Improved assessment of functional severity of coronary artery stenosis by analysis of combined intracoronary pressure and flow velocity signals

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Chapter 3

Coronary pressure-flow relations as basis for the understanding of coronary physiology

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Abstract

Recent technological advancements in the area of intracoronary physiology, as well as non-invasive contrast perfusion imaging, allow to make clinical decisions with respect to percutaneous coronary interventions and to identify microcirculatory coronary pathophysiology. The basic characteristics of coronary hemodynamics, as described by pressure-flow relations in the normal and diseased heart, need to be understood for a proper interpretation of these physiological measurements. Especially the hyperemic coronary pressure-flow relation, as well as the influence of cardiac function on it, bears great clinical significance. The interaction of a coronary stenosis with the coronary pressure-flow relation can be understood from the stenosis pressure drop-flow velocity relationship. Based on these relationships the clinically applied concepts of coronary flow velocity reserve, fractional flow reserve, stenosis resistance and microvascular resistance are discussed. Attention is further paid to the heterogeneous nature of myocardial perfusion, the vulnerability of the subendocardium and the role of collateral flow on hyperemic coronary pressure-flow relations.
Introduction

The oxygen extraction from the coronary circulation is high and even at baseline conditions approximates 75%, while the overall oxygen extraction in the systemic circulation amounts to 25–30% (1). In extreme exercise in dogs, coronary venous saturation may be reduced further from 25% to approximately 10% (2), but this increased extraction is much too small to account for the 4 to 5 times increase in oxygen demand that may occur and consequently necessitates an increase in coronary blood flow (1). Normally, coronary blood flow is well controlled and matched to the oxygen needs of the heart by adapting the caliber of the coronary resistance arteries, including arterioles, via inter-related processes involving mechanisms intrinsic to the vascular wall, as well as metabolic and neurohumoral factors (3, 4). One of the first observations on coronary physiology several centuries ago was that coronary arterial flow is pulsatile, high in diastole and low in systole (5). This is opposite to the flow pattern in arteries feeding other organs where flow is high in systole. The particular coronary bi-phasic flow pattern is the result of compressive forces that are exerted by the contracting heart muscle on the embedded microvessels. Hence, the heart impedes its own perfusion by the contraction that is needed to fulfill its principal function. Many of the physiological phenomena underlying coronary flow regulation have been studied in conscious and unconscious animal preparations where there is great freedom in instrumentation and interventions. More recently, investigation of human coronary physiology has become possible in clinical studies owing to the miniaturization of pressure and flow sensors at the tip of coronary guide wires used during cardiac catheterization and by myocardial perfusion imaging via magnetic resonance imaging, positron emission tomography and contrast echocardiography (6, 7). The purpose of this paper is to provide a brief overview of some principles of coronary physiology, and how these principles translate to diagnostic applications in clinical practice.

Characteristics and limits of coronary blood flow control

In functional terms, the two major determinants of coronary flow are coronary arterial pressure and myocardial oxygen consumption. It was found very early on that, at constant oxygen consumption, coronary flow is relatively independent of arterial pressure which is referred to as coronary autoregulation (8). Similarly, at a given coronary arterial pressure, coronary flow increases with oxygen consumption, which is defined as metabolic adaptation. These two mechanisms are interrelated and may even be due to the same control mechanism designed to maintain the controlled variable at a desired level. The controlled variable may be tissue oxygen pressure or a different factor related to metabolism. Since in the intact circulation coronary pressure equates to aortic pressure and aortic pressure is a main determinant of myocardial oxygen consumption, it is difficult to study metabolic flow adaptation and autoregulation independently in an intact preparation. This can best be studied in a system where the coronary blood supply is controlled independently, e.g. by an extracorporeal system.
Conceptually, it is important to have a clear picture of the two manifestations of coronary flow control as illustrated in Figure 1. The left panel schematically depicts coronary pressure-flow relations at rest and during maximal vasodilation. The steepest line (hyperemia) represents the situation where flow control is abolished. Hyperemic flow increases with pressure, but not proportional, since this relation does not pass through the origin. The hyperemic pressure-flow relation bears great clinical significance as will be discussed below. The autoregulatory action of the coronary system is indicated by the lines with a smaller slope at two different levels of constant oxygen consumption, demonstrating the characteristic parallel shift with oxygen consumption. Coronary flow is kept fairly constant over a large range of perfusion pressure by adjusting coronary microvascular resistance to changing perfusion pressures. Note that coronary autoregulation is not perfect, which would correspond to horizontal plateaus in the autoregulation range. The right panel in Figure 1 depicts results from an experiment where oxygen consumption of the heart was altered at two different coronary pressures (9). Coronary flow increases with oxygen consumption, but also not in a proportional manner and oxygen extraction becomes less efficient at higher coronary pressure. Clearly, metabolic adaptation is not perfect either, since at the same oxygen consumption, flow rate is higher for a higher coronary pressure. Obviously, the pressure dependence of metabolic adaptation corresponds to the slope of the autoregulation curve. In a conceptual model, control of coronary blood flow can best be understood as a system designed to maintain tissue oxygen pressure ($P_{O_2}$) at a constant level. In such a model, factors causing a decrease of tissue $P_{O_2}$ will lower coronary resistance by inducing vasodilatation (10, 11). Similarly, vasoconstriction will result via factors inducing an increase in tissue $P_{O_2}$. This does not imply that tissue $P_{O_2}$ is the controlled variable in real life, since such model behaviour can be realized in several ways. However, the concept of tissue $P_{O_2}$ control has guided the design of experiments to unravel the specific role of mechanisms involved in blood flow control using coronary venous $P_{O_2}$ as a surrogate for myocardial tissue $P_{O_2}$ (1, 12, 13). In this way a direct vasoactive effect of a drug may be distinguished from an indirect effect via alterations in oxygen consumption (14).

Coronary blood pressure declines only little along the larger epicardial vessels and starts to drop sharply in arteries with a diameter below 400 μm. Those vessels are referred to as resistance vessels and are involved in the regulation of coronary blood flow. It has been shown that resistance vessels respond to stimuli in a diameter-dependent manner. These selective responses serve a functional purpose. The smallest vessels are in more direct contact with the metabolic stimuli from the myocytes (15). The local dilatory response to such a stimulus affects the flow rate and pressure in more upstream segments and activates flow and pressure-mediated diameter changes in those upstream vessel segments (16, 17).

**Effect of stenosis resistance**

**Stenosis pressure gradient-flow velocity relationship**

In order to properly assess the physiological significance of an epicardial stenosis on coronary blood flow, it is important to understand the hemodynamic effect of a focal
Figure 1: (A) Schematic pressure-flow relations illustrating autoregulation and maximal vasodilatation (hyperemia). The hyperemic relationship is incremental-linear with a non-zero intercept. Autoregulation is shown at two levels of constant oxygen consumption, which induces a parallel shift. (B) Coronary blood flow (CBF) as a function of oxygen consumption (MV02) for two different values of the coronary arterial pressure (PC). Data from (9).

Figure 2: (A) Human stenosis pressure-drop-flow velocity relations at different stages of treatment obtained by a dual-sensor equipped guide wire. Note that the relations are curvilinear and become less steep at subsequent stages. The bottom curve is measured in a reference vessel. (Data redrawn from (19)). (B) Effect of pressure loss (ΔP) across a stenosis on coronary flow reserve. The progressively decreasing coronary pressure (PC) with increasing coronary blood flow (CBF) strongly reduces maximal hyperemic blood flow. v, blood flow velocity.
diameter reduction formed by a stenosis. Total pressure drop across a stenosis is the sum of viscous losses due to friction (Law of Poiseuille) and losses incurred at the exit after acceleration along the throat of the lesion (Law of Bernoulli). The relationship between pressure drop ($\Delta P$) and velocity ($v$) can be described by a quadratic equation of the form $\Delta P = A \cdot v + B \cdot v^2$, where the coefficients $A$ and $B$ are a function of stenosis morphology and rheological properties of blood (18). The most important geometric parameter is the minimum diameter of the stenosis, which enters both terms with the inverse fourth power as $(1/D_s^4)$. The flow-limiting behaviour of a coronary stenosis is mainly determined by the second term which increases with the square of the flow. Without a stenosis (no diameter reduction), the nonlinear exit losses are removed and the equation reduces to the linear (Poiseuille) part. This is illustrated in Figure 2 (left panel), which shows the $\Delta P$-$v$ relationships obtained in a patient before and after stepwise expansion of stenosis diameter by balloon angioplasty and stent placement (19). Coronary flow was briefly increased by distal vasodilation with adenosine. Note that each relationship represents the hemodynamic effect of a given stenosis geometry. The position along the curve is determined by flow through the stenosis, which changes with microvascular resistance. With autoregulation intact, baseline flow can be maintained by compensatory dilation of the resistance vessels. However, coronary perfusion pressure decreases with the square of flow through the stenosis and hence strongly reduces the maximal flow that can be obtained at full vasodilation (Figure 2, right panel). This reduction in perfusion pressure by a stenosis has particular consequences for minimal microvascular resistance as will be discussed below.

**Physiological indices to assess functional stenosis severity**

Current clinical practice guidelines advise percutaneous coronary intervention as the preferred treatment for culprit coronary artery stenoses responsible for ischemic events (20, 21). Since every procedure carries a small risk of possible adverse events treatment should be deferred when such an intervention is not strictly indicated. This approach, consequently, requires functionally relevant criteria for such a deferral. It may be clear from the above section that even detailed information on stenosis geometry e.g. as obtained by quantitative coronary angiogram analysis, is not sufficient to evaluate the physiological impact of a stenosis on myocardial perfusion. After all, an image-based analysis can at best yield a prediction of the stenosis $\Delta P$-$v$ relationship, but not the position along that curve for a particular patient and flow condition. The use of sensor-equipped guide wires in the catheterization laboratory has enabled the functional assessment of stenosis severity based on intracoronary pressure and/or flow velocity measurement and several indices have been introduced to identify stenoses responsible for reversible ischemia. The physiological basis underlying these clinically used indices is outlined in this section. It should be noted that these indices rely on elicitation of maximal coronary flow, i.e. elimination of all active vasomotor tone. As recently pointed out by Heusch (22), this may not completely be achieved by administration of adenosine, a powerful small vessel coronary vasodilator that does, however, not alleviate effects of prevailing alpha-adrenergic or endothelin-induced vasoconstriction common in diseased coronary arteries.
Coronary flow velocity reserve

Coronary flow reserve is defined as the ratio of maximal flow to flow at rest at the same perfusion pressure (23, 24). In clinical practice, Doppler-derived cross-sectional peak velocity is measured rather than volume flow, and coronary flow velocity reserve (CFVR) is determined as the ratio of mean (time-averaged) velocity during hyperemia to mean velocity at rest. Values for minimally diseased vessels in patients with coronary risk factors average 2.7±0.6, with values up to 4.5±0.7 being reported for healthy males (25). The threshold for reversible ischemia has been established at CFVR<2.0 (26). As recently summarized by Hoffman (27), CFVR depends on the prevailing physiologic conditions that affect the coronary pressure-flow relationship at baseline and/or hyperemia. Factors that influence baseline flow (e.g., workload, heart rate, gender) and age were identified as major determinants of CFVR, whereas coronary risk factors or cardiomyopathies affecting the functional capacity of the small resistance vessels tend to reduce CFVR by impairing maximal flow (16, 28, 29).

In order to minimize the influence of the various factors, Baumgart and colleagues (30) introduced the relative CFVR that relates the CFVR in the target vessel to the CFVR in another, presumably normal artery in the same patient (and under the same conditions). This practice requires the presence of a normal reference vessel. Although a relative CFVR=1 indicates that the target and reference artery have the same CFVR, this does not necessarily reflect the presence of normal vascular territories, as e.g. in patients with global microvascular dysfunction. It is important to realize that CFVR is not uniform and a profound regional heterogeneity exists both transmurally and between adjacent perfusion areas (31–33).

Fractional flow reserve

Young et al. proposed in 1977 to characterize stenosis severity by its limiting effect on maximal flow (34). The ratio of hyperemic flow in the presence of a stenosis to that in the absence of the stenosis was later extended to the concept of fractional flow reserve (FFR) by Pijls et al. (35). Based on a simplified model of the hyperemic coronary pressure-flow relation, they expressed the relative maximal flow in terms of the ratio between pressure distal and proximal to the stenosis at full vasodilation. A major assumption in this concept is that a change in perfusion pressure induced by a stenosis is proportional to a change in inflow. This implies that the hyperemic pressure-flow relation would be straight and passes through the origin (proportional rather than incremental linear), neglecting the effects of cardiac contraction on hyperemic coronary flow as discussed below. In addition, it is assumed that minimal coronary resistance downstream of a stenosis is equal to that in a tissue region subtended by a normal vessel. However, this assumption is in conflict with the pressure-dependent diameter and resistance of vessels without tone (36–38). Although FFR avoids the dependence on baseline flow, it is influenced by conditions that affect hyperemic microvascular resistance such as tachycardia, inflow pressure, or microvascular disease (39–42). Studies proclaiming hemodynamic independence of FFR either did not assess the equivalence of pressure-based FFR and true relative maximal flow for a given stenosis (35) or induced small changes in heart rate or pressure, which could furthermore not be executed independently due to physiological interaction.
While initially a value of FFR≥0.75 was adopted for treatment deferral, more recent guidelines raised the threshold to 0.8 (21). Interestingly (but not surprisingly), comparison of stenosis severity assessed by both pressure-based (FFR) and velocity-based (CFVR) indices leads to conflicting outcomes in about 30% of cases (44), which can be attributed to the differences in microvascular resistance (45). A change in hyperemic microvascular resistance affects FFR and CFVR in opposite directions. A higher microvascular resistance reduces CFVR and increases FFR (reduced maximal flow and hence higher distal pressure). Conversely, for the same stenosis, a low hyperemic microvascular resistance may well indicate sufficient flow reserve (CFVR≥2), but the higher maximal flow comes at the expense of an increased stenosis pressure gradient, which in turn may result in FFR<0.8. It is precisely in this group of intermediate lesions with discordance between CFVR and FFR that the stenosis resistance index (see below) performs better in predicting reversible ischemia (46). Furthermore, deferral in this subgroup of patients was associated with a higher risk of future adverse events (47).

**Stenosis resistance index**

The simultaneous measurement of pressure and flow velocity allows the separate derivation of indices that are determined by the stenosis severity only. The most straightforward index in this regard is the hyperemic stenosis resistance index, HSR, defined as the ratio between the average pressure drop over the stenosis and the average flow velocity during hyperemia (46). HSR was compared to FFR and CFVR in a cohort of 151 patients with single-photon emission computed tomography as gold standard for reversible ischemia (46). A deferral threshold of HSR≤0.8 mmHg/cm/s was established. In this study it was also found that the diagnostic predictive power of HSR was significantly higher than that of FFR and CFVR.

**Which physiological index to use**

Based on epidemiological evidence it seems that any physiological index performs better than angiographic derived stenosis parameters in guiding clinical decision making (48, 49). However, currently, there is no consensus which physiological parameter should be most preferred. The popularity of these indices is not only determined by the strength of their theoretical and physiological foundation but also by the practicalities involved. However, practical consideration may change by technological advancements. Currently, FFR is the most popular index of stenosis severity, primarily owing to the practical ease of pressure measurements compared to flow velocity measurements. FFR is even considered by some as the clinical standard for the determination of physiological significance of a stenosis. However, in light of the aforementioned limitations, it should be noted that FFR lacks the theoretical solid foundation to be a gold standard and most probably, invasive stenosis assessment will be replaced in the future by methods that actually measure perfusion directly such as MRI perfusion imaging (7, 50, 51). Moreover, the combined measurement of pressure and flow velocity distal of a stenosis provides more comprehensive information on stenosis severity and microvascular resistance (26). For a comprehensive comparison of currently used indices, the reader is referred to the tables provided in recent reviews by Siebes (18) and Kern et al. (26). It is the rate of technological advancements that will determine what principle will be used in the end.
Microvascular resistance and the distribution of myocardial perfusion

Up to this point we have discussed the myocardium as an entity and its perfusion at the level of epicardial arteries. However, perfusion of the myocardium is far from homogeneous and the hemodynamic characteristics measured at the epicardial level reflect a space average state. This implies that overall, the myocardium is perfused well but that certain local areas are predisposed for ischemia. Heterogeneity occurs at different spatial scales, and it is well established that especially the subendocardium is vulnerable for ischemia (52–55). Furthermore, heterogeneity exists also at a smaller scale. Hence, over a distance of a few millimeters, a small area may be perfused well while neighboring areas may show signs of ischemia (31, 32). This corresponds to observations of micro-infarctions in the heart (56).

Vulnerability of the subendocardium

Structural and functional reasons explain perfusion heterogeneity. The structure of the vascular bed at the subendocardium is different from that of the subepicardium (57). Furthermore, the vascular capacity of the myocardium increases across the wall depth, with a coronary arterial volume lowest at the most superficial subepicardial layer (58). This corresponds with a much smaller hyperemic coronary resistance per gram of tissue in the subendocardium than in the subepicardium when the heart is arrested. Hence, intrinsically, the vascular bed allows for a higher level of perfusion at the subendocardium than at the subepicardium. This finding would contradict the observation of predisposition of the subendocardium to ischemia. The explanation is that cardiac contraction adds to the impediment of tissue perfusion especially at the subendocardium. In dog hearts it was found that at hyperemia and a perfusion pressure of about 100 mmHg, subendocardial perfusion is 50% higher at cardiac arrest, equal at a HR=100 bpm and 50% lower at a HR=180 bpm compared to subepicardial perfusion (59). Hence, the intramural vascular structure is adapted to compensate for the impeding effect of cardiac contraction on subendocardial perfusion (60).

Intramural vessels are compressed during systole, reducing intramural blood volume which results in an increase of coronary venous and decrease of coronary arterial flow. During diastole, the compressive forces recede and the intramural vascular volume is restored. As a result, the intramural vessels continuously vary in diameter during the cardiac cycle (61). The rate of change of diameters depends on the actual resistances of the microcirculation between the vascular segments and the coronary arteries and veins. The larger these resistances, the slower the rate of change in diameters. This corresponds to findings that the diameter pulsations during the cardiac cycle are less in the smaller than in larger arterioles and in the smaller than in larger venules (62, 63).

The periodic compression of intramural vessels and the resulting periodic swing in coronary arterial and venous coronary flow is evidence for intramycardial pump action (64). The role of the microvascular resistance in impeding the swing of
coronary arterial flow is clear from the observation that diastolic-systolic differences are smaller at higher perfusion pressure than at lower perfusion pressure due to the effect of autoregulatory action on the coronary circulation, increasing coronary resistance proximal to the capillary bed with arterial pressure. The importance of diastole for refilling the intramural microcirculation is clear from measurements of regional hemodynamic hyperemic conductance as a function of the diastolic time fraction (DTF) as illustrated in Figure 3 (40). At the subendocardium the conductance increases with DTF at constant pressure and is clearly higher than at the epicardium for larger values but lower at smaller values of DTF. In addition, at constant DTF, conductance increases with increasing pressure both at the subepicardium and subendocardium. Hence, the factors that promote the rate of filling of intramural vessels in diastole, DTF and coronary pressure, result in an increased microvascular conductance or decreased microvascular resistance at the subendocardium. At the subepicardium there is an opposite tendency for conductance to decrease with DTF but also here conductance increases with coronary pressure. There are a variety of mechanisms suggested for the impeding effect of cardiac contraction on coronary flow (65, 66). One of the suggested mechanisms is tissue pressure related to left ventricular cavity pressure at the endocardium and thoracic pressure at the epicardium. This mechanism concurs with the observation that the contraction related impeding effect is stronger at the subendocardium than at the subepicardium. However, it was demonstrated that also in the empty beating heart, coronary arterial flow was still pulsatile (67) and subendocardial perfusion is reduced more strongly (68). It has been suggested that direct compression effects of myocardial fibers on the microvessels are responsible for perfusion impediment (67, 69). However, this is in contrast with the finding that contraction has hardly an effect on subepicardial perfusion as is demonstrated in Figure 3.

The impeding effect of contraction on coronary perfusion is the result of the synergy of factors including tissue pressure, direct compression effects by tissue elastance and deformations (52, 70). In fact, most likely, the stiffer muscle in systole protects the intramural vessels from extreme compressions by tissue pressure in systole, since left ventricular pressure has a strong effect on the coronary arterial waveform in early systole with low grade of elastance but not in mid systole where elastance is much higher (65). It has been shown that at constant heart rate, DTF is increasing with reduced coronary pressure, an effect that may also act as a protective mechanism for the myocardium (71).

At present, clinical diagnostic methods are in development directed to the estimation of perfusion and oxygenation distribution by imaging methods such as perfusion MRI (50, 72, 73). These methods indeed demonstrate the vulnerability of the subendocardium in the presence of a stenosis, since in patients with ischemia resulting from a severe stenosis, contrast arrives at the subendocardium much later and at smaller amounts. However, the interpretation of such images requires more detailed analysis since these results are strongly dependent on hemodynamic factors as well.
Figure 3: The conductances in the subepicardium (A) and subendocardium (B) as function of diastolic time fraction and perfusion pressure ($P_C$). Data from (40). HR, heart rate.

Figure 4: Hyperemic pressure-flow relations in the arrested and beating state. Both relationships are curvilinear but incremental linear in the physiological pressure range. The dashed lines connect venous pressure with possible points on the pressure-flow lines. The inverse of the slope of the dashed lines is coronary resistance per definition. Hence, coronary resistance decreases with coronary pressure and increases with cardiac contraction. Data from (74). LV, left ventricle; $P_v$, venous pressure.
Resistance definition and coronary pressure-flow relations

Hemodynamic dependencies of myocardial perfusion relate to epicardial pressure-flow relations and the microvascular resistance measured at the epicardial level as demonstrated in Figure 4 based on data of Downey and Kirk (74). A main coronary artery was cannulated and artificially perfused at different flow rates during continuous vasodilation with adenosine infusion. The decrease in pressure due to arresting the heart was then measured at each flow rate. In the range of physiological pressures, the pressure-flow relations in the arrested and beating state are incremental linear, implying that they are straight but their extrapolations do not pass through the origin.

The effect of cardiac contraction on the pressure-flow relation is clear and results in a parallel shift of the curve. Often the slope of the pressure-flow relation is considered erroneously to reflect coronary vascular resistance. The resistance of a vascular system is defined as the pressure drop between inlet and outlet divided by the flow through it. How this definition relates to the pressure-flow relation is demonstrated in Figure 4. The dashed lines connect the venous pressure (Pv) to several points on the two pressure-flow relations, each point corresponding to a possible measuring condition. Per definition, the inverse of the slope of such a line is the vascular resistance at that measuring condition. It is then clear from Figure 4 that the resistance in each state decreases with increasing pressure and that for a certain pressure or flow the resistance increases from the arrested to the beating state. Hence, the hemodynamic influences on the coronary arterial pressure-flow relations are fully consistent with the hemodynamic dependences of perfusion distribution in the myocardium. The pressure-dependence of coronary microvascular resistance has also been confirmed in humans (75).

Diastolic pressure-flow relations

It has been frequently assumed that diastolic perfusion of the myocardial tissue could be characterized without the confounding influence of cardiac contraction. Hence, Gregg and Green proposed the concept of end-diastolic resistance, defined as the coronary arterial-right atrial pressure difference divided by coronary arterial flow at the end of diastole (76). When Bellamy described that in diastoles longer than normal, coronary flow ceases at a perfusion pressure far above right atrial pressure (77), it was also assumed that this finding was free of preceding systoles (78). However, the intramyocardial vasculature represents a large compliance (79) and the time constants for emptying in systole and filling in diastole are much larger than a heartbeat. Moreover, venous outflow continued after cessation of flow in such a long diastole, a clear proof of the “Windkessel” function of the intramyocardial compliance (80).

Effects of collateral flow

The non-linearity of the collateral system and its interaction with myocardial perfusion has been demonstrated by Messina et al. (81). In isolated dog hearts, the LCX was perfused separately from the remaining left main territory such that these two territories could be perfused independently and studied in the presence and absence of a pressure gradient with the main stem. It was shown that with
increasing interarterial pressure gradients, the LCX pressure-flow relation diverged only over the lower range of perfusion pressure and the effect of collateral flow was only measureable below 40 mmHg perfusion pressure. Obviously, depending on the state of the heart and species, collateral flow is a factor to be considered in the interpretation of coronary pressure-flow relations. In general, the pig has a low innate collateralization (82), but it is higher in the dog. In humans, it has been found that only with a wedge pressure larger than 25 mmHg or some alternative indication, a physiological effect of collateral flow can be found (81, 83–85).

Conclusions

Coronary pressure-flow relations are at the heart of the mechanistic interpretation of coronary hemodynamics. The autoregulation curves with their parallel shift depending on oxygen consumption are essential for understanding the interplay between coronary pressure and oxygen consumption with the control of blood flow. The hyperemic pressure-flow relation describes the maximal flow that is possible at a given coronary pressure and plays an important role in the definition of coronary flow velocity reserve, CFVR, and fractional flow reserve, FFR, which are indices for clinical decision making with respect to deferral of percutaneous coronary interventions. It was noted that in the clinical literature the models underlying the concepts of CFVR and FFR are often oversimplified by assuming linear pressure-flow relations for the fully vasodilated coronary microcirculation and stenosis while these relationships are essentially incremental linear or curvilinear, respectively. These deviations from linearity are well founded by fluid dynamic principles for a stenosis, the physical effect of coronary pressure on distensible microvessels, and contraction related compression of the microcirculation. The field of human coronary physiology as applied by the cardiology community would benefit from combined measurement of pressure and flow velocity distal to the stenosis, since information on both stenosis and microvascular resistance is obtained simultaneously. Moreover, perfusion distribution measurements as obtainable by echo and MRI contrast methods could evolve into reliable noninvasive methods to detect subendocardial ischemia in humans.
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Coronary pressure-flow relations


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Coronary pressure-flow relations


Chapter 3

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