

FEATURES

Dynamic mechanisms in human coronary stenosis

B. GREG BROWN, M.D., PH.D., EDWARD L. BOLSON, M.S., AND HAROLD T. DODGE, M.D.

CORONARY STENOSES behave in a dynamic fashion. One needs only to interview patients to reach this conclusion. Most anginal syndromes are exertional, but the effort threshold for pain is commonly variable; angina may occur with very little activity on arising despite a surprisingly good exercise capacity later in the day. Emotional stress, exposure to cold, and isometric handgrip can lower the anginal threshold or even provoke pain de novo. Conversely, in the variant angina syndrome, episodes of severe transmural ischemia commonly occur at rest or even during sleep but are frequently not provoked by exercise or emotional stress.¹ Paradoxically, potent dilators of the coronary arteriolar resistance bed may provoke angina.² Clinical episodes of coronary insufficiency may develop in a crescendo pattern and mysteriously ameliorate with rest and symptomatic therapy. Our understanding of the dynamic mechanisms in coronary stenosis that account for this spectrum of clinical observations is currently incomplete. But new insights continue to emerge from such diverse fields as fluid dynamics, pathologic anatomy, smooth muscle physiology, pharmacology, vascular biology, thrombosis, and arteriography. We will attempt to provide a current perspective on the interaction among stenosis blood flow, morphologic features of the atherosclerotic lesion, and mechanisms of arterial vasomotion, each of which may contribute to this dynamic behavior.

Hemodynamic effects

Energy (pressure) is lost as blood traverses a stenosis. The myocardial microvasculature has a substantial vasodilatory reserve to compensate for reduced perfu-

sion pressure distal to a stenosis. Thus flow is maintained by distal arteriolar dilation in the face of increasing stenosis severity. This reserve is exhausted first in the subendocardial zone when distal pressure falls below about 55 mm Hg. Thus pressure loss in the stenosis is an important determinant of ischemia. To estimate this loss, the appropriate principles of fluid mechanics have been adapted to the geometry of the nonuniform stenosis lumen encountered in practice.³ This adaptation has been validated experimentally.⁴ The following expression provides a good approximation of the hemodynamic behavior of a typical high-grade human coronary stenosis³:

$$\Delta P_s = \frac{1.8 Q_s}{d_{\min}^4} + \frac{6.1 Q_s^2}{d_{\min}^5}$$

This expression for calculating the drop in stenosis pressure (ΔP_s , mm Hg) in terms of stenosis flow (Q_s , ml/sec) and minimum lumen diameter (d_{\min} , mm) characterizes the principal modes of energy loss in the stenosis. The first term accounts for frictional losses caused by blood viscosity. The second term accounts for a transfer of energy, first from the "pressure energy" of normal arterial flow to the kinetic energy of high-velocity stenosis flow, and then to the turbulent energy of distal flow eddies. As blood accelerates in flowing to the point of greatest narrowing, pressure falls but total energy is conserved; the irreversible energy loss occurs distally as most of this kinetic energy is transferred to turbulent eddies that form in the region of stenosis flow separation and then dissipate by viscous processes.

There are two salient features of the above expression. First, when flow is normal (approximately 1.1 ml/sec in the left anterior descending coronary artery [LAD]), over 75% of the loss is due to the turbulent term, in which the square of flow appears. Thus, for clinical reasoning, the viscous (first) term may be neglected except in the case of exceedingly long tubular stenoses. Second, a stenosis in the LAD approaches

From the Department of Medicine, Cardiology Division, University of Washington School of Medicine, Seattle.

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Address for correspondence: B. Greg Brown, M.D., Ph.D., Cardiology Division RG-22, University of Washington Hospital, Seattle, WA 98195.

Dr. Brown is an Established Investigator of the American Heart Association.

hemodynamic significance when its minimum diameter approaches 1 mm; in general, any coronary stenosis approaches physiologic importance as its flow/minimum area ratio approaches about 130 cm/sec. Thus smaller branches, with less flow demand, would have a correspondingly smaller diameter of critical stenosis. We found, for example, that minimum stenosis lumen diameter averaged 0.88 mm in patients with refractory unstable angina and proximal single-vessel disease.³ In similar patients with subendocardial infarction this value averaged 0.64 mm. In this range, because of the inverse fourth-power effect, small changes (e.g., 0.1 to 0.2 mm) in minimum lumen diameter have large effects on stenosis resistance and thus, potentially, on myocardial perfusion.

The Q_s^2 term in the expression for stenosis loss becomes physiologically important in three common situations. (1) Exercise, which can cause a fourfold increase in coronary flow, should thus increase pressure loss by 16-fold in a fixed stenosis. This would be physiologically impossible in the case of a high-grade lesion. Instead, the exertional increase in regional perfusion is blunted.⁵ (2) Anemia is poorly tolerated in the presence of a critical coronary stenosis. Since the myocardium cannot greatly increase its already large fractional oxygen extraction, anemia must be compensated in large part by increased coronary flow, for which distal myocardial perfusion pressure pays a Q_s^2 penalty. And since blood viscosity is not a factor in the dominant turbulent component of resistance, its reduction with anemia is of little advantage in the arterial stenosis. (3) Pharmacologic vasodilation of the coronary arteriolar resistance bed, which occurs with drugs such as dipyridamole, hydralazine, and nifedipine, may increase the stenosis flow and pressure loss and result in an adverse redistribution of perfusion ("steal") from the subendocardium to the subepicardium.^{2, 6}

Effects of stenosis morphology

"Hardening of the arteries" refers to the palpably rigid texture of atherosclerotic arterial segments. This term has fostered the misconception that stenoses are "fixed" in a rigidly immobile shell of calcified, cholesterol-laden fibrotic atheroma. Stenosis morphology is actually variable; some diseased segments fit the above description and are indeed fixed. But most lesions have a morphology similar to that of the histologic section of figure 1, which was cut through a surgically resected stenosis of the right coronary artery responsible for the variant angina syndrome. Lesions of such morphology are not limited to patients with classic spasm, but they are typical of the majority of all

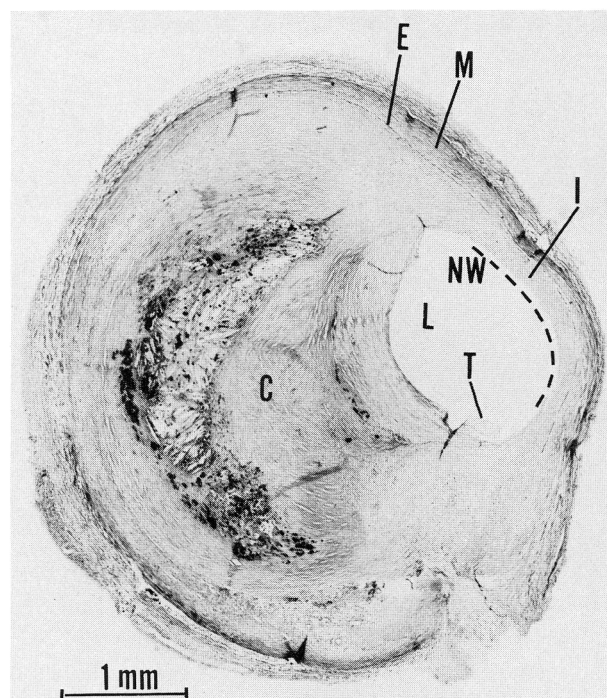


FIGURE 1. Histologic section cut through a pressure-fixed stenosis of the right coronary artery surgically resected from a patient with variant angina. E = internal elastic lamina; M = arterial media; I = intimal smooth muscle; L = lumen; T = focal mural thrombus; C = collagen (fibrosis) surrounding crystalline cholesterol deposit; NW = the arc of normal wall partly surrounding the remaining lumen.

coronary stenoses. Histologic sections cut through pressure-fixed diseased arterial segments display the morphologic spectrum illustrated in figure 2. In about 70% of these significantly narrowed ($\geq 50\%$) histologic sections, the residual arterial lumen was considered eccentric and was partially circumscribed by an arc of at least 60 degrees of normal arterial wall.⁷ Usually the intima of this normal wall is mildly thickened. This observation is extremely important for the understanding of dynamic stenosis behavior. The presence of this pliable, musculoelastic arc of normal wall in 70% of all significantly diseased arterial segments provides a mechanism whereby variations in intraluminal pressure and/or vasomotor tone may affect lumen caliber and thus flow resistance. This is particularly important when we recall that changes in lumen diameter of 0.1 to 0.2 mm can substantially alter the flow resistance of a high-grade proximal arterial lesion.

Thus the majority of human coronary stenoses are compliant. The implications of this concept and some supportive observations are presented below.

Effects of active vasoconstriction

If the compliant stenosis contains a normal mural arc, then drugs and stresses that constrict the normal arterial wall should have a comparable effect on the

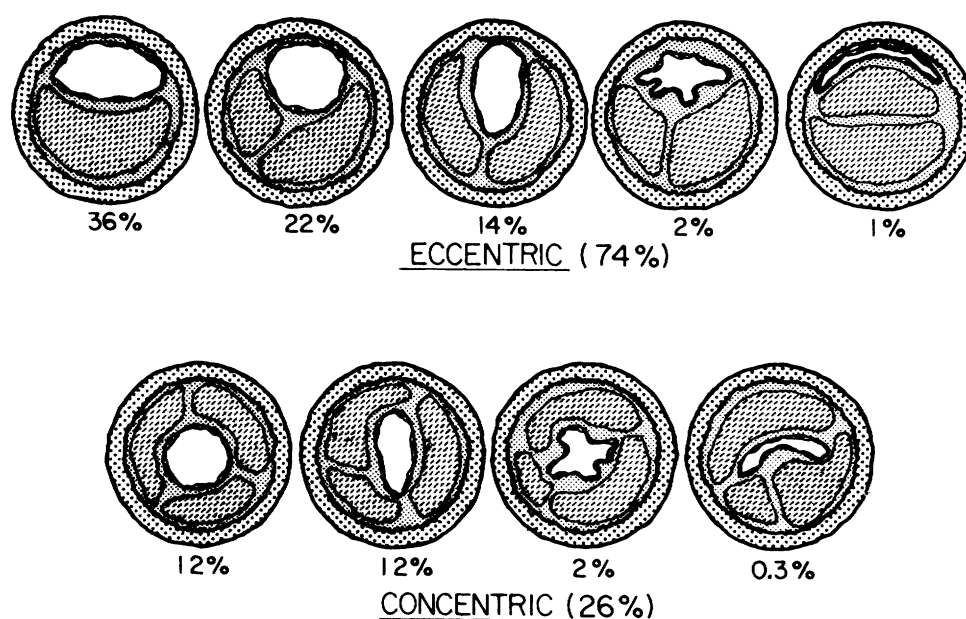


FIGURE 2. Idealized drawings of the various types of lesion structure observed in histologic sections cut through diseased coronary arteries. Approximately three-fourths of all significantly obstructed vessels demonstrated the potential for compliant behavior by having at least 16% of the residual lumen surrounded by an arc of normal wall. (Adapted from Freudenberg H, Lichtlen PR: *Z Kardiol* 70: 863, 1981.)

compliant stenosis. In fact, the morphology of certain stenoses (e.g., upper right section in figure 2) may amplify the effects of ordinary amounts of smooth muscle shortening to produce severe transient focal obstruction. Although drug effects on human coronary tone have been reported,⁸ little is known of the magnitude of inducible shortening or lengthening of human coronary smooth muscle. However, we have accumulated a considerable body of data on the effects of a number of agents on arteriographic coronary lumen diameter. With use of the approximation that normal arterial wall thickness is one-tenth of normal lumen diameter, it is possible to derive circumferential changes in smooth muscle length from changes in measured diameter. These estimates, based on studies of 1117 angiographically normal arterial segments in 227 patients, are presented in figure 3. Two points are obvious. First, the magnitude of mural smooth muscle vasomotion is greater in the proximal epicardial arteries (2.0 to 2.8 mm dia.) or the mid vessels and their major branches (1.0 to 2.0 mm) than in the larger arteries of the size of the left main (4.0 to 5.0 mm). Second, there appear to be four classes of vasoactive stimuli: (1) the "nitro" drugs (nitroglycerin, isosorbide dinitrate, and nitroprusside) and prostaglandin (PG) E₁ appear to be effective arterial dilators. (2) "Vasodilators" at the arteriolar level (dipyridamole and hydralazine) and, surprisingly, diltiazem and verapamil, in clinically effective doses, are not significant large-vessel dilators. (3) Adrenergic receptor stimuli

(propranolol, propranolol plus epinephrine, and isometric handgrip) are modest coronary smooth muscle constrictors. The rise in blood pressure with handgrip (25 mm Hg) and with propranolol plus epinephrine (40 mm Hg) almost certainly distends the arteries passively and thus prevents a greater constriction. (4) The serotonergic receptor agonist, ergonovine, is the most potent of the coronary constrictors we have studied. The magnitude of this constriction may, in part, be caused by the usual lack of a large increase in distending pressure with ergonovine.

Prinzmetal originally proposed that severe arterial obstruction by an atheroma interacted with normal mural vasomotor shortening to cause many of the clinical features of coronary "spasm." According to this hypothesis, true coronary spasm (abnormally great smooth muscle shortening) is not required.⁹ Figure 4, constructed by planimetry, demonstrates that this hypothesis is plausible. It shows how lumen caliber would be changed by 10% circumferential shortening in the *compliant* portions of various normal and diseased arterial segments. The choice of 10% mural shortening as "normal" for an epicardial artery of this size is a conservative estimate, somewhat greater than that seen with adrenergic stimulation, somewhat less than that with ergonovine (figure 3). Activation of serotonergic receptors is plausibly the best model for spontaneous vasoconstriction, since the ergonovine response most reliably mimics the clinical syndrome. The percent reduction from the normal lumen diameter

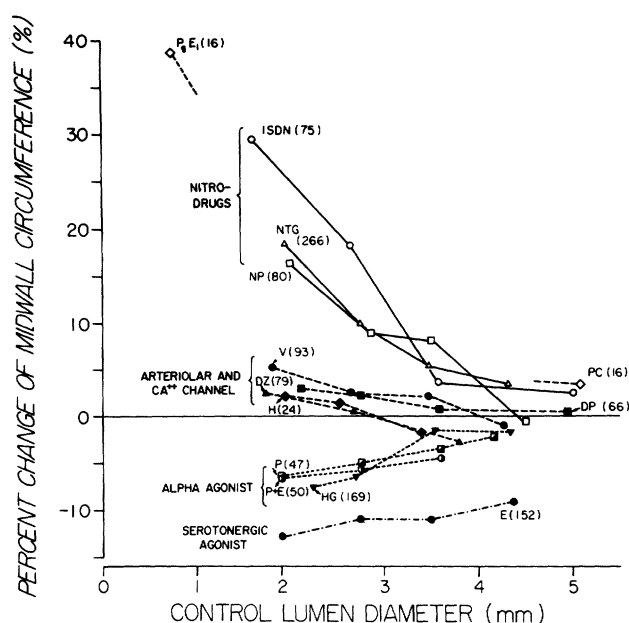


FIGURE 3. Effect of arterial size on response to vasoactive drugs. Changes in circumferential length of arterial smooth muscle were estimated from angiographic diameter changes measured in 1117 "normal" coronary segments in 227 patients. Vasomotion depended strongly on initial arterial size and the vasoactive intervention studied. The latter fell into four categories: large-vessel dilators (nitroglycerin [NTG], 0.4 to 0.8 mg sublingual; isosorbide dinitrate [ISDN], 5 to 10 mg sublingual; nitroprusside [NP], 1.0 to 1.5 mg/kg/min iv; PGE₁ iv), arteriolar dilators (verapamil [V], 0.0075 mg/kg/min iv; diltiazem [DZ], 0.003 mg/kg/min iv; hydralazine [H], 10 to 20 mg iv; dipyridamole [DP], 0.56 mg/kg iv over 4 min), α -agonists (propranolol [P], 0.2 mg/kg load over 20 min; propranolol plus epinephrine [P + E], 1 mg sc; handgrip [HG] at 25% of max for 4 to 5 min), and serotonergic agonists (ergonovine maleate [E], 0.2 mg iv). Computations are based on assumed wall thickness of $0.1 \times$ lumen diameter. Dimensional changes in vivo are a summation of active vasomotion and passive elastic response to changes in blood pressure.

of 2.8 mm is illustrated in figure 4 in the relaxed and the 10% constricted state. In this illustration, 49%, 60%, and 76% stenoses correspond to minimum lumen areas of 1.7, 1.0, and 0.35 mm², which are clinically associated with no symptoms, exertional angina, and subendocardial infarction,³ respectively.

Figure 4 depicts a hypothesis that explains the various combinations of rest and exertional pain observed in patients with angina pectoris. The pieces of the puzzle, which include an understanding of the histopathologic spectrum of stenosis morphology,⁷ of the lumen dimensions of critical stenosis,³ and of vasoconstriction in normal arterial segments, fit together nicely to provide a plausible mechanistic explanation for many of our clinical observations.

Effects of active vasodilation

By similar reasoning, relaxation of smooth muscle in the compliant portions of the stenosis permits small

increases in minimum lumen diameter, which translate through $1/d_{\min}^4$ to a substantial reduction in stenosis flow resistance. Our results with nitroglycerin^{10, 11} support this perception. About 70% of all coronary lesions, mild or severe, dilate measurably after nitroglycerin. This agrees with the histologic prediction that about 70% of all significant lesions are compliant.⁷ On the average, flow resistance in severe lesions ($\geq 65\%$ stenosis) is reduced 38% by nitroglycerin. We believe that stenosis dilation is among the most potent of the beneficial effects of nitroglycerin.¹⁰

Passive collapse in compliant stenoses

When blood is accelerated from about 10 cm/sec to higher velocities to pass through a coronary constriction, part of its pressure is converted into kinetic energy. This principle of reduced pressure with increased velocity, deduced by Bernoulli in 1734, is the principal basis for the common laboratory suction device, for the lift of an airplane wing, and for the dominant second term in the above equation for loss of pressure in the stenosis. Thus intraluminal pressure reaches a minimum in the stenosis at the point of greatest narrowing. Little pressure is recovered distally, as this kinetic energy is largely dissipated in turbulence. The following two examples illustrate the magnitude of this effect. At a normal rate of steady flow (1.1 ml/sec) through 60%, 70%, and 80% LAD stenoses, minimum pressures are, respectively, 5, 14, and 72 mm Hg less than aortic pressure. Doubling the LAD flow through a 70% stenosis would increase the pressure drop at mid-stenosis from 14 to 52 mm Hg.

Predictably, such substantial variations in intraluminal pressure could alter lumen diameter passively in a compliant stenosis. Passive collapse has been demonstrated experimentally in severe stenoses and in the clinical setting. Dipyridamole-induced coronary hyperemia in patients at catheterization resulted in a measurable decrease in minimum lumen diameter, only in severe stenoses, with a mean 45% increase in estimated stenosis resistance.²

Effects of injury, thrombosis, and atherogenesis

Vascular injury, thrombosis, and atherogenesis are the least understood of the mechanisms potentially contributing to dynamic stenosis behavior. Yet these are likely, in some way, to account for an episode of acute coronary insufficiency that subsequently ameliorates over the course of days to weeks. A complete treatment of existing information in this area is beyond the scope of this report. However, we can list some of the crucial questions. For example:

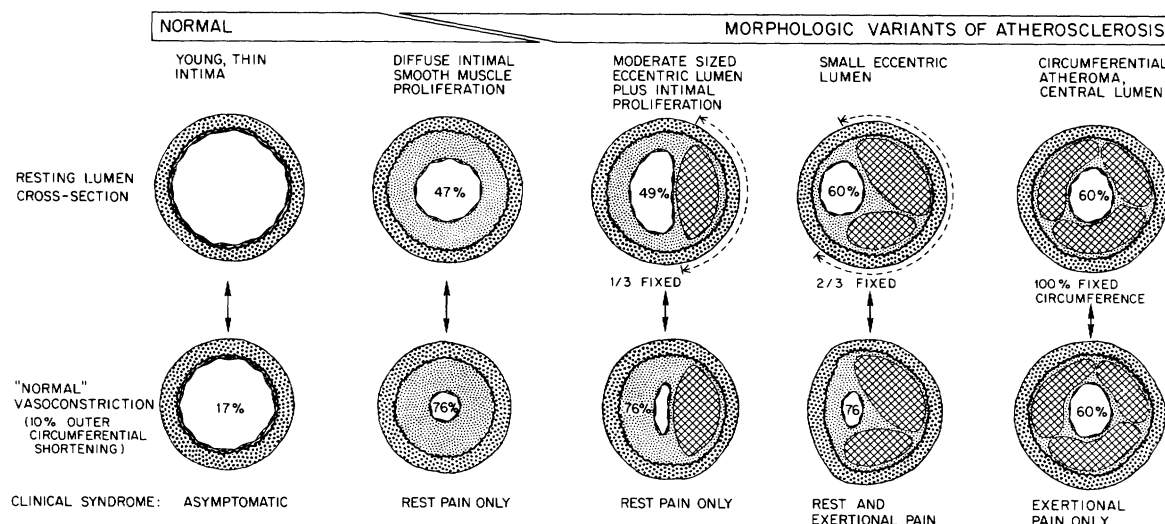


FIGURE 4. Relationship of lesion structure to clinical presentation in the spectrum of angina syndromes; effects of ordinary vasoconstriction in normal and diseased coronary arteries. In portions of the vessel with relatively normal wall, transient 10% isovolumetric circumferential shortening may cause dramatic change in lumen caliber. Percent diameter reduction is relative to original 2.8 mm lumen and corresponds to an absolute lumen area and an associated anginal syndrome: 49% stenosis, 1.7 mm², no symptoms; 60%, 1.0 mm², exertional angina; 76%, 0.35 mm², subendocardial infarction.³ (From Brown BG: Arch Intern Med 141: 716, 1981. Copyright 1981, American Medical Association.)

- (1) Does mural thrombus contribute to luminal narrowing in unstable angina?
- (2) Does hemorrhage into the plaque make a significant contribution to transient worsening of stenosis?
- (3) Does the intimal smooth muscle proliferation associated with injury and/or atherogenesis contribute in an important way to dynamic stenosis behavior?
- (4) Does intimal injury foster a hypercontractile state in adjacent mural smooth muscle?
- (5) Do platelets adherent to sites of endothelial injury in the stenosis trigger vasoconstriction by releasing vasoactive substances?

These and other important questions are still under investigation and cannot be considered definitively answered. For example, there are conflicting observations on the effect of thrombolytic agents in patients with unstable angina. Plaque hemorrhage and rupture have been described in cases of myocardial infarction,^{12, 13} but it is not clear how frequently these events occur. Vascular injury appears to predispose to increased coronary tone. An example is the vasoconstriction demonstrated in deendothelialized regions of balloon-injured carotid arteries of the rat,¹⁴ which persists unabated until endothelial coverage is restored. Such an effect could be due to injury-induced smooth muscle hypersensitivity, increased concentration of circulating or platelet-derived vasoconstrictor agents, or the failure of the injured vessel to produce a vasodilating substance. PGI₂ and PGE₁, vascular wall prod-

ucts and coronary dilators (see figure 3) are intriguing hypothetical candidates for this latter role. However, drugs that inhibit the production of PGI₂ and platelet adherence and their release of vasoactive substances do not alter the frequency or severity of acute vasospastic angina.

Dynamic interactions among flow, vasomotor tone, and pressure

Two or more of the phenomena discussed above commonly occur simultaneously. Consider, for example, a patient with unstable angina caused by a "critical" 70% stenosis ($d_{\min} = 0.9$ mm).³ For this example, let us suppose that he experiences sympathetic activation, which may occur with sustained isometric handgrip, the cold pressor response, or emotional distress. At the peak of his sustained handgrip effort, myocardial flow demand increases about 50% and stenosis lumen area is reduced by an average of 25%.² Pressure in the stenosis, initially predicted to be 14 mm Hg lower than aortic pressure by the above equation, falls during handgrip to 53 mm Hg below aortic pressure. Despite a typical 25 mm Hg rise in aortic pressure, stenosis pressure during handgrip is 14 mm Hg lower than it was at rest. Thus the measured 25% constriction of stenosis area during handgrip is a composite effect of active smooth muscle shortening and passive stenosis collapse.

Dynamic interactions of this sort occur principally in severe stenoses in which small changes in lumen caliber produce large changes in resistance and intralu-

minal pressure. They also occur in "vasospastic" lesions in which smooth muscle shortening and lesion morphology interact to dramatically alter stenosis hemodynamics.

Summary

At the clinical level, coronary stenoses frequently behave as though the obstruction to flow were variable and not as rigidly fixed as previously imagined. Pressure (energy) lost in flow through a stenosis is the primary determinant of its hemodynamic impact. Ischemic episodes occur when pressure distal to the stenosis falls below that needed to perfuse the subendocardium. Three important properties of the stenosis contribute to variation in its pressure loss. First, loss is proportional to the square of stenosis flow. Thus proper distribution of perfusion is doubly vulnerable to conditions such as exercise, anemia, or pharmacologic vasodilation, which ordinarily increase myocardial blood flow. Second, pressure loss is proportional to the inverse fourth power of minimum lumen diameter. As a result, seemingly small changes in diameter are amplified to large changes in stenosis resistance. Third, a compliant arc of normal arterial wall borders part of the lumen in the majority of coronary lesions. This extremely important morphologic feature of stenoses permits transient variation in stenosis lumen diameter in response to drugs or to variation in endogenous vasomotor activity or intraluminal pressure.

Although our understanding is incomplete, many of the clinical features of coronary disease and its pharmacologic responses are explained in terms of these stenosis properties and their interaction.

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