Chapter 5

Coronary Physiology and Atherosclerosis

Benjamin Hibbert, MD, PhD • Howard J. Nathan, MD • Trevor Simard, MD • Edward R. O'Brien, MD

Key Points

1. To care for patients with coronary artery disease in the perioperative period safely, the clinician must understand how the coronary circulation functions in health and disease.
2. Coronary endothelium modulates myocardial blood flow by producing factors that relax or contract the underlying vascular smooth muscle.
3. Vascular endothelial cells help maintain the fluidity of blood by elaborating anticoagulant, fibrinolytic, and antiplatelet substances.
4. One of the earliest changes in coronary artery disease, preceding the appearance of stenoses, is the loss of the vasoregulatory and antithrombotic functions of the endothelium.
5. Although sympathetic activation increases myocardial oxygen demand, activation of α-adrenergic receptors causes coronary vasoconstriction.
6. It is unlikely that one substance alone (eg, adenosine) provides the link between myocardial metabolism and myocardial blood flow under a variety of conditions.
7. As coronary perfusion pressure decreases, the inner layers of myocardium nearest the left ventricular cavity are the first to become ischemic and display impaired relaxation and contraction.
8. The progression of an atherosclerotic lesion is similar to the process of wound healing.
9. Lipid-lowering therapy can help restore endothelial function and prevent coronary events.

When caring for patients with coronary artery disease (CAD), the anesthesiologist must prevent or minimize myocardial ischemia by maintaining optimal conditions for perfusion of the heart. This goal can be achieved only with an understanding of the many factors that determine myocardial blood flow in both health and disease.

ANATOMY AND PHYSIOLOGY OF BLOOD VESSELS

The coronary vasculature has been traditionally divided into three functional groups: (1) large conductance vessels visible on coronary angiography, which offer little resistance to blood flow; (2) small resistance vessels ranging in size from approximately 250 nm to 10 μm in diameter; and (3) veins. Although it has been taught that arterioles (precapillary vessels <50 μm in size) account for most coronary resistance, studies indicate that, under resting conditions, 45% to 50% of total coronary vascular resistance

resides in vessels larger than 100 μm in diameter. The reason may be, in part, the relatively great length of the small arteries.

Normal Artery Wall

The arterial lumen is lined by a monolayer of endothelial cells that overlies smooth muscle cells). The inner layer of smooth muscle cells, known as the intima, is circumscribed by the internal elastic lamina. Between the internal elastic lamina and external elastic lamina is another layer of smooth muscle cells, the media. Outside the external elastic lamina is an adventitia that is sparsely populated by cells but consists of complex extracellular matrix (primarily collagen and elastin fibers) and the microvessels that comprise the vasa vasorum.

Endothelium

Although the vascular endothelium was once thought of as an inert lining for blood vessels, it is more accurately characterized as a very active, distributed organ with many biologic functions. It has synthetic and metabolic capabilities and contains receptors for a variety of vasoactive substances.

Endothelium-Derived Relaxing Factors

The first vasoactive endothelial substance to be discovered was prostacyclin (PGI_2), a product of the cyclooxygenase pathway of arachidonic acid metabolism (Fig. 5.1 and Box 5.1). The production of PGI_2 is activated by shear stress, pulsatility of flow, hypoxia, and a variety of vasoactive mediators. On production it leaves the endothelial cell and acts in the local environment to cause relaxation of the underlying smooth muscle or to inhibit platelet aggregation. Both actions are mediated by the stimulation of adenylyl cyclase in the target cell to produce cyclic adenosine monophosphate (cAMP).

It has been shown that many physiologic stimuli cause vasodilation by stimulating the release of a labile, diffusible, nonprostanoid molecule termed *endothelium-derived relaxing factor* (EDRF), now known to be nitric oxide (NO). NO is a very small lipophilic molecule that can readily diffuse across biologic membranes and into the cytosol of nearby cells. The half-life of the molecule is less than 5 seconds so that only the local environment can be affected. NO is synthesized from the amino acid L-arginine by NO synthase (NOS). When NO diffuses into the cytosol of the target cell, it binds with the heme group of soluble guanylate cyclase; the result is a 50- to 200-fold increase in production of cyclic guanosine monophosphate (cGMP), its secondary messenger. If the target cells are vascular smooth muscle cells, vasodilation occurs; if the target cells are platelets, adhesion and aggregation are inhibited. NO is probably the final common effector molecule of nitrovasodilators. The cardiovascular system is in a constant state of active vasodilation that depends on the generation of NO. The molecule is more important in controlling vascular tone in veins and arteries compared with arterioles. Abnormalities in the ability of the endothelium to produce NO likely play a role in diseases such as diabetes, atherosclerosis, and hypertension. The venous circulation of humans seems to have a lower basal release of NO and an increased sensitivity to nitrovasodilators compared with the arterial side of the circulation.

Endothelium-Derived Contracting Factors

Contracting factors produced by the endothelium include prostaglandin H_2, thromboxane A_2 (generated by cyclooxygenase), and the peptide endothelin. Endothelin is a potent vasoconstrictor peptide (100-fold more potent than norepinephrine). In vascular smooth muscle cells, endothelin 1 (ET-1) binds to specific membrane receptors

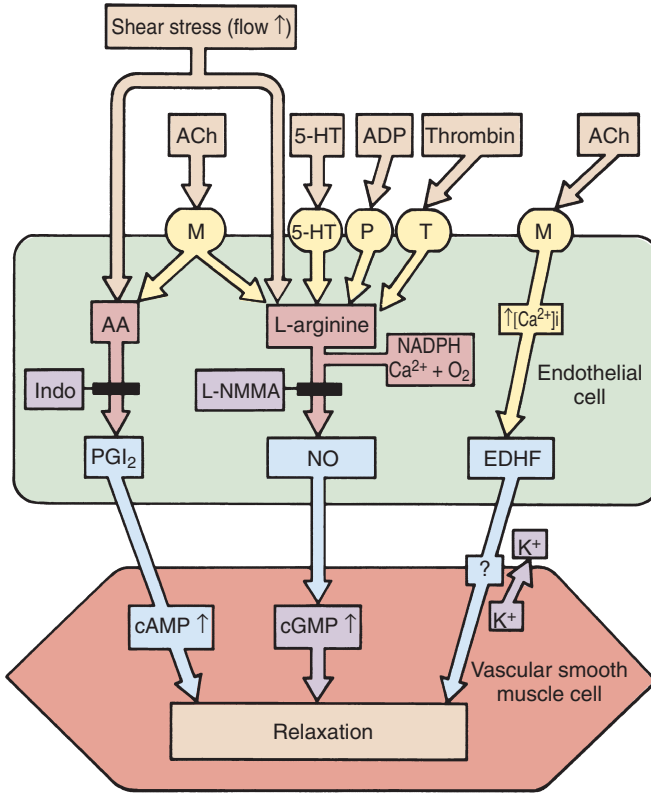
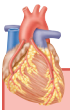


Fig. 5.1 The production of endothelium-derived vasodilator substances. Prostacyclin *(PGI_2)* is produced by the cyclooxygenase pathway of arachidonic acid *(AA)* metabolism, which can be blocked by indomethacin *(Indo)* and aspirin. PGI_2 stimulates smooth muscle adenylyl cyclase and increases cyclic adenosine monophosphate *(cAMP)* production, actions that cause relaxation. Endothelium-derived relaxing factor *(EDRF),* now known to be nitric oxide *(NO),* is produced by the action of NO synthase on L-arginine in the presence of reduced nicotinamide adenine dinucleotide phosphate *(NADPH),* oxygen *(O_2),* and calcium *(Ca^{2+})* and calmodulin. This process can be blocked by arginine analogs such as N^G-monomethyl-L-arginine *(LNMMA).* NO combines with guanylate cyclase in the smooth muscle cell to stimulate production of cyclic guanosine monophosphate *(cGMP),* which results in relaxation. Less well characterized is an endothelium-derived hyperpolarizing factor *(EDHF),* which hyperpolarizes the smooth muscle membrane and probably acts by activation of potassium *(K^+)* channels. *ACh,* Acetylcholine; *ADP,* adenosine diphosphate; *$[Ca^{2+}]_i$,* intracellular calcium; *5-HT,* serotonin; *M,* muscarinic receptor; *P,* purinergic receptor; *T,* thrombin receptor. (From Rubanyi GM. Endothelium, platelets, and coronary vasospasm. *Coron Artery Dis.* 1990;1:645.)

(ET_A) and, through phospholipase C, induces an increase in intracellular calcium resulting in long-lasting contractions. It is also linked by a guanosine triphosphate (GTP)-binding protein (G_i) to voltage-operated calcium channels. This peptide has greater vasoconstricting potency than any other cardiovascular hormone, and in pharmacologic doses it can abolish coronary flow, thereby leading to ventricular fibrillation and death.

Endothelial Inhibition of Platelets

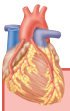
A primary function of endothelium is to maintain the fluidity of blood. This is achieved by the synthesis and release of anticoagulant (eg, thrombomodulin, protein C), fibrinolytic (eg, tissue-type plasminogen activator), and platelet inhibitory



BOX 5.1 *Endothelium-Derived Relaxing and Contracting Factors*

Healthy endothelial cells have an important role in modulating coronary tone by producing:

- vascular muscle-relaxing factors
  - prostacyclin
  - nitric oxide
  - hyperpolarizing factor
- vascular muscle-contracting factors
  - prostaglandin H_2
  - thromboxane A_2
  - endothelin



BOX 5.2 *Endothelial Inhibition of Platelets*

Healthy endothelial cells have a role in maintaining the fluidity of blood by producing:

- anticoagulant factors: protein C and thrombomodulin
- fibrinolytic factor: tissue-type plasminogen activator
- platelet inhibitory substances: prostacyclin and nitric oxide

(eg, PGI_2, NO) substances (Box 5.2). Mediators released from aggregating platelets stimulate the release from intact endothelium of NO and PGI_2, which act together to increase blood flow and decrease platelet adhesion and aggregation (Fig. 5.2).

DETERMINANTS OF CORONARY BLOOD FLOW

Under normal conditions, coronary blood flow has four major determinants: (1) perfusion pressure; (2) myocardial extravascular compression; (3) myocardial metabolism; and (4) neurohumoral control.

Perfusion Pressure and Myocardial Compression

Coronary blood flow is proportional to the pressure gradient across the coronary circulation (Box 5.3). This gradient is calculated by subtracting downstream coronary pressure from the pressure in the root of the aorta.

During systole, the heart throttles its own blood supply. The force of systolic myocardial compression is greatest in the subendocardial layers, where it approximates intraventricular pressure. Resistance resulting from extravascular compression increases with blood pressure, heart rate, contractility, and preload.

The most appropriate measure of the driving pressure for flow is the average pressure in the aortic root during diastole. This value can be approximated by aortic diastolic or mean pressure.

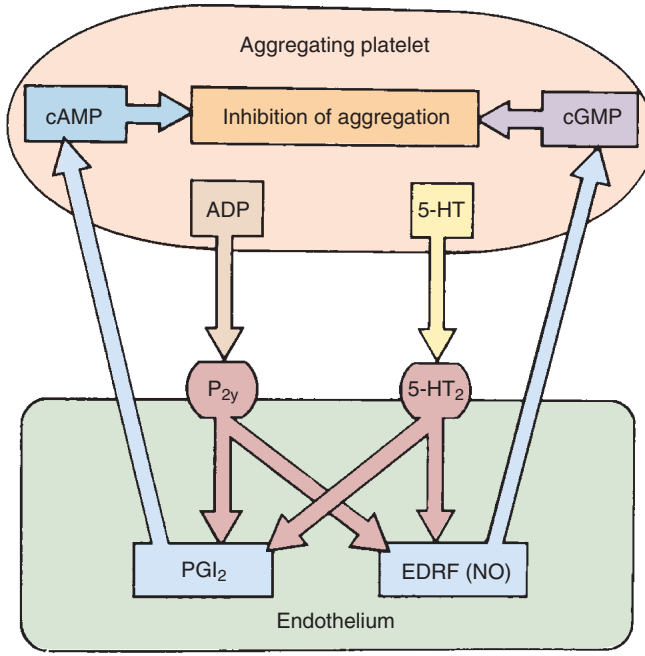
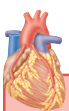


Fig. 5.2 Inhibition of platelet adhesion and aggregation by intact endothelium. Aggregating platelets release adenosine diphosphate *(ADP)* and serotonin *(5-HT),* which stimulate the synthesis and release of prostacyclin (*PGI_2*) and endothelium-derived relaxing factor (*EDRF;* nitric oxide *[NO]*), which diffuse back to the platelets and inhibit further adhesion and aggregation and can cause disaggregation. PGI_2 and EDRF act synergistically by increasing platelet cyclic adenosine monophosphate *(cAMP)* and cyclic guanosine monophosphate *(cGMP),* respectively. By inhibiting platelets and also increasing blood flow by causing vasodilation, PGI_2 and EDRF can flush away microthrombi and prevent thrombosis of intact vessels. *P_{2y}*, Purinergic receptor. (From Rubanyi GM. Endothelium, platelets, and coronary vasospasm. *Coron Artery Dis.* 1990;1:645.)



BOX 5.3 *Determinants of Coronary Blood Flow*

The primary determinants of coronary blood flow are:

- perfusion pressure
- myocardial extravascular compression
- myocardial metabolism
- neurohumoral control

Although the true downstream pressure of the coronary circulation is likely close to the coronary sinus pressure, other choices may be more appropriate in clinical circumstances. The true downstream pressure of the left ventricular subendocardium is the left ventricular end-diastolic pressure, which can be estimated by pulmonary artery occlusion pressure. When the right ventricle is at risk of ischemia (eg, severe pulmonary hypertension), right ventricular diastolic pressure or central venous pressure may be a more appropriate choice for measuring downstream pressure.

Myocardial Metabolism

Myocardial blood flow is primarily under metabolic control. Even when the heart is cut off from external control mechanisms (neural and humoral factors), its ability to match blood flow to its metabolic requirements is almost unaffected. Because coronary venous oxygen tension is normally 15 to 20 mm Hg, only a small amount of oxygen is available through increased extraction. A major increase in myocardial oxygen consumption ($M\dot{V}O_2$), beyond the normal resting value of 80 to 100 mL O_2/100 g of myocardium, can occur only if oxygen delivery is increased by augmentation of coronary blood flow. Normally, flow and metabolism are closely matched, so that over a wide range of oxygen consumption coronary sinus oxygen saturation changes little. Flow and metabolism could be coupled either through feedback or feedforward control or a combination of both. Feedback control requires myocardial oxygen tension to fall and provide a signal that can then increase flow. That would require vascular tone to be linked either to a substrate that is depleted, such as oxygen or adenosine triphosphate (ATP), or to the accumulation of a metabolite such as carbon dioxide or hydrogen ion. The mediator or mediators linking myocardial metabolism so effectively to myocardial blood flow are still unknown (Box 5.4).

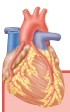
Neural and Humoral Control

Coronary Innervation

The heart is supplied with branches of the sympathetic and parasympathetic divisions of the autonomic nervous system. Large and small coronary arteries and veins are richly innervated. The sympathetic nerves to the heart and coronary vessels arise from the superior, middle, and inferior cervical sympathetic ganglia and the first four thoracic ganglia. The stellate ganglion (formed when the inferior cervical and first thoracic ganglia merge) is a major source of cardiac sympathetic innervation. The vagus nerve supplies the heart with efferent cholinergic nerves.

Parasympathetic Control

Vagal stimulation causes bradycardia, decreased contractility, and lower blood pressure. The resultant fall in $M\dot{V}O_2$ causes metabolically mediated coronary vasoconstriction. These effects can be abolished by atropine.



BOX 5.4 ***Myocardial Metabolism***

Several molecules have been proposed as the link between myocardial metabolism and myocardial blood flow, including:

- oxygen
- reactive oxygen species
- carbon dioxide
- adenosine

Current evidence suggests that a combination of local factors, each with differing importance during rest, exercise, and ischemia, acts together to match myocardial oxygen delivery to demand.

β-Adrenergic Coronary Dilation

β-Receptor activation causes dilation of both large and small coronary vessels, even in the absence of changes in blood flow.

α-Adrenergic Coronary Constriction

Activation of the sympathetic nerves to the heart results in increases in heart rate, contractility, and blood pressure that lead to a marked, metabolically mediated increase in coronary blood flow. The direct effect of sympathetic stimulation is coronary vasoconstriction, which is in competition with the metabolically mediated dilation of exercise or excitement. Whether adrenergic coronary constriction is powerful enough to diminish blood flow in ischemic myocardium further or whether it can have some beneficial effect in the distribution of myocardial blood flow is controversial.

CORONARY PRESSURE-FLOW RELATIONS

Autoregulation

Autoregulation is the tendency for organ blood flow to remain constant despite changes in arterial perfusion pressure. Autoregulation can maintain flow to myocardium served by stenotic coronary arteries despite low perfusion pressure distal to the obstruction. This is a local mechanism of control and can be observed in isolated, denervated hearts. If $M\dot{V}O_2$ is fixed, coronary blood flow remains relatively constant between mean arterial pressures of 60 and 140 mm Hg.

Coronary Reserve

Myocardial ischemia causes intense coronary vasodilation. After a 10- to 30-second coronary occlusion, restoration of perfusion pressure is accompanied by a marked increase in coronary flow. This large increase in flow, which can be five or six times resting flow, is termed *reactive hyperemia*. The repayment volume is greater than the debt volume. However, no overpayment of the oxygen debt occurs because oxygen extraction falls during the hyperemia. The presence of high coronary flows when coronary venous oxygen content is high suggests that mediators other than oxygen are responsible for this metabolically induced vasodilation. The difference between resting coronary blood flow and peak flow during reactive hyperemia represents the autoregulatory coronary flow reserve—the further capacity of the arteriolar bed to dilate in response to ischemia.

Transmural Blood Flow

When coronary perfusion pressure is inadequate, the inner one-third to one-fourth of the left ventricular wall is the first region to become ischemic or necrotic. This increased vulnerability of the subendocardium may reflect an increased demand for perfusion or a decreased supply, compared with the outer layers.

If coronary artery pressure is gradually reduced, autoregulation is exhausted, and flow decreases in the inner layers of the left ventricle before it begins to decrease in the outer layers (Fig. 5.3). This finding indicates less flow reserve in the subendocardium than in the subepicardium. Three mechanisms have been proposed to explain the decreased coronary reserve in the subendocardium: (1) differential systolic intramyocardial pressure; (2) differential diastolic intramyocardial pressure; and (3) interactions between systole and diastole.

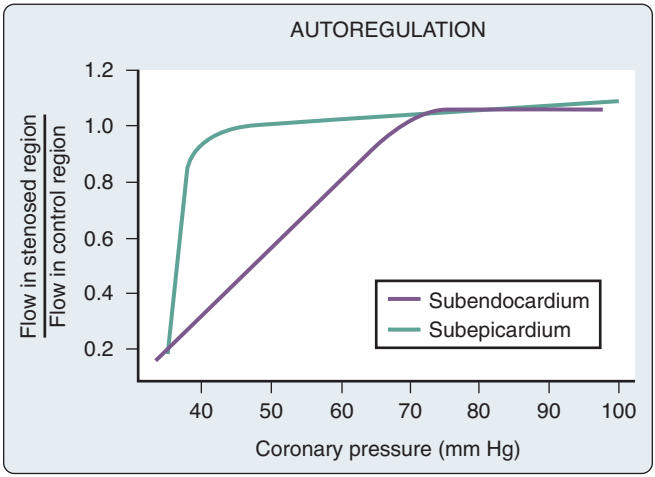
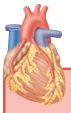


Fig. 5.3 Pressure-flow relationships of the subepicardial and subendocardial thirds of the left ventricle in anesthetized dogs. In the subendocardium, autoregulation is exhausted and flow becomes pressure-dependent when pressure distal to a stenosis falls to less than 70 mm Hg. In the subepicardium, autoregulation persists until perfusion pressure falls to less than 40 mm Hg. Autoregulatory coronary reserve is less in the subendocardium. (Redrawn from Guyton RA, McClenathan JH, Newman GE, Michaelis LL. Significance of subendocardial ST segment elevation caused by coronary stenosis in the dog. *Am J Cardiol.* 1977;40:373.)



BOX 5.5 ***Atherosclerosis***

- The atherosclerotic process begins in childhood and adolescence.
- The progression of an atherosclerotic lesion resembles the process of wound healing.
- Inflammation, lipid infiltration, and smooth muscle proliferation have important roles in atherogenesis.
- Impairment of endothelial function is an early consequence of atherosclerosis.
- Statin therapy has been shown to improve endothelial function, impede development of atherosclerosis, and, in some cases, reverse established disease.

ATHEROSCLEROSIS

The atherosclerotic lesion consists of an excessive accumulation of smooth muscle cells in the intima, with quantitative and qualitative changes in the noncellular connective tissue components of the artery wall and intracellular and extracellular deposition of lipoproteins and mineral components (eg, calcium) (Box 5.5). By definition, *atherosclerosis* is a combination of "atherosis" and "sclerosis." The term *sclerosis* refers to the hard, collagenous material that accumulates in lesions and is usually more voluminous than the pultaceous "gruel" of the atheroma (Fig. 5.4).

The earliest detectable change in the evolution of coronary atherosclerosis is the accumulation of intracellular lipid in the subendothelial region that gives rise to lipid-filled macrophages or "foam cells." Grossly, a collection of foam cells may give the artery wall the appearance of a "fatty streak." In general, fatty streaks are covered by a layer of intact endothelium and are not characterized by excessive smooth muscle cell accumulation. At later stages of atherogenesis, extracellular lipoproteins accumulate

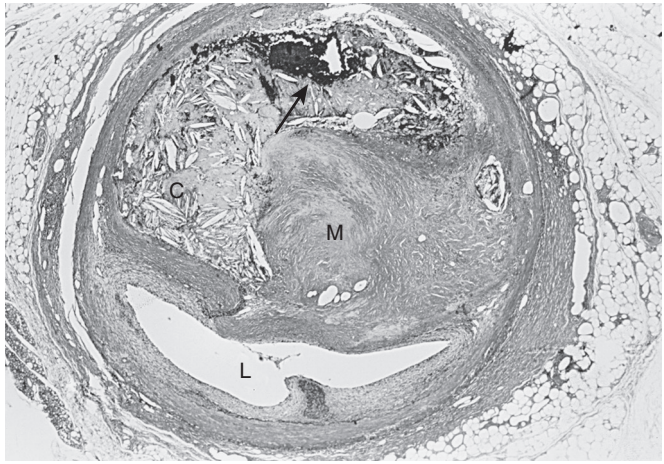


Fig. 5.4 Atherosclerotic human coronary artery of an 80-year-old man. He has severe narrowing of the central arterial lumen *(L).* The intima consists of a complex collection of cells, extracellular matrix *(M),* and a necrotic core with cholesterol *(C)* deposits. Rupture of plaque microvessels has resulted in intraplaque hemorrhage *(arrow)* at the base of the necrotic core (Movat's pentachrome–stained slide; original magnification ×40).

in the musculoelastic layer of the intima and eventually form an avascular core of lipid-rich debris that is separated from the central arterial lumen by a fibrous cap of collagenous material. Foam cells are not usually seen deep within the atheromatous core but are frequently found at the periphery of the lipid core.

Arterial Wall Inflammation

Monocytes or macrophages and T lymphocytes are found in arteries not only with advanced lesions but also in arteries with early atherosclerotic lesions in young adults. Leukocyte infiltration into the vascular wall is known to precede smooth muscle cell hyperplasia. Once inside the artery wall, mononuclear cells may play several important roles in lesion development. For example, monocytes may transform into macrophages and become involved in the local oxidation of low-density lipoproteins (LDLs) and accumulation of oxidized LDLs. Alternatively, macrophages in the artery wall may act as a rich source of factors that promote cell proliferation, migration, or the breakdown of local tissue barriers. The process of local tissue degradation may be important for the initiation of acute coronary artery syndromes because loss of arterial wall integrity may lead to plaque fissuring or rupture.

Role of Lipoproteins in Lesion Formation

The clinical and experimental evidence linking dyslipidemias with atherogenesis is well established. However, the exact mechanisms by which lipid moieties contribute to the pathogenesis of atherosclerosis remain elusive. Although the simple concept of cholesterol accumulating in artery walls until flow is obstructed may be correct in certain animal models, this theory is not correct for human arteries.

One of the major consequences of cholesterol accumulation in the artery wall is thought to be impairment of endothelial function. The endothelium is more than a physical barrier between the bloodstream and the artery wall. Under normal conditions,

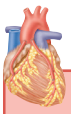
the endothelium is capable of modulating vascular tone (eg, through NO), thrombogenicity, fibrinolysis, platelet function, and inflammation. In the presence of traditional risk factors, particularly dyslipidemias, these protective endothelial functions are reduced or lost. The loss of these endothelium-derived functions may occur in the presence or absence of an underlying atherosclerotic plaque and may simply imply that atherogenesis has begun. Aggressive attempts to normalize atherosclerotic risk factors (eg, diet and lipid-lowering therapies) may markedly attenuate endothelial dysfunction, even in the presence of extensive atherosclerosis. Some clinical studies demonstrated dramatic improvements in endothelial function, as well as in cardiovascular morbidity and mortality, with the use of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, or "statins."

PATHOPHYSIOLOGY OF CORONARY BLOOD FLOW

Coronary Artery Stenoses and Plaque Rupture

Coronary atherosclerosis is a chronic disease that develops over decades and remains clinically silent for prolonged periods (Box 5.6). Clinical manifestations of CAD occur when the atherosclerotic plaque mass encroaches on the vessel lumen and obstructs coronary blood flow to cause angina. Alternatively, cracks or fissures may develop in the atherosclerotic lesions and result in acute thromboses that cause unstable angina or myocardial infarction.

Patients with stable angina typically have lesions with smooth borders on angiography. Only a few coronary lesions are concentric; most have complex geometry varying in shape over their length. Eccentric stenoses, with a remaining pliable, musculoelastic arc of normal wall, can vary in diameter and resistance in response to changes in vasomotor tone or intraluminal pressure. Most human coronary artery stenoses are compliant. The intima of the normal portion of the vessel wall is often thickened, thus making endothelial dysfunction probable. In contrast, patients with unstable angina usually have lesions characterized by overhanging edges, scalloped or irregular borders, or multiple irregularities. These complicated stenoses likely represent ruptured plaque or partially occlusive thrombus, or both. On angiography these lesions may appear segmental, confined to a short segment of an otherwise normal proximal coronary artery. At autopsy, however, the most common pathologic finding is *diffuse* vessel involvement with superimposed segmental obstruction of greater severity. In a diffusely narrowed vessel, even modest progression of luminal narrowing can be significant. In such an artery, rating the significance of the obstruction by the percentage of diameter reduction relative to adjacent vessel segments



BOX 5.6 ***Pathophysiology of Coronary Blood Flow***

- In most patients experiencing a myocardial infarction, the coronary occlusion occurs at the site of less than 50% stenosis.
- Plaque rupture leads to incremental growth of coronary stenoses and can cause coronary events.
- Plaque rupture occurs at the shoulder of the plaque where inflammatory cells are found.

underestimates its physiologic importance. Therefore understanding the characteristics of atherosclerotic plaques is of central importance to the management of acute coronary artery syndromes.

The intuitive notion that the severity of coronary artery stenoses should correlate with the risk of complications from CAD was disproved. The coronary angiograms of 38 patients who had had Q-wave myocardial infarction in the interval between serial studies were reviewed. On the preinfarct angiograms, the mean percentage of stenosis at the coronary segment that was later responsible for infarction was only 34%. Therefore, although the revascularization of arteries with critical stenoses in target lesions is appropriately indicated to reduce symptoms and myocardial ischemia, a risk of further cardiac events remains because atherosclerosis is a diffuse process, and mild or modest angiographic stenoses are more likely to result in subsequent myocardial infarction than are severe stenoses.

With this background comes the problem of predicting which arterial segments with minimal angiographic disease will later develop new critical stenoses. Superficial intimal injury (plaque erosions) and intimal tears of variable depth (plaque fissures) with overlying microscopic mural thrombosis are commonly found in atherosclerotic plaques. In the absence of obstructive luminal thrombosis, these intimal injuries do not cause clinical events. However, disruption of the fibrous cap, or plaque rupture, is a more serious event that typically results in the formation of clinically significant arterial thromboses. From autopsy studies it is known that rupture-prone plaques tend to have a thin, friable fibrous cap. The site of plaque rupture is thought to be the shoulder of the plaque, in which substantial numbers of mononuclear inflammatory cells are commonly found. The mechanisms responsible for the local accumulation of these cells at this location in the plaque are unknown; presumably, monocyte chemotactic factors, the expression of leukocyte cell adhesion molecules, and specific cytokines are involved. Currently, no effective strategies have been designed to limit the possibility of plaque rupture; however, aggressive lipid-lowering therapy may be a helpful preventive measure.

Hemodynamics

If accurate angiographic assessment of the geometry of a coronary stenosis is made, hydrodynamic principles can be used to estimate the physiologic significance of the obstruction.

Resting flow remains constant as lumen diameter decreases because the coronary arterioles progressively dilate, thereby reducing the resistance of the distal coronary bed sufficiently to compensate for the resistance of the stenosis. As the severity of the stenosis increases further, the arteriolar bed can no longer compensate, and flow begins to fall. As stenosis severity increases, distal perfusion pressure falls, arterioles dilate to maintain flow until autoregulation is exhausted (in the subendocardium first), and flow becomes pressure-dependent.

The frequently used term *critical stenosis* is usually defined as coronary constriction sufficient to prevent an increase in flow over resting values in response to increased myocardial oxygen demands. This is a greater degree of obstruction than angiographically significant stenosis, which is usually defined as a reduction in cross-sectional area of 75%, equivalent to a 50% decrease in the diameter of a concentric stenosis.

Coronary Collaterals

Coronary collaterals are anastomotic connections, without an intervening capillary bed, between different coronary arteries or between branches of the same artery. In

the normal human heart, these vessels are small and have little or no functional role. In patients with CAD, well-developed coronary collateral vessels may play a critical role in preventing death and myocardial infarction. Individual differences in the capability of developing a sufficient collateral circulation are determinants of the vulnerability of the myocardium to coronary occlusive disease.

In humans, perfusion through collaterals can equal perfusion through a vessel with a 90% diameter obstruction. Although coronary collateral flow can be sufficient to preserve structure and resting myocardial function, muscle dependent on collateral flow usually becomes ischemic when oxygen demand rises to more than resting levels. Among patients with stable CAD, the presence of "high collateralization" is associated with a reduction in mortality rates of greater than 30% compared with patients with low collateralization. It is possible that evidence from patients with angina underestimates collateral function of the population of all patients with CAD. Perhaps persons with coronary obstructions but excellent collateralization remain asymptomatic and are not studied.

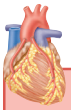
PATHOGENESIS OF MYOCARDIAL ISCHEMIA

Ischemia is the condition of oxygen deprivation accompanied by inadequate removal of metabolites consequent to reduced perfusion. Clinically, myocardial ischemia is a decrease in the blood flow supply-to-demand ratio that results in impaired function. No universally accepted gold standard exists for the presence of myocardial ischemia. In practice, symptoms, ECG changes, anatomic findings, and evidence of myocardial dysfunction must be combined before concluding that myocardial ischemia is present.

Determinants of Ratio of Myocardial Oxygen Supply to Demand

An increase in myocardial oxygen requirement beyond the capacity of the coronary circulation to deliver oxygen results in myocardial ischemia (Box 5.7). This is the most common mechanism leading to ischemic episodes in chronic stable angina and during exercise testing. Intraoperatively, the anesthesiologist must measure and control the determinants of $M\dot{V}O_2$ and protect the patient from "demand" ischemia. The major determinants of $M\dot{V}O_2$ are heart rate, myocardial contractility, and wall stress (chamber pressure × radius/wall thickness).

An increase in heart rate can reduce subendocardial perfusion by shortening diastole. Coronary perfusion pressure may fall in response to reduced systemic pressure or increased left ventricular end-diastolic pressure (LVEDP). With the onset of ischemia, perfusion may be further compromised by delayed ventricular relaxation (decreased



BOX 5.7 ***Determinants of Myocardial Oxygen Supply-to-Demand Ratio***

The major determinants of myocardial oxygen consumption are:
- heart rate
- myocardial contractility
- wall stress (chamber pressure × radius/wall thickness)

subendocardial perfusion time) and decreased diastolic compliance (increased LVEDP). Anemia and hypoxia can also compromise delivery of oxygen to the myocardium.

Dynamic Stenosis

Patients with CAD can have variable exercise tolerance during the day and between days. Ambulatory monitoring of the electrocardiogram has demonstrated that ST-segment changes indicative of myocardial ischemia, in the absence of changes in oxygen demand, are common. These findings are explained by variations over time in the severity of the obstruction to blood flow imposed by coronary stenoses.

Although the term *hardening of the arteries* suggests rigid, narrowed vessels, in fact most stenoses are eccentric and have a remaining arc of compliant tissue. A modest amount (10%) of shortening of the muscle in the compliant region of the vessel can cause dramatic changes in lumen caliber. The term *spasm* is reserved for "situations where coronary constriction is both focal, sufficiently profound to cause transient coronary occlusion, and is responsible for reversible attacks of angina at rest" (ie, variant angina). Although this syndrome is rare, lesser degrees of obstruction in response to vasoconstrictor stimuli are common among patients with CAD.

Coronary Steal

Steal occurs when the perfusion pressure for a vasodilated vascular bed (in which flow is pressure-dependent) is lowered by vasodilation in a parallel vascular bed, with both beds usually distal to a stenosis. Two kinds of coronary steal are illustrated: collateral and transmural (Fig. 5.5).

Fig. 5.5A shows collateral steal in which one vascular bed (R_3), distal to an occluded vessel, is dependent on collateral flow from a vascular bed (R_2) supplied by a stenotic artery. Because collateral resistance is high, the R_3 arterioles are dilated to maintain flow in the resting condition (autoregulation). Dilation of the R_2 arterioles increases flow across the stenosis R_1 and decreases pressure P_2. If R_3 resistance cannot further decrease sufficiently, flow there decreases, thus producing or worsening ischemia in the collateral-dependent bed.

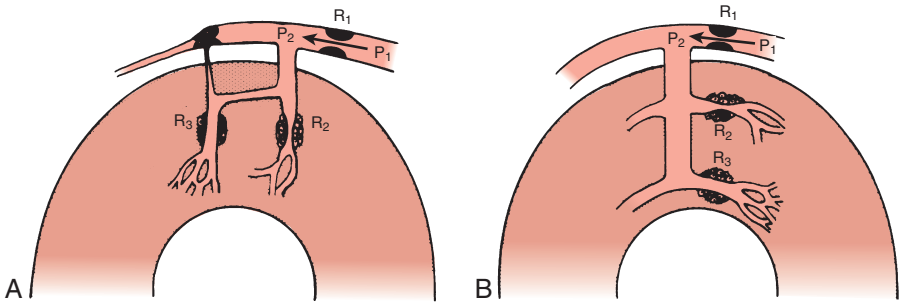


Fig. 5.5 Conditions for coronary steal in different areas of the heart and between the subendocardial and subepicardial layers of the left ventricle. (A) Collateral steal. (B) Transmural steal. See text for details. *P_1*, Aortic pressure; *P_2*, pressure distal to the stenosis; *R_1*, stenosis resistance; *R_2* and *R_3*, resistance of autoregulating and pressure-dependent vascular beds, respectively. (From Epstein SE, Cannon RO, Talbot TL. Hemodynamic principles in the control of coronary blood flow. *Am J Cardiol.* 1985;56:4E.)

Transmural steal is illustrated in Fig. 5.5B. Normally, vasodilator reserve is less in the subendocardium. In the presence of stenosis, flow may become pressure-dependent in the subendocardium, whereas autoregulation is maintained in the subepicardium.

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