

Ischemic Heart Disease

6

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In 1772, the British physician William Heberden reported a disorder in which patients developed an uncomfortable sensation in the chest when walking. Labeling it angina pectoris, Heberden noted that this discomfort would disappear soon after the patient stood still but would recur with similar activities. Although he did not know the cause, it is likely that he was the first to describe the symptoms of ischemic heart disease, a condition of imbalance between myocardial oxygen supply and demand most often caused by atherosclerosis of the coronary arteries. Ischemic heart disease now afflicts millions of Americans and is the leading cause of death in industrialized nations.

The clinical presentation of ischemic heart disease can be highly variable and forms a spectrum of syndromes (Table 6-1). For example, ischemia may be accompanied by the same exertional symptoms described by Heberden. In other cases, it may occur without any clinical manifestations at all, a condition termed silent ischemia. This chapter describes the causes and consequences of chronic ischemic heart disease syndromes and provides a framework for the diagnosis and treatment of affected patients.

Angina pectoris remains the most common manifestation of ischemic heart disease and literally means “strangling in the chest.” Although other conditions may lead to similar discomfort, angina refers specifically to the uncomfortable sensation in the chest and neighboring structures that arises from an imbalance between myocardial oxygen supply and demand.

TABLE 6-1 Clinical Definitions

Syndrome	Description
Ischemic heart disease	Condition in which imbalance between myocardial oxygen supply and demand results in myocardial hypoxia and accumulation of waste metabolites, most often caused by atherosclerotic disease of the coronary arteries (often termed coronary artery disease)
Angina pectoris	Uncomfortable sensation in the chest and neighboring anatomic structures produced by myocardial ischemia
Stable angina	Chronic pattern of transient angina pectoris, precipitated by physical activity or emotional upset, relieved by rest within a few minutes; episodes often associated with temporary depression of the ST segment, but permanent myocardial damage does not result
Variant angina	Typical anginal discomfort, usually at rest, which develops because of coronary artery spasm rather than an increase of myocardial oxygen demand; episodes often associated with transient shifts of the ST segment, usually ST elevation (also termed Prinzmetal angina)
Silent ischemia	Asymptomatic episodes of myocardial ischemia; can be detected by electrocardiogram and other laboratory techniques
Unstable angina	Pattern of increased frequency and duration of angina episodes produced by less exertion or at rest; high frequency of progression to myocardial infarction if untreated
Myocardial infarction	Region of myocardial necrosis usually caused by prolonged cessation of blood supply; most often results from acute thrombus at site of coronary atherosclerotic stenosis; may be a first clinical manifestation of ischemic heart disease, or there may be a history of angina pectoris

DETERMINANTS OF MYOCARDIAL OXYGEN SUPPLY AND DEMAND

In the normal heart, the oxygen requirements of the myocardium are continuously matched by the coronary arterial supply. Even during vigorous exercise, when the metabolic needs of the heart increase, so does the delivery of oxygen to the myocardial cells so that the balance is maintained. The following sections describe the key determinants of myocardial oxygen supply and demand in a normal person (Fig. 6-1) and how they are altered by the presence of atherosclerotic coronary artery disease (CAD).

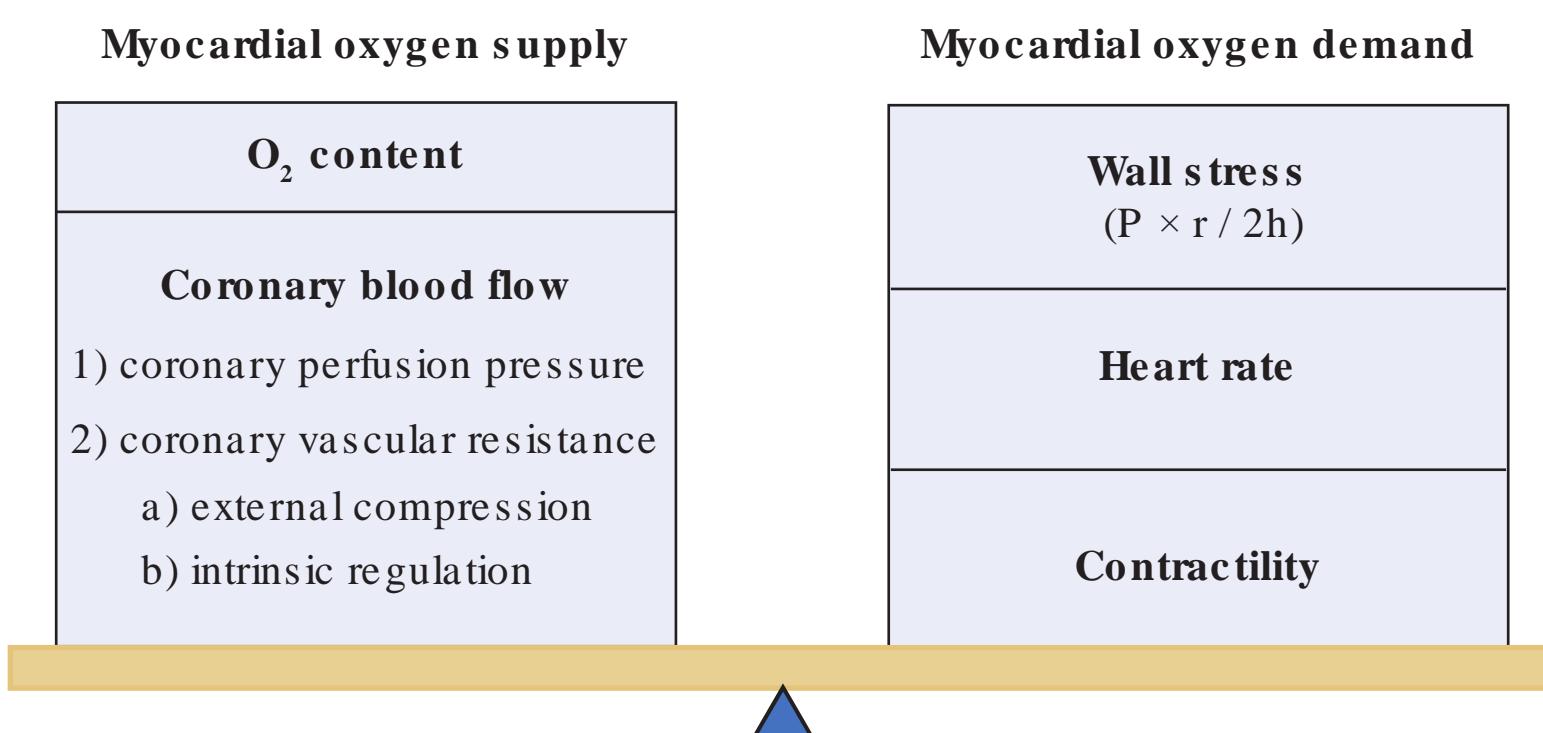


FIGURE 6-1. Major determinants of myocardial oxygen supply and demand. P, ventricular pressure; r, ventricular radius; h, ventricular wall thickness.

Myocardial Oxygen Supply

The supply of oxygen to the myocardium depends on the **oxygen content** of the blood and the rate of **coronary blood flow**. The oxygen content is determined by the hemoglobin concentration and the degree of systemic oxygenation. In the absence of anemia or lung disease, oxygen content remains fairly constant. In contrast, coronary blood flow is much more dynamic, and regulation of that flow is responsible for matching the oxygen supply with metabolic requirements.

As in all blood vessels, coronary artery flow (Q) is directly proportional to the vessel's perfusion pressure (P) and is inversely proportional to coronary vascular resistance (R). That is,

$$Q \propto \frac{P}{R}$$

However, unlike other arterial systems in which the greatest blood flow occurs during systole, the predominance of coronary perfusion takes place during diastole. The reason for this is that systolic flow is impaired by the compression of the small coronary branches as they course through the contracting myocardium. Coronary flow is unimpaired in diastole because the relaxed myocardium does not compress the coronary vasculature. Thus, in the case of the coronaries, **perfusion pressure** can be approximated by the aortic diastolic pressure. Conditions that decrease aortic diastolic pressure (such as hypotension or aortic valve regurgitation) decrease coronary artery perfusion pressure and may lessen myocardial oxygen supply.

Coronary vascular resistance is the other major determinant of coronary blood flow. In the normal artery, this resistance is dynamically modulated by (1) forces that externally compress the coronary arteries and (2) factors that alter intrinsic coronary tone.

External Compression

External compression is exerted on the coronary vessels during the cardiac cycle by contraction of the surrounding myocardium. The degree of compression is directly related to intramyocardial pressure and is therefore greatest during systole, as described in the previous section. Moreover, when the myocardium contracts, the subendocardium, adjacent to the high intraventricular pressure, is subjected to greater force than are the outer muscle layers. This is one reason that the subendocardium is the region most vulnerable to ischemic damage.

Intrinsic Control of Coronary Arterial Tone

Unlike most tissues, the heart cannot increase oxygen extraction on demand because in its basal state, it removes nearly as much oxygen as possible from its blood supply. Thus, any additional oxygen requirement must be met by an increase in blood flow, and autoregulation of coronary vascular resistance is the most important mediator of this process. Factors that participate in the regulation of coronary vascular resistance include the accumulation of local metabolites, endothelium-derived substances, and neural innervation.

Metabolic Factors

The accumulation of local metabolites significantly affects coronary vascular tone and acts to modulate myocardial oxygen supply to meet changing metabolic demands. During states of hypoxemia, aerobic metabolism and oxidative phosphorylation in the mitochondria are inhibited and generation of high-energy phosphates, including adenosine triphosphate (ATP), is impaired. Consequently, adenosine diphosphate (ADP) and adenosine monophosphate (AMP) accumulate and are subsequently degraded to adenosine. Adenosine is a potent

vasodilator and is thought to be the prime metabolic mediator of vascular tone. By binding to receptors on vascular smooth muscle, adenosine decreases calcium entry into cells, which leads to relaxation, vasodilatation, and increased coronary blood flow. Other metabolites that act locally as vasodilators include lactate, acetate, hydrogen ions, and carbon dioxide.

Endothelial Factors

Endothelial cells of the arterial wall produce numerous vasoactive substances that contribute to the regulation of vascular tone. Vasodilators produced by the endothelium include nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF). Endothelin 1 is an example of an endothelium-derived vasoconstrictor.

The discovery and significance of **endothelium-derived NO** are highlighted in Box 6-1. In brief, NO regulates vascular tone by diffusing into and then relaxing neighboring arterial

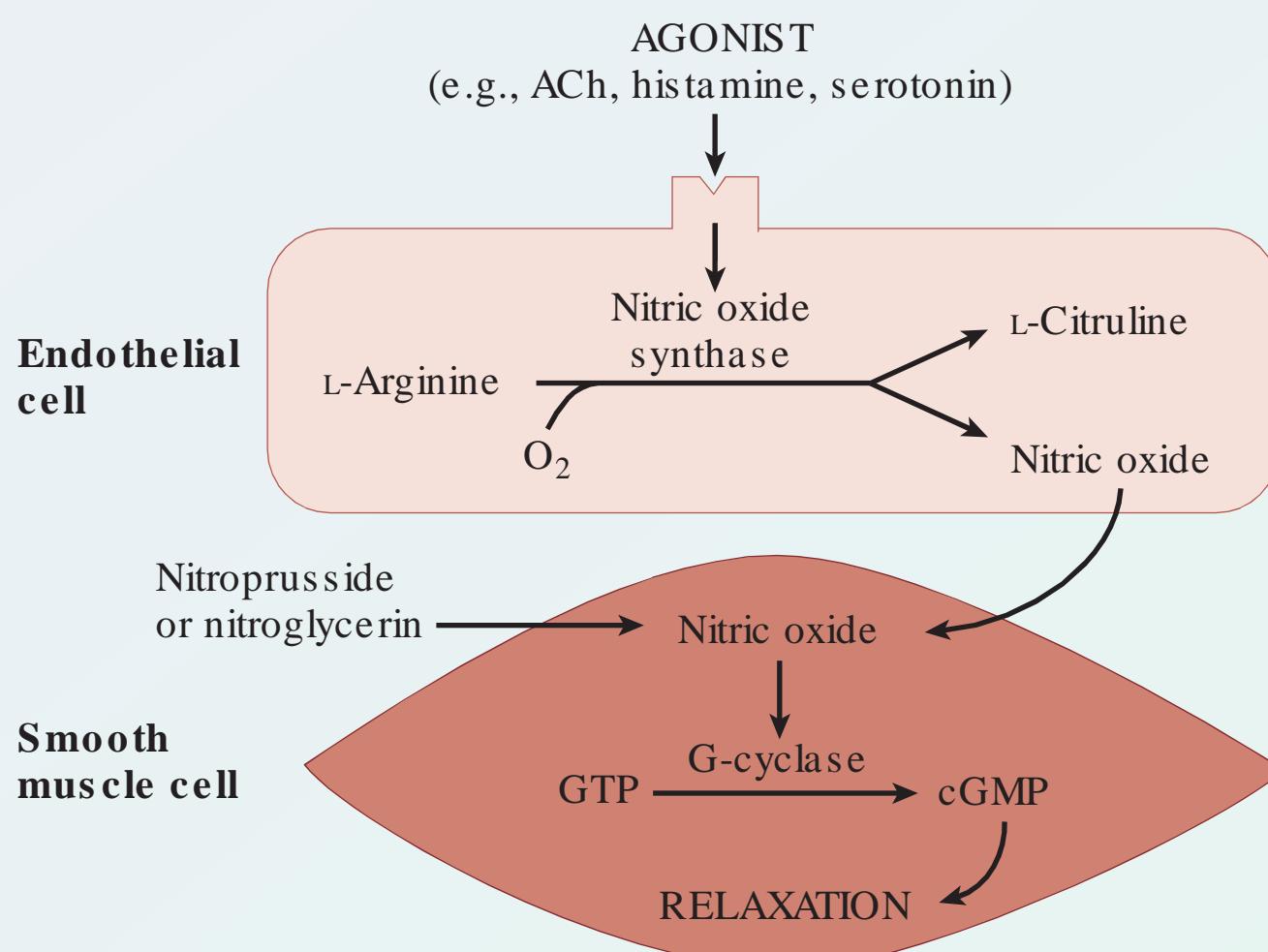
BOX 6-1

Endothelium-Derived Relaxing Factor, Nitric Oxide, and the Nobel Prize

Normal arterial endothelial cells synthesize potent vasodilator substances that contribute to the modulation of vascular tone. Among the first of these to be identified were prostacyclin (an arachidonic acid metabolite) and a substance termed endothelium-derived relaxing factor (EDRF).

EDRF was first studied in the 1970s. In experimental preparations, it was shown that acetylcholine (ACh) has two opposite actions on blood vessels. Its direct effect on vascular smooth muscle cells is to cause vasoconstriction, but when an intact endothelial lining overlies the smooth muscle cells, vasodilatation occurs instead. Subsequent experiments showed that ACh causes the endothelial cells to release a chemical mediator (that was termed EDRF), which quickly diffuses to the adjacent smooth muscle cells and results in their relaxation with subsequent vasodilatation of the vessel.

Further research demonstrated that the mysterious EDRF is actually the nitric oxide (NO) radical. Binding of ACh (or another endothelial-dependent vasodilator such as serotonin or histamine) to endothelial cells catalyzes the formation of NO from the amino acid L-arginine (see figure). NO then diffuses to the adjacent vascular smooth muscle, where it activates guanylyl cyclase (G-cyclase). G-cyclase in turn forms cyclic guanosine monophosphate (cGMP), which results in smooth muscle cell relaxation through mechanisms that involve a reduction in cytosolic Ca^{++} .



(continues on page 138)

BOX 6-1**Endothelium-Derived Relaxing Factor, Nitric Oxide, and the Nobel Prize (continued)**

In contrast to the endothelial-dependent vasodilators, some agents cause smooth muscle relaxation independent of the presence of endothelial cells. For example, the drugs sodium nitroprusside and nitroglycerin result in vasodilatation by providing an exogenous source of NO to vascular smooth muscle cells, thereby activating G_s-cyclase and forming cGMP without endothelial cell participation.

In the cardiac catheterization laboratory, the intracoronary administration of ACh in a normal person causes vasodilatation of the vessel, presumably through the release of NO. However, in conditions of endothelial dysfunction, such as atherosclerosis, intracoronary ACh administration results in paradoxical vasoconstriction instead. This likely reflects reduced production of NO by the dysfunctional endothelial cells, resulting in unopposed direct vasoconstriction of the smooth muscle by ACh. Of particular interest is that the loss of vasodilatory response to infused ACh is evident in persons with certain cardiac risk factors (e.g., elevated LDL cholesterol, hypertension, cigarette smoking) even before the physical appearance of atheromatous plaque. Thus, the impaired release of NO may be an early and sensitive predictor for the later development of atherosclerotic lesions.

The significance of these discoveries was highlighted in 1998, when the Nobel Prize in medicine was awarded to the scientists who discovered the critical role of NO as a cardiovascular signaling molecule.

smooth muscle by a cyclic guanosine monophosphate (cGMP)-dependent mechanism. The production of NO by normal endothelium occurs in the basal state and is additionally stimulated by many substances and conditions. For example, its release is augmented when the endothelium is exposed to acetylcholine (ACh), thrombin, products of aggregating platelets (e.g., serotonin and ADP), or even the shear stress of blood flow. Although the direct effect of many of these substances on vascular smooth muscle is to cause vasoconstriction, the induced release of NO from the normal endothelium results in vasodilatation instead (Fig. 6-2).

Prostacyclin, an arachidonic acid metabolite, has vasodilator properties similar to those of NO (see Fig. 6-2). It is released from endothelial cells in response to many stimuli, including hypoxia, shear stress, ACh, and platelet products (e.g., serotonin). It causes relaxation of vascular smooth muscle by a cyclic AMP-dependent mechanism.

EDHF also appears to have important vasodilatory properties. Like endothelial-derived NO, it is a diffusible substance released by the endothelium that hyperpolarizes (and therefore relaxes) neighboring vascular smooth muscle cells. EDHF is released by some of the

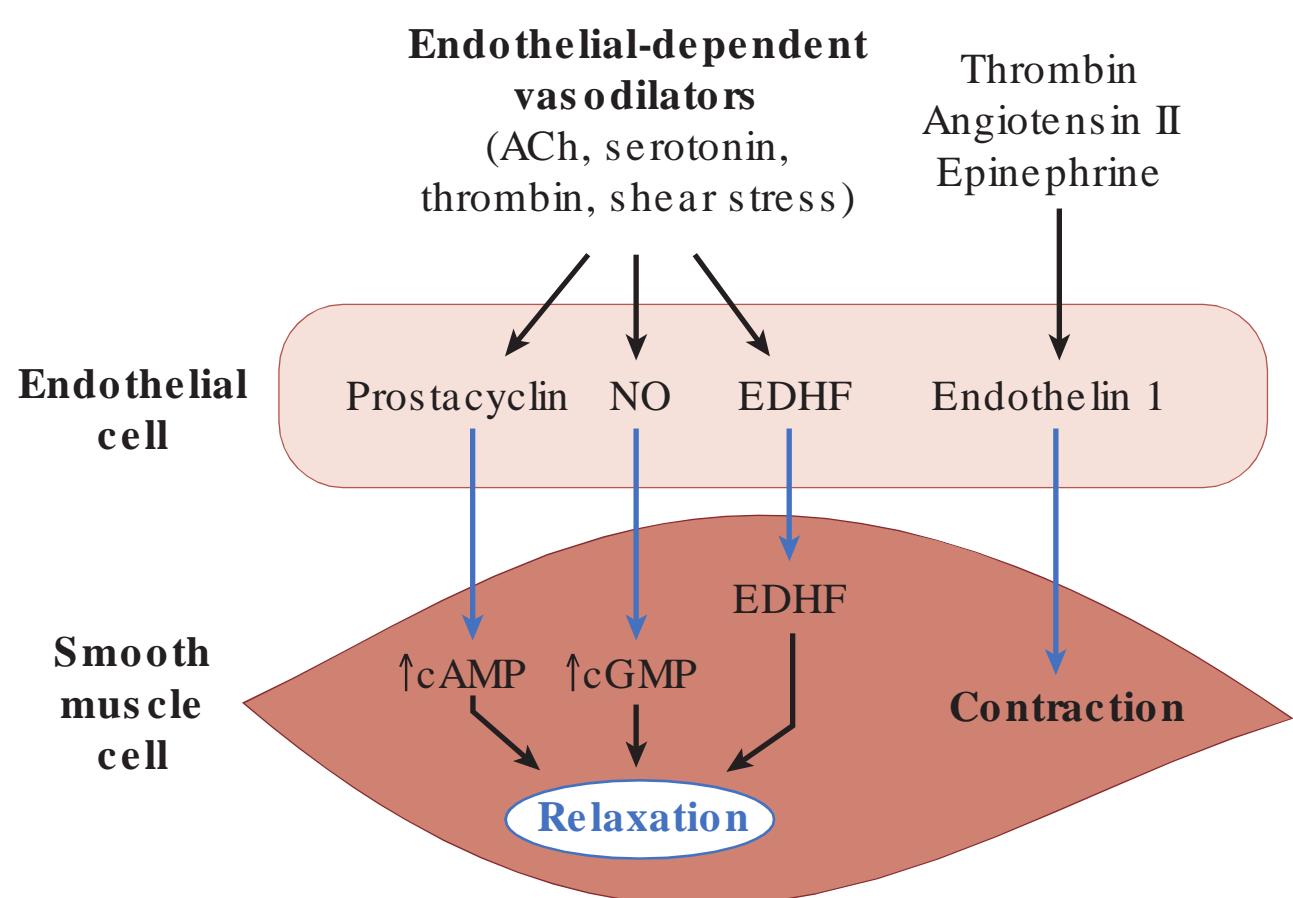


FIGURE 6-2. Endothelium-derived vasoactive substances and their regulators. Endothelium-derived vasodilators are shown on the left and include nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF). Endothelin 1 is an endothelium-derived vasoconstrictor. In the normal state, the vasodilator influence predominates over that of vasoconstriction. ACh, acetylcholine; cGMP, cyclic guanosine monophosphate; cAMP, cyclic adenosine monophosphate.

same factors that stimulate NO, including ACh and normal pulsatile blood flow. In the coronary circulation, EDHF appears to be more important in modulating relaxation in small arterioles than in the large conduit arteries.

Endothelin 1 is a potent vasoconstrictor produced by endothelial cells that partially counteracts the actions of the endothelial vasodilators. Its expression is stimulated by several factors, including thrombin, angiotensin II, epinephrine, and the shear stress of blood flow.

Under normal circumstances, the healthy endothelium promotes vascular smooth muscle relaxation (vasodilatation) through elaboration of substances such as NO and prostacyclin, the influences of which predominate over the endothelial vasoconstrictors (see Fig. 6-2). However, as described later in the chapter, dysfunctional endothelium (e.g., in atherosclerotic vessels) secretes reduced amounts of vasodilators, causing the balance to shift toward vasoconstriction instead.

Neural Factors

The neural control of vascular resistance has both sympathetic and parasympathetic components. Under normal circumstances, the contribution of the parasympathetic nervous system appears minor, but sympathetic receptors play an important role. Coronary vessels contain both α -adrenergic and β_2 -adrenergic receptors. Stimulation of α -adrenergic receptors results in vasoconstriction, whereas β_2 -receptors promote vasodilatation.

It is the interplay among the metabolic, endothelial, and neural regulating factors that determines the net impact on coronary vascular tone. For example, catecholamine stimulation of the heart may initially cause coronary vasoconstriction via the α -adrenergic receptor neural effect. However, catecholamine stimulation also increases myocardial oxygen consumption through increased heart rate and contractility (β_1 -adrenergic effect), and the resulting increased production of local metabolites induces net coronary dilatation instead.

Myocardial Oxygen Demand

The three major determinants of myocardial oxygen demand are (1) ventricular wall stress, (2) heart rate, and (3) contractility (which is also termed the inotropic state). Additionally, very small amounts of oxygen are consumed in providing energy for basal cardiac metabolism and electrical depolarization.

Ventricular **wall stress** (σ) is the tangential force acting on the myocardial fibers, tending to pull them apart, and energy is expended in opposing that force. Wall stress is related to intraventricular pressure (P), the radius of the ventricle (r), and ventricular wall thickness (h) and is approximated by Laplace's relationship:

$$\sigma = \frac{P \times r}{2h}$$

Thus, wall stress is directly proportional to systolic ventricular pressure. Circumstances that increase pressure in the left ventricle, such as aortic stenosis or hypertension, augment wall stress and myocardial oxygen consumption. Conditions that decrease ventricular pressure, such as antihypertensive therapy, reduce myocardial oxygen consumption.

Because wall stress is also directly proportional to the radius of the left ventricle, conditions that augment left ventricular (LV) filling (e.g., mitral or aortic regurgitation) raise wall stress and oxygen consumption. Conversely, any physiologic or pharmacologic maneuver that decreases LV filling and size (e.g., nitrate therapy) reduces wall stress and myocardial oxygen consumption.

Finally, wall stress is inversely proportional to ventricular wall thickness because the force is spread over a greater muscle mass. A hypertrophied heart has lower wall stress and oxygen

consumption per gram of tissue than a thinned-wall heart. Thus, when hypertrophy develops in conditions of chronic pressure overload, such as aortic stenosis, it serves a compensatory role in reducing oxygen consumption.

The second major determinant of myocardial oxygen demand is **heart rate**. If the heart rate accelerates—during physical exertion, for example—the number of contractions and the amount of ATP consumed per minute increases and oxygen requirements rise. Conversely, slowing the heart rate (e.g., with a β-blocker drug) decreases ATP utilization and oxygen consumption.

The third major determinant of oxygen demand is myocardial **contractility**, a measure of the force of contraction (see Chapter 9). Circulating catecholamines, or the administration of positive inotropic drugs, directly increase the force of contraction, which augments oxygen utilization. Conversely, negative inotropic effectors, such as β-adrenergic-blocking drugs, decrease myocardial oxygen consumption.

In the normal state, autoregulatory mechanisms adjust coronary tone to match myocardial oxygen supply with oxygen requirements. In the absence of obstructive coronary disease, these mechanisms maintain a fairly constant rate of coronary flow, as long as the aortic perfusion pressure is approximately 60 mm Hg or greater. In the setting of advanced coronary atherosclerosis, however, the fall in perfusion pressure distal to the arterial stenosis, along with dysfunction of the endothelium of the involved segment, sets the stage for a mismatch between the available blood supply and myocardial metabolic demands.

PATHOPHYSIOLOGY OF ISCHEMIA

The traditional view has been that myocardial ischemia in CAD results from fixed atherosclerotic plaques that narrow the vessel's lumen and limit myocardial blood supply. However, research has demonstrated that the reduction of blood flow in this condition results from the combination of fixed vessel narrowing and abnormal vascular tone, contributed to by atherosclerosis-induced endothelial cell dysfunction.

Fixed Vessel Narrowing

The hemodynamic significance of fixed atherosclerotic coronary artery stenoses relates to both the fluid mechanics and the anatomy of the vascular supply.

Fluid Mechanics

Poiseuille's law states that for flow through a vessel,

$$Q = \frac{\Delta P \pi r^4}{8\eta L}$$

in which Q is flow, ΔP is the pressure difference between the points being measured, r is the vessel radius, η is the fluid viscosity, and L is the vessel length. By analogy to Ohm's law, flow is also equal to the pressure difference divided by the resistance (R) to flow:

$$Q = \frac{\Delta P}{R}$$

By combining these two formulas and rearranging, resistance to blood flow in a vessel can be expressed as

$$R = \frac{8\eta L}{\pi r^4}$$

Thus, vascular resistance is governed, in part, by the geometric component L/r^4 . That is, the hemodynamic significance of a stenotic lesion depends on its length and, far more importantly, on the degree of vessel narrowing (i.e., the reduction of r) that it causes.

Anatomy

The coronary arteries consist of large, proximal epicardial segments and smaller, distal resistance vessels (arterioles). The proximal vessels are subject to overt atherosclerosis that results in stenotic plaques. The distal vessels are usually free of flow-limiting plaques and can adjust their vaso-motor tone in response to metabolic needs. These resistance vessels serve as a reserve, increasing their diameter with exertion to meet increasing oxygen demand and dilating, even at rest, if a proximal stenosis is sufficiently severe.

The hemodynamic significance of a coronary artery narrowing depends on both the degree of stenosis of the epicardial portion of the vessel and the amount of compensatory vasodilatation the distal resistance vessels are able to achieve (Fig. 6-3). If a stenosis narrows the lumen diameter by less than 60%, the maximal potential blood flow through the artery is not significantly altered and, in response to exertion, the resistance vessels can dilate to provide adequate blood flow. When a stenosis narrows the diameter by more than approximately 70%, resting blood flow is normal, but maximal blood flow is reduced even with full dilatation of the resistance vessels. In this situation, when oxygen demand increases (e.g., from the elevated heart rate and force of contraction during physical exertion), coronary flow reserve is inadequate, oxygen demand exceeds supply, and myocardial ischemia results. If the stenosis compromises the vessel lumen by more than approximately 90%, then even with maximal dilatation of the resistance vessels, blood flow may be inadequate to meet basal requirements and ischemia can develop at rest.

Although collateral connections (see Chapter 1) may become apparent between unobstructed coronaries and sites distal to atherosclerotic stenoses, and such flow can buffer the fall in myocardial oxygen supply, it is often not sufficient to prevent ischemia during exertion in critically narrowed vessels.

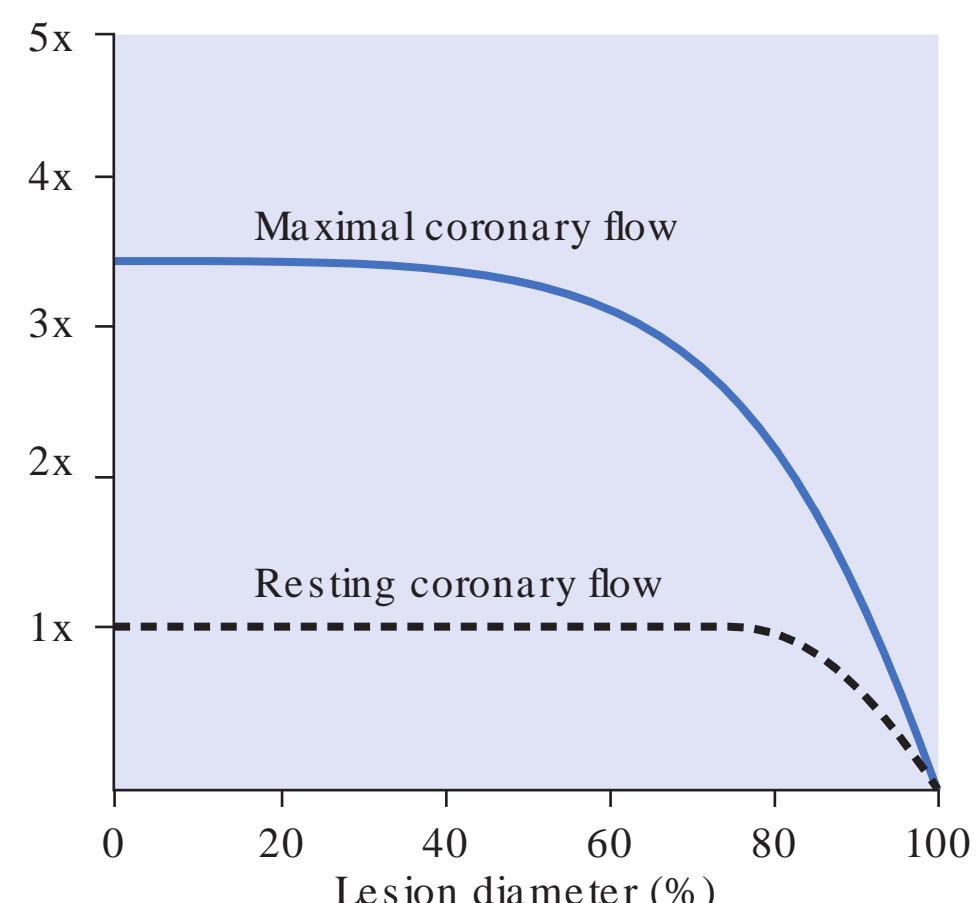


FIGURE 6-3. Resting and maximal coronary blood flows are affected by the magnitude of proximal arterial stenosis (percent lesion diameter). The dotted line indicates resting blood flow, and the solid line represents maximal blood flow (i.e., when there is full dilatation of the distal resistance vessels). Compromise of maximal blood flow is evident when the proximal stenosis reduces the coronary lumen diameter by more than approximately 70%. Resting flow may be compromised if the stenosis exceeds approximately 90%. (Modified from Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. Am J Cardiol. 1974;34:50.)

The graph illustrates the relationship between lesion diameter and blood flow. The y-axis represents blood flow as a multiple of resting flow (1x), ranging from 1x to 5x. The x-axis represents the lesion diameter as a percentage of the original vessel diameter, ranging from 0% to 100%. A horizontal dotted line at 1x represents 'Resting coronary flow'. A solid blue line represents 'Maximal coronary flow' at 3.5x. Both lines remain flat until approximately 70% stenosis, then drop sharply. The maximal flow curve reaches zero at 100% stenosis, while resting flow drops to approximately 0.5x at 100% stenosis.

Endothelial Cell Dysfunction

In addition to fixed vessel narrowing, the other major contributor to reduced myocardial oxygen supply in chronic CAD is endothelial dysfunction. Abnormal endothelial cell function can contribute to the pathophysiology of ischemia in two ways: (1) by inappropriate vasoconstriction of coronary arteries and (2) through loss of normal antithrombotic properties.

Inappropriate Vasoconstriction

In normal persons, physical activity or mental stress results in measurable coronary artery vasodilatation. This effect is thought to be regulated by activation of the sympathetic nervous system, with increased blood flow and shear stress stimulating the release of endothelial-derived vasodilators, such as NO. It is postulated that in typical people, the relaxation effect of NO outweighs the direct α -adrenergic constrictor effect of catecholamines on arterial smooth muscle, such that vasodilatation results. However, in patients with dysfunctional endothelium (e.g., atherosclerosis), an impaired release of endothelial vasodilators leaves the direct catecholamine effect unopposed, such that relative vasoconstriction occurs instead. The resultant decrease in coronary blood flow contributes to ischemia. Even the vasodilatory effect of local metabolites (such as adenosine) is attenuated in patients with dysfunctional endothelium, further uncoupling the regulation of vascular tone from metabolic demands.

In patients with risk factors for CAD, such as hypercholesterolemia, diabetes mellitus, hypertension, and cigarette smoking, impaired endothelial-dependent vasodilatation is noted even before visible atherosclerotic lesions have developed. This suggests that endothelial dysfunction occurs very early in the atherosclerotic process.

Inappropriate vasoconstriction also appears to be important in acute coronary syndromes, such as unstable angina and myocardial infarction (MI). As described in Chapter 7, the usual cause of acute coronary syndromes is disruption of atherosclerotic plaque, with superimposed platelet aggregation and thrombus formation. Normally, the products of platelet aggregation in a developing clot (e.g., serotonin and ADP) result in vasodilatation because they stimulate the endothelial release of NO. However, with dysfunctional endothelium, the direct vasoconstricting actions of platelet products predominate (Fig. 6-4), further compromising flow through the arterial lumen.

Loss of Normal Antithrombotic Properties

In addition to their vasodilatory actions, factors released from endothelial cells (including NO and prostacyclin) also exert antithrombotic properties by interfering with platelet aggregation (see Fig. 6-4). However, in states of endothelial cell dysfunction, release of these substances is reduced; therefore, the antithrombotic effect is attenuated. Thus, in syndromes characterized by thrombosis (i.e., the acute coronary syndromes described in Chapter 7), the impaired release of NO and prostacyclin allows platelets to aggregate and to secrete their potentially harmful procoagulants and vasoconstrictors.

Other Causes of Myocardial Ischemia

In addition to atherosclerotic CAD, other conditions may result in an imbalance between myocardial oxygen supply and demand and result in ischemia. Other common causes of decreased myocardial oxygen supply include (1) decreased perfusion pressure due to hypotension (e.g., in a patient with hypovolemia or septic shock) and (2) a severely decreased blood oxygen content (e.g., marked anemia, or impaired oxygenation of blood by the lungs). For example, a patient with massive bleeding from the gastrointestinal tract may develop myocardial ischemia and angina pectoris, even in the absence of atherosclerotic coronary disease, because of reduced oxygen supply (i.e., the loss of hemoglobin and hypotension).

On the other side of the balance, a profound increase in myocardial oxygen demand can cause ischemia even in the absence of coronary atherosclerosis. This can occur, for example, with rapid tachycardias, acute hypertension, or severe aortic stenosis.

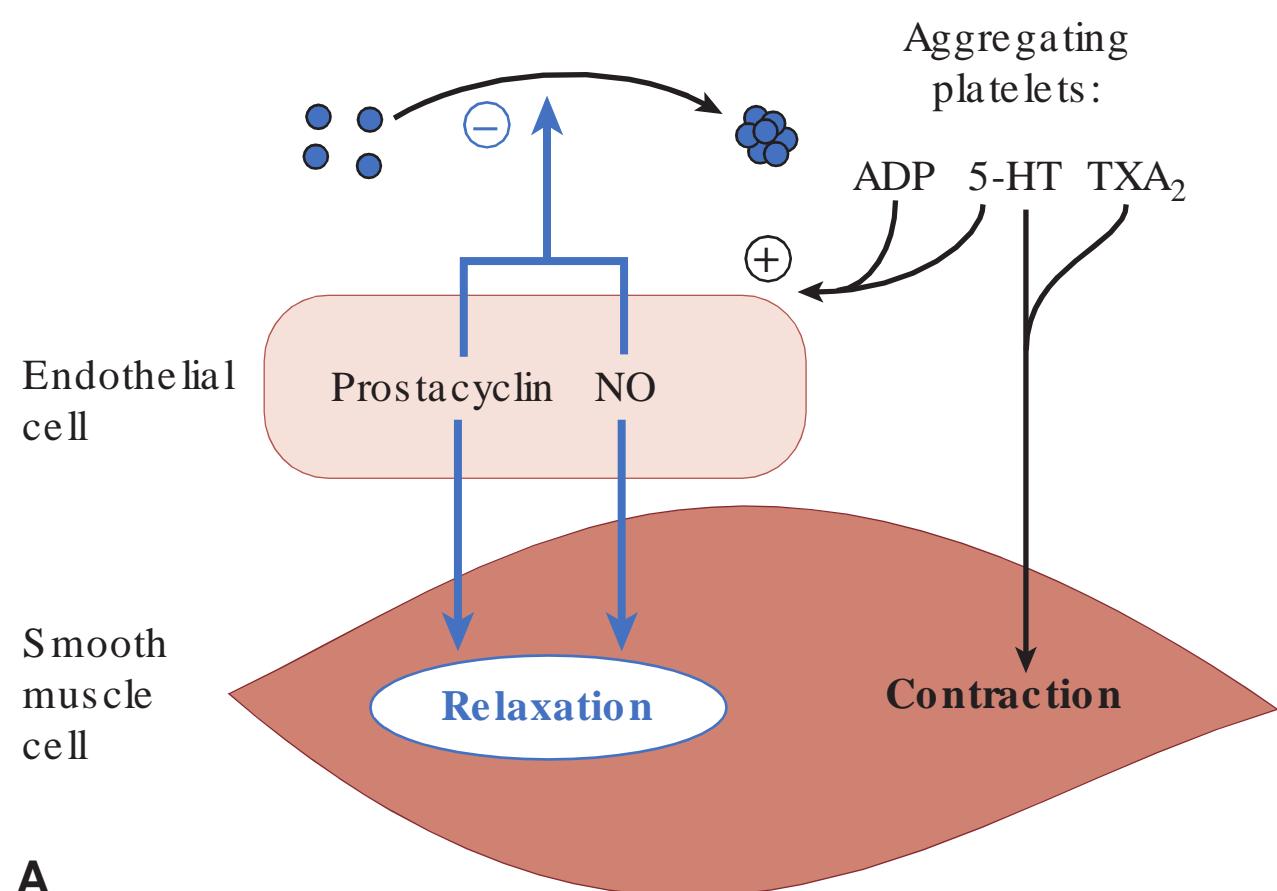
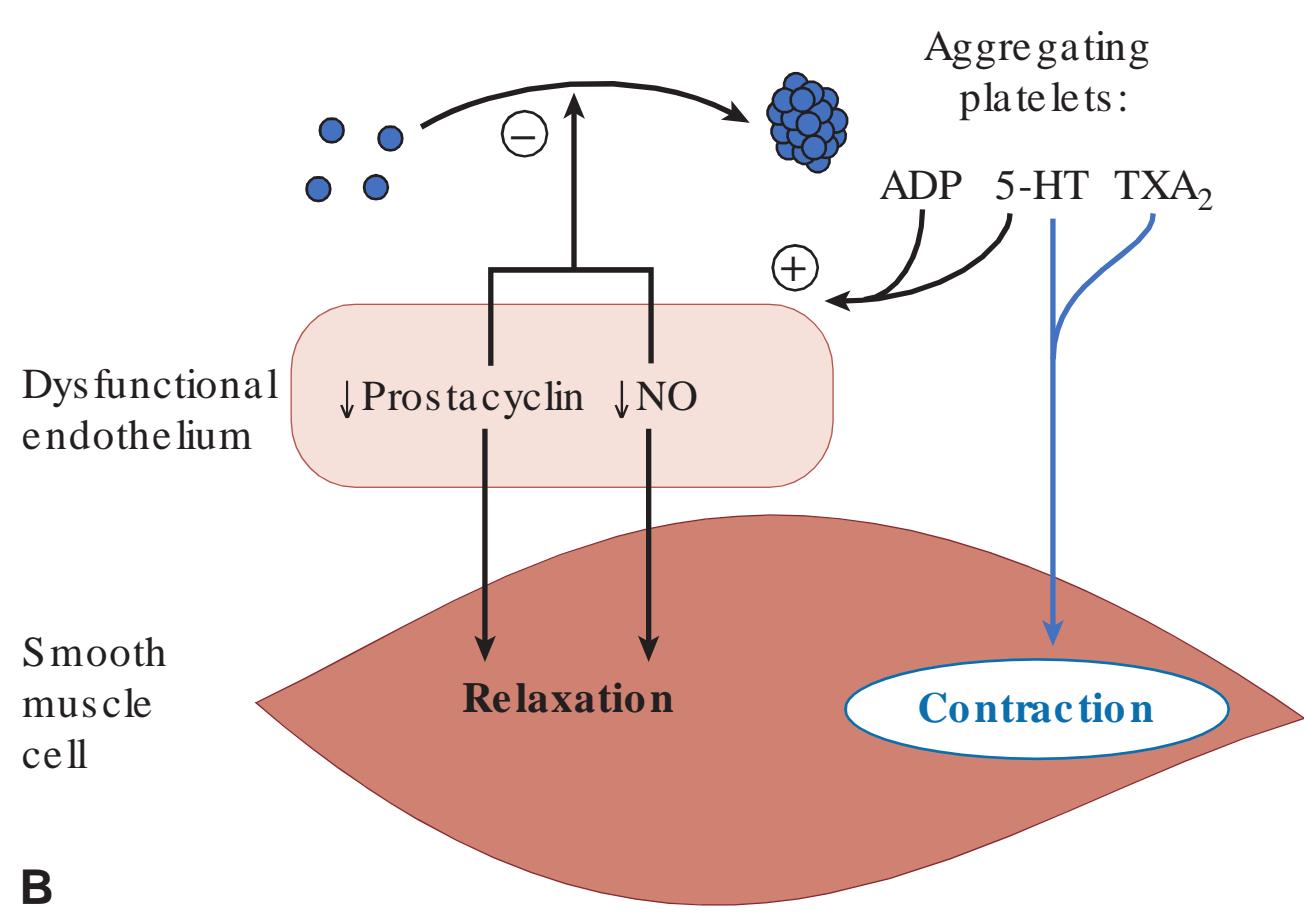


FIGURE 6-4. The interaction between platelets and endothelial cells. **A.** Normal endothelium.

Aggregating platelets release thromboxane (TXA₂) and serotonin (5-HT), the direct vascular effects of which cause contraction of vascular smooth muscle and vasoconstriction. However, platelet products (e.g., ADP and 5-HT) also stimulate the endothelial release of the potent vasodilators nitric oxide (NO) and prostacyclin, such that the net effect is smooth muscle relaxation instead. Endothelial production of NO and prostacyclin also serves antithrombotic roles, which limit further platelet aggregation. ADP, adenosine diphosphate. **B.** Dysfunctional endothelium demonstrates impaired release of the vasodilator substances, such that net smooth muscle contraction and vasoconstriction supervene. The reduced endothelial release of NO and prostacyclin diminishes their antiplatelet effect, such that thrombosis proceeds unchecked.



CONSEQUENCES OF ISCHEMIA

The consequences of ischemia reflect the inadequate myocardial oxygenation and local accumulation of metabolic waste products. For example, during ischemia, myocytes convert from aerobic to anaerobic metabolic pathways. The reduced generation of ATP impairs the interaction of the contractile proteins and results in a transient reduction of both ventricular systolic contraction and diastolic relaxation, as each are energy-dependent processes. The consequent elevation of LV diastolic pressure is transmitted (via the left atrium and pulmonary veins) to the pulmonary capillaries and can precipitate pulmonary congestion and the symptom of dyspnea (shortness of breath). In addition, metabolic products such as lactate, serotonin, and adenosine accumulate locally. It is suspected that one or more of these compounds activate peripheral pain receptors in the C7 through T4 distribution and may be the mechanism by which the discomfort of angina is produced. The accumulation of local metabolites and transient abnormalities of myocyte ion transport may also precipitate arrhythmias (see Chapter 11).

The ultimate fate of myocardium subjected to ischemia depends on the severity and duration of the imbalance between oxygen supply and demand. It was previously thought that ischemic cardiac injury results in either irreversible myocardial necrosis (i.e., MI) or rapid and full recovery of myocyte function (e.g., after a brief episode of typical angina). It is now known that in addition

to those outcomes, ischemic insults can sometimes result in a period of prolonged contractile dysfunction without myocyte necrosis, and recovery of normal function may ultimately follow.

For example, **stunned myocardium** refers to tissue that, after suffering an episode of severe acute, transient ischemia (but not necrosis), demonstrates prolonged systolic dysfunction even after the return of normal myocardial blood flow. In this setting, the functional, biochemical, and structural abnormalities following ischemia are reversible and contractile function gradually recovers. The mechanism responsible for this delayed recovery of function involves myocyte calcium overload and the accumulation of oxygen-derived free radicals during ischemia. In general, the magnitude of stunning is proportional to the degree of the preceding ischemia, and this state is likely the pathophysiologic response to an ischemic insult that just falls short of causing irreversible necrosis.

In contrast, **hibernating myocardium** refers to tissue that manifests chronic ventricular contractile dysfunction due to a persistently reduced blood supply, usually because of multivessel CAD. In this situation, irreversible damage has not occurred and ventricular function can promptly improve if appropriate blood flow is restored by percutaneous or surgical revascularization. Special “viability” imaging studies (e.g., positron emission tomography or dobutamine echocardiography, as described in Chapter 3) of patients with CAD and contractile dysfunction can differentiate hibernating from infarcted myocardium. That distinction can help guide the decision of whether to undertake coronary revascularization, because hibernating myocardium would be expected to regain contractile function with restoration of blood flow, whereas infarcted myocardium would not.

Ischemic Syndromes

Depending on the underlying pathophysiologic process and the timing and severity of a myocardial ischemic insult, a spectrum of distinct clinical syndromes may result, as illustrated in Figure 6-5.

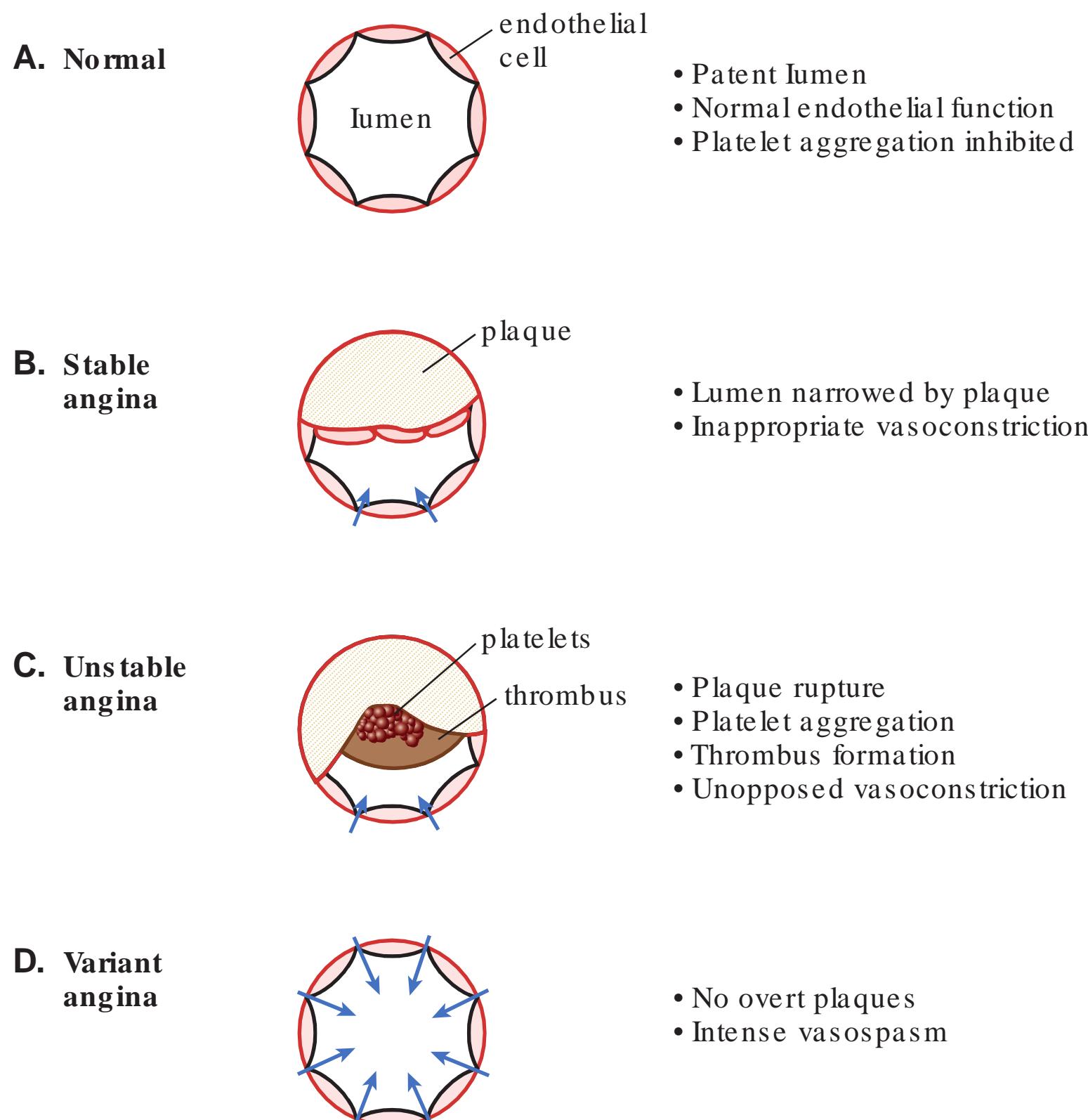


FIGURE 6-5. Pathophysiologic findings in anginal syndromes.

A. Normal coronary arteries are widely patent, and the endothelium functions normally. **B.** In stable angina, atherosclerotic plaque and inappropriate vasoconstriction (caused by dysfunctional endothelium) reduce the vessel lumen's size and coronary blood flow. **C.** In unstable angina, disruption of the plaque triggers platelet aggregation, thrombus formation, and vasoconstriction, all of which contribute to reduced coronary blood supply. **D.** In variant angina, atherosclerotic plaques are absent; rather, ischemia is due to intense vasospasm that reduces myocardial oxygen supply.

Stable Angina

Chronic stable angina manifests as a pattern of predictable, transient chest discomfort during exertion or emotional stress. It is generally caused by fixed, obstructive atheromatous plaque in one or more coronary arteries (see Fig. 6-5B). The pattern of symptoms is usually related to the degree of stenosis. As described in the earlier section on pathophysiology, when atherosclerotic stenoses narrow a coronary artery lumen diameter by more than approximately 70%, the reduced flow capacity may be sufficient to serve the low cardiac oxygen needs at rest but is insufficient to compensate for any significant increase in oxygen demand (see Fig. 6-3). During physical exertion, for example, activation of the sympathetic nervous system results in increased heart rate, blood pressure, and contractility, all of which augment myocardial oxygen consumption. During the period that oxygen demand exceeds available supply, myocardial ischemia results, often accompanied by the chest discomfort of angina pectoris. The ischemia and symptoms persist until the increased demand is alleviated and oxygen balance is restored.

Potentially contributing to the inadequate oxygen supply in stable angina is inappropriate coronary vasoconstriction caused, at least in part, by atherosclerosis-associated endothelial dysfunction. Recall that normally, the high myocardial oxygen demand during exertion is balanced by an increased supply of blood as the accumulation of local metabolites induces vasodilatation. With endothelial cell dysfunction, however, vasodilatation is impaired and the vessels may paradoxically vasoconstrict instead, in response to exercise-induced catecholamine stimulation of α -adrenergic receptors on the coronary artery smooth muscle cells.

As a result, the extent of coronary artery narrowing in patients with atherosclerosis is not necessarily constant. Rather, it can vary from moment to moment because of changes in the superimposed coronary vascular tone. For some patients with stable angina, alterations in tone play a minimal role in the decreased myocardial oxygen supply, and the level of physical activity required to precipitate angina is fairly constant. These patients have fixed-threshold angina. In other cases, the degree of dynamic obstruction caused by vasoconstriction or vasospasm plays a more prominent role, and such patients may have variable-threshold angina. For example, on a given day, a patient with variable-threshold angina can exert herself or himself without chest discomfort, but on another day, the same degree of myocardial oxygen demand does produce symptoms. The difference reflects alterations in vascular tone over the sites of fixed stenosis. Other clinical features of chronic stable angina are described in greater detail later in the chapter.

Unstable Angina

A patient with chronic stable angina may experience a sudden increase in the tempo and duration of ischemic episodes, occurring with lesser degrees of exertion and even at rest. This acceleration of symptoms is known as unstable angina, which can be a precursor to an acute MI. Unstable angina and acute MI are also known as acute coronary syndromes and result from specific pathophysiologic mechanisms, most commonly rupture of an unstable atherosclerotic plaque with subsequent platelet aggregation and thrombosis (see Fig. 6-5C). These syndromes are described in detail in Chapter 7.

Variant Angina

A small minority of patients manifest episodes of focal coronary artery spasm in the absence of overt atherosclerotic lesions, and this syndrome is known as variant angina or Prinzmetal angina. In this case, intense vasospasm alone reduces coronary oxygen supply and results in angina (see Fig. 6-5D). The mechanism by which such profound spasm develops is not completely understood but may involve increased sympathetic activity in combination with

endothelial dysfunction. It is thought that many patients with variant angina may actually have early atherosclerosis manifested only by a dysfunctional endothelium, because the response to endothelium-dependent vasodilators (e.g., ACh and serotonin) is often abnormal.

Variant angina often occurs at rest because ischemia in this case results from transient reduction of the coronary oxygen supply rather than an increase in myocardial oxygen demand.

Silent Ischemia

Episodes of cardiac ischemia sometimes occur in the absence of perceptible discomfort or pain, and such instances are referred to as silent ischemia. These asymptomatic episodes can occur in patients who on other occasions experience typical symptomatic angina. Conversely, in some patients, silent ischemia may be the only manifestation of CAD. It may be difficult to diagnose silent ischemia on clinical grounds, but its presence can be detected by laboratory techniques such as continuous ambulatory electrocardiography or it can be elicited by exercise stress testing, as described later in the chapter. One study estimated that silent ischemic episodes occur in 40% of patients with stable symptomatic angina and in 2.5% to 10% of asymptomatic middle-aged men. When considering the importance of anginal discomfort as a physiologic warning signal, the asymptomatic nature of silent ischemia becomes all the more concerning.

The reason why some episodes of ischemia are silent whereas others are symptomatic has not been elucidated. The degree of ischemia cannot fully explain the disparity, because even MI may present without symptoms in some patients. Silent ischemia has been reported to be more common among diabetic patients (possibly due to impaired pain sensation from peripheral neuropathy), the elderly, and in women.

Syndrome X

The term syndrome X refers to patients with typical symptoms of angina pectoris who have no evidence of significant atherosclerotic coronary stenoses on coronary angiograms. Some of these patients may show definite laboratory signs of ischemia during exercise testing. The pathogenesis of ischemia in this situation may be related to inadequate vasodilator reserve of the coronary resistance vessels. It is thought that the resistance vessels (which are too small to be visualized by coronary angiography) may not dilate appropriately during periods of increased myocardial oxygen demand. Microvascular dysfunction, vasospasm, and hypersensitive pain perception may each contribute to this syndrome. Patients with syndrome X have a better prognosis than those with overt atherosclerotic disease.

CLINICAL FEATURES OF CHRONIC STABLE ANGINA

History

The most important part of the clinical evaluation of ischemic heart disease is the history described by the patient. Because chest pain is such a common complaint, it is important to focus on the characteristics that help distinguish myocardial ischemia from other causes of discomfort. From a diagnostic standpoint, it would be ideal to interview and examine a patient during an actual episode of angina, but most people are asymptomatic during routine clinic examinations. Therefore, a careful history probing several features of the discomfort should be elicited.

Quality

Angina is most often described as a “pressure,” “discomfort,” “tightness,” “burning,” or “heaviness” in the chest. It is rare that the sensation is actually described as a “pain,” and often a patient will correct the physician who refers to the anginal symptom as such.

Sometimes, a patient likens the sensation to “an elephant sitting on my chest.” Anginal discomfort is neither sharp nor stabbing, and it does not vary significantly with inspiration or movement of the chest wall. It is a steady discomfort that lasts a few minutes, yet rarely more than 5 to 10 minutes. It always lasts more than a few seconds, and this helps to differentiate it from sharper and briefer musculoskeletal pains.

While describing angina, the patient may place a clenched fist over his or her sternum, referred to as the **Levine sign**, as if defining the constricting discomfort by that tight grip.

Location

Anginal discomfort is usually diffuse rather than localized to a single point. It is most often located in the retrosternal area or in the left precordium but may occur anywhere in the chest, back, arms, neck, lower face, or upper abdomen. It often radiates to the shoulders and inner aspect of the arms, especially on the left side.

Accompanying Symptoms

During the discomfort of an acute anginal attack, generalized sympathetic and parasympathetic stimulation may result in tachycardia, diaphoresis, and nausea. Ischemia also results in transient dysfunction of LV systolic contraction and diastolic relaxation. The resultant elevation of LV diastolic pressure is transmitted to the pulmonary vasculature and often causes dyspnea during the episode. Transient fatigue and weakness are also common, particularly in elderly patients. When such symptoms occur as a consequence of myocardial ischemia but are unaccompanied by typical chest discomfort, they are referred to as “anginal equivalents.”

Precipitants

Angina, when not caused by pure vasospasm, is precipitated by conditions that increase myocardial oxygen demand (e.g., increased heart rate, contractility, or wall stress). These include physical exertion, anger, and other emotional excitement. Additional factors that increase myocardial oxygen demand and can precipitate anginal discomfort in patients with CAD include a large meal or cold weather. The latter induces peripheral vasoconstriction, which in turn augments myocardial wall stress as the left ventricle contracts against the increased resistance.

Angina is generally relieved within minutes after the cessation of the activity that precipitated it and even more quickly (within 3 to 5 minutes) by sublingual nitroglycerin. This response can help differentiate myocardial ischemia from many of the other conditions that produce chest discomfort.

Patients who experience angina primarily due to increased coronary artery tone or vasospasm often develop symptoms at rest, independent of activities that increase myocardial oxygen demand.

Frequency

Although the level of exertion necessary to precipitate angina may remain fairly constant, the frequency of episodes varies considerably because patients quickly learn which activities cause their discomfort and avoid them. It is thus important to inquire about reductions in activities of daily living when taking the history.

Risk Factors

In addition to the description of chest discomfort, a careful history should uncover risk factors that predispose to atherosclerosis and CAD, including cigarette smoking, dyslipidemia, hypertension, diabetes, and a family history of premature coronary disease (see Chapter 5).

Differential Diagnosis

Several conditions can give rise to symptoms that mimic the transient chest discomfort of angina pectoris, including other cardiac causes (e.g., pericarditis), gastrointestinal disorders (e.g., gastroesophageal reflux, peptic ulcer disease, esophageal spasm, or biliary pain), and musculoskeletal conditions (including chest wall pain, spinal osteoarthritis, and cervical radiculitis). The history remains of paramount importance in distinguishing myocardial ischemia from these disorders. In contrast to angina pectoris, gastrointestinal causes of recurrent chest pain are often precipitated by certain foods and are unrelated to exertion. Musculoskeletal causes of chest discomfort tend to be more superficial or can be localized to a discrete spot (i.e., the patient can point to the pain with one finger) and often vary with changes in position. Similarly, the presence of pleuritic pain (sharp pain aggravated by respiratory movements) argues against angina as the cause; this symptom is more likely a result of pericarditis, or an acute pulmonary condition such as pulmonary embolism or acute pneumothorax. Useful differentiating features of recurrent chest pain are listed in Table 6-2.

TABLE 6-2 Causes of Recurrent Chest Pain

Condition	Differentiating Features
Cardiac	
Myocardial ischemia	<ul style="list-style-type: none"> • Retrosternal tightness or pressure; typically radiates to the neck, jaw, or left shoulder and arm • Lasts a few minutes (usually <10) • Brought on by exertion, relieved by rest or nitroglycerin • ECG transient ST depressions or elevations, or flattened or inverted T waves
Pericarditis	<ul style="list-style-type: none"> • Sharp, pleuritic pain that varies with position; friction rub may be present on auscultation • Can last for hours to days • ECG diffuse ST elevations and PR deviation (see Chapter 14)
Gastrointestinal	
Gastroesophageal reflux	<ul style="list-style-type: none"> • Retrosternal burning • Precipitated by certain foods, worsened by supine position, unaffected by exertion • Relieved by antacids
Peptic ulcer disease	<ul style="list-style-type: none"> • Epigastric ache or burning • Occurs after meals, unaffected by exertion • Relieved by antacids, not by nitroglycerin
Esophageal spasm	<ul style="list-style-type: none"> • Retrosternal pain accompanied by dysphagia • Precipitated by meals, unaffected by exertion • May be relieved by nitroglycerin
Biliary colic	<ul style="list-style-type: none"> • Constant, deep pain in right upper quadrant; can last for hours • Brought on by fatty foods, unaffected by exertion • Not relieved by antacids or nitroglycerin
Musculoskeletal	
Costochondral syndrome	<ul style="list-style-type: none"> • Sternal pain worsened by chest movement • Costochondral junctions tender to palpation • Relieved by anti-inflammatory drugs, not by nitroglycerin
Cervical radiculitis	<ul style="list-style-type: none"> • Constant ache or shooting pains, may be in a dermatomal distribution • Worsened by neck motion

ECG, electrocardiogram.

Physical Examination

If it is possible to examine a patient during an anginal attack, several transient physical signs may be detected (Fig. 6-6). An increased heart rate and blood pressure are common because of the augmented sympathetic response. Myocardial ischemia may lead to papillary muscle dysfunction and therefore mitral regurgitation. Ischemia-induced regional ventricular contractile abnormalities can sometimes be detected as an abnormal bulging impulse on palpation of the left chest. Ischemia decreases ventricular compliance, producing a stiffened ventricle and therefore an S₄ gallop on physical examination during atrial contraction (see Chapter 2). However, if the patient is free of chest discomfort during the examination, there may be no abnormal cardiac findings.

Physical examination should also assess for signs of atherosclerotic disease in more accessible vascular beds. For example, carotid bruits may indicate the presence of cerebrovascular disease, whereas femoral artery bruits or diminished pulses in the lower extremities can be a clue to peripheral arterial disease (see Chapter 15).

Diagnostic Studies

Once angina is suspected, several diagnostic procedures may be helpful in confirming myocardial ischemia as the cause. Because many of these tests are costly, it is important to choose the appropriate studies for each patient.

Electrocardiogram

One of the most useful tools is an electrocardiogram (ECG) obtained during an anginal episode. Although this is easy to arrange when symptoms occur in hospitalized patients, it may not be possible to “catch” episodes in people seen on an outpatient basis. During myocardial ischemia, ST-segment and T-wave changes can appear (Fig. 6-7). Acute ischemia usually results in transient horizontal or downsloping ST-segment depressions and T-wave flattening or inversions. Occasionally, ST-segment elevations are seen, suggesting more severe transmural myocardial ischemia, and can also be observed during the intense vasospasm of variant angina. In contrast to the ECG of a patient with an acute MI, the ST deviations seen in patients with stable angina quickly normalize with resolution of the patient’s symptoms. In fact,

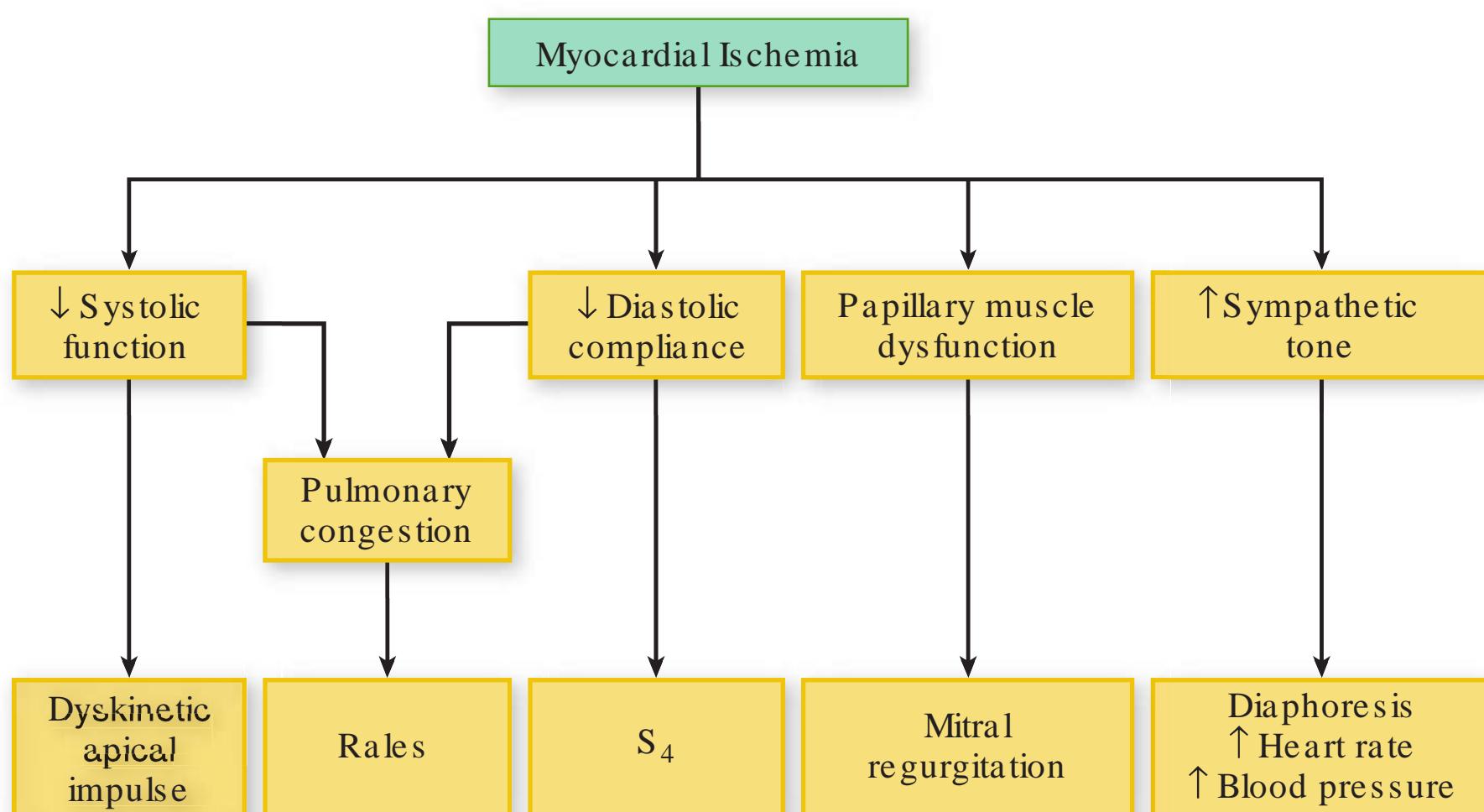


FIGURE 6-6. Pathophysiology of physical signs during acute myocardial ischemia.

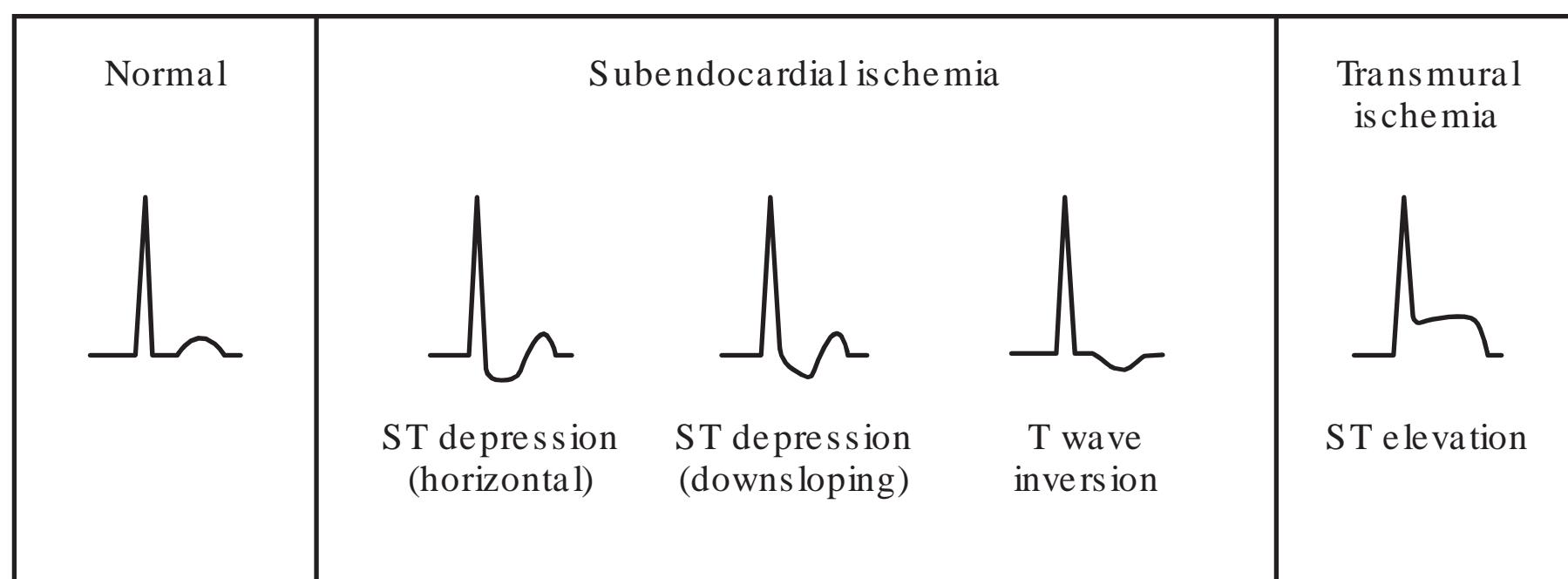


FIGURE 6-7. Common transient ECG abnormalities during ischemia. Subendocardial ischemia causes ST-segment depressions and/or T-wave flattening or inversions. Severe transient transmural ischemia can result in ST-segment elevations, similar to the early changes in acute myocardial infarction. When transient ischemia resolves, so do the electrocardiographic changes.

ECGs obtained during periods free of ischemia are completely normal in approximately half of patients with stable angina. In others, chronic “nondiagnostic” ST and T-wave deviations may be present. Evidence of a previous MI (e.g., pathologic Q waves) on the ECG also points to the presence of underlying coronary disease.

Stress Testing

Because ECGs obtained during or between episodes of chest discomfort may be normal, such tracings do not rule out underlying ischemic heart disease. For this reason, provocative **exercise or pharmacologic stress tests** are valuable diagnostic and prognostic aids.

Standard Exercise Testing

For many patients suspected of having CAD, a standard exercise test is performed. During this test, the patient exercises on a treadmill or a stationary bicycle to progressively higher workloads and is observed for the development of chest discomfort or excessive dyspnea. The heart rate and ECG are continuously monitored, and blood pressure is checked at regular intervals. The test is continued until angina develops, signs of myocardial ischemia appear on the ECG, a target heart rate is achieved (85% of the maximal predicted heart rate [MHR]; the MHR is calculated as 220 beats/min minus the patient’s age), or the patient becomes too fatigued to continue.

The test is considered abnormal if the patient’s typical chest discomfort is reproduced or if ECG abnormalities consistent with ischemia develop (i.e., greater than 1 mm horizontal or downsloping ST-segment depressions). Among patients who later undergo diagnostic coronary angiography, the ECG changes noted above have a sensitivity of approximately 65% to 70% and specificity of 75% to 80% for the detection of anatomically significant CAD.

The stress test is considered markedly positive if one or more of the following signs of severe ischemic heart disease occur: (1) ischemic ECG changes develop in the first 3 minutes of exercise or persist 5 minutes after exercise has stopped; (2) the magnitude of the ST-segment depressions is greater than 2 mm; (3) the systolic blood pressure abnormally falls during exercise (i.e., resulting from ischemia-induced impairment of contractile function); (4) high-grade ventricular arrhythmias develop; or (5) the patient cannot exercise for at least 2 minutes because of cardiopulmonary limitations. Patients with markedly positive tests are more likely to have severe multivessel coronary disease.

The utility of a stress test may be affected by the patient’s medications. For example, β -blockers or certain calcium channel blockers (verapamil, diltiazem) may blunt the ability to

achieve the target heart rate. In these situations, one must consider the purpose of the stress test. If it is to determine whether ischemic heart disease is present, then those medications are typically withheld for 24 to 48 hours before the test. On the other hand, if the patient has known ischemic heart disease and the purpose of the test is to assess the efficacy of the current medical regimen, testing should be performed while the patient takes his or her usual antianginal medications.

Nuclear Imaging Studies

Since a standard exercise test relies on ischemia-related changes on the ECG, the test is less useful in patients with baseline abnormalities of the ST segments (e.g., as seen in left bundle branch block or LV hypertrophy). In addition, the standard exercise stress test sometimes yields equivocal results in patients for whom the clinical suspicion of ischemic heart disease is high. In these situations, radionuclide imaging can be combined with exercise testing to overcome these limitations and to increase the sensitivity and specificity of the study.

As described in Chapter 3, during such myocardial perfusion imaging, a radionuclide (commonly either a technetium-99m-labeled compound or thallium-201) is injected intravenously at peak exercise, after which imaging is performed. The radionuclide accumulates in proportion to the degree of perfusion of viable myocardial cells. Therefore, areas of poor perfusion (i.e., regions of ischemia) during exercise do not accumulate radionuclide and appear as “cold spots” on the image. However, irreversibly infarcted areas also do not take up the radionuclide, and they too will appear as cold spots. To differentiate between transient ischemia and infarcted tissue, imaging is also performed at rest (either before or several hours after the exercise portion of the test). If the cold spot fills in, a region of transient ischemia has been identified (Fig. 3-18). If the cold spot remains unchanged, a region of irreversible infarction is likely.

Standard radionuclide exercise tests are 80% to 90% sensitive and approximately 80% specific for the detection of clinically significant CAD. Positron emission tomography (PET; see Chapter 3), another form of nuclear stress imaging that is not as widely available, offers superior spatial and temporal resolution, with sensitivity and specificity of 90% or greater. Because these nuclear imaging techniques are expensive, their use in screening for CAD should be reserved for (1) patients in whom baseline ECG abnormalities preclude interpretation of a standard exercise test or for (2) improvement in test sensitivity when standard stress test results are discordant with the clinical suspicion of coronary disease.

Exercise Echocardiography

Exercise testing with echocardiographic imaging is another technique to diagnose myocardial ischemia in patients with baseline ST or T-wave abnormalities or in those with equivocal standard stress tests. In this procedure, LV contractile function is assessed by echocardiography at baseline and immediately after treadmill or bicycle exercise. The test indicates inducible myocardial ischemia if regions of ventricular contractile dysfunction develop with exertion and has a sensitivity of approximately 80% and a specificity of about 90% for the detection of clinically significant CAD.

Pharmacologic Stress Tests

For patients unable to exercise (e.g., those with hip or knee arthritis), pharmacologic stress testing can be performed instead using various agents, including vasodilators or inotropes. The most common approach is to use a coronary vasodilator such as adenosine, regadenoson,

or dipyridamole. Adenosine and regadenoson bind to adenosine A_{2a} receptors on vascular smooth muscle cells, resulting in coronary vasodilatation. As ischemic regions are already maximally dilated (in compensation for the epicardial coronary stenoses), the vasodilatation induced by these agents increases flow to the myocardium perfused by healthy coronary arteries and thus “steals” blood away from the diseased segments. Dipyridamole causes a similar effect indirectly, as it blocks normal cellular uptake and destruction of adenosine, thereby increasing adenosine’s circulating concentration and subsequent stimulation of the A_{2a} receptor. Administration of these pharmacologic agents is typically coupled with nuclear imaging, to reveal regions of impaired myocardial perfusion.

An alternative to vasodilating agents, pharmacologic stress testing can also be performed using the inotrope dobutamine, which increases myocardial oxygen demand by augmenting heart rate and the force of contraction, thus simulating some of the effects of exercise. Accompanying imaging (typically nuclear imaging or echocardiography) reveals regions of drug-induced ischemia. Vasodilator pharmacologic stress testing is generally preferred over dobutamine testing for the assessment of ischemia, as the former produces greater incremental myocardial blood flow, and is technically easier and faster to perform. However, the vasodilator agents can cause bronchospasm in patients with reactive airways disease (by stimulating bronchiolar adenosine A_{2b} receptors) and should be avoided in that population, in whom dobutamine pharmacologic testing is therefore preferred. In addition, a vasodilator study cannot be performed successfully in a patient who has been exposed to methylxanthines (e.g., caffeine consumption or use of the bronchodilator theophylline) on the day of the study, as such agents competitively antagonize adenosine’s interaction with its receptor and blunt its effect.

Coronary Angiography

The most direct means of identifying coronary artery stenoses is by coronary angiography, in which atherosclerotic lesions are visualized radiographically following the injection of radiopaque contrast material into the artery (Fig. 6-8; also see Chapter 3). Although generally safe, the procedure is associated with a small risk of complications directly related to its invasive nature. Therefore, coronary angiography is typically

reserved for patients whose anginal symptoms do not respond adequately to pharmacologic therapy, for those with an unstable presentation, or when the results of noninvasive testing are so abnormal that severe CAD warranting revascularization is likely.

When the degree of stenosis of a region of intracoronary plaque, or its hemodynamic significance, is not clear, additional techniques can be applied in the cardiac catheterization laboratory. For example, **fractional flow reserve (FFR)** measurement is a technique that can assess the functional severity of a stenosis identified at angiography. A special manometer-tipped guidewire inserted through the catheter measures the pressure in the coronary artery distal to the stenosis during induced vasodilatation. The FFR value is equal to the pressure distal to the stenosis (P_d) relative to the pressure proximal to the stenosis in the aorta (P_{ao}).

$$FFR = P_d / P_{ao}$$



FIGURE 6-8. Example of coronary angiography.
Injection of the right coronary artery demonstrates a stenosis in the midportion of the vessel, indicated by the arrow. (Courtesy of Pinak B. Shah, MD, Brigham and Women's Hospital, Boston, MA)

A higher FFR value indicates a less severe stenosis. FFR values less than 0.75 to 0.80 identify severe stenoses that typically warrant mechanical intervention.

Although coronary angiography is considered the “gold standard” for the diagnosis of CAD, it should be noted that it provides only anatomic information. The clinical significance of lesions detected by angiography depends on both the degree of narrowing and also on the pathophysiologic consequences. Therefore, treatment decisions are made not only on the finding of such stenoses but also by their functional effects, manifested by the patient’s symptoms, the viability of the myocardial segments served by stenotic vessels, and the degree of ventricular contractile dysfunction. Furthermore, standard arteriography does not reveal the composition of coronary atherosclerotic plaque or its vulnerability to rupture (see Chapter 5).

Noninvasive Imaging of Coronary Arteries

Diagnostic alternatives to coronary angiography have been developed to noninvasively visualize the coronary arteries. Coronary CT angiography (CCTA) performed with administration of intravenous contrast (see Fig. 3.21) can visualize stenoses of greater than 50% of the coronary lumen with an approximate sensitivity of 90% and specificity of 65% to 90%. CCTA is considered an alternative to stress testing to help exclude significant CAD in low- to intermediate-risk patients who present with undifferentiated chest pain. The quality of images in CCTA is limited by cardiac motion, which can be reduced by slowing the heart rate with administration of a beta-blocker.

Cardiac CT without contrast administration can be used as a screening test to detect coronary artery calcification (CAC) as described in Chapter 3. CAC correlates with the extent of atherosclerosis and thus estimates plaque burden, but does not quantify individual coronary stenoses. The absence of CAC is a clinically useful finding as it strongly predicts the absence of CAD.

Natural History

The patient with chronic angina may show no change in a stable pattern of ischemia for many years. In some patients, however, the course may be punctuated by the occurrence of unstable angina, MI, or sudden cardiac death. These complications are often related to acute thrombosis at the site of disrupted atherosclerotic plaque (see Chapter 7). Why some patients, but not others, sustain these complications remains a subject of intense clinical and basic science investigation and may relate to the vulnerability of plaque to rupture.

The mortality associated with CAD has declined significantly in recent decades: the age-adjusted death rate has fallen by more than 50%. This is likely related to (1) atherosclerotic risk reduction through improved lifestyle changes (e.g., less tobacco use, less dietary fat consumption, and more exercise); (2) improved therapeutic strategies and longevity following acute coronary syndromes (see Chapter 7); and (3) advances in the pharmacologic and mechanical therapies for chronic CAD.

TREATMENT

The goals of therapy in chronic ischemic heart disease are to decrease the frequency of anginal attacks, to prevent acute coronary syndromes such as MI, and to prolong survival. A long-term crucial step is to address the risk factors that led to the development of atherosclerotic coronary disease. Data convincingly demonstrate the benefit of smoking cessation, cholesterol improvement, and blood pressure control in lowering the risk of coronary disease events (see Chapter 5). Improvements in other risk factors for CAD, including serum glucose in diabetics,

obesity and physical inactivity, may also reduce the risk of adverse outcomes although the benefits of these interventions are less well documented.

The following sections describe medical and surgical strategies to (1) reduce ischemia and its symptoms by restoring the balance between myocardial oxygen supply and demand and (2) prevent acute coronary syndromes and death in patients with chronic CAD.

Medical Treatment of an Acute Episode of Angina

When experiencing acute angina, the patient should cease physical activity. Sublingual nitroglycerin, an organic nitrate, is the drug of choice in this situation. Placed under the tongue, this medication produces a slight burning sensation as it is absorbed through the mucosa, and it begins to take effect in 1 to 2 minutes. Nitrates relieve ischemia primarily through vascular smooth muscle relaxation, particularly venodilatation. Venodilatation reduces venous return to the heart, with a subsequent decline in LV volume (a determinant of wall stress). The latter decreases myocardial oxygen consumption, thus helping to restore oxygen balance in the ischemic heart.

A second action of nitrates is to dilate the coronary vasculature, with subsequent augmentation of coronary blood flow. This effect may be of little value in patients with angina in whom maximal coronary dilatation has already resulted from the accumulation of local metabolites. However, when coronary vasospasm plays a role in the development of ischemia, nitrate-induced coronary vasodilatation may be particularly beneficial.

Medical Treatment to Prevent Recurrent Ischemic Episodes

Pharmacologic agents are also the first line of defense in the prevention of anginal attacks. The goal of these agents is to decrease the cardiac workload (i.e., reduce myocardial oxygen demand) and to increase myocardial perfusion. The three classes of medications most commonly used are β -adrenergic blockers, organic nitrates, and calcium channel blockers (Table 6-3).

β -Blockers (see Chapter 17) exert their antianginal effect primarily by reducing myocardial oxygen demand. They are directed against β -receptors, of which there are two classes: β_1 -adrenergic receptors are restricted to the myocardium, whereas β_2 -adrenergic receptors are located throughout the blood vessels and the bronchial tree. The stimulation of β_1 -receptors by endogenous catecholamines and exogenous sympathomimetic drugs increases heart rate and contractility. Consequently, β -adrenergic antagonists decrease the force of ventricular contraction and heart rate, thereby relieving ischemia by reducing myocardial oxygen demand. In addition, slowing the heart rate may benefit myocardial oxygen supply by augmenting the time spent in diastole, the phase when coronary perfusion primarily occurs.

In addition to suppressing angina, several studies have shown that β -blockers decrease the rates of recurrent infarction and mortality following an acute MI (see Chapter 7). Moreover, they have been shown to reduce the likelihood of an initial MI in patients with hypertension. Thus, β -blockers are first-line chronic therapy in the treatment of CAD.

β -Blockers are generally well tolerated but have several potential side effects. For example, they may precipitate bronchospasm in patients with underlying asthma by antagonizing β_2 -receptors in the bronchial tree. Although β_1 -selective blockers are theoretically less likely to exacerbate bronchospasm in such patients, drug selectivity for the β_1 -receptor is not complete, and in general, all β -blockers should be used cautiously, or avoided, in patients with significant obstructive airway disease.

β -Blockers are also generally not used in patients with acutely decompensated LV dysfunction because they could intensify heart failure symptoms by further reducing inotropy. (However, as described in Chapter 9, β -blockers actually improve outcomes in patients with

TABLE 6-3**Pharmacologic Agents Used in the Prevention and Treatment of Angina**

Drug Class	Mechanism of Action	Adverse Effects
Organic nitrates	\downarrow Myocardial O ₂ demand \downarrow Preload (venodilatation) \uparrow O ₂ supply \uparrow Coronary perfusion \downarrow Coronary vasospasm	<ul style="list-style-type: none"> • Headache • Hypotension • Reflex tachycardia
β -Blockers	\downarrow Myocardial O ₂ demand \downarrow Contractility \downarrow Heart rate	<ul style="list-style-type: none"> • Excessive bradycardia • \downarrow LV contractile function • Bronchoconstriction • May mask hypoglycemic symptoms • Fatigue
Calcium channel blockers (agent specific; see footnote)	\downarrow Myocardial O ₂ demand \downarrow Preload (venodilatation) \downarrow Wall stress (\downarrow BP) \downarrow Contractility (V, D) \downarrow Heart rate (V, D) \uparrow O ₂ supply \uparrow Coronary perfusion \downarrow Coronary vasospasm	<ul style="list-style-type: none"> • Headache, flushing • \downarrow LV contractility (V, D) • Marked bradycardia (V, D) • Edema (especially N, D) • Constipation (especially V)
Ranolazine	\downarrow Late phase inward sodium current	<ul style="list-style-type: none"> • Dizziness, headache • Constipation, nausea

BP, blood pressure; D, diltiazem; LV, left ventricular; N, nifedipine and other dihydropyridine calcium channel antagonists; V, verapamil.

stable chronic heart failure conditions.) β -Blockers are also relatively contraindicated in patients with marked bradycardia or certain types of heart block to avoid additional impairment of electrical conduction.

β -Blockers sometimes cause fatigue and sexual dysfunction. They should be used with caution in insulin-treated diabetic patients because they can mask tachycardia and other catecholamine-mediated responses that can warn of hypoglycemia. One might also expect that β -blockers would decrease myocardial blood perfusion by blocking the vasodilating β_2 -adrenergic receptors of the coronary arteries. However, this effect is usually attenuated by autoregulation and vasodilatation of the coronary vessels owing to the accumulation of local metabolites.

Organic nitrates (e.g., nitroglycerin, isosorbide dinitrate, isosorbide mononitrate), as previously mentioned, relieve ischemia primarily through venodilatation (i.e., lower wall stress results from a smaller ventricular radius) and possibly through coronary vasodilatation. The organic nitrates are the oldest of the antianginal drugs and come in several preparations (also described in Chapter 17). Sublingual nitroglycerin tablets or sprays are used in the treatment of acute attacks because of their rapid onset of action. In addition, when taken immediately before a person engages in activities known to provoke angina, these rapidly acting nitrates are useful as prophylaxis against anginal attacks.

Longer-acting anginal prevention can be achieved through a variety of nitrate preparations, including oral tablets of isosorbide dinitrate (or mononitrate) or a transdermal nitroglycerin patch, which is applied once a day. A limitation to chronic nitrate therapy is the development of drug tolerance (i.e., decreased effectiveness of the drug during continued

administration), which occurs to some degree in most patients. This undesired effect can be overcome by providing a nitrate-free interval for several hours each day, usually while the patient sleeps.

There is no evidence that nitrates improve survival or prevent infarctions in patients with chronic CAD, and they are used purely for symptomatic relief. Common side effects include headache, light-headedness, and palpitations induced by vasodilatation and reflex sinus tachycardia. The latter can be prevented by combining a β -blocker with the nitrate regimen.

Calcium channel blockers (see Chapter 17) antagonize voltage-gated L-type calcium channels, but the actions of the individual drugs of this group vary. The dihydropyridines (e.g., nifedipine and amlodipine) are potent vasodilators. They relieve myocardial ischemia by (1) decreasing oxygen demand (venodilatation reduces ventricular filling and size, arterial dilation reduces the resistance against which the left ventricle contracts, and both actions reduce wall stress) and (2) increasing myocardial oxygen supply via coronary dilatation. By the latter mechanism, they are also potent agents for the relief of coronary artery vasospasm.

Nondihydropyridine calcium channel blockers (verapamil and diltiazem) also act as vasodilators but are not as potent in this regard as the dihydropyridines. However, these agents have additional beneficial antianginal effects stemming from their more potent cardiac depressant actions: they reduce the force of ventricular contraction (contractility) and slow the heart rate. Accordingly, verapamil and diltiazem also decrease myocardial oxygen demand by these mechanisms.

Questions have been raised about the safety of short-acting calcium channel-blocking drugs in the treatment of ischemic heart disease. In meta-analyses of randomized trials, these drugs have been associated with an increased incidence of MI and mortality. The adverse effect may relate to the rapid hemodynamic effects and blood pressure swings induced by the short-acting agents. Therefore, only long-acting calcium channel blockers (i.e., preparations taken once a day) are recommended in the treatment of chronic angina, generally as second-line drugs if symptoms are not controlled by β -blockers and nitrates.

The three standard groups of antianginal drugs described in this section can be used alone or in combination. However, care should be taken in combining a β -blocker with a nondihydropyridine calcium channel blocker (verapamil or diltiazem) because the additive negative chronotropic effect can cause excessive bradycardia and the combined negative inotropic effect could precipitate heart failure in patients with LV contractile dysfunction.

Ranolazine, a fourth type of anti-ischemic therapy, has been shown to decrease the frequency of anginal episodes and improve exercise capacity in patients with chronic CAD but differs from other anti-ischemic drugs in that it does not affect the heart rate or blood pressure. Although its mechanism of action has not been fully elucidated, it is believed to inhibit the late phase of the action potential's inward sodium current (I_{Na^+}) in ventricular myocytes. That late phase tends to be abnormally enhanced in ischemic myocardium, and the associated increased sodium influx results in higher-than-normal intracellular Ca^{++} (mediated by the trans-sarcolemmal Na^+-Ca^{++} exchanger; see Fig. 1.10). Such calcium overload is thought to result in impaired diastolic relaxation and contractile inefficiency. Inhibition of the late I_{Na^+} by ranolazine counters these pathologic effects. Clinical studies have supported ranolazine's effectiveness in reducing angina, and its long-term safety, when used alone or in combination with other antianginal agents.

Although useful in controlling symptoms of angina, none of the antianginal drug groups has been shown to slow or reverse the atherosclerotic process responsible for the arterial lesions of chronic CAD. Moreover, although β -blockers have demonstrated mortality benefits in patients after MI, none of these agents has been shown to improve longevity in patients with chronic stable angina and preserved LV function.

Medical Treatment to Prevent Acute Cardiac Events

Platelet aggregation and thrombosis are key elements in the pathophysiology of acute MI and unstable angina (see Chapter 7). **Antiplatelet therapy** reduces the risk of these acute coronary syndromes in patients with chronic angina and should be a standard part of the regimen used to treat CAD. For example, **aspirin** has antithrombotic actions through the inhibition of synthesis of thromboxane A₂, a mediator of platelet activation and aggregation, as well as anti-inflammatory properties that may be important in stabilizing atherosomatous plaque. Unless contraindications are present (e.g., allergy or gastric bleeding), aspirin should be continued indefinitely in all patients with CAD.

Platelet P2Y₁₂ ADP receptor antagonists, such as clopidogrel, also prevent platelet activation and aggregation (see Chapter 17). They can be used as an antiplatelet substitute in patients who are allergic to aspirin. In addition, the combination of aspirin and a P2Y₁₂ inhibitor is superior to aspirin alone in reducing death and ischemic complications in patients with acute coronary syndromes, in those undergoing elective percutaneous coronary stenting, and in patients with a history of MI.

Lipid-regulating therapy is an additional approach to reduce cardiovascular clinical events in patients with CAD. In particular, HMG-CoA reductase inhibitors (“statins”) lower MI and death rates in patients with established coronary disease and in those at high risk of developing CAD. The benefits of statin therapy are believed to extend beyond their lipid-altering effects, because there is evidence that they decrease vascular inflammation and improve endothelial cell dysfunction and thus may help stabilize atherosclerotic plaques. Moreover, trials of patients with established atherosclerotic disease have demonstrated a linear relationship between the magnitude of LDL lowering and the reduction in cardiovascular risk. Thus, high-intensity lipid lowering (resulting in reduction of LDL by more than 50%) is superior to less intense lipid-lowering therapy in preventing future ischemic events and cardiovascular death. An LDL less than 70 mg/dL is a common goal for patients with CAD, and recent evidence suggests that even patients with a baseline LDL of 70 mg/dL benefit from high-intensity lipid lowering. As a result, current national guidelines no longer recommend treating to a specific target LDL level. Rather, it is recommended that all patients with CAD receive a high-intensity statin regimen, with the goal of at least 50% reduction in LDL.

Angiotensin-converting enzyme (ACE) inhibitors, beneficial in the treatment of hypertension (see Chapter 13), heart failure (see Chapter 9), and following MI (see Chapter 7), have also been studied as chronic therapy for patients with stable CAD not complicated by heart failure. Some (but not all) of these trials have shown reduced rates of death, MI, and stroke. Thus, many cardiologists recommend that an ACE inhibitor be included in the medical regimen of patients with chronic CAD.

Revascularization

Patients with angina that becomes asymptomatic during pharmacologic therapy are usually monitored by their physicians with continued emphasis on cardiac risk factor reduction. However, coronary revascularization is pursued if (1) the patient’s symptoms of angina do not respond adequately to antianginal drug therapy, (2) unacceptable side effects of medications occur, or (3) the patient is found to have high-risk coronary disease for which revascularization is known to improve survival (as described in the next section). The two techniques used to accomplish mechanical revascularization are percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery.

PCI includes **percutaneous transluminal coronary angioplasty (PTCA)**, a procedure performed under fluoroscopy in which a balloon-tipped catheter is inserted through a peripheral artery (usually femoral, radial, or brachial) and maneuvered into the stenotic segment of a

coronary vessel. The balloon at the end of the catheter is then inflated under high pressure to dilate the stenosis, after which the balloon is deflated and the catheter is removed from the body. The improvement in the size of the coronary lumen increases coronary perfusion and myocardial oxygen supply. Effective dilatation of the stenosis results from compression of the atherosclerotic plaque and often by creating a fracture within the lesion and stretching the underlying media. The risk of MI during the procedure is less than 1.5%, and mortality is less than 1%. Unfortunately, approximately one third of patients who undergo balloon angioplasty develop recurrent symptoms within 6 months owing to restenosis of the dilated artery and require additional coronary interventions.

For this reason, **coronary stents** were developed for implantation at the time of PCI, and have been shown to significantly reduce the rate of restenosis. Such stents are slender, cage-like metal support devices that in their collapsed configuration can be threaded into the region of stenosis by a catheter. Once in position, the stent is expanded into its open position by inflating a high-pressure balloon in its interior (Fig. 6-9). The balloon and attached catheter are then removed, but the stent is left permanently in place to serve as a scaffold to maintain arterial patency. Because stents are thrombogenic, a combination of oral antiplatelet agents (commonly, aspirin plus a platelet P2Y₁₂ receptor antagonist, such as clopidogrel) is crucial after stent implantation.

Compared with conventional balloon angioplasty, stent implantation decreases restenosis rates and reduces the need for repeat PCIs. Although restenosis resulting from vessel elastic recoil is greatly diminished by standard metal stent placement, neointimal proliferation (i.e., migration of smooth muscle cells and production of extracellular matrix) remains an important cause of in-stent restenosis and recurrent anginal symptoms.

To address the problem of in-stent restenosis after PCI, **drug-eluting stents** were devised. These special stents are fabricated with a polymer coat that incorporates an antiproliferative medication such as sirolimus (an immunosuppressive agent that inhibits T-cell activation), everolimus (an immunosuppressive similar to sirolimus), or paclitaxel (which interferes with cellular microtubule function). The medication is released from the stent over a period of 2 to 4 weeks, and this approach has shown great effect at preventing neointimal proliferation

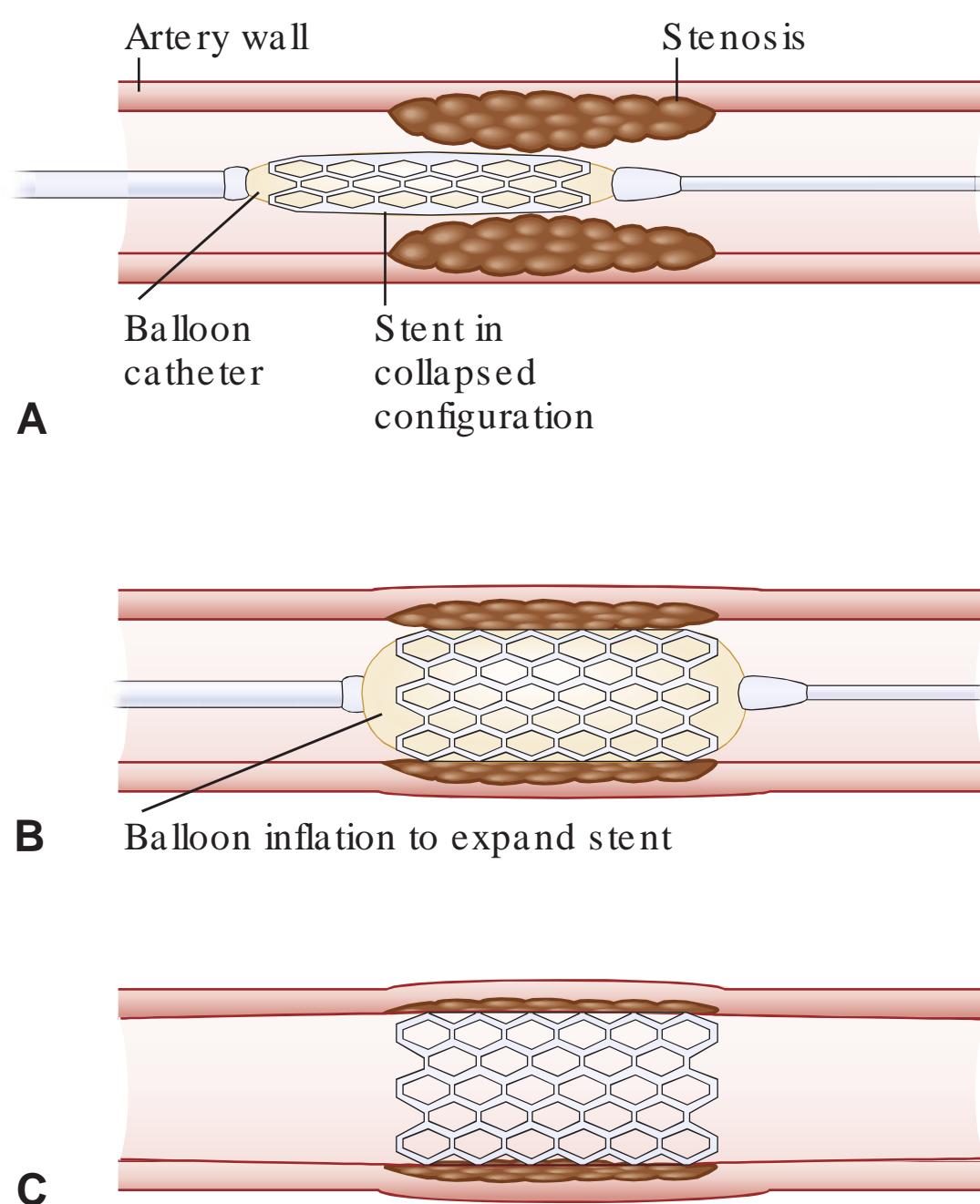


FIGURE 6-9. Placement of a coronary artery stent.

A A stent, in its original collapsed state, is advanced into the coronary stenosis on a balloon catheter. **B** The balloon is inflated to expand the stent. **C** The balloon is deflated, and the catheter is removed from the body, leaving the stent permanently in place.

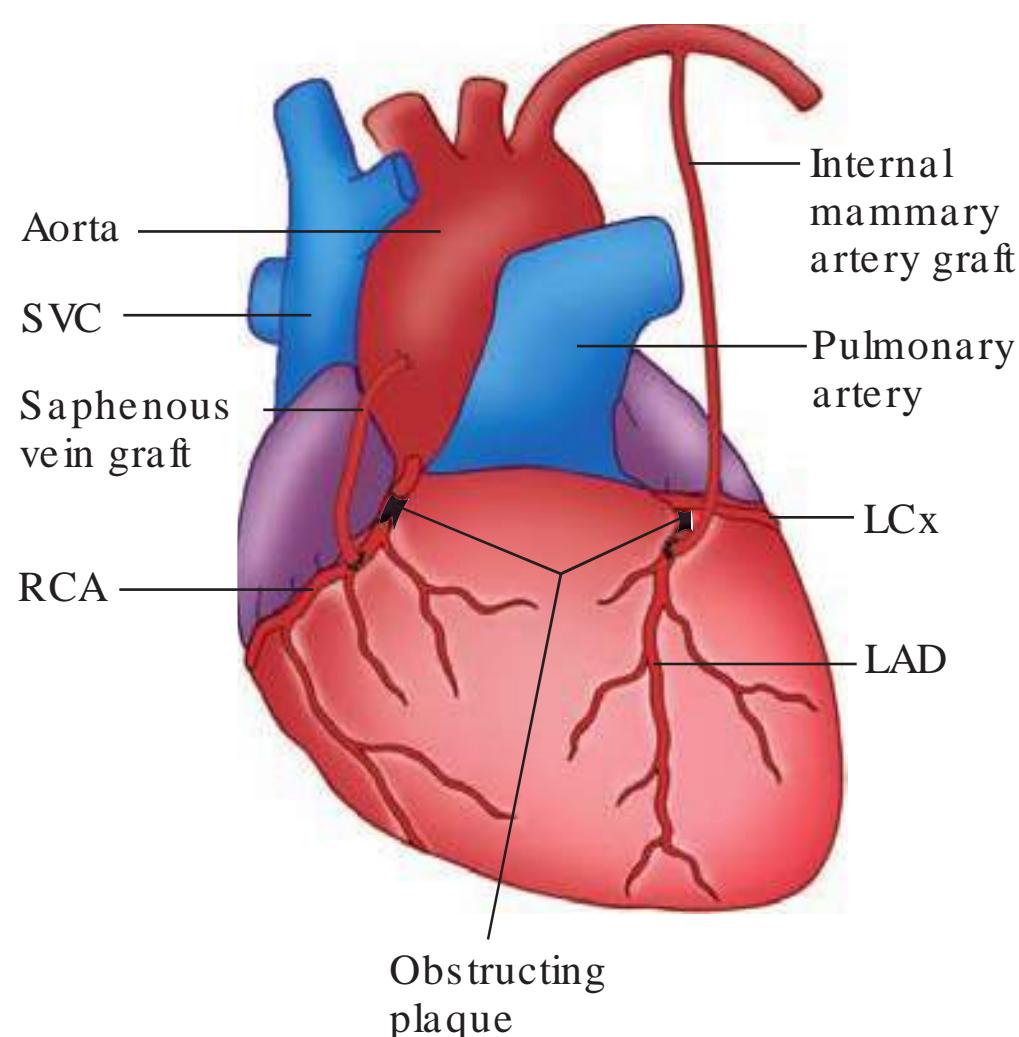


FIGURE 6-10. Coronary artery bypass surgery. Two types of bypasses are illustrated: (1) the left internal mammary artery originates from the left subclavian artery, and in this schematic, it is anastomosed to the left anterior descending (LAD) coronary artery distal to obstructing plaque; (2) one end of a saphenous vein graft is sutured to the proximal aorta and the other end to the right coronary artery (RCA) distal to a stenotic segment.

(IMA, a “superfluous” branch of each subclavian artery) that can be directly anastomosed distal to a stenotic coronary site. Vein grafts have a patency rate of up to 80% at 12 months but are vulnerable to accelerated atherosclerosis; 10 years after surgery, more than 50% have occluded. In contrast, IMA grafts are more resistant to atherosclerosis with a patency rate of 90% at 10 years. Therefore, IMA grafts are often used to perfuse sites of critical flow such as the left anterior descending artery. Clinical trial evidence supports the use of aggressive lipid-lowering drug therapy after CABG to improve the long-term patency rates of bypass grafts.

In recent years, less invasive surgical alternatives to conventional CABG have been explored. These include “minimally invasive” operations with smaller incisions, the use of transcutaneous ports with videoscopic robotic assistance, and “off-pump” procedures, which avoid the use of cardiopulmonary bypass (heart–lung) machines. While there are theoretical advantages of avoiding the latter, studies examining off-pump procedures in comparison with standard CABG have shown comparable mortality benefit, but poorer graft patency over time and an increased need for future revascularization. Additionally, there have been no major high-quality studies comparing benefits of minimally invasive operations to conventional CABG. In general, patient-specific risks and characteristics are considered by the surgeon when selecting which type of bypass procedure to undertake.

Medical versus Revascularization Therapy

Many patients with chronic, stable angina can be successfully managed with pharmacologic therapy alone. However, if anginal symptoms prove refractory despite maximal pharmacologic therapy, or if intolerable drug side effects develop, coronary angiography is recommended for further therapeutic planning. Moreover, for patients whose angina is controlled by medications, it is standard to perform noninvasive testing (e.g., exercise testing, echocardiography) to identify those with high-risk disease, because the long-term prognosis for such patients can

and reducing the need for repeat revascularization by more than half. However, just as neointimal proliferation is slowed, so too is protective endothelialization of the stent. The delay in endothelial cell coverage of the metal struts leaves patients at risk for thrombus formation within the stent should antiplatelet agents be discontinued prematurely. Therefore, prolonged courses of combination antiplatelet therapy (e.g., aspirin plus a platelet P2Y₁₂ receptor antagonist for at least 12 months) followed by aspirin indefinitely are necessary for patients who receive drug-eluting stents.

Although percutaneous revascularization techniques are generally superior to standard medical therapy for relief of angina, it is important to note that in the setting of stable coronary disease (i.e., not an acute coronary syndrome), they have not been shown to reduce the risk of MI or death.

CABG surgery entails grafting portions of a patient’s native blood vessels to bypass obstructed coronary arteries. Two types of surgical grafts are used (Fig. 6-10). The first employs native veins—typically, a section of the saphenous vein (a “superfluous” vessel removed from the leg) that is sutured from the base of the aorta to a coronary segment downstream from the region of stenosis. The second method uses arterial grafts—most commonly, an internal mammary artery

IMA, a “superfluous” branch of each subclavian artery)—that can be directly anastomosed distal to a stenotic coronary site. Vein grafts have a patency rate of up to 80% at 12 months but are vulnerable to accelerated atherosclerosis; 10 years after surgery, more than 50% have occluded. In contrast, IMA grafts are more resistant to atherosclerosis with a patency rate of 90% at 10 years. Therefore, IMA grafts are often used to perfuse sites of critical flow such as the left anterior descending artery. Clinical trial evidence supports the use of aggressive lipid-lowering drug therapy after CABG to improve the long-term patency rates of bypass grafts.

TABLE 6-4 Coronary Revascularization Procedures

Percutaneous Coronary Interventions (PCI)	Coronary Artery Bypass Graft Surgery (CABG)
Less invasive than CABG	More effective for long-term relief of angina than PCI or pharmacologic therapy
Shorter hospital stay and easier recuperation than CABG	Most complete revascularization
Superior to pharmacologic therapy for relief of angina	Survival advantage in patients with <ul style="list-style-type: none"> • >50% left main coronary artery stenosis • Multivessel coronary disease, especially if LV contractile function is impaired

LV, left ventricle.

be improved by coronary revascularization. Those with high-risk noninvasive test findings then typically proceed to coronary angiography.

In general, patients with stable angina found to have a large amount of myocardium at ischemic risk, such as those with severe ($\geq 70\%$) stenoses in all three major coronary arteries (especially when LV contractile function is reduced), those with multivessel disease that includes a critical narrowing of the proximal left anterior descending artery (which thereby threatens a large portion of the left ventricle), or those with a high-grade ($\geq 50\%$) stenosis of the left main coronary artery, achieve a survival benefit from CABG compared with medical therapy. More recent studies that have compared percutaneous coronary revascularization with CABG have demonstrated that CABG leads to a survival benefit in patients with stable angina who have severe stenoses in all three coronary arteries, a high-grade stenosis in the left main coronary artery, or diabetes (especially with multivessel disease). In contrast, PCI is a reasonable approach in patients with less extensive disease (in whom survival benefit of CABG over PCI has not been shown) and in those at high risk of undergoing surgery (Table 6-4).

Each of the described approaches for the treatment of coronary disease is benefiting from rapidly developing research advancements. New surgical techniques (increased use of various arterial grafts, less invasive operations), new drug-eluting stents (e.g., incorporation of bioabsorbable/biodegradable polymers to decrease late stent thrombosis), novel adjuncts to stenting (potent antithrombotic drugs), and progress in pharmacologic management (e.g., aggressive use of statins and antithrombotic drugs) will likely further improve outcomes and better define the best therapeutic approaches for specific subsets of patients with chronic CAD.

SUMMARY

- Cardiac ischemia results from an imbalance between myocardial oxygen supply and demand.
- Determinants of myocardial oxygen supply are (1) the oxygen content of the blood and (2) coronary blood flow (which is dependent on the coronary perfusion pressure and coronary vascular resistance).
- Key regulators of myocardial oxygen demand include (1) the heart rate, (2) contractility, and (3) myocardial wall stress.
- In the presence of coronary artery disease, myocardial oxygen supply is compromised by atherosclerotic plaques that narrow the vascular lumen (reducing coronary blood flow) and by endothelial cell dysfunction that causes inappropriate vasoconstriction of coronary resistance vessels.

- Angina pectoris is the most frequent symptom of intermittent myocardial ischemia.
- The diagnosis of angina relies heavily on the patient's description of the discomfort and can be aided by laboratory studies (e.g., exercise or pharmacologic stress testing).
- Angina may be accompanied by signs and symptoms of adrenergic stimulation, pulmonary congestion, and transient left ventricular systolic and diastolic dysfunction.
- Standard pharmacologic therapy for chronic angina includes agents to prevent ischemia and relieve symptoms (β -blockers, nitrates, calcium channel antagonists, alone or in combination) as well as agents that reduce the risk of acute coronary syndromes and death (aspirin, statins, angiotensin-converting enzyme inhibitors).
- Modifiable risk factors for atherosclerosis (i.e., dyslipidemia, smoking, hypertension, and diabetes) should be addressed.
- Revascularization with PCI or CABG surgery provides relief from ischemia in patients with chronic angina who are refractory to, or unable to tolerate, medical therapy. CABG confers improved survival rates to certain high-risk groups.

Acknowledgments

Contributors to previous editions of this chapter were June-Wha Rhee, MD; Haley Naik, MD; Christopher P. Chiodo, MD; Carey Farquhar, MD; Anurag Gupta, MD; Rainu Kaushal, MD; William Carlson, MD; Michael E. Mendelsohn MD; and Patrick T. O'Gara, MD.

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