7 Acute Coronary Syndromes

Jayme Wilder
Marc S. Sabatine
Leonard S. Lilly

Chapter Outline

Acute coronary syndromes (ACSs) are life-threatening conditions that can punctuate the course of patients with coronary artery disease at any time. These syndromes form a continuum that ranges from an unstable pattern of angina pectoris to the development of a large acute myocardial infarction (MI), a condition of irreversible necrosis of heart muscle (Table 7-1). All forms of ACS share a common initiating pathophysiologic mechanism, as this chapter examines.

The frequency of ACS is staggering: more than 1.4 million people are admitted to hospitals in the United States each year with these conditions. Within the year after a first MI, 19% of men and 26% of women will die. Despite these daunting statistics, mortality associated with ACS has actually substantially and continuously declined in recent decades as a result of major therapeutic and preventive advances. This chapter considers the events that lead to an ACS, the pathologic and functional changes that follow, and therapeutic approaches that ameliorate the aberrant pathophysiology.

PATHOGENESIS OF ACUTE CORONARY SYNDROMES

More than 90% of ACSs result from disruption of an atherosclerotic plaque with subsequent platelet aggregation and formation of an intracoronary thrombus. The thrombus transforms a region of plaque narrowing to one of severe or complete occlusion, and the impaired blood flow causes a marked imbalance between myocardial oxygen supply and demand. The form of ACS that results depends on the degree of coronary obstruction and associated ischemia (see Table 7-1). A partially occlusive thrombus is the typical cause of the closely related syndromes **unstable angina (UA)** and **non–ST-elevation myocardial infarction**

TABLE 7-1 Spectrum of Acute Coronary Syndromes

	Unstable Angina	Non–ST-Elevation MI	ST-Elevation MI
Usual coronary pathology	Partially occlusive thrombus	Partially occlusive thrombus	Completely occlusive thrombus
Myocyte necrosis	No	Yes	Yes

MI, myocardial infarction.

(**NSTEMI**), with the latter being distinguished from the former by the presence of myocardial necrosis. At the other end of the spectrum, if the thrombus completely obstructs the coronary artery, the results are more severe ischemia and a larger amount of necrosis, manifesting as an **ST-elevation myocardial infarction** (**STEMI**).

The responsible thrombus in ACS is generated by interactions among the atherosclerotic plaque, the coronary endothelium, circulating platelets, and the dynamic vasomotor tone of the vessel wall, which overwhelm the natural antithrombotic mechanisms described in the next section.

Normal Hemostasis

When a normal blood vessel is injured, the endothelial surface becomes disrupted and thrombogenic connective tissue is exposed. Primary hemostasis is the first line of defense against bleeding. This process begins within seconds of vessel injury and is mediated by circulating platelets, which adhere to collagen in the vascular subendothelium and aggregate to form a "platelet plug." While the primary hemostatic plug forms, the exposure of subendothelial tissue factor triggers the plasma coagulation cascade, initiating the process of secondary hemostasis. The plasma coagulation proteins involved in secondary hemostasis are sequentially activated at the site of injury and ultimately form a fibrin clot by the action of thrombin. The resulting clot stabilizes and strengthens the platelet plug.

The normal hemostatic system minimizes blood loss from injured vessels, but there is little difference between this physiologic response and the pathologic process of coronary thrombosis triggered by disruption of atherosclerotic plaques.

Endogenous Antithrombotic Mechanisms

Normal blood vessels, including the coronary arteries, are replete with safeguards that prevent spontaneous thrombosis and occlusion, some examples of which are shown in Figure 7-1.

Inactivation of Clotting Factors

Several natural inhibitors tightly regulate the coagulation process to oppose clot formation and maintain blood fluidity. The most important of these are antithrombin, proteins C and S, and tissue factor pathway inhibitor (TFPI).

Antithrombin is a plasma protein that irreversibly binds to thrombin and other clotting factors, inactivating them and facilitating their clearance from the circulation (see mechanism 1 in Fig. 7-1). The effectiveness of antithrombin is increased 1,000-fold by binding to heparan sulfate, a heparin-like molecule normally present on the luminal surface of endothelial cells.

Protein C, protein S, and **thrombomodulin** form a natural anticoagulant system that inactivates the "acceleration" factors of the coagulation pathway (i.e., factors Va and VIIIa). Protein C is synthesized in the liver and circulates in an inactive form. Thrombomodulin is a thrombin-binding receptor normally present on endothelial cells. Thrombin bound to thrombomodulin cannot convert fibrinogen to fibrin (the final reaction in clot formation). Instead,

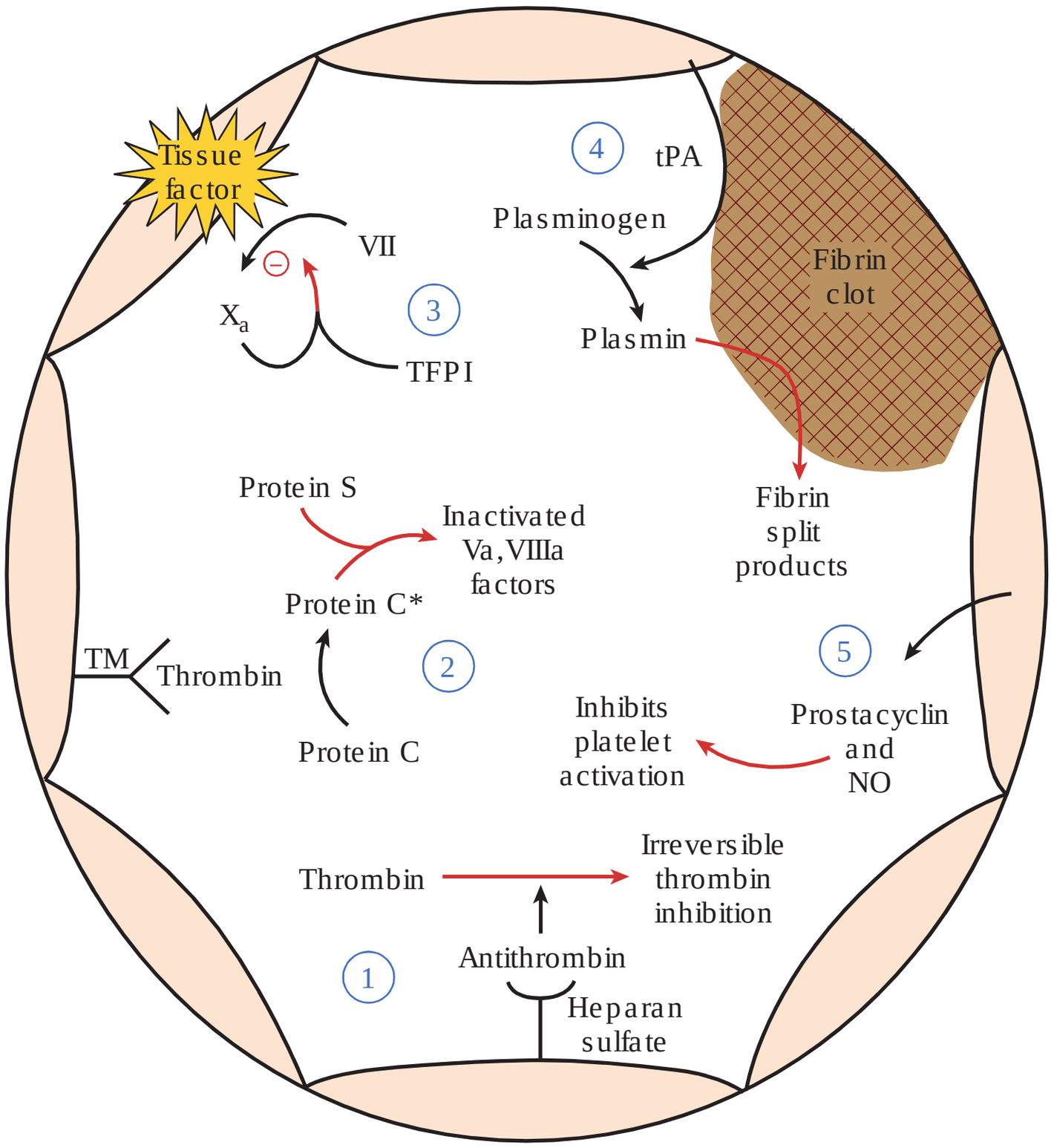

FIGURE 7-1. Endogenous protective mechanisms against thrombosis and vessel occlusion. (1) Inactivation of thrombin by antithrombin (AT), the effectiveness of which is enhanced by binding of AT to heparan sulfate. (2) Inactivation of clotting factors Va and VIIIa by activated protein C (protein C*), an action that is enhanced by protein S. Protein C is activated by the thrombomodulin (TM)–thrombin complex. (3) Inactivation of factor VII/tissue factor complex by tissue factor pathway inhibitor (TFPI). (4) Lysis of fibrin clots by tissue plasminogen activator (tPA). (5) Inhibition of platelet activation by prostacyclin and nitric oxide (NO).

the thrombin–thrombomodulin complex activates protein C. Activated protein C degrades factors Va and VIIIa (see mechanism 2 in Fig. 7-1), thereby inhibiting coagulation. The presence of protein S in the circulation enhances the inhibitory function of protein C.

TFPI is a plasma serine protease inhibitor that is activated by coagulation factor Xa. The combined factor Xa–TFPI binds to and inactivates the complex of tissue factor with factor VIIa that normally triggers the extrinsic coagulation pathway (see mechanism 3 in Fig. 7-1). Thus, TFPI serves as a negative feedback inhibitor that interferes with coagulation.

Lysis of Fibrin Clots

Tissue plasminogen activator (tPA) is a protein secreted by endothelial cells in response to many triggers of clot formation. It cleaves the protein plasminogen to form active plasmin, which in turn enzymatically degrades fibrin clots (see mechanism 4 in Fig. 7-1). When tPA binds to fibrin in a forming clot, its ability to convert plasminogen to plasmin is greatly enhanced.

Endogenous Platelet Inhibition and Vasodilatation

Prostacyclin is synthesized and secreted by endothelial cells (see mechanism 5 in Fig. 7-1), as described in Chapter 6. Prostacyclin increases platelet levels of cyclic AMP and thereby strongly inhibits platelet activation and aggregation. It also indirectly inhibits coagulation via its potent vasodilating properties. Vasodilatation helps guard against thrombosis by augmenting blood flow (which minimizes contact between procoagulant factors) and by reducing shear stress (an inducer of platelet activation).

Nitric oxide (NO) is similarly secreted by endothelial cells, as described in Chapter 6. It acts locally to inhibit platelet activation, and it too serves as a potent vasodilator.

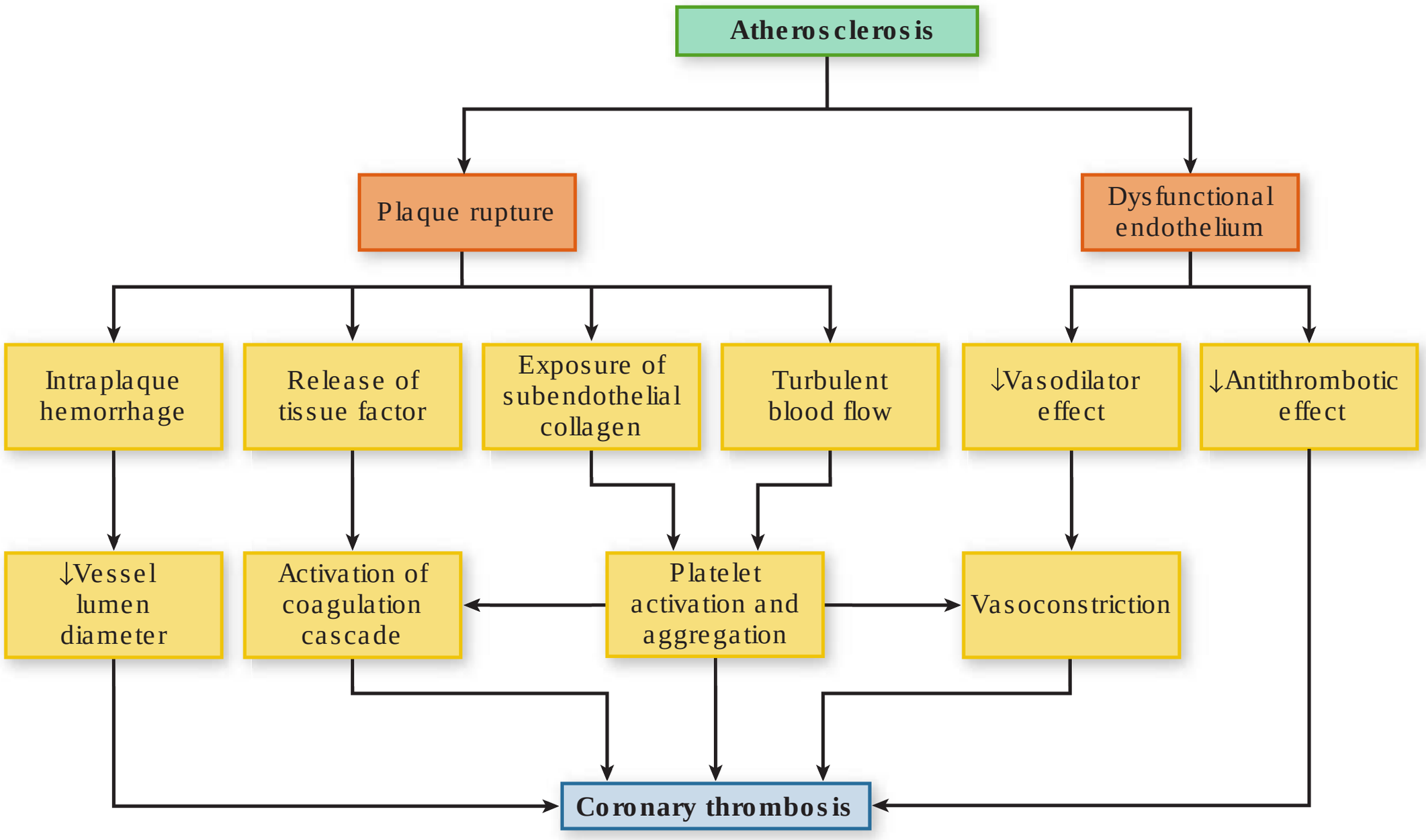

FIGURE 7-2. Mechanisms of coronary thrombus formation. Factors that contribute to this process include plaque disruption (e.g., rupture) and inappropriate vasoconstriction and loss of normal antithrombotic defenses because of dysfunctional endothelium.

Pathogenesis of Coronary Thrombosis

Normally, the mechanisms shown in Figure 7-1 serve to prevent spontaneous intravascular thrombus formation. However, abnormalities associated with atherosclerotic lesions may overwhelm these defenses and result in coronary thrombosis and vessel occlusion (Fig. 7-2). Atherosclerosis contributes to thrombus formation by (1) plaque rupture, which exposes the circulating blood elements to thrombogenic substances, and (2) endothelial dysfunction with the loss of normal protective antithrombotic and vasodilatory properties.

Atherosclerotic **plaque rupture** is considered the major trigger of coronary thrombosis. The underlying causes of plaque disruption are (1) chemical factors that destabilize atherosclerotic lesions and (2) physical stresses to which the lesions are subjected. As described in Chapter 5, atherosclerotic plaques consist of a lipid-laden core surrounded by a fibrous external cap. Substances released from inflammatory cells within the plaque can compromise the integrity of the fibrous cap. For example, T lymphocytes release interferon-γ (IFN-γ), which inhibits collagen synthesis by smooth muscle cells and thereby interferes with the usual strength of the cap. Additionally, cells within atherosclerotic lesions produce enzymes (e.g., metalloproteinases) that degrade the interstitial matrix, further compromising plaque stability. A weakened or thin-capped plaque is subject to rupture, particularly in its "shoulder" region (the border with the normal arterial wall that is subjected to high circumferential stress) either spontaneously or by physical forces, such as intraluminal blood pressure and torsion from the beating myocardium.

ACSs sometimes occur in the setting of certain triggers, such as strenuous physical activity or emotional upset. The activation of the sympathetic nervous system in these situations increases the blood pressure, heart rate, and force of ventricular contraction—actions that may stress the atherosclerotic lesion, thereby causing the plaque to fissure or rupture. In addition, MI is most likely to occur in the early morning hours. This observation may relate to the tendency of key physiologic stressors (such as systolic blood pressure, blood viscosity, and

plasma epinephrine levels) to be most elevated at that time of day, and these factors subject vulnerable plaques to rupture.

While rupture of the f brous cap is responsible for the majority of ACSs, superf cial erosion without rupture is a less common, important mechanism of plaque disruption and thrombus formation. Eroded plaques often do not have a substantial lipid burden but have been associated with smoking and are also frequently found to be the cause of ACS in premenopausal women.

Following plaque disruption, thrombus formation is provoked via mechanisms shown in Figure 7-2. For example, during plaque rupture, the exposure of tissue factor from the atheromatous core triggers the coagulation pathway, while subendothelial collagen activates platelets. Activated platelets release the contents of their granules, which include facilitators of platelet aggregation (e.g., adenosine diphosphate [ADP] and f brinogen), activators of the coagulation cascade (e.g., factor Va), and vasoconstrictors (e.g., thromboxane and serotonin). The developing intracoronary thrombus, intraplaque hemorrhage, and vasoconstriction all contribute to narrowing the vessel lumen, creating turbulent blood flow that contributes to shear stress and further platelet activation.

Dysfunctional endothelium, which is apparent even in mild atherosclerotic coronary disease, also increases the likelihood of thrombus formation. In the setting of endothelial dysfunction, reduced amounts of vasodilators (e.g., NO and prostacyclin) are released and inhibition of platelet aggregation by these factors is impaired, resulting in the loss of a key defense against thrombosis.

Not only is dysfunctional endothelium less equipped to prevent platelet aggregation but also is less able to counteract the vasoconstricting products of platelets. During thrombus formation, vasoconstriction is promoted both by platelet products (thromboxane and serotonin) and by thrombin within the developing clot. The normal platelet-associated vascular response is vasodilatation, because platelet products stimulate endothelial NO and prostacyclin release, the influences of which predominate over direct platelet-derived vasoconstrictors (see Fig. 6-4). However, reduced secretion of endothelial vasodilators in atherosclerosis allows vasoconstriction to proceed unchecked. Similarly, thrombin in a forming clot is a potent vascular smooth muscle constrictor in the setting of dysfunctional endothelium. Vasoconstriction causes torsional stresses that can contribute to plaque rupture or can transiently occlude the stenotic vessel through heightened arterial tone. The reduction in coronary blood flow caused by vasoconstriction also reduces the washout of coagulation proteins, thereby enhancing thrombogenicity.

Signif cance of Coronary Thrombosis

The formation of an intracoronary thrombus results in one of the several potential outcomes (Fig. 7-3). For example, plaque rupture is sometimes superf cial, minor, and self-limited, such that only a small, nonocclusive thrombus forms. In this case, the thrombus may simply become incorporated into the growing atheromatous lesion through f brotic organization, or it may be lysed by natural f brinolytic mechanisms. Recurrent asymptomatic plaque ruptures of this type may cause gradual progressive enlargement of the coronary stenosis.

However, deeper plaque rupture may result in greater exposure of subendothelial collagen and tissue factor, with formation of a larger thrombus that more substantially occludes the vessel's lumen. Such obstruction may cause prolonged severe ischemia and the development of an ACS. If the intraluminal thrombus at the site of plaque disruption totally occludes the vessel, blood flow beyond the obstruction will cease, prolonged ischemia will occur, and an MI (usually an ST-elevation MI) will result. Conversely, if the thrombus partially occludes the vessel (or if it totally occludes the vessel but only transiently because of spontaneous recanalization or by relief of superimposed vasospasm), the severity and duration of

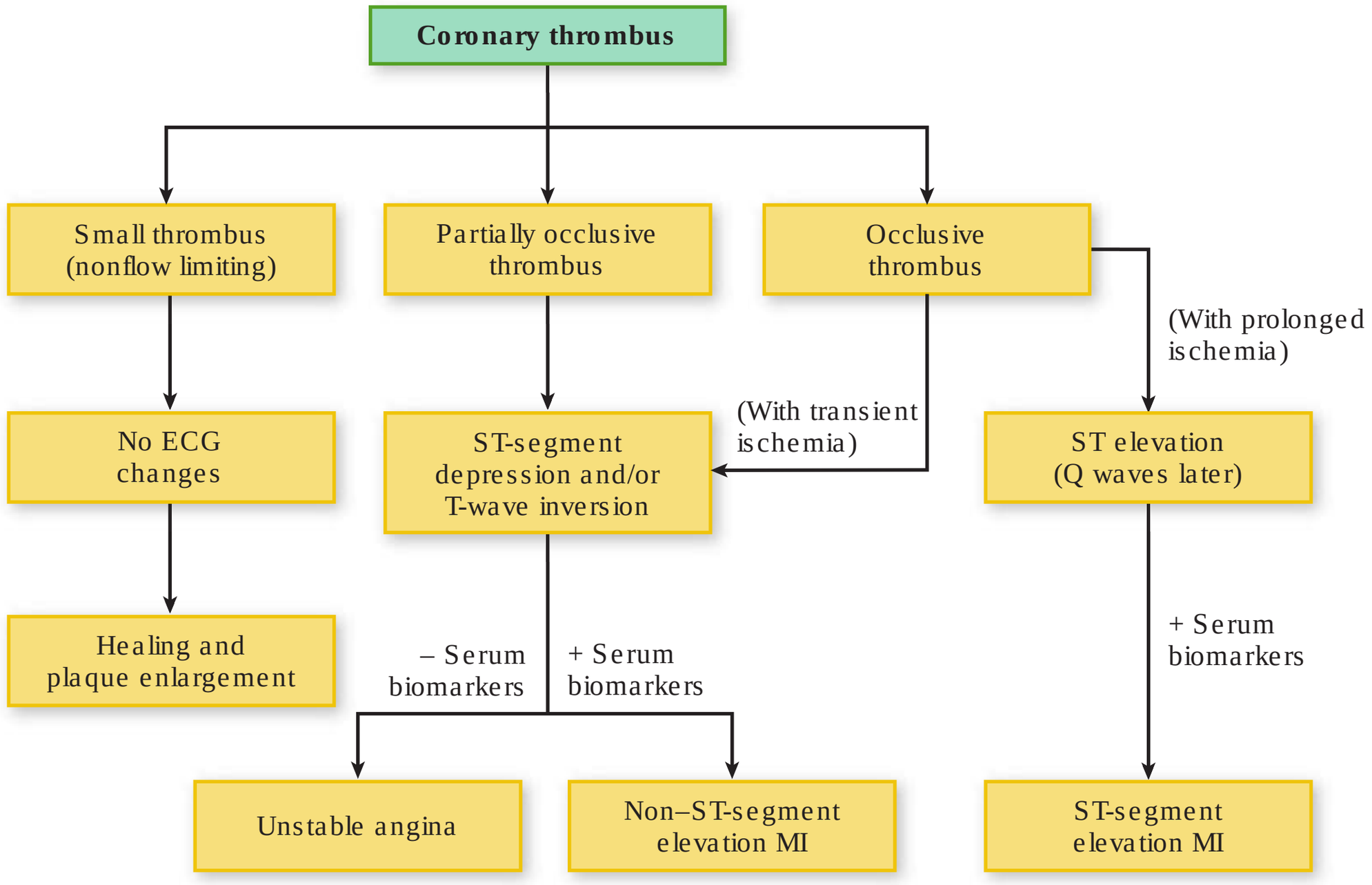

FIGURE 7-3. Consequences of coronary thrombosis. A small thrombus formed on superficial plaque rupture may not result in symptoms or electrocardiogram (ECG) abnormalities, but healing and fibrous organization may incorporate the thrombus into the plaque, causing the atherosclerotic lesion to enlarge. A partially occlusive thrombus narrows the arterial lumen, restricts blood flow, and can cause unstable angina or a non–ST-elevation MI, either of which may result in ST-segment depression and/or T-wave inversion on the ECG. A totally occlusive thrombus with prolonged ischemia is the most common cause of ST-elevation MI, in which the ECG initially shows ST-segment elevation, followed by Q-wave development if early reperfusion is not achieved. An occlusive thrombus that recanalizes, or one that develops in a region served by adequate collateral blood flow, may result in less prolonged ischemia and a non–ST-elevation MI instead. Serum biomarkers of myocardial necrosis include cardiac-specific troponins and creatine kinase MB isoenzyme.

ischemia will be less, and a smaller NSTEMI or UA is the more likely outcome. The distinction between NSTEMI and UA is based on the degree of the ischemia and whether the event is severe enough to cause necrosis, indicated by the presence of certain serum biomarkers (see Fig. 7-3). Nonetheless, NSTEMI and UA act quite alike, and the management of these entities is similar.

Occasionally, a non–ST-elevation infarct may result from total coronary occlusion. In this case, it is likely that a substantial collateral blood supply (see Chapter 1) limits the extent of necrosis, such that a larger ST-elevation MI is prevented.

Nonatherosclerotic Causes of Acute Myocardial Infarction

Infrequently, mechanisms other than acute thrombus formation can precipitate an acute MI (Table 7-2). These should be suspected when an ACS occurs in a young patient or a person without atherosclerotic risk factors. For example, coronary emboli from mechanical or infected cardiac valves may lodge in the coronary circulation, inflammation from acute vasculitis can initiate coronary occlusion, or patients with connective tissue disorders, or peripartum women, can rarely experience a spontaneous coronary artery dissection (a tear in

TABLE 7-2 Causes of Myocardial Infarction

- Atherosclerotic plaque rupture with superimposed thrombus
- Vasculitic syndromes (see Chapter 15)
- Coronary embolism (e.g., from endocarditis, artif cial heart valves)
- Congenital anomalies of the coronary arteries
- Coronary trauma or aneurysm
- Spontaneous coronary artery dissection
- Severe coronary artery spasm (primary or cocaine-induced)
- Increased blood viscosity (e.g., polycythemia vera, thrombocytosis)
- Markedly increased myocardial oxygen demand (e.g., severe aortic stenosis)

the vessel wall that may lead to occlusion, described in Chapter 15). Occasionally, intense transient coronary spasm can suff ciently reduce myocardial blood supply to result in UA or infarction.

Cocaine abuse can also lead to an ACS. Cocaine increases sympathetic tone by blocking the presynaptic reuptake of norepinephrine and by enhancing the release of adrenal catecholamines, which can lead to vasospasm and therefore decreased myocardial oxygen supply. An ACS may ensue because of increased myocardial oxygen demand resulting from cocaine-induced sympathetic myocardial stimulation (increased heart rate and blood pressure) in the face of the decreased oxygen supply.

These nonatherosclerotic causes are relatively rare causes of acute MI. However, they are important to recognize as their treatments differ from those of typical ACSs due to plaque rupture and superimposed thrombus formation, as discussed in this chapter.

PATHOLOGY AND PATHOPHYSIOLOGY

MI (either STEMI or NSTEMI) results when myocardial ischemia is suff ciently severe to cause myocyte necrosis. Although by def nition UA does not result in necrosis, it may subsequently progress to MI if the underlying pathophysiology is not promptly corrected.

In addition to their clinical classif cations, infarctions can be described pathologically by the extent of necrosis they produce within the myocardial wall. **Transmural infarcts** span the entire thickness of the myocardial wall and result from total, prolonged occlusion of an epicardial coronary artery. Conversely, **subendocardial infarcts** exclusively involve the innermost layers of the myocardium. The subendocardium is particularly susceptible to ischemia because it is the zone subjected to the highest pressure from the ventricular chamber, has few collateral connections that supply it, and is perfused by vessels that must pass through layers of contracting myocardium.

Infarction represents the culmination of a disastrous cascade of events, initiated by ischemia, that progresses from a potentially reversible phase to irreversible cell death. Myocardium that is supplied directly by an occluded vessel may die quickly. The adjacent tissue may not necrose immediately because it may be suff ciently perfused by nearby patent vessels. However, the neighboring cells may become increasingly ischemic over time, as demand for oxygen continues in the face of reduced oxygen supply. Thus, the region of infarction may subsequently extend outward. The amount of tissue that ultimately succumbs to infarction therefore relates to (1) the mass of myocardium perfused by the occluded vessel, (2) the magnitude and duration of impaired coronary blood flow, (3) the oxygen demand of the affected region, (4) the adequacy of collateral vessels that provide blood flow from neighboring nonoccluded coronary arteries, and (5) the degree of tissue response that modif es the ischemic process.

Pathologic Evolution of Infarction

The pathophysiologic alterations that transpire during MI occur in two stages: early changes at the time of acute infarction and late changes during myocardial healing and remodeling (Table 7-3).

Early Changes in Infarction

Early changes include the histologic evolution of the infarct and the functional impact of oxygen deprivation on myocardial contractility. These changes culminate in coagulative necrosis of the myocardium in 2 to 4 days.

As oxygen levels fall in the myocardium supplied by an abruptly occluded coronary vessel, there is a rapid shift from aerobic to anaerobic metabolism (Fig. 7-4). Because mitochondria can no longer oxidize fats or products of glycolysis, high-energy phosphate production drops dramatically and anaerobic glycolysis leads to the accumulation of lactic acid, resulting in a lowered pH.

Furthermore, the paucity of high-energy phosphates such as adenosine triphosphate (ATP) interferes with transmembrane Na^+ –K^+ -ATPase, with resultant elevation in the concentrations of intracellular Na^+ and extracellular K^+ . Rising intracellular Na^+ contributes to cellular edema. Membrane leak and rising extracellular K^+ concentration contributes to alterations in the transmembrane electrical potential, predisposing the myocardium to lethal arrhythmias. Intracellular calcium accumulates in the damaged myocytes and is thought to contribute to the final common pathway of cell destruction through the activation of degradative lipases and proteases.

Collectively, these metabolic changes decrease myocardial function as early as 2 minutes following occlusive thrombosis. Without intervention, irreversible cell injury ensues in 20 minutes and is marked by the development of membrane defects. Proteolytic enzymes leak across the myocyte's altered membrane, damaging adjacent myocardium, and the release of certain macromolecules into the circulation serves as a clinical marker of acute infarction.

Early histological changes include myocardial edema, wavy myofibers, and the presence of contraction bands (see Table 7-3). Edema of the myocardium develops within 4 to 12 hours, as vascular permeability increases and interstitial oncotic pressure rises (because of the leak of intracellular proteins). **Wavy myofibers** appear as intercellular edema separates the myocardial

TABLE 7-3 Pathologic Time Line in Transmural Infarction

Time	Event
Early changes	
1–2 min	ATP levels fall; cessation of contractility
10 min	50% depletion of ATP; cellular edema, decreased membrane potential, and susceptibility to arrhythmias
20–24 min	Irreversible cell injury
1–3 h	Wavy myofibers
4–12 h	Hemorrhage, edema, PMN infiltration begins
18–24 h	Coagulation necrosis (pyknotic nuclei with eosinophilic cytoplasm), edema
2–4 d	Total coagulation necrosis (no nuclei or striations, rimmed by hyperemic tissue); monocytes appear; PMN infiltration peaks
Late changes	
5–7 d	Yellow softening from resorption of dead tissue by macrophages
7+ d	Granulation tissue forms, ventricular remodeling
7 wk	Fibrosis and scarring complete

ATP, adenosine triphosphate; PMN, polymorphonuclear leukocyte.

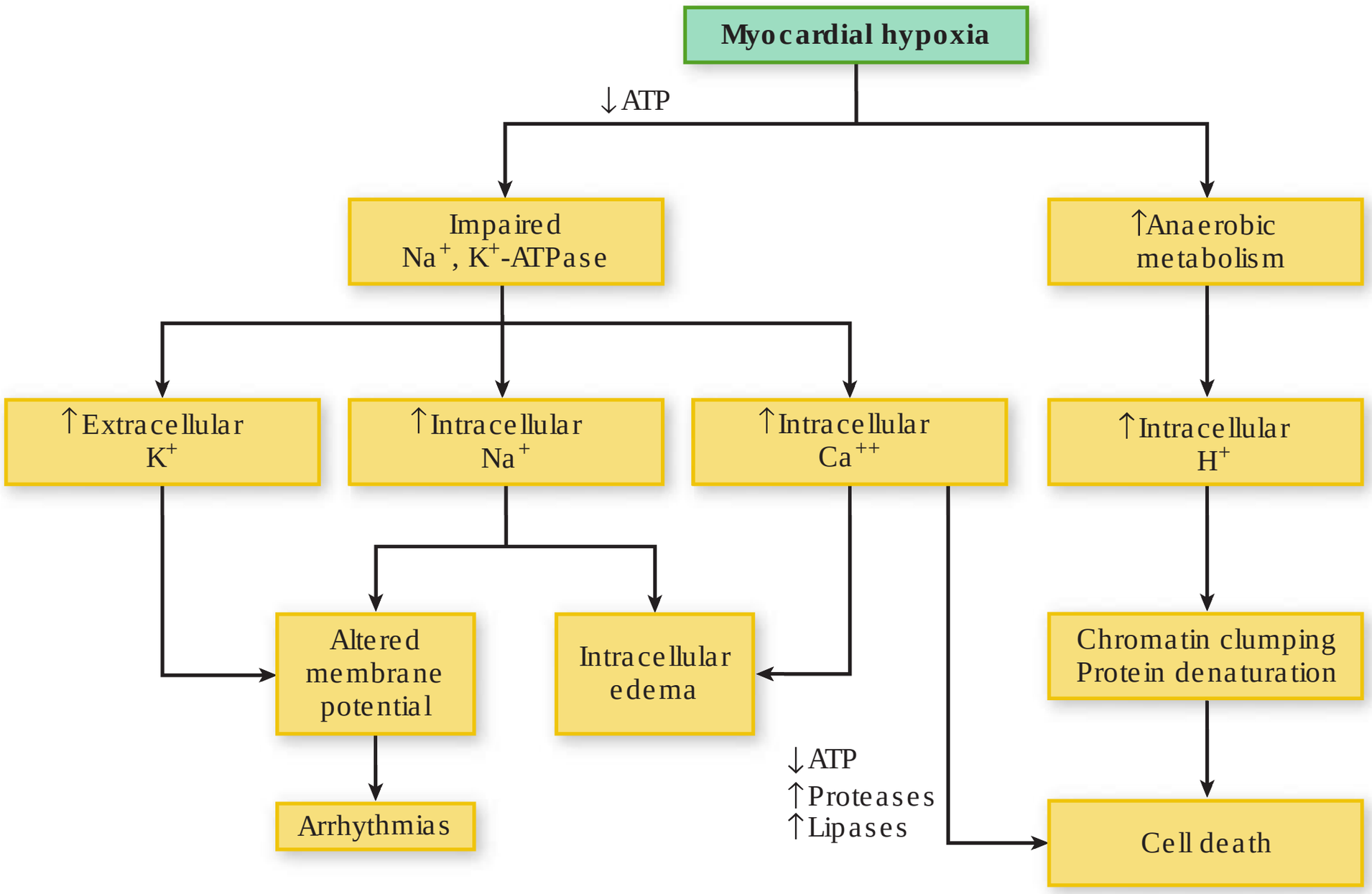

FIGURE 7-4. Mechanisms of cell death in myocardial infarction. Acute ischemia rapidly depletes the intracellular supply of adenosine triphosphate (ATP) as aerobic metabolism fails. Subsequent intracellular acidosis and impairment of ATP-dependent processes culminate in intracellular calcium accumulation, edema, and cell death.

cells that are tugged about by the surrounding, functional myocardium. **Contraction bands** can often be seen near the borders of the infarct: sarcomeres are contracted and consolidated and appear as bright eosinophilic belts (Fig. 7-5A).

An acute inflammatory response, with inf ltration of neutrophils, begins after approximately 4 hours and incites further tissue damage. Within 18 to 24 hours, **coagulation necrosis** is evident on light microscopy (Fig. 7-5B) with pyknotic nuclei and bland eosinophilic cytoplasm.

Gross morphologic changes (dark, mottled discoloration of infarcted tissue) do not appear until 18 to 24 hours after coronary occlusion, although certain staining techniques (e.g., tetrazolium) permit the pathologist to identify regions of infarction earlier.

Late Changes in Infarction

Late pathologic change in the course of an MI includes (1) the clearing of necrotic myocardium and (2) the deposition of collagen to form scar tissue.

Five to seven days after infarction, the process of wound healing progresses. Irreversibly injured myocytes do not regenerate; rather, the cells are removed and replaced by f brous tissue. Macrophages invade the inflamed myocardium shortly after neutrophil inf ltration and remove necrotic tissue (Fig. 7-5C). This period of tissue resorption is termed **yellow softening** because connective tissue elements are destroyed and removed along with dead myocardial cells. The phagocytic clearing, combined with thinning and dilatation of the infarcted zone, results in structural weakness of the ventricular wall and the possibility of myocardial wall rupture at this stage.

Approximately 1 week after infarction, granulation tissue appears, representing the beginning of the scarring process (Fig. 7-5D). This is observed grossly as a red border at the edge of the infarct. **Fibrosis** subsequently ensues, and scarring is complete by 7 weeks after infarction (Fig. 7-5E).

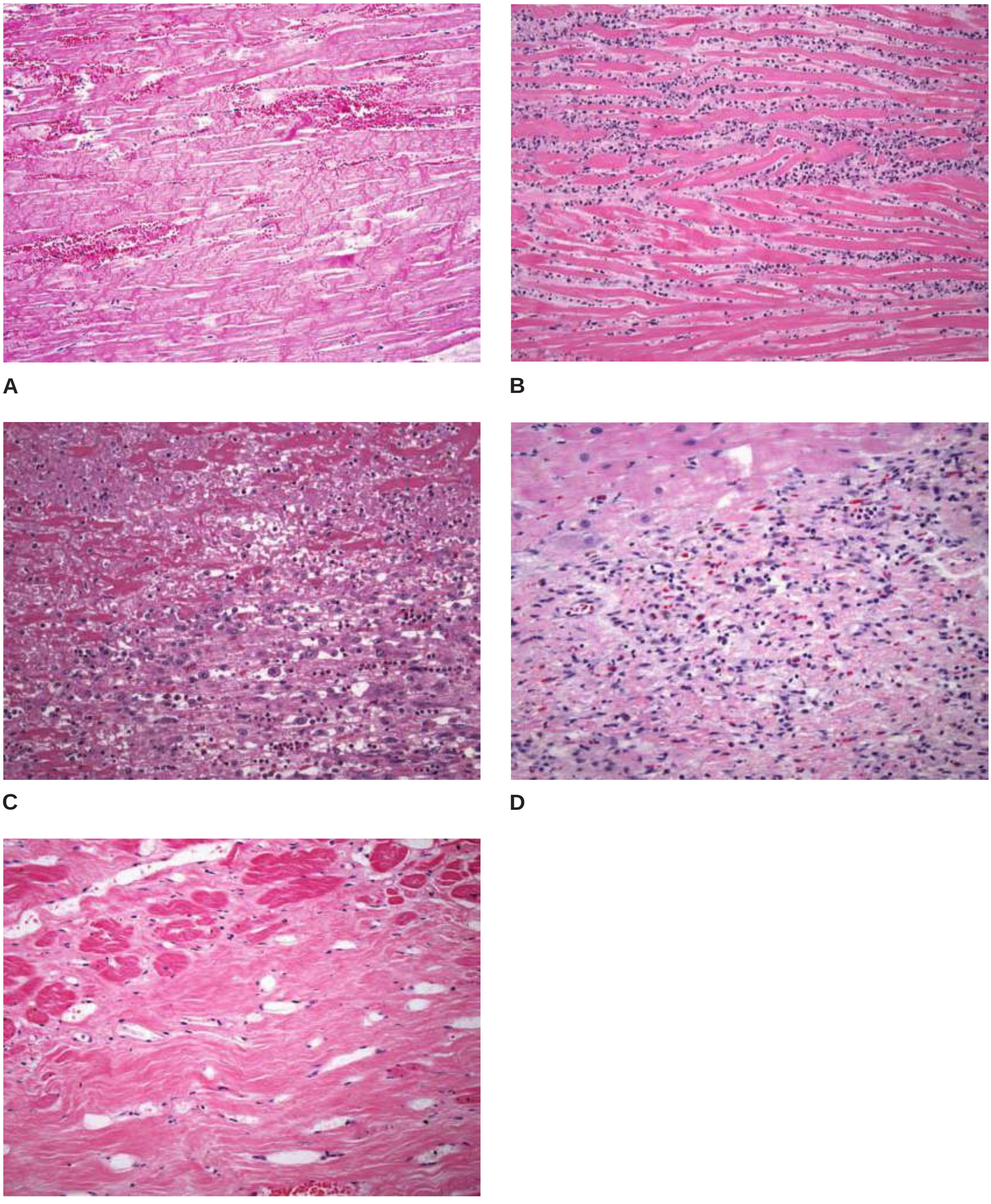

FIGURE 7-5. Pathologic evolution in myocardial infarction. A. Acute infarct approximately 12 hours old showing contraction band necrosis, nuclear karyolysis, focal hemorrhage, and an absence of inflammation. **B.** Acute infarct approximately 24 to 48 hours old showing coagulation necrosis and dense infiltration of neutrophils. **C.** Healing infarct approximately 5 days old showing necrotic myocytes undergoing removal by macrophages, with the neutrophilic response having largely dissipated. **D.** Healing infarct approximately 10 days old showing granulation tissue with new blood vessels (neovascularization), mild chronic inflammation (macrophages and lymphocytes), fibroblasts, and early collagen deposition; viable myocardium is present at the upper left. **E.** Healed infarct approximately 1 to 2 months old showing dense fibrosis; the inflammation and new vessels have largely regressed; viable myocardium is present at the upper left. All images are hematoxylin and eosin–stained sections.(Courtesy of Robert Padera, MD, PhD, Brigham and Women's Hospital, Boston, MA).

Functional Alterations

Impaired Contractility and Compliance

The destruction of functional myocardial cells in infarction quickly leads to impaired ventricular contraction **(systolic dysfunction)**. Cardiac output is further compromised because synchronous contraction of myocytes is lost. Specif c terms are used to describe the types of wall motion abnormalities that can result. A localized region of reduced contraction is termed hypokinetic, a segment that does not contract at all is called akinetic, and a dyskinetic region is one that bulges outward during contraction of the remaining functional portions of the ventricle.

During an ACS, the left ventricle is also adversely compromised by **diastolic dysfunction**. Ischemia and/or infarction impair diastolic relaxation (an energy-dependent process; see Chapter 1), which reduces ventricular compliance and contributes to elevated ventricular f lling pressures.

Stunned Myocardium

Sometimes transient myocardial ischemia can result in a very prolonged, but gradually reversible, period of contractile dysfunction. For example, as described in Chapter 6, **stunned myocardium** is tissue that demonstrates prolonged systolic dysfunction after a discrete episode of severe ischemia, despite restoration of adequate blood flow, and gradually regains contractile force days to weeks later. For example, stunning may occur following reperfusion therapy for acute STEMI, in which case prolonged contractile dysfunction of affected ventricular segments may simulate infarcted tissue. However, if the tissue is simply stunned rather than necrotic, its function will recover over time.

Ischemic Preconditioning

Brief ischemic insults to a region of myocardium may render that tissue more resistant to subsequent episodes, a phenomenon termed **ischemic preconditioning**. The clinical relevance is that patients who sustain an MI in the context of recent angina experience less morbidity and mortality than those without preceding ischemic episodes. The mechanism of this phenomenon is not fully understood but appears to involve multiple signaling pathways that involve both local and systemic mediators. Substances released during ischemia, including adenosine and bradykinin, are believed to be key triggers of these pathways.

Ventricular Remodeling

Following an MI, changes occur in the geometry of both infarcted and noninfarcted ventricular muscle. Such alterations in chamber size and wall thickness affect long-term cardiac function and prognosis.

In the early post-MI period, infarct expansion may occur, in which the affected ventricular segment enlarges without additional myocyte necrosis. Infarct expansion represents thinning and dilatation of the necrotic zone of tissue, likely because of “slippage” between the muscle f bers, resulting in a decreased volume of myocytes in the region. Infarct expansion can be detrimental because it increases ventricular size, which (1) augments wall stress, (2) impairs systolic contractile function, and (3) increases the likelihood of aneurysm formation.

In addition to early expansion of the infarcted territory, remodeling of the ventricle may also involve dilatation of the overworked noninfarcted segments, which are subjected to increased wall stress. This dilatation begins in the early postinfarct period and continues over the ensuing weeks and months. Initially, chamber dilatation serves a compensatory role because it increases

cardiac output via the Frank–Starling mechanism (see Chapter 9), but progressive enlargement may ultimately lead to heart failure and predisposes to ventricular arrhythmias.

Adverse ventricular remodeling can be beneficially modified by certain interventions. At the time of infarction, for example, reperfusion therapies limit infarct size and therefore decrease the likelihood of infarct expansion. In addition, drugs that interfere with the renin–angiotensin system have been shown to attenuate progressive remodeling and to reduce short- and long-term mortality after infarction (as discussed later in the chapter).

CLINICAL FEATURES OF ACUTE CORONARY SYNDROMES

Because ACSs represent disorders along a continuum, their clinical features overlap. In general, the severity of symptoms and associated laboratory findings progress from UA on one side of the continuum, through NSTEMI, to STEMI on the other end of the continuum. Distinguishing among these syndromes is based on the clinical presentation, electrocardiographic findings, and serum biomarkers of myocardial damage. To institute appropriate immediate therapy, the most important distinction to make is between an ACS that causes ST-segment elevation on the electrocardiogram (STEMI) and those acute syndromes that do not (UA and NSTEMI).

Clinical Presentation

Unstable Angina

UA presents as an acceleration of ischemic symptoms in one of the following three ways: (1) a crescendo pattern in which a patient with chronic stable angina experiences a sudden increase in the frequency, duration, and/or intensity of ischemic episodes; (2) episodes of angina that unexpectedly occur at rest, without provocation; or (3) the new onset of anginal episodes, described as severe, in a patient without previous symptoms of coronary artery disease. These presentations are different from the pattern of chronic stable angina, in which instances of chest discomfort are predictable, brief, and nonprogressive, occurring only during physical exertion or emotional stress. Patients with UA may progress further along the continuum of ACS and develop evidence of necrosis (i.e., acute NSTEMI or STEMI) unless the condition is recognized and promptly treated.

Acute Myocardial Infarction

The symptoms and physical findings of acute MI (both STEMI and NSTEMI) can be predicted from the pathophysiology described earlier in this chapter and are summarized in Table 7-4. The discomfort experienced during an MI resembles angina pectoris qualitatively but is usually more severe, lasts longer, and may radiate more widely. Like angina, the sensation may result from the release of mediators such as adenosine and lactate from ischemic myocardial cells onto local nerve endings. Because ischemia in acute MI persists and proceeds to necrosis, these provocative substances continue to accumulate and activate afferent nerves for longer periods. The discomfort is often referred to other regions of the C7 through T4 dermatomes, including the neck, shoulders, and arms. Initial symptoms are usually rapid in onset and briskly crescendo to leave the patient with a profound “feeling of doom.” Unlike a transient attack of angina, the pain does not wane with rest, and there may be little response to the administration of sublingual nitroglycerin.

The chest discomfort associated with an acute MI is often severe but not always. In fact, up to 25% of patients who sustain an MI are asymptomatic during the acute event, and the diagnosis is made only in retrospect. This is particularly common among diabetic patients who may not adequately sense pain because of associated neuropathy.

TABLE 7-4 Signs and Symptoms of Myocardial Infarction

1. Characteristic pain	• Severe, persistent, typically substernal
2. Sympathetic effect	• Diaphoresis • Cool and clammy skin
3. Parasympathetic (vagal effect)	• Nausea, vomiting • Weakness
4. Inflammatory response	• Mild fever
5. Cardiac findings	• S_4 (and S_3 if systolic dysfunction present) gallop • Dyskinetic bulge (in anterior wall MI) • Systolic murmur (if mitral regurgitation or VSD)
6. Other	• Pulmonary rales (if heart failure present) • Jugular venous distention (if heart failure or right ventricular MI)

MI, myocardial infarction; S_3, third heart sound; S_4, fourth heart sound; VSD, ventricular septal defect.

The combination of intense discomfort and baroreceptor unloading (if hypotension is present) may trigger a dramatic sympathetic nervous system response. Systemic signs of subsequent catecholamine release include diaphoresis (sweating), tachycardia, and cool and clammy skin caused by vasoconstriction.

If the ischemia affects a sufficiently large amount of myocardium, left ventricular (LV) contractility can be reduced (systolic dysfunction), thereby decreasing the stroke volume and causing the diastolic volume and pressure within the LV to rise. The increase in LV pressure, compounded by the ischemia-induced stiffness of the chamber (diastolic dysfunction), is conveyed to the left atrium and pulmonary veins. The resultant pulmonary congestion decreases lung compliance and stimulates juxtacapillary receptors. These J receptors effect a reflex that results in rapid, shallow breathing and evokes the subjective feeling of dyspnea. Transudation of fluid into the alveoli exacerbates this symptom.

Physical findings during an acute MI depend on the location and extent of the infarct. The S_4 sound, indicative of atrial contraction into a noncompliant left ventricle, is frequently present (see Chapter 2). An S_3 sound, indicative of volume overload in the presence of failing LV systolic function, may also be heard. A systolic murmur may appear if ischemia-induced papillary muscle dysfunction causes mitral valvular insufficiency or if the infarct ruptures through the interventricular septum to create a ventricular septal defect (as discussed later in the chapter).

Myocardial necrosis also activates systemic responses to inflammation. Cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) are released from macrophages and vascular endothelium in response to tissue injury. These mediators evoke an array of clinical responses, including low-grade fever.

Not all patients with severe chest pain are in the midst of MI or UA. Table 7-5 lists other common causes of acute chest discomfort and clinical, laboratory, and radiographic features to differentiate them from an ACS.

Diagnosis of Acute Coronary Syndromes

The diagnosis of, and distinctions among, the ACSs is made on the basis of (1) the patient's presenting symptoms, (2) acute ECG abnormalities, and (3) detection of specific serum markers of myocardial necrosis (see Table 7-6 and Fig. 7-3). Specifically, UA is a clinical diagnosis supported by the patient's symptoms, transient ST abnormalities on the ECG (usually ST depression and/or T-wave inversion), and the absence of serum biomarkers of myocardial necrosis. Non–ST-segment elevation MI is distinguished from UA by the detection of serum markers of necrosis and often more persistent ST or T-wave abnormalities. The hallmark of ST-elevation MI is an appropriate clinical history coupled with ST elevations on the ECG plus detection of serum markers of myocardial necrosis.

TABLE 7-5 Conditions That May Be Confused with Acute Coronary Syndromes

Condition	Differentiating Features
Cardiac	
Acute coronary syndrome	• Retrosternal pressure, radiating to the neck, jaw, or left shoulder and arm; more severe and lasts longer than previous anginal attacks • ECG: localized ST elevations or depressions
Pericarditis	• Sharp pleuritic pain (worsens with inspiration) • Pain varies with position (relieved by sitting forward) • Friction rub auscultated over precordium • ECG: diffuse ST elevations (see Chapter 14)
Aortic dissection	• Tearing, ripping pain that migrates over time (chest and back; see Chapter 15) • Asymmetry of arm blood pressures • Widened mediastinum on chest radiograph
Pulmonary	
Pulmonary embolism	• Localized pleuritic pain, accompanied by dyspnea • Pleural friction rub may be present • Predisposing conditions for venous thrombosis
Pneumonia	• Pleuritic chest pain • Cough and sputum production • Abnormal lung auscultation and percussion (i.e., consolidation) • Infiltrate on chest radiograph
Pneumothorax	• Sudden sharp, pleuritic unilateral chest pain • Decreased breath sounds and hyperresonance of affected side • Chest radiograph: increased lucency and absence of pulmonary markings
Gastrointestinal	
Esophageal spasm	• Retrosternal pain, worsened by swallowing • History of dysphagia
Acute cholecystitis	• Right upper quadrant abdominal tenderness • Often accompanied by nausea • History of fatty food intolerance

ECG Abnormalities

ECG abnormalities, which reflect abnormal electrical currents during an ACS, are usually manifest in characteristic ways. In UA or NSTEMI, ST-segment depression and/or T-wave inversions may occur (Fig. 7-6). These abnormalities may be transient, occurring just during chest pain episodes in UA, or they may persist in patients with NSTEMI. In contrast, as described in Chapter 4, STEMI presents with a temporal sequence of abnormalities: initial ST-segment

TABLE 7-6 Distinguishing Features of Acute Coronary Syndromes

		Myocardial Infarction	
Feature	Unstable Angina	NSTEMI	STEMI
Typical symptoms	Crescendo, rest, or new-onset severe angina	Prolonged "crushing" chest pain, more severe and wider radiation than usual angina	
Serum biomarkers	No	Yes	Yes
Electrocardiogram initial findings	ST depression and/or T-wave inversion	ST depression and/or T-wave inversion	ST elevation (and Q waves later)

NSTEMI, non–ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

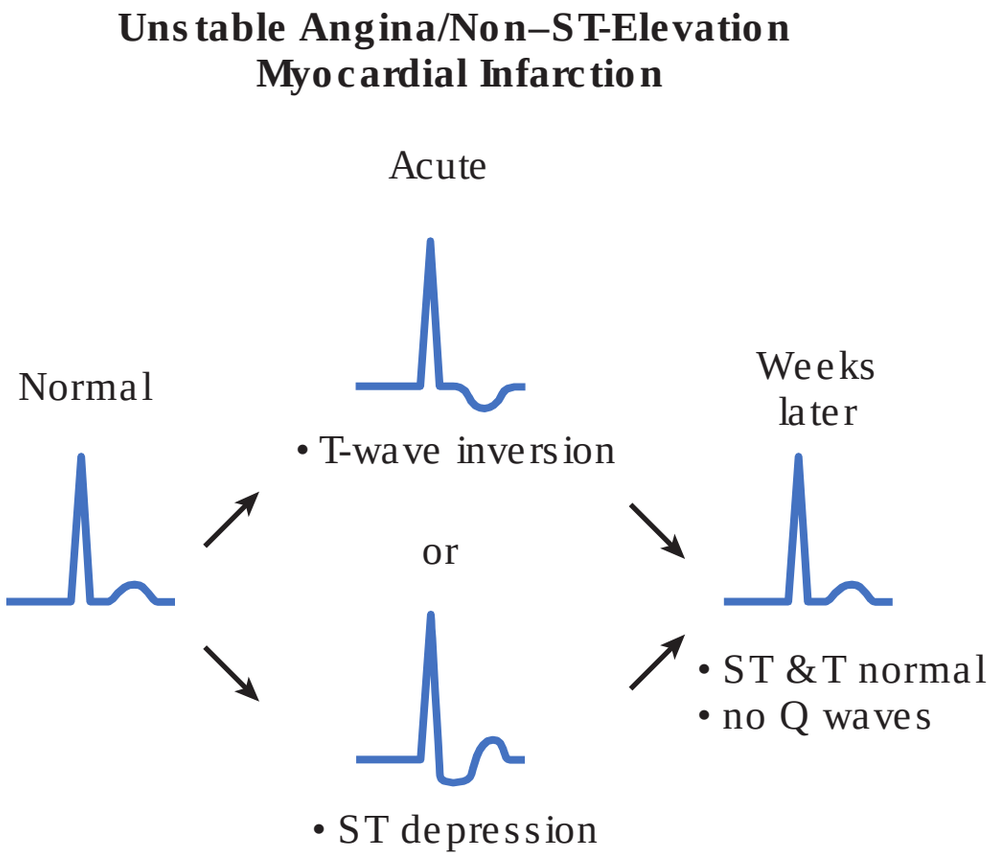

FIGURE 7-6. ECG abnormalities in unstable angina and non–ST-elevation myocardial infarction.

elevation, followed over the course of several hours by inversion of the T wave and the appearance of pathologic Q waves (Fig. 7-7). Importantly, these characteristic patterns of ECG abnormalities in ACS can be minimized or prevented by early therapeutic interventions.

Historically, MIs had been classified as "Q-wave" or "non–Q-wave" infarctions before the advent of the terms "STEMI" and "NSTEMI," respectively. The older terminology, which is still occasionally encountered, reflected the fact that pathologically transmural infarctions typically produce pathologic Q waves (after an initial period of ST elevation), whereas subendocardial infarctions do not. However, it is now known that the development of Q waves does not reliably correlate with pathologic findings and that much overlap exists among the types of infarction. Moreover, the finding of new pathologic Q waves to classify ACSs now has little therapeutic relevance because Q waves, when they occur, take hours to develop and therefore are not helpful in making acute treatment decisions.

Serum Markers of Infarction

Necrosis of myocardial tissue causes disruption of the sarcolemma, so that intracellular macromolecules leak into the cardiac interstitium and ultimately into the bloodstream (Fig. 7-8). Detection of such molecules in the serum, particularly cardiac-specific troponins, serves important diagnostic and prognostic roles. In patients with STEMI or NSTEMI, these markers rise above a threshold level in a defined temporal sequence.

Cardiac-specific Troponins

Troponin is a regulatory protein in muscle cells that controls interactions between myosin and actin (see Chapter 1). It consists of three subunits: TnC, TnI, and TnT. Although these subunits are found in both skeletal and cardiac muscles, the cardiac forms of troponin I (cTnI) and troponin T (cTnT) are structurally unique, and highly specific and sensitive assays for their detection in the serum are in wide clinical use. The presence of even minor serum elevations of these biomarkers serves as evidence of cardiomyocyte injury, is diagnostic of infarction in the appropriate clinical setting, and conveys powerful prognostic information. However, as new generations of these assays have become ever more sensitive, small serum

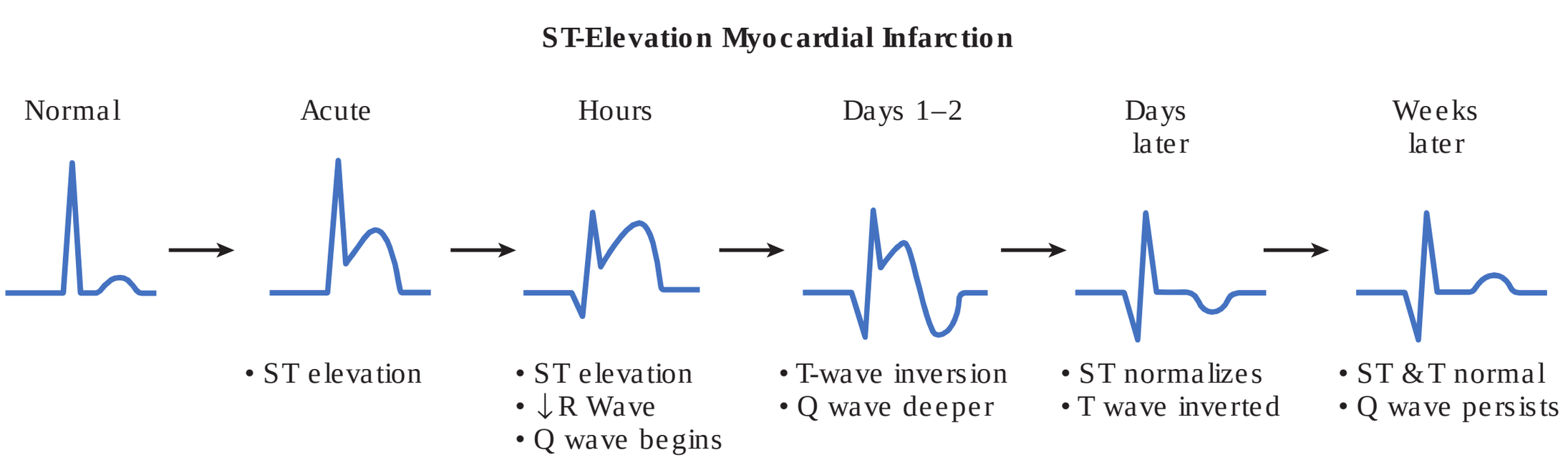

FIGURE 7-7. ECG evolution during ST-elevation myocardial infarction.

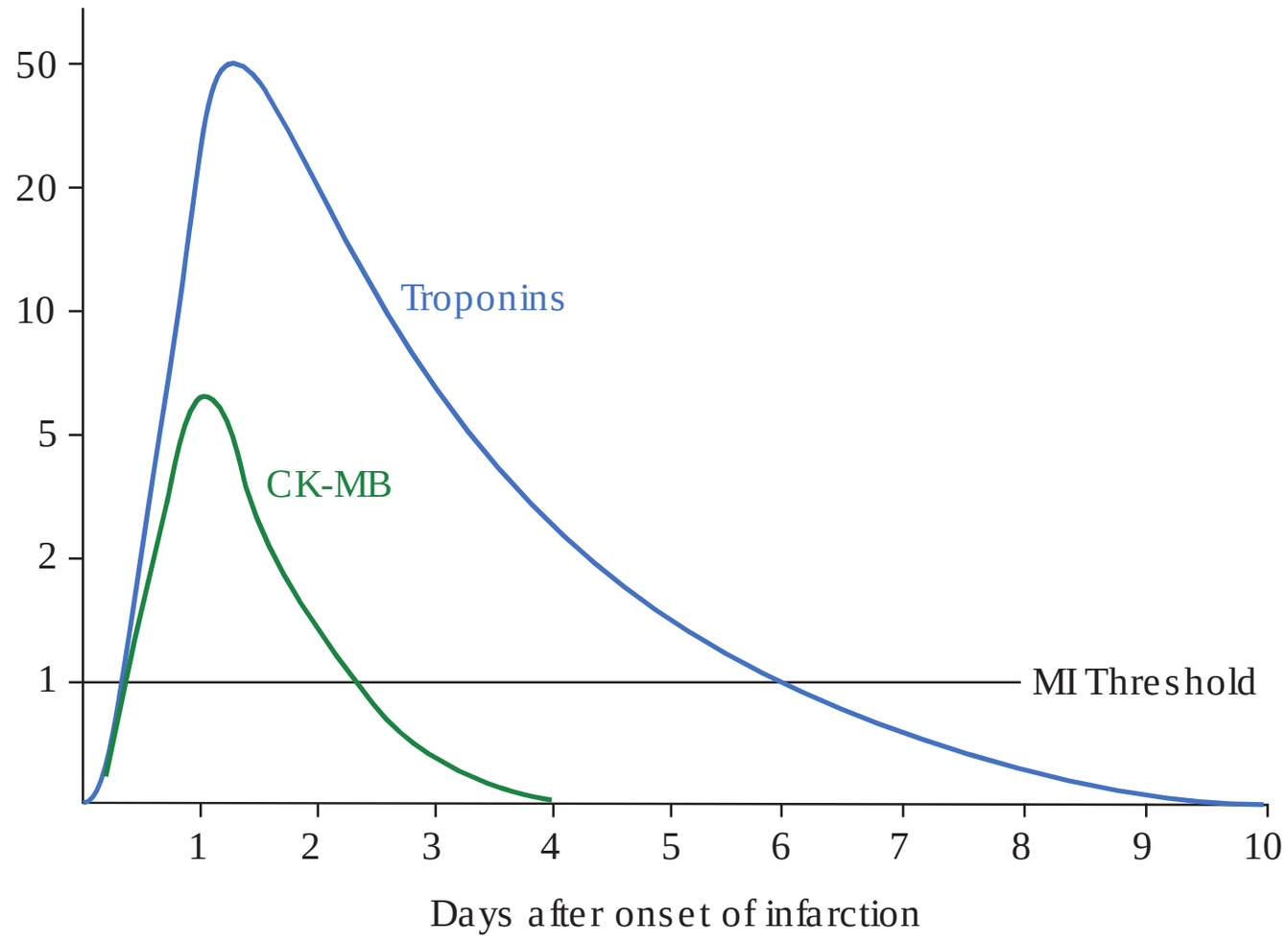

FIGURE 7-8. Evolution of serum biomarkers in acute myocardial infarction (MI).

elevations can also be detected in conditions other than MI, related to acute cardiac strain or inflammation (e.g., in heart failure, myocarditis, hypertensive crises, or pulmonary embolism [due to right ventricular strain]).

In the case of MI, cardiac troponin serum levels begin to rise 3 to 4 hours after the onset of chest discomfort, achieve a peak level between 18 and 36 hours, and then decline slowly, allowing for detection for 10 days or more after a large MI. Thus, their measurement may be helpful for detection of MI for nearly 2 weeks after the event occurs. Given their high sensitivity and specif city, cardiac troponins are the preferred serum biomarkers to detect myocardial necrosis.

Creatine Kinase

The enzyme creatine kinase (CK) is found in the heart, skeletal muscle, brain, and other organs. Injury to any of these tissues may lead to elevation in serum concentrations of the enzyme. There are, however, three isoenzymes of CK that improve diagnostic specif city of its origin: CK-MM (found mainly in skeletal muscle), CK-BB (located predominantly in the brain), and **CK-MB** (localized mainly in the heart). Elevation of CK-MB is highly suggestive of myocardial injury. To facilitate the diagnosis of MI using this marker, it is common to calculate the ratio of CK-MB to total CK. The ratio is usually greater than 2.5% in the setting of myocardial injury and less than that when CK-MB elevation is from another source. The serum level of CK-MB starts to rise 3 to 8 hours following infarction, peaks at 24 hours, and returns to normal within 48 to 72 hours (see Fig. 7-8). As CK-MB is not as sensitive or specif c for detection of myocardial injury as is cardiac troponin, the latter is the preferred diagnostic biomarker in clinical use. Because troponin and CK-MB levels do not become elevated in the serum until at least a few hours after the onset of MI symptoms, a single normal value drawn early in the course of evaluation (e.g., in the hospital emergency department) does not rule out an acute MI; thus, the diagnostic utility of these biomarkers is limited in that critical period. As a result, early decision making in patients with ACS often relies most heavily on the patient's history and ECG f ndings.

Imaging

Sometimes, the early diagnosis of MI can remain uncertain even after careful evaluation of the patient's history, ECG, and serum biomarkers. In such a situation, an additional diagnostic study that may be useful in the acute setting is echocardiography, which often reveals new abnormalities of ventricular contraction in the region of ischemia or infarction.

TREATMENT OF ACUTE CORONARY SYNDROMES

Successful management of ACS requires rapid initiation of therapy to limit myocardial damage and minimize complications. Therapy must address the intracoronary thrombus that incited the syndrome and provide anti-ischemic measures to restore the balance between myocardial oxygen supply and demand. Although certain therapeutic aspects are common to all ACS, there is a critical difference in the approach to patients who present with ST-segment elevation (STEMI) compared with those without ST-segment elevation (UA and NSTEMI). Patients with STEMI typically have total occlusion of a coronary artery and for optimal therapy require very rapid reperfusion therapy (mechanical or pharmacologic), whereas patients without ST elevation generally do not (see Fig. 7-9 and as discussed later in the chapter).

General in-hospital measures for any patient with ACS include admitting the patient to an intensive care setting where **continuous ECG monitoring** for arrhythmias is undertaken. The patient is initially maintained at **bed rest** to minimize myocardial oxygen demand, while supplemental **oxygen** is provided (by face mask or nasal cannula), if there is any degree of hypoxemia, to improve oxygen supply. Analgesics, such as **morphine**, may be administered to reduce chest pain and associated anxiety.

Acute Treatment of Unstable Angina and Non–ST-Elevation Myocardial Infarction

The management of UA and NSTEMI is essentially the same and is therefore discussed as one entity, whereas the approach to STEMI is described later. The primary focus of treatment for UA and NSTEMI consists of anti-ischemic medications to restore the balance between myocardial oxygen supply and demand, and antithrombotic therapy to prevent further growth, and to facilitate resolution of, the underlying partially occlusive coronary thrombus.

Anti-ischemic Therapy

The same pharmacologic agents used to decrease myocardial oxygen demand in chronic stable angina are appropriate in UA and NSTEMI but are often administered more aggressively. **β-Blockers** decrease sympathetic drive to the myocardium, thus reducing oxygen demand, and contribute to electrical stability. This group of drugs reduces the likelihood of progression from UA to MI and lowers mortality rates in patients who present with infarction. In the absence of contraindications (e.g., marked bradycardia, bronchospasm, decompensated heart failure, or hypotension), a β-blocker is usually initiated in the first 24 hours to achieve a target heart rate of approximately 60 beats/min. Such therapy is usually continued indefinitely after hospitalization because of proven long-term mortality benefits following an MI.

Nitrates help bring about anginal relief through venodilation, which lowers myocardial oxygen demand by diminishing venous return to the heart (reduced preload and therefore less ventricular wall stress). Nitrates may also improve coronary flow and prevent vasospasm through coronary vasodilation. In UA or NSTEMI, nitroglycerin is often initially administered by the sublingual route, followed by a continuous intravenous infusion. In addition to providing symptomatic relief of angina, intravenous nitroglycerin is useful as a vasodilator in patients with ACS accompanied by heart failure or severe hypertension.

Nondihydropyridine **calcium channel antagonists** (i.e., verapamil and diltiazem) exert anti-ischemic effects by decreasing heart rate and contractility and through their vasodilatory properties (see Chapter 6). These agents do not confer mortality benefit to patients with ACS and are reserved for those in whom ischemia persists despite β-blocker and nitrate therapies or for those with contraindications to β-blocker use. They should not be prescribed to patients with LV systolic dysfunction, because clinical trials have shown adverse outcomes in that case.

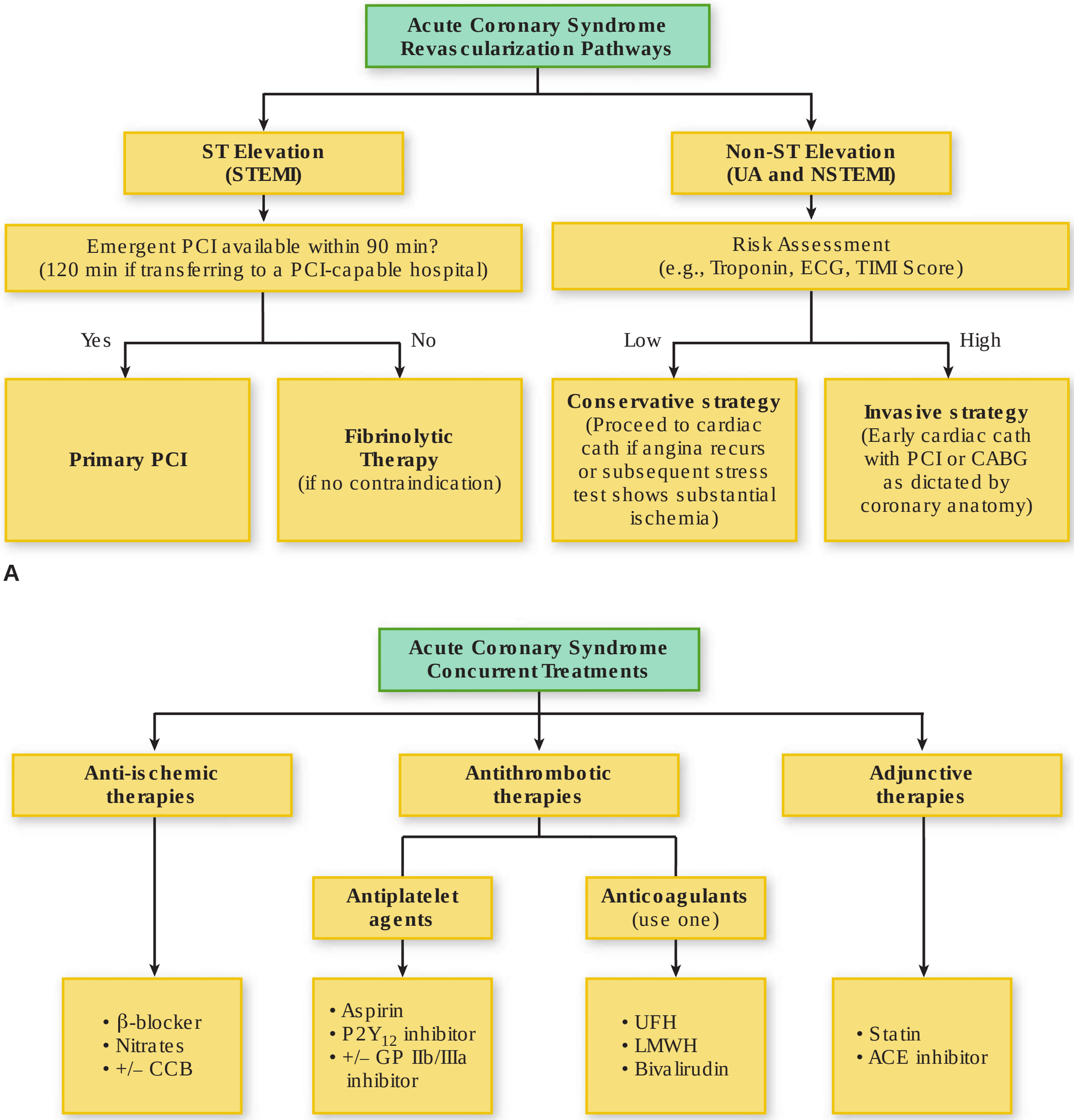

FIGURE 7-9. Initial management strategies in acute coronary syndromes (ACS). A. Revascularization options. Primary percutaneous coronary intervention (PCI) is the preferred approach for STEMI patients if it is available rapidly. In UA/NSTEMI, early invasive assessment is advised in patients with high-risk features. **B.** Pharmacologic agents that are typically indicated in ACS. Platelet $P2Y_{12}$ inhibitors include clopidogrel, ticagrelor, and prasugrel. Note that when a glycoprotein (GP) IIb/IIIa receptor antagonist is used as an additional antiplatelet agent, it is typically initiated at the time of PCI. Bivalirudin is an anticoagulant option for patients with ACS undergoing PCI. ECG, electrocardiogram; CCB, calcium channel blocker; LMWH, low molecular weight heparin; UFH, unfractionated intravenous heparin; ACE, angiotensin-converting enzyme.

Antithrombotic Therapy

The purpose of antithrombotic therapy, including antiplatelet and anticoagulant medications, is to prevent further propagation of the partially occlusive intracoronary thrombus while facilitating its dissolution by endogenous mechanisms.

Antiplatelet Drugs

The majority of patients with UA or NSTEMI should receive at least two forms of antiplatelet therapy, typically aspirin and an inhibitor of the platelet $P2Y_{12}$ ADP receptor.

Aspirin inhibits platelet synthesis of thromboxane A_2, a potent mediator of platelet activation (see Chapter 17), and is one of the most important interventions to reduce mortality in patients with all forms of ACS. It should be administered immediately on presentation and continued indef nitely in patients without contraindications to its use (e.g., allergy or underlying bleeding disorder).

Aspirin inhibits only a single pathway of platelet activation. Another important agonist is ADP, which activates platelets in part by binding to the platelet $P2Y_{12}$ receptor (see Chapter 17). Antagonists of this receptor inhibit platelet activation and include clopidogrel, prasugrel, and ticagrelor. **Clopidogrel** is an oral thienopyridine derivative (described in Chapter 17) that further reduces cardiovascular death, recurrent MI, and stroke rates in patients with UA or NSTEMI who are treated with aspirin.

However, not all patients respond to clopidogrel with similar benef t as it is a prodrug that requires cytochrome P-450–mediated biotransformation to its active metabolite. Patients with reduced function polymorphisms of the CYP2C19 gene produce lower concentrations of clopidogrel's activate metabolite, less platelet inhibition, and attenuated clinical benef ts. Thus, newer $P2Y_{12}$ ADP receptor blockers have been developed that do not have this metabolic shortcoming, have more rapid onsets of action, and achieve greater degrees of platelet inhibition than clopidogrel. For example, **prasugrel** is also a thienopyridine derivative. Compared to clopidogrel, it reduces coronary event rates in patients with ACS who undergo percutaneous coronary intervention (PCI), but because it is more potent, it also increases the risk of bleeding complications.

Both clopidogrel and prasugrel are irreversible platelet inhibitors. **Ticagrelor** is a nonthienopyridine drug that is a reversible $P2Y_{12}$ ADP receptor blocker. Compared to clopidogrel, it has been shown to further decrease major cardiovascular events and mortality, without an increased risk of life-threatening bleeding episodes; minor bleeding is, however, more common than with clopidogrel.

In some circumstances, even more powerful antiplatelet agents are utilized in ACSs. The **glycoprotein (GP) IIb/IIIa receptor antagonists** (which include the monoclonal antibody abciximab and the small molecules eptif batide and tirof ban) are potent antiplatelet agents that block the f nal common pathway of platelet aggregation (see Chapter 17). These agents are effective in reducing adverse coronary events in patients undergoing PCI. In patients presenting with UA or NSTEMI, their benef t is manifest primarily in those at the highest risk of complications (e.g., the presence of elevated serum troponin levels or recurrent episodes of chest pain). When used, GP IIb/IIIa receptor antagonists are most commonly initiated in the cardiac catheterization laboratory at the time of PCI.

Anticoagulant Drugs

Intravenous **unfractionated heparin (UFH)** has long been standard anticoagulant therapy for UA and NSTEMI. It binds to antithrombin, which greatly increases the potency of that plasma protein in the inactivation of clot-forming thrombin. UFH additionally inhibits coagulation factor Xa, slowing thrombin formation and thereby further impeding clot development. In patients with UA or NSTEMI, UFH improves cardiovascular outcomes and reduces the likelihood of progression from UA to MI. It is administered as a weight-based bolus, followed by continuous intravenous infusion. Because of a high degree of pharmacodynamic variability, its anticoagulant effect must be monitored and its dose adjusted, through serial measurements of the serum activated partial thromboplastin time (aPTT). It is the least expensive of the anticoagulant drugs described in this section.

To overcome the pharmacologic shortcomings of UFH, **low molecular weight heparins (LMWHs)** were developed. Like UFH, LMWHs interact with antithrombin but preferentially inhibit coagulation factor Xa. They provide a more predictable pharmacologic response than UFH. As a result, LMWHs are easier to use, prescribed as one or two daily subcutaneous injections based on the patient's weight. Unlike UFH, repeated monitoring of blood tests and dosage adjustments are not generally necessary. In clinical trials in patients with UA or NSTEMI, the LMWH enoxaparin (see Chapter 17) has demonstrated reduced death and ischemic event rates compared with UFH.

Two other types of anticoagulants have also been shown to be beneficial in UA and NSTEMI and are sometimes used in place of UFH or LMWH. **Bivalirudin** is an intravenous direct thrombin inhibitor (see Chapter 17), which is equivalent to UFH plus a GP IIb/IIIa inhibitor in preventing adverse ischemic outcomes, with less associated bleeding, in patients with UA or NSTEMI treated with an early invasive strategy. **Fondaparinux** is a subcutaneously administered agent that is a very specific factor Xa inhibitor (see Chapter 17). Its effect is similar to the LMWH enoxaparin at reducing cardiac adverse events but with fewer bleeding complications.

With all of these choices, the decision of which anticoagulant to prescribe to an individual patient often depends on whether an initial conservative versus invasive approach is followed.

Conservative versus Early Invasive Management of UA and NSTEMI

Many patients with UA or NSTEMI stabilize following institution of the therapies described in the previous section, while others have recurrent ischemic events. There is currently no definitive way to predict which direction a patient will take or to quickly determine which individuals have such severe underlying CAD that coronary revascularization is warranted. These uncertainties have led to two therapeutic strategies in UA/NSTEMI: (1) an early invasive approach, in which urgent cardiac catheterization is performed and coronary revascularization undertaken as indicated, and (2) a conservative approach, in which the patient is managed with medications (as detailed in the previous section) and undergoes angiography only if ischemic episodes spontaneously recur or if the results of a subsequent stress test indicate substantial residual inducible ischemia. The conservative approach offers the advantage of avoiding costly and potentially risky invasive procedures. Conversely, an early invasive strategy allows rapid identification and definitive treatment (i.e., revascularization) for those with critical coronary disease.

In general, an early invasive approach is recommended to patients with refractory angina, with complications such as shock or ventricular arrhythmias, or those with the most concerning clinical features. Risk assessment algorithms consider such features and help identify patients at high likelihood of a poor outcome. One commonly used tool is the **Thrombolysis in Myocardial Infarction (TIMI) risk score** that employs seven variables to predict a patient's risk level:

1. Age greater than 65 years old
2. ≥3 risk factors for coronary artery disease (as described in Chapter 5)
3. Known coronary stenosis of ≥50% by prior angiography
4. ST-segment deviations on the ECG at presentation
5. At least two anginal episodes in prior 24 hours
6. Use of aspirin in prior 7 days (i.e., implying resistance to aspirin's effect)
7. Elevated serum troponin or CK-MB

Clinical studies have confirmed that a patient's TIMI risk score predicts the likelihood of death or subsequent ischemic events, such that an early invasive strategy is recommended in patients with higher scores (≥3). If an early invasive approach is adopted, the patient should undergo angiography within 72 hours, or within 24 hours for patients at especially high risk.

Acute Treatment of ST-Elevation Myocardial Infarction

In contrast to UA and NSTEMI, the culprit artery in STEMI is typically completely occluded. Thus, to limit myocardial damage, the major focus of acute treatment is to achieve very rapid reperfusion of the jeopardized myocardium using either percutaneous coronary mechanical revascularization or fibrinolytic drugs. These approaches reduce the extent of myocardial necrosis and greatly improve survival. To be effective, they must be undertaken as soon as possible; the earlier the intervention occurs, the greater the amount of myocardium that can be salvaged. Decisions about therapy must be made within minutes of a patient's assessment, based on the history and electrocardiographic findings, often before serum markers of necrosis would be expected to rise.

In addition, as is the case in UA and NSTEMI, specific medications should be initiated promptly to prevent further thrombosis and to restore the balance between myocardial oxygen supply and demand. For example, antiplatelet therapy with **aspirin** decreases mortality rates and rates of reinfarction after STEMI. It should be administered immediately on presentation (by chewing a tablet to facilitate absorption) and continued orally daily thereafter. An **anticoagulant** (e.g., intravenous UFH) is typically initiated to help maintain patency of the coronary vessel and is an important adjunct to PCI and fibrinolytic regimens. **β-Blockers** reduce myocardial oxygen demand and lower the risk of recurrent ischemia, arrhythmias, and reinfarction. In the absence of contraindications (e.g., asthma, hypotension, or significant bradycardia), an oral β-blocker should be administered to achieve a heart rate of 50 to 60 beats/min. Intravenous β-blocker therapy should be reserved for patients who are hypertensive at presentation, as that route of administration has otherwise been associated with an increased risk of cardiogenic shock in STEMI. **Nitrate** therapy, usually intravenous nitroglycerin, is used to help control ischemic pain and also serves as a beneficial vasodilator in patients with heart failure or severe hypertension.

Primary Percutaneous Coronary Intervention

The preferred method of reperfusion therapy in patients with acute STEMI is immediate cardiac catheterization and percutaneous coronary intervention of the lesion responsible for the infarction. This approach, termed primary PCI, is a very effective method for reestablishing coronary perfusion and, in clinical trials performed at highly experienced medical centers, has achieved optimal flow in the infarct-related artery in more than 95% of patients. During the procedure, performed under fluoroscopy, a catheter is inserted into a peripheral artery and directed to the site of coronary occlusion. A balloon at the end of the catheter is then inflated, compressing the thrombus and atherosclerotic plaque, and a stent is usually inserted (see Chapter 6), thereby restoring and maintaining coronary blood flow. In order to salvage as much myocardium as possible, the goal is that the time from first medical contact to PCI be less than 90 minutes. At medical centers without PCI availability, the decision to transfer a patient to a PCI-capable hospital or to treat with fibrinolytic therapy (discussed in next section) must be made rapidly. A delay in reperfusion leads to worse outcomes for patients regardless of the mechanism chosen, and the longer the delay, the less benefit primary PCI has over fibrinolytic therapy. Generally, transfer to a PCI-capable hospital is recommended if the procedure can be performed within 120 minutes of first medical contact.

To reduce thrombotic complications, patients undergoing primary PCI receive a combination of medications. **Aspirin** and a **$P2Y_{12}$ receptor inhibitor** (e.g., ticagrelor, prasugrel, or clopidogrel) are the antiplatelet agents typically administered prior to the procedure. A more potent **GP IIb/IIIa platelet inhibitor** is also sometimes used with PCI. Anticoagulation therapy consists of either **UFH** or **bivalirudin** as the primary choices. Recent evidence shows that bivalirudin results in lower rates of bleeding in STEMI when compared to UFH plus a GP IIb/IIIa inhibitor. However, it is also associated with a higher rate of acute stent thrombosis in this setting.

After primary PCI, aspirin is continued indefinitely. For patients who receive coronary stents during PCI, a prolonged course of a $P2Y_{12}$ receptor inhibitor reduces the risk of ischemic complications and stent thrombosis.

Fibrinolytic Therapy

Primary PCI is the preferred reperfusion approach in acute STEMI, as it leads to greater survival with lower rates of reinfarction and bleeding when compared to fibrinolytic therapy. However, if PCI is not available or is likely to be delayed, fibrinolytic therapy is the reperfusion alternative. Fibrinolytic drugs accelerate lysis of the occlusive intracoronary thrombus in STEMI, thereby restoring blood flow and limiting myocardial damage. This section does not pertain to patients with UA or NSTEMI, as such individuals do not benefit from fibrinolytic therapy.

Currently used fibrinolytic agents include **recombinant tissue–type plasminogen activator (alteplase, tPA), reteplase (rPA)**, and **tenecteplase (TNK-tPA)**. Each drug functions by stimulating the natural fibrinolytic system, transforming the inactive precursor plasminogen into the active protease plasmin, which lyses fibrin clots. Although the intracoronary thrombus is the target, plasmin has poor substrate specificity and can degrade other proteins, including fibrin's precursor fibrinogen. As a result, bleeding is the most common complication of these drugs. Administration of fibrinolytic agents in the early hours of an acute STEMI restores blood flow in most (70% to 80%) coronary occlusions and significantly reduces the extent of tissue damage. Improved artery patency translates into substantially increased survival rates and fewer postinfarction complications. The rapid initiation of fibrinolysis is crucial: patients who receive therapy within 2 hours of the onset of symptoms of STEMI have half the mortality rate of those who receive it after 6 hours.

To prevent immediate vessel reocclusion after successful thrombolysis, anticoagulants (UFH or LMWHs) and antiplatelet therapy, including aspirin and a platelet $P2Y_{12}$ inhibitor, are administered. For those initially treated with fibrinolytic therapy who do not demonstrate an adequate acute response, including expeditious resolution of symptoms and ST-segment elevations, transfer of the patient to a hospital capable of performing "rescue" PCI is recommended as soon as possible.

Because the major risk of thrombolysis is bleeding, contraindications to such therapy include situations in which necessary fibrin clots within the circulation would be jeopardized (e.g., patients with active peptic ulcer disease or an underlying bleeding disorder, patients who have had a recent stroke, or patients who are recovering from recent surgery). Consequently, approximately 30% of patients may not be suitable candidates for thrombolysis.

Adjunctive Therapies

Angiotensin-converting enzyme (ACE) inhibitors limit adverse ventricular remodeling and reduce the incidence of heart failure, recurrent ischemic events, and mortality following an MI. Their benefit is additive to that of aspirin and β-blocker therapies, and they have shown favorable improvements especially in higher-risk patients—those with anterior wall infarctions or LV systolic dysfunction.

Cholesterol-lowering **statins** (HMG-CoA reductase inhibitors) reduce mortality rates of patients with coronary artery disease (see Chapter 5). Clinical trials of patients with ACS have demonstrated that it is safe to begin statin therapy early during hospitalization and that a high-intensity lipid-lowering regimen, designed to reduce low-density lipoprotein (LDL) levels by greater than 50% (ideally to < 70 mg/dL), provides greater protection against subsequent cardiovascular events and death than less intense regimens. The benefits of statin therapy may extend beyond lipid lowering, because this group of drugs has attributes that can improve endothelial dysfunction, inhibit platelet aggregation, and impair thrombus formation. Additional LDL lowering with the cholesterol absorption inhibitor ezetimibe (see Chapter 17) after an ACS was recently shown to further reduce subsequent cardiovascular event rates.

In addition to the short-term use of heparin anticoagulation described earlier, a more prolonged course, followed by oral anticoagulation (i.e., warfarin), is appropriate for patients at high risk of thromboembolism. This includes patients with documented intraventricular thrombus (typically identified by echocardiography), those with atrial fibrillation, and persons who have suffered a large acute anterior MI with akinesis of that territory (which is susceptible to thrombus formation because of the stagnant blood flow).

As discussed later in the chapter, impaired ventricular contractility after MI can lead to heart failure. Patients with a left ventricular ejection fraction of less than 40% and symptoms of heart failure after STEMI should be considered for therapy with an **aldosterone antagonist** (spironolactone or eplerenone) in addition to an ACE inhibitor and beta-blocker. Aldosterone augments sodium reabsorption from the distal nephron (contributing to fluid retention, an undesired effect in heart failure) and also promotes inflammation and myocardial fibrosis. Chronic administration of an aldosterone antagonist mitigates these effects and has been shown to decrease mortality following MI in patients with left ventricular dysfunction.

COMPLICATIONS

In UA, potential complications include death (5% to 10% of patients) or progression to infarction (10% to 20% of patients) over the ensuing days and weeks. Once infarction has transpired, especially STEMI, complications can result from the inflammatory, mechanical, and electrical abnormalities induced by regions of necrosing myocardium (Fig. 7-10). Early complications result from myocardial necrosis itself. Those that develop several days to weeks later reflect the inflammation and healing of necrotic tissue.

Recurrent Ischemia

Postinfarction angina has been reported in 20% to 30% of patients following an MI. This rate has not been reduced by the use of thrombolytic therapy, but it is lower in those who have undergone acute percutaneous coronary revascularization. Indicative of inadequate residual

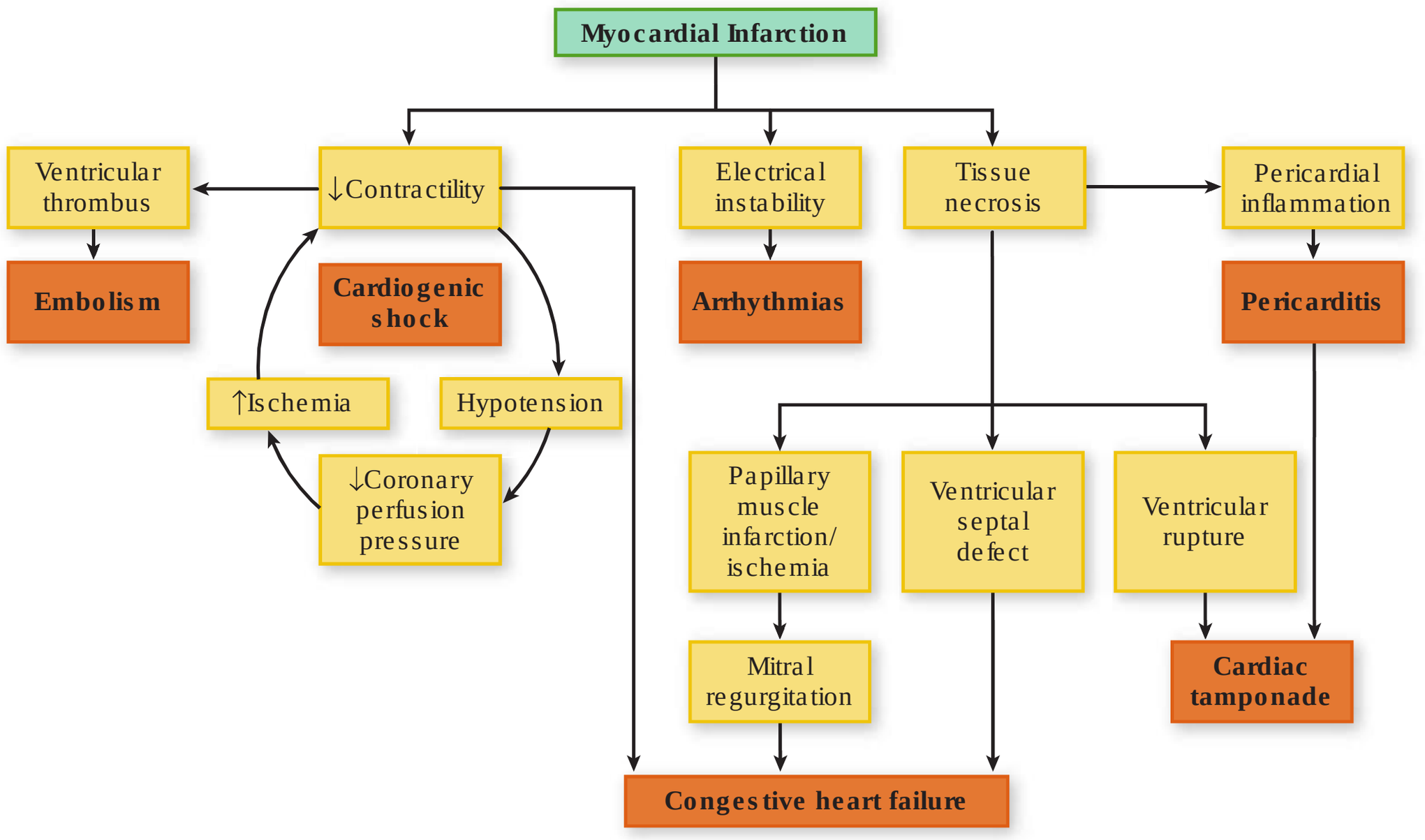

FIGURE 7-10. Complications of MI. Infarction may result in decreased contractility, electrical instability, and tissue necrosis, which can lead to the indicated sequelae.

TABLE 7-7 Arrhythmias in Acute Myocardial Infarction

Rhythm	Cause
Sinus bradycardia	• ↑Vagal tone • ↓SA nodal artery perfusion
Sinus tachycardia	• Pain and anxiety • Heart failure • Volume depletion • Chronotropic drugs (e.g., dopamine)
APBs, atrial fibrillation	• Heart failure • Atrial ischemia
VPBs, VT, VF	• Ventricular ischemia • Heart failure
AV block (1°, 2°, 3°)	• IMI: ↑vagal tone and ↓AV nodal artery flow • AMI: extensive destruction of conduction tissue

AMI, anterior myocardial infarction; APBs, atrial premature beats; AV, atrioventricular; IMI, inferior myocardial infarction; SA, sinoatrial; VPBs, ventricular premature beats; VF, ventricular fibrillation; VT, ventricular tachycardia.

coronary blood flow, it is a poor omen and correlates with an increased risk for reinfarction. Such patients usually require urgent cardiac catheterization, often followed by revascularization by percutaneous techniques or coronary artery bypass surgery.

Arrhythmias

Arrhythmias occur frequently during acute MI and are a major source of mortality prior to hospital arrival. Fortunately, modern coronary care units are highly attuned to the detection and treatment of rhythm disturbances; thus, once a patient is hospitalized, arrhythmia-associated deaths are uncommon. Mechanisms that contribute to arrhythmogenesis after MI include the following (Table 7-7):

1. Anatomic interruption of blood flow to structures of the conduction pathway (e.g., sinoatrial node, atrioventricular node, and bundle branches); the normal perfusion of pertinent components of the conduction system is summarized in Table 7-8.
2. Accumulation of toxic metabolic products (e.g., cellular acidosis) and abnormal transcellular ion concentrations owing to membrane leaks.
3. Autonomic stimulation (sympathetic and parasympathetic).
4. Administration of potentially arrhythmogenic drugs (e.g., dopamine).

TABLE 7-8 Blood Supply of the Conduction System

Conduction Pathway	Primary Arterial Supply
SA node	• RCA (70% of patients)
AV node	• RCA (85% of patients)
Bundle of His	• LAD (septal branches)
Right bundle branch	• Proximal portion by LAD • Distal portion by RCA
Left bundle branch	
Left anterior fascicle	• LAD
Left posterior fascicle	• LAD and PDA

AV, atrioventricular; LAD, left anterior descending coronary artery; PDA, posterior descending artery; RCA, right coronary artery; SA, sinoatrial.

Ventricular Fibrillation

Ventricular fibrillation (rapid, disorganized electrical activity of the ventricles) is largely responsible for sudden cardiac death during the course of acute MI. Most fatal episodes occur before hospital arrival, a trend that can be impacted by increasing availability of automatic external defibrillators in public places. Episodes of ventricular fibrillation that occur during the first 48 hours of MI are often related to transient electrical instability, and the long-term prognosis of survivors of such events is not adversely affected. However, ventricular fibrillation occurring later than 48 hours after the acute MI usually reflects severe LV dysfunction and is associated with high subsequent mortality rates.

Ventricular ectopic beats, ventricular tachycardia, and ventricular fibrillation during an acute MI arise from either reentrant circuits or enhanced automaticity of ventricular cells (see Chapter 11). Ventricular ectopic beats are common and usually not treated unless the beats become consecutive, multifocal, or frequent. Cardiac care unit personnel are proficient at arrhythmia detection and institution of treatment should more malignant ventricular arrhythmias develop. Therapy for ventricular arrhythmias is described in Chapter 12.

Supraventricular Arrhythmias

Supraventricular arrhythmias are also common in acute MI. Sinus bradycardia results from either excessive vagal stimulation or sinoatrial nodal ischemia, usually in the setting of an inferior wall MI. Sinus tachycardia occurs frequently and may result from pain and anxiety, heart failure, drug administration (e.g., dopamine), or intravascular volume depletion. Because sinus tachycardia increases myocardial oxygen demand and could exacerbate ischemia, identifying and treating its cause are important. Atrial premature beats and atrial fibrillation (see Chapter 12) may result from atrial ischemia or atrial distention secondary to LV failure.

Conduction Blocks

Conduction blocks (atrioventricular nodal block and bundle branch blocks) develop commonly in acute MI. They may result from ischemia or necrosis of conduction tracts, or in the case of atrioventricular blocks, they may develop transiently because of increased vagal tone. Vagal activity may be increased because of stimulation of afferent fibers by the inflamed myocardium or as a result of generalized autonomic activation in association with the discomfort of an acute MI.

Myocardial Dysfunction

Heart Failure

Acute cardiac ischemia results in impaired ventricular contractility (systolic dysfunction) and increased myocardial stiffness (diastolic dysfunction), both of which may lead to symptoms of heart failure. In addition, ventricular remodeling, arrhythmias, and acute mechanical complications of MI (described later in the chapter) may culminate in heart failure. Signs and symptoms of such decompensation include dyspnea, pulmonary rales, and a third heart sound (S_3). Treatment consists of standard heart failure therapy, which typically includes diuretics for relief of volume overload, and ACE inhibitor and β-blocker therapies for long-term mortality benefit (see Chapter 9). As noted earlier, for patients with post-MI heart failure and an LV ejection fraction less than 40%, an aldosterone antagonist (spironolactone or eplerenone—described in Chapter 17) should be considered. However, when an aldosterone antagonist is prescribed concurrently with an ACE inhibitor, the serum potassium level should be carefully monitored to prevent hyperkalemia.

Cardiogenic Shock

Cardiogenic shock is a condition of severely decreased cardiac output and hypotension (systolic blood pressure < 90 mm Hg) with inadequate perfusion of peripheral tissues that develops when more than 40% of the LV mass has infarcted. It may also follow certain severe mechanical complications of MI described later. Cardiogenic shock is self-perpetuating because (1) hypotension leads to decreased coronary perfusion, which exacerbates ischemic damage, and (2) decreased stroke volume increases LV size and therefore augments myocardial oxygen demand (see Fig. 7-10). Cardiogenic shock occurs in up to 10% of patients after MI, and the mortality rate is greater than 70%. Early cardiac catheterization and revascularization can improve the prognosis.

Patients in cardiogenic shock require intravenous inotropic agents (e.g., dobutamine) to increase cardiac output and, once the blood pressure has improved, arterial vasodilators to reduce the resistance to LV contraction. Patients may be stabilized by the placement of an **intra-aortic balloon pump**. Inserted into the aorta through a femoral artery, the pump consists of an inflatable, flexible chamber that expands during diastole to increase intra-aortic pressure, thus augmenting perfusion of the coronary arteries. During systole, it deflates to create a "vacuum" that serves to reduce the afterload of the left ventricle, thus aiding the ejection of blood into the aorta and improving cardiac output and peripheral tissue perfusion.

If more extensive and prolonged hemodynamic support is required, a **percutaneous left ventricular assist device (LVAD)** can be placed. Using cannulae inserted via the femoral vessels, a motor pumps oxygenated blood from the LA or the LV (depending on the model) to the aorta and its branches, bypassing or "assisting" the LV.

Right Ventricular Infarction

Approximately one third of patients with infarction of the LV inferior wall also develop necrosis of portions of the right ventricle, because the same coronary artery (usually the right coronary) perfuses both regions in most individuals. The resulting abnormal contraction and decreased compliance of the right ventricle lead to signs of right-sided heart failure (e.g., jugular venous distention) out of proportion to signs of left-sided failure. In addition, profound hypotension may result when the right ventricular dysfunction impairs blood flow through the lungs, leading to the left ventricle becoming underf lled. In this setting, intravenous volume infusion serves to correct hypotension, often guided by hemodynamic measurements via a transvenous pulmonary artery catheter (see Chapter 3).

Mechanical Complications

Mechanical complications following MI result from cardiac tissue ischemia and necrosis.

Papillary Muscle Rupture

Ischemic necrosis and rupture of an LV papillary muscle may be rapidly fatal because of acute severe mitral regurgitation, as the valve leaflets lose their anchoring attachments. Partial rupture, with more moderate regurgitation, is not immediately lethal but may result in symptoms of heart failure or pulmonary edema. Because it has a more precarious blood supply, the posteromedial LV papillary muscle is more susceptible to infarction than the anterolateral one.

Ventricular Free Wall Rupture

An infrequent but deadly complication, rupture of the LV free wall through a tear in the necrotic myocardium may occur within the f rst 2 weeks following MI. It is more common

among women and patients with a history of hypertension. Hemorrhage into the pericardial space owing to LV free wall rupture results in rapid cardiac tamponade, in which blood fills the pericardial space and severely restricts ventricular filling (see Chapter 14). Survival is rare.

On occasion, a **pseudoaneurysm** results if rupture of the free wall is incomplete and held in check by thrombus formation that "plugs" the hole in the myocardium. This situation is the cardiac equivalent of a time bomb, because subsequent complete rupture into the pericardium and tamponade could follow. If detected (usually by imaging studies), surgical repair may prevent an otherwise disastrous outcome.

Ventricular Septal Rupture

This complication is analogous to LV free wall rupture, but the abnormal flow of blood is not directed across the LV wall into the pericardium. Rather, blood is shunted across the ventricular septum from the left ventricle to the right ventricle, usually precipitating congestive heart failure because of subsequent volume overload of the pulmonary capillaries. A loud systolic murmur at the left sternal border, representing transseptal flow, is common in this situation. Although each results in a systolic murmur, ventricular septal rupture can be differentiated from acute mitral regurgitation by the location of the murmur (see Fig. 2-11), by Doppler echocardiography, or by measuring the O_2 saturation of blood in the right-sided heart chambers through a transvenous catheter. The O_2 content in the right ventricle is abnormally higher than that in the right atrium if there is shunting of oxygenated blood from the left ventricle across the septal defect.

True Ventricular Aneurysm

A late complication of MI, a true ventricular aneurysm, may come to attention weeks to months after the acute infarction. It develops as the ventricular wall is weakened, but not perforated, by the phagocytic clearance of necrotic tissue, and it results in a localized outward bulge (dyskinesis) when the residual viable heart muscle contracts. Unlike the pseudoaneurysm described earlier, a true aneurysm does not involve communication between the LV cavity and the pericardium, so that rupture and tamponade do not develop. Potential complications of LV aneurysm include (1) thrombus formation within this region of stagnant blood flow, serving as a source of emboli to peripheral organs; (2) ventricular arrhythmias associated with the stretched myofibers; and (3) heart failure resulting from reduced forward cardiac output, because some of the LV stroke volume is "wasted" by filling the aneurysm cavity during systole.

Clues to the presence of an LV aneurysm include persistent ST-segment elevations on the ECG weeks after an acute ST-elevation MI and a bulge at the LV border on chest radiography. The abnormality can be confirmed by echocardiography or other imaging modalities.

Pericarditis

Acute pericarditis may occur in the early (in-hospital) post-MI period as inflammation extends from the myocardium to the adjacent pericardium. Sharp pain, fever, and a pericardial friction rub are typically present in this situation and help distinguish pericarditis from the discomfort of recurrent myocardial ischemia (see Chapter 14). The symptoms usually promptly respond to aspirin therapy. Anticoagulants are relatively contraindicated in MI complicated by pericarditis to avoid hemorrhage from the inflamed pericardial lining. The frequency of MI-associated pericarditis has declined since the introduction of acute reperfusion strategies, because those approaches limit the extent of myocardial damage and inflammation.

Dressler Syndrome

Dressler syndrome is now a rare form of pericarditis that can occur weeks following an MI. The cause is unclear, but an immune process directed against damaged myocardial tissue is suspected to play a role. The syndrome is heralded by fever, malaise, and sharp; pleuritic chest pain typically accompanied by leukocytosis; an elevated erythrocyte sedimentation rate; and a pericardial effusion. Similar to other forms of acute pericarditis, Dressler syndrome generally responds to aspirin or other nonsteroidal anti-inflammatory therapies.

Thromboembolism

Stasis of blood flow in regions of impaired LV contraction after an MI may result in intracavity thrombus formation, especially when the infarction involves the LV apex or when a true aneurysm has formed. Subsequent thromboemboli can result in infarction of peripheral organs (e.g., a cerebrovascular event [stroke] caused by embolism to the brain).

RISK STRATIFICATION AND MANAGEMENT FOLLOWING MYOCARDIAL INFARCTION

The most important predictor of post-MI outcome is the extent of LV dysfunction. Other features that portend adverse outcomes include early recurrence of ischemic symptoms, a large volume of residual myocardium still at risk because of severe underlying coronary disease, and high-grade ventricular arrhythmias.

To identify patients at high risk for complications who may benef t from cardiac catheterization and revascularization, exercise treadmill testing is often performed (unless the patient has already undergone catheterization and corrective percutaneous revascularization for the presenting coronary syndrome). Patients with signif cantly abnormal results, or those who demonstrate an early spontaneous recurrence of angina, are customarily referred for cardiac catheterization to def ne their coronary anatomy.

Standard postdischarge therapy for the long-term includes aspirin, a β-blocker, and a high-intensity HMG-CoA reductase inhibitor (statin). A $P2Y_{12}$ platelet inhibitor is continued for 12 months or longer. ACE inhibitors are prescribed to patients who have LV contractile dysfunction; an aldosterone antagonist should be considered in those with heart failure symptoms. Rigorous attention to underlying cardiac risk factors, such as smoking, hypertension, and diabetes, is mandatory, and a formal exercise rehabilitation program often speeds convalescence.

Patients who have an LV ejection fraction of $\leq$30% after MI are at high risk of sudden cardiac death and are candidates for prophylactic placement of an implantable cardioverter–def brillator. Current guidelines recommend postponing such implantation for at least 40 days post-MI because clinical trials have not shown a survival benef t at earlier stages.

SUMMARY

- Acute coronary syndromes (ACSs) include unstable angina (UA), non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).
- Most ACS episodes are precipitated by intracoronary thrombus formation at the site of atherosclerotic plaque disruption.
- Distinctions among types of ACS are based on the severity of ischemia and whether myocardial necrosis results: STEMI is associated with an occlusive thrombus and severe ischemia

with necrosis, whereas ACSs without ST elevation (NSTEMI and UA) usually result from partially occlusive thrombi with less intense ischemia; however, compared with UA, the insult in NSTEMI is of sufficient magnitude to cause some myocardial necrosis.

- ACSs result in biochemical and mechanical changes that impair systolic contraction, decrease myocardial compliance, and predispose to arrhythmias; infarction initiates an inflammatory response that clears necrotic tissue and leads to scar formation.
- The diagnosis of specific ACS relies on the patient's history, ECG abnormalities, and the presence of specific biomarkers in the serum (e.g., cardiac troponin T or troponin I).
- Acute treatment of UA and NSTEMI includes anti-ischemic therapy to restore the balance between myocardial oxygen supply and demand (e.g., β-blockers, nitrates), antithrombotic therapy to facilitate resolution of the intracoronary thrombus (e.g., aspirin, a $P2Y_{12}$ ADP receptor antagonist, an anticoagulant [e.g., intravenous or low molecular weight heparin], and sometimes a glycoprotein IIb/IIIa receptor antagonist), and high-intensity statin therapy.
- Early coronary angiography, with subsequent coronary revascularization, is beneficial for UA or NSTEMI patients with high-risk features.
- Acute treatment of STEMI includes rapid coronary reperfusion, ideally with percutaneous catheter-based intervention if available or else fibrinolytic therapy.
- Other important therapies for STEMI include antiplatelet therapy (aspirin, $P2Y_{12}$ receptor antagonist), an anticoagulant, a β-blocker, sometimes nitrate therapy, and a statin; an ACE inhibitor is frequently appropriate.
- Potential complications of infarction include arrhythmias (e.g., ventricular tachycardia and fibrillation, and supraventricular tachycardias) and conduction blocks (atrioventricular blocks and bundle branch blocks).
- Heart failure or cardiogenic shock may develop because of ventricular dysfunction or mechanical complications (e.g., acute mitral regurgitation or ventricular septal defect); wall motion abnormalities of the infarcted segment may predispose to thrombus formation.
- Right ventricular infarction results in signs of right heart failure out of proportion to left heart failure, often with intravascular volume sensitivity and hypotension.
- Standard pharmacologic therapy following discharge from the hospital after an ACS includes measures to reduce the risks of thrombosis (aspirin and a $P2Y_{12}$ receptor antagonist), recurrent ischemia (a β-blocker), progressive atherosclerosis (high-intensity statin), and adverse ventricular remodeling (an ACE inhibitor, especially if left ventricular [LV] dysfunction is present).
- Adding an aldosterone antagonist should be considered for patients with heart failure.
- Systemic anticoagulation with warfarin is indicated if an intraventricular thrombus, a large akinetic segment, or atrial fibrillation is present.

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