1 Perfusion and function in the normal and abnormal heart

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Introduction

This chapter is intended to summarize the salient features of the normal physiology and pathophysiology of the coronary circulation and myocardial function. The intent is to provide physicians and scientists involved in imaging myocardial perfusion and function a basic understanding of the mechanisms involved in these processes.

Balance between myocardial oxygen demand and supply

The continuous work of the heart throughout life requires a high level of supply of nutrients. Because the heart has a limited and short-lived capacity for anaerobic metabolism, the functional adequacy of the coronary circulation depends on its ability to supply sufficient oxygen to meet metabolic requirements over a wide range of ventricular activity [1]. The necessary balance between myocardial oxygen demand and supply is illustrated schematically in Fig. 1.1.

The primary physiologic factors governing myocardial oxygen demand include afterload, heart rate, and contractile state:

1 Afterload, the stress developed by myocardial fibers during shortening, is directly proportional to systolic pressure and the ventricular radius of curvature and inversely proportional to ventricular wall thickness. Systolic arterial pressure is a clinically useful surrogate for afterload, although it cannot account for changes in either ventricular cavity dimension or wall thickness. Wall tension, which takes chamber radius into account but pertains only to thin wall structures, is less frequently substituted for wall stress.

2 The effect of heart rate on myocardial oxygen demand depends primarily on the number of contractions per minute. Positive inotropic effects of increased rate are involved to a lesser degree.

3 Contractile state. Myocardial contractility is an additional important factor related to the strength of contraction. It remains difficult to evaluate quantitatively in humans (as reflected by the numerous indices that have been proposed to evaluate it).

4 Preload. Changes in ventricular volume can alter afterload (via changes in wall thickness) and contractile state (via the Starling effect).

These four parameters normally account for approximately 80% of myocardial oxygen consumption. Stroke volume has a limited independent effect on oxygen usage.

Another important factor when considering the need to balance oxygen demand and supply is the coronary circulation's high degree (70–80%) of oxygen extraction under basal conditions. The heart has only limited ability to adjust to increasing oxygen demand by increasing transmyocardial oxygen extraction. Thus, changes in oxygen demand mandate changes in coronary blood flow on essentially a 1:1 basis.

Because of the ease with which it can be measured, the "double product" of peak systolic blood pressure and heart rate continues to be used frequently as an index of left ventricular oxygen demand [2]. Experimental studies supporting the use of double product have been summarized elsewhere [3]. The index correlates usefully with left ventricular oxygen consumption during exercise [4] and other activities. It also remains valid in the presence of beta blockade [5]. As noted above, limitations may arise during interventions involving substantial changes in ventricular volume.

Factors controlling coronary blood flow

As in other organs, the primary physiologic factors controlling blood flow in the heart are driving pressure and

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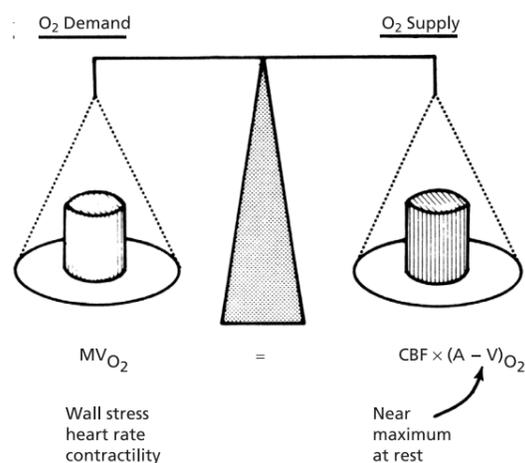
Figure 1.1 Normal balance between myocardial oxygen demand (MV_{O2}) and supply. As discussed in the text, the double product of peak systolic pressure and heart rate is used clinically as a surrogate index of oxygen demand. (Reprinted with permission from [1])

impedance (resistance). However, each of these parameters has unique features in the heart.

Driving pressure

Coronary driving pressure, traditionally considered to be the difference between coronary arterial and coronary venous pressures, is usually calculated as the difference between mean aortic and right atrial pressures. There is now evidence that the effective back pressure in the coronary bed is actually higher than right atrial pressure [6,7]. Often referred to as "zero-flow pressure," this back pressure is at least a few mm Hg higher than right atrial pressure during maximum coronary vasodilation, and substantially higher when microvascular vasomotor tone is operative. Although mechanisms underlying zero-flow pressure remain unsettled, it can be affected substantially by changes in vasomotor tone and increases in ventricular diastolic pressure, and probably varies transmurally.

Impedance (resistance)

Although impedance to flow is often considered only in terms of resistance, it includes capacitive and inertial as well as resistive components. Capacitive effects are prominent in the heart because of its large intravascular volume (6–15% of total heart weight) [8] and fluctuations and redistribution of blood volume during the cardiac cycle. Resistance nonetheless remains the dominant component of impedance.

Coronary resistance – functional components

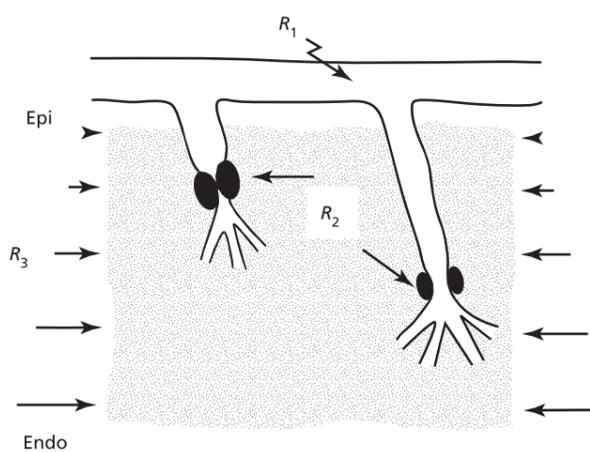Coronary vascular resistance can be considered in terms of three functional components (Fig. 1.2).

Conduit artery resistance ("R_1")

General features

The contribution of epicardial arteries to total coronary vascular resistance is trivial under normal conditions. However, epicardial artery diameter is affected by vasoactive substances produced by local endothelium and/or autonomic activation and is subject to coronary spasm. Effects of the vasoactive substances are relevant to normal coronary circulatory control and have increased importance in abnormal states.

Effects of endothelial and autonomic factors

Nitric oxide produced locally in conduit artery endothelium exerts a small tonic vasodilating effect under resting conditions [9,10]. Increases in coronary flow increase local shear stress; if endothelial function is intact, the conduit artery dilates further [11–13]. Increased production of nitric oxide is importantly involved in the additional dilation. However, an endothelium-derived hyperpolarizing factor also plays a role in flow-induced dilation of conduit arteries in experimental animals [14], and seems likely to participate in humans as well.

Figure 1.2 Schematic representation of the three functional components of coronary vascular resistance. R_1, conduit artery resistance; R_2, microvascular resistance, i.e., small arteries and arterioles; R_3, compressive resistance. R_3 increases in magnitude from epicardium (Epi) to endocardium (Endo), while R_2 compensates by varying transmurally in a directionally opposite manner. (Reprinted with permission from [1].)

Conduit arteries are subject to α-adrenergic vaso-constrictorand β-adrenergic vasodilator influences. α_1-Adrenergic constriction appears not to be active under resting conditions in normal human epicardial arteries [15] but can become important in pathologic states. α_1-Adrenergic constriction in intramural portions of conduit arteries during exercise may assist in maintaining subendocardial perfusion by reducing to-and-fro oscillation of blood during vigorous myocardial contraction [16]. β-Adrenergic activation contributes to epicardial artery dilation during exercise [17].

Microvascular (autoregulatory) resistance ("R_2")

General features

Coronary vascular resistance resides primarily at the arteriolar and small artery level and relates to both the number of microvessels and their degree of vasodilation. As indicated by Poiseuille's law, resistance in individual vessels is inversely proportional to the fourth power of vessel radius. Under normal conditions, approximately 25% of total resistance is located in vessels greater than 200 μm in diameter, 20% in vessels between 100 and 200 μm, and 55% in vessels less than 100 μm [18]. These size-related values of small vessel resistance become important when evaluating effects of vasoactive stimuli; i.e., different stimuli have predominant effects on different microvessels.

Adjustments in microcirculatory resistance play the dominant role in maintaining a normal balance between myocardial oxygen demand and supply. The process by which resistance adjusts to keep coronary flow constant when coronary artery pressure is reduced is referred to as *autoregulation*.

Major controlling factors

Factors affecting microcirculatory resistance can be summarized under four headings.

Metabolic factors

In view of the tight coupling between coronary flow and myocardial oxygen requirements, it is not surprising that metabolic factors play a major role in coronary flow regulation.

Metabolic vasodilation occurs primarily in arterioles less than 100 μm in diameter [19]. Over the years many products of local metabolism have been proposed as *the* metabolic regulator of resistance. These include adenosine, ATP, local O_2 and/or CO_2 tension, and local tissue pH or lactic acid concentration. Berne and coworkers amassed a large body of evidence supporting the role of adenosine, which is continuously produced by local metabolism and removed by reentry into cardiomyocytes and conversion

to other substances [20]. As well known clinically, adenosine has a powerful vasodilating effect on microcirculatory resistance vessels. Its interstitial concentration in the heart varies directly with metabolic activity and importantly modulates the tone of resistance vessels. However, Feigl and colleagues have presented evidence indicating that vasodilation induced by metabolites can occur despite inhibition of adenosine receptors [21].

The vasodilating action of adenosine is mediated through A_{2A} receptors and K_{ATP} channels in humans [22–24] as well as experimental animals [25]. Adenosine acts primarily at the level of small arterioles (<100 m) and its action is generally classified as endothelial-independent vasodilation. Nonetheless, as described below, endothelial function plays a secondary role of further increasing flow during adenosine vasodilation.

Endothelial factors

Vasoactive substances produced locally by coronary endothelium have received increasing attention in recent years. Vasodilation primarily governed by this process is termed endothelial-dependent vasodilation.

Nitric oxide is produced locally by microcirculatory as well as conduit vessels [26]. In vivo microvascular vasodilation mediated by nitric oxide appears to involve primarily vessels greater than 100 μm, i.e., small arteries rather than arterioles [27]. When flow increases, e.g., in response to increased metabolic activity, nitric oxide production increases concurrently. This may be a mechanism responsive to shear stress in small arteries similar to that in conduit arteries. Increased nitric oxide production augments effects of other vasodilating factors and can serve as a "braking" factor on concurrently active vasoconstrictor mechanisms [28].

An endothelium-derived hyperpolarizing factor also plays a role in flow-induced dilation in microvessels. Studies from Gutterman's laboratory indicate that this mechanism is quantitatively important in human coronary arterioles [29], and involves endothelial-release of H_2O_2 [23].

Additional endothelial-derived products of interest include prostacyclins (vasodilators) and endothelins (vasoconstrictors). Although it is not proven, endothelium-derived agents other than nitric oxide may also have their primary effect on microvessels greater than 100 μm.

Neurohumoral factors

Microcirculatory resistance vessels are affected by both the autonomic nervous system and circulating vasoactive substances. The importance of autonomic innervation has become increasingly apparent in recent years. Our understanding of the signaling processes involved, and their various interactions, remains in evolution.

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Sympathetic-induced constriction of microvascular smooth muscle is mediated primarily through postsynaptic α_2-adrenergic receptors. α_2-Adrenergic vasoconstriction is not demonstrable under normal resting conditions [30] but can become evident when the normal vasodilating action of endothelium-generated nitric oxide is attenuated.

When evaluating sympathetic-induced microvascular vasodilation, direct neural effects on microvessels must be distinguished from metabolic effects resulting from concurrent myocardial stimulation [31]. Microvascular sympathetic dilation is mediated through two receptor mechanisms.

β_2-*Adrenergic receptors*
β_2-Adrenergic vasodilation has been demonstrated directly in human coronary arterioles [32]. In addition, the degree of augmentation of myocardial flow during cold pressor testing in cardiac transplant recipients depends on the degree of regional sympathetic reinnervation [33]. The functional importance of neurally induced β-adrenergic vasodilation in ordinary activities is supported by canine studies indicating that this factor accounts for approximately 25% of total coronary vasodilation during exercise [34].

α_2-*Adrenergic receptors*
α_2-Adrenergic receptors have been reported to be present on microvascular endothelium as well as microvascular smooth muscle [35]. The endothelial receptors may reduce the constrictor effect of the smooth muscle receptors when α_2 agonists are administered. Reduced constriction would apparently depend on increased endothelial production of nitric oxide and, in human coronary microvessels, involve local kinin synthesis as an intermediate step [26].

Autonomic effects on coronary microvascular resistance involve reflex as well as direct stimuli. Parasympathetic activation during baroreceptor and chemoreceptor reflexes produces vasodilation by augmenting local production of nitric oxide [36].

Myogenic factors
Coronary arterioles also exhibit myogenic effects; i.e., increases in intraluminal pressure stimulate smooth muscle vasoconstriction, and decreases cause vasodilation. Myogenic effects may have a particular role in modulating precapillary pressure and therefore tissue exchange.

Overview
The net magnitude of microcirculatory resistance depends on the summated effects of these several, sometimes competing factors. Under basal conditions, metabolic factors predominate. During exercise and other forms of increased activity, endothelial and neurohumoral mechanisms are activated and contribute importantly to maintaining the appropriate balance between oxygen demand and supply. When endothelial and/or neurohumoral mechanisms are not normally active, responses to metabolic stimuli can be blunted.

Compressive resistance ("R_3")

General features

Compressive resistance refers to the effects on coronary blood vessels of local forces within the ventricular wall during individual cardiac cycles. These forces produce the well-known difference in coronary flow between systole and diastole; i.e., left ventricular contraction normally reduces flow into the epicardial arteries during systole to less than one-third of that in diastole.

When superimposed on conduit and microvascular resistance during systole, compressive forces narrow intramural arteries and other vessels substantially, displacing their contained blood retrogradely and antegradely and greatly reducing incoming flow in epicardial arteries. These forces also produce a large gradient in intramyocardial tissue pressure across the ventricular wall. Pressure in the subendocardial myocardium approximates intracavitary ventricular pressure while subepicardial tissue pressure remains close to intrapericardial pressure.

A finite period in early diastole is required for reexpansion and refilling of vessels compressed during systole, thereby delaying early diastolic inner wall perfusion. An inner-to-outer gradient in intramyocardial tissue pressure also occurs in diastole [37]. Although normally much smaller than the systolic gradient, the diastolic gradient is also affected by changes in ventricular diastolic pressure or intrapericardial pressure [38].

Transmural variations in perfusion and resistance

The general principles governing overall left ventricular perfusion require refinement when considering perfusion in different transmural portions of the full-thickness ventricular wall. Compressive effects cause the inner layers of the ventricular wall to be particularly dependent on diastolic perfusion. Increasing epi- to endocardial compressive effects are normally counterbalanced by directionally opposite differences in microcirculatory resistance (Fig. 1.2).

In addition, myocardial oxygen demand can vary transmurally. Myocardial oxygen consumption has been reported to be approximately 20% greater in the subendocardium than the subepicardium [39]. Relative

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increases in subendocardial oxygen demand are consistent with models of transmural variations in developed stress [40] and in vivo measurements of transmural variations in diastolic sarcomere length [41]. Increased subendocardial oxygen extraction can reduce but does not negate the need for the full-cycle level of subendocardial flow to at least equal that in the subepicardium. Accordingly, flow per unit weight of myocardium (ml/(min g)) is usually 10–30% greater in the subendocardium than the subepicardium [42].

Since the mechanical effects of ventricular contraction impede systolic perfusion to the greatest extent in the inner layers of the heart, the inner layers are particularly dependent on diastolic perfusion. Transmural differences in driving pressure and microvascular resistance exert opposing effects in order to maintain subendocardial perfusion at the level needed to meet local oxygen demand [3]. The pressure drop in arteries upstream of the microcirculation is greater in arteries supplying the subendocardium than the subepicardium, presumably because of the longer intramural path of the vessels supplying the inner myocardial layers [43]. The back pressure opposing coronary flow is probably also greater in the subendocardium than the subepicardium [37,44]. The resulting reduction in subendocardial driving pressure is potentially counterbalanced by an intrinsically greater subendocardial vasodilatory capacity (i.e., smaller minimum resistance) [45]. Increased microvascular vasodilation successfully maintains the required level of subendocardial flow in most situations in normal hearts. Nonetheless, when demand is high or inflow is restricted by a process such as progressive coronary artery constriction, vasodilator reserve becomes exhausted sooner in the inner layers of the heart than the outer, resulting in subendocardial ischemia [46].

Summary

Coronary vascular resistance at any point in the heart depends on the summated effect of these three functional components. Microvascular resistance normally predominates.

Techniques used clinically to evaluate conduit artery and microvascular resistance

Cold pressor test

The cold pressor test has been used frequently to assess the vasoactivity of epicardial conduit arteries and microcirculatory resistance vessels. When the subject's forearm is immersed in ice water, blood pressure and heart rate rise reflexly as the sympathetic nervous system is activated.

Coronary flow normally increases proportionally to the increase in myocardial oxygen demand.

The normal coronary vascular response to cold pressor testing includes dilation of both epicardial arteries and microcirculatory resistance vessels. It involves activation of myocardial β_1 receptors, microvascular α_2- and β_2-adrenergic receptors [47], and endothelial flow-induced dilation [48]. Since dilatory components of the response are reduced when endothelium is dysfunctional, the test is often utilized as a noninvasive probe of endothelium-dependent vasomotion [49]. Reductions in neurally mediated adrenergic vasodilation can participate in the response through reduced stimulation of β_2-receptors in microvascular smooth muscle [32,33] and/or α_2-receptors on microvascular endothelium [26].

Intracoronary acetylcholine

Intracoronary injection of acetylcholine normally causes epicardial artery diameter to increase in a dose-dependent manner [50]. The increase is mediated through increased endothelial synthesis of nitric oxide and is frequently used as a test of conduit artery endothelial function.
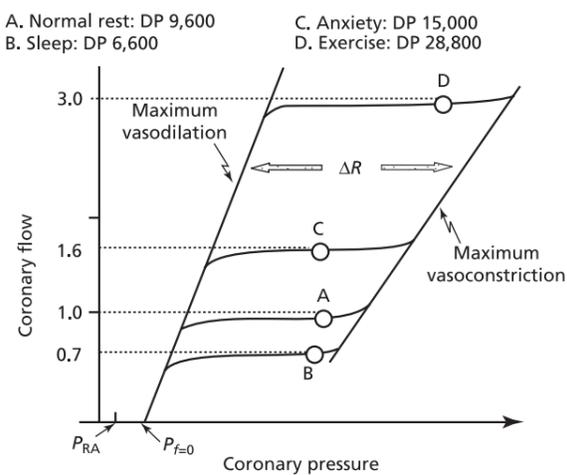
Coronary pressure–flow relationships in vivo

Full-thickness myocardium

Functional aspects of coronary circulatory behavior can be illustrated using diagrams depicting steady-state relationships between coronary arterial pressure and coronary flow. These are usually constructed using average values of flow for the full-thickness myocardial wall. Figure 1.3 illustrates four situations in normal individuals.

Transmural differences

As noted previously, myocardial oxygen consumption is frequently greater in the subendocardium than the subepicardium, necessitating a correspondingly greater subendocardial flow. Figure 1.4 is taken from the work of Canty [51,52], who has provided steady-state transmural pressure–flow relationships in conscious chronically instrumented dogs. As coronary artery pressure is reduced at constant myocardial oxygen demand, autoregulatory microvascular dilation maintains flow at the necessary level until vasodilator reserve is exhausted. Because subendocardial flow requirements exceed those in the subepicardium, the pressure "breakpoint" at which flow begins to fall is higher in the subendocardium than the subepicardium (Fig. 1.4a). The "breakpoint" pressure

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Figure 1.3 Pressure–flow diagrams depicting steady-state relationships between mean coronary artery pressure and coronary flow in the full-thickness myocardial wall in normal individuals. The line depicting the pressure–flow relation during maximum vasodilation intersects the pressure axis at a "zero-flow" pressure ($P_{f=0}$), which is higher than right atrial pressure (P_{RA}). The space between the lines representing maximum vasodilation and maximum constriction is the potential operating range for changes in coronary resistance (ΔR).

1 Normal resting conditions (point A). Typical values of BP (blood pressure) and HR (heart rate) might be 120/70 mmHg (mean 87) and 80 bpm, producing a double product of 9600. The normal resting value of flow is designated 1.0.

2 Sleep (Point B). BP and HR would probably be lower, e.g., 110/70 (mean 83) and 60 with a double product of 6600. The lower double product would require a coronary flow only 69% of that needed at rest when awake.

3 Anxiety-producing situation, with tachycardia and systemic vasodilation (Point C): BP and HR might be 110/70 (mean 83) and 140. The double product of 15,000 is 160% of that under normal resting conditions.

4 Treadmill exercise (Point D): A BP of 180/80 (113) and HR of 160 would represent an increase in double product to 300% of that under resting conditions. The threefold increase would presumably have had to be accompanied by an increase in coronary flow to 300% of its resting value.

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also varies with changes in flow requirement, and can rise substantially during rapid tachycardia (Fig. 1.4b).

Quantitative measurements of coronary flow

General considerations

When considering absolute values of coronary flow, several points need to be kept in mind. Individual values need to be considered in relation to concomitant myocardial oxygen demand. Because of its practical availability, the "double product" index is most frequently used [53,54].

Quantitative measurements of flow are usually confined to the left ventricle. Measurements employing positron emission tomography (PET) provide values in terms of flow per unit weight, i.e., ml/(min g) [54,55]. Measurements employing an intraarterial Doppler velocity catheter and angiographic measurements of arterial cross-sectional area provide absolute values in ml/min for the area supplied by the artery. Sequential measurements before and following an intervention assume that the area supplied is not altered by the intervention. If only velocity is measured, the intervention is also assumed not to alter arterial cross-sectional area. Gullberg et al. have recently demonstrated that measurements of absolute flow (and flow reserve) can also be obtained by dynamic SPECT [56], although systems with sufficient count sensitivity to allow rapid sequential monitoring of the myocardial and blood concentrations of radioactivity needed for these measurements to date have not become widely available commercially.

All measurement techniques have significant methodological limitations. Since flow normally varies within the ventricle on both macroscopic [57] and microscopic [58,59] levels, an average value for the entire left ventricle represents the mean value of some distribution of flow.

Measurements employing invasive techniques in normal individuals have necessarily been limited in number. Most "normal" measurements have been obtained in patients undergoing cardiac catheterization for clinical indications and proving to have normal or near-normal findings. A frequent example would be individuals with atypical chest pain in whom coronary arteriography is needed to exclude coronary artery disease.

Measurements employing noninvasive techniques have frequently included normal volunteers as well as individuals undergoing cardiac evaluation. PET has played the dominant role in this area. All quantitative measurements involve assumptions concerning blood-tissue tracer exchange and some form of flow modeling. These differ somewhat, depending on both the tracer employed (^{13}N-ammonia, ^{15}O-oxygen) and the laboratory in which the measurement is made. Schelbert has recently provided an excellent review of cardiac PET methodology and findings in normal and disease states [54].

"Normal" values at rest

Measurements employing PET have now been reported in substantial numbers of normal individuals. Schelbert has tabulated measurements in 12 studies involving 214 patients [54, Table 10]. Resting left ventricular flows averaged 0.89 ± 0.15 (SD) ml/(min g). Camici and colleagues have reported resting values averaging 0.99 ± 0.23 ml/(min g)
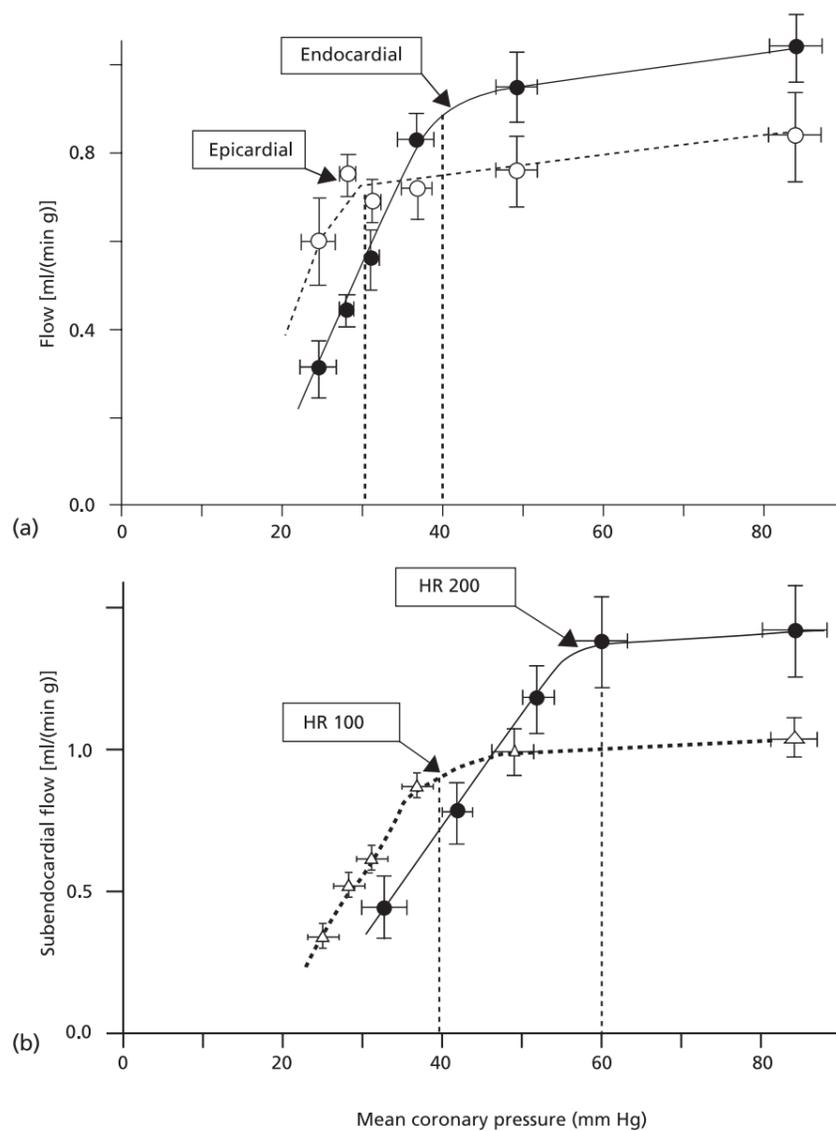
Figure 1.4 (a) Subendocardial and subepicardial pressure–flow relationships in the circumflex bed of conscious chronically instrumented dogs. Data are from Canty [51]. Under control conditions (coronary pressure 84 ± 10 mm Hg), subendocardial flow is 26% higher than subepicardial flow (1.06 ± 0.22 vs. 0.82 ± 0.24 ml/(min g)), reflecting higher oxygen demand in the subendocardial myocardium. When coronary pressure is reduced by progressive circumflex artery constriction, normal autoregulatory mechanisms maintain control flows until circumflex pressure falls below 40 mm Hg. At that "breakpoint" subendocardial flow begins to decrease. Subepicardial flow is maintained until coronary pressure falls below 30 mm Hg, when it too begins to decrease. The subendocardial/subepicardial flow ratio falls progressively when subendocardial flow begins to decrease (Redrawn from [51]). (b) Changes in the subendocardial pressure–flow relationship during tachycardia. Data are again from Canty et al. [52]. When heart rate increases from 100 to 200 bpm, subendocardial flow increases by approximately 40% and the "breakpoint" pressure at which subendocardial flow begins to fall increases from 40 to 60 mm Hg. (Redrawn with permission from [52].)

in 169 normal volunteers in their own studies [60]. Their coefficient of variation (27%) improved only slightly (to 24%) when values were normalized for differences in double product.

The relatively wide range of normal flow values emphasizes the difficulty in classifying an individual measurement in a patient as "normal" or "abnormal." The variability is probably more physiologic than methodologic; e.g., arithmetic mental stress increases resting flow and double product by approximately 30% [61]. Reproducibility of individual measurements in Schelbert's laboratory is approximately 16%, and improves to

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approximately 10% when normalized for differences in double product [62].

PET measurements indicate that average resting left ventricular flow increases with age greater than 50, concomitant with age-related increases in double product [53,60]. Resting flow has been reported to be higher in females than males in some [57,63] but not all [53] studies.

Maximum coronary vasodilation

Transient coronary artery occlusion is the most consistent stimulus for producing maximum coronary vasodilation, i.e., for minimizing coronary resistance. In humans, coronary flow normally peaks at four to eight times its resting value during the "reactive" hyperemia, which follows release of a coronary artery occlusion lasting 20 or more seconds [64,65]. The relationship between coronary flow and arterial pressure during maximum vasodilation is depicted by the line on the left in Fig. 1.3.

Because total coronary resistance depends on compressive as well as microcirculatory factors, flow during maximum vasodilation varies with heart rate; i.e., tachycardia can produce a moderate reduction in the slope of the pressure–flow line representing maximum vasodilation. A reduction in slope also occurs when left ventricular preload is elevated or the left ventricle is hypertrophied. Conversely, anemia (reduced blood viscosity) increases the slope of the maximum vasodilation line.

When coronary flow is measured during vasodilation, vasodilation is usually produced pharmacologically. The most commonly employed agent is adenosine, usually given as an intravenous infusion $(140\ \mu g/(kg\ min))$ but occasionally injected directly into a coronary artery $(12–18\ \mu g)$ during invasive studies. Dipyridamole $(0.56\ mg/(kg\ min))$ infused intravenously over 4 min) continues to be used by some laboratories. Selective adenosine A_2 receptor agonists which reduce uncomfortable side effects of systemically administered adenosine [66] are likely to become available in the near future. Papaverine, which is injected directly into a coronary artery, can produce ventricular arrhythmias and is now used infrequently.

As noted previously, it is now clear that a portion of the vasodilatory response to pharmacological agents involves the release of endothelium-derived vasodilating factors as flow (and local shear stress) increase in response to the pharmacological agent [25]. In normal individuals studied by Buus et al., adenosine-induced hyperemia decreased by an average of 21% when endogenous nitric oxide synthesis was inhibited [67]. Thus, the total response to a pharmacological vasodilating agent reflects the combined effect of agent-induced relaxation of vascular smooth muscle and endothelium-mediated vasodilation. The distribution of microvascular resistance bears importantly on this response.

As noted previously, metabolic vasodilation occurs primarily in arterioles less than 100 μm in diameter [19]. Adenosine and related compounds also have their primary vasodilating effect on microvessels of this size. Since these vessels represent only 55% of total coronary resistance, microvessels greater than 100 μm are also involved in maximal vasodilatory responses. When flow increases in response to dilation of less than 100-μm-diameter vessels, endothelial shear stress increases in larger microvessels, resulting in increased production of nitric oxide (and perhaps hyperpolarzing and other vasodilatory agents as well). Thus, metabolic or pharmacological dilation of small arterioles leads to dilation of larger resistance vessels and, if endothelial function is compromised, vasodilatory responses to metabolic stimuli and adenosine are reduced.

PET flows during adenosine- or dipyridamole-induced vasodilation averaged $3.71 \pm 0.62\ ml/(min\ g)$ in the tabulation by Schelbert mentioned above [54]. Similar values in the Camici lab's normal volunteers were $3.54 \pm 1.01\ ml/(min\ g)$ (coefficient of variation 29%) [57].

Coronary flow reserve

Coronary flow reserve is defined as the ratio of coronary flow during maximum vasodilation to that immediately preceding vasodilation. The clinical advantage of the flow reserve measurement is that a region is compared to itself, between rest and stress, avoiding the issues of underdetection of regional abnormality in the presence of balanced reduction of flow. Several methodological considerations need to be kept in mind during measurements of flow reserve. Because of variations in individual response, standard doses of adenosine and/or dipyridamole do not always produce maximum reductions in microvascular resistance. Since numerical values of flow reserve depend on flow immediately prior to as well as during vasodilation, basal conditions during the prevasodilation measurement are also important. Increases in heart rate and ventricular preload reduce reserve and need to be considered in interpreting measurements [68,69]. The same is true for adenosine- or dipyridamole-associated reductions in arterial pressure and reflex tachycardia.

"Normal" values of flow reserve also vary more than is sometimes appreciated. Marcus and colleagues pioneered Doppler measurements of coronary flow velocity in humans in the early 1980s. In initial measurements at the time of open heart surgery, ratios of peak to resting velocity were similar in the right and left ventricles and averaged 5.8 ± 2.2 [64]. Wilson et al. subsequently reported values ranging from 3.8 to 7.0 and averaging 5.0 in a small group of individuals with atypical chest pain and normal coronary arteriograms studied in the cardiovascular

laboratory [70]. Using the same approach, McGinn et al. reported values ranging from 3.0 to 7.5 and averaging 4.0 ± 1.1 in 25 cardiac transplant recipients with heart rates of 100 and normal coronary arteries and myocardium [68].

More recent "normal" values obtained using Doppler velocity measurements have varied among laboratories. For example, Kern et al. report values averaging 2.8 ± 0.6 in 85 patients with chest pain syndromes and arteriographically normal arteries and 3.1 ± 0.9 in 108 heart transplant recipients [71], whereas Houghton et al. find values averaging 4.4 ± 2.3 and 4.1 ± 2.0 in 96 African-Americans and Caucasian-Americans [72].

In Schelbert's tabulation of PET data, values of flow reserve in individual studies ranged from 3.0 to 5.4 and averaged 4.0 ± 0.66 [54, Table 10]. In the study of Camici et al., values in normal volunteers ranged from 1.4 to 8.1 and averaged 3.8 ± 1.2 [57]. Spatial heterogeneity of flow reserve was evident regionally. In addition, as reported in animal studies [73], baseline and hyperemic flows in individual myocardial segments did not correlate; i.e, resting and maximal flows were sometimes discordant.

Attempts to define a single "cut-point" separating normal and abnormal values of coronary flow reserve are complicated by the wide range of normal values. There is agreement that flow reserve measured using PET is reduced moderately at ages greater than 50 [53,57]. Gender differences have not been identified [53,57,63]. The variability of normal values can be especially problematic when attempting to classify an individual value as normal or abnormal. Nevertheless, given the potential of flow reserve measurements for adding to the detection of perfusion limitations, continued exploration of clinical applications remains important as detectors, modeling, and computing systems improve over time.

Effects of physical training and deconditioning

Physical training has beneficial effects on both myocardial oxygen demand and the coronary circulation. It is well established that myocardial oxygen requirements for any given level of activity are less in a trained individual. Heart rate is the major factor in this response. The trained individual has a lower resting rate, and achieves any given level of exercise at a lower rate, than the untrained individual [74]. In addition to reducing myocardial oxygen demand, the slower rate increases the duration of diastolic perfusion, thereby augmenting coronary flow reserve. Studies in experimental animals indicate that physical training also increases the diameter of conduit coronary arteries by a few percent, and may increase myocardial capillary density [75]. Small degrees of ventricular hypertrophy have also been reported [76].

Conversely, deconditioning increases myocardial oxygen requirements at any given level of activity [74]. The higher heart rate needed to generate the required cardiac output in the deconditioned individual is the major factor involved. Conduit coronary artery diameter and ventricular mass may diminish slightly [75,76].

Measures of myocardial function in humans

The importance of measurements of cardiac function in clinical decision making underscores the value of assessing chamber size and contractile function concurrently with myocardial perfusion. Parameters of particular interest include left ventricular volumes and ejection fraction, regional wall motion, and myocardial mass. Beller has provided a cogent discussion of the relative clinical strengths and limitations of measurement techniques now used widely [77]. These include echocardiography, angiography, and gated magnetic resonance imaging as well as gated SPECT and equilibrium radionuclide angiography.

Global ventricular function

Global ventricular function is most commonly assessed by measuring ejection fraction (end-diastolic − end-systolic volume/end-diastolic volume). Ejection fraction has proven to have enormous clinical value despite its known variability with loading conditions (particularly afterload) and heart rate, and sometimes challenging measurement issues. Measurements of chamber volume frequently involve an assumed geometric model, e.g., a prolate ellipsoid for the left ventricle and a crescentic solid for the right ventricle [78]. Options for avoiding an assumed geometry include summing data from multiple transverse slices, reconstructing three-dimensional volumes from two-dimensional images, and gated imaging of the ventricular blood pool following labeling with a radionuclide tracer. The latter is particularly useful in right ventricular studies. All volume measurements cannot deal fully with the complex pattern of ventricular motion during contraction (which includes rotational and translational motion as well as transverse and apex-to-base shortening). Accurate definition of endocardial borders can also be problematic. Despite these limitations, the value of ejection fraction as an indicator of prognosis and an important determinant in therapeutic decisions is unquestioned.

M-mode echocardiographic measurements of fractional shortening provide an additional ejection phase index of left ventricular function. Isovolumic phase indices continue to be used occasionally. The rate of change of ventricular pressure (dP/dt) is affected by preload,

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i.e., end-diastolic ventricular pressure. More complex parameters, e.g., end-systolic pressure-dimension indices, can provide relatively load-independent estimates of contractility.

Regional ventricular function

Regional contractile performance is usually assessed by evaluating endocardial wall motion or transmural wall thickening. The latter is generally considered preferable. The clinical importance of detecting, and at least semi-quantifying, regional contractile abnormalities is well established. An important recent development has been the agreement on "Standardized Myocardial Segmentation and Nomenclature for Tomographic Imaging of the Heart" developed under the auspices of the American Heart Association by the American Society of Echocardiography, American Society of Nuclear Cardiology, North American Society of Cardiac Imaging, Society for Cardiac Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance [79]. Consensus recommendations are provided for orientation of the heart, names for cardiac planes, number of myocardial segments, selection and thickness of cardiac slices for display and analysis, nomenclature and location of segments, and assignment of segments to coronary arterial territories. The resulting 17-segment system for assessing the myocardium and left ventricular cavity (Fig. 1.5) is suitable for evaluating perfusion as well as function.

Regional myocardial function is usually assessed visually, often with semiquantitative characterization as normal, hypokinetic, akinetic, or dyskinetic. The clinical value of this approach is reflected in its continued widespread usage and acceptance. However, several complexities of regional contractile behavior discussed by Mulhern and Skorton in an earlier edition of this book [78] need to be recognized. The complex and nonuniform nature of ventricular muscle fiber architecture results in some degree of nonuniformity of contraction pattern in even the normal left ventricle. This nonuniformity may underlie some of the nonuniformity of regional blood flow in normal ventricles. Generally accepted criteria for normal endocardial motion or wall thickening in all portions of the ventricle are not available. Estimates of regional contraction can also be confounded by rotational and translational motion during systole which is unrelated to contraction. Approaches for dealing with noncontractile motion include the centerline approach developed by Sheehan and colleagues [80] and floating- and fixed-axis analyses discussed by Force and Parisi [81]. Finally, in slice-based approaches, efforts to image the same portion of myocardium at end-systole and end-diastole are complicated by base-to-apex shortening and/or translational movement during contraction. Techniques such as myocardial tagging
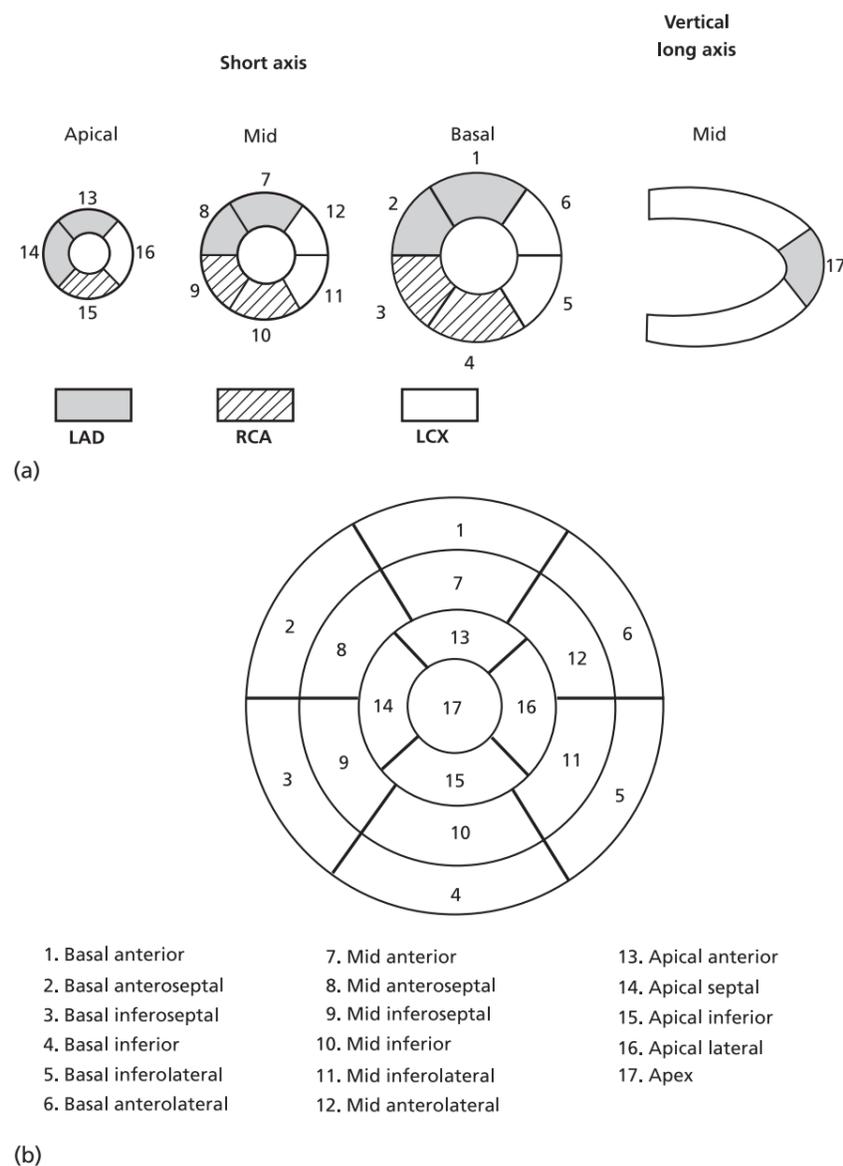
with magnetic resonance imaging (MRI) can be helpful in addressing these problems.

Ventricular remodeling

Structural and functional changes in the left ventricle following myocardial infarction or other injury, referred to as remodeling, have received increasing attention in recent years. Myocardial dysfunction involving areas not included in the infarction is of particular concern. Initially compensatory ventricular dilation sometimes progresses to an adverse degree, resulting in deteriorating overall function and ejection fraction. Early measurements of ejection fraction, infarct size and location, and TIMI-grade flow in the infarct-related artery can assist in identifying individuals at high risk of adverse remodeling [82].

Remodeling is ordinarily identified using an imaging technique, most commonly echocardiography. The recent development of delayed contrast-enhanced magnetic resonance imaging [83,84] has added the capability to identify infarcted tissue selectively with high resolution. Thus, it is now possible to define the circumferential, longitudinal, and transmural extent of infarctions, and to identify otherwise unappreciated subendocardial infarctions. Due principally to limitations of resolution, definition of the extent of infarction is currently less precise with most other imaging techniques. Delayed contrast enhancement using multislice computed tomography (CT), however, has shown promise in this regard. With MRI, infarct size can be followed throughout the period of acute injury and subsequent resorption and scar formation. When imaging is performed during the first few days, areas of microvascular obstruction can be identified within the zone of infarction (the "no-reflow" phenomenon) [85–87]. Recent data suggest that this phenomenon is predictive of adverse remodeling. The direct visualization of infarctions with MRI and possibly CT also offers advantages over surrogate measures based on wall motion abnormalities or resting perfusion scans. Wall motion abnormalities related to areas of infarction can be distinguished from those representing viable hypocontractile myocardium, i.e., stunned or hibernating myocardium. Abnormalities in perfusion scans resulting from areas of infarction can be distinguished from those caused by flow reductions in viable myocardium [88]. Theoretically, these distinctions are also possible with radionuclide methods such as rest/redistribution thallium SPECT, but would require improved resolution over that currently available. Hypertrophy of viable noninfarcted muscle can be identified and quantified even when total ventricular mass does not change (because of concurrent reductions in infarct size as necrotic tissue is resorbed and replaced by scar) [89].

(a)

1. Basal anterior
2. Basal anteroseptal
3. Basal inferoseptal
4. Basal inferior
5. Basal inferolateral
6. Basal anterolateral

7. Mid anterior
8. Mid anteroseptal
9. Mid inferoseptal
10. Mid inferior
11. Mid inferolateral
12. Mid anterolateral

13. Apical anterior
14. Apical septal
15. Apical inferior
16. Apical lateral
17. Apex

(b)

Figure 1.5 Recommended 17-segment system for assessing regional ventricular function and/or perfusion (reprinted with permission from [79]). (a) Assignment of the 17 myocardial segments to the territories of the left anterior descending (LAD), right (RCA), and left circumflex (LCX) coronary arteries. (b) Display, on a circumferential polar plot, of the 17 myocardial segments and the recommended nomenclature for tomographic imaging of the heart.
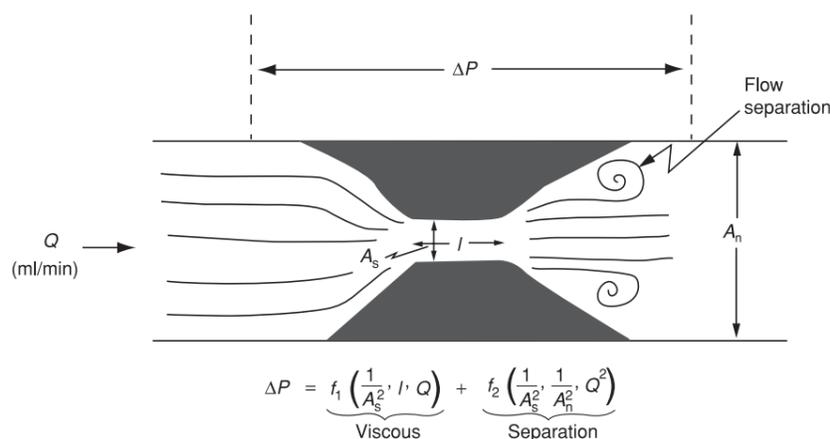
Pathophysiologic alterations in coronary artery disease

Hemodynamics of stenotic lesions

In considering pathophysiologic alterations in coronary artery disease, it is useful to begin by examining effects of stenotic lesions independently of the distal coronary vasculature. Building on Gould's original experimental studies [90–92], several groups have contributed to our current understanding of factors governing energy losses across a stenosis. These are illustrated schematically in Figs. 1.6 and 1.7. As depicted in the figures, small increments in severity of an established stenosis can have important clinical effects [93,94]. Such an increment might represent static progression of the underlying atherosclerotic process but can also result dynamically from local vasomotion, a platelet aggregate or small thrombus, or intramural hemorrhage. Conversely, small

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$$\Delta P \;=\; f_1 \underbrace{\left(\frac{1}{A_s^2}, l, Q\right)}_{\text{Viscous}} \;+\; f_2 \underbrace{\left(\frac{1}{A_s^2}, \frac{1}{A_n^2}, Q^2\right)}_{\text{Separation}}$$

Figure 1.6 Factors governing the pressure drop (ΔP) across a stenosis. Q, flow; l, stenosis length; A_s, minimum cross-sectional area within the stenosis; A_n, cross-sectional area in adjacent section of the artery (reprinted with permission from [93]). The pressure drop across a stenosis varies with flow and is influenced by both frictional (viscous) and separation losses. Four points are noteworthy: (1) Frictional losses are proportional to flow and vary linearly with stenosis length; (2) separation losses are proportional to flow raised to the second power and become increasingly important as flow increases; (3) separation losses also increase nonlinearly with severity of stenosis; (4) for any given level of flow, the most important determinant of stenosis severity is the minimum cross-sectional area within the stenosis, which appears as a second-order term in the expression of both frictional and separation losses.
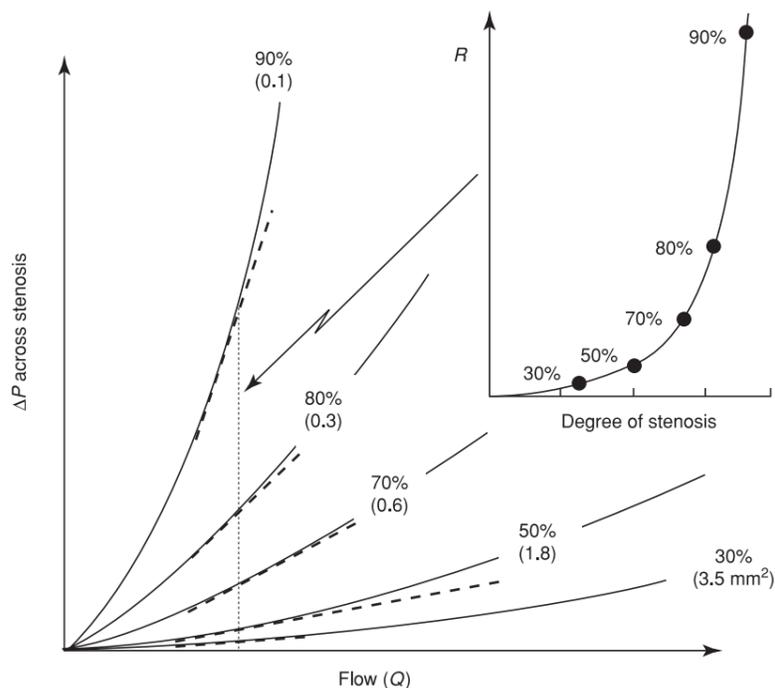
Figure 1.7 Additional features of the relationship between pressure drop across a stenosis (ΔP) and flow (Q) through the stenosis. As usually done clinically, degree of stenosis is expressed as percent diameter narrowing (assuming circular stenosis geometry). The dashed tangent lines represent the resistance (R) offered by individual stenoses at a particular level of flow (vertical dotted line) (Reprinted with permission from [93]). Although the figure has been derived using fluid mechanics equations for steady flow of an incompressible fluid in rigid tubes, it applies in principle to the in vivo coronary circulation. Two points are noteworthy: (1) Because the relationship between pressure drop and flow is alinear, the pressure drop across a stenosis increases progressively more rapidly as flow rises; i.e., the resistance of even a rigid stenosis increases with flow. (2) At any given level of flow, stenosis resistance also increases alinearly and progressively more rapidly with stenosis severity. As shown in the inset, this latter point is especially relevant for greater than 50% diameter stenoses; e.g., stenosis resistance doubles as the degree of narrowing increases from 70 to 80%, and doubles again between 80 and 90%.
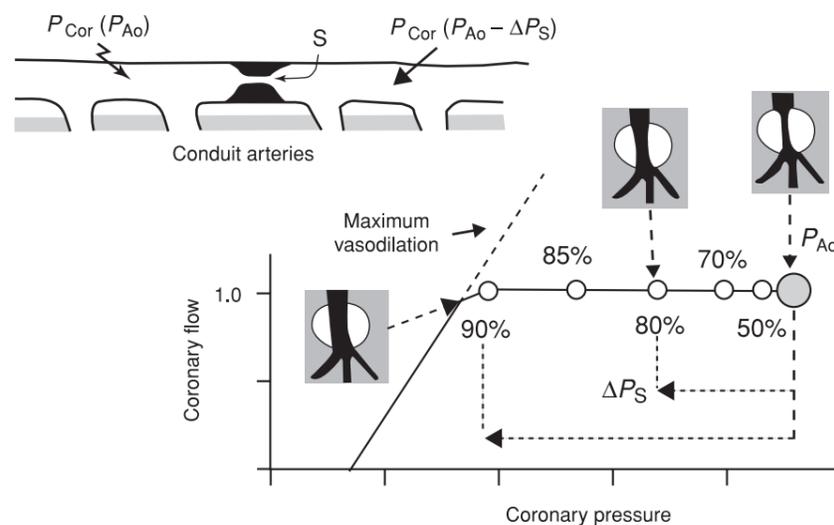
Figure 1.8 Schematic representation of in vivo effects of stenoses (redrawn with permission from [1,94]). (a) Coronary artery pressure (P_{Cor}) is the same as aortic pressure (P_{Ao}) upstream of a stenosis (S) within an epicardial artery but is reduced beyond the stenosis by the transstenotic pressure gradient (ΔP_S). The magnitude of reduction depends on the factors illustrated in Figs. 1.6 and 1.7. (b) Pressure–flow relationships under resting conditions for varying degrees of stenosis. Values of poststenotic pressure corresponding to different degrees of stenoses are shown by open circles. Reductions in poststenotic pressure are modest for less than 70% diameter stenoses but increase rapidly thereafter. Compensatory microcirculatory vasodilation is able to maintain resting flow at its normal level but is almost exhausted at the 90% stenosis level.

decreases in stenosis severity, either static or dynamic, can have important benefit.

Since coronary lesions frequently do not involve the entire circumferential vessel wall, dynamic changes in the severity of atherosclerotic stenoses are expected. Abnormalities in endothelium-mediated vasodilation blunt flow-induced dilatory responses and increase susceptibility to α-adrenergic vasoconstriction, e.g., α-adrenergic activation during exercise can constrict atherosclerotic epicardial arteries [95]. Conversely, reductions in conduit artery caliber can often be counteracted by nitroglycerin.

Stenosis effects in the intact circulation

Effects of coronary stenoses on the resting pressure–flow relationship are depicted schematically in Fig. 1.8. Reductions in poststenotic pressure are modest for less than 70% diameter stenoses but increase rapidly thereafter. Compensatory microcirculatory vasodilation is able to maintain resting flow at its normal level but is almost exhausted at the 90% stenosis level.

Figure 1.9 shows the pressure–flow relationship throughout the full range of coronary vasodilation. Maximum vasodilated flow is reduced by approximately 20% for a 50% stenosis, approximately 40% for a 70% stenosis, and approximately 60% for an 80% stenosis. Flow reserve is essentially absent for stenoses greater than 90%. The additional factor of transmural differences in perfusion is illustrated in Fig. 1.10.

Arterial remodeling and estimates of stenosis severity

The limitations of estimating stenosis severity by comparing an area of arteriographic narrowing to an adjacent area of an artery involved with a diffuse abnormality such as atherosclerosis are well recognized. Because of the eccentric nature of many stenoses, percent diameter narrowing is usually defined as the maximum narrowing observed in views taken from various angles and positions. Complexities of remodeling of the arterial wall [96] also need to be considered. As illustrated in Fig. 1.11, the atherosclerotic process proceeds in an outward as well as inward direction, and frequently involves an increase in external arterial diameter as well as a reduction in luminal diameter. Increases in diameter which precede luminal narrowing can lengthen the asymptomatic phase of developing coronary disease. When evaluating a stenosis arteriographically, the area of luminal narrowing and adjacent "reference" area each represent the result of a process involving both atherosclerotic proliferation and arterial enlargement. The stenosis reflects a relative local difference in the proliferative-enlargement process, the factors governing which remain incompletely understood.

In vivo measurements of transstenotic pressure gradients: fractional flow reserve

The development in recent years of pressure-monitoring guide wires only 0.10–0.15 in. in diameter has enabled

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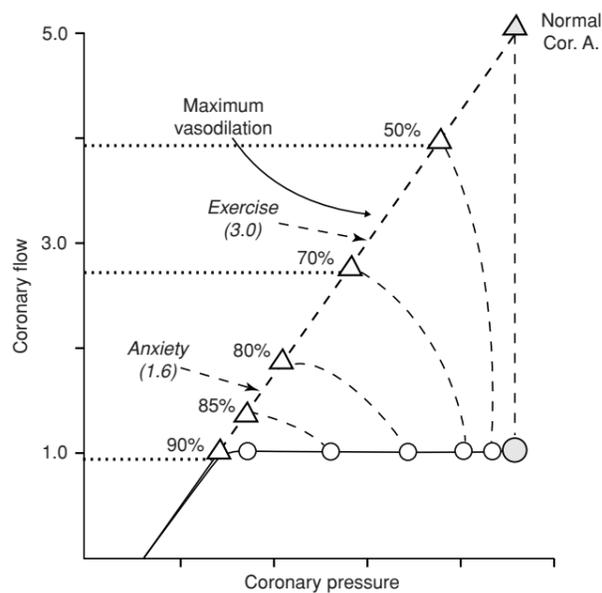
Figure 1.9 In vivo pressure–flow relationship throughout the full range of coronary vasodilation. The heavy line represents flow during maximum vasodilation; i.e., when total coronary resistance ($R_1 + R_2 + R_3$) is minimum. Maximum flow is reduced from 5 to approximately 4 ml/(min g) by a 50% diameter stenosis, and to approximately 2.7, 1.9, 1.4, and 1.1 ml/(min g) by 70, 80, 85, and 90% stenoses, respectively. The dashed lines connecting resting and vasodilated points for individual stenoses are curvilinear because of the curvilinear relationships between pressure gradient and flow in the stenoses. In this schematic illustration, the increases in flow required in the examples for exercise (3.0) and anxiety (1.6) in Fig. 1.3 would fail to be met when stenoses reached 70 and 85%, respectively. (Redrawn with permission from [94].)

pressure gradients across individual stenoses to be measured precisely in coronary patients. In 1993 Pijls and colleagues proposed that stenosis severity could be evaluated in terms of *fractional flow reserve* (FFR), defined as "the maximally achievable flow in the presence of a stenosis divided by the maximum flow expected in the same distribution in the absence of a stenosis" [97]. Using a model modified from Gould's previous studies [98], FFR was calculated by measuring transstenotic gradients during maximum coronary vasodilation and expressing poststenotic pressure as a fraction of prestenotic (aortic) pressure. Application to coronary patients followed quickly [99,100]. The technique appears advantageous in relation to velocity-based measures of reserve [101] and is now utilized in a number of catheterization laboratories. It can evaluate sequential stenoses in a single artery [102] and has demonstrated abnormal pressure drops in arteries of coronary patients not showing focal stenoses arteriographically [103]. A recent commentary by Pijls summarizes additional clinical applications [104].

As discussed subsequently in the section on collateral circulation, the availability of poststenotic pressure measurements offers opportunities for studying the distal coronary bed as well as conduit arteries. However, studies based on the model utilized by Pijls et al. [97] involve additional assumptions concerning coronary back pressure (zero-flow pressure), capacitance, collateral circulation, and effects of compressive resistance. This remains an evolving area of study.

Concurrent abnormalities in conduit artery and microvascular vasodilation

Intrinsic vasodilating mechanisms are noticeably blunted in conduit and resistance vessels in patients with coronary atherosclerosis. As early as 1976 Mudge et al. demonstrated abnormal responses of total coronary resistance during cold pressor testing in patients with coronary disease [105]. The abnormality was subsequently shown to involve both conduit and resistance vessels [12,47] and reflects endothelial dysfunction in both vessel types [106]. The defect in endothelium-mediated vasodilation involves reduced production of nitric oxide and appears to predate the development of clinically evident disease; i.e., it is evident in patients with risk factors for coronary disease who still have angiographically normal coronary arteries [10]. With blunting of normal endothelium-mediated vasodilation, vasoconstrictor mechanisms can become evident [15,30]. As discussed by Heusch et al. [15], α_2-adrenergic microvascular vasoconstriction probably contributes frequently to exercise-induced ischemia.

Collateral circulation

It has long been recognized that a well-developed coronary collateral circulation has a clinically important impact [107,108]. However, the reasons why substantial collaterals develop in only a minority of coronary patients remain unclear. Heterogeneity among individuals involves genetic factors in at least some cases, e.g., collateral development correlates with a particular haptoglobin phenotype in diabetics [109]. It has also been associated with the ability to augment production of vascular endothelial growth factor in response to hypoxia [110].

Coronary collaterals arise from preexisting microvascular interconnections that remodel into functional conductance arteries [111]. Collateralized human hearts show a predominance of collateralization through intramural vessels, with variable additional contributions of larger anastomoses at the epicardial level [112]. Collateral channels connect into the recipient bed primarily at the arteriolar level, i.e., at vessels with diameters of 20–100 µm [113]. Capillary density is not increased after the initial phase of collateral development but increased numbers
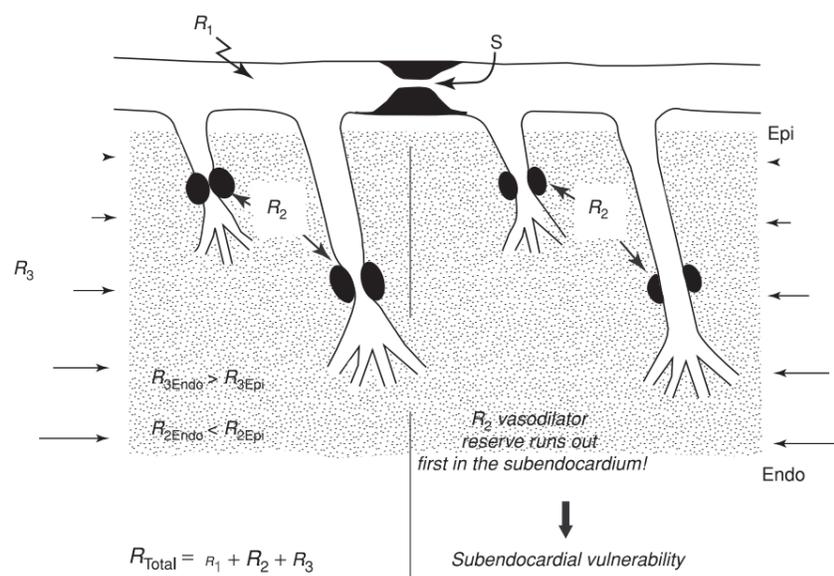
Figure 1.10 Normal transmural differences in perfusion and effects of a coronary stenosis. As discussed previously, microvascular resistance (R_2) is normally less in the inner (Endo) than outer (Epi) layers of the ventricular wall; i.e., subendocardial dilation compensates for the transmural gradient in compressive resistance (R_3). Vasodilator reserve is consequently less in the subendocardium than the subepicardium. Thus, as also illustrated in Fig. 1.4, an inability to maintain the normal balance between myocardial oxygen demand and coronary flow occurs initially in the subendocardium. (Redrawn with permission from [1].)
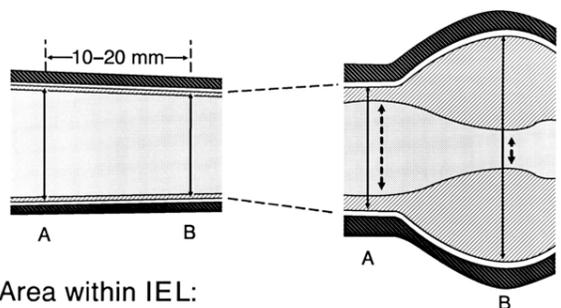
Figure 1.11 Atherosclerotic coronary artery remodeling, illustrated using data from Stiel et al. [95], in human coronary arteries fixed at a normal arterial pressure. The proximal portion of a normal coronary artery is shown on the left and a stenotic atherosclerotic artery on the right. The atherosclerotic process (hatched area) encroaches on luminal area but the degree of encroachment is attenuated by an increase in overall arterial diameter. The local increase in enlargement can be expressed as the ratio of the areas contained within the internal elastic membrane (IEL) at points B and A. In the series of Stiel et al. this ratio averaged 1.79 in diseased arteries, as opposed to 0.93 in nondiseased normally tapering arteries. The percent luminal narrowing that would be calculated arteriographically depends on the relative luminal diameters at points A and B in the atherosclerotic artery. (Reprinted with permission from [94].)

of 20–100 μm distribution vessels persist. Experimental studies indicate that collateral vessels exhibit endothelium-dependent vasodilation [114,115] and are responsive to a variety of vasoactive stimuli. Nitric oxide [116] and prostacyclin [117] appear to have tonic vasodilating activity. Aspirin-induced blockade of cyclooxygenase activity (and presumably prostaglandin production) reduces collateral flow at least transiently but the reduction is reversible with nitroglycerin [118].

Even when coronary collaterals are well developed, the amount of flow that can be provided is limited. The ability to measure distal coronary artery pressure during angioplasty has provided more quantitative estimates of collateral efficacy than can be obtained angiographically. When an artery is occluded distal to a stenosis, the steady-state occlusion pressure represents the inflow pressure generated by collaterals in the artery's distal bed. This pressure exceeded 30 mm Hg in only 26 of 120 patients reported by Pijls et al. in 1995 [119, Fig. 1.3]. Values less than 30 mm Hg have a very limited flow supplying capacity (see Figs. 1.4, 1.8, and 1.9) and usually cannot maintain a normal demand/supply balance under even resting conditions. They may be sufficient if demand is reduced, e.g., in hibernating myocardium [120].

In their original study describing the use of fractional flow reserve to evaluate stenosis severity [97], Pijls and colleagues also proposed a pressure-based collateral flow index based on the relative values of distal coronary pressure

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(P_w) and aortic pressure (P_a) during balloon occlusion. The model on which the index is based assumes a coronary back pressure equal to central venous pressure (P_v) and is calculated as $(P_w - P_v)/(P_a - P_v)$. In their 1995 study of 120 coronary patients, an index "cut-point" of 0.24 was felt to be optimal in separating patients with and without ECG signs of ischemia during balloon occlusion [119]. More recently, using an assumed P_v of 5 mm Hg, Seiler and colleagues have reported values averaging 0.17 ± 0.09 in 40 patients with, and 0.44 ± 0.16 in 11 patients without, ECG signs of ischemia during balloon occlusion [121]. This group also calculated a collateral flow index based on Doppler flow velocities in the stenotic artery before and following angioplasty and found it similar to the pressure-based index (average difference $= 0.03 \pm 0.10$, linear $r^2 = 0.64$). They have now extended their experience to 450 patients and confirm that two-thirds of patients do not have sufficient collateral flow to prevent myocardial ischemia during coronary occlusion [122]. Not withstanding these limitations, even a level of collateral flow that cannot prevent ischemia can often reduce its adverse consequences [123]. While collaterals may provide adequate flow to preserve viability, and perhaps even normal resting flow in some patients, collaterals that increase coronary flow sufficiently to prevent ischemia during peak exercise are uncommon, even when they are prominent angiographically.

Clinical importance of regional differences in perfusion

As noted in an earlier section of this chapter, maximum coronary vasodilation involves endothelium-mediated vasodilation as well as direct relaxation of arteriolar smooth muscle. Because of the abnormalities summarized above, coronary flow reserve in patients with coronary artery disease can be decreased moderately throughout the left ventricle independently of the effects of arterial stenoses. Thus, regional differences in perfusion are usually more important than absolute reductions in flow reserve for evaluating the effects of a stenosis during exercise, pharmacological vasodilation, or other stresses.

Because radionuclide approaches for evaluating perfusion depend on assessing the entrance and/or retention of blood-borne tracer in the myocardium, it is important to understand the relationship between flow and transmyocardial extraction of tracer. With the exception of ^{15}O-water, virtually all tracers exhibit a reduction in the proportion extracted during circulation through the myocardium as flow exceeds approximately two times normal. For example, a number of studies have documented that the fractional extractions of ^{201}Tl and ^{99m}Tc-sestamibi or -tetrofosmin decrease as flow increases above approximately 2 ml/(min g) [124,125]. This property is also
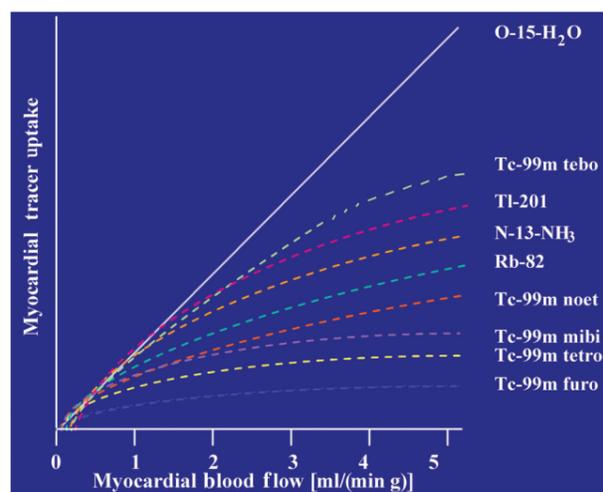
Figure 1.12 Schematic representation of relative extraction fractions of PET and SPECT radiopharmaceuticals.

observed with PET agents such as ^{82}Rb and ^{13}N-ammonia. Since the flow during maximum vasodilation is normally at least 4 ml/(min g), modest reductions in vasodilated flow – as illustrated schematically for a 70% stenosis in Fig. 1.9 – can be difficult to appreciate [126]. While issues of tissue retention through the imaging time are also important, the reduction of extraction fraction with increasing flow is the fundamental limiting variable in detectibility of mild stenoses with the tracer method. ^{99m}Tc-teboroxime, a tracer that was commercially available in the early 1990s in the United States, was reported to have extraction fraction at high flow rates exceeding that of ^{201}Tl, suggesting that in combination with vasodilator stress, this agent might be more sensitive than other radionuclide methods in detecting mild stenoses. Rapid washout of this tracer from the myocardium, and avid accumulation in the liver, resulted in little practical clinical use. The relative extraction fractions of the various PET and SPECT radiopharmaceuticals are schematically illustrated in Fig. 1.12. Quantitative measurements of perfusion using PET and tracers such as ^{13}NH$_3$, ^{15}O, and ^{82}Rb involve additional complexities that Schelbert has summarized [54]; those involved in the use of dynamic SPECT have been summarized by Gullberg [56].

Although data addressing the minimal difference in regional flow needed for a defect to be identified are limited, a difference of at least 30% seems a reasonable estimate but depends on the detection system being employed. Transmural differences resulting in full-thickness flow reductions of less than 30% require higher-than-usual resolution with most tracer techniques. Figure 1.13 presents interpretive issues for three situations that might be expected to produce similar defects on perfusion images but would have different clinical implications.
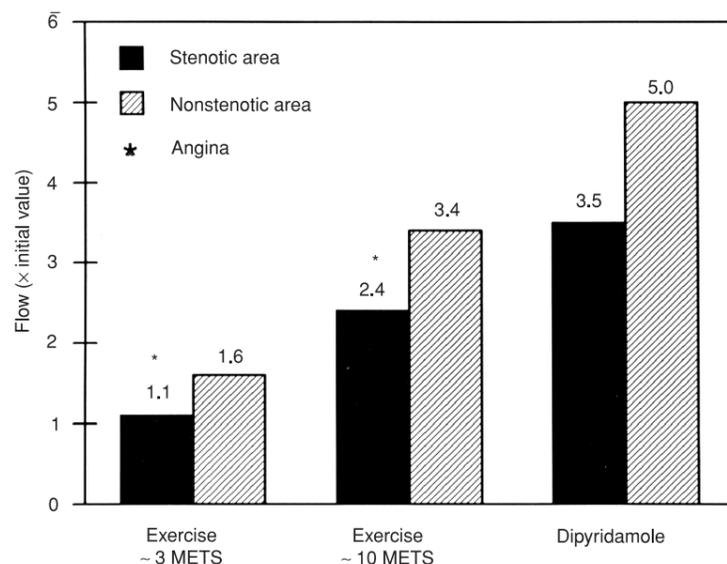
Figure 1.13 Examples of 30% reductions in regional flow having different clinical implications. The paired columns on the left depict exercise with angina at a low work load. Extrapolating from the studies of Kitamura et al. [4], an exercise level of 3 metabolic equivalents (METS) would require an increase to 1.6 times resting flow (1.0). The center columns represent exercise with angina at a high work load (10 METS), requiring a flow of 3.4 times the resting value. Although the relative perfusion deficits are similar, the therapeutic implications of ischemia at 3 and 10 METS differ. The columns on the right represent findings that might occur during maximum pharma-cological vasodilation with a 60% stenosis. A 30% regional reduction in flow corresponds to a regional increase to 3.5 (rather than 5.0) times resting flow and occurs without a corresponding increase in myocardial oxygen demand. Thus, the relative perfusion deficit is not associated with ischemia. Although a finding of this type can be diagnostically useful in identifying an asymptomatic stenosis, it may be difficult to discern using tracer techniques in which transmyocardial tracer extraction decreases progressively as flow exceeds twice resting values. (Reprinted with permission from [94].)

Pathophysiologic alterations in microvascular function and conduit artery caliber without apparent coronary artery disease

Information is now available concerning conduit artery and microvascular function in a variety of clinically relevant situations in which coronary artery disease is not apparent. Abnormalities in endothelial-mediated coronary vasomotion have been identified in individuals with coronary risk factors and in the early stages of several disease processes. Four situations are illustrative.

Cigarette smoking

It is well established that cigarette smoking produces acute increases in heart rate, arterial pressure, and myocardial contractility. These are mediated through the sympathetic nervous system and involve both cardiostimulatory (β-adrenergic) and vasoconstrictor (α-adrenergic) influences [127].

Since cigarette smoking acutely increases the double product index, increases in resting coronary flow are expected and do occur in otherwise healthy young adults with relatively short smoking histories (6 ± 3 pack years) [128]. However, flow during dipyridamole-induced vasodilation is reduced in these individuals, resulting in substantial transient decreases in flow reserve. In long-term smokers (27 ± 13 years) without cardiovascular risk factors, expected increases in resting coronary flow during smoking are blunted or reversed [129]. Long-term smokers also show blunted flow responses to cold pressor testing [130,131], which can be normalized by intravenous administration of L-arginine and are therefore felt to reflect sustained endothelial dysfunction [130].

Abnormal responses to smoking are accentuated in individuals with coronary artery disease. It has been known since the 1980s that expected increases in coronary flow accompanying smoking-induced increases in double product are blunted or reversed in coronary patients [132–135]. The abnormal response involves constriction of both epicardial conduit arteries and microcirculatory resistance vessels [136,137]. It can be reversed by nonspecific α-adrenergic blockade [135] and probably involves α_1-adrenergic constriction of conduit arteries and α_2-adrenergic constriction of resistance vessels as well as blunted endothelial-dependent vasodilatory mechanisms.

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It can also be prevented by the administration of calcium antagonists or nitroglycerin [138].

Hyperinsulinemia and diabetes mellitus

Indications that hyperinsulinemia is an independent risk factor for developing ischemic heart disease have stimulated a variety of studies of insulin's effects on the coronary circulation. Effects on conduit arteries have been examined using intracoronary acetlycholine or the cold pressor test. Effects on microvascular resistance have been evaluated by responses of coronary flow to cold pressor testing, intravenous adenosine infusion, or intracoronary papaverine injection.

Because insulin increases sympathetic nerve activity, modest increases in basal levels of coronary flow following insulin administration have to be considered in relation to concomitant changes in myocardial oxygen demand [139]. McNulty et al. attempted to circumvent this issue using intracoronary infusion of small doses of insulin in patients undergoing coronary arteriography [140]. They report approximately 20% consistent increases in coronary sinus flow without increases in myocardial oxygen consumption. In addition, Sundell and colleagues find that insulin increases adenosine-stimulated flow and coronary flow reserve in a dose-dependent manner in healthy young subjects [141]. Flow during adenosine infusion increased by an average of 20% during physiological hyperinsulinemia (∼65 mU/l), and by an additional 19% when insulin levels were increased to pharmacological levels (∼460 mU/l). Thus, insulin appears to have vasodilator as well as hypoglycemic activity.

Insulin-induced dilation of the coronary vasculature involves activation of both the sympathetic nervous system and endothelium-dependent mechanisms. Since insulin-induced increments in coronary flow reserve in healthy young men are not affected by dexamethasone pretreatment, local endothelium-dependent mechanisms (rather than central sympathetic activation) are thought normally to predominate [142]. However, although insulin-induced increments in coronary reserve are initially similar in young men with and without type 1 diabetes, the increments in diabetic patients can be abolished by dexamethasone pretreatment [142]. Central sympathetic activation therefore seems to play an important role in diabetes, possibly by augmenting adrenergic microvascular dilation to compensate for endothelial dysfunction. Studies of Di Carli et al. support this view [33]. Increases in coronary flow in partially reinnervated transplanted hearts during cold pressor testing were greater in regions of the left ventricle showing sympathetic reinnervation (as assessed with ^{11}C-hydroxyephedrine uptake) than in those remaining denervated. In addition, despite similar responses to intravenous adenosine, diabetic patients with autonomic dysfunction showed systematically smaller increases in coronary flow during cold pressor testing than diabetic patients without autonomic neuropathy [143].

Coronary vascular dysfunction can be demonstrated in the early stages of diabetes. Increases in coronary flow during cold pressor testing are blunted in insulin-resistant individuals without glucose intolerance, and the abnormality can be normalized by insulin-sensitizing thiazolidinedione therapy [144]. Abnormal responses to cold pressor testing also occur in approximately one-third of asymptomatic, non-insulin-treated type 2 diabetic patients [145]. As diabetes progresses and becomes evident clinically, abnormal responses to cold pressor testing and reductions in coronary flow reserve become present consistently [143,146–148]. Reduced hyperemic responses to adenosine can, at least in young otherwise healthy type I diabetics, be ameliorated by raising insulin levels to supraphysiologic levels (93 ± 27 mU/l) [149].

Mechanisms possibly underlying abnormal coronary vascular responses in diabetic patients continue to be explored. Miura et al. have demonstrated that K_{ATP} channel-mediated coronary arteriolar dilation is intrinsically impaired [150]. Nitenberg and colleagues report that abnormal responses to cold pressor testing and reductions in flow reserve can be ameliorated by inhibition of oxygen-derived free radical production [151,152]. Johansson et al. find that administration of proinsulin C-peptide, which is cleaved from proinsulin and released into the circulation in amounts equimolar with insulin, can restore reduced levels of adenosine-stimulated coronary flow to those of healthy controls while plasma insulin concentrations remain in the normal physiological range [153]. Hansen et al. have reported similarly beneficial effects of C-peptide using contrast echocardiographic indices of flow [154].

The possibility that occult coronary artery disease in diabetic patients played a role in some of the findings in this section cannot be excluded, particularly in studies of individuals undergoing diagnostic cardiac catheterization who proved to have arteriographically normal or "near normal" coronary arteries. Hemodynamically significant coronary stenoses would no doubt accentuate diabetes-related abnormalities in cold pressor testing and coronary flow reserve. It remains clear, however, that diabetics often have abnormal flow reserve in the absence of epicardial stenoses, probably secondary to endothelial dysfunction.

Lipid abnormalities

Schelbert has summarized several studies indicating systematic reductions in hyperemic flows (∼25%) and coronary flow reserve in hypercholesterolemic and hypertriglyceridemic patients without clinically detectible coronary artery disease [54, Table 14]. Reductions in hyperemic flow and coronary reserve probably again reflect

endothelial dysfunction. Responses to cholesterol-lowering therapies indicate that these abnormalities are at least partially reversible [54, Table 15]. Leung and Lau have reported that acetylcholine-induced epicardial artery constriction in hypercholesterolemic patients with angiographically normal coronary arteries can also be reversed by cholesterol lowering [155].

Hypertension and ventricular hypertrophy

Endothelium-dependent coronary vasomotion is frequently abnormal in hypertensive patients. Constriction of conduit arteries to acetylcholine was identified in the early 1990s [156–159]. Coronary flow reserve was subsequently reported to be reduced in hypertensive patients without other coronary risk factors [106,160], and in asymptomatic young men with borderline hypertension and no signs of angina or left ventricular hypertrophy [161]. Microvascular abnormalities have been suggested to underlie anginal chest pain in hypertensive patients without left ventricular hypertrophy [162]. In part, reduced coronary flow reserve is related to increased resting flow levels in these patients; however, there is also a reduced vasomotion component.

When left ventricular hypertrophy becomes demonstrable in hypertensive individuals, coronary flow reserve is reduced consistently. Reductions averaging 33% were reported by Strauer as early as 1979 [163]. This finding was confirmed in the early 1980s [164,165], has been observed consistently in subsequent studies, and has been suggested to underlie angina pectoris in hypertensive patients with hypertrophied ventricles [165]. The degree of reduction in flow reserve in hypertensive disease varies directly with the magnitude of hypertrophy [166] and is greater in African-Americans than Caucasian-Americans [72]. Consistent with the reduction in reserve, Polese et al. have reported that the "breakpoint" pressure at which autoregulatory vasodilation is exhausted (see Fig. 1.4) is increased in hypertensive patients with left ventricular hypertrophy [167]. Experimental studies suggest that increases in coronary back pressure, i.e., "zero-flow pressure," also play a role in the reduced reserve of hypertrophied ventricles [168]. Reductions in reserve can, at least in some cases, involve structural as well as functional changes [169]. Although several groups have demonstrated treatment-induced regression of hypertrophy, information about changes in flow reserve is limited. Studies thus far indicate improvement [170–172].

Reductions in coronary flow reserve also occur regularly in ventricular hypertrophy caused by conditions other than essential hypertension. Early studies in humans with aortic stenosis and volume overload hypertrophy were performed by Marcus and colleagues [65,173,174]. Studies during the past two decades have addressed a number of additional abnormalities [175,176].

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