, 7, 15]. It is postulated that the flow patterns in such regions promote endothelial dysfunction and increased contact of endothelium with leukocytes and platelets. 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 [3–5]. Areas of predilection for severe atherosclerosis in the coronary system include the proximal left anterior descending coronary artery and the proximal and distal right coronary arteries (Fig. 1.1).

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 [13, 15–17]. 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") [13]. Quantitative coronary arteriography can provide more objective measurements of absolute coronary dimensions and flow. Fractional flow reserve (FFR) provides the most accurate measure of the severity of a otenous [18].

Coronary Thrombosis and Other Acute Coronary Lesions

Acute ischemic heart disease is often initiated by acute changes superimposed on atherosclerotic plaques (Fig. 1.3) [1–3, 10–23]. The spectrum of thrombotic lesions includes platelet aggregates, mural (nonocclusive) thrombi, and occlusive thrombi (Figs. 1.4, 1.5, 1.6, and 1.7) [1–3, 10–23]. Major thrombi are frequently associated with significant disruptions of the plaque surface, which may appear as fissures, erosion, ulceration, or rupture (Figs. 1.4, 1.5, and 1.6). 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. 1.5) [12, 13, 22, 23]. However, endothelial erosion predisposing to thrombosis can involve fibrocellular plaques without significant lipid content [19, 20].

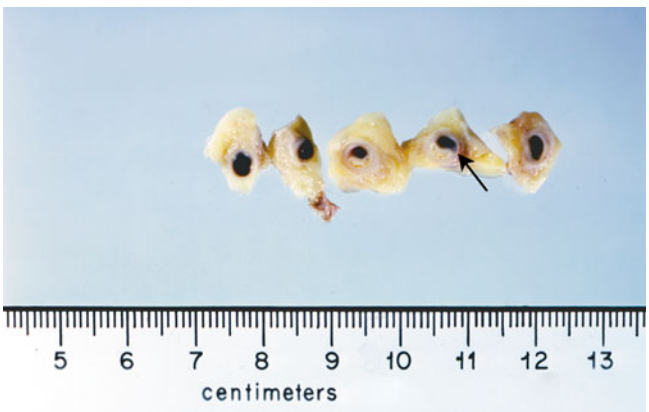

Fig. 1.4 Gross photograph of sections of a coronary artery with an atherosclerotic plaque and occlusive thrombus. A break in the plaque capsule has given rise to plaque hemorrhage (*arrow*) and occlusive thrombosis (From Buja and McAllister [3]. Reprinted with permission from Springer)

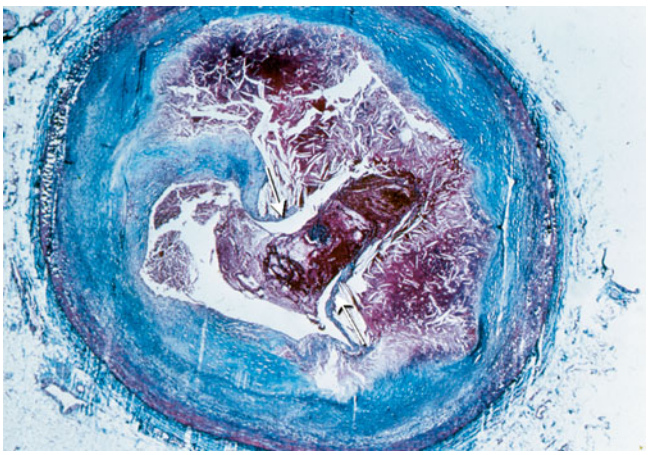

Fig. 1.5 Coronary artery shows a ruptured plaque capsule (*arrows*) and intraluminal and intraplaque thrombus. Low power photomicrograph (From Buja and McAllister [3]. Reprinted with permission from Springer)

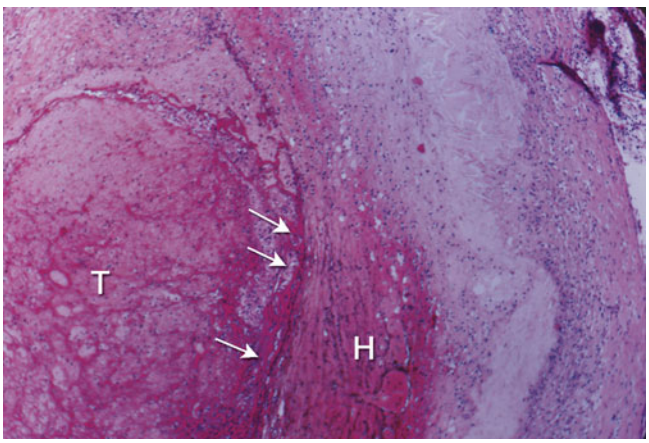

Fig. 1.6 Coronary artery shows an erosion of the endothelial surface (*arrows*) leading to superficial hemorrhage in the plaque (*H*) and thrombosis (*T*) of the lumen. Low power photomicrograph (From Buja and McAllister [3]. Reprinted with permission from Springer)

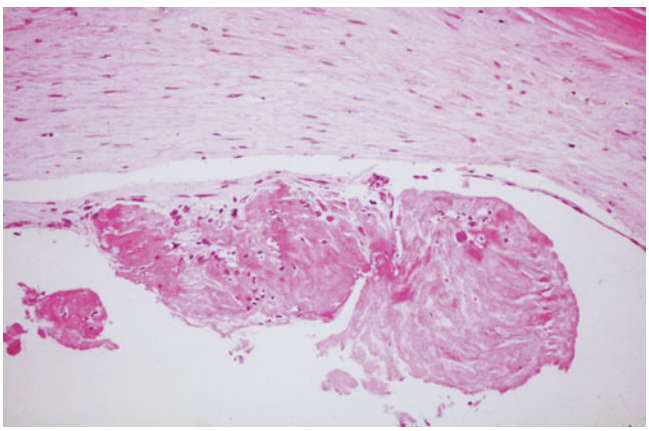

Fig. 1.7 Coronary artery with a small mural thrombus attached to the surface of an atherosclerotic plaque. High power photomicrograph (From Buja and McAllister [3]. Reprinted with permission from Springer)

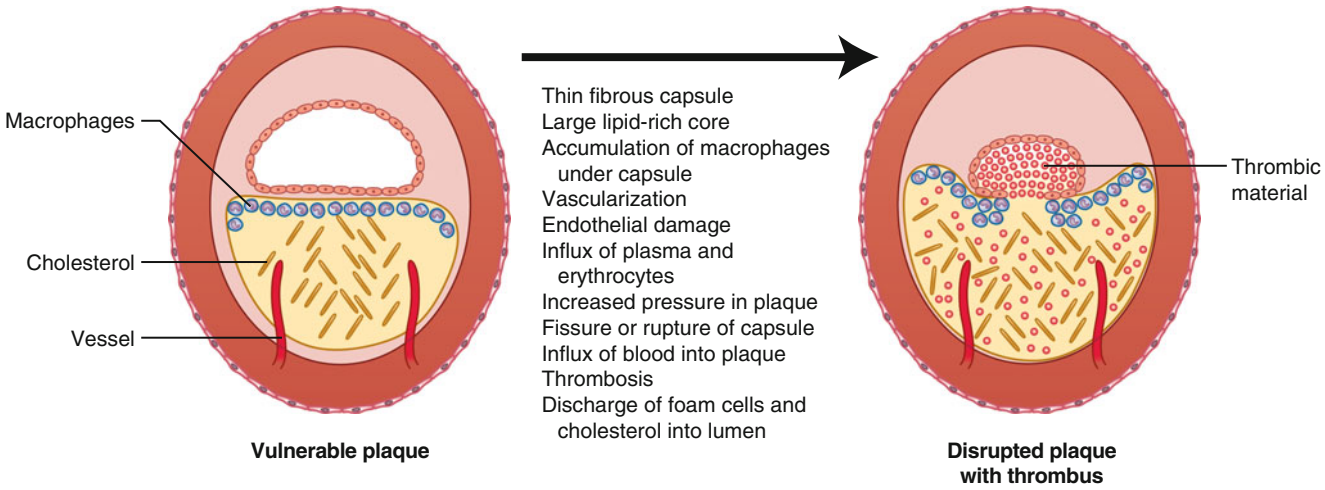

Fig. 1.8 Characteristics of the vulnerable plaque and mechanisms contributing to disruption of the plaque capsule and thrombosis (From Buja and McAllister [3]. Reprinted with permission from Springer)

Inflammation adjacent to the plaque surface is important in the pathogenesis of alterations predisposing to thrombosis regardless of the plaque morphology [11–13]. Thus, high risk or vulnerable plaques are characterized by inflammation associated with a variety of plaque morphologies [19–21]. Factors that 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. 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. 1.8) [1–3, 19–23]. Localized erosion and plaque fissuring also can give rise to platelet aggregation and thrombosis. Disruption of the plaque surface, by any mechanism, predisposes to formation of intraluminal and intramural (intraplaque) thrombus (Fig. 1.5).

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 [1–3, 19–23]. Due to coronary remodeling, plaque rupture and occlusive thrombosis often occurs without prior significant luminal narrowing by the vulnerable plaque [22, 23].

Little information is available regarding anatomic correlates of coronary spasm [3, 24, 25]. Spasm is usually associated with atherosclerotic lesions but in some cases occurs without angiographically evident disease. Prominent adventitial inflammation and increased mast cells have 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 supporting a role for inflammatory mediators in the pathophysiology of coronary spasm [26]. Mechanisms for coronary artery spasm involve alterations of the vessel wall, including endothelial injury and hyperreactivity of vascular smooth muscle cells, coupled with a vasoconstrictive stimulus [25].

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. 1.9 and 1.10), emboli, vasculitis, and other conditions of the coronary arteries [27]. Cocaine use can precipitate acute myocardial ischemia and infarction as a result of coronary spasm and/or thrombosis [28].

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 [1–3, 19–21]. However, there is considerable variation in the anatomic extent of large vessel 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

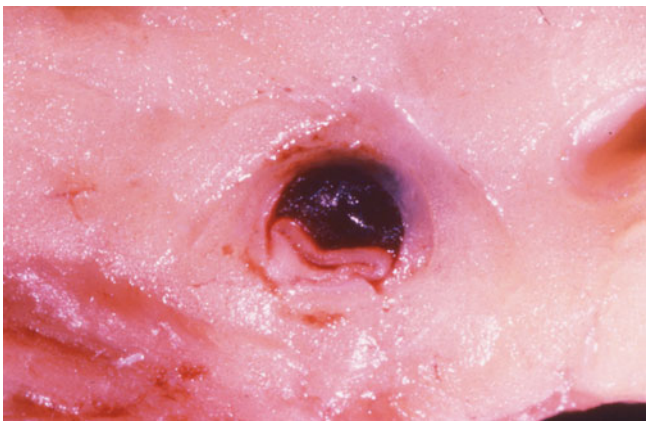

Fig. 1.9 Gross photograph of a spontaneously dissected coronary artery with a hematoma in the wall and marked compression of the lumen (From Buja and McAllister [3]. Reprinted with permission from Springer)

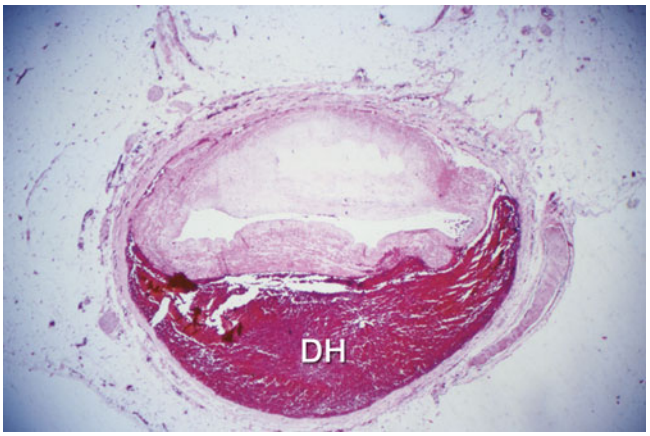

Fig. 1.10 Coronary artery with spontaneous dissecting hematoma (*H*) in the vessel wall. Low power photomicrograph (From Buja and McAllister [3]. Reprinted with permission from Springer)

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 myocardial infarct (MI) or to little or no myocardial damage. Thus, the myocardium can develop a spectrum of responses to alterations in coronary perfusion (Table 1.1) [29].

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 [1–3, 19–21]. The accumulation of macrophages at sites of unstable, vulnerable plaques, indicates an inflammatory component to these vascular lesions, has also been demonstrated [11–13].

Coronary atherosclerosis is the most frequent anatomic substrate of sudden cardiac death [30, 31]. In large series, approximately 90 % of cases exhibit significant

Table 1.1 Myocardial responses to alterations in coronary perfusion

Dysfunction during transient ischemia (angina pectoris)
Stunning following acute ischemia
Hibernation during chronic ischemia
Ischemic preconditioning
Against stunning
Against infarction
Acute myocardial infarction (AMI)
Subendocardial, transmural
Extension, expansion
Complications
Reperfusion effects
On myocardial function
On myocardial injury
Postconditioning
Remodeling
Chronic ischemic heart disease
Ischemic cardiomyopathy

Modified from Buja [29]. With permission from Nature Publishing Group

atherosclerotic narrowing of at least one coronary artery [31]. Many of the cases also show evidence of previous myocardial injury, manifest as multifocal myocardial scarring and/or healed infarction [31]. Although most cases do not exhibit an anatomically demonstrable acute MI, a subset of cases of sudden death are related to acute MI [31–34]. There is considerable variability in the reported incidence of acute plaque alterations and thrombotic lesions [31–34]. 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 [31–34]. Such patients also frequently show evidence of platelet aggregation in the coronary microcirculation.

Women and men exhibit differences regarding sudden cardiac death [3, 33, 34]. Sudden cardiac death occurs more frequently in men than 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. There is evidence of a higher incidence of plaque rupture in men dying suddenly during exertion than in men dying suddenly at rest. Furthermore, plaque rupture with exertion is characterized by a relatively thin fibrous capsule, relatively numerous vasa vasorum, and rupture in mid-cap, whereas plaque rupture at rest tends to occur at the shoulder region of the fibrous cap. In summary, clinicopathologic studies support the concept of three major mechanisms of sudden cardiac death: 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. 1.3) [30, 31].

Pathology of Acute Myocardial Infarction

MI is defined as the death of heart muscle resulting from severe, prolonged ischemia [1–3, 35–40]. MIs usually involve the LV. 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. MIs are designated as subendocardial (non-Q-wave) when the necrosis is limited to the inner half of the ventricular wall (Fig. 1.11) 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. 1.12 and 1.13). The electrocardiographic (ECG) correlates are the ST segment elevation with subsequent Q-wave pattern for transmural infarcts (STEMI) and the ST segment depression without Q-wave pattern for subendocardial infarcts (NSTEMI) [1–3, 35–40].

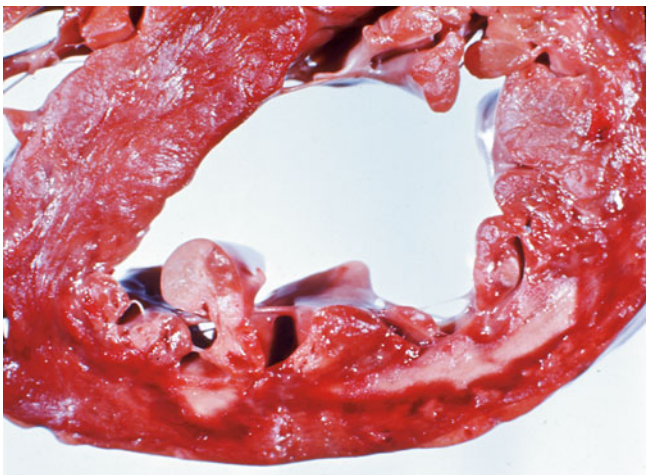

Fig. 1.11 Heart section demonstrates an acute subendocardial myocardial infarct involving the anterior left ventricle. The necrotic subendocardial myocardium is *pale yellow* and rimed by a *red area* of congestion (From Buja and McAllister [3]. Reprinted with permission from Springer)

The overall incidence of occlusive coronary thrombosis and associated plaque fissure or rupture is high (greater than 75 %) for acute MI [1–3]. 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 (STEMI) MI but in only about one-third of cases of subendocardial (NSTEMI) MI [1–3]. Subendocardial MI without occlusive thrombosis is related to the influence of other factors, such as more subtle coronary lesions (platelet aggregation, nonocclusive thrombi) and/or factors that increase myocardial oxygen demand (e.g., aortic stenosis, systemic hypertension, cardiac hypertrophy, excessive stress, or exertion) (Fig. 1.3). The occurrence of subendocardial MI without occlusive thrombosis highlights 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

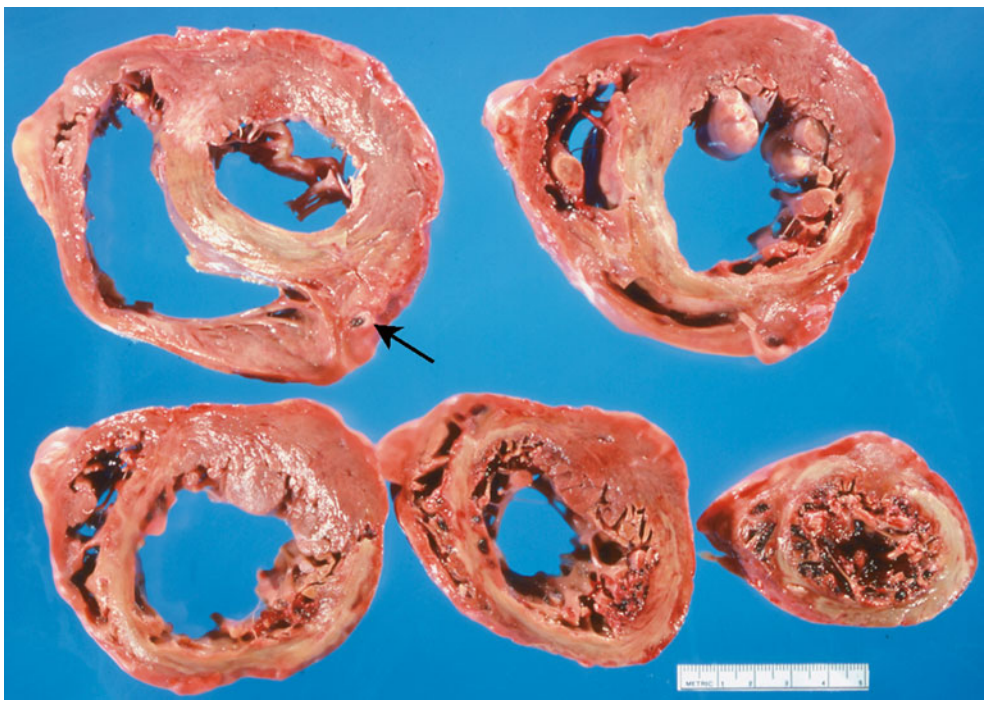

Fig. 1.12 Transverse sections of the heart demonstrate a large acute transmural anteroseptal myocardial infarct (*yellow area*) related to an occlusive thrombus (*arrow*) of the proximal left anterior descending coronary artery (From Buja and McAllister [3]. Reprinted with permission from Springer)

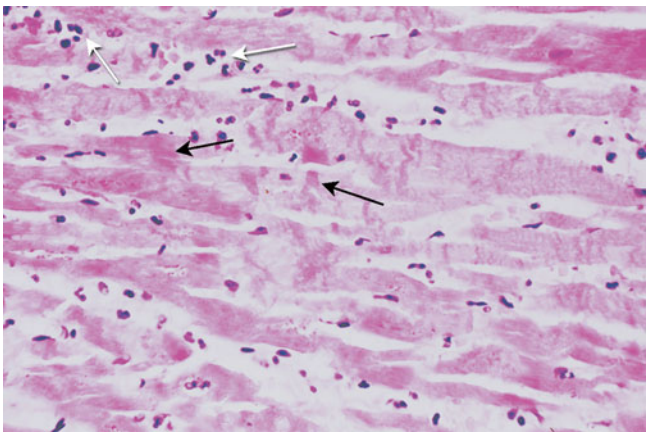

Fig. 1.13 Acutely infarcted myocardium contains necrotic myocytes with contraction bands (*black arrows*) and an infiltrate of neutrophils (*white arrows*). High magnification micrograph (From Buja and McAllister [3]. Reprinted with permission from Springer)

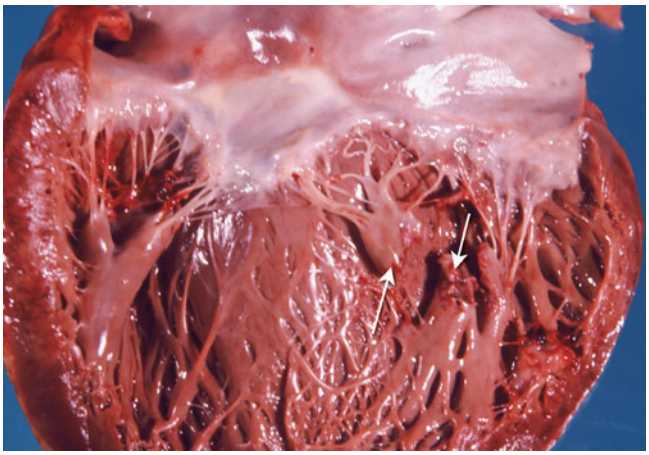

Fig. 1.14 Heart shows a rupture of the posterior papillary muscle (*arrows*) due to an acute myocardial infarct (From Buja and McAllister [3]. Reprinted with permission from Springer)

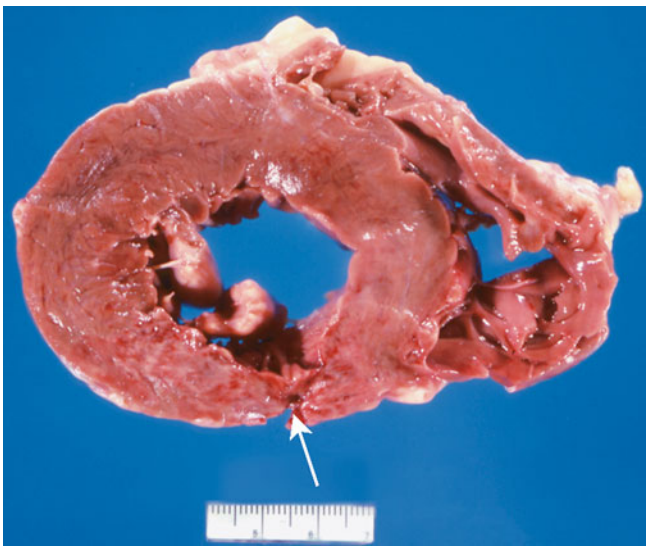

Fig. 1.15 Section of heart shows an acute transmural posterior myocardial infarct with an external rupture site (*arrow*) (From Buja and McAllister [3]. Reprinted with permission from Springer)

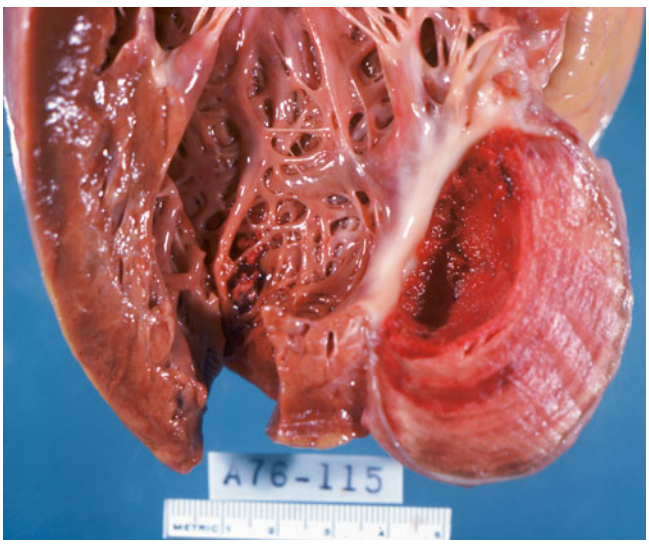

Fig. 1.16 Left ventricular aneurysm with mural thrombus resulting from healing of a transmural myocardial infarct (From Buja and McAllister [3]. Reprinted with permission from Springer)

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 [1–3].

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/or recurrent ventricular arrhythmias related to large infarct size (generally greater than 33–40 % of LV mass), papillary muscle dysfunction, papillary muscle rupture (Fig. 1.14), external cardiac rupture (Fig. 1.15), ventricular aneurysm (Fig. 1.16), ventricular pseudoaneurysm (due to sealing off of a relatively slowly evolving rupture), ventricular septal rupture, pericarditis (nonspecific and autoimmune, e.g., Dressler's syndrome) systemic embolization from an LV mural thrombus, and pulmonary thromboembolism [38–40].

The risk for infarct rupture is significant during the first week of MI before significant organization of the necrotic tissue [38–40]. 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 2–3 weeks. Thereafter, the granulation tissue is converted to a dense scar; this process is completed in 2–3 months.

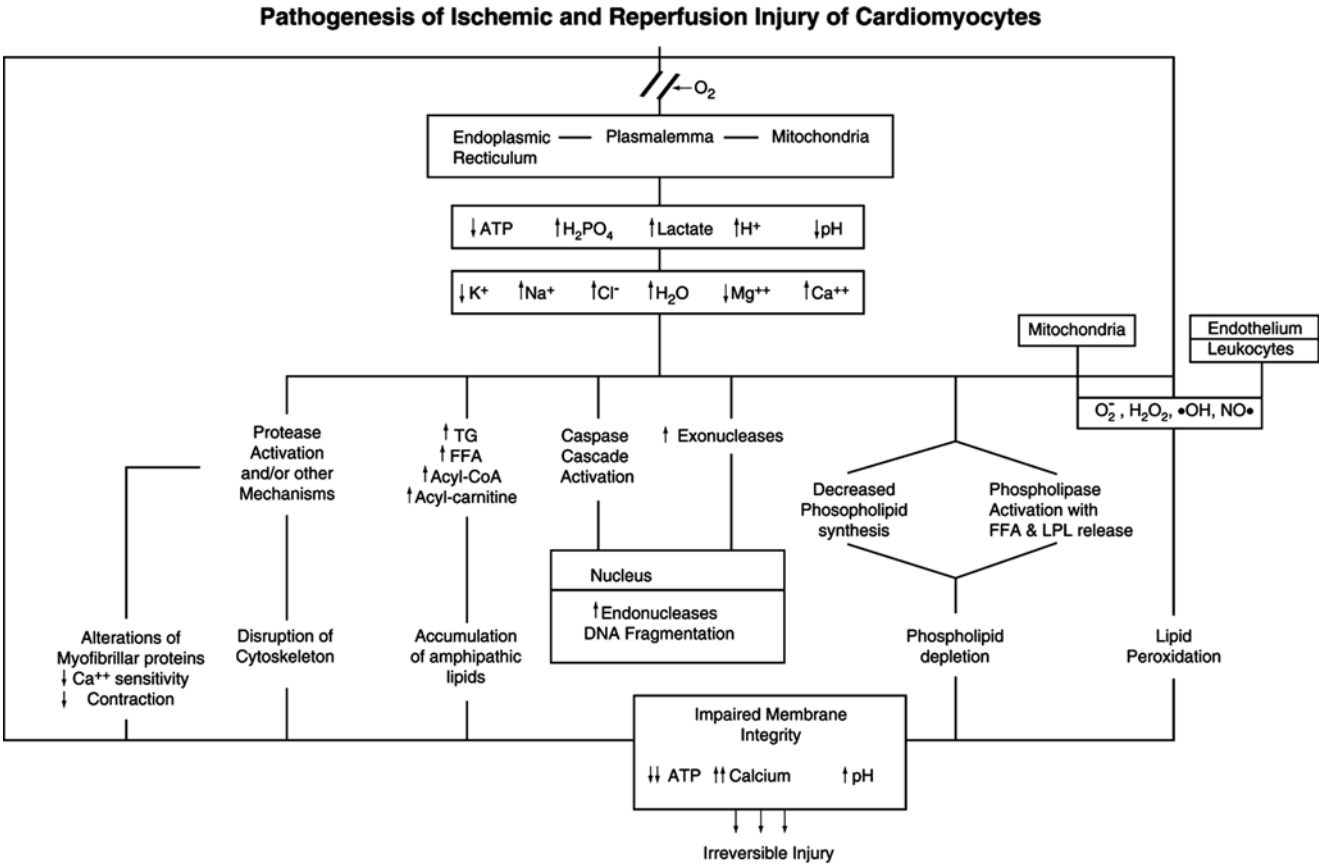

Fig. 1.17 Postulated sequence of alterations involved in the pathogenesis of irreversible myocardial ischemic injury and reperfusion injury. The potential exists for activation of apoptotic (caspase-mediated) and oncotic (multisystem metabolic) pathways in the same perturbed cardiomyocytes. Oxygen deficiency induces metabolic changes, including decreased ATP, decreased pH, and lactate accumulation, in ischemic myocytes. The irreversible phase of oncotic injury in energy depleted cardiomyocytes is mediated by severe membrane damage produced by phospholipid loss, lipid peroxidation and cytoskeletal damage. In cardiomyocytes with some preservation of ATP, activation of the caspase cascade can lead to a predominant apoptotic type of cell death. *FFA* free fatty acids, *LPL* lysophospolipids, *TG* triglycerides (From Buja and Weerashinghe [41]. Reprinted with permission from Elsevier Limited)

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. 1.17) [29, 35–37, 42–44]. As a result of oxygen deprivation, mitochondrial oxidative phosphorylation rapidly ceases, with resultant loss of the major source of 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 [29, 35].

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 [29]. The initial alteration is loss of intracellular K^+ due to increased efflux of the ion. Although the mechanism is unclear, it may involve activation of ATP-dependent K^+ channels due to change in the ATP/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^+ -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 [29]. Alterations in myofibrillar proteins leads to decreased sensitivity to Ca^{2+} resulting in impaired contractility in spite of the elevated cytosolic Ca^{2+} [44, 45]. As a result of the metabolic derangements, a key transitional event involves the opening of the mitochondrial permeability transition pore (mPTP) in the inner membrane of the

mitochondria. Opening of the mPTP causes immediate loss of the electrical potential difference across the inner membrane ($\Delta_{\Psi m}$) leading to cessation of ATP synthesis, influx of solute, and severe mitochondrial swelling [45, 46].

Advanced ischemic myocardial cell injury is mediated by progressive membrane damage involving several contributory factors (Fig. 1.17) [29, 37]. 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 species, including long-chain acyl 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 is physical disruption of the sarcolemma of the swollen myocyte [29, 37]. The progression and pattern of injury are impacted importantly by the extent of reperfusion [41, 47–49].

The sequence of abnormalities described above constitute the well documented pathophysiological 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 cardiomyocytes, as with other cells and tissues, are subject to three major modes of cell injury and death, namely, apoptosis (programmed cell death Type I), dysregulated autophagy (programmed cell death Type II), and oncosis (apparently passive cell death) [50–54]. Non-apoptotic cell death is commonly referred to as necrosis. But necrosis more precisely is defined as the final common pathway of cell degeneration following any mode of cell injury and death. Non-apoptotic oncotic cell death is increasingly being recognized to follow integrated and regulated steps, i.e., a different form of programmed injury. This has given rise to the use of new terms of programmed necrosis, necroptosis and Type III necrosis to characterize this process [52–54].

Following the recognition of apoptosis as a major and distinctive mode of cell death, reports have been published implicating apoptosis in myocardial infarction, reperfusion injury, and other forms of cardiovascular pathology [56]. Apoptosis is characterized by a series of integrated (programmed) molecular and biochemical events, including: (a) gene activation (programmed cell death); (b) perturbations of mitochondria, including membrane permeability transition and cytochrome c release; (c) activation of a cascade of cytosolic aspartate-specific cysteine proteases (caspases); (d) endonuclease activation leading to double-stranded DNA fragmentation; and (e) altered phospholipid distribution of cell membranes and other surface properties with preservation of selective membrane permeability [57–61]. Apoptosis can be triggered by activation of a death receptor pathway or a mitochondrial pathway [57–61]. Apoptosis is also characterized by distinctive morphological alterations featuring cell and nuclear shrinkage and fragmentation, with subsequent phagocytosis of apoptotic bodies by adjacent viable cells without exudative inflammation [45, 50, 51].

Apoptosis and oncosis are mediated by distinct but overlapping pathways involving cell surface death receptors, mitochondria and endoplasmic reticulum. The critical event in apoptosis is mitochondrial outer membrane permeabilization (MOMP) which promotes release of cytochrome c and other molecules leading to caspase activation. Conversely, the critical mitochondrial event in oncosis is early opening of the mitochondrial permeability transition pore (mPTP) in the inner membrane, which occurs without cytochrome c release [52–54]. The rate and magnitude of ATP reduction may be a critical determinant of whether an injured myocyte progresses to death by apoptosis or oncosis. Studies using caspase inhibitors and mutant mouse models indicate that apoptosis as well as oncosis contribute to the overall magnitude of ischemic necrosis, with the dominant mechanism being apoptosis and oncosis in approximately equal percentage of ischemic myocytes, respectively [41, 45, 60]. Apoptotic and oncotic mechanisms likely are operative in the same myocytes during progression to irreversible ischemic injury and necrosis [51]. 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 (Fig. 1.17) [41]. Thus, the cell injury and death induced by severe coronary blood flow reduction appears to represent a hybrid pattern best designated as ischemic cell injury and cell death. In contrast to primary oncotic necroptosis, secondary necrotic change follows apoptosis if the rapid removal of apoptotic bodies does not occur. In this event, necrotic events, such as loss of the mitochondrial membrane potential, can occur in close temporal relationship to cytochrome c release from the mitochondria [52–54].

Recently, autophagy has been identified as another mode of cell modulation that can contribute to various forms of ischemic injury [61, 62]. Autophagy, or macroautophagy, is an intracellular catabolic process involving the incorporation

of cytoplasmic proteins and intracellular organelles in double membrane-lined autophagosomes that fuse with lysosomes followed by degradation of the material. Controlled autophagy is important in the normal turnover of organelles. However, unregulated autophagy can lead to a form of cell death. Interactions between autophagy and apoptosis contribute to the myocardial response to acute and chronic ischemic injury [61, 62].

Determinants of Infarct Development and Size and Remodeling

After coronary artery occlusion, the myocardium can withstand up to about 20 min of severe ischemia without developing irreversible injury. However, after about 20–30 min of severe ischemia, irreversible myocardial injury begins [36, 37]. The subsequent degenerative changes give rise to recognizable myocardial necrosis (Fig. 1.13). 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 3–4 h, irreversible myocardial injury progresses in a wavefront pattern from the subendocardium into the subepicardium (Fig. 1.18) [36]. In the experimental animal and probably in humans as well, most MIs are completed within approximately 4 h after the onset of coronary occlusion. However, a slower pattern of evolution of MI can occur when the coronary collateral perfusion is abundant and/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. 1.19) [29, 37]. 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 peripheral 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.

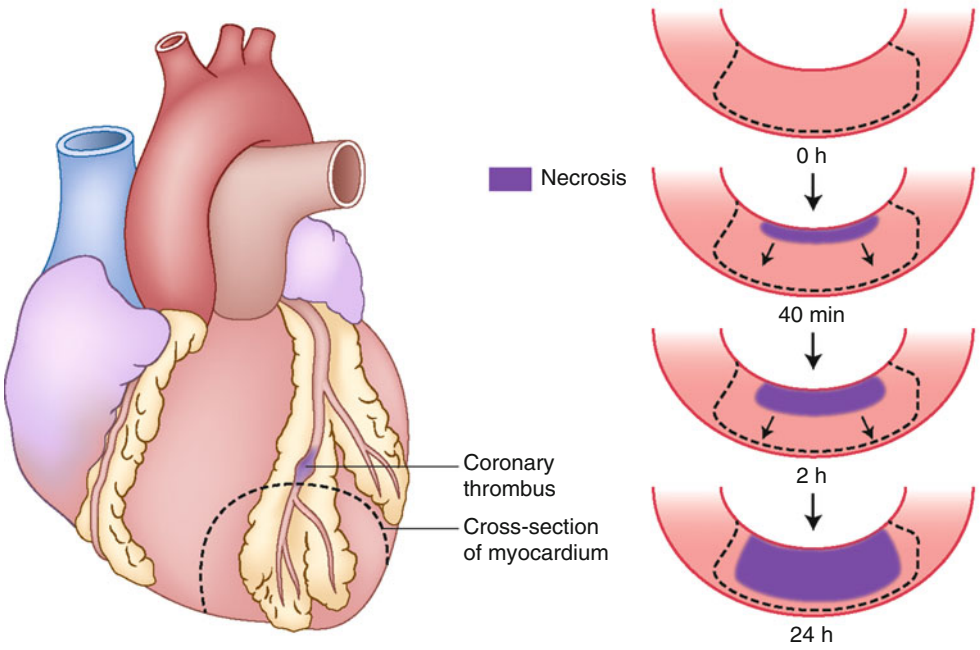

Fig. 1.18 Progression of cell death versus time as a wavefront of necrosis at various time intervals after coronary occlusion. Necrosis occurs first in the subendocardial myocardium. With longer intervals of occlusion, a wavefront of cell death moves from the subendocardial zone across the wall to involve 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 min after occlusion and are sharply defined by the anatomic boundaries of the ischemic bed (From Buja and McAllister [3]. Reprinted with permission from Springer)

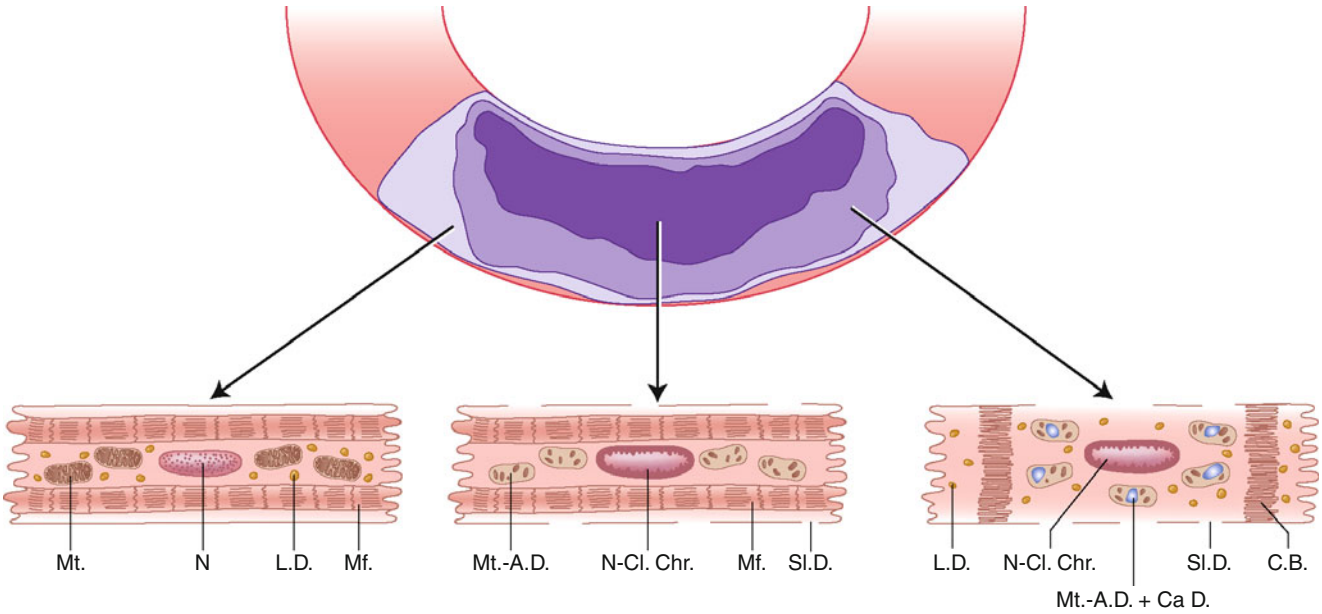

Fig. 1.19 Patterns of myocardial injury in an acute transmural myocardial infarct. *C.B.* myofibrillar contraction band, *L.D.* lipid droplet, *Mf.* myofibril, *Mt.* mitochondrion, *Mt.-A.D.* mitochondrion with amorphous matrix (flocculent) densities, *Mt.-A.D. + CaD.* mitochondrion with amorphous matrix densities and calcium phosphate deposits, *N.* nucleus, *N.-Cl. Chr.* nucleus with clumped chromatin, *Sl.D.* sarcolemmal defect (From Buja [43]. Reprinted with permission from Springer)

The ultrastructural features correlate with the three histopathological patterns of coagulation necrosis, coagulative myocytolysis (contraction band necrosis) and colliquative myocytolysis (myocytolysis) [1, 29].

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 (Fig. 1.18) [36]. 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. 1.18) [36, 37]. The bed-at-risk will also contain viable but injured myocardium. The border zone refers to the non-necrotic 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, involving activation of endogenous stem cells and/or division of pre-existing myocytes [17, 51, 62, 63]. 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 [64, 65].

Reperfusion, Preconditioning, Stunning, Postconditioning and Hibernation

A number of factors can significantly modulate the myocardial response and subsequent outcome following an ischemic episode [29]. The progression of myocardial ischemia can be

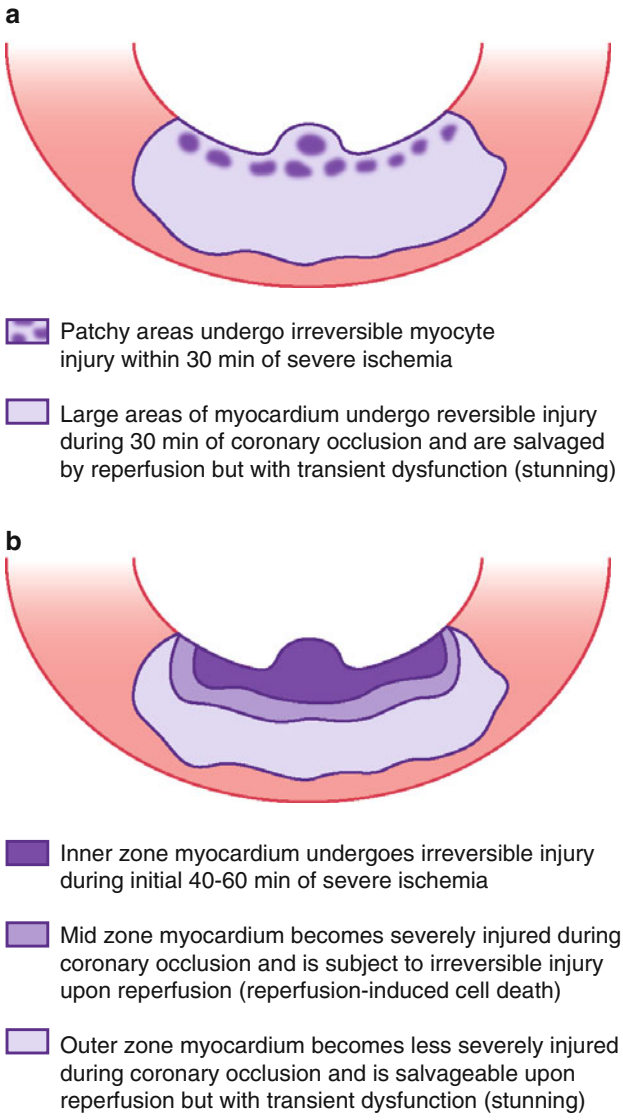

Fig. 1.20 Influences of duration of coronary occlusion and timing of reperfusion on the response of the ischemic myocardium. (**a**) When reperfusion is achieved within 30 min of coronary occlusion, minimal irreversible injury occurs and most of the ischemic myocardium is salvaged but with transient dysfunction (stunning). (**b**) When reperfusion occurs within 2 h 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 (From Buja [29]. Reprinted with permission from Nature Publishing Group)

profoundly influenced by reperfusion (Fig. 1.20). However, the effects of reperfusion are complex [41, 45, 47–49]. 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 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/or progression to cell death [29, 41, 45, 47–49]. Major mediators of reperfusion injury are oxygen radicals and neutrophils. The oxygen radicals are generated by injured myocytes and non-myocytes in the ischemic zone due to an oxidative burst upon reperfusion as well as neutrophils which can access to the ischemic zone and become activated upon reperfusion [45, 58–60]. The neutrophils also contribute to microvascular obstruction and the no-reflow phenomenon in the reperfused myocardium [29, 41, 45, 47–49].

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 60–90 min of coronary occlusion is significantly less in animals that had been pretreated with one or more 5-min intervals of coronary occlusion before the induction of permanent occlusion. However, after 120 min of coronary occlusion, the effect on infarct size is lost. This phenomenon is known as preconditioning (Fig. 1.21) [66]. A reduced rate of ATP depletion correlates with the beneficial effects of preconditioning [66]. Further studies have indicated that classical preconditioning involves activation of receptors for adenosine and other agonists, G-protein-coupled protein kinase C, and sarcolemmal and mitochondrial ATP-dependent potassium channels, with a key role for the mitochondrial K channels [67, 68]. 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) [69]. SWOP is related to ischemia-induced gene activation with production of various gene products, including superoxide dismutase, nitric oxide synthase, and stress (heat shock) proteins [67, 68]. 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 [69].

Prolonged functional depression, requiring up to 24 h or longer for recovery, develops on reperfusion even after relatively brief periods of coronary occlusion, on the order of

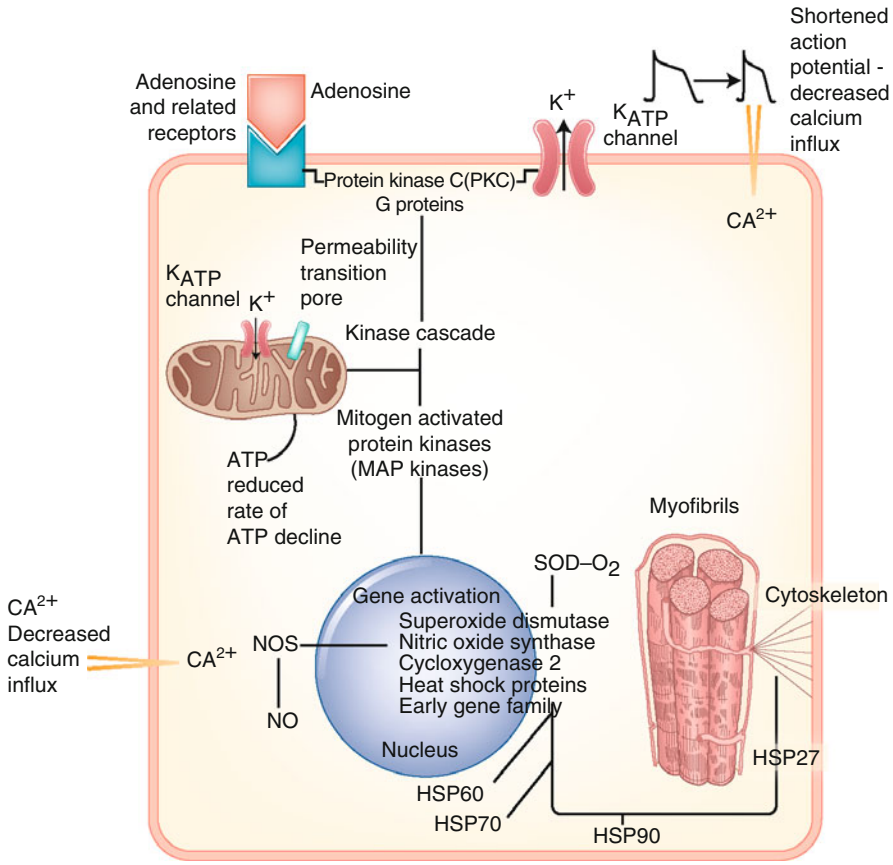

Fig. 1.21 Postulated mechanisms of early ischemic myocardial preconditioning and second window of protection. Brief periods of coronary occlusion lead to an initially slower rate of ATP decline and reduced rate of progression to irreversible injury and necrosis during subsequent prolonged coronary occlusion; 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 (NFκB). 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 (From Buja [29]. Reprinted with permission from Nature Publishing Group)

15 min, which are insufficient to cause myocardial necrosis. This phenomenon has been referred to as myocardial stunning [70]. A related condition, termed hibernation, refers to chronic depression of myocardial function owing to a chronic moderate reduction of perfusion [29, 49]. 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 [29, 45, 70]. After longer intervals of coronary occlusion, on the order of 2–4 h, necrosis of the subendocardium develops and even more severe and persistent functional depression occurs [71]. In experimental studies, after 2 h of coronary occlusion LV regional sites of moderate dysfunction during ischemia recovered normal or near-normal regional contractile function after 1–4 weeks of reperfusion, whereas after 4 h of coronary occlusion, contractile dysfunction persisted after 4 weeks of reperfusion [71]. Degenerative changes in cardiomyocytes develop in chronically underperfused, hibernating myocardium [29, 45]. These changes can influence the degree of functional recovery upon complete restoration of blood flow.

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 [29, 41, 47–50]. 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.

Therapeutic Interventions to Limit Ischemic Damage

Continuing efforts have been made to develop therapeutic approaches to limiting infarct size since the extent of myocardial necrosis is a major determinant of prognosis following myocardial infarction. Experimental studies have shown that evaluation of a therapeutic agent should take into account both the influence of the size of the myocardial bed-at-risk and the amount of collateral perfusion over a given time interval of coronary occlusion (Fig. 1.22) [29, 40, 42]. If an intervention produces a smaller infarct as a percentage of the bed-at-risk at any given level of residual perfusion, then it can be concluded that the intervention has an independent effect on myocardial ischemic cell injury. Various pharmacological approaches have been aimed at improving myocardial metabolism, increasing myocardial blood flow, reducing cellular calcium overload and preventing free radical-mediated effects (Table 1.2) [29, 41, 42, 45–49]. In spite of the promise of experimental studies, demonstration of major reduction of infarct size by pharmacological means has not been forthcoming in man [48, 49].

Recent studies have documented that reperfusion also leads to activation of a group of protein kinases that act to promote cell survival and, therefore constitute a reperfusion injury salvage kinase (RISK) pathway [41, 45, 49]. One intermediate pathway involves phosphatidylinositol-3 kinase (PI-3K) acting on Akt and the mammalian target of rapamycin (MTOR). The other involves mitogen-associated protein kinase (MAPK) and p42/p44 extracellular signal-regulated kinase (ERK). The pathways converge on p70s6 kinase which activates glycogen synthase kinase ß which acts to prevent opening of the mitochondrial PTP. Activation of the RISK pathway exerts effects on inhibiting the mitochondrial PTP opening, enhanced uptake of calcium into the sarcoplasmic reticulum, and activation of antiapoptotic pathways. The RISK pathway appears to represent a mechanism for programmed cell survival (Table 1.3).

The most important clinical advance in recent years has been the advent of percutaneous coronary (PCI) interventions, including thrombolytic therapy and stent placement, to provide reperfusion of the ischemic myocardium. This approach is the hallmark of the current era of treatment of acute myocardial infarction. Ongoing investigations are aimed at developing pharmacological interventions which can be coupled with thrombolytic therapy to provide optimal protection and salvage of the ischemic myocardium [72–77]. Control and treatment of arrhythmias and conduction disturbances include both pharmacological approaches, pacemakers and defibrillators.

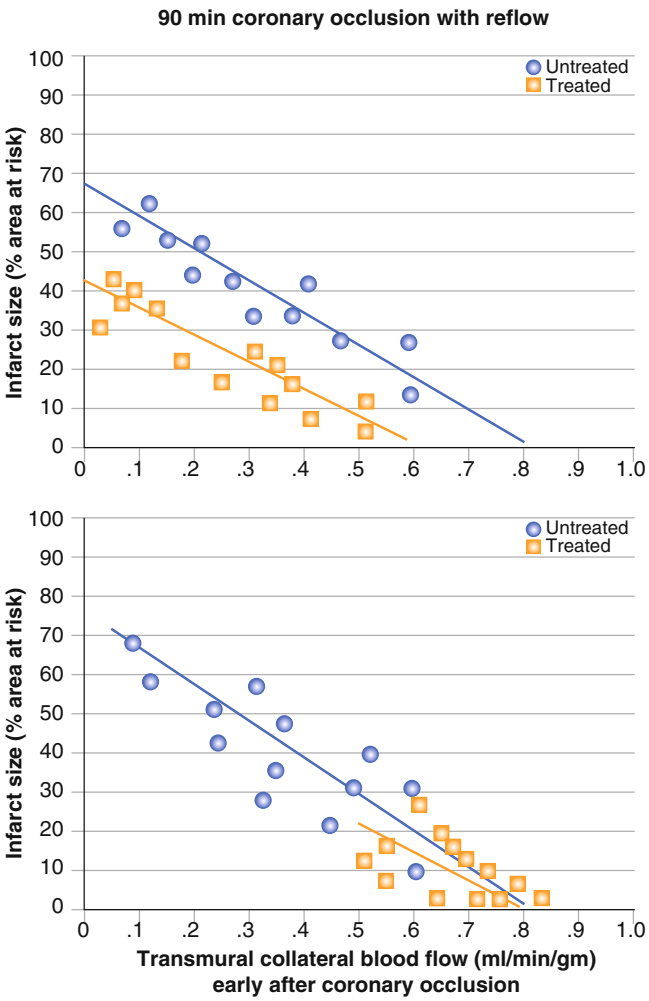

Fig. 1.22 Theoretical outcomes of experiments performed to determine the potential effect of an intervention on limiting infarct size after 90 min of temporary coronary occlusion and reperfusion in the dog. Infarct size, expressed as a percentage of the area at risk, is plotted against transmural collateral blood flow measured shortly after coronary occlusion. Smaller infarct size at any level of residual collateral blood flow is shown in the treated versus untreated group (*top*). This result supports the conclusion that the intervention reduced infarct size by a direct effect on the ischemic myocytes without affecting coronary blood flow. The treated group had smaller infarcts associated with greater collateral blood flow compared with the untreated group (*bottom*). This result supports the conclusion that the intervention reduced infarct size by increasing collateral blood flow and decreasing the severity of ischemia rather than by a direct effect on the ischemic myocytes. Alternatively, this result could have occurred by bias in selecting animals with greater native collaterals for the treated group (From Buja and Willerson [42]. Reprinted with permission from Elsevier Limited)

Table 1.2 Previous problematic approaches to reduce lethal reperfusion injury in patients with acute myocardial infarction

Antioxidants
Reduction of intracellular Ca^{2+} overload and Na^{+}-H^{+} exchange inhibitors
Anti-inflammatory agents
Adenosine
Metabolic modulation (glucose, insulin, and potassium)
Magnesium
Nicorandil
Therapeutic hypothermia

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Table 1.3 New cardioprotective strategies for reducing lethal reperfusion injury in patients with acute myocardial infarction

Ischemic postconditioning
Remote ischemic postconditioning
RISK pathway activators
Atrial natriuretic peptide
Glucagon-like peptide 1
Darbepoetin alfa (long-acting erythropoietin analogue)
Atorvastatin
Protein kinase c-delta inhibitor (KAI-9803)
Mitochondrial PTP inhibition
Cyclosporin
Other

From Buja and Weerashinghe [41]. Reprinted with permission from Elsevier Limited
RISK reperfusion injury salvage kinase pathway, *PTP* permeability transition pore

Pathology of Interventionally Treated Coronary Artery Disease

Myocardial revascularization by coronary artery bypass graft (CABG) surgery has been employed for many years. The responses of various types of grafts have been established. Saphenous vein coronary artery bypass grafts (SVCABG) develop diffuse fibrocellular intimal thickening, medial degeneration and atrophy, and vascular dilatation within several months after implantation (Figs. 1.23 and 1.24) [78, 79]. Subsequently, the grafts are prone to development of eccentric intimal plaques with lipid deposition (atherosclerosis) [79]. Plaque fissuring and thrombosis also may develop (Figs. 1.25 and 1.26). 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 (internal thoracic) arteries for coronary bypass has taken on more widespread

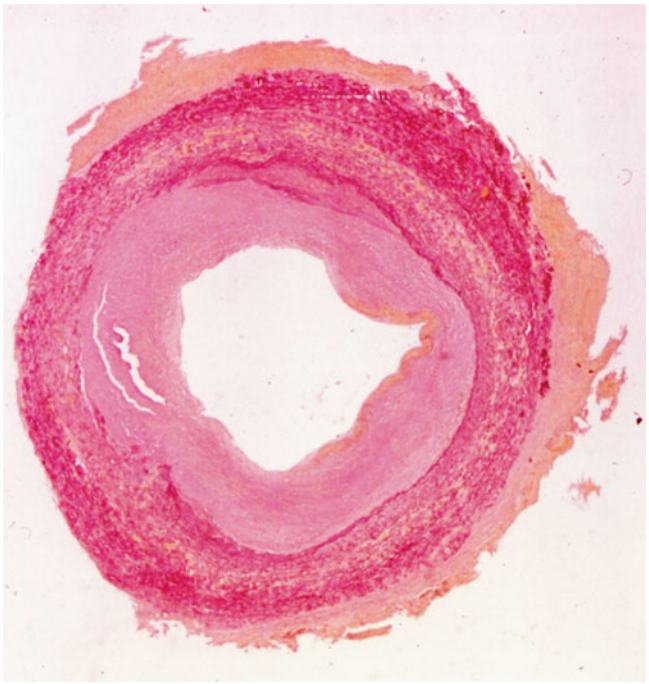

Fig. 1.23 Saphenous vein-coronary artery bypass graft implanted for several months. The vein graft shows diffuse concentric fibromuscular intimal thickening. Low power photomicrograph (From Buja and McAllister [3]. Reprinted with permission from Springer)

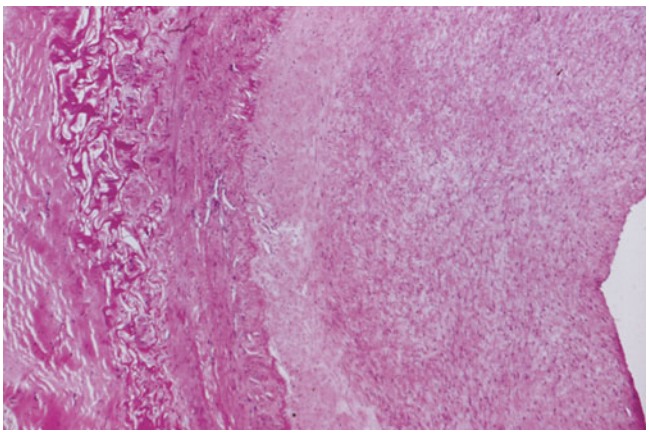

Fig. 1.24 Further detail of the fibrocellular intimal proliferation in a saphenous vein-coronary artery bypass graft. Medium power photomicrograph (From Buja and McAllister [3]. Reprinted with permission from Springer)

application [80, 81]. 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 [80, 81]. Other free arterial conduits also are being used [80, 81].

A variety of catheter-based interventional approaches have been explored to reduce coronary atherosclerotic

Fig. 1.25 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 (From Willerson et al. [1]. Reprinted with permission from Wolters Kluwer)

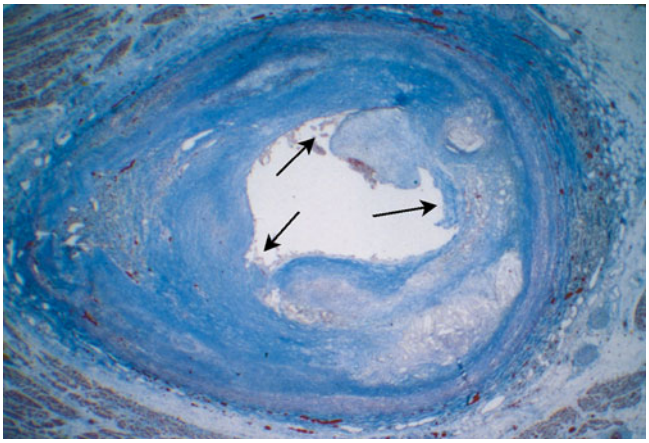

Fig. 1.27 Coronary artery after percutaneous transluminal coronary angioplasty shows areas of plaque disruption (*arrows*) with microthrombus on the surface. Low magnification photomicrograph (From Buja and McAllister [3]. Reprinted with permission from Springer)

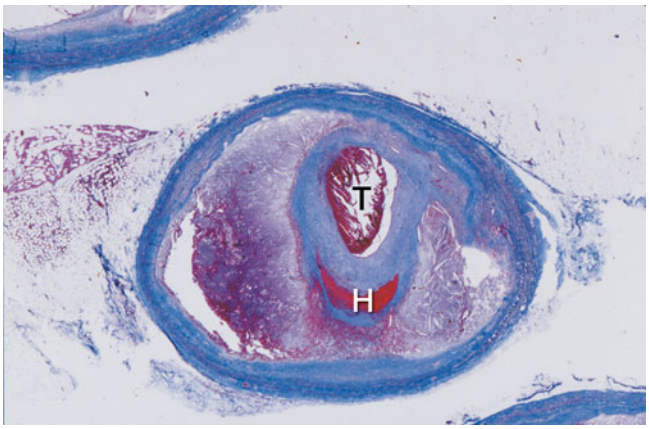

Fig. 1.26 This segment of vein graft is involved by a large atheroma with lipid-laden core and thin fibrous capsule. Hemorrhage is present in the plaque core (*H*). The lumen is occluded by recent thrombus (*T*). Low power photomicrograph (From Willerson et al. [1]. Reprinted with permission from Wolters Kluwer)

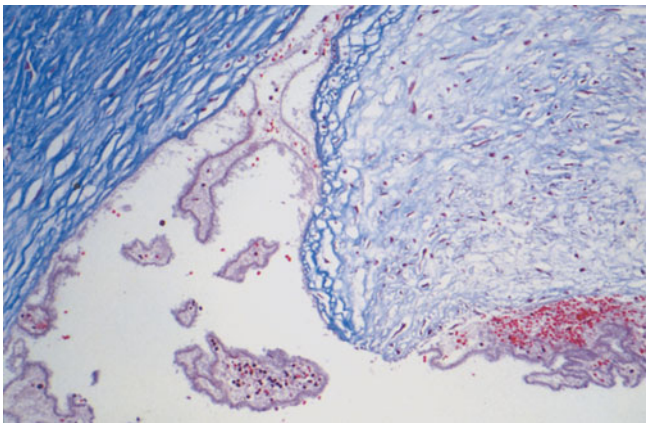

Fig. 1.28 Close up view of microthrombus on surface of a fissured plaque following percutaneous transluminal coronary angioplasty. High magnification phtomicrograph (From Buja and McAllister [3]. Reprinted with permission from Springer)

stenosis and relieve myocardial ischemic symptoms [82–84]. 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. 1.27 and 1.28) [85–89]. The acute injury initiates a reparative response which leads to intimal proliferation [85–89]. Similar effects occur after atherectomy and laser angioplasty. The resultant fibrocellular tissue is composed of modified smooth muscle cells (myofibroblasts) and connective tissue matrix without lipid deposits. Experimental evidence supports a role for platelet activation in the pathogenesis of the lesion [90]. This process of intimal proliferation leads to restenosis of lesions in 30–40 % 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. Bare metal stents have been used to treat patients with symptomatic angina pectoris as well as patients with a major acute coronary syndrome (Fig. 1.29). Drug-eluting stents have improved long-term outcomes [86, 87]. However, coronary arteries with drug eluting stents are subject to late thrombosis due to incomplete endothelial healing and replacement. They also are subject to intimal proliferation (Fig. 1.30). Secondary atheromatous change can also develop [87–89].

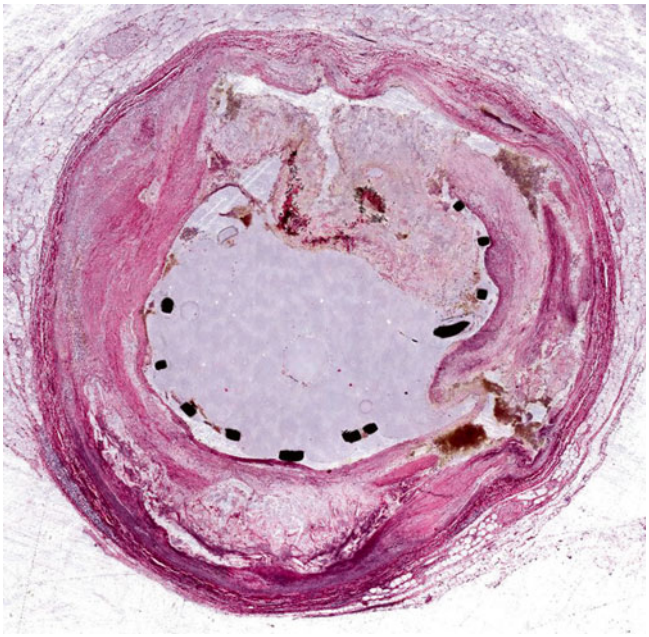

Fig. 1.29 Coronary artery with acute coronary plaque rupture and drug-eluting (paclitaxel) coronary stent in place. A specialized technique was used to prepare the specimen shown in this figure and Fig. 1.33. See: Clubb et al. [88]

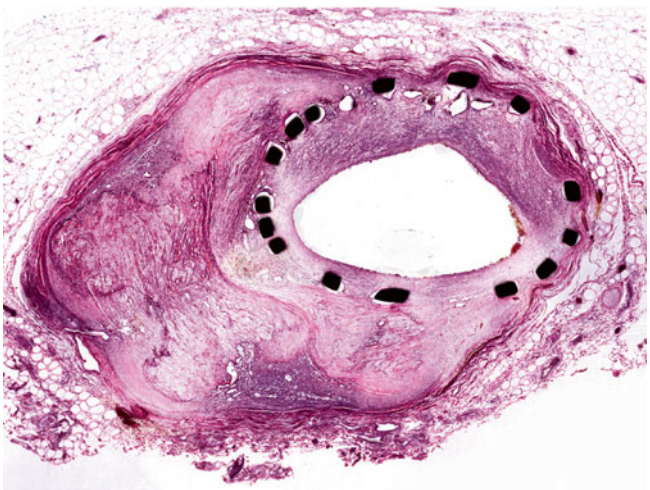

Fig. 1.30 Coronary artery with bare metal stent in place for 2 years shows variability in the arrangement of the stent struts and evidence of intimal proliferation and luminal narrowing in response to the angioplasty and stent placement. Note the irregular spacing of the struts of the stent

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 [91–93]. Alternative approaches are being explored for the treatment of intractable angina pectoris, including the intravascular delivery of genetically engineered growth factors, including VEGF and FGF [94, 95]. The debate regarding whether or not the myocardium is composed of terminally differentiated cardiac myocytes has been revived [51, 62, 96]. 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 [51, 96]. Bone marrow derived stem cells also have the potential to differentiate into mature cardiac cells when these cells home to the myocardium or are injected, particularly after myocardial injury. These insights have opened the promising field of regenerative cardiology. Initially, some positive results have been obtained with the use of autologous stem cells for the treatment of patients with MI and heart failure [97, 98]. While these approaches have considerable promise for the treatment of ischemic myocardial disease, pitfalls have been identified [98]. Much is yet to be determined about the effects of stem cells on the pathobiology of the myocardium [99, 100].

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