



ST-Elevation Myocardial Infarction: Pathology, Pathophysiology, and Clinical Features

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Pathologic diagnosis of myocardial infarction (MI) requires evidence of myocardial cell death caused by ischemia. Characteristic findings include coagulation necrosis and contraction band necrosis, often with patchy areas of myocytolysis at the periphery of the infarct. During the acute phase of MI, myocytes die in the infarct zone, with subsequent inflammation, clearance of necrotic debris, and repair eventually in scar formation.

Clinical diagnosis of MI requires a clinical syndrome indicative of myocardial ischemia with some combination of evidence of myocardial necrosis on biochemical, electrocardiographic, or imaging modalities. The sensitivity and specificity of the clinical tools for diagnosing MI vary considerably depending on the timing of evaluation after the onset of infarction. Cardiac professional societies have jointly established updated criteria for the diagnosis of MI (**Table 51-1**).¹ The revised universal definition of myocardial infarction classifies MI into five types, depending on the circumstances in which the MI occurs (**Table 51-2**).¹ These revisions to the definition of MI and a shift to more sensitive biomarkers of myocardial injury have important implications not only for the clinical care of patients but also for epidemiologic study, public policy, and clinical trials.^{2,3}

The contemporary approach to patients with ischemic discomfort is to consider them to be experiencing an acute coronary syndrome (ACS), which encompasses the diagnoses of unstable angina, non-ST-segment elevation MI (NSTEMI), and ST-segment elevation MI (STEMI) (**Fig. 51-1**). The principal diagnostic tool for patients with suspected ACS is the 12-lead electrocardiogram (ECG), which discriminates those with ST-segment elevation, the subject of **Chapters 51 and 52**, and those without ST-segment elevation, the subject of **Chapter 53**.

CHANGING PATTERNS IN INCIDENCE AND CARE

Despite advances in diagnosis and management, STEMI remains a major public health problem in the industrialized world and is on the rise in developing countries (see **Chapter 1**).⁴ In the United States, almost 600,000 patients are admitted to the hospital each year with a primary diagnosis of ACS. The number exceeds 1 million with the inclusion of ACS as a secondary diagnosis.⁵ The rate of MI rises sharply in both men and women with increasing age, and racial differences exist, with MI occurring more frequently in black men and women regardless of age. The proportion of patients with ACS events who have STEMI varies across observational studies—from 29% to 47% of patients admitted with ACS. This estimate does not include “silent” MI, which may not prompt hospitalization. Between 1999 and

2008, the proportion of patients with an ACS and STEMI declined by almost 50% (**Fig. 51-2A**; see also Fig. 53-2).⁶

Of particular concern from a global perspective, the burden of MI in developing countries may be approaching that now afflicting developed countries.⁴ The limited resources available to treat STEMI in developing countries mandate major international efforts to strengthen primary prevention programs (see also **Chapter 1**).

IMPROVEMENTS IN OUTCOME

The overall number of deaths from STEMI has declined steadily over the past 30 years, but it has stabilized over the past decade (**Fig. 51-2B**).⁶⁻⁹ Both a decreased incidence of STEMI and a decline in the case fatality rate after STEMI have contributed to this trend.⁵ According to estimates from the American Heart Association, the short-term mortality rate of patients with STEMI ranges from 5% to 6% during the initial hospitalization and from 7% to 18% at 1 year.¹⁰ Mortality rates in clinical trial populations tend to be approximately half of those observed in registries of consecutive patients, most likely because of the exclusion of patients with more extensive comorbid medical conditions.

Improvements in the management of patients with STEMI have occurred in several phases.¹¹ The “clinical observation phase” of coronary care consumed the first half of the 20th century and focused on detailed recording of physical and laboratory findings, with little active treatment of the infarction. The “coronary care unit phase” began in the mid-1960s and emphasized early detection and management of cardiac arrhythmias based on the development of monitoring and cardioversion/defibrillation capabilities. The “high-technology phase,” heralded by the introduction of the pulmonary artery balloon flotation catheter, set the stage for bedside hemodynamic monitoring and directed hemodynamic management. The modern “reperfusion era” of STEMI care began with intracoronary and then intravenous fibrinolysis, increased use of aspirin (see **Chapter 52**), and subsequently the development of primary percutaneous coronary intervention (PCI) (see **Chapter 55**).

Contemporary care of patients with STEMI has entered an “evidence-based coronary care phase,” which is increasingly being influenced by guidelines and performance measures for clinical practice.^{10,12,13} Implementation of guideline-directed medical treatment (GDMT) and regional quality initiatives has significantly decreased heterogeneity in care, increased compliance with evidence-based therapies, and improved outcomes.^{14,15} Mandatory outcome and procedural reporting has resulted in the establishment of benchmarks for procedural success and mortality rates in patients with MI cared for at various hospitals (www.hospitalcompare.hhs.gov).

**TABLE 51-1** Universal Definition of Myocardial Infarction**Criteria for Acute Myocardial Infarction**

The term *acute MI* should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any of the following criteria meet the diagnosis for MI:

- Detection of a rise and/or fall in cardiac biomarker values (preferably cTn), with at least one value above the 99th percentile of the URL and with at least one of the following:
 - Symptoms of ischemia
 - New or presumed new significant ST-segment T wave (ST-T) changes or new LBBB
 - Development of pathologic Q waves on the ECG
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
 - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic changes on the ECG or new LBBB but death occurred before cardiac biomarkers were determined or before cardiac biomarker values would be increased.
- PCI-related MI is arbitrarily defined by elevation of cTn values ($>5 \times$ the 99th percentile of the URL) in patients with normal baseline values (≤ 99 th percentile of the URL) or a rise in cTn values $>20\%$ if the baseline values are elevated and are stable or falling. In addition, either (1) symptoms suggestive of myocardial ischemia, (2) new ischemic changes on the ECG, (3) angiographic findings consistent with a procedural complication, or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall in cardiac biomarker values and at least one value higher than the 99th percentile of the URL.
- CABG-related MI is arbitrarily defined by elevation of cardiac biomarker values ($>10 \times$ the 99th percentile of the URL) in patients with normal baseline cTn values (≤ 99 th percentile of the URL). In addition, either (1) new pathologic Q waves or new LBBB, (2) angiographically documented new graft or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality is required.

Criteria for Previous Myocardial Infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathologic Q waves with or without symptoms in the absence of nonischemic causes
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract in the absence of a nonischemic cause
- Pathologic findings of previous MI

CABG = coronary artery bypass grafting; cTn = cardiac troponin; LBBB = left bundle branch block; URL = upper reference limit.

From Thygesen K, Alpert JS, White HD, et al: *Universal definition of myocardial infarction*. *J Am Coll Cardiol* 60:1581, 2012.

TABLE 51-2 Universal Myocardial Infarction Classification of Type**Type 1: Spontaneous Myocardial Infarction**

Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries that leads to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion nonobstructive or no CAD.

Type 2: Myocardial Infarction Secondary to Ischemic Imbalance

In instances of myocardial injury with necrosis in which a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachyarrhythmias/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LV hypertrophy.

Type 3: Myocardial Infarction Resulting in Death When Biomarker Values Are Unavailable

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic changes on the ECG or new LBBB but death occurring before blood samples could be obtained, before cardiac biomarkers could rise, or in rare cases, when cardiac biomarkers were not collected.

Type 4a: Myocardial Infarction Related to Percutaneous Coronary Intervention

MI associated with PCI is arbitrarily defined by elevation of cTn values to $>5 \times$ the 99th percentile of the URL in patients with normal baseline values (≤ 99 th percentile of the URL) or a rise in cTn values $>20\%$ if the baseline values are elevated and are stable or falling. In addition, either (1) symptoms suggestive of myocardial ischemia, (2) new ischemic changes on the ECG or new LBBB, (3) angiographic loss of patency of a major coronary artery or a side branch or persistent slow flow or no flow or embolization, or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.

Type 4b: Myocardial Infarction Related to Stent Thrombosis

MI associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall in cardiac biomarkers values with at least one value above the 99th percentile of the URL.

Type 5: Myocardial Infarction Related to Coronary Artery Bypass Grafting

MI associated with CABG is arbitrarily defined by elevation of cardiac biomarker values to $>10 \times$ the 99th percentile of the URL in patients with normal baseline cTn values (<99 th percentile of the URL). In addition, either (1) new pathologic Q waves or new LBBB, (2) angiographically documented new graft or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality is required.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; cTn = cardiac troponin; LBBB = left bundle branch block; URL = upper reference limit.

From Thygesen K, Alpert JS, White HD, et al: *Universal definition of myocardial infarction*. *J Am Coll Cardiol* 60:1581, 2012.

Limitations of Current Therapy

Rates of appropriate initiation of reperfusion therapy vary widely, with up to 30% of patients with STEMI who are eligible to receive reperfusion therapy not receiving this lifesaving treatment in some registries.¹⁶ Therefore initiatives to increase timely administration of guideline-directed reperfusion therapy are important to achieve improvements in care (see Chapter 52).

Advanced age is a principal determinant of mortality in patients with STEMI.^{17,18} Cardiac catheterization and other invasive procedures are being performed more commonly during hospitalization in elderly patients with STEMI. Nevertheless, evidence suggests that the greatest reductions in mortality in elderly patients are gained by strategies used during the first 24 hours, a time frame in which prompt and appropriate use of lifesaving reperfusion therapy is

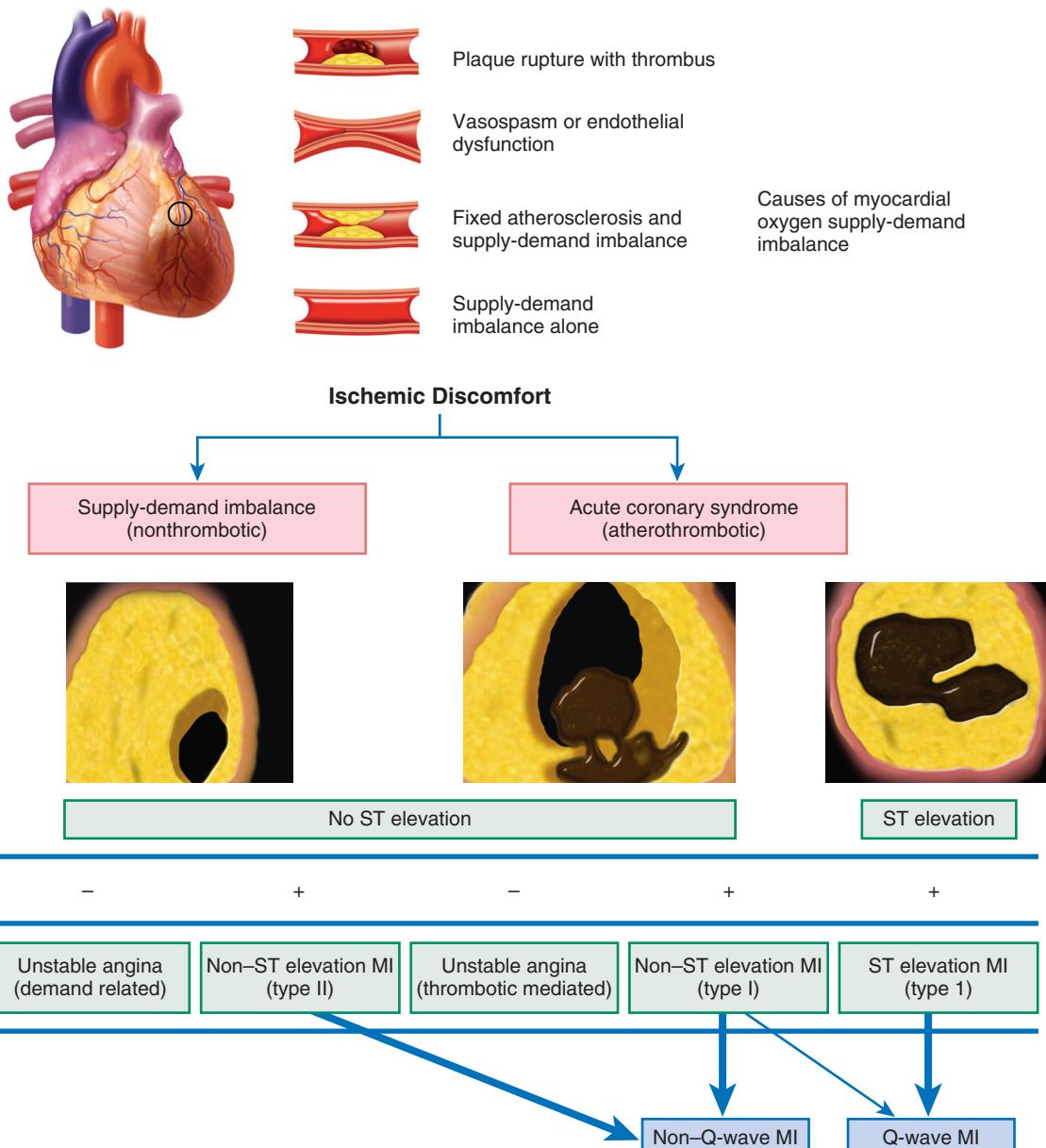


FIGURE 51-1 Myocardial ischemia and infarction. Myocardial ischemia and infarction can result from various coronary disease processes, including vasospasm, increased myocardial demand in the setting of a fixed coronary lesion, and erosion or rupture of vulnerable atherosclerotic plaque leading to acute thrombus formation and subsequent ischemia. All result in myocardial oxygen supply-demand mismatch and can precipitate ischemic symptoms, and all processes, when severe or prolonged, will lead to myocardial necrosis or infarction. Nonthrombotically mediated events (bottom half, left side) typically occur without ST-segment elevations on the ECG but can have elevated levels of cardiac biomarkers if the ischemia is severe and long enough, in which case they are classified as having type II MI. The atherothrombotic lesion is the hallmark pathobiologic event of an ACS. The reduction in flow may be caused by a completely occlusive thrombus (bottom half, right side) or by a subtotally occlusive thrombus (bottom half, middle). Ischemic discomfort may occur with or without ST-segment elevation on the ECG. Of patients with ST-segment elevation, Q-wave MI ultimately develops in most, whereas non-Q-wave MI develops in a few. Patients without ST-segment elevation are suffering from either unstable angina or NSTEMI, a distinction that is ultimately made by the presence or absence of a serum cardiac marker such as CK-MB or cardiac troponin detected in blood. Non-Q-wave MI ultimately develops in most patients with NSTEMI on the ECG; Q-wave MI may develop in a few. MI that develops as the result of the atherothrombotic lesion of an ACS is classified as type I MI. (Modified from Thygesen K, Alpert JS, Jaffe AS, et al: Third universal definition of myocardial infarction. *J Am Coll Cardiol* 60:1581, 2012.)

paramount—thus emphasizing the need to extend advances in GDMT for STEMI to older adults.¹⁹

Management and outcomes of patients with STEMI appear to vary substantially depending on the volume of such patients cared for within a hospital system.^{20,21} Mortality rates in patients with STEMI are lower in hospitals with a high clinical volume, a high rate of invasive procedures, and a top ranking in quality reports. Conversely, patients with STEMI not cared for by a cardiovascular specialist have higher mortality rates. Variation also occurs in the treatment patterns of certain population subgroups with STEMI, notably women and blacks, although after adjusting for comorbid

conditions and the degree of atherosclerosis, outcomes appear to be similar.²²

PATHOLOGIC FINDINGS

Based on research beginning in the 1970s, we now recognize that almost all ACS events result from coronary atherosclerosis, generally with superimposed coronary thrombosis caused by rupture or erosion of an atherosclerotic lesion.^{23,24} Nonatherogenic forms of coronary artery disease are discussed later in this chapter, and causes of MI without coronary atherosclerosis are presented in Table 51-3.

TABLE 51-3 Causes of Myocardial Infarction Without Coronary Atherosclerosis

Coronary Artery Disease Other than Atherosclerosis	
Arteritis	
Luetic	
Granulomatous (Takayasu disease)	
Polyarteritis nodosa	
Mucocutaneous lymph node (Kawasaki) syndrome	
Disseminated lupus erythematosus	
Rheumatoid spondylitis	
Ankylosing spondylitis	
Trauma to coronary arteries	
Laceration	
Thrombosis	
Iatrogenic	
Radiation (radiation therapy for neoplasia)	
Coronary mural thickening with metabolic disease or intimal proliferative disease	
Mucopolysaccharidoses (Hurler disease)	
Homocystinuria	
Fabry 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 angina with normal coronary arteries)	
Spasm after nitroglycerin withdrawal	
Dissection of the aorta	
Dissection of the coronary artery	
Emboli to Coronary Arteries	
Infective endocarditis	
Nonbacterial thrombotic endocarditis	
Prolapse of the mitral valve	
Mural thrombus from the left atrium, left ventricle, or pulmonary veins	
Prosthetic valve emboli	
Cardiac myxoma	
Associated with cardiopulmonary bypass surgery and coronary arteriography	
Paradoxical emboli	
Papillary fibroelastoma of the aortic valve ("fixed embolus")	
Thrombi from intracardiac catheters or guidewires	
Congenital Coronary Artery Anomalies	
Anomalous origin of the left coronary from the pulmonary artery	
Left coronary artery from the anterior sinus of Valsalva	
Coronary arteriovenous and arteriocameral fistulas	
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	
Takotsubo cardiomyopathy	
Hematologic (In Situ Thrombosis)	
Polycythemia vera	
Thrombocytosis	
Disseminated intravascular coagulation	
Hypercoagulability, thrombosis, thrombocytopenic purpura	
Miscellaneous	
Cocaine abuse	
Myocardial contusion	
Myocardial infarction with normal coronary arteries	
Complication of cardiac catheterization	

Modified from Cheitlin MD, McAllister HA, de Castro CM: Myocardial infarction without atherosclerosis. *JAMA* 231:951, 1975. Copyright 1975, American Medical Association.

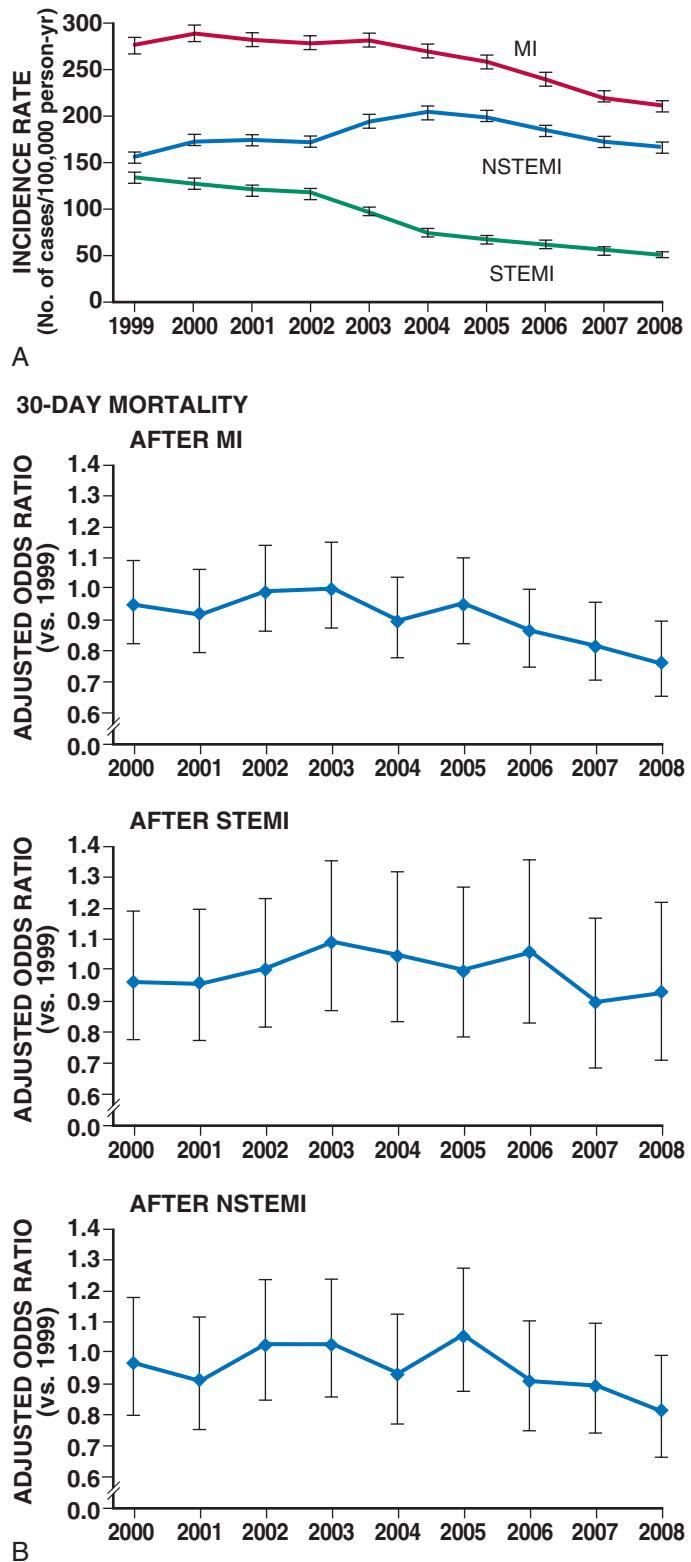


FIGURE 51-2 **A**, Age- and sex-adjusted incidence rates of acute MI from 1999 to 2008. *I* bars represent 95% confidence intervals. **B**, Adjusted odds ratios are shown for 30-day mortality according to year after any MI (**B**, top), STEMI (**B**, middle), and NSTEMI (**B**, bottom). Models were adjusted for patient demographic characteristics, previous cardiovascular disease, cardiovascular risk factors, chronic lung disease, and systemic cancer. The reference year is 1999. See also Figure 53-2. (From Yeh RW, Sidney S, Chandra M, et al: Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med* 362:2155, 2010.)

When acute coronary atherosclerotic thrombosis occurs, the resulting intracoronary thrombus may be partially obstructive, which generally leads to myocardial ischemia in the absence of ST-segment elevation, or be completely occlusive and cause transmural myocardial ischemia and STEMI. Before the fibrinolytic era, clinicians typically divided patients with MI into those in whom a Q wave developed on the ECG and those with non-Q-wave MI based on evolution of the ECG pattern over several days. The term *Q-wave infarction* was frequently considered to be virtually synonymous with *transmural infarction*, whereas *non-Q-wave infarctions* were often referred to as *subendocardial infarctions*. Contemporary studies using cardiac magnetic resonance (CMR) indicate that the development of a Q wave on the ECG is determined more by the size of the infarct than by the depth of mural involvement. Thus use of ACS as the more appropriate broad conceptual framework has replaced this terminology, anchored by the underlying unifying pathophysiology (see Fig. 51-1). Further classification of patients by the presence of ST-segment elevation (STEMI) or by its absence (non-ST-segment elevation ACS) rather than by the evolution of Q waves is preferable because immediate clinical decisions such as fibrinolysis or primary PCI depend on identification of diagnostic ST-segment elevation on the initial ECG.

Plaque (See also Chapter 41)

Atherosclerotic plaque begins early in life and grows slowly over decades.²⁵ Evidence of some atherosclerosis is almost ubiquitous in the modern world, yet most plaque remains asymptomatic throughout a lifetime. Other plaques may develop slowly and elicit stable symptoms. Plaque that precipitates an ACS event through the abrupt and catastrophic transition from a vulnerable, yet stable plaque to an unstable one characterized by plaque disruption or erosion and then subsequent overlying thrombosis is rare.^{23,26} Traditional risk factors and consequent chronic inflammation promote much of the development of atherosclerosis, although some patients have a systemic predisposition to plaque disruption that is independent of traditional risk factors. Plaque disruption exposes substances that promote platelet activation and aggregation, thrombin generation, and ultimately thrombus formation.^{23,26} The resultant thrombus interrupts blood flow and leads to an imbalance between oxygen supply and demand and, if this imbalance is severe and persistent, to myocardial necrosis (Fig. 51-3).

Composition of Plaque

The atherosclerotic plaque associated with total thrombotic occlusion of an epicardial coronary artery, located in infarct-related vessels, is generally more complex and irregular than the plaque in vessels not associated with STEMI.^{23,26} Histologic studies of these lesions often reveal plaque rupture or erosion (see Chapter 41). Thrombus composition may vary at different levels: white thrombi contain platelets, fibrin, or both, and red thrombi contain erythrocytes, fibrin, platelets, and leukocytes (see Chapter 82).

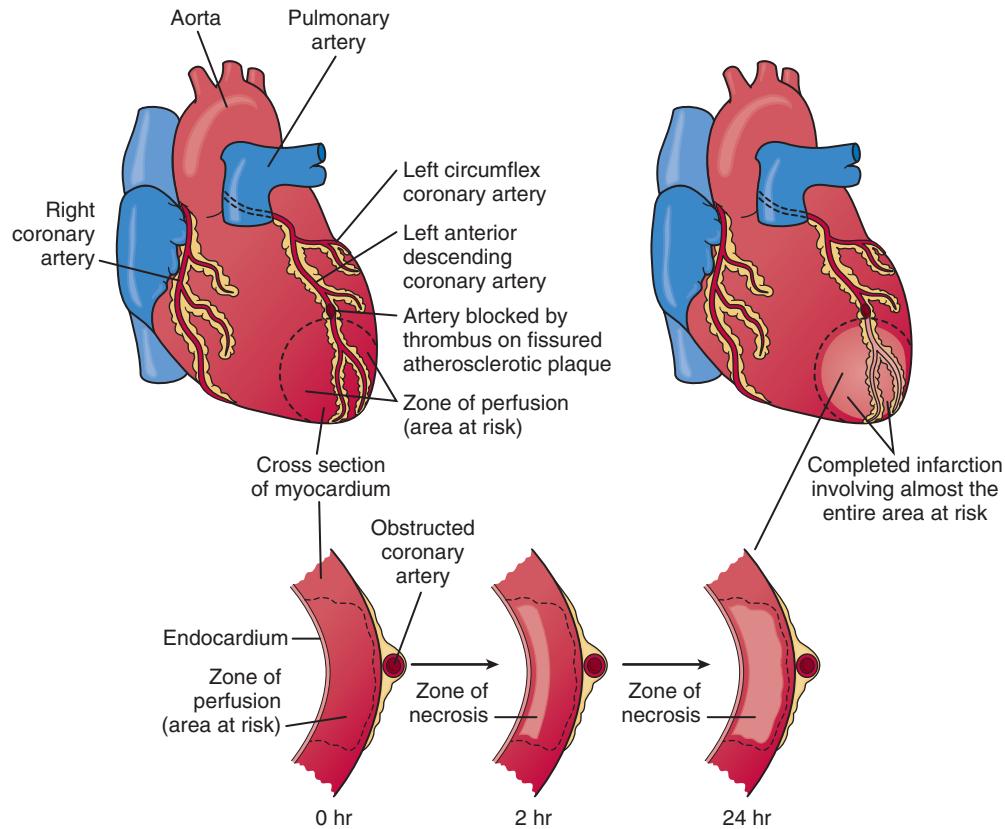


FIGURE 51-3 Schematic representation of the progression of myocardial necrosis after coronary artery occlusion. Necrosis begins in a small zone of the myocardium beneath the endocardial surface in the center of the ischemic zone. This entire region of myocardium (dashed outline) depends on the occluded vessel for perfusion and is the area at risk. A narrow zone of myocardium immediately beneath the endocardium is spared from necrosis because it can be oxygenated by diffusion from the ventricle. (From Schoen FJ: The heart. In Kumar V, Abbas AK, Fausto N [eds]: Robbins & Cotran Pathologic Basis of Disease. 8th ed. Philadelphia, WB Saunders, 2009.)

Plaque Fissuring and Disruption

In autopsy studies, plaque rupture and plaque erosion are the most common underlying causes of MI and sudden cardiac death. Plaque rupture is present in almost three quarters of cases and is more prevalent in men. Plaque erosion is more frequent in women younger than 50 years, although the prevalence of rupture increases as women age.²³ Atherosclerotic plaque considered prone to disruption or erosion is most likely plaque that has evolved to a morphology that includes a necrotic core filled with lipids and inflammatory cells and covered by a thin and inflamed fibrous cap. A prospective study of 697 patients with ACS who underwent three-vessel coronary angiography and gray-scale radiofrequency intravascular ultrasonographic imaging after PCI found that three lesion characteristics—lipid burden greater than 70%, thin-cap fibroatheroma morphology, and a minimal luminal area of 4.0 mm^2 or smaller—were independent correlates of future atherosclerotic events (Fig. 51-4).²⁷ Other morphologic characteristics associated with rupture-prone plaque include expansive remodeling that minimizes luminal obstruction (mild stenosis by angiography), neovascularization (angiogenesis), plaque hemorrhage, adventitial inflammation, and a “spotty” pattern of calcification.²³

Inflammation stimulates the overexpression of enzymes that degrade components of the plaque's extracellular matrix.^{23,26} Activated macrophages and mast cells, abundant at the site of plaque disruption in patients who die of STEMI, can elaborate these proteases. In addition to these structural aspects of vulnerable or high-risk plaque, stress induced by intraluminal pressure, coronary vasoconstriction, tachycardia (cyclical stretching and compression), and disruption of microvessels combine to produce plaque disruption at the margin of the fibrous cap near an adjacent, less involved segment of the coronary artery wall (shoulder region of the plaque).²⁵ Several key

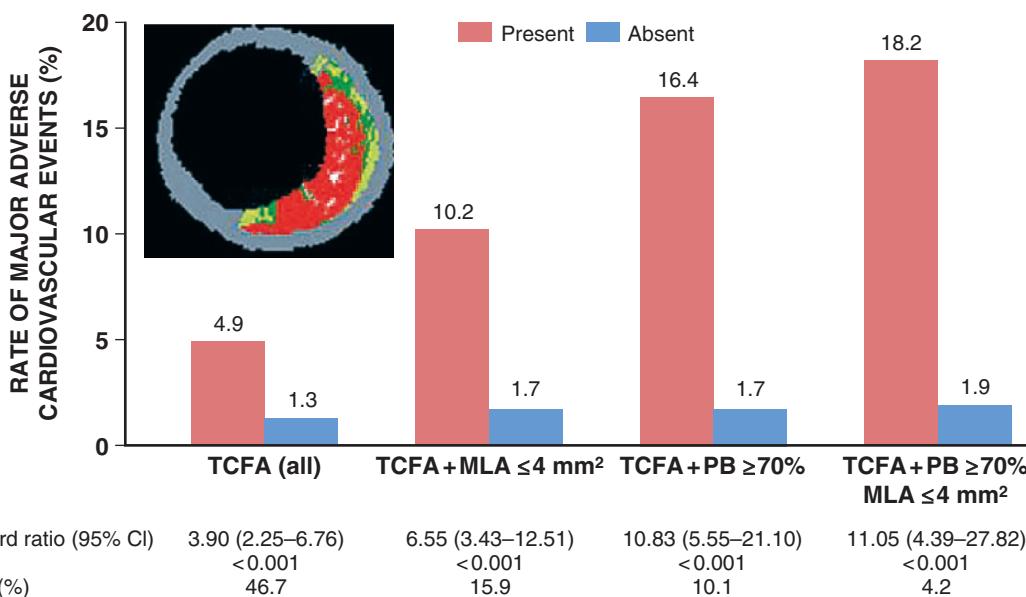


FIGURE 51-4 Comparison of cardiovascular event rates for lesions that were and those that were not thin-cap fibroatheromas (TCFAs). This figure shows the event rates associated with 595 nonculprit lesions that were characterized as TCFAs and 2114 that were not by means of gray-scale radiofrequency intravascular ultrasonographic imaging according to minimal luminal area (MLA) and plaque burden (PB). Lesions that had a larger plaque burden, signifying greater atherosclerotic content, and smaller lumen were at greatest risk for subsequently triggering an acute coronary event. The inserted image is an example of a TCFA imaged by radiofrequency ultrasonography. Red indicates necrotic core, dark green indicates fibrous tissue, white indicates confluent dense calcium, and light green indicates fibrofatty tissue. CI = confidence interval. (From Stone GW, Maehara A, Lansky AJ, et al: A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 364:226, 2011.)

physiologic variables—such as systolic blood pressure, heart rate, blood viscosity, endogenous tissue plasminogen activator (t-PA) activity, plasminogen activator inhibitor-1 (PAI-1) levels, plasma cortisol levels, and plasma epinephrine levels—exhibit circadian and seasonal variations and increase at times of stress. These factors act in concert to heighten the propensity for plaque disruption and coronary thrombosis, with the result that STEMI clusters in the early morning hours, especially in the winter and after natural disasters.²⁸⁻³⁰

Acute Coronary Syndromes

Plaque disruption exposes thrombogenic substances that may produce an extensive thrombus in the infarct-related artery (see Fig. 51-1). An adequate collateral network that prevents necrosis from occurring can result in clinically silent episodes of coronary occlusion; in addition, many plaque ruptures are asymptomatic if the thrombosis is not occlusive. Characteristically, completely occlusive thrombi lead to transmural injury to the ventricular wall in the myocardial bed subtended by the affected coronary artery (Fig. 51-5; see also Figs. 51-1 and 51-3). Infarction alters the sequence of depolarization ultimately reflected as changes in the QRS.³¹ The most characteristic change in the QRS that develops in most patients with STEMI is the evolution of Q waves in leads overlying the infarct zone (see Figs. 51-1 and 51-5).³¹ In a minority of patients with ST elevation, no Q waves develop but other abnormalities in the QRS complex occur frequently, such as diminution in R wave height and notching or splintering of the QRS (see Chapter 12). Patients who have ischemic symptoms without ST elevation are initially diagnosed as suffering either from unstable angina or, with evidence of myocardial necrosis, from NSTEMI (see Fig. 51-1).

Patients with persistent ST-segment elevation are candidates for reperfusion therapy (either pharmacologic or catheter based) to restore flow in the occluded epicardial infarct-related artery (see Chapter 52).¹⁰ ACS patients without ST-segment elevation are not candidates for pharmacologic reperfusion but should receive anti-ischemic therapy, followed in most cases by PCI (see Chapter 53). Thus the 12-lead ECG remains at the center of the decision pathway for the management of patients with ACS to distinguish between those with ST elevation and those without it (see Figs. 51-1 and Fig. 55-5).³²

Heart Muscle

The cellular effects of ischemia commence within seconds of the onset of hypoxia with the loss of adenosine triphosphate (ATP) production. Myocardial relaxation-contraction is compromised, and irreversible cell injury begins within as early as 20 minutes. Necrosis is usually complete in 6 hours unless reperfusion occurs or an extensive collateral circulation is present (Fig. 51-6).

Gross Pathologic Findings. On gross inspection, MI falls into two major types: transmural infarcts, in which myocardial necrosis involves the full thickness (or almost full thickness) of the ventricular wall, and subendocardial (nontransmural) infarcts, in which the necrosis involves the subendocardium, the intramural myocardium, or both without extending all the way through the ventricular wall to the epicardium (Fig. 51-7).

Occlusive coronary thrombosis appears to be far more common when the infarction is transmural and localized to the distribution of a single coronary artery (see Fig. 51-5). Nontransmural infarctions, however, frequently occur in the presence of severely narrowed but still patent coronary arteries or when the infarcted region has sufficient collateral circulation. Patchy nontransmural infarction may arise secondary to fibrinolysis or PCI of an originally occlusive thrombus with restoration of blood flow before the wave front of necrosis has extended from the subendocardium across the full thickness of the ventricular wall (see Fig. 51-3).

Histologic and Ultrastructural Findings. Gross alterations in the myocardium are difficult to identify until at least 6 to 12 hours has elapsed following the onset of necrosis (Fig. 51-8), but a variety of histochemical stains can identify zones of necrosis after only 2 to 3 hours (Fig. 51-9).³³ Subsequently, the infarcted myocardium undergoes a sequence of gross pathologic changes (Fig. 51-10; see also Fig. 51-8).³⁴ Within hours of death from MI, the presence of an infarct can often be detected by immersing slices of myocardium in triphenyltetrazolium chloride, which turns noninfarcted myocardium a brick red color while the infarcted area remains unstained (see Fig. 51-7).

Microscopic Findings. Histologic evaluation of MI reveals various stages of the healing process (see Figs. 51-8 to 51-10). In experimental infarction, the earliest ultrastructural changes in cardiac muscle following ligation of a coronary artery, noted within 20 minutes, consist of a reduction in the size and number of glycogen granules; intracellular edema; and swelling and distortion of the transverse tubular system, sarcoplasmic reticulum, and mitochondria (see Fig. 51-8).³⁵

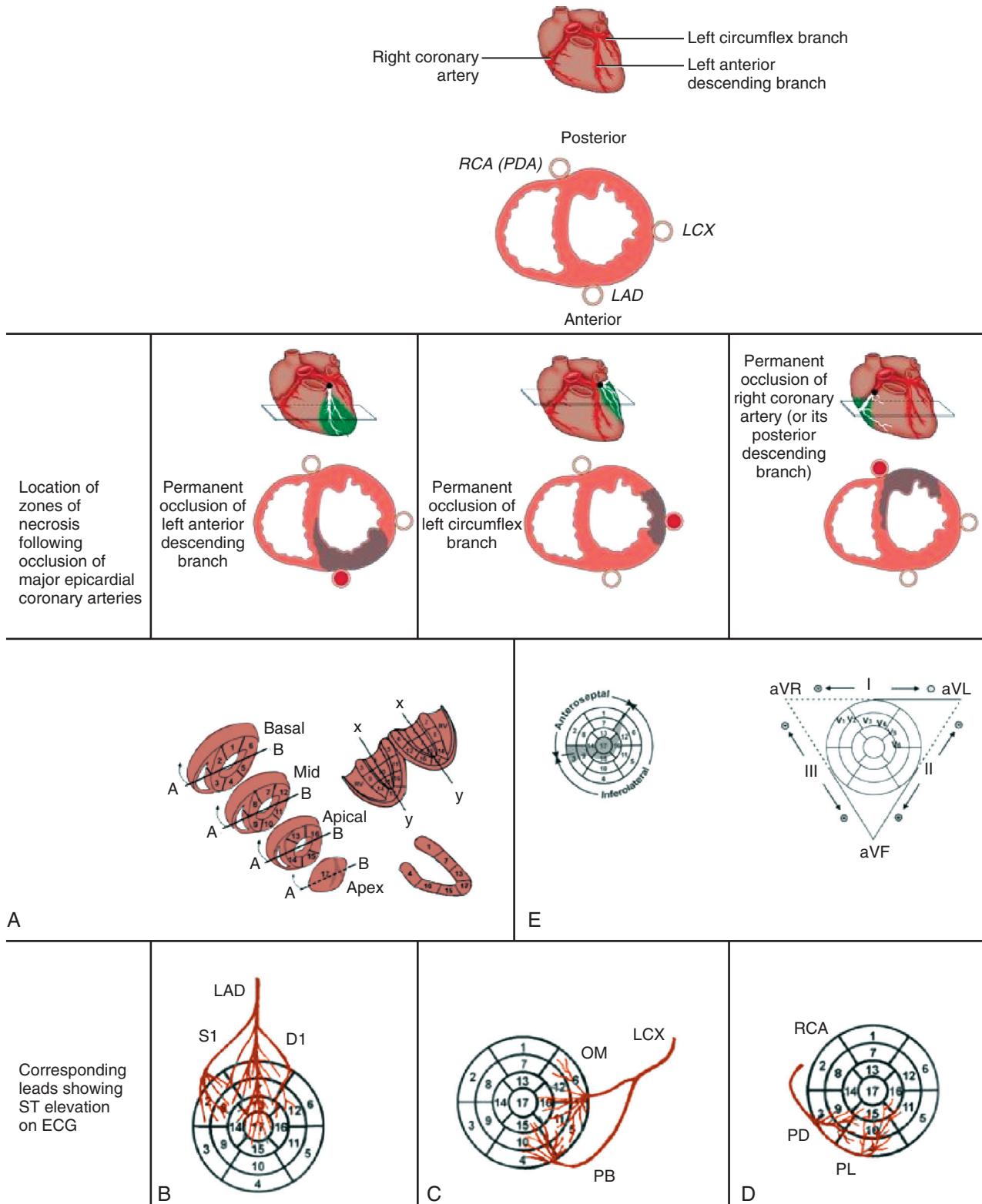


FIGURE 51-5 Correlation of sites of coronary occlusion, zones of necrosis, and abnormalities on the ECG. At the top is a schematic diagram of the heart with the location of the major epicardial coronary arteries. Immediately below, another schematic diagram depicts a short-axis view of the left and right ventricles and approximate location of the left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA); the latter gives rise to the posterior descending artery (PDA) in most patients. The middle of the figure shows the location of the zones of necrosis following occlusion of a major epicardial coronary artery. Identification of the infarct artery from the 12-lead ECG is shown at the bottom. The 17 myocardial segments in a polar map format (**A**) are shown with superimposition of the arterial supply provided by the LAD artery (**B**), RCA (**C**), and LCX artery (**D**). **E**, Position of the standard ECG leads relative to the polar map. The infarct artery can be deduced by identifying the leads that show ST elevation and referencing that information to **A** to **D**. For example, ST elevation seen most prominently in the leads overlying segments 1, 2, 7, 8, 13, 14, and 17 indicates that the LAD is the infarct artery. D₁ = first diagonal; OM = obtuse marginal; PB = posterobasal; PD = posterior descending; PL = posterolateral; S₁ = first septal. (From Bayes-de-Luna A, Wagner G, Birnbaum Y, et al: A new terminology for the left ventricular walls and location of myocardial infarcts that present Q wave based on the standard of cardiac magnetic resonance imaging. Circulation 114:1755, 2006.)

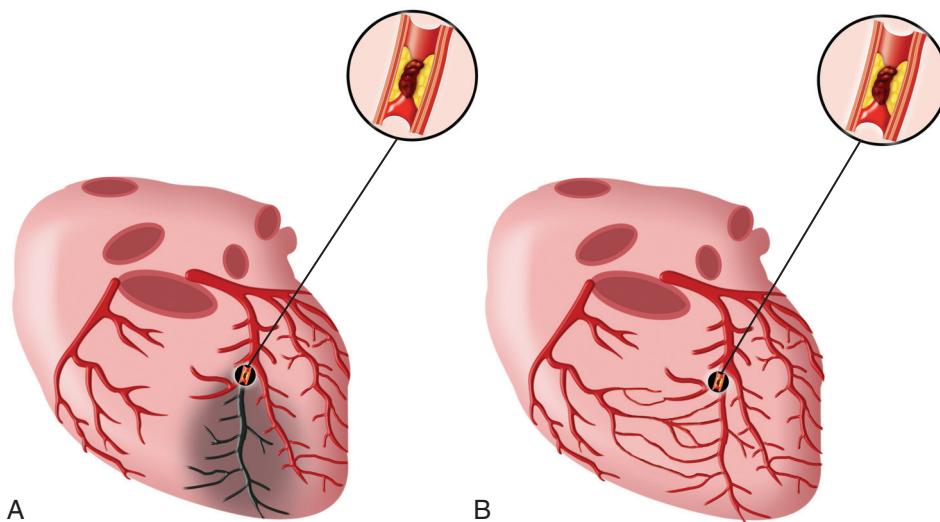


FIGURE 51-6 Schematic drawing of the coronary artery circulation without (A) and with (B) interarterial anastomoses between the right coronary artery and the occluded left anterior descending artery (occluded downstream of the third diagonal branch). A, The gray area indicates the ischemic area at risk for MI (finally corresponding to infarct size) in the case of left anterior descending artery occlusion and in the absence of collaterals. B, The area at risk for MI is equal to zero because of the extended collaterals. (From Traupe T, Gloekler S, de Marchi SF, et al: Assessment of the human coronary collateral circulation. *Circulation* 122:1210, 2010.)

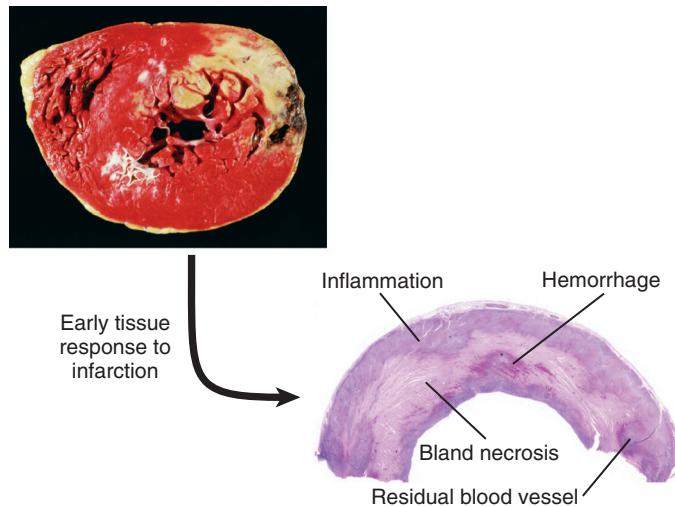


FIGURE 51-7 Top, Acute MI, predominantly of the posterolateral left ventricle, demonstrated histochemically by lack of staining with triphenyltetrazolium chloride in areas of necrosis. The staining defect is caused by leakage of the enzyme following cell death. The myocardial hemorrhage at one edge of the infarct was associated with cardiac rupture, and the anterior scar (lower left) was indicative of an old infarct. The specimen was oriented with the posterior wall at the top. Bottom, The early tissue response to the infarction process involves a mixture of bland necrosis, inflammation, and hemorrhage. (From Schoen FJ: The heart. In Kumar V, Abbas AK, Fausto N [eds]: *Robbins & Cotran Pathologic Basis of Disease*. 8th ed. Philadelphia, WB Saunders, 2009.)

These early changes are reversible. Changes after 60 minutes of occlusion include myocyte swelling, swelling and internal disruption of mitochondria, development of amorphous, flocculent aggregation and margination of nuclear chromatin, and relaxation of myofibrils. After 20 minutes to 2 hours of ischemia, the changes in some cells become irreversible and progression of these alterations occurs.³⁴

Patterns of Myocardial Necrosis

Coagulation Necrosis. Coagulation necrosis results from severe, persistent ischemia and is usually present in the central region of infarcts; it causes arrest of muscle cells in the relaxed state and passive stretching of ischemic muscle cells. The tissue exhibits stretched myofibrils, many cells with pyknotic nuclei, congested microvessels, and phagocytosis of necrotic muscle cells (see Fig. 51-8). Mitochondrial damage with prominent amorphous (flocculent) densities occurs, but no calcification is evident.

Necrosis with Contraction Bands. This form of myocardial necrosis, also termed contraction band necrosis or coagulative myocytolysis, results primarily from severe ischemia followed by reflow.³⁴ It is characterized by hypercontracted myofibrils with contraction bands and mitochondrial damage, frequently with calcification, marked vascular congestion, and healing by lysis of muscle cells. Necrosis with contraction bands is caused by increased influx of Ca^{2+} into dying cells, which results in the arrest of cells in the contracted state in the periphery of large infarcts and, to a greater extent, in nontransmural than in transmural infarcts. The entire infarct may show this form of necrosis after reperfusion (see Fig. 51-9).

Myocytolysis. Ischemia without necrosis generally causes no acute changes visible on light microscopy, but severe prolonged ischemia can result in myocyte vacuolization, often termed myocytolysis. Prolonged severe ischemia, which is potentially reversible, causes cloudy swelling, as well as hydropic, vascular, and fatty degeneration.

Apoptosis. An additional pathway of myocyte death involves apoptosis, or programmed cell death. In contrast to coagulation necrosis, myocytes undergoing apoptosis exhibit shrinkage of cells, fragmentation of DNA, and phagocytosis but without the usual cellular infiltrate indicative of inflammation.³⁴ The role of apoptosis in the setting of MI is less well understood than that of classic coagulation necrosis. Apoptosis may occur shortly after the onset of myocardial ischemia, but its major impact appears to be on late myocyte loss and ventricular remodeling after MI.³⁶

Current Concepts of the Cellular Events During Myocardial Infarction and Healing

Classic studies defined the sequence of cellular events that occur during human MI by careful histologic studies.³⁷ Accumulation of granulocytes characterized the first days following MI. After the first days, mononuclear phagocytes accumulated in the infarct in tissue. Finally, granulation tissue characterized by neovascularization and accumulation of extracellular matrix (fibrosis) followed. Recent experimental work in mice has revealed a sequence of accumulation of subpopulations of mononuclear phagocytes.³⁸ The first wave, occurring about days 1 to 3 following coronary ligation, consists of a proinflammatory subset of monocytes characterized by high proteolytic and phagocytic capacity and elaboration of proinflammatory cytokines. During a later phase (days 3 to 7), less inflammatory monocytes predominate and produce the angiogenic mediator vascular endothelial growth factor (VEGF) and the fibrogenic mediator transforming growth factor-beta (TGF- β). This highly orchestrated sequential recruitment of subpopulations of monocytes probably plays an important role in myocardial healing. The first wave of proinflammatory and phagocytically active mononuclear cells constitutes a "cleanup

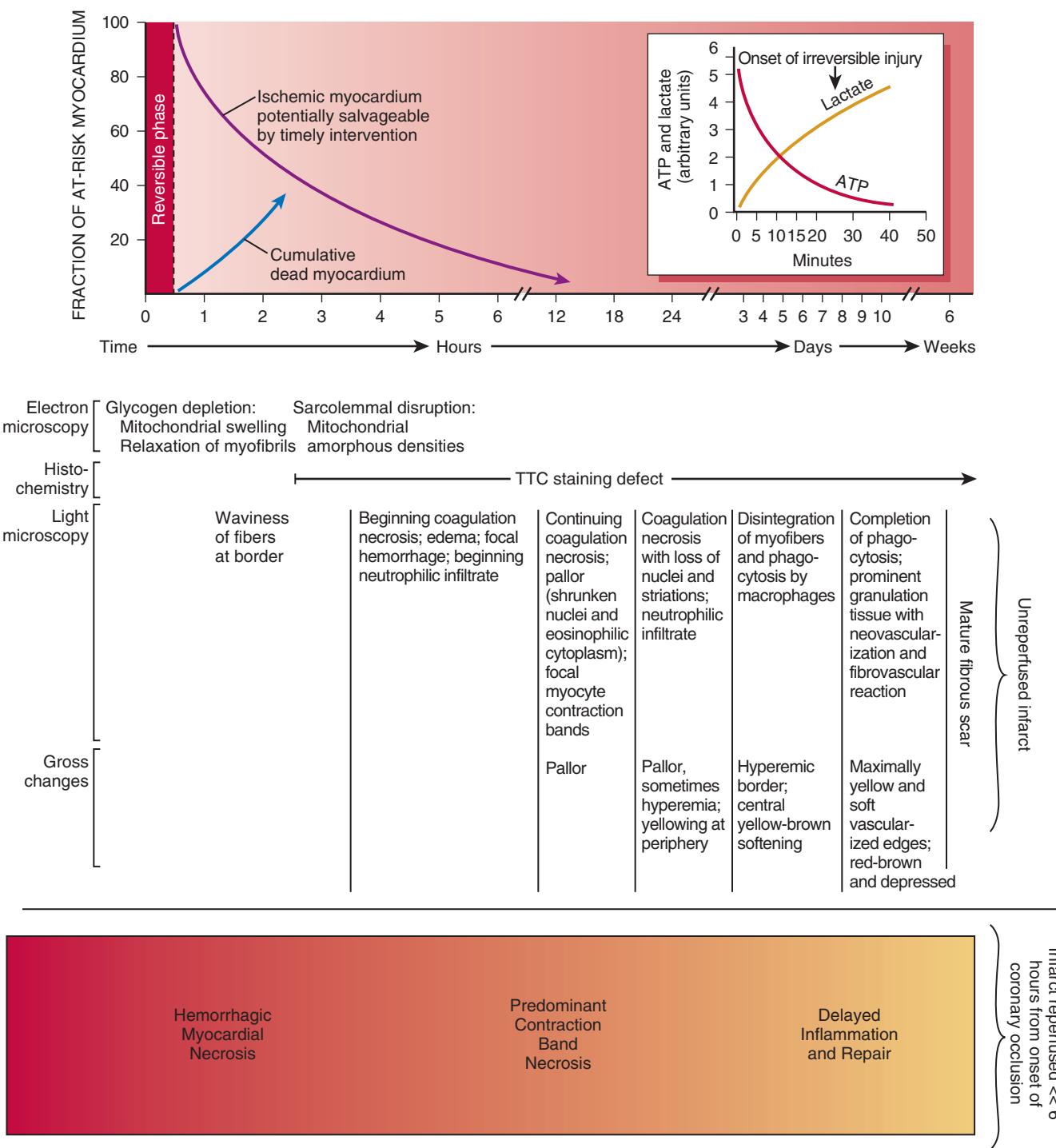


FIGURE 51-8 Temporal sequence of early biochemical, ultrastructural, histochemical, and histologic findings after the onset of MI. **Top,** Schematics of the time frames for early and late reperfusion of the myocardium supplied by an occluded coronary artery. For approximately 30 minutes after the onset of even the most severe ischemia, myocardial injury is potentially reversible; after this point, progressive loss of viability occurs and is complete by 6 to 12 hours. The benefits of reperfusion are greatest when it is achieved early, with progressively smaller benefits occurring as reperfusion is delayed. Note the alterations in the temporal sequence in the reperfused infarct. The pattern of pathologic findings following reperfusion varies depending on the timing of reperfusion, previous infarction, and collateral flow. TTC = triphenyltetrazolium chloride. (From Schoen F: The heart. In Kumar V, Abbas AK, Fausto N [eds]: Robbins & Cotran Pathologic Basis of Disease. 8th ed. Philadelphia, WB Saunders, 2009.)

“crew” that clears necrotic debris and paves the way for the second wave of less inflammatory monocytes, which contribute to healing by promoting the formation of granulation tissue.

Modification of Pathologic Changes by Reperfusion

When reperfusion of myocardium undergoing the evolutionary changes from ischemia to infarction occurs sufficiently early (i.e.,

within 15 to 20 minutes), it can successfully prevent necrosis from developing. Beyond this early stage, the number of salvaged myocytes—and therefore the amount of salvaged myocardial tissue (area of necrosis/area at risk)—is directly related to the length of time of total coronary artery occlusion, the level of myocardial oxygen consumption, and collateral blood flow (Fig. 51-11). Reperfused infarcts typically show a mixture of necrosis, hemorrhage within zones

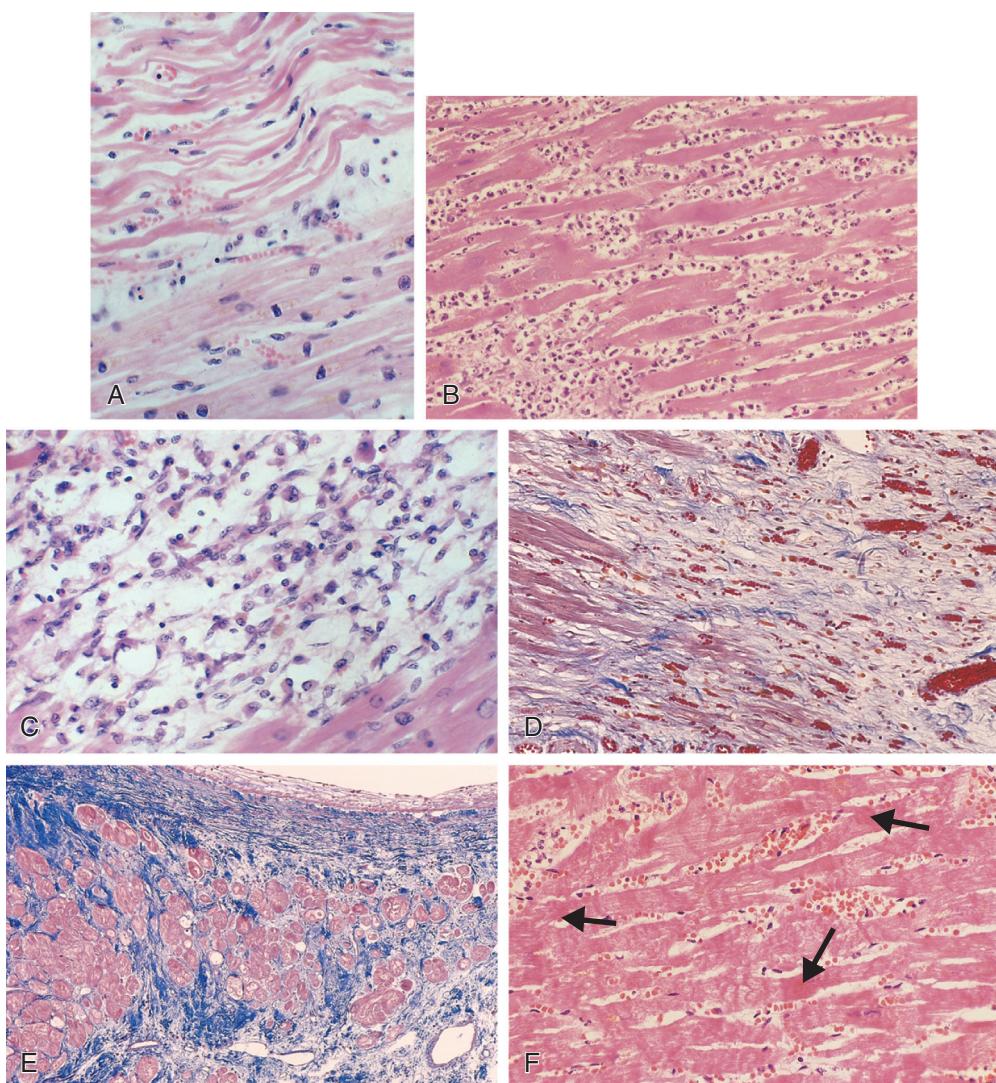


FIGURE 51-9 Microscopic features of MI. **A**, One-day-old infarct showing coagulative necrosis, wavy fibers with elongation, and narrowing as compared with adjacent normal fibers (lower right). Widened spaces between the dead fibers contain edema fluid and scattered neutrophils. **B**, Dense polymorphonuclear leukocytic infiltrate in an area of acute MI of 3 to 4 days' duration. **C**, Almost complete removal of necrotic myocytes by phagocytosis (\approx 7 to 10 days). **D**, Granulation tissue with a rich vascular network and early collagen deposition, approximately 3 weeks after infarction. **E**, Well-healed myocardial infarct with replacement of necrotic fibers by dense collagenous scar. A few residual cardiac muscle cells are present. (In **D** and **E**, collagen is highlighted as blue in this Masson trichrome stain.) **F**, Myocardial necrosis with hemorrhage and contraction bands, visible as dark bands spanning some myofibers (arrows). This is the characteristic appearance of markedly ischemic myocardium that has been reperfused. (From Schoen FJ: The heart. In Kumar V, Abbas AK, Fausto N [eds]. *Robbins & Cotran Pathologic Basis of Disease*. 8th ed. Philadelphia, WB Saunders, 2009.)

of irreversibly injured myocytes, coagulative necrosis with contraction bands, and distorted architecture of cells in the reperfused zone (Fig. 51-12). Reperfusion of infarcted myocardium accelerates the washout of leaked intracellular proteins, thereby producing an exaggerated and early peak value of substances such as the MB fraction of creatine kinase (CK-MB) and cardiac-specific troponin T and I (see below).³⁹

Coronary Anatomy and Location of Infarction

Angiographic studies performed in the earliest hours of STEMI have revealed an approximately 90% incidence of total occlusion of the infarct-related vessel. Recanalization as a result of spontaneous thrombolysis diminishes angiographic total occlusion in the period following the onset of MI. Pharmacologic fibrinolysis and PCI markedly increase the proportion of patients with a patent infarct-related artery early after STEMI.

A STEMI with transmural necrosis typically occurs distal to an acutely totally occluded coronary artery with thrombus superimposed on a ruptured plaque (see Fig. 51-5). Yet chronic total occlusion of a coronary artery does not always cause MI. Collateral blood flow and other factors such as the level of myocardial metabolism, the presence and location of stenoses in other coronary arteries, the rate

of development of the obstruction, and the quantity of myocardium supplied by the obstructed vessel all influence the viability of myocardial cells distal to the occlusion. In many series of patients studied at necropsy or by coronary arteriography, a small number (5%) of those with STEMI have normal coronary vessels. An embolus that has lysed, a transiently occlusive platelet aggregate, or a prolonged episode of severe coronary spasm may cause the infarct in these patients.

Studies of patients in whom STEMI ultimately develops after having undergone coronary angiography at some time before its occurrence have helped clarify the coronary anatomy before infarction. Although high-grade stenoses, when present, more frequently lead to STEMI than do less severe lesions, most occlusions occur in vessels with a previously identified stenosis of less than 50% on angiograms performed months to years earlier.²⁷ This finding supports the concept that STEMI results from sudden thrombotic occlusion at the site of rupture of previously nonobstructive but lipid-rich plaque. When collateral vessels perfuse an area of the ventricle, an infarct may occur at a distance from a coronary occlusion. For example, following gradual obliteration of the lumen of the right coronary artery, collateral vessels arising from the left anterior descending coronary artery

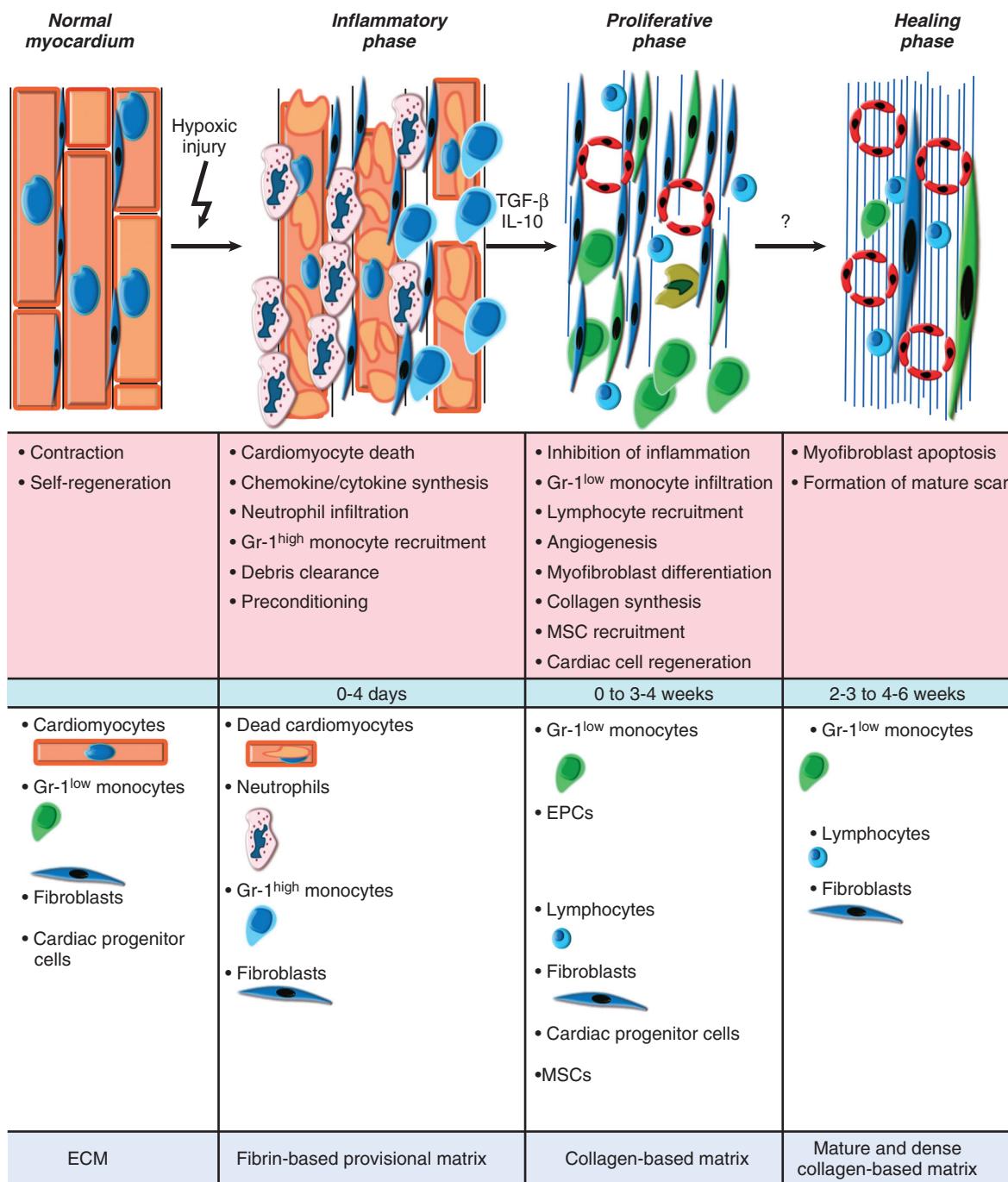


FIGURE 51-10 Healing after MI involves three overlapping phases: inflammatory, proliferative, and healing. Each is characterized by specific events and processes (red boxes) mediated by different cells controlled by specific chemokines. TGF- β and IL-10 signal transition from the inflammatory to proliferative phase. Extracellular matrix (ECM) evolves to mature scar (dark blue in top right), which ensures the stability and function of the heart. GR-1^{high} monocytes induce inflammation and phagocytosis whereas GR-1^{low} monocytes facilitate healing. EPCs = endothelial progenitor cells; IL = interleukin; MSC = mesenchymal stem cell; TGF = transforming growth factor. (From Liehn EA, Postea O, Curaj A, Marx N: Repair after myocardial infarction, between fantasy and reality: The role of chemokines. *J Am Coll Cardiol* 2011;58:2357, 2011.)

can keep the inferior wall of the left ventricle viable. Later, an occlusion of the left anterior descending artery may cause infarction of the diaphragmatic wall.

Right Ventricular Infarction

Approximately 50% of patients with inferior infarction have some involvement of the right ventricle.⁴⁰ Among these patients, right ventricular (RV) infarction occurs exclusively in those with transmural infarction of the inferoposterior wall and the posterior portion of the septum. RV infarction almost invariably develops in association with infarction of the adjacent septum and inferior left ventricular (LV) walls, but isolated infarction of the right ventricle is seen in just 3%

to 5% of autopsy-proven cases of MI. RV infarction occurs less commonly than would be anticipated from the frequency of atherosclerotic lesions involving the right coronary artery. The right ventricle can sustain long periods of ischemia but still demonstrate excellent recovery of contractile function after reperfusion.

Atrial Infarction

This type of infarction occurs in up to 10% of patients with STEMI if PR-segment displacement is used as the criterion. Although isolated atrial infarction is observed in only 3.5% of patients with STEMI at autopsy, it often occurs in conjunction with ventricular infarction and can cause rupture of the atrial wall.⁴¹ This type of infarction is more

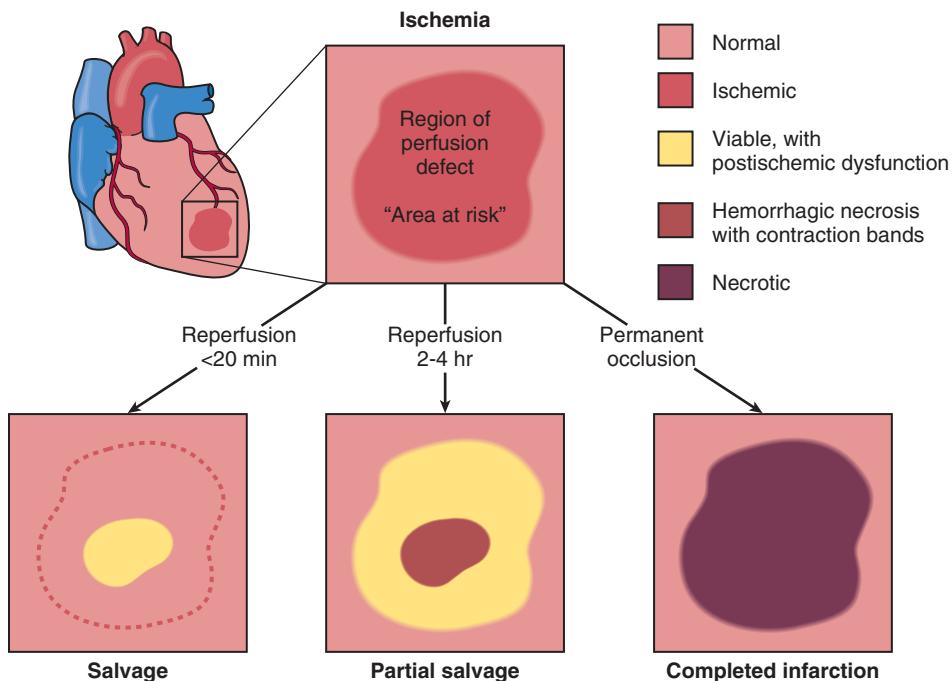


FIGURE 51-11 Consequences of reperfusion at various times after coronary adhesion. In this example the midportion of the left anterior descending coronary artery is occluded and a large zone of ischemic myocardium develops—the “area at risk.” Reperfusion in less than 20 minutes does not result in permanent loss of tissue, but there may be a period of contractile dysfunction of the reperfused myocardium—a condition referred to as “stunning.” Later reperfusion results in hemorrhagic necrosis with contraction bands. Permanent occlusion results in necrosis of myocardium. (From Schoen FJ: *The heart*. In Kumar V, Abbas AK, Fausto N [eds]: *Robbins & Cotran Pathologic Basis of Disease*. 8th ed. Philadelphia, WB Saunders, 2009.)

common on the right side than on the left side, occurs more frequently in the atrial appendages than in the lateral or posterior walls of the atrium, and can result in thrombus formation. Atrial infarction is frequently accompanied by atrial arrhythmias and has been linked to reduced secretion of atrial natriuretic peptide and to a low–cardiac output syndrome when RV infarction coexists.

Collateral Circulation in Acute Myocardial Infarction (See Chapter 49)

The coronary collateral circulation is particularly well developed in patients with coronary occlusive disease, especially with reduction of the luminal cross-sectional area by more than 75% in one or more major vessels; in patients with chronic hypoxia, as occurs in cases of severe anemia, chronic obstructive pulmonary disease, and cyanotic congenital heart disease; and in patients with LV hypertrophy (see Fig. 51-6).⁴²

The magnitude of coronary collateral flow is a principal determinant of infarct size. Indeed, patients with abundant collateral vessels commonly have totally occluded coronary arteries without evidence of infarction in the distribution of that artery; thus survival of myocardium distal to such occlusions depends largely on collateral blood flow. Even if the collateral perfusion existing at the time of coronary occlusion does not prevent infarction, it may still exert a beneficial effect by preventing the formation of LV aneurysms. The presence of a high-grade stenosis (90%), possibly with periods of intermittent total occlusion, probably permits the development of collateral vessels that remain only as potential conduits until a total occlusion occurs or recurs. Total occlusion then brings these channels into full operation. Patients with angiographic evidence of collateral formation have improved angiographic and clinical outcomes after MI.

Nonatherosclerotic Causes of Acute Myocardial Infarction

Numerous pathologic processes other than atherosclerosis can involve the coronary arteries and result in STEMI (see Table 51-3).

For example, coronary arterial occlusions can result from embolization of a coronary artery. The causes of coronary embolism are numerous: infective endocarditis and nonbacterial thrombotic endocarditis (see Chapter 64), mural thrombi, prosthetic valves, neoplasms, air introduced at the time of cardiac surgery, and calcium deposits from manipulation of calcified valves at surgery. In situ thrombosis of coronary arteries can occur secondary to chest wall trauma (see Chapter 72).

A variety of inflammatory processes can cause coronary artery abnormalities, some of which mimic atherosclerotic disease and may predispose to true atherosclerosis. Epidemiologic evidence suggests that viral infections, particularly with Coxsackie B virus, may uncommonly cause MI. Viral illnesses occasionally precede MI in young persons who are later shown to have normal coronary arteries.

Syphilitic aortitis can produce marked narrowing or occlusion of one or both coronary ostia, whereas Takayasu arteritis can result in obstruction of the coronary arteries. Necrotizing arteritis, polyarteritis nodosa, mucocutaneous lymph node syndrome (Kawasaki disease), systemic lupus erythematosus (see Chapter 84), and giant cell arteritis can cause coronary occlusion. Therapeutic levels of mediastinal radiation can

result in coronary arteriosclerosis⁴³ with subsequent infarction. MI can also result from coronary arterial involvement in patients with amyloidosis (see Chapter 65), Hurler syndrome, pseudoxanthoma elasticum, and homocystinuria. Cocaine can cause MI in patients with normal coronary arteries, preexisting MI, documented coronary artery disease, or coronary artery spasm (see Chapter 68).

Myocardial Infarction with Angiographically Normal Coronary Vessels

Patients with STEMI and normal coronary arteries tend to be young with relatively few coronary risk factors except that they often have a history of cigarette smoking (Table 51-4). Usually, they have no history of angina pectoris before the infarction. These patients do not generally have a prodrome before infarction, but the clinical, laboratory, and electrocardiographic features of STEMI otherwise resemble those present in the overwhelming majority of patients with STEMI who have classic obstructive atherosclerotic coronary artery disease.

Patients who recover frequently have areas of localized dyskinesis and hypokinesis identified at LV angiography. Many of these cases result from coronary artery spasm and/or thrombosis, perhaps with underlying endothelial dysfunction or plaque not apparent on coronary angiography. The transient LV apical ballooning syndrome (takotsubo cardiomyopathy) is characterized by transient wall motion abnormalities involving the LV apex and midventricle (Fig. 51-13). This syndrome occurs in the absence of obstructive epicardial coronary disease and can mimic STEMI.^{44,45} Typically, an episode of psychological stress precedes the development of takotsubo cardiomyopathy. Initial ECGs demonstrate significant and often diffuse ST-segment elevations that when coupled with the typical (frequently severe) chest discomfort, prompts the appropriate immediate referral for coronary angiography. The cause is not clear, but catecholamine-mediated myocardial stunning and microvascular dysfunction play important roles.⁴⁶

Additional suggested causes include (1) coronary emboli (perhaps from a small mural thrombus, a prolapsed mitral valve, or a myxoma);

POTENTIAL OUTCOMES OF ISCHEMIA

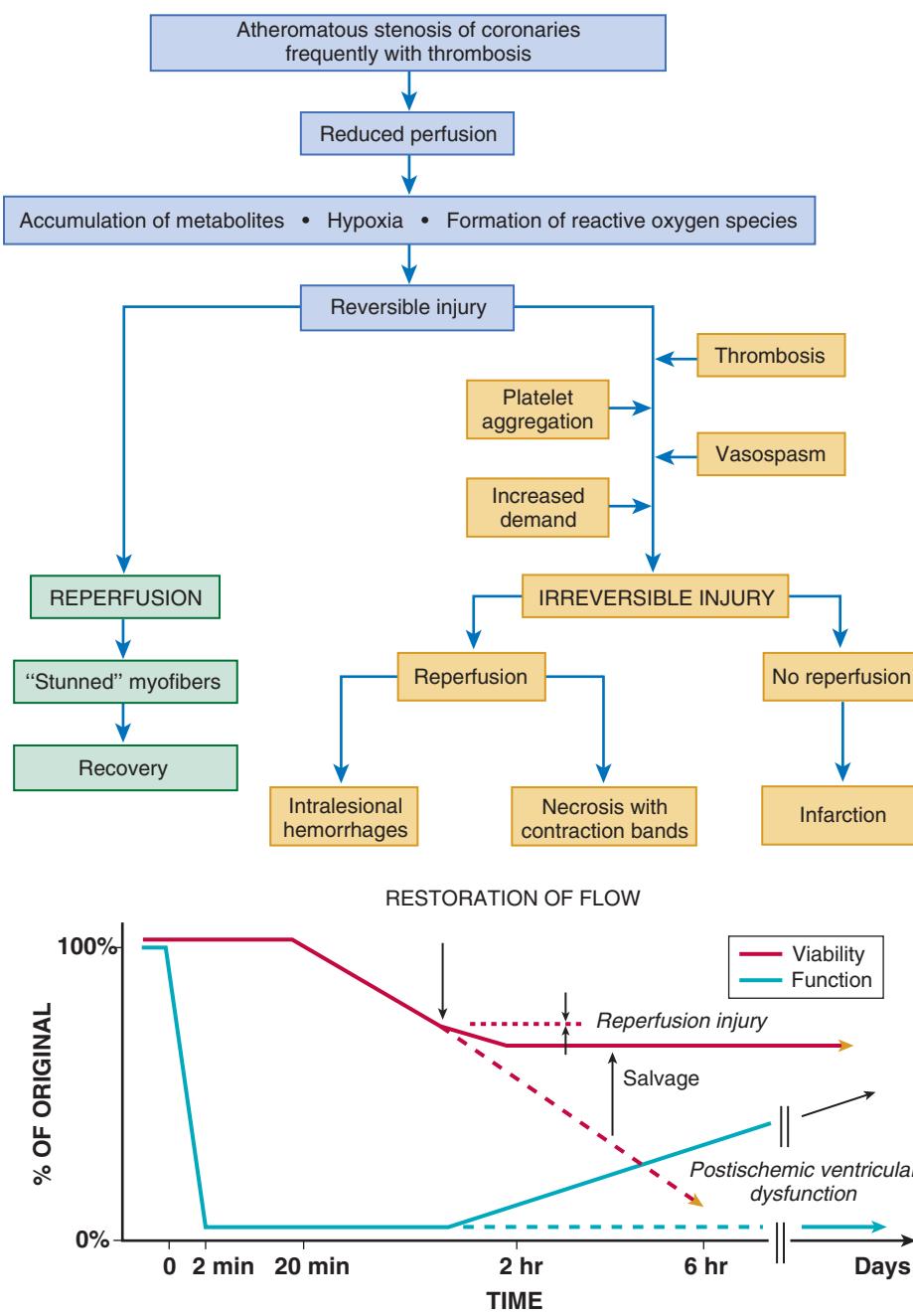


FIGURE 51-12 Several potential outcomes of reversible and irreversible ischemic injury to the myocardium. The schematic diagram at the bottom depicts the timing of changes in function and viability. A key point is that although function drops dramatically after coronary occlusion, the tissue is still viable for a period. This is the basis for early aggressive efforts at reperfusion of patients with STEMI. (From Schoen FJ: The heart. In Kumar V, Abbas AK, Fausto N [eds]: Robbins & Cotran Pathologic Basis of Disease. 8th ed. Philadelphia, WB Saunders, 2009.)

(2) coronary artery disease in vessels too small to be visualized on coronary arteriography or coronary arterial thrombosis with subsequent recanalization; (3) a hematologic disorder (polycythemia vera, cyanotic heart disease with polycythemia, sickle cell anemia, disseminated intravascular coagulation, thrombocytosis, and thrombotic thrombocytopenic purpura) causing *in situ* thrombosis in the presence of normal coronary arteries; (4) augmented oxygen demand (e.g., thyrotoxicosis, amphetamine use); (5) hypotension secondary to sepsis, blood loss, or pharmacologic agents; and (6) anatomic variations such as anomalous origin of a coronary artery (see Chapter 20), coronary arteriovenous fistula, or a myocardial bridge.

Prognosis

The long-term outlook for patients who have survived STEMI with angiographically normal coronary vessels appears to be brighter than for those with STEMI and obstructive coronary artery disease.⁴⁵ After recovery from the initial infarct, recurrent infarction, heart failure, and death are unusual in patients with normal coronary arteries. Indeed, most of these patients have normal finding on the exercise ECG, and very few develop angina pectoris.

PATHOPHYSIOLOGY

Left Ventricular Function

Systolic Function

On interruption of antegrade flow in an epicardial coronary artery, the zone of myocardium supplied by that vessel immediately loses its ability to shorten and perform contractile work (see Fig. 51-12). Four abnormal contraction patterns develop in sequence: (1) dyssynchrony, or dissociation of the time course of contraction of adjacent segments; (2) hypokinesis, or a reduction in the extent of shortening; (3) akinesis, or cessation of shortening; and (4) dyskinesis, paradoxical expansion, and systolic bulging. Hyperkinesis of the remaining normal myocardium initially accompanies dysfunction of the infarct. The early hyperkinesis of the noninfarcted zones probably results from acute compensation, including increased activity of the sympathetic nervous system and the Frank-Starling mechanism. A portion of this compensatory hyperkinesis is ineffective work because contraction of the noninfarcted segments of myocardium causes dyskinesis of the infarct zone. The increased motion of the noninfarcted region subsides within 2 weeks of infarction, during which time some degree of recovery often occurs in the infarct region as well, particularly if reperfusion of the infarcted area occurs and myocardial stunning diminishes.

Patients with STEMI also often have reduced myocardial contractile function in noninfarcted zones. This finding may result from previous obstruction of the coronary artery supplying the noninfarcted region of the ventricle and loss of collaterals from the freshly occluded infarct-related vessel, a condition termed *ischemia at a distance*. Conversely, the development of collaterals before STEMI occurs may allow greater

preservation of regional systolic function in an area of distribution of the occluded artery and improvement in the LV ejection fraction early after infarction (see Fig. 51-6).⁴²

If a sufficient quantity of myocardium undergoes ischemic injury (see Fig. 51-12), LV pump function becomes depressed; cardiac output, stroke volume, blood pressure, and peak dP/dt decline; and end-systolic volume increases. The degree to which end-systolic volume increases is perhaps the most powerful hemodynamic predictor of mortality following STEMI.⁴⁷ Paradoxical systolic expansion of an area of ventricular myocardium further decreases LV stroke volume.⁴⁸ As necrotic myocytes slip past each other, the infarct zone thins and elongates, especially in patients with large anterior infarcts, thereby

TABLE 51-4 Causes of Myocardial Injury

Injury Related to Primary Myocardial Ischemia
Plaque rupture
Intraluminal coronary artery thrombus formation
Injury Related to the Supply-Demand Imbalance of Myocardial Ischemia
Tachyarrhythmias/bradyarrhythmias
Aortic dissection or severe aortic valve disease
Hypertrophic cardiomyopathy
Cardiogenic, hypovolemic, or septic shock
Severe respiratory failure
Severe anemia
Hypertension with or without LV hypertrophy
Coronary spasm
Coronary embolism or vasculitis
Coronary endothelial dysfunction without significant coronary artery disease
Injury Not Related to Myocardial Ischemia
Cardiac contusion, surgery, ablation, pacing, or defibrillator shocks
Rhabdomyolysis with cardiac involvement
Myocarditis
Cardiotoxic agents (e.g., anthracyclines, trastuzumab [Herceptin])
Multifactorial or Indeterminate Myocardial Injury
Heart failure
Stress (takotsubo) cardiomyopathy
Severe pulmonary embolism or pulmonary hypertension
Sepsis and critically ill patients
Renal failure
Severe acute neurologic diseases (e.g., stroke, subarachnoid hemorrhage)
Infiltrative diseases (e.g., amyloidosis, sarcoidosis)
Strenuous exercise

From Thygesen K, Alpert JS, White HD, et al: Universal definition of myocardial infarction. *J Am Coll Cardiol* 60:1581, 2012.

leading to expansion of the infarct. In some patients a vicious circle of dilation begetting further dilation ensues. The degree of ventricular dilation, which depends closely on infarct size, patency of the infarct-related artery, and activation of the renin-angiotensin-aldosterone system (RAAS), can be favorably modified by inhibitors of this system, even in the absence of symptomatic LV dysfunction.^{49,50}

With time, edema and ultimately fibrosis increase the stiffness of the infarcted myocardium back to and beyond control values. Increasing stiffness in the infarcted zone of myocardium improves LV function because it prevents paradoxical systolic wall motion (dyskinesia).

The likelihood of clinical symptoms developing correlates with specific parameters of LV function. The earliest abnormality is ventricular stiffness in diastole (see later), which is observed with infarcts involving only a small portion of the left ventricle on angiographic examination. When the abnormally contracting segment exceeds 15%, the ejection fraction may decline and LV end-diastolic pressure and volume increase. Risk for the development of physical signs and symptoms of LV failure also increases in proportion to increasing areas of abnormal LV wall motion. Clinical heart failure accompanies areas of abnormal contraction exceeding 25%, and cardiogenic shock, often fatal, is associated with loss of more than 40% of the LV myocardium.

Unless extension of the infarct occurs, some improvement in wall motion takes place during the healing phase, with recovery of function occurring in initially reversibly injured (stunned) myocardium (see Figs. 51-11 and 51-12). Regardless of the age of the infarct, patients who continue to demonstrate abnormal wall motion involving 20% to 25% of the left ventricle will probably manifest hemodynamic signs of LV failure, with its attendant poor prognosis for long-term survival.

Diastolic Function

The diastolic properties of the left ventricle (see Chapters 21, 22, and 27) change in infarcted and ischemic myocardium. These

alterations are associated with a decrease in the peak rate of decline in LV pressure (peak—dP/dt), an increase in the time constant of the fall in LV pressure, and an initial rise in LV end-diastolic pressure. Over a period of several weeks, end-diastolic volume increases and diastolic pressure begins to fall toward normal. As with impairment of systolic function, the magnitude of the diastolic abnormality appears to be related to the size of the infarct.

Circulatory Regulation

Patients with STEMI have an abnormality in circulatory regulation. The process begins with an anatomic or functional obstruction in the coronary vascular bed that results in regional myocardial ischemia and, if the ischemia persists, in infarction (Fig. 51-14). If the infarct is of sufficient size, it depresses overall LV function such that LV stroke volume falls and filling pressure rises.⁵¹ A marked depression in LV stroke volume ultimately lowers aortic pressure and reduces coronary perfusion pressure; this condition may intensify myocardial ischemia and thereby initiate a vicious circle (Fig. 51-14) leading to cardiogenic shock, which occurs in 5% to 8% of patients with STEMI.^{52,53} Systemic inflammation secondary to myocardial injury leads to the release of cytokines that contribute to the vasodilation and decreased systemic vascular resistance.⁵² The inability of the left ventricle to empty normally also increases preload; that is, it dilates the well-perfused, normally functioning portion of the left ventricle. This compensatory mechanism tends to restore stroke volume to normal levels, but at the expense of a reduced ejection fraction. Dilation of the left ventricle also elevates ventricular afterload, however, because Laplace's law dictates that at any given arterial pressure, the dilated ventricle must develop higher wall tension. This increased afterload not only depresses LV stroke volume but also elevates myocardial oxygen consumption, which in turn intensifies the myocardial ischemia. When regional myocardial dysfunction is limited and the function of the remainder of the left ventricle is normal, compensatory mechanisms—especially hyperkinesis of the nonaffected portion of the ventricle—sustain overall LV function. If a large portion of the left ventricle ceases to function, pump failure occurs.

Ventricular Remodeling (See also Chapter 22)

As a consequence of STEMI, the changes in LV size, shape, and thickness involving both the infarcted and noninfarcted segments of the ventricle described earlier occur and are collectively referred to as *ventricular remodeling*—which in turn can influence ventricular function and prognosis.⁵⁴ Changes in LV dilation combined with hypertrophy of residual noninfarcted myocardium cause remodeling. After infarct size, other important factors driving the process of LV dilation are ventricular volume, loading conditions, and infarct artery patency.^{48,55} Elevated ventricular pressure contributes to increased wall stress and the risk for infarct expansion, but a patent infarct artery accelerates myocardial scar formation and increases tissue turgor in the infarct zone, thereby reducing the risk for infarct expansion and ventricular dilation.

Infarct Expansion

An increase in the size of the infarcted segment, known as *infarct expansion*, is defined as “acute dilation and thinning of the area of infarction not explained by additional myocardial necrosis.” Infarct expansion appears to result from a combination of slippage between muscle bundles, which reduces the number of myocytes across the infarct wall; disruption of normal myocardial cells; and destruction of extracellular matrix within the necrotic zone.⁵⁶ Infarct expansion involves thinning and dilation of the infarct zone before the formation of a firm, fibrotic scar. The degree of infarct expansion appears to be related to preinfarction wall thickness, with existing hypertrophy possibly protecting against infarct thinning. On a cellular level, the degree of expansion and worsening remodeling depends on the intensity of the inflammatory response to the necrotic cells. Suppression of cytokine expression and stimulation may minimize the degree of inflammation and thus final infarct size.⁵⁶ The apex, the thinnest



EMOTIONAL AND PHYSICAL STRESS

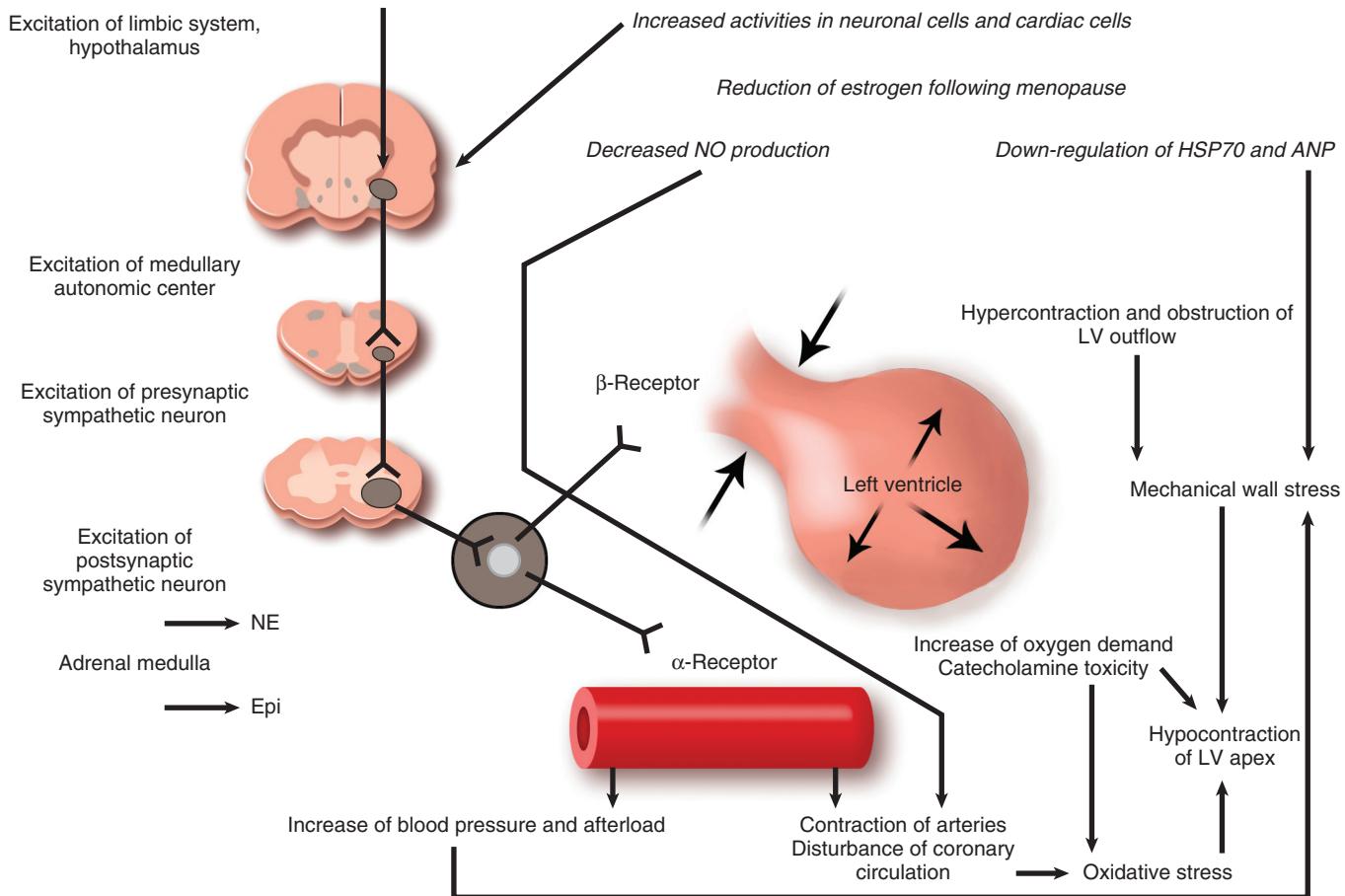


FIGURE 51-13 A proposed mechanism for takotsubo, or stress-mediated, cardiomyopathy begins with sudden and severe emotional stress, which activates central autonomic network neurons expressing estrogen receptors. Simultaneously, sympathetic neuronal and adrenomedullary hormonal outflow increases dramatically and results in release of epinephrine (Epi) from the adrenal medulla combined with the release of norepinephrine (NE) from cardiac and extracardiac sympathetic nerves, which stimulate adrenoceptors in the blood vessels of the heart. Contraction of resistance vessels rapidly increases systemic blood pressure and cardiac afterload. High circulating levels of NE and Epi can precipitate catecholamine toxicity in cardiomyocytes via occupation of adrenoceptors. The typical hypercontraction of the basal sections of the heart, which leads to functional basal obstruction of LV outflow, further exacerbates LV wall stress and increases end-diastolic pressure. ANP = atrial natriuretic peptide; HSP70 = heat shock protein 70; NO = nitric oxide. (From Akashi YJ, Goldstein DS, Barbaro G, Ueyama T: Takotsubo cardiomyopathy: A new form of acute, reversible heart failure. *Circulation* 118:2754, 2008.)

region of the left ventricle, is particularly vulnerable to infarct expansion. Infarction of the apex secondary to occlusion of the left anterior descending coronary artery causes the radius of curvature at the apex to increase, thereby exposing this normally thin region to a marked elevation in wall stress.

Infarct expansion is associated with both higher mortality and a higher incidence of nonfatal complications, such as heart failure and ventricular aneurysm. Infarct expansion is best recognized as elongation of the noncontractile region of the ventricle on echocardiography or CMR. When the expansion is severe enough to cause symptoms, the most characteristic clinical findings are deterioration of systolic function, new or worsening pulmonary congestion, and the development of ventricular arrhythmias.

Ventricular Dilatation

Although infarct expansion plays an important role in the ventricular remodeling that occurs early following MI, remodeling is also caused by dilation of the viable portion of the ventricle, which commences immediately after STEMI and progresses for months or years thereafter. A shift of the pressure-volume curve of the left ventricle to the right, which results in a larger LV volume at any given diastolic pressure, may accompany dilation. This dilation of the noninfarcted zone can be viewed as a compensatory mechanism that maintains stroke volume in the presence of a large infarction. STEMI places an

extra load on the residual functioning myocardium, a burden that presumably causes the compensatory hypertrophy of the noninfarcted myocardium. This hypertrophy could help compensate for the functional impairment caused by the infarct and may be responsible for some of the hemodynamic improvement seen in some patients in the months after infarction.

Effects of Treatment

Several factors can affect ventricular remodeling after STEMI, notably infarct size (see Figs. 51-11 and 51-12). Acute reperfusion and other measures to restrict the extent of myocardial necrosis limit the increase in ventricular volume after STEMI. Multiple pharmacologic agents aimed at limiting infarct size have undergone evaluation in clinical trials, although few have produced significant results in adequately powered phase III investigations (see Chapter 52). The second factor is scar formation in the infarct. Glucocorticosteroids and nonsteroidal anti-inflammatory agents given early after MI can cause scar thinning and greater infarct expansion, whereas RAAS inhibitors attenuate the ventricular enlargement.⁴⁹ Additional beneficial consequences of inhibition of angiotensin II that may contribute to myocardial protection include attenuation of endothelial dysfunction and direct antiatherogenic effects. Inhibition of aldosterone action may limit excessive fibrosis and decrease the development of ventricular arrhythmias.⁵⁷

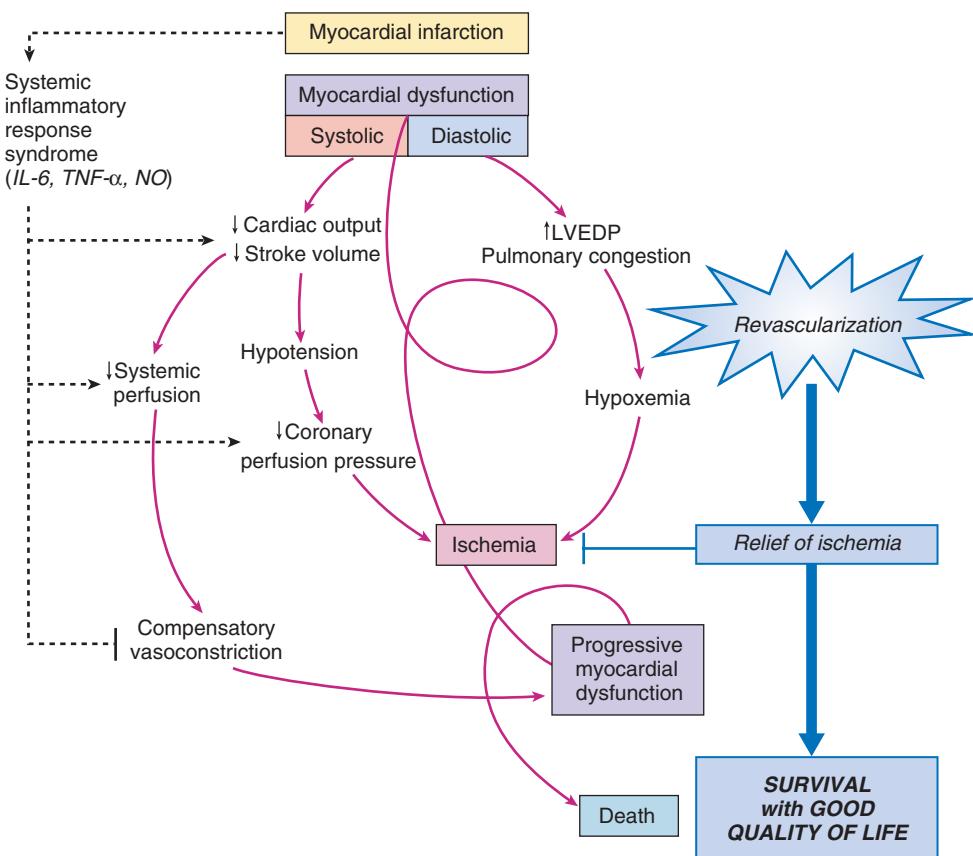


FIGURE 51-14 Current concept of the pathophysiology of cardiogenic shock. Myocardial injury causes systolic and diastolic dysfunction. A decrease in cardiac output leads to a decrease in systemic and coronary perfusion. The decreased perfusion exacerbates ischemia and causes cell death in the infarct border zone and the remote zone of myocardium. Inadequate systemic perfusion triggers reflex vasoconstriction, which is usually insufficient. Systemic inflammation may play a role in limiting the peripheral vascular compensatory response and may contribute to the myocardial dysfunction. Whether inflammation plays a causal role or is only an epiphenomenon remains unclear. Revascularization leads to relief of ischemia. Demonstration of an increase in cardiac output or the LV ejection fraction as the mechanism of benefit of revascularization has not been possible, but revascularization significantly increases the likelihood of survival with good quality of life. IL-6 = interleukin-6; LVEDP = LV end-diastolic pressure; NO = nitric oxide; TNF- α = tumor necrosis factor-alpha. (From Reynolds HR, Hochman JS: Cardiogenic shock: Current concepts and improving outcomes. *Circulation* 117:686, 2008.)

Pathophysiology of Other Organ Systems

Pulmonary Function

Arterial oxygen tension is inversely related to pulmonary artery diastolic pressure, which suggests that if patients with STEMI become hypoxic, the increased pulmonary capillary hydrostatic pressure can promote interstitial edema and consequently result in arteriolar and bronchiolar compression that ultimately causes perfusion of poorly ventilated alveoli with resultant hypoxemia (see Chapter 22). In addition to hypoxemia, diffusion capacity decreases. Hyperventilation often occurs in patients with STEMI and may cause hypocapnia and respiratory alkalosis, particularly in restless, anxious patients with pain. Pulmonary extravascular (interstitial) water content, LV filling pressure, and the clinical signs and symptoms of LV failure are correlated. The increase in pulmonary extravascular water may cause the alterations in pulmonary mechanics observed in patients with STEMI (i.e., reduction in airway conductance, pulmonary compliance, forced expiratory volume, and midexpiratory flow rate and an increase in closing volume, presumably related to the widespread closure of small, dependent airways during the first 3 days after STEMI). Ultimately, severe increases in extravascular water may lead to pulmonary edema. Virtually all lung volume indices—total lung capacity, functional residual capacity, and residual volume, as well as vital capacity—fall during STEMI.

Reduction of the Affinity of Hemoglobin for Oxygen

In patients with MI, particularly when complicated by LV failure or cardiogenic shock, the affinity of hemoglobin for oxygen falls (i.e., P50 increases). The increase in P50 results from increased levels of

erythrocyte 2,3-diphosphoglycerate, which is an important compensatory mechanism that is responsible for an estimated 18% increase in release of oxygen from oxyhemoglobin in patients with cardiogenic shock.

Endocrine Function

Pancreas. Although patients with STEMI often have absolute concentrations of blood insulin in the normal range, these levels are usually inappropriately low for their blood sugar concentration, and relative insulin resistance may be present as well. Patients with cardiogenic shock frequently have marked hyperglycemia with depressed levels of circulating insulin. Abnormalities in insulin secretion and the resultant impaired glucose tolerance appear to be due to a reduction in pancreatic blood flow as a consequence of the splanchnic vasoconstriction accompanying severe LV failure. In addition, increased activity of the sympathetic nervous system with augmented circulating catecholamines inhibits insulin secretion and increases glycogenolysis, which also contributes to elevated blood sugar.⁵⁸

Glucose permits the generation of ATP by anaerobic glycolysis, as opposed to free fatty acids, which require aerobic conditions to furnish ATP.⁵⁹ Because hypoxic heart muscle derives a considerable proportion of its energy from the metabolism of glucose (see Chapter 21) and because glucose uptake by the myocardium requires insulin, insulin deficiency can jeopardize the availability of energy. These metabolic considerations, combined with epidemiologic observations that patients with diabetes have a markedly worse prognosis, served as the foundation for efforts to administer insulin-glucose infusions to diabetic patients with STEMI. To date, however, none of these studies has demonstrated clear benefit (see Chapter 52).^{60,61}

Adrenal Medulla. Plasma and urinary catecholamine levels peak during the first 24 hours after the onset of chest pain, with the



greatest rise in plasma catecholamine secretion occurring during the first hour after the onset of STEMI. These high levels of circulating catecholamines in patients with STEMI correlate with the occurrence of serious arrhythmias and result in an increase in myocardial oxygen consumption, both directly and indirectly, as a consequence of catecholamine-induced elevation of circulating free fatty acids. The concentration of circulating catecholamines correlates with the extent of myocardial damage and the incidence of cardiogenic shock, as well as with both early and late mortality rates.

Circulating catecholamines enhance platelet aggregation; when this occurs in the coronary microcirculation, release of the potent local vasoconstrictor thromboxane A₂ may further impair cardiac perfusion. The marked increase in sympathetic activity associated with STEMI serves as the foundation for beta-adrenergic receptor blocker (beta-blocking agent) regimens in the acute phase.

Activation of the Renin-Angiotensin-Aldosterone System. Noninfarcted regions of the myocardium appear to exhibit activation of the tissue RAAS with increased production of angiotensin II. Both locally and systemically generated angiotensin II can stimulate the production of various growth factors, such as platelet-derived growth factor and TGF- β , that promote compensatory hypertrophy in the noninfarcted myocardium, as well as control the structure and tone of the infarct-related coronary and other myocardial vessels. Additional potential actions of angiotensin II that have a more negative impact on the infarction process include the release of endothelin, PAI-1, and aldosterone, which may cause vasoconstriction, impaired fibrinolysis, and increased sodium retention, respectively.

Natriuretic Peptides. The peptides atrial natriuretic factor (ANF) and N-terminal pro-ANF are released from the cardiac atria in response to an elevation in atrial pressure. B-type natriuretic peptide (BNP) and its precursor N-terminal pro-BNP are secreted by atrial and ventricular myocardium. Given the larger mass of ventricular than atrial myocardium, the total amount of mRNA for BNP is higher in the ventricles than in the atria. Natriuretic peptides are released early after STEMI, with a peak at approximately 16 hours. Evidence shows that the natriuretic peptides released from the left ventricle during STEMI originate both from the infarcted myocardium and from viable non-infarcted myocardium. The rise in BNP and N-terminal pro-BNP after STEMI correlates with infarct size and regional wall motion abnormalities. Measurement of natriuretic peptides can provide useful information both early and late in the course of STEMI.^{62,63}

Adrenal Cortex. Plasma and urinary 17-hydroxycorticosteroids and ketosteroids, as well as aldosterone, rise markedly in patients with STEMI. Their concentrations correlate directly with the peak level of serum CK, thus implying an association between the stress imposed by larger infarcts and greater secretion of adrenal steroids. The magnitude of the elevation in cortisol correlates with infarct size and mortality. Glucocorticosteroids also contribute to impaired glucose tolerance.

Thyroid Gland. Although patients with STEMI are generally euthyroid clinically, serum triiodothyronine (T₃) levels can decrease transiently, a fall that is most marked on approximately the third day after the infarct. A rise in reverse T₃ usually accompanies this fall in T₃, with variable changes or no change in thyroxine (T₄) and thyroid-stimulating hormone levels. The alteration in peripheral T₄ metabolism appears to correlate with infarct size and may be mediated by the rise in endogenous levels of cortisol that accompanies STEMI.

Renal Function. Both prerenal azotemia and acute renal failure can complicate the marked reduction in cardiac output that occurs in cardiogenic shock. On the other hand, an increase in circulating atrial natriuretic peptide occurs following STEMI and correlates with the severity of LV failure. An increase in natriuretic peptide also occurs when RV infarction accompanies inferior wall infarction, thus suggesting that this hormone may contribute to the hypotension that accompanies RV infarction.

Hematologic Alterations

Platelets. STEMI generally occurs in the presence of extensive coronary and systemic atherosclerotic plaque, which may serve as the site for the formation of platelet aggregates—a sequence suggested as the initial step in the process of coronary thrombosis, coronary occlusion, and subsequent MI. Platelets from patients with STEMI have an increased propensity for aggregation both systemically and locally in the area of disrupted plaque, and they release vasoactive substances.⁶⁴

Hemostatic Markers. Elevated levels of serum fibrinogen degradation products, an end product of thrombosis, as well as release of distinctive proteins when platelets are activated (such as platelet factor 4 and beta-thromboglobulin), occur in some patients with STEMI. Fibrinopeptide A (FPA), a protein released from fibrin by thrombin, is a marker of ongoing thrombosis and increases during the early hours

of STEMI. Marked elevation of hemostatic markers such as FPA, TAT, and F1.2 is associated with an increased risk for mortality in patients with STEMI. Interpretation of coagulation test results in patients with STEMI may be complicated by elevated blood levels of catecholamines, concomitant shock, and/or pulmonary embolism—conditions that may alter various tests of platelet and coagulation function. Additional factors that affect coagulation test results in patients with STEMI include the type and dosage of antithrombotic agent and reperfusion of the infarct artery.

Leukocytes. Leukocytosis usually accompanies STEMI in proportion to the magnitude of the necrotic process, elevated glucocorticoid levels, and possibly inflammation in the coronary arteries. The magnitude of the elevation in leukocyte count is associated with in-hospital mortality after STEMI.⁶⁵ Experimental evidence suggests that the surge in catecholamines after coronary occlusion can mobilize leukocyte progenitors from bone marrow, thereby sustaining the inflammatory response following infarction.⁶⁶

Blood Viscosity. Clinical and epidemiologic studies suggest that several hemostatic and hemorheologic factors (e.g., fibrinogen, factor VII, plasma viscosity, hematocrit, red blood cell aggregation, total white blood cell count) participate in the pathophysiology of atherosclerosis and play an integral role in acute thrombotic events. An increase in blood viscosity also occurs in patients with STEMI and can be attributed to hemoconcentration during the first few days and later to elevated serum concentrations of alpha₂-globulin and fibrinogen, components of the acute-phase response to tissue necrosis that also cause the elevated sedimentation rate characteristic of STEMI.

CLINICAL FEATURES

Predisposing Factors

Up to half of patients with STEMI have an identifiable precipitating factor or prodromal symptoms. Unusually heavy exercise (particularly in fatigued or habitually inactive patients) and emotional stress can precipitate STEMI.⁶⁷ Such infarctions could result from marked increases in myocardial oxygen consumption in the presence of severe coronary arterial narrowing.

Accelerating angina and rest angina, two patterns of unstable angina, may culminate in STEMI (see Fig. 51-1). Noncardiac surgical procedures may also precede STEMI. Perioperative risk stratification and preventive measures may limit STEMI and cardiac-related mortality (see Chapter 80).⁶⁸ Reduced myocardial perfusion secondary to hypotension (e.g., hemorrhagic or septic shock) and the increased myocardial oxygen demands caused by aortic stenosis, fever, tachycardia, and agitation can also contribute to myocardial necrosis. Other factors reported to predispose to STEMI include respiratory infections, hypoxemia from any cause, pulmonary embolism, hypoglycemia, administration of ergot preparations, cocaine use, sympathomimetics, serum sickness, allergy, and rarely, wasp stings. In patients with Prinzmetal angina (see Chapter 54), STEMI may develop in the territory of the coronary artery that repeatedly undergoes spasm.

Circadian Periodicity

The time of onset of STEMI has a pronounced circadian periodicity, with the peak incidence of events occurring in the morning.²⁸ Circadian rhythms affect many physiologic and biochemical variables; the early morning hours are associated with increases in plasma catecholamines and cortisol and in platelet aggregability. Interestingly, the characteristic circadian peak is *absent* in patients receiving a beta-blocking agent or aspirin before the development of STEMI. The concept of “triggering” a STEMI is complex and probably involves the superimposition of multiple factors such as the time of day, season, and the stress of natural disasters.⁶⁹

History (See also Chapters 11, 50, and 53) Prodromal Symptoms

The patient's history remains crucial to establishing a diagnosis of STEMI. Chest discomfort resembling classic angina pectoris usually

characterizes the prodrome, but it occurs at rest or with less activity than usual. Yet the symptoms are often not disturbing enough to induce patients to seek immediate medical attention, and if they do, they may not be hospitalized. A feeling of general malaise or frank exhaustion frequently accompanies other symptoms preceding STEMI.

Nature of the Pain

Pain in patients with STEMI varies in intensity; in most patients it is severe and in some instances is intolerable. The pain is prolonged—it generally lasts for more than 30 minutes and frequently for several hours. The patient usually describes the discomfort as constricting, crushing, oppressing, or compressing and often complains of a sensation of a heavy weight or a squeezing in the chest. Although patients typically describe the discomfort as a choking, viselike, or heavy pain, it can also be characterized as a stabbing, knifelike, boring, or burning discomfort. The discomfort usually localizes retrosternally and frequently spreads to both sides of the anterior part of the chest, with a predilection for the left side. Often the pain radiates down the ulnar aspect of the left arm and produces a tingling sensation in the left wrist, hand, and fingers. Some patients note only a dull ache or numbness of the wrists in association with severe substernal or precordial discomfort. In some patients, pain from STEMI may begin in the epigastrium and simulate a variety of abdominal disorders, which often causes STEMI to be misdiagnosed as “indigestion.” In other patients the discomfort of STEMI radiates to the shoulders, upper extremities, neck, jaw, and interscapular region, again usually favoring the left side. In patients with preexisting angina pectoris, the pain of infarction generally resembles that of angina with respect to location, but it is normally much more severe, lasts longer, and is not relieved by rest and nitroglycerin.

STEMI pain may subside by the time that the physician first encounters the patient (or the patient reaches the hospital), or it may persist for many hours. Opiates, particularly morphine, usually relieve the pain (see Chapter 52). Both angina pectoris and STEMI pain are thought to arise from nerve endings in ischemic or injured, but not necrotic myocardium. Thus in cases of STEMI, stimulation of nerve fibers in an ischemic zone of myocardium surrounding the necrotic central area of infarction probably gives rise to the pain.

The pain often disappears suddenly and completely following restoration of blood flow to the infarct territory. In patients in whom reocclusion occurs after fibrinolysis, pain recurs if the initial reperfusion has left viable myocardium. Thus what has previously been thought of as the “pain of infarction,” sometimes lasting for many hours, probably represents pain caused by ongoing ischemia. The recognition that pain implies ischemia and not infarction heightens the importance of seeking ways to relieve the ischemia, for which the pain is a marker. This finding suggests that clinicians should *not* be complacent about ongoing cardiac pain in any circumstances. In some patients—particularly older adults, patients with diabetes, and heart transplantation recipients—STEMI is manifested clinically not by chest pain but rather by symptoms of acute LV failure and chest tightness or by marked weakness or frank syncope. Diaphoresis, nausea, and vomiting may accompany these symptoms.

Other Symptoms

Nausea and vomiting may occur, presumably because of activation of the vagal reflex or stimulation of LV receptors as part of the Bezold-Jarisch reflex. These symptoms occur more commonly in patients with inferior STEMI than in those with anterior STEMI. Moreover, nausea and vomiting are common side effects of opiates. When the pain of STEMI is epigastric in location and associated with nausea and vomiting, the clinical picture can easily be confused with that of acute cholecystitis, gastritis, or peptic ulcer. Occasionally, a patient complains of diarrhea or a violent urge to defecate during the acute phase of STEMI. Other symptoms include feelings of profound weakness, dizziness, palpitations, cold perspiration, and a sense of impending doom. On occasion, symptoms arising from an episode of cerebral embolism or other systemic arterial embolism can herald STEMI. Chest discomfort may not accompany these symptoms.

Differential Diagnosis

STEMI pain may simulate that of acute pericarditis (see Chapter 71), which is usually associated with some pleuritic features—it is aggravated by respiratory movements and coughing and often involves the shoulder, ridge of the trapezius, and neck. An important feature that distinguishes pericardial pain from ischemic discomfort is that ischemic discomfort does not radiate to the trapezius ridge, a characteristic site of radiation of pericardial pain. Pleural pain is generally sharp, knifelike, and aggravated in a cyclical fashion by each breath, which distinguishes it from the deep, dull, steady pain of STEMI. Pulmonary embolism (see Chapter 73) typically produces pain laterally in the chest, is often pleuritic in nature, and may be associated with hemoptysis. The pain caused by acute aortic dissection (see Chapter 57) is usually localized to the center of the chest, is extremely severe and described by the patient as a “ripping” or “tearing” sensation, is at its maximal intensity shortly after onset, persists for many hours, and frequently radiates to the back or lower extremities. Often, one or more major arterial pulses are absent. Pain arising from the costochondral and chondrosternal articulations may be associated with localized swelling and redness; it is generally sharp and “darting” and is characterized by marked localized tenderness. Episodes of retrosternal discomfort induced by peristalsis in patients with increased esophageal stiffness and episodes of sustained esophageal contraction can mimic the pain of STEMI.

Silent ST-Elevation Myocardial Infarction with Atypical Features

Nonfatal STEMI can go unrecognized by the patient and be manifested only on subsequent routine electrocardiographic or postmortem examinations. Of these unrecognized infarctions, approximately half are truly silent, with patients unable to recall any symptoms whatsoever. The other half of patients with so-called *silent infarction* can recall an event characterized by symptoms compatible with acute infarction when leading questions are posed after the electrocardiographic abnormalities are discovered. Unrecognized or silent infarction occurs more commonly in patients without antecedent angina pectoris and in patients with diabetes and hypertension and are typically detected by identification of new wall motion abnormalities, fixed perfusion defects, or pathologic Q waves.⁷⁰ Silent STEMI is often followed by silent ischemia (see Chapter 54). The prognosis of patients with silent and symptomatic manifestations of STEMI appears to be quite similar.^{71,72}

Atypical features of STEMI include the following: (1) heart failure (i.e., dyspnea without pain beginning de novo or worsening of established failure), (2) classic angina pectoris without a particularly severe or prolonged episode, (3) atypical location of the pain, (4) central nervous system manifestations resembling those of stroke secondary to a sharp reduction in cardiac output in a patient with cerebral arteriosclerosis, (5) apprehension and nervousness, (6) sudden mania or psychosis, (7) syncope, (8) overwhelming weakness, (9) acute indigestion, and (10) peripheral embolization. Women are seen more frequently than men with “atypical” features, and hence a high “index of suspicion” is required by the clinician (see Chapter 77).

Physical Examination (See also Chapter 11)

General Appearance

Patients suffering from STEMI often appear anxious and in considerable distress. An anguished facial expression is common, and—in contrast to patients with severe angina pectoris, who often lie, sit, or stand still because all forms of activity increase the discomfort—some patients suffering from STEMI may be restless and move about in an effort to find a comfortable position. They often massage or clutch their chests and frequently describe their pain with a clenched fist held against the sternum (the Levine sign, named after Dr. Samuel A. Levine). In patients with LV failure and sympathetic stimulation, cold perspiration and skin pallor may be evident; they typically sit or are propped up in bed and gasp for breath. Between breaths they may complain of chest discomfort or a feeling of suffocation. Cough producing frothy, pink, or blood-streaked sputum may occur.



Patients in cardiogenic shock often lie listlessly and make few spontaneous movements. Their skin is cool and clammy, with a bluish or mottled color over the extremities, and there is marked facial pallor with severe cyanosis of the lips and nail beds. Depending on the degree of cerebral perfusion, a patient in shock may converse normally or be confused.

Heart Rate

The heart rate can vary from marked bradycardia to a rapid regular or irregular tachycardia, depending on the underlying rhythm and degree of LV failure. Most commonly the pulse is rapid and regular initially (sinus tachycardia at 100 to 110 beats/minute) and slows as the patient's pain and anxiety are relieved; premature ventricular beats are common.

Blood Pressure

Most patients with uncomplicated STEMI are normotensive, although the reduced stroke volume accompanying the tachycardia can cause declines in systolic and pulse pressure and elevation of diastolic pressure. In previously normotensive patients, a hypertensive response is occasionally seen during the first few hours, presumably as a consequence of adrenergic discharge secondary to pain, anxiety, and agitation. Previously hypertensive patients often become normotensive without treatment after STEMI, although many of them eventually regain their elevated levels of blood pressure, generally 3 to 6 months after infarction. In patients with massive infarction, arterial pressure falls acutely because of LV dysfunction and may be exacerbated by morphine and/or nitrates, which cause venous pooling; as recovery occurs, arterial pressure tends to return to preinfarction levels.

Patients in cardiogenic shock by definition have systolic pressure below 90 mm Hg and evidence of end-organ hypoperfusion. Hypotension alone does not necessarily signify cardiogenic shock, however; some patients with inferior infarction and activation of the Bezold-Jarisch reflex may also transiently have systolic blood pressure below 90 mm Hg. Their hypotension eventually resolves spontaneously, although the process can be accelerated by intravenous atropine (0.5 to 1 mg) and assumption of the Trendelenburg position. Other patients who are initially only slightly hypotensive may demonstrate gradually falling blood pressure with a progressive reduction in cardiac output over a period of several hours or days as cardiogenic shock develops because of increasing ischemia and extension of infarction (Fig. 51-14). Evidence of autonomic hyperactivity is common and varies in type with the location of the infarction. More than half of patients with inferior STEMI have evidence of excess parasympathetic stimulation, with hypotension, bradycardia, or both evident during initial evaluation, whereas approximately half of patients with anterior STEMI show signs of sympathetic excess and have hypertension, tachycardia, or both.

Temperature and Respiration

Fever, a nonspecific response to tissue necrosis, develops in most patients with extensive STEMI within 24 to 48 hours of the onset of infarction. Body temperature often begins to rise within 4 to 8 hours after the onset of infarction, and rectal temperature may reach 38.3°C to 38.9°C (101°F to 102°F). The fever usually resolves by the fourth or fifth day after infarction.

The respiratory rate may rise slightly soon after the development of STEMI; in patients without heart failure, it results from anxiety and pain and returns to normal with treatment of the physical and psychological discomfort. In patients with LV failure, the respiratory rate correlates with the severity of the failure; patients with pulmonary edema may have respiratory rates exceeding 40 per minute. However, the respiratory rate is not necessarily elevated in patients with cardiogenic shock. Cheyne-Stokes (periodic) respiration may occur in elderly individuals with cardiogenic shock or heart failure, particularly after opiate therapy or in the presence of cerebrovascular disease.

Jugular Venous Pulse

The jugular venous pulse is usually normal. The α wave may be prominent in patients with pulmonary hypertension secondary to LV

failure or reduced compliance. In contrast, RV infarction (regardless of whether it accompanies LV infarction) often results in marked jugular venous distention and, when complicated by necrosis or ischemia of RV papillary muscles, in the tall $c-v$ waves of tricuspid regurgitation. Patients with STEMI and cardiogenic shock generally have elevated jugular venous pressure. In patients with STEMI, hypotension, and hypoperfusion (findings that may resemble those of patients with cardiogenic shock) who have flat neck veins, the depression in LV performance is probably related, at least in part, to hypovolemia. Differentiation can be made only by assessing LV performance with echocardiography or by measuring LV filling pressure with a pulmonary artery flotation catheter.

Carotid Pulse

Palpation of the carotid arterial pulse provides a clue to LV stroke volume: a small pulse suggests reduced stroke volume, whereas a sharp, brief upstroke often occurs in patients with mitral regurgitation or a ruptured ventricular septum with a left-to-right shunt. Pulsus alternans reflects severe LV dysfunction.

The Chest

Moist rales are audible in patients in whom LV failure and/or a reduction in LV compliance with STEMI develops. Diffuse wheezing can occur in patients with severe LV failure. Cough with hemoptysis, suggesting pulmonary embolism with infarction, can also occur. In 1967, Thomas Killip proposed a prognostic classification scheme on the basis of the presence and severity of rales in patients with STEMI. Class I patients are free of rales and a third heart sound. Class II patients have rales, but only to a mild to moderate degree (<50% of lung fields), and may or may not have an S_3 . Patients in class III have rales in more than half of each lung field and frequently have pulmonary edema. Finally, class IV patients are in cardiogenic shock. Despite the overall improvement in the mortality rate that has now been achieved in each class, when compared with data observed during original development of the classification scheme, it still remains useful today, as evidenced by data from large MI trials of patients with STEMI.^{73,74}

Cardiac Examination

Palpation

Palpation of the precordium may yield normal results, but in patients with transmural STEMI, it more commonly reveals a presystolic pulsation synchronous with an audible fourth heart sound, a finding reflecting vigorous left atrial contraction filling a ventricle with reduced compliance. In patients with LV systolic dysfunction, an outward movement of the left ventricle can be palpated in early diastole, coincident with a third heart sound.

Auscultation

HEART SOUNDS. The heart sounds, particularly the first sound, are frequently muffled and occasionally inaudible immediately after an infarct, and their intensity increases during convalescence. A soft first heart sound may also reflect prolongation of the PR interval. Patients with marked ventricular dysfunction and/or left bundle branch block may have paradoxical splitting of the second heart sound.

A fourth heart sound is almost universally present in patients in sinus rhythm with STEMI, but it has limited diagnostic value because it is commonly audible in most patients with chronic ischemic heart disease and is recordable, although not often audible, in many normal subjects older than 45 years.

A third heart sound in patients with STEMI usually reflects severe LV dysfunction with elevated ventricular filling pressure. It is caused by rapid deceleration of transmural blood flow during protodiastolic filling of the left ventricle and is typically heard in patients with large infarctions. This sound is detected best at the apex with the patient in the left lateral recumbent position. A third heart sound may be caused not only by LV failure but also by increased inflow into the left ventricle, as occurs when mitral regurgitation or a ventricular septal defect complicates STEMI. Third and fourth heart sounds

emanating from the left ventricle are heard best at the apex; in patients with RV infarcts, these sounds can be heard along the left sternal border and increase on inspiration.

MURMURS. Systolic murmurs—transient or persistent—are commonly audible in patients with STEMI and generally result from mitral regurgitation secondary to dysfunction of the mitral valve apparatus (papillary muscle dysfunction, LV dilation). A new, prominent, apical holosystolic murmur accompanied by a thrill may represent rupture of a head of a papillary muscle (see Chapter 52). The findings in cases of rupture of the interventricular septum are similar, although the murmur and thrill are usually most prominent along the left sternal border and may be audible at the right sternal border as well. The systolic murmur of tricuspid regurgitation (caused by RV failure because of pulmonary hypertension and/or RV infarction or by infarction of an RV papillary muscle) is also heard along the left sternal border. It is characteristically intensified by inspiration and is accompanied by a prominent *c-v* wave in the jugular venous pulse and an RV fourth sound.

FRiction RUBS. Pericardial friction rubs may be heard in patients with STEMI, especially in those sustaining large transmural infarctions.⁷⁵ Rubs are notorious for their evanescence and hence are probably even more common than reported. Although friction rubs can be heard within 24 hours or as late as 2 weeks after the onset of infarction, they occur most commonly on the second or third day. Occasionally, in patients with extensive infarction, a loud rub can be heard for many days. Patients with STEMI and a pericardial friction rub may have a pericardial effusion on echocardiographic study, but it only rarely causes the classic electrocardiographic changes of pericarditis. Delayed onset of the rub and the associated discomfort of pericarditis (as late as 3 months after infarction) is characteristic of the now rare post-MI (Dressler) syndrome.

Pericardial rubs are most readily audible along the left sternal border or just inside the apical impulse. Loud rubs may be audible over the entire precordium and even over the back. Occasionally, only the systolic portion of a rub is heard, which requires distinction from a systolic murmur, such as might result from rupture of the ventricular septum or mitral regurgitation.

Other Findings

Fundi

Hypertension, diabetes, and generalized atherosclerosis commonly accompany STEMI and can produce characteristic changes in the fundus. A funduscopic examination may provide information concerning the underlying vascular status, which can be particularly useful in patients unable to provide a detailed history.

Abdomen

Patients often interpret pain in the abdomen associated with nausea, vomiting, restlessness, and even abdominal distention as a sign of “indigestion,” and it results in self-medication with antacids; it can also suggest an acute abdominal process to the physician. Right-sided heart failure, characterized by hepatomegaly and a positive abdominojugular reflux, is unusual in patients with acute LV infarction but occurs in patients with severe and prolonged LV failure or RV infarction.

Extremities

Coronary atherosclerosis is often associated with systemic atherosclerosis, and therefore patients with STEMI may have a history of intermittent claudication and demonstrate the physical findings of peripheral vascular disease (see Chapter 58). Thus diminished peripheral arterial pulses, loss of hair, and atrophic skin in the lower extremities may be noted in patients with coronary artery disease. Peripheral edema is a manifestation of RV failure and, like congestive hepatomegaly, is unusual in patients with acute LV infarction. Cyanosis of the nail beds is common in patients with severe LV failure and is particularly striking in patients in cardiogenic shock.

Neuropsychiatric Findings

Except for the altered mental status that occurs in patients with STEMI who have markedly reduced cardiac output and cerebral

hypoperfusion, findings on neurologic examination are normal unless the patient has suffered cerebral embolism secondary to a mural thrombus. The coincidence between these two conditions can be explained by systemic hypotension caused by STEMI precipitating a cerebral infarction and the converse, as well as by mural emboli from the left ventricle causing cerebral emboli.

Patients with STEMI frequently exhibit alterations in their emotional state, including intense anxiety, denial, and depression. Medical staff caring for patients with STEMI must be sensitive to changes in the patient's emotional state; a calm, professional atmosphere, with thorough explanations of equipment and prognosis, can help alleviate the distress associated with STEMI.

Laboratory Findings

Serum Markers of Cardiac Damage

Myocardial injury can be detected by the presence of circulating proteins released from damaged myocardial cells. Even though the availability of serum and plasma cardiac markers with markedly enhanced sensitivity for myocardial injury has enabled clinicians to identify much lower levels of injury, it is important to clarify that biochemical tests of myocardial injury do not provide any direct insight into the cause of the damage.^{76,77} MI is the diagnosis given to myocardial injury that results from ischemia (Fig. 51-15).¹ Other nonischemic insults, such as myocarditis or direct myocardial toxins, may result in myocardial injury but should not be labeled MI. Moreover, the enhanced ability to detect myocardial damage has increased the number of cases of myocardial injury that result from non-plaque-related clinical events, thus necessitating the establishment of new criteria for MI (see Table 51-1, 51-2, and 51-4) that place the injury in clinical context.¹

Although the following section applies more to diagnostic decision making for patients with suspected ACS without ST-segment elevation (see Chapter 53), this chapter contains a general discussion of cardiac biomarkers because of the overlapping pathophysiologic concepts and methodology when biomarkers are used to evaluate patients with STEMI. It should be emphasized that clinicians should *not* wait for the results of biomarker assays to initiate treatment of patients with STEMI. Given the time urgency for reperfusion in patients with STEMI, the 12-lead ECG should serve to initiate such strategies.

Necrosis compromises the integrity of the sarcolemmal membrane; intracellular macromolecules (serum and plasma cardiac markers) begin to diffuse into the cardiac interstitium and ultimately into the microvasculature and lymphatics in the region of the infarct (Fig. 51-16; also see Table 51-4). The rate of appearance of these macromolecules in the peripheral circulation depends on several factors, including intracellular location, molecular weight, local blood and lymphatic flow, and the rate of elimination from blood.⁷⁸

Cardiac-Specific Tropionins

The preferred biomarker to detect myocardial injury is cardiac troponin, which consists of three subunits that regulate the calcium-mediated contractile process of striated muscle.¹ These subunit include troponin C, which binds Ca^{2+} ; troponin I (TnI), which binds to actin and inhibits actin-myosin interactions; and troponin T (TnT), which binds to tropomyosin, thereby attaching the troponin complex to the thin filament (Fig. 51-16). Although most TnT is incorporated in the troponin complex, approximately 6% to 8% is dissolved in the cytosol; in contrast, approximately 2% to 3% of TnI is found in a cytosolic pool. Following myocyte injury, the initial release of cardiac-specific TnT and TnI is from the cytosolic pool, followed subsequently by release from the structural (myofilament-bound) pool (Fig. 51-16).⁷⁸ Different genes encode TnT and TnI in cardiac and skeletal muscle, thus permitting the production of specific antibodies for the cardiac forms (cTnT and cTnI), which enables quantitative measurement of them (Fig. 51-16).^{78,79} Detection of a rise and fall in cTnT or cTnI in the appropriate clinical setting is now at the center of the new diagnostic criteria for MI.¹

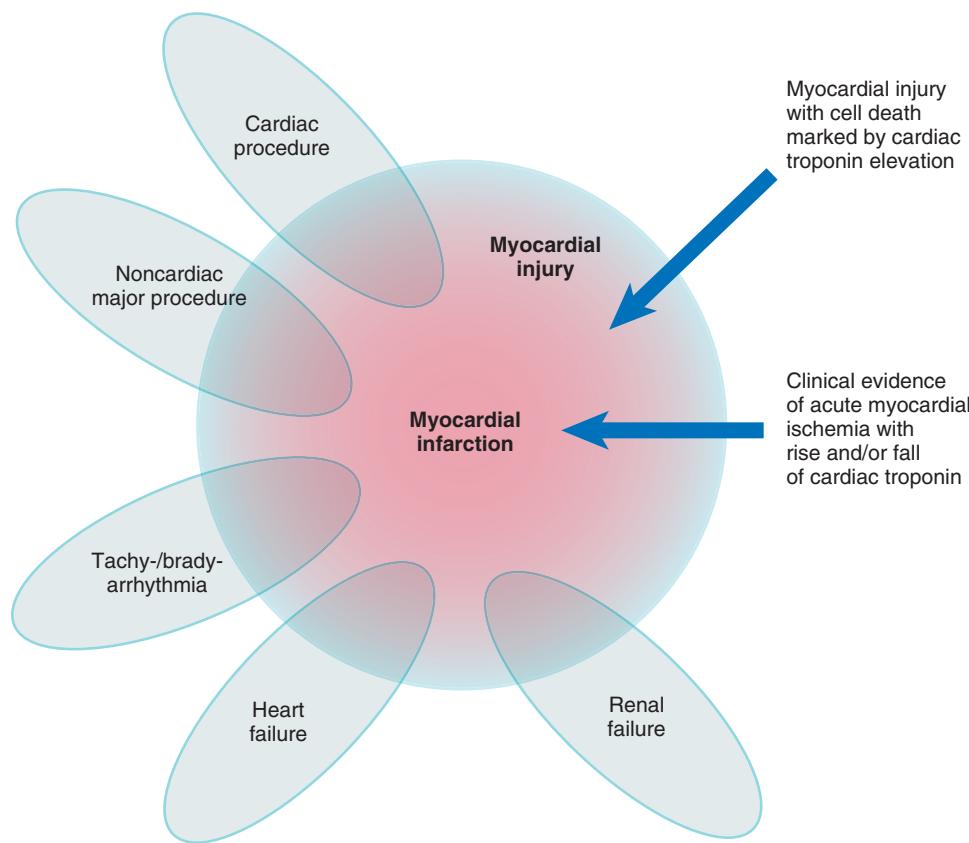


FIGURE 51-15 Myocardial ischemia and subsequent myocardial injury can result from a variety of clinical entities, including renal failure, heart failure, tachyarrhythmia or bradycardia, and cardiac or noncardiac procedures. Each of these scenarios can result in myocardial injury with cell death marked by the release of detectable circulating levels of cardiac troponin. However, each of these entities can also be associated with MI when there is clinical evidence of acute myocardial ischemia with a typical rise and/or fall in cardiac troponin levels. (From Thygesen K, Alpert JS, Jaffe AS, et al: *Third universal definition of myocardial infarction*. *J Am Coll Cardiol* 60:1581, 2012.)

When interpreting the results of assays for cTnT or cTnI, clinicians must recognize several analytic issues.^{77,80} cTnI assays are produced by multiple manufacturers using different troponin epitopes for detection, which has resulted in varying reference levels.^{78,79} A single manufacturer has commercialized cTnT, thereby leading to greater uniformity of the recommended cutoff. The release pattern of troponin complexes, conformational changes, and degradation into various troponin fragments may differentially affect the results of various commercial assays. Such post-translational modifications may provide insight into the underlying cause and timing of release (e.g., differentiating ischemia from myocarditis), but such applications remain investigational.

CUTOFF VALUES. Variations in the cutoff concentration for abnormal levels of cTnI in the clinically available immunoassays result in part from the different specificities of the antibodies used for detecting free and complexed cTnI. Thus clinicians should apply evidence-based cutoff values for the particular assay used in their laboratory.^{78,79} For both cTnT and cTnI, the definition of an abnormally increased level is a value exceeding that of 99% of a reference control group. Assays that have a level of imprecision (i.e., coefficient of variation) of less than 10% at the specific 99th percentile cutoff are optimal for clinical practice.¹

In patients with MI, cTnT and cTnI first begin to rise by approximately 3 hours after the onset of chest pain. Because of continuous release from a degenerating contractile apparatus in necrotic myocytes, elevations in cTnI may persist for 7 to 10 days after MI; elevations in cTnT may persist for up to 10 to 14 days. The prolonged time course of the elevation in cTnT and cTnI is advantageous for the late diagnosis of MI (Fig. 51-16). Patients with STEMI who undergo successful recanalization of the infarct-related artery have a rapid release of cardiac troponins, which can indicate reperfusion (Fig. 51-17).

HIGH-SENSITIVITY CARDIAC TROPONIN

Newer high-sensitivity assays that deliver enhanced analytic performance enable more precise measurement of very low concentrations of cardiac-specific troponin. Experts recommend that the term high-sensitivity troponin (hsTn) be reserved for assays that can detect cardiac troponin in more than 50% of an apparently healthy population.^{78,79} Such assays are substantially more sensitive than previous-generation assays but also have diminished clinical specificity for MI because they detect true myocardial injury in a variety of other clinical settings.⁷⁶ Nevertheless, in multiple studies of patients with nontraumatic chest pain, hsTn assays have improved overall diagnostic accuracy and enabled earlier detection of myocardial injury^{81,82} (see Fig. 51-16). Moreover, even low-level elevations in cardiac troponin detected with sensitive assays are associated with a worse prognosis.⁸³

Creatine Kinase-MB

If a cardiac-specific troponin assay is not available, CK-MB measured with a mass assay is the best alternative. Cardiac muscle contains both the MM and MB isoenzymes of CK. Other tissues can contain small quantities of the MB isoenzyme of CK, including the small intestine, tongue, diaphragm, uterus, and prostate. Strenuous exercise, particularly in trained long-distance runners or professional athletes, can cause an elevation in both total CK and CK-MB.

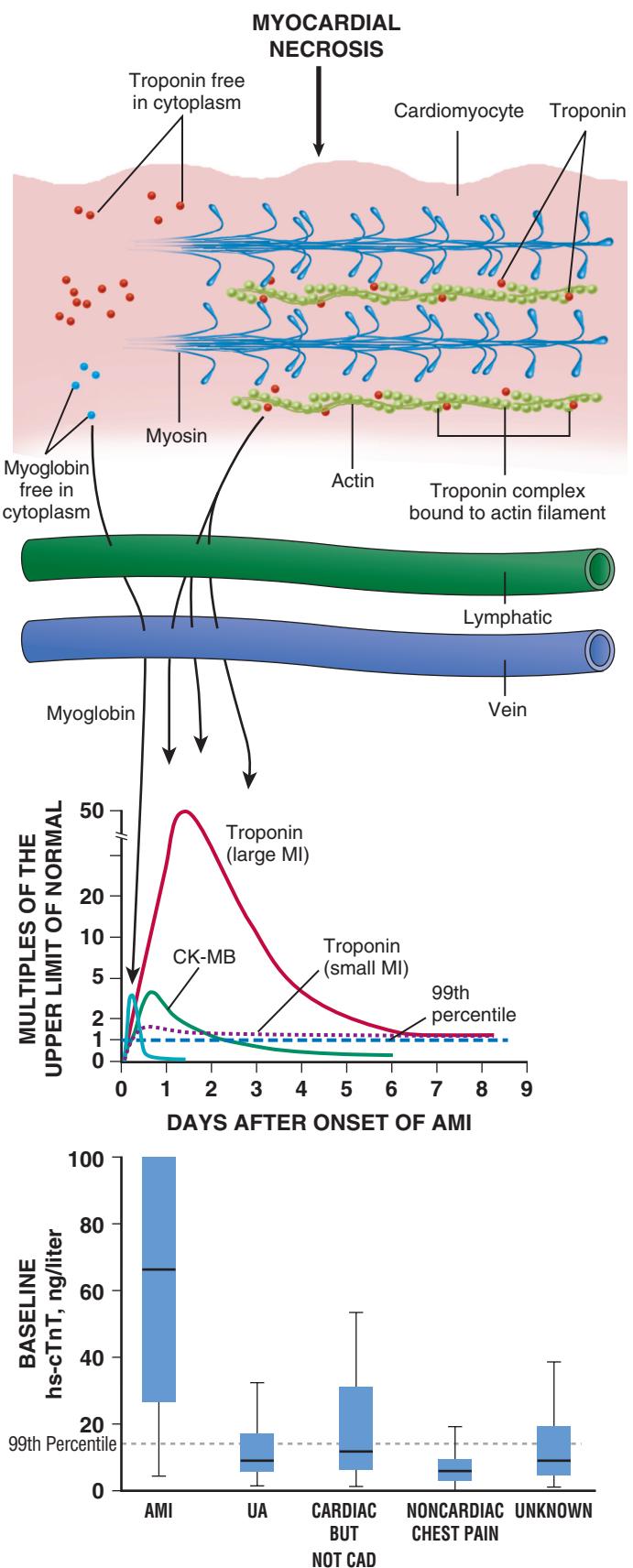
Because CK-MB can be detected in the blood of healthy subjects, the cutoff value for abnormal elevation of CK-MB is usually set a few units above the upper reference limit for a given laboratory (see Fig. 51-16). Like cardiac-specific troponin, the diagnosis of MI requires a maximal concentration of CK-MB exceeding the 99th percentile of values for sex-specific reference levels on two successive samples in a rise and fall pattern.¹ CK-MB is inaccurate in circumstances involving skeletal muscle injury.

Recommendations for Measurement of Serum Markers

All patients with suspected MI should undergo measurement of cardiac-specific troponin as soon as possible after the initial encounter. In patients with STEMI, the results of biomarker assessment should not delay interventions to achieve immediate reperfusion. From a cost-effectiveness perspective, measuring both a cardiac-specific troponin and CK-MB is unnecessary.¹ Routine diagnosis of MI can be accomplished by obtaining measurements at initial evaluation and then 3 to 6 hours later (see Table 50-1).¹ Later testing is required only when uncertainty exists regarding the onset of pain or when stuttering symptoms occur.

The universal definition of MI recommends classifying infarctions into five types (see Table 51-2), along with the magnitude of the infarction expressed as the fold elevation in cardiac biomarkers above the 99th percentile of the upper reference limit. An example from a clinical trial comparing prasugrel with clopidogrel as supportive antiplatelet therapy for moderate- to high-risk ACS patients undergoing PCI is shown in Figure 51-18.⁸⁴

Other Biomarkers. Other biomarkers may be used to noninvasively assess the potential causes and complications of MI. C-reactive protein (CRP) rises substantially in the setting of STEMI as a result of



the inflammatory response to myocyte necrosis and is associated with the subsequent risk for death or heart failure. BNP and related peptides reflect the hemodynamic impact of the MI and are associated with prognosis. Although both BNP and CRP enhance risk assessment, no clear guidance is available on how to structure specific therapeutic maneuvers in the setting of STEMI in response to these biomarkers.⁸⁵

FIGURE 51-16 Release of biomarkers into the circulation begins with prolonged ischemia and subsequent necrosis that results in loss of integrity of the cellular membranes. After disruption of the sarcolemmal membrane of the cardiomyocyte, the cytoplasmic pool of biomarkers is released first (left-most arrow in the bottom portion of the figure). Markers such as myoglobin and CK isoforms are released rapidly, and blood levels rise quickly above the cutoff limit. More protracted release of biomarkers from the disintegrating myofilaments follows and may continue for several days (three-headed arrow). Cardiac troponin levels rise to about 20 to 50 times the upper reference limit (the 99th percentile of values in a reference control group) in patients who have "classic" acute MI and sustain sufficient myocardial necrosis that results in abnormally elevated levels of CK-MB. Clinicians can now diagnose episodes of microinfarction by more sensitive assays that detect even small elevations in cardiac troponin above the upper reference limit, even though levels of CK-MB and troponin determined from older generations of assays may still be below the MI decision limit. Other causes of myocardial injury, such as renal failure or pulmonary embolism, can lead to detectable levels of cardiac troponin even without any coronary artery disease (lower panel). AMI = acute MI; CAD = coronary artery disease; UA = unstable angina. (Modified from Antman EM: Decision making with cardiac troponin tests. *N Engl J Med* 346:2079, 2002; Jaffe AS, Babuin L, Apple FS: Biomarkers in acute cardiac disease: The present and the future. *J Am Coll Cardiol* 48:1, 2006; and Reichlin T, Schindler C, Drexler B, et al: One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin. *T. Arch Intern Med* 172:1211, 2012.)

Future studies evaluating novel biomarkers should focus on unmet clinical scenarios such as earlier detection of MI, differentiation of type I from type II MI, and improved risk stratification.⁸⁶ Markers such as copeptin, pregnancy-associated plasma protein-A (PAPP-A), fms-like tyrosine kinase (Flt-1), heart-type fatty acid-binding protein (H-FABP), and growth differential factor-15 (GDF-15) may offer insight into the different pathophysiologic processes in MI.^{63,87}

Other Laboratory Measurements

Serum Lipids (See Chapter 45). During the first 24 to 48 hours after admission, total cholesterol and high-density lipoprotein (HDL) cholesterol remain at or near baseline values, but they generally fall after that. The fall in HDL cholesterol after STEMI is greater than the fall in total cholesterol; thus the ratio of total cholesterol to HDL cholesterol is no longer useful for risk assessment unless measured early after MI. A lipid profile should be obtained on all patients with STEMI who are admitted within 24 hours of symptoms.⁸⁸ Lipid levels may still be clinically useful for patients admitted beyond 24 to 48 hours,⁸⁹ although more accurate determinations of serum lipid levels are obtained about 8 weeks after the infarction has occurred.

Hematologic Findings. Elevation of the white blood cell count usually develops within 2 hours after the onset of chest pain, reaches a peak 2 to 4 days after infarction, and returns to normal in 1 week; the peak white blood cell count generally ranges between 12 and $15 \times 10^3/\text{mL}$ but occasionally rises to as high as $20 \times 10^3/\text{mL}$ in patients with large STEMI. Frequently there is an increase in the percentage of polymorphonuclear leukocytes and a shift of the differential count to band forms. An epidemiologic association has been reported, with a worse angiographic appearance of the culprit lesions and increased risk for adverse clinical outcomes the higher the white blood cell count at initial evaluation in patients with an ACS.⁹⁰

The erythrocyte sedimentation rate (ESR) is usually normal during the first day or two after infarction, even though fever and leukocytosis may be present. It then rises to a peak on the fourth or fifth day and may remain elevated for several weeks. The increase in the ESR does not correlate well with the size of the infarction or with prognosis. The hematocrit often increases during the first few days after infarction as a consequence of hemoconcentration.

The hemoglobin value at initial evaluation of a patient with STEMI powerfully and independently predicts major cardiovascular events. Of note is a J-shaped relationship between baseline hemoglobin values and clinical events. Cardiovascular mortality increases progressively as the initial hemoglobin value falls below 14 to 15 g/dL; conversely, it also rises as the hemoglobin level increases above 17 g/dL. The increased risk from anemia is probably related to diminished tissue delivery of oxygen, whereas the increased risk with polycythemia may be related to an increase in blood viscosity.⁹¹

Electrocardiography (See Chapter 12)

Serial changes on the ECG develop in most patients with STEMI, but many factors limit the usefulness of the ECG in diagnosing and localizing MI: the extent of myocardial injury, the age of the infarct, its

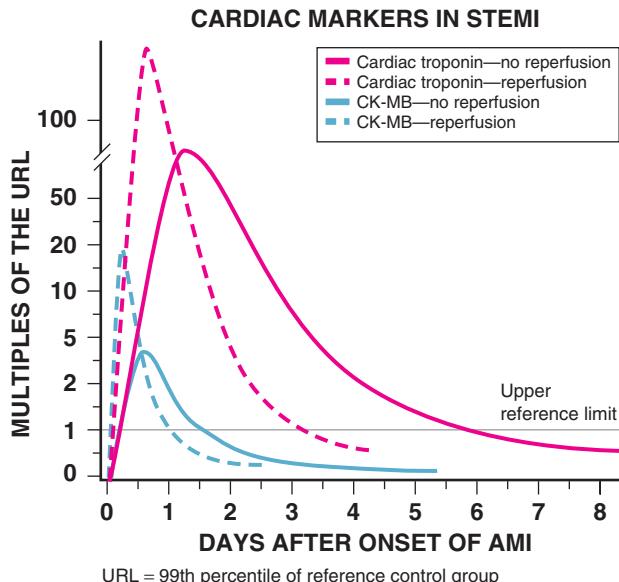


FIGURE 51-17 The kinetics of the release of CK-MB and cardiac troponin in patients who do not undergo reperfusion is shown in the solid blue and red curves as multiples of the URL. When patients with STEMI undergo reperfusion, as depicted in the dashed blue and red curves, the cardiac biomarkers are detected sooner and rise to a higher peak value but decline more rapidly, which results in a smaller area under the curve and limitation of infarct size. AMI = acute MI. (Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. *Circulation* 110:e82, 2004.)

location, the presence of conduction defects, the presence of previous infarcts or acute pericarditis, changes in electrolyte concentrations, and the administration of cardioactive drugs. Abnormalities in the ST segment and T wave are quite nonspecific and may occur in a variety of conditions, including stable and unstable angina pectoris, ventricular hypertrophy, acute and chronic pericarditis, myocarditis, early repolarization, electrolyte imbalance, shock, and metabolic disorders, as well as following the administration of digitalis. Serial ECGs help in differentiating these conditions from STEMI. Transient changes favor angina or electrolyte disturbances, whereas persistent changes argue for infarction if other causes such as shock, administration of digitalis, and persistent metabolic disorders can be eliminated. Nevertheless, serial standard 12-lead ECGs remain an extremely useful method for the detection and localization of MI.⁹²

Analysis of the constellation of ECG leads showing ST elevation may also be useful for identifying the site of occlusion in the infarct artery (see Fig. 51-5).³¹ The extent of ST deviation on the ECG, location of the infarction, and the QRS duration correlate with the risk for adverse outcomes. Even when left bundle branch block is present on the ECG, MI can be diagnosed when striking ST-segment deviation is present beyond what can be explained by the conduction defect (Table 51-5). In addition to the diagnostic and prognostic information contained within the 12-lead ECG, the degree of ST-segment resolution provides valuable noninvasive information about the success of reperfusion for STEMI, regardless of whether it was achieved with fibrinolysis or primary coronary intervention (see Chapter 52).^{93,94}

Although general agreement exists on electrocardiographic and vector cardiographic criteria for the recognition of infarction of the anterior and inferior myocardial walls, less agreement exists on criteria for lateral and posterior infarcts. A consensus group has recommended elimination of the term “posterior” and suggests using “lateral” to be consistent with current understanding of the segmental anatomy of the heart as it sits in the thorax.³¹ The most recent universal definition of MI, however, retains the category of posterior MI.¹ Patients with an abnormal R wave in V₁ (0.04 second in duration and/or R/S ratio ≥ 1 in the absence of preexcitation or RV hypertrophy)

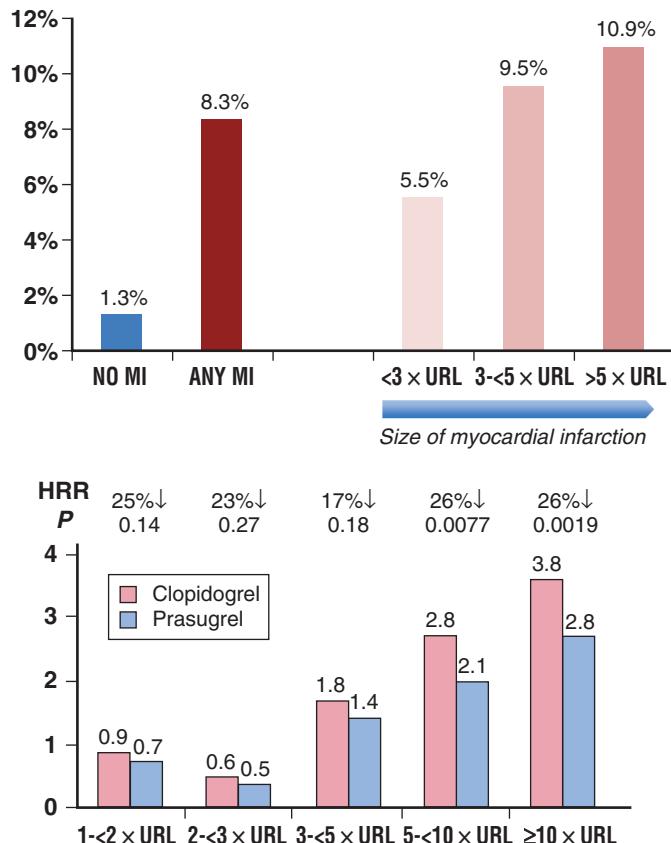


FIGURE 51-18 **Top panel.** Risk for cardiovascular death associated with new or recurrent type I MI stratified according to MI size. **Bottom panel.** Rates of the effect of prasugrel versus clopidogrel with respect to the total number of new or recurrent MIs; the incidence of MI (%) is classified by using the biomarker categories recommended by the universal definition of MI (see Table 51-2). The biomarker categories are groupings of fold elevations above the upper reference limit (URL) of normal. The data shown for each bar are derived from Kaplan-Meier estimates for the incidence of MI; the percent reductions represent the relative reductions in the hazard ratio for the development of an MI in the prasugrel versus clopidogrel groups. HRR = hazard ratio reduction. (From Morrow DA, Wiviott SD, White HD, et al: Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38. An application of the classification system from the universal definition of myocardial infarction. *Circulation* 119:2758, 2009; and Bonaca MP, Wiviott SD, Braunwald E, et al: American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation universal definition of myocardial infarction classification system and the risk of cardiovascular death: Observations from the TRITON-TIMI 38 trial [Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38]. *Circulation* 125:577, 2012.)

and inferior or lateral Q waves have an increased incidence of isolated occlusion of a dominant left circumflex coronary artery without collateral circulation; such patients have a lower ejection fraction, increased end-systolic volume, and higher complication rate than do those with inferior infarction because of isolated occlusion of the right coronary artery.

Although most patients bear the changes from an MI on the ECG for the rest of their lives, particularly if Q waves evolve, in a substantial minority the typical changes disappear, the Q waves regress, and findings on the ECG can even return to normal after a number of years. Under many circumstances, Q wave patterns simulate MI. Conditions that may mimic the electrocardiographic features of MI by producing a pattern of “pseudoinfarction” include ventricular hypertrophy, conduction disturbances, preexcitation, primary myocardial disease, pneumothorax, pulmonary embolism, amyloid heart disease, primary and metastatic tumors of the heart, traumatic heart disease, intracranial hemorrhage, hyperkalemia, pericarditis, early repolarization, and cardiac sarcoidosis.

TABLE 51-5 Electrocardiographic Manifestations of Myocardial Infarction

ELECTROCARDIOGRAPHIC MANIFESTATIONS OF ACUTE MYOCARDIAL ISCHEMIA (IN THE ABSENCE OF LEFT BUNDLE BRANCH BLOCK)	
ST Elevation	
New ST elevation at the J point in two contiguous leads with the following cut points:	
• ≥0.1 mV in all leads (except V ₂ -V ₃)	
• In leads V ₂ -V ₃ the following cut points apply:	
• ≥0.2 mV in men ≥40 years	
• ≥0.25 mV in men <40 years	
• ≥0.15 mV in women	
ST Depression and T Wave Changes	
• New horizontal or down sloping ST depression ≥0.05 mV in two contiguous leads	
• T-wave inversion ≥0.1 mV in two contiguous leads with a prominent R wave or R/S ratio >1	
ELECTROCARDIOGRAPHIC MANIFESTATIONS OF ISCHEMIA IN THE SETTING OF LEFT BUNDLE BRANCH BLOCK	
Electrocardiographic Criterion	Points
ST-segment elevation ≥1 mm and concordant with the QRS complex	5
ST-segment depression ≥1 mm in lead V ₁ , V ₂ , or V ₃	3
ST-segment elevation ≥5 mm and discordant with the QRS complex	2
A score of ≥3 had a specificity of 98% for acute MI	
ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH PREVIOUS MYOCARDIAL INFARCTION (IN THE ABSENCE OF LEFT VENTRICULAR HYPERTROPHY AND LEFT BUNDLE BLOCK)	
Any Q wave in leads V ₂ -V ₃ ≥0.02 sec or a QS complex in leads V ₂ and V ₃	
Q wave ≥0.03 sec and ≥0.1-mV deep or QS complex in leads I, II, aVL, aVF, or V ₄ -V ₆ in any 2 leads of a contiguous lead grouping (I, aVL; V ₁ -V ₅ ; II, III, aVF)	
R wave ≥0.04 sec in V ₁ -V ₂ and R/S ≥1 with a concordant positive T wave in absence of a conduction defect	

Based on criteria from O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61:e78, 2013.

Q-Wave and Non-Q-Wave Infarction

The presence or absence of Q waves on the surface ECG does not reliably distinguish between transmural and nontransmural (subendocardial) MI. Q waves on the ECG signify abnormal electrical activity but are not synonymous with irreversible myocardial damage. Also, the absence of Q waves may simply reflect the insensitivity of the standard 12-lead ECG, especially in zones of the left ventricle supplied by the left circumflex artery (see Fig. 51-5).³¹

Ischemia at a Distance

Patients with new Q waves and ST-segment elevation diagnostic of STEMI in one territory often have ST-segment depression in other territories. These additional ST-segment changes, which imply a poor prognosis, result either from ischemia in a territory other than the area of infarction, termed *ischemia at a distance*, or from reciprocal electrical phenomena. Much attention has been directed toward associated ST-segment depression in the anterior leads when it occurs in patients with acute inferior STEMI. Yet despite the clinical importance of differentiation among causes of anterior ST-segment depression in such patients, including anterior ischemia, inferolateral wall infarction, and true reciprocal changes, such differentiation cannot be made reliably by electrocardiographic or even

vector cardiographic techniques. Although precordial ST-segment depression is more commonly associated with extensive infarction of the lateral or inferior septal segments than with anterior wall subendocardial ischemia, imaging techniques such as echocardiography are necessary to ascertain whether an anterior wall motion abnormality is present.

Right Ventricular Infarction

ST-segment elevation in the right precordial leads (V₁, V₃R through V₆R) is a relatively sensitive and specific sign of RV infarction.³¹ Occasionally, ST-segment elevation in leads V₂ and V₃ results from acute RV infarction; this appears to occur only when injury to the left inferior wall is minimal.⁹⁵ Usually, the concurrent inferior wall injury suppresses this anterior ST-segment elevation resulting from RV injury. Similarly, RV infarction appears to reduce the anterior ST-segment depression often observed with inferior wall MI. A QS or QR pattern in leads V₃R and/or V₄R also suggests RV myocardial necrosis but has less predictive accuracy than does ST-segment elevation in these leads.

Imaging

Noninvasive imaging provides important diagnostic and prognostic information in patients with MI. In most cases of STEMI, unless the ECG is nondiagnostic or the clinical scenario is questionable, imaging is not required for diagnosis—but imaging plays many roles after diagnosis, including determining the extent of the infarct, the presence of mechanical complications, and the overall function of the right and left ventricles.

Roentgenography (See Chapter 15)

The initial chest roentgenogram in patients with STEMI is almost invariably a portable film obtained in the emergency department or cardiac care unit. When present, prominent pulmonary vascular markings on the roentgenogram reflect elevated LV end-diastolic pressure, but significant temporal discrepancies can occur because of what have been termed *diagnostic lags* and *post-therapeutic lags*. Up to 12 hours can elapse before pulmonary edema accumulates after ventricular filling pressure has become elevated. The post-therapeutic phase lag represents a longer time interval; up to 2 days is required for pulmonary edema to be resorbed and the radiographic signs of pulmonary congestion to clear after ventricular filling pressure has returned toward normal. The degree of congestion and the size of the left side of the heart on the chest film are useful for defining groups of patients with STEMI who have an increased risk for fatal complications.

Echocardiography (See Chapter 14)

The relative portability of echocardiographic equipment makes this technique ideal for the assessment of patients with MI.⁹⁶ In patients with chest pain compatible with MI but with a nondiagnostic ECG, the finding on echocardiography of a distinct region of disordered contraction can support the diagnosis of myocardial ischemia. Echocardiography can also provide some help in evaluating patients with chest pain and a nondiagnostic ECG who are suspected of having aortic dissection. Identification of an intimal flap consistent with aortic dissection is a critical observation because the finding would drive critical changes in therapeutic strategy (see Chapter 57), but transthoracic echocardiography has poor sensitivity for detecting aortic dissection in comparison to other imaging modalities such as computed tomography (CT) angiography.

LV function estimated from echocardiograms correlates well with measurements from angiography and is useful in establishing the prognosis after MI.⁹⁶ Furthermore, early use of echocardiography can aid in early detection of potentially viable but stunned myocardium (contractile reserve), residual provokable ischemia, patients at risk for the development of congestive heart failure after MI, and mechanical complications of MI. Newer techniques also provide information regarding the success of myocardial tissue-level reperfusion.⁹⁷ Although transthoracic imaging is adequate in most patients, some patients have poor echocardiographic windows, especially if they are

undergoing mechanical ventilation. In such patients, transesophageal echocardiography can be performed safely and may help in evaluating ventricular septal defects and papillary muscle dysfunction.¹⁰

Doppler techniques allow assessment of blood flow in the cardiac chambers and across cardiac valves. When used in conjunction with echocardiography, Doppler interrogation can help in detecting and assessing the severity of mitral or tricuspid regurgitation after STEMI, the site of acute ventricular septal rupture, quantification of shunt flow across the resulting defect, and assessment of acute cardiac tamponade.¹⁰

Magnetic Resonance Imaging (See Chapter 17)

In addition to localizing and sizing the area of infarction, magnetic resonance imaging (MRI) techniques permit early recognition of MI and can provide an assessment of the severity of the ischemic insult. This modality is attractive because of its ability to assess perfusion of infarcted and noninfarcted tissue, as well as reperfused myocardium; to identify areas of jeopardized but not infarcted myocardium; to identify myocardial edema, fibrosis, wall thinning, and hypertrophy; to assess ventricular chamber size and segmental wall motion; and to identify the temporal transition between ischemia and infarction (Fig. 51-19).⁹⁸⁻¹⁰¹ MRI has limited application during the acute phase because of the need to transport patients with MI to the MRI

facility, but as discussed later, it is an extremely useful imaging technique during the subacute and chronic phases of MI.

Contrast-enhanced CMR with gadolinium can define areas of myocardial necrosis accurately. The transmural extent of late gadolinium enhancement (LGE) in regions of dysfunctional myocardium accurately predicts the likelihood of recovery of contractile function after successful restoration of coronary flow via mechanical revascularization.¹⁰² Numerous clinical studies have also demonstrated the high sensitivity of LGE ("delayed hyperenhancement") of CMR in detecting small amounts of myonecrosis. LGE accurately identifies the infarct zone when compared with histologic examination. The best predictor of return to normal ventricular wall thickening is less than 25% transmurality of LGE. LGE is also a sensitive technique for detecting RV infarcts.⁹⁹

In patients with a previous MI, estimation of the size of the peri-infarct zone by CMR with the delayed-enhancement technique provides incremental prognostic value beyond LV volume and ejection fraction. Besides detecting infarction, this imaging technique can characterize the presence and size of microvascular obstruction as a result of infarction, which may be an even poorer prognostic finding than LGE is. Clinically unrecognized myocardial scar detected by LGE imaging is associated with high risk for adverse cardiac events in patients with signs and symptoms of coronary artery disease but without a history of infarction.¹⁰⁰

Nuclear Imaging (See Chapter 16)

Radionuclide angiography, perfusion imaging, infarct-avid scintigraphy, and positron emission tomography can all be used to evaluate patients with STEMI.^{100,103} Nuclear cardiac imaging techniques can detect MI; assess infarct size, collateral flow, and jeopardized myocardium; determine the effects of the infarct on ventricular function; and establish the prognosis of patients with STEMI. Yet the necessity of moving a critically ill patient from the coronary care unit to the nuclear medicine department limits practical application.

Computed Tomography (See Chapter 18)

CT can provide an assessment of cavity dimensions and wall thickness, can detect LV aneurysms, and—of particular importance in patients with STEMI—can identify intracardiac thrombi. In the acute setting, contrast-enhanced CT detects focal areas of MI as decreased areas of enhancement. Older infarcts show hyperenhancement. Although cardiac CT is a less convenient technique, it is probably more sensitive than echocardiography for thrombus detection.¹⁰⁴ Coronary CT angiography is sensitive in detecting coronary obstructions, particularly in the proximal third of the coronary anatomy, and may improve the diagnostic evaluation of patients with a low to intermediate probability of ACS, but it does not have a role in the management of suspected STEMI.¹⁰⁵

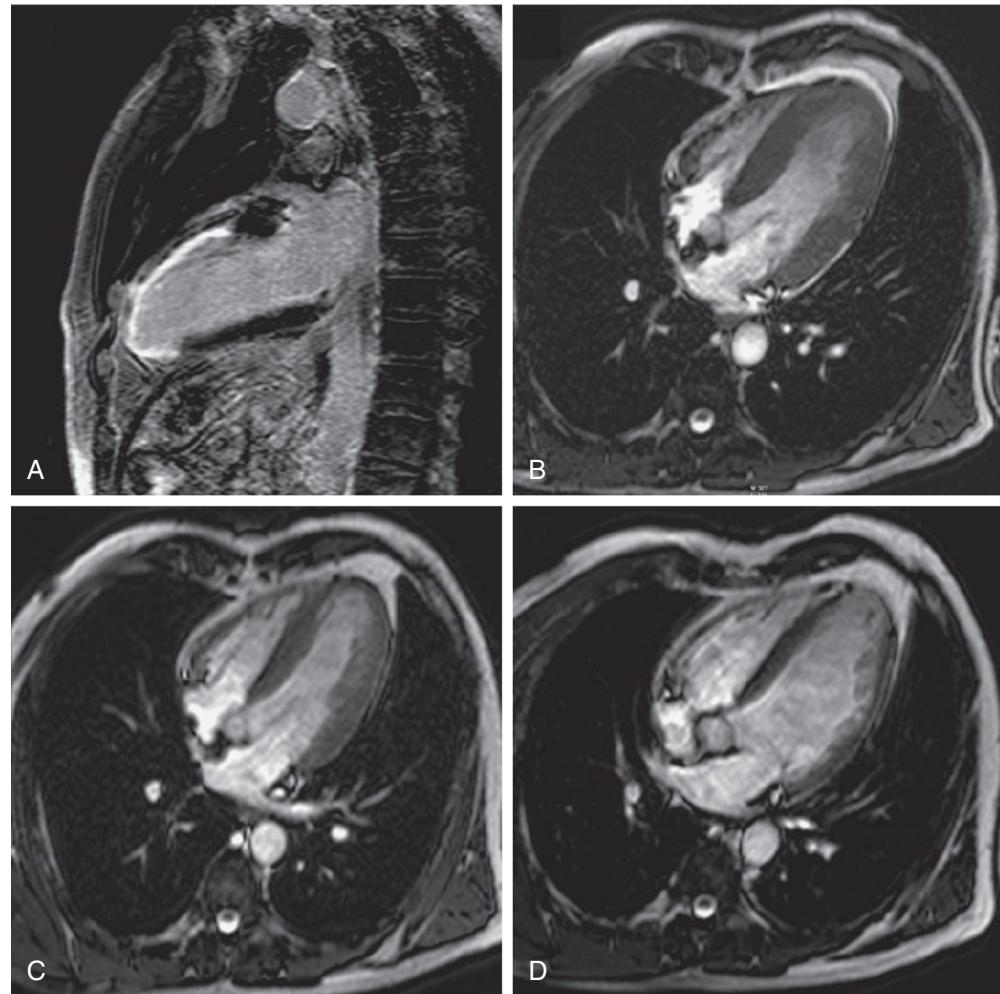


FIGURE 51-19 Vertical long-axis delayed-enhancement MRI in a patient with extensive transmural anteroapical MI (**A**). Horizontal long-axis cine-MRI at baseline (**B**), at 4 months (**C**), and at 1 year (**D**) shows progressive LV dilation (LV end-diastolic volume index of 81.9 mL/m^2 at baseline, 88.2 mL/m^2 at 4 months, and 112.7 mL/m^2 at 1 year) with progressive thinning of the LV wall. (From Ganame J, Messali G, Masci PG, et al: Time course of infarct healing and left ventricular remodelling in patients with reperfused STEMI using comprehensive magnetic resonance imaging. Eur Radiol 21:693, 2011.)

Estimation of Infarct Size

ELECTROCARDIOGRAPHY. Interest in limiting infarct size, largely because of the recognition that the quantity of infarcted myocardium has important prognostic implications, has focused attention on accurate determination of MI size. The sum of ST-segment elevations measured from multiple precordial leads correlates with the extent of myocardial injury in patients with anterior MI.⁹² Yet a relationship exists between the number of ECG leads showing ST-segment elevation and the mortality rate: patients with 8 or 9 of 12 leads showing ST-segment elevation have three to four times the mortality of those with only 2 or 3 leads demonstrating ST-segment elevation.

CARDIAC MARKERS. Estimation of infarct size by analysis of serum or plasma cardiac markers requires accounting for the quantity of the marker lost from the myocardium, its volume of distribution, and its release ratio. Serial measurements of proteins released by necrotic myocardium can be used to help determine MI size. Clinically, the peak CK, CK-MB, or troponin level provides an approximate estimate of infarct size. Coronary artery reperfusion dramatically changes the wash-out kinetics of necrosis markers from myocardium, thereby resulting in early and exaggerated peak levels (see Fig. 51-17). Measuring a cardiac-specific troponin level several days after STEMI, even in cases of successful reperfusion, may provide a reliable estimate of infarct size because such late troponin measurements reflect delayed release from the myofilament-bound pool in damaged myocytes.

NONINVASIVE IMAGING TECHNIQUES. The imaging modalities discussed above can aid in experimental and clinical assessment of infarct size. Echocardiography remains the most commonly used modality for assessing infarct size and LV function, although contrast-enhanced CMR can detect smaller degrees of ischemia and identify areas of injury that are permanently damaged myocardium versus “stunned” regions, which may recover. CMR can also discern the regional heterogeneity of infarction patterns in patients with persistently occluded infarct arteries or severe microvascular occlusion versus those with a successfully reperfused macrocirculation and microcirculation.¹⁰⁰

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