Physiological Assessment of Coronary Stenoses and the Microcirculation

Javier Escaned
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Editors

Springer

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ISBN 978-1-4471-5244-6 ISBN 978-1-4471-5245-3 (eBook)
DOI 10.1007/978-1-4471-5245-3

Library of Congress Control Number: 2017940189

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer-Verlag London Ltd.
The registered company address is: 236 Gray's Inn Road, London WC1X 8HB, United Kingdom

Preface

This book was completed in 2016, when coronary physiology probably reached its maturity.

Forty years had passed since the publication of the landmark articles linking stenosis severity and coronary flow impairment. The impact of this research was enormous and triggered the development of numerous invasive and non-invasive technologies aimed at interrogating the coronary circulation with a new index, coronary flow reserve.

Twenty years later, fractional flow reserve (FFR) demonstrated its diagnostic utility as a pressure-derived index of stenosis severity. Over the next decades, FFR was used in clinical trials to demonstrate the importance of functional guidance of coronary revascularization and demonstrated, this time without any residual doubt, that angiography is a deceptive technique in assessing functional relevance of coronary stenoses.

Today, two decades later, a new revolution in coronary physiology is occurring applying computational fluid dynamics and in silico simulations to coronary imaging with the aim of calculating FFR-like indices without the need for intracoronary instrumentation. Furthermore, new indices such as the instantaneous wave free ratio (iFR) have been developed to facilitate easier pressure guidewire interrogation of the coronary arteries and hopefully increase its use.

Despite this progress and the growing interest generated by these developments, adoption of coronary physiology in clinical practice is still lagging. The main aim of this book is to serve both as an introduction to coronary physiology for all those interested in the field of cardiovascular disease and as a companion for practicing clinical and interventional cardiologists.

In that regard, this book provides a comprehensive approach to the interrogation of different domains of the coronary circulation. In 2016, coronary physiology is still largely stenosis centered. Assessment of the coronary microcirculation is seldom performed in the catheterization laboratory, and few centers routinely perform coronary vasomotion tests. This occurs despite growing information on the implications that microcirculatory and vasomotion disorders have for both patient's symptoms and prognosis. It is quite likely that a more extensive interest in these topics will foster the development and availability of diagnostic methods to interrogate the coronary circulation beyond the stenoses. And if this happens, surely new avenues for research and patient care will follow.

We are extremely grateful to all the authors for sharing their expertise in the topics covered in the many chapters of this book. We are also indebted to our Deputy Editors Hernán Mejía-Rentería, MD, and Nicola Ryan, MB, BCh, for their support throughout the edition of this book, and to Sara Fernández, MSc, for valuable technical assistance.

Madrid, Spain — Javier Escaned
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The Physiology of the Coronary Circulation

Contents

Hemodynamic Effects of Epicardial Stenoses

Lorena Casadonte and Maria Siebes

J. Escaned, J. Davies (eds.), *Physiological Assessment of Coronary Stenoses and the Microcirculation*,
DOI 10.1007/978-1-4471-5245-3_1

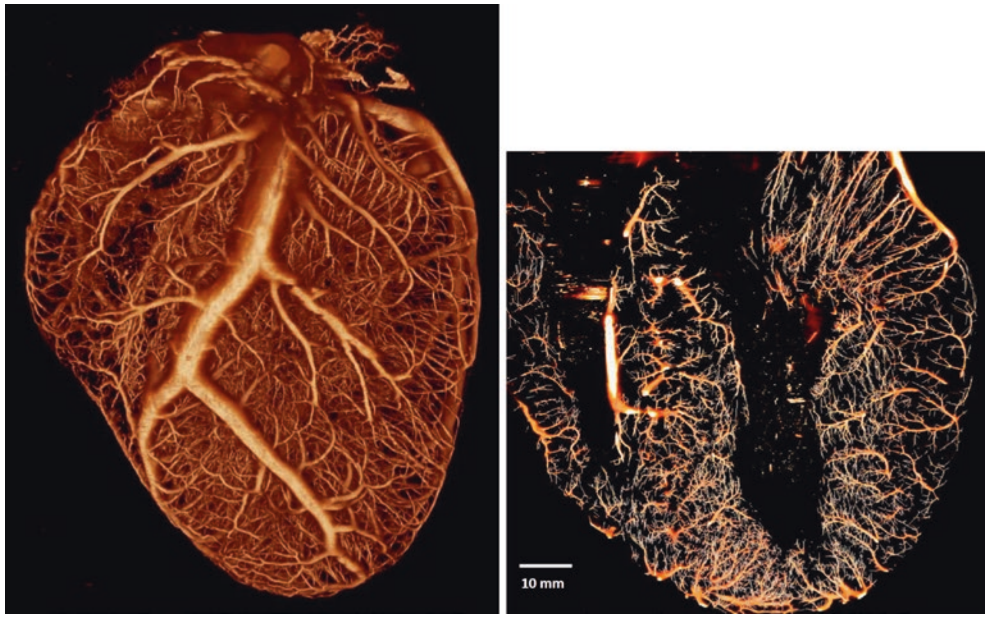

Fig. 1.1 3D image of coronary arteries of a dog heart obtained by a novel cryomicrotome technique with epifluorescence imaging. The vessels were filled with fluorescent cast material, and the frozen heart was alternately sliced at 40 µm and the bulk surface imaged with a high-resolution CCD camera [4]. The right panel shows a longitudinal cross section of a 2-mm-thick maximal intensity projection of transmural vessels (partially skeletonized) where the branching pattern of penetrating vessels is clearly visible

1.1 Principles of Coronary Physiology

A comprehensive understanding of coronary physiology is fundamental to aid in the interpretation of coronary pressure and flow signals obtained in patients with coronary artery disease. The heart is perfused by an intricate network of arteries that supply oxygen and nutrients to this continuously active muscle. Multiple branching vessels arise from epicardial conduit arteries (Fig. 1.1) and perfuse small volumes at the subepicardial layer of the myocardium, whereas the subendocardium is perfused by penetrating arteries that pass through the outer layers of the myocardium and only branch out into numerous vessels once they have reached the inner layer, where they supply larger volumes of myocardial tissue [1–4].

From a physical standpoint, minimal vascular resistance is principally determined by the segmental dimensions (length and diameter) of the distributed maximally dilated network. Thus, in the absence of epicardial coronary artery stenosis, maximal coronary flow is a function of the coronary driving pressure and of the maximal surface area of the dilated coronary resistance vessels. In this respect it is important to recall that all blood vessels are essentially elastic tubes when active smooth muscle tone is minimal. Once coronary arterioles are maximally dilated, they passively react to changes in distending and extravascular pressure, i.e., their diameter becomes pressure dependent [5–7].

Coronary pressure-flow relations Oxygen extraction from the coronary circulation is near maximal at rest, and raised myocardial oxygen demand is met by a corresponding change in coronary blood flow. The dynamic match to oxygen consumption at constant arterial pressure is denoted as metabolic flow adaptation or functional hyperemia. For a given cardiac workload, coronary blood flow remains constant over a wide range of arterial perfusion pressures (typically from about 60 to 140 mmHg) by an intrinsic mechanism denoted as autoregulation [8]. This entails coronary resistance changes in a direction parallel to the change in perfusion pressure. Importantly, autoregulation fails at higher pressures in subendocardial than subepicardial vessels [9, 10]. All arteries and arterioles contribute to flow control by changing their smooth muscle tone. Resistance to flow is negligible in large epicardial vessels, and most of coronary resistance resides in the intramural microvessels smaller than approximately 300 µm in diameter [11]. The regulation of coronary microvascular resistance includes integrative mechanisms of metabolic, myogenic, and flow-dependent vascular control, discussed in more detail elsewhere in this book. Distributed vasodilation decreases local microvascular resistance in the normal heart to maintain resting flow at the autoregulatory level as coronary pressure falls, e.g., in the presence of an epicardial coronary stenosis [12]. Substantial vasodilator reserve exists to increase flow above resting level during exercise, and values of 4–5 times above resting flow levels have been reported for humans [13–17]. Vasodilation results in a substantial redistribution of microvascular resistance compared to baseline conditions. Chilian and colleagues [11] reported that the resistance of arterial microvessels (<170 µm diameter) decreased nearly 15-fold for a sixfold increase in flow after dipyridamole administration, while papaverine caused preferential vasodilation of larger arterioles (>200 µm diameter) [18].

At low pressures the pressure-flow curve declines in a convex fashion toward the flow axis, and actual zero-flow pressure (P_{zf}) is only 2–4 mmHg above coronary sinus pressure at steady state [19]. The curvature reflects the progressive increase in resistance that results from the decrease in vascular transmural pressure. The curvilinear shape of this

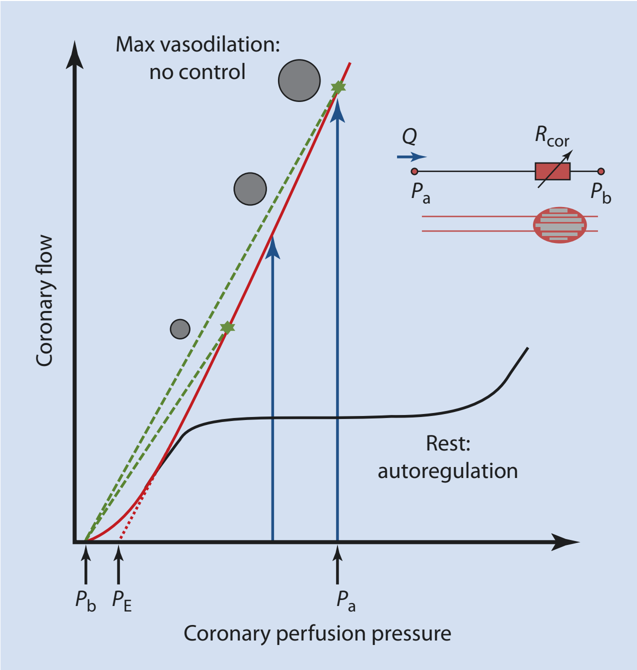

Fig. 1.2 Coronary pressure-flow relations in the absence of a stenosis. At rest, flow (Q) is maintained over a large range of arterial perfusion pressures. At maximal vasodilation (*red line*), flow can increase 4–5 times at normal arterial pressure (P_a); however, control is exhausted and flow reserve depends on pressure (blue arrows). The line curves at low pressures toward a zero flow intercept, which is the effective back pressure (P_b) to flow and only slightly above venous pressure. P_E is obtained by linear extrapolation of the straight part of the pressure-flow curve. As pressure falls, the diameter of the passive resistance vessels decreases (*circles*), and microvascular resistance (R_{cor}) gradually increases. The *dashed lines* (*green*) indicate pressure-flow lines at constant minimal resistance, shown here for a normal and a reduced perfusion pressure (*stars*). The inverse of the slope of these lines represents minimal resistance

pressure-flow curve is important in defining coronary vascular resistance, and the influence of distributed capacitive effects should be kept in mind when approximating zero-flow pressure by linear extrapolation to the pressure axis from data obtained after cessation of flow in epicardial vessels [19]. Moreover, data in isolated maximally dilated dog hearts suggest that P_{zf} is likely distributed across the left ventricular wall rather than being a function of global flow [20].

Typical coronary pressure-flow relations at autoregulation and at maximal vasodilation are schematically shown in Fig. 1.2.

The coronary pressure-flow relation at maximal vasodilation is a steep line with a nonzero pressure intercept, and flow is now a function of perfusion pressure. Although the pressure-flow curve at vasodilation (without control) appears relatively straight at pressures above about 40 mmHg, this line is likely the result of interacting mechanisms which are obscured from signals obtained at the epicardial arteries [21]. These include time constants involved in emptying microvascular compliance and coronary resistance changes that are affected by the greater narrowing of microvessels at the lower pressure range due to the strong nonlinear pressure-distensibility relation for vessels with relaxed smooth muscle tone [6, 22–26].

Coronary blood flow is principally determined by the driving pressure and the resistance of the coronary vascular bed. In the absence of an epicardial stenosis, the driving pressure is the difference between aortic input pressure P_a and the effective back pressure P_b at which flow becomes zero. Since steady-state P_b is difficult to assess in humans, venous pressure can be used as a reasonable approximation. In equivalence to Ohm's law, the resistance R of a vascular compartment is defined as the pressure drop ΔP across that compartment divided by flow Q:

$$R = \Delta P / Q \quad (1.1)$$

By analogy, coronary resistance at vasodilation is then the inverse slope of the line connecting P_b on the pressure axis with the data point on the pressure-flow line at a certain arterial pressure (star symbol in Fig. 1.2). The decreasing slope of these lines reflects the increased coronary resistance at lower perfusion pressure, e.g., distal to a stenosis.

At vasodilation, coronary pressure and flow are *not* linearly related and do not pass through the origin. The intercept on the pressure axis makes this relation incremental linear, and the change in flow is not proportional to the change in pressure [26, 27]. Hence, the inverse slope of the hyperaemic pressure-flow line is not a measure of coronary resistance. Although the units are those of resistance, the inverse slope is the change in pressure divided by the *change* in flow. For example, the parallel rightward shift of this relationship from the arrested to the beating heart [28] clearly implies an increase in resistance due to cardiac contraction, but resistance determined from the slope would remain constant. Minimal coronary resistance has been shown to increase with decreasing perfusion pressure (and vice versa) in animals and humans [5, 6, 29, 30], and models that assume a pressure-independent microvascular resistance at maximal dilation are rather unrealistic.

Other influences can independently alter the coronary pressure-flow relationships illustrated schematically in Fig. 1.3.

An increase in oxygen consumption at rest shifts the autoregulatory plateau upward (1), which implies that autoregulation fails at higher pressure. Additionally, an increased resistance with lower maximal flow at the same pressure ensues when the slope of the pressure-flow relation for maximally dilated vessels decreases (2), as with left ventricular hypertrophy, increased blood viscosity in polycythemia, or small vessel disease due to, e.g., hypertension [31, 32]. Notably, a rise in myocardial wall stress due to cardiac contraction induces a rightward shift of the hyperemic pressure-flow curve. This parallel shift between a non-beating and a beating heart was shown to amount to half of the mean left ventricular pressure [26, 28]. Several other factors can raise zero-flow pressure (3), such as elevated left ventricular end-diastolic pressure or coronary venous pressure [33, 34], and collateral flow, which tends to decrease the curvature at the low-pressure range [35, 36]. It is possible for several factors to operate

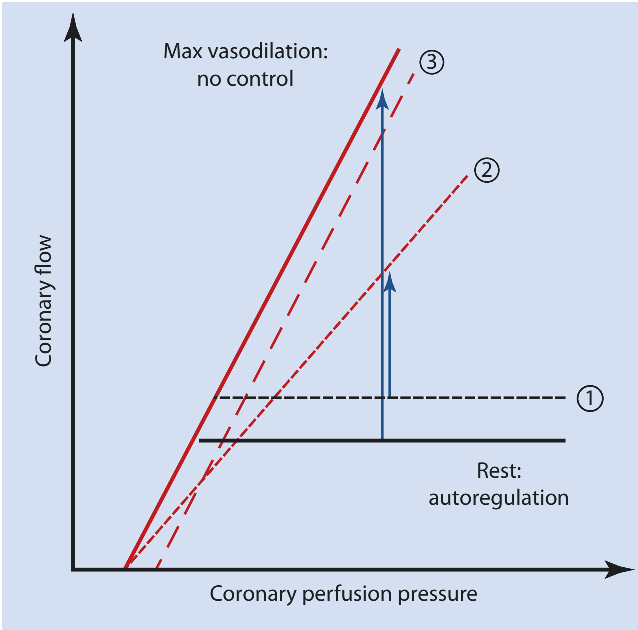

Fig. 1.3 Factors that decrease coronary flow reserve at any perfusion pressure. (*1*) A raised autoregulated flow, e.g., due to increased oxygen consumption. (*2*) When the slope of the pressure-flow line during maximal vasodilation is reduced, the maximum flow falls. (*3*) A parallel shift to the right of the pressure-flow relationship during vasodilation increases zero-flow pressure. Note that autoregulation fails at higher pressures for each condition

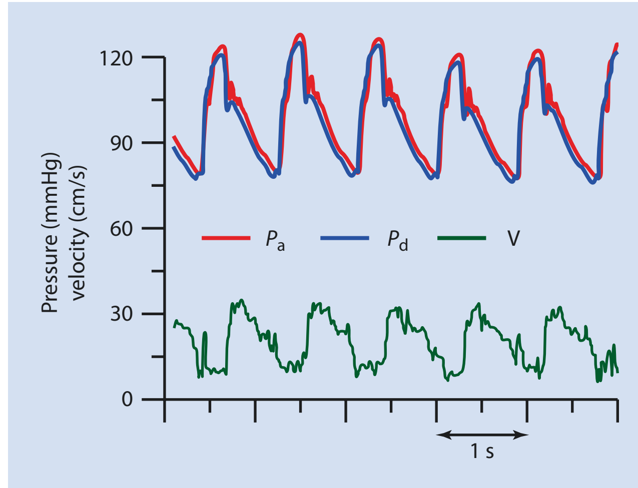

Fig. 1.4 Typical pressure and flow velocity waveforms obtained in a normal coronary artery at rest. Coronary flow is maximal during the diastolic phase. P_a aortic pressure, P_d distal coronary pressure, *v* flow velocity

synergistically, leading to a more pronounced reduction in flow reserve for any given perfusion pressure and to failure of autoregulation at a higher pressure. These concepts have been summarized in several publications [10, 26, 32, 37, 38].

Determinants of coronary blood flow The main cause for the pulsatile behavior of coronary blood flow is cardiac contraction. In contrast to the systemic circulation, coronary inflow is low in systole despite higher input pressure and highest in diastole when aortic input pressure declines (Fig. 1.4).

The forces exerted by the squeezing action of the heart muscle on the compressible vessels embedded in the myocardium vary the intramural blood volume throughout a heartbeat and lead to an impediment of systolic inflow and augmentation of venous outflow during systole. The out-of-phase behavior of these signals can be explained by the intramyocardial pump model [22, 23, 39] and varying elastance concept [40]. Basically, the transmural tissue pressure gradient generated by the intramyocardial pump that acts on the intramyocardial compliance is modulated by the time-varying elastance of the myocardium and vessels during the cardiac cycle [25, 41]. Both models assume that coronary resistance is volume dependent. The distensibility of the intramural vessels in interaction with the surrounding myocardial tissue constitutes the so-called intramyocardial compliance. The rate of volume exchange between systole and diastole (capacitive flow) modifies the microvascular inflow and outflow resistances [42, 43]. Due to the longtime constants involved in changing the blood volume of the large intramyocardial compliance, microvascular resistance is varying throughout the cardiac cycle and cannot simply be divided into systolic and diastolic components.

Transmural flow and subendocardial vulnerability A dense network of branching elastic vessels delivers blood flow across the myocardium; however, the flow distribution across the myocardium is not uniform. Studies in animals and humans have demonstrated a profound perfusion heterogeneity both across and within layers [44–46], which makes it difficult to assess subendocardial perfusion from epicardial intracoronary measurements.

Several mechanisms contribute to the subendocardial vulnerability to ischemia [47]. The impeding effect of extravascular compression during cardiac contraction is stronger at the subendocardium. This is partially compensated by the larger total volume of the resistance vessels in the inner than the outer layer of the heart wall, yielding a lower intrinsic resistance at full dilation [48]. Subendocardial perfusion was shown to be about 50 % higher than at the subepicardium in the non-beating dog heart [2]. Transmural perfusion during maximal coronary vasodilation was nearly uniform at a heart rate of 100 bpm, whereas subendocardial flow was about half of subepicardial flow at a heart rate of about 200 bpm [49]. This implies that over heart rates ranging from 0 to 200 bpm, heart contraction may reduce subendocardial flow by a factor of 3, while subepicardial flow may even slightly increase at elevated heart rates [50].

Clearly, factors that affect the rate of filling of intramural vessels in diastole, such as perfusion pressure and the duration of diastole [51], modulate microvascular conductance at the subendocardium. Perfusion pressure is generally lower in the subendocardial layer due to the longer path length (greater longitudinal pressure drop) for blood to reach the subendocardium via transmural penetrating vessels. A decreased perfusion pressure tends to redistribute blood flow away from the subendocardium and causes a reduction of the subendocardial/subepicardial blood flow ratio [52]. Further reduction in perfusion pressure distal to a stenosis decreases the diameter of subendocardial arterioles more than the subepicardial arterioles, and additionally, a stenosis selectively decreases the dilatory response of subendocardial arterioles [53]. Another confounding factor is inadequate perfusion time, expressed as the diastolic time fraction, DTF, which leads to insufficient flow to subendocardium, while the more superficial layers may still be adequately perfused. Moreover, the effect of DTF on subendocardial blood flow is exacerbated at low perfusion pressure distal to a stenosis [54–56]. Interestingly, DTF was shown to be prolonged at reduced coronary pressure distal to a stenosis, which may act as a protective regulatory mechanism when vasodilatory reserve is exhausted [57].

1.2 Stenosis Hemodynamics

This section provides an overview of stenosis fluid dynamics and its mathematical description as derived from in vitro and in vivo experiments.

Stenosis pressure drop-flow (Δ*P*-*Q*) characteristics Pressure is lost due to viscous friction, when blood flows through a vessel. For steady and laminar flow, the pressure drop ΔP over a uniform tube of length L is given by Poiseuille's law as

$$\Delta P = \frac{32\ \mu L}{D^2} v \qquad (1.2)$$

where μ is the viscosity, D is the diameter of the tube, and v is the mean cross-sectional velocity. In terms of volume flow Q and diameter D, this equation becomes

$$\Delta P = \frac{128\ \mu L}{\pi D^4} Q \qquad (1.3)$$

This implies that for a given tube dimension and length, the resistance $R = \Delta P/Q$ is constant. Viscous shear determines viscous energy losses along the entire length of an artery. The pressure drop increases with the inverse fourth power of the tube diameter, i.e., when the diameter is reduced by factor of 2, the resistance increases 16 times for the same flow and unit length. This relationship clearly shows the dominant influence of vessel diameter, and both active and passive mechanisms can substantially change vessel resistance and flow.

The main assumptions for Poiseuille's law are (1) a rigid, straight tube of uniform cross section, (2) steady, laminar flow with a parabolic velocity profile, and (3) constant viscosity, i.e., blood is considered a Newtonian fluid. These assumptions are far from true in curved, branching, and compliant vessels with pulsatile blood flow, but Poiseuille's law can serve as a first-order approximation.

For a change in diameter along the tube, conservation of mass applied to fluid transport comes into play. Conservation of mass states that the volume of blood entering a vessel per unit time is equal to the rate at which it leaves the vessel. This is described by the so-called continuity equation, with A the cross-sectional area:

$$Q = A_1 v_1 = A_2 v_2 = \text{constant} \qquad (1.4)$$

Bernoulli's law relates blood pressure to flow velocity v and is based on the conservation of energy and conservation of momentum. It states that the sum of static pressure, hydrostatic pressure (potential energy), and dynamic pressure (kinetic energy) remains constant:

$$P_{tot} = P + \rho g h + \tfrac{1}{2}\rho v^2 = \text{constant} \qquad (1.5)$$

where ρ is the blood density, g is the gravitational acceleration, and h is the height of the fluid column above a reference level. Pressure losses due to friction are neglected (inviscid flow is assumed), and the fluid is considered incompressible, with constant density. Note that for a blood density of 1.06 g/cm^3, a difference in hydrostatic pressure (mmHg) is related to a change in the height (h, cm) by $\Delta P = \Delta h \cdot 0.78$. If the height is constant, then Eq. 1.5 reduces to

$$P_1 + \tfrac{1}{2}\rho v_1^2 = P_2 + \tfrac{1}{2}\rho v_2^2 \qquad (1.6)$$

As blood enters a narrowed section, the velocity v increases proportional to the decrease in cross-sectional area of the vessel, and pressure is lost ($P_2 < P_1$) due to convective acceleration ($v_2 > v_1$), with conversion of pressure to kinetic energy, as depicted in Fig. 1.5. In addition, there is a pressure drop due to viscous losses as blood moves through the stenosis.

Under ideal circumstances, pressure would be recovered once the diverging section is reached where the flow decelerates. However, blood emerges from the stenosis as an inertial jet, leading to flow separation and formation of a recirculation zone, with eddies and viscous shear stresses between slow and fast moving fluid particles. The extent of this recirculation zone depends on stenosis area reduction and varies with flow [58, 59]. In addition, significant irreversible losses are incurred due to viscous friction along the length of the converging and narrowed section, which can be approximated by Poiseuille's law for the reduced diameter in the narrowed section. As a result, pressure is lowest inside the narrowed stenosis section, close to the point of flow separation, and only a small portion of kinetic energy is converted back to pressure energy downstream of the stenosis.

Based on a series of experiments with steady and pulsatile flows through models of concentric and eccentric stenoses in the 1970s, Young and co-workers [60–62] developed an empirical relationship describing the pressure drop across as a function of stenosis geometry. In essence, the total pressure drop across a stenosis is a quadratic function of flow and equals the sum of viscous losses along the entrance and throat of the stenosis, ΔP_v, that are linearly related to flow and inertial losses at the exit of the stenosis, ΔP_e, that scale with the square of the flow:

$$\Delta P = \Delta P_v + \Delta P_e \qquad (1.7)$$

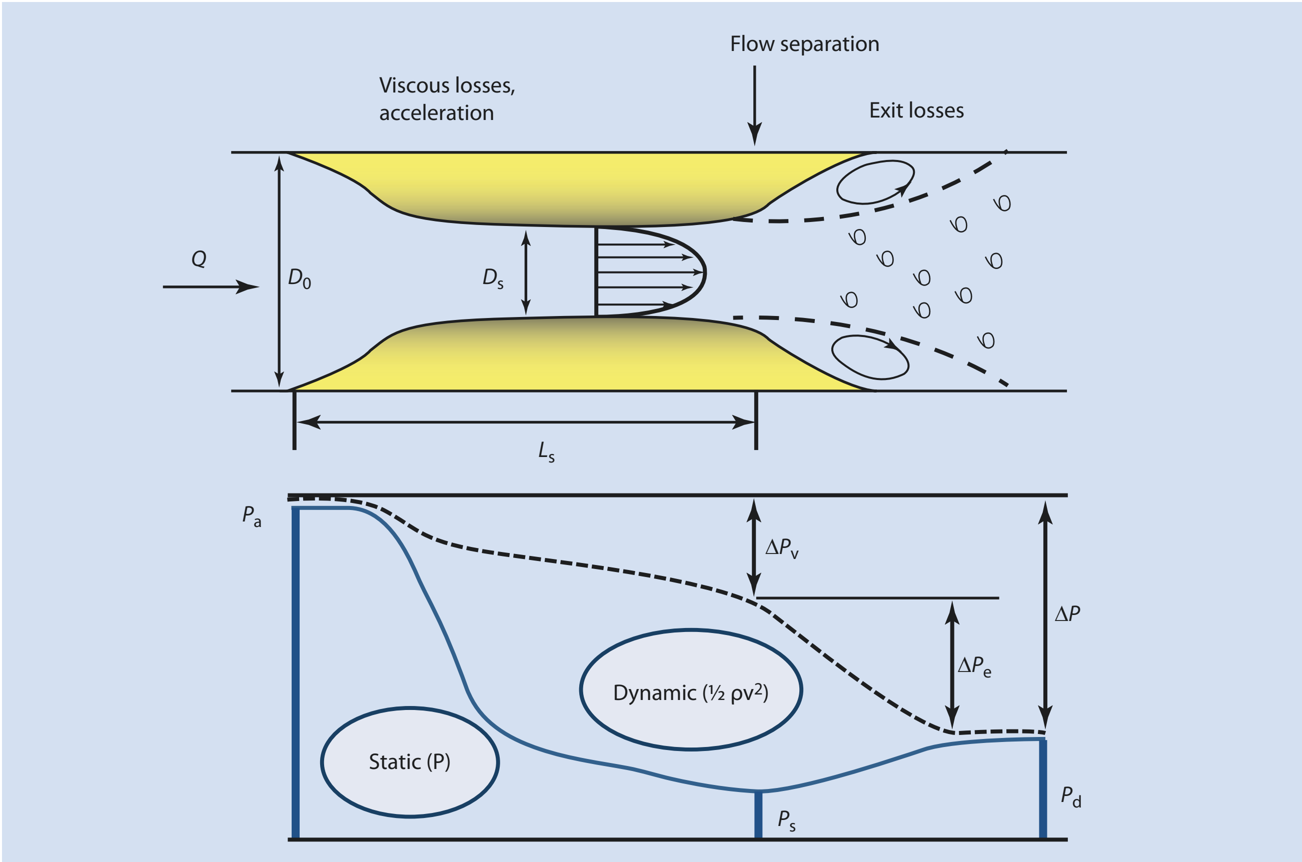

Fig. 1.5 Stenosis flow field (*top*) and energy loss (*bottom*). Pressure is lost by viscous friction along the converging and narrowed section. The convective acceleration due to diameter reduction causes conversion from static pressure energy to kinetic energy, with minimal pressure close to the point of flow separation. Exit losses are incurred at the expansion zone where the high-velocity jet leaving the narrowed section leads to formation of eddies and energy is converted to heat. The total pressure drop (ΔP) is the sum of viscous losses (ΔP_v) that scale linearly with flow and exit losses (ΔP_e) that increase with the square of flow. D_0 *and* D_s normal and stenosis diameter, resp., L_s length of converging section and throat up to the point of flow separation, Q flow rate, P_a aortic input pressure, P_s minimal stenosis pressure, P_d distal pressure, v velocity, ρ fluid density

Or expressed in terms of flow, Q

$$\Delta P = AQ + BQ^2 \quad (1.8)$$

where A and B are constants that derive from stenosis geometry and rheological properties of blood:

$$A = 32\frac{L_s}{D_0}\left(\frac{A_0}{A_s}\right)^2 \frac{\mu}{A_0 D_0} \quad (1.8a)$$

$$B = \frac{\rho}{2}\frac{k_e}{A_0^2}\left(\frac{A_0}{A_s}-1\right)^2 \quad (1.8b)$$

where k_e is an exit coefficient that was originally determined to average 1.52 for blunt-ended stenoses with L_s/D_0=2 [60]. A series of additional experiments in the 1980s [63, 64] has shown that not only the stenosis area reduction A_0/A_s and length L_s but also the shape of the entrance and exit sections influence the overall pressure drop by altering the velocity profile as it develops along the entrance and throat of the constriction. This boundary-layer growth from the inlet to the outlet of a stenosis could empirically be accounted for by adjusting L_s/D_0 in Eq. 1.8a to

$$L_s^{'} / D_0 = 0.45 + 0.86\left(L_s / D_0\right) \quad (1.8c)$$

and by expressing the exit loss coefficient k_e in Eq. 1.8b as a function of L_s/D_0:

$$k_e = 1.21 + 0.08\left(L_s / D_0\right) \quad (1.8d)$$

The gradually changing area reduction along the stenosis can be taken into account by integration of differential viscous losses over the stenosis length. The effect of the stenosis entrance region was also more recently investigated by Huo et al. [65] who proposed a second-order polynomial to determine the diffusive energy loss coefficients for different uniform (blunt/parabolic) velocity profiles at the entrance and outlet region.

Because resistance is per definition equal to pressure drop divided by the flow, Eq. 1.8 implies that stenosis resistance is given by

$$R_S = A + BQ \quad (1.9)$$

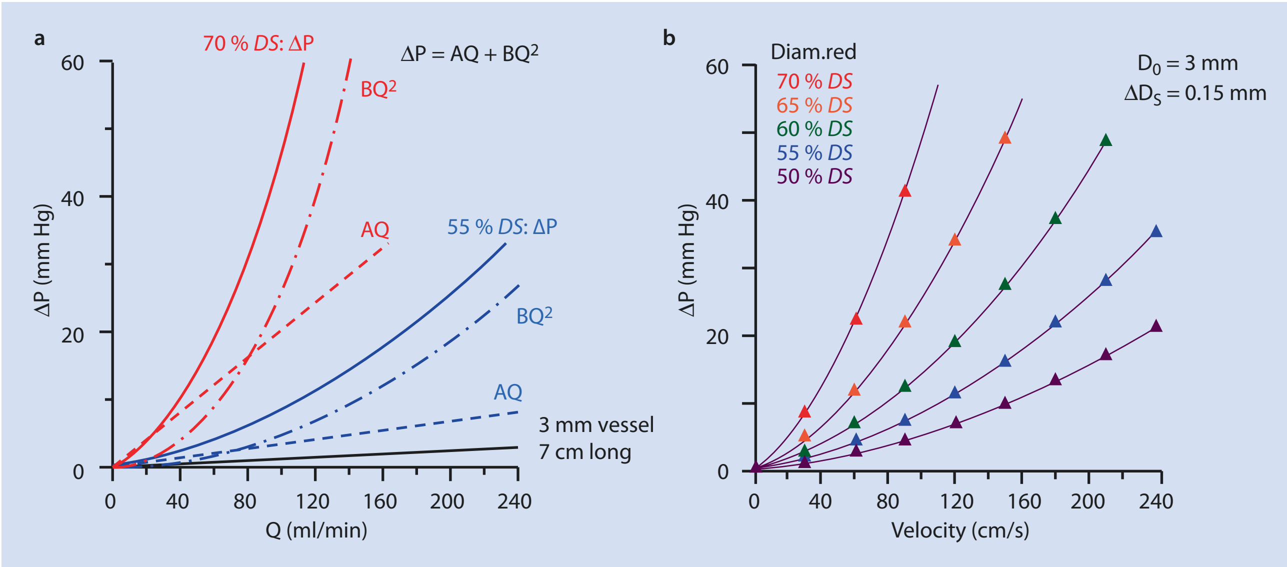

Fig. 1.6 Illustrations of stenosis pressure drop-flow relationship. **a** The total pressure gradient (ΔP) is the sum of linear viscous pressure losses (AQ) and quadratic exit losses (BQ^2). Theoretical relationships are shown for a 55 % and a 70 % diameter stenosis in a 3-mm vessel. The lower black line indicates pressure loss in the unobstructed vessel. **b** Effect of small changes in stenosis diameter (ΔD_s) in a vessel with 3-mm normal diameter (D_0). The pressure drop for a given flow rate increases progressively with each reduction in stenosis diameter by 0.15 mm

The first term on the right represents the viscous resistance which is constant for a given stenosis geometry, and the second term relates to exit losses that increase with flow.

The two additive components of stenosis pressure drop (Eq. 1.7) are graphically shown in Fig. 1.6a for a moderate and severe lesion with $L_s/D_0 = 2$ in a 3-mm vessel. Note that viscous losses dominate at low flow rates, while the nonlinear exit losses grow more quickly with increasing flow through the stenosis and makes up the larger contribution to the total pressure drop at elevated flow. The major geometric factor is the minimum stenosis diameter, which enters with its inverse fourth power into both terms of the ΔP-Q relationship. Even small changes in stenosis dimensions can have a large effect, as is illustrated in Fig. 1.6b. The difference between the ΔP-Q curves stems from a reduction in stenosis diameter by <0.2 mm, which produces a progressively larger incremental rise in pressure drop with increasing stenosis severity, even for moderate flow. This example highlights the influence of a small thrombus in the narrowed section, or the effect of passive changes in stenosis dimensions with variations in intraluminal pressure when a compliant plaque or wall section is present (see below).

The mean value of pulsatile flow (time averaged over a cardiac cycle) was shown to differ less than 5 % from the steady-state value in the coronary circulation [62, 65], and the general quadratic equation relating pressure drop to flow (Eq. 1.8) is applicable to both steady and pulsatile flow. Studies of coronary stenoses in unsedated dogs have shown that throughout diastole and mid-systole, the measured instantaneous data followed the theoretical form and that inertial effects due to rapid flow deceleration and acceleration during the cycle were limited to brief periods at the end of systole and beginning of diastole [66]. The general form of Eq. 1.8 has been used to derive hemodynamic characteristics of coronary artery stenoses in patients based on per-beat averages of pressure drop and flow velocity throughout the hyperemic response to a vasodilator stimulus [67]. Stenosis pressure drop-velocity relations also served to successfully assess hemodynamic stenosis severity by evaluating the pressure gradient at a fixed flow velocity of 50 cm/s for instantaneous diastolic flow and at 30 cm/s for cycle-averaged flow velocity [68, 69]. The advantage of this approach is that maximal vasodilation is not required (e.g., contrast injection can be used to increase flow), and potential pitfalls of baseline measurements associated with autoregulation or measurement errors are avoided.

1.3 Effects of Stenosis on Coronary Blood Flow

As outlined above, maximum myocardial perfusion depends on the sum of all resistances, and distal coronary pressure is the major determinant of microvascular perfusion. An epicardial stenosis represents an additional resistance to flow in the coronary system (Fig. 1.7). It is important to realize that stenosis resistance is directly dependent on flow and hence is variable, even for a stenosis of fixed geometry. Moreover, coronary microvascular resistance includes an active component governed by mechanisms of flow control and a passive component that is pressure dependent and determines minimal resistance of the dilated vessels without tone. Hence, all resistances are variable and functions of flow and pressure.

The hemodynamic effect of an epicardial stenosis in the context of coronary perfusion is schematically illustrated in Fig. 1.8, where the stenosis ΔP-Q relationship is combined with the pressure-flow relations of the coronary circulation at rest and at maximal vasodilation. The x-axis represents (distal) coronary perfusion pressure, and flow is shown on the y-axis.

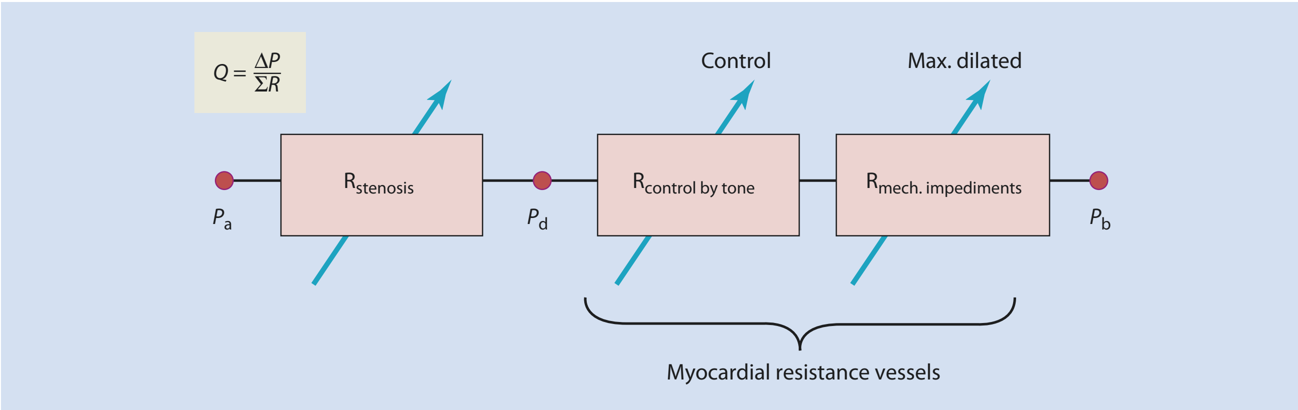

Fig. 1.7 Stenosis resistance is in series with microvascular resistance. Flow (Q) in a stenosed artery is determined by the total pressure gradient ($\Delta P = P_a - P_b$) divided by the sum of all resistances. Myocardial resistance vessels include a resistance that is controlled by tone and a minimum resistance at maximal vasodilation that is determined by the structure of the vascular tree and altered by mechanical impediments. P_d is the perfusion pressure for the microcirculation downstream of the stenosis. Note that all resistances are variable

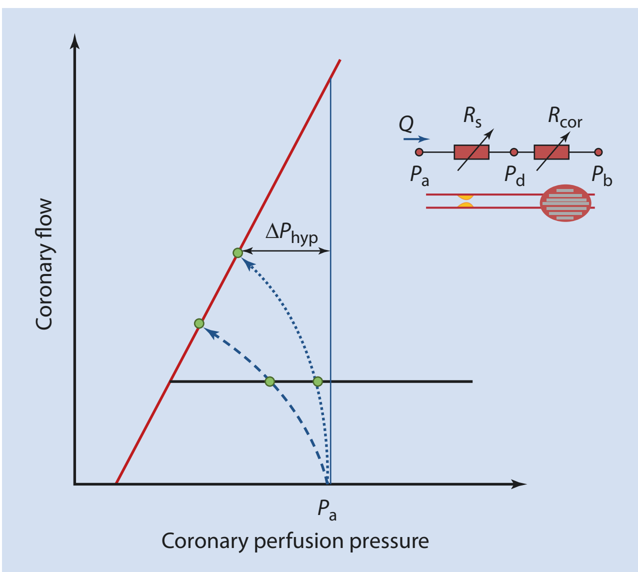

Fig. 1.8 Coronary pressure-flow relation and stenosis pressure drop-flow relations (*dashed lines*) shown for two stenoses of different severities. While the pressure drop at rest is compensated by a reduction in microvascular resistance, maximal flow is reduced with increasing stenosis severity (*dotted vs. dashed curve*), with an increase in hyperemic pressure drop (ΔP_{hyp})

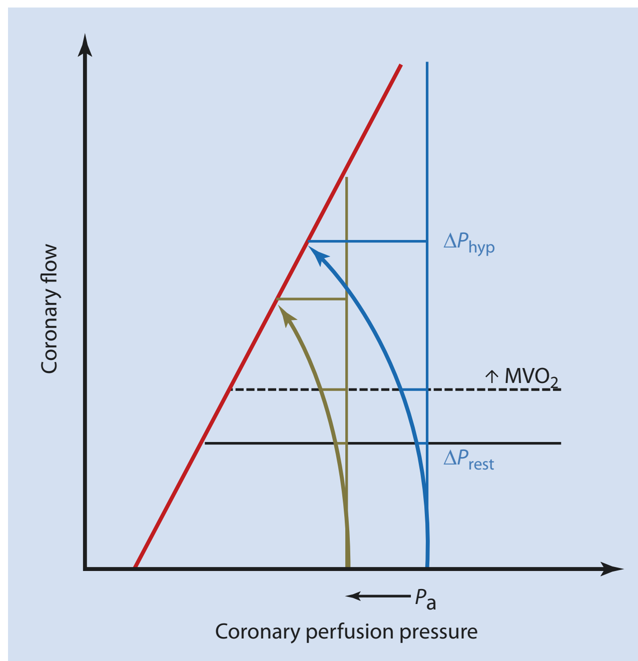

Fig. 1.9 Effect of decreasing perfusion pressure and increased resting flow on stenosis resistance for a given stenosis. The stenosis pressure drop-flow relation shifts to the left (*blue to brown*) when aortic pressure is reduced (P_a). The hyperemic pressure gradient (ΔP_{hyp}) is reduced because of a lower maximal flow that can be achieved, while pressure gradient at baseline (ΔP_{rest}) is unchanged. However, when resting flow is increased due to a higher oxygen consumption (MVO_2), resting pressure gradient is increased, while hyperemic pressure gradient is not affected. Note that stenosis resistance increases linearly with flow ($R_s = A + BQ$)

Starting from no-pressure drop at no flow ($P_d = P_a$), the curve representing stenosis pressure drop as a function of flow (Eq. 1.8) turns left toward lower distal perfusion pressure with increasing flow, reflecting the nonlinear loss in pressure across the stenosis with increasing flow. In order to maintain baseline flow at rest, the coronary microcirculation adapts to the presence of a stenosis and compensates for the additional pressure loss by lowering microvascular resistance, which in turn reduces the vasodilatory reserve. The maximal flow value is prescribed by the pressure-flow line at maximal vasodilation, which can turn downward or shift to the right in certain cardiovascular conditions, as discussed earlier. The difference between aortic pressure and the intersection with the hyperemic pressure-flow line is the stenosis pressure drop at maximal dilation.

If oxygen demand increases at rest, the intersection with the autoregulation plateau occurs at a higher flow (Fig. 1.9), which on fluid dynamic principles implies an increase in basal stenosis resistance commensurate with the nonlinear relationship between flow and stenosis pressure drop. Conversely, a

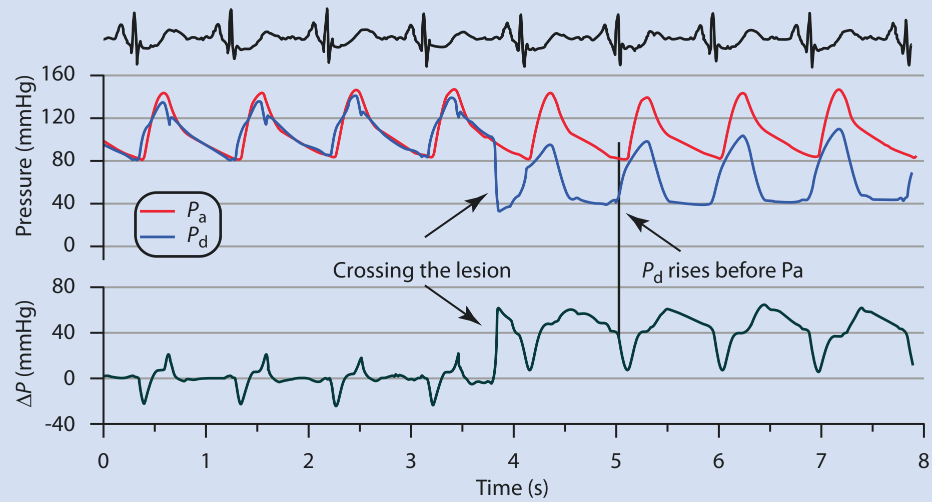

Fig. 1.10 Phasic tracings of aortic (P_a) and distal pressure (P_d) obtained in a patient's left anterior descending artery with a 75 % diameter stenosis. As the stenosis is crossed, a substantial pressure gradient (ΔP) is clearly seen that is higher during diastole. The distal pressure profile resembles a left ventricular pressure pattern. Note that coronary pressure downstream of the stenosis rises slightly before aortic pressure

decrease in aortic pressure will shift the pressure drop-flow relationship of this stenosis to the left resulting in a lower maximal flow, despite the same baseline resistance. Both examples entail a reduced capacity to increase flow above resting levels.

Effect of stenosis on pulsatile flow and pressure signals Development of an epicardial stenosis has a profound effect on pulsatile pressure and flow waveform patterns. An example obtained in a patient with a severe lesion (Fig. 1.10) shows how the pressure signal changes from an aortic to a ventricular pattern (not unlike that of the intramyocardial pump model) as the stenosis is crossed. This is explained by the higher diastolic flow and corresponding higher pressure loss during this part of the cardiac cycle. Note that the rise in distal pressure occurs earlier than the rise in aortic pressure. It is known from animal studies that distal pressure starts to increase during isovolumic contraction, whereas the pressure proximal to the stenosis rises with aortic pressure at the onset of aortic valve opening.

The availability of sensor-equipped guidewires allows the simultaneous acquisition of pulsatile coronary pressure and flow velocity data in patients. Figure 1.11 shows an example of coronary hemodynamic signals obtained in a left circumflex vessel with a severe lesion during increasing flow induced by intracoronary administration of adenosine, before (left) and after (right) percutaneous coronary intervention. In the presence of the stenosis, the distal pressure signal clearly reveals the hemodynamic stenosis severity. Although only a small increase in average flow velocity was attained during hyperemia (from 20 to 31 cm/s), the predominantly diastolic pressure gradient is exacerbated, with additionally a substantial pressure gradient during systole. Conversely, after revascularization, the distal pressure profile hardly changes despite a large rise in flow velocity (from 23 to 75 cm/s). The corresponding ΔP-Q relationships (lower panel) unequivocally illustrate the improvement in stenosis hemodynamics that was accomplished by revascularization, and the post-intervention ΔP-Q relationship closely approaches that obtained in an undiseased reference vessel of this patient. The solid lines represent least-squares quadratic fits through the data (Eq. 1.8). Note that the post-intervention and reference ΔP-Q relationships are almost straight, which indicates the dominance of viscous losses along the vessel (between the P_a at the ostium and the location of distal pressure sensor). This implies a lack of energy losses due to convective acceleration in a narrowed section (second term in Eq. 1.8) and confirms a successful hemodynamic outcome without further constrictions along the interrogated vessel path.

Compliant stenosis Pathological studies and intravascular imaging have shown that only a minority of coronary artery stenoses is concentric with a fixed, rigid geometry. Most plaques develop at the inner curvature of the epicardial vessel or at bifurcations, with a D-shaped, concentric, or elliptical residual lumen [70–73]. The eccentric location of the plaque implies that in most cases, an arc of normal wall circumference is present which provides a mechanism whereby variations in intraluminal pressure or vasomotor tone can affect the luminal dimensions and thus alter flow resistance. Moreover, the plaque itself can be compliant [74–77]. The hemodynamic significance of dynamic changes in stenosis dimensions has received much attention in the past, and both active and passive mechanisms have been demonstrated in vivo [78–85]. Especially when vasomotor tone of epicardial vessels is minimized after giving nitroglycerin, a passive change in stenosis geometry can take place during the hyperemic response, when flow velocity increases at the expense of intraluminal pressure in the narrowed section [67, 84]. For a stenosis with an arc of compliant wall, the decrease in pressure may lead to extra narrowing by partial passive collapse, thereby worsening the situation.

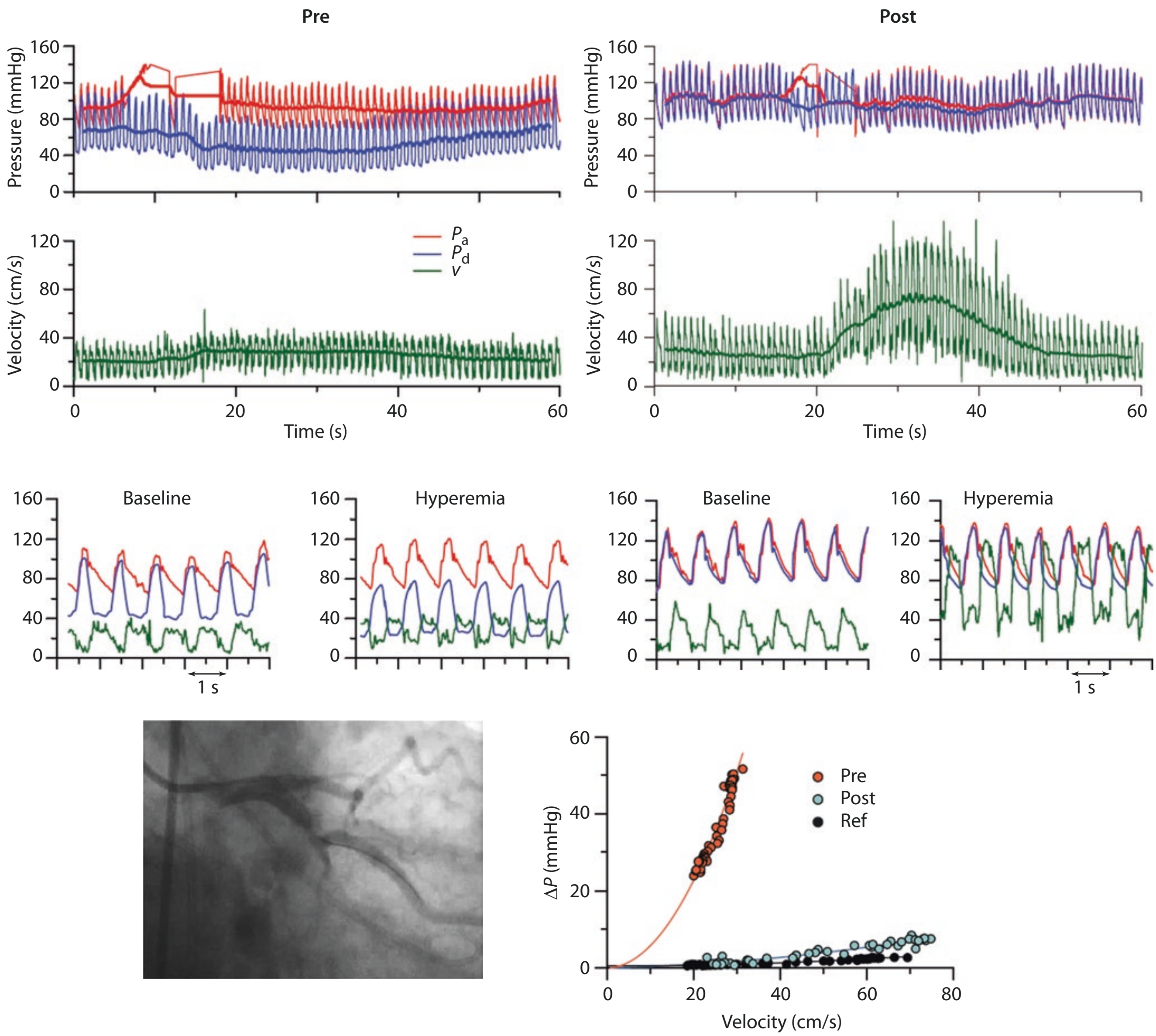

Fig. 1.11 Hyperemic response to an intracoronary adenosine injection. Simultaneous pressure and velocity measurements were obtained in a 63-year-old patient with a 85 % diameter stenosis in the left circumflex artery (angiogram) before (pre, *left*) and after (post, *right*) interventional revascularization. Middle panels show proximal (P_a) and distal (P_d) pressure and flow velocity (v) at baseline and maximal hyperemia for each condition. On the lower right, the corresponding pressure drop (ΔP)-velocity relations are shown for cycle-averaged values from baseline to hyperemia. Post intervention the ΔP-velocity relation closely approaches that of an undiseased reference vessel (Ref)

As outlined above (see Fig. 1.6b), even very small changes in minimum diameter can lead to large changes in pressure drop. In terms of the ΔP-Q relationship, stenosis hemodynamics is then no longer characterized by a single curve, but by a family of curves that reflect the changing stenosis geometry with time during the waxing and waning of flow [67]. The resulting ΔP-Q relationship of such a stenosis then displays in the form of a loop (Fig. 1.12), with two different pressure gradients at the same flow velocity, reflecting the passive dynamic change in stenosis dimensions.

Serial lesions Many lesions do not appear in isolation, but multiple stenoses are frequently present along a coronary artery. If the distance separating two lesions is sufficiently large, the overall pressure drop is simply the sum of the pressure drops across the individual stenoses. However, as the distance between the lesions decreases, interaction between the upstream and downstream lesion causes the overall pressure drop to be less than the sum. This interaction depends on the severity of the lesions, the distance between them, and the flow. At low flow rates, the expansion loss is small and two similar lesions act as a single lesion of summed length [60]. With increasing flow, two stenoses in series can undergo a transition from a single lesion of twice the length to two independent lesions with twice the overall pressure drop, as shown in Fig. 1.13. The flow rate at which this transition occurs decreases with increasing distance between the lesions, i.e., two lesions that are close together behave as a single lesion of twice

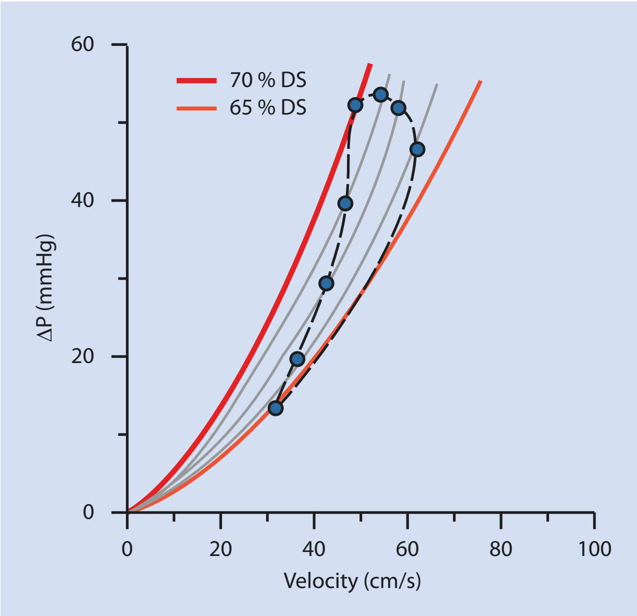

Fig. 1.12 Effect of stenosis compliance on the pressure drop (ΔP)-velocity relation. As intraluminal pressure declines with increasing velocity, partial collapse leads to a worsening of stenosis severity. The resulting loop is a composite of a family of unique curves that are traversed during the hyperemic response. Note that the change in stenosis geometry results in different pressure gradients for the same velocity

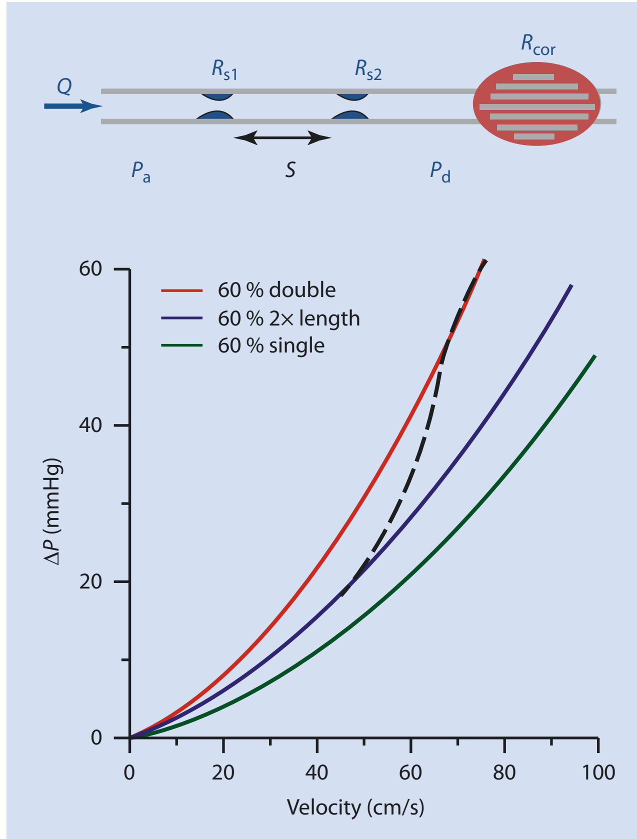

Fig. 1.13 Effect of two 60 % diameter stenoses in series on the pressure drop (ΔP)-velocity relation. A single stenosis is indicated by the *green line*. At low flow rates, two lesions act as a single lesion of twice the length (*blue line*). But with increasing flow, they undergo a transition (*dashed trajectory*) to two independent lesions with twice the pressure gradient (*red line*). This transition depends on the distance (*S*) between the lesions and on the sequence and severity of the stenoses. *Q* flow, R_s stenosis resistance, R_{cor} coronary resistance, P_a aortic pressure, P_d distal pressure

the length over a larger flow range compared to lesions that are further apart [86].

For a given flow rate, the "critical" separation distance for two lesions to act independently depends on stenosis severity and distance. This is in line with the extent of the flow expansion zone of the upstream stenosis mentioned earlier. If the jet leaving the proximal lesion can fully expand before the distal lesion is encountered, the lesions are fluid dynamically independent, and pressure loss is maximal. This reattachment length is longer at elevated flow and for more severe lesions (up to 5–10 normal diameters). Intermediate lesions (55 % diameter reduction) at moderate flow (physiological range) tended to act independently when the distance between the lesions, *S*, exceeding six times the normal diameter, i.e., when $S/D_0 > 6$ [86]. For lesions that are closer together, the overall energy loss is reduced, since energy diffusion in the expanding jet is limited by the distal lesion and flow tends to remain more laminar [61]. Steady flow studies have shown that if a severe lesion is closely ($S/D_0 = 2$) followed by a mild or moderate stenosis, the overall pressure drop was even less than that across the single severe stenosis [87]. If the upstream stenosis is compliant, increasing the severity of the downstream stenosis in a coronary artery can lead to expansion of the upstream stenosis lumen area, thereby decreasing its hemodynamic effect and increasing flow through both lesions [88, 89].

Selecting the most appropriate stenosis of serial lesions to be dilated is challenging. A method to predict the theoretical pressure drop across the remaining individual lesion after virtual stepwise revascularization is complicated and involves obtaining a wedge pressure requiring balloon inflation [90]. In the case of a left main stenosis in the presence of a downstream left anterior or circumflex lesion, it was proposed to measure distal pressure in the uninvolved epicardial artery instead [91]. However, both methods assume a constant hyperemic microvascular resistance regardless of distending pressure to the downstream myocardial bed, and the effect of distance between the lesions on mutual interaction was not investigated. A practical approach to identify the culprit lesion may be to determine sudden steps in pressure gradient by pressure wire pullback along the length of a coronary artery during hyperemia [92].

In summary, the overall effect of serial stenoses not only depends on the severity of the stenoses and the distance between them but also on the sequence of lesion severities, on stenosis compliance, and on flow. Clearly, more studies are needed in this area, but it is certain that multiple noncritical stenoses can cause a significant pressure loss, especially in the presence of underlying diffuse narrowing.

Diffuse disease The importance of diffuse coronary artery disease underlying a focal stenosis has long been recognized [93] and continues to be an active focus of research attention [94, 95]. A tandem development of focal and diffuse coronary artery disease is common and is associated with an increased risk of coronary events [17, 95, 96]. Recent studies using computed tomography imaging have shown that the cumulative plaque burden proximal to a focal stenosis plays an important role in determining the functional significance of that stenosis [97, 98].

Detection of diffuse disease by conventional angiographic imaging remains a problem for interventional cardiologists. The true extent of plaque accumulation cannot be appreciated by luminal angiography that may show smooth vessels, falsely suggesting the absence of atherosclerotic disease, and errors in angiographic assessment of plaque burden are exacerbated by the frequent occurrence of eccentric plaques that may present angiographically as a marginally narrowed circular lumen [99]. Yet the absence of focal disease does not imply the absence of increased flow resistance. Diffuse segmental narrowing can lead to substantial loss in distal perfusion pressure [100, 101] and can conceptually be modeled as a uniform relative reduction in normal segmental diameter with or without an overlaying focal obstruction [102]. Normal coronary artery size in humans is not easy to assess [103, 104]. Several approaches have employed length-area relations based on scaling laws that relate the size of the coronary tree to regional perfused mass via cumulative distal artery branch length [105, 106] or tried to assess the size of normal vessels via bifurcation analysis, where deviation from normal scaling law patterns can reveal the severity of diffuse disease [107–109]. Based on this approach, the extent of diffuse disease in the epicardial coronary artery tree of patients with metabolic syndrome was reflected by a 28 % decrease of mean cross-sectional area along the entire epicardial coronary artery tree and an 18% decrease of the sum of intravascular volume as a result of reduced cross-sectional area in distal coronary arteries [108].

Recapitulating, the hemodynamics of an epicardial stenosis can be summarized as follows:

1. Stenosis pressure drop (and therefore flow through the vessel) is influenced by stenosis geometry (shape of converging and diverging section, plaque location, length, lumen area of the stenosis, and lumen area of the vessel), velocity, blood viscosity and density, and blood flow waveform. Of these, the most important factors are flow velocity and minimum stenosis diameter.
2. The pressure drop varies nonlinearly with flow velocity, and the resistance of a stenosis is therefore not constant. For a fixed geometry, stenosis resistance increases linearly with velocity. In this regard, it should be recognized that microvascular resistance influences stenosis hemodynamics via its direct influence on flow velocity.
3. The major geometric factor influencing the pressure drop is the reduction in lumen area. This effect is relatively small for mild lesions, but escalates nonlinearly with increasing stenosis severity, where even a small worsening in stenosis diameter causes a steep rise in pressure drop.
4. Stenosis shape and lumen eccentricity do not strongly affect the pressure drop for moderate to severe lesions for which lumen reduction dominates. However, in case of partially compliant lesions (compliant plaque or an arc of flexible wall circumference), dynamic behavior can be introduced by small changes in effective lesion diameter with decreasing distending pressure, e.g., at elevated flow rates (passive) or induced by changes in tone (active).
5. The effect of multiple stenoses depends on the severity of the lesions, sequence of different severities, spacing between the lesions, and flow. If the distal lesion is close enough to the proximal one, it interferes with the expanding jet emerging from the upstream stenosis, thereby reducing its pressure loss. Based on experimental findings, sequential lesions can be regarded as independent (overall pressure drop is determined by the sum of individual lesions) when the distance between the lesions is greater than 6 times the adjacent vessel diameter.
6. Diffuse coronary artery disease underlying a focal lumen obstruction is common and independently modulates the physiological effect of an epicardial stenosis.

1.4 Distal Perfusion Beyond the Epicardial Lesion: Integrated Measures of Physiological Stenosis Severity

Considering that flow velocity is a major physiological determinant of epicardial stenosis hemodynamics for any given driving pressure, the level of microvascular resistance at the time of measurement is of paramount importance. After all, the value of basal and maximal flow during physiological lesion assessment determines the position along the stenosis ΔP-Q relationship, and clinically relevant functional parameters are derived from these values.

The power of conveying stenosis hemodynamics in terms of combined pressure and flow velocity information is further depicted in Fig. 1.14 showing stenosis ΔP-Q relationships for a selection of clinical cases. Data were obtained during a diagnostic procedure with intracoronary adenosine administration in coronary arteries of six patients with various degrees of anatomical stenosis severity.

In line with observations and simulations by others [94, 102], it becomes clear that percent diameter reduction alone is not a defining measure for the functional severity of a lesion. As shown in Fig. 1.14a, two lesions of 55 % DS (light blue and green) have very different ΔP-Q relationships (due to different diameters of the stenosed coronary vessel), whereas the fluid dynamic relationship of the 50 % DS (orange) is on the same curve as that of a 55 % DS (shown in green), albeit at a much lower flow velocity range. When pressure gradient is expressed in terms of aortic pressure ($1-\Delta P/P_a = P_d/P_a$), it can be seen