Physiological Basis of Clinically Used Coronary Hemodynamic Indices

Jos A.E. Spaan, PhD; Jan J. Piek, MD; Julien I.E. Hoffman, MD; Maria Siebes, PhD

Abstract—In deriving clinically used hemodynamic indices such as fractional flow reserve and coronary flow velocity reserve, simplified models of the coronary circulation are used. In particular, myocardial resistance is assumed to be independent of factors such as heart contraction and driving pressure. These simplifying assumptions are not always justified. In this review we focus on distensibility of resistance vessels, the shape of coronary pressure-flow lines, and the influence of collateral flow on these lines. We show that (1) the coronary system is intrinsically nonlinear because resistance vessels at maximal vasodilation change diameter with pressure and cardiac function; (2) the assumption of collateral flow is not needed to explain the difference between pressure-derived and flow-derived fractional flow reserve; and (3) collateral flow plays a role only at low distal pressures. We conclude that traditional hemodynamic indices are valuable for clinical decision making but that clinical studies of coronary physiology will benefit greatly from combined measurements of coronary flow or velocity and pressure. (Circulation. 2006;113:446-455.)

Key Words: blood flow velocity ■ blood pressure ■ collateral circulation ■ coronary disease ■ hemodynamics

Coronary physiology has a rich history, founded on numerous animal and theoretical models, and significant milestones were reached as new measuring techniques were developed. Recent progress has been made by applying techniques to measure intracoronary flow, flow velocity, and pressure to aid in clinical decision making, thereby advancing our understanding of human coronary physiology beyond what could be extrapolated from animal studies. One unresolved issue that has arisen from these studies, however, concerns conflicting interpretations of coronary microvascular resistance, a quantity with crucial relevance for clinical decision making.1–4

There are 2 conflicting interpretations of coronary pressure-flow lines during hyperemia: (1) coronary pressure-flow relations are straight and, in the absence of collateral flow, intercept the pressure axis at venous pressure (Pv); or (2) coronary pressure-flow relations are straight at physiological pressures and, when linearly extrapolated, intercept the pressure axis at a value well above venous pressure (extrapolated zero flow pressure [PzfE]); at lower pressures, however, they curve toward the pressure axis, intercepting it at a lower pressure (actual zero flow pressure [Pzf]) that is still higher than Pv.

The purpose of this article is to review the physiological literature with respect to coronary pressure-flow relations as relevant to myocardial microvascular resistance. This key issue relates to important assumptions underlying the frequently used model of myocardial fractional flow reserve (FFRmyo). We conclude with a synopsis of physiological studies demonstrating the curved nature of pressure-flow relations and how this shape relates to the pressure dependence of minimal coronary microvascular resistance.

This focused review of coronary physiology is intended to help the clinical reader to translate the physiological analysis of microvascular resistance from bench to bedside and to encourage the use and further development of hemodynamic indices in the clinical setting.

Coronary Flow Reserve

The concept of coronary flow reserve (CFR) was developed to describe the flow increase available to the heart in response to an increase in oxygen demand.5 Because the perfused tissue mass cannot always be measured, CFR was expressed as the ratio between maximal hyperemic flow and resting flow, with the hyperemic condition implicitly assumed as a standard value.6,7 A pressure drop across a stenosis causes compensatory vasodilatation at rest, thereby diminishing the ability of the coronary circulation to adapt to an increase in oxygen demand. In other words, a stenosis reduces CFR. Investigators also recognized that flow per gram of tissue varied throughout the cardiac muscle and that subendocardial perfusion in particular was impeded by forces related to cardiac contraction.8–11 Consequently, CFR varies regionally within the myocardium and is first exhausted in the subendocardium, especially at higher heart rates.12 Reduced subendocardial CFR is a good paradigm to explain why ischemia and infarction start predominantly in this vulnerable region.7 We expect that the concept of subendocardial CFR will...
Figure 1. Model of the coronary circulation. Top and bottom circuits represent equivalent myocardial mass. Without stenosis in the bottom, \( \text{Rmin}_n = \text{Rmin}_s, Q_n = 0, Q_S = Q_s, \text{and} \ P_d = P_a. \) \( Q_S \) indicates hyperemic flow with stenosis; \( Q_n \) hyperemic flow without stenosis; and \( Q_c \), collateral flow.

become used in clinical diagnosis once new technological modalities mature.13

Coronary flow velocity reserve (CFVR) measured by Doppler ultrasound was introduced as a surrogate for CFR and was first measured during open heart surgery by applying Doppler suction probes to epicardial arteries for stenosis evaluation. This pioneering work of Marcus and colleagues14 is the clinical precursor of the present-day guidewire-based measuring techniques. Marcus et al demonstrated that CFVR could also be reduced in normal coronary arteries of hearts with hypertrophy resulting from valvar stenosis. The development of intracoronary catheters and Doppler velocity sensor–equipped guidewires allowed the application of CFVR during catheterization procedures.15,16 A threshold value of CFVR indicative of reversible ischemia varies between 1.7 and 2.17

An important problem in applying CFVR and CFR is their dependence on the level of control resistance, which in turn is affected by oxygen demand or impaired autoregulatory capacity.18 However, as discussed below, hyperemic microvascular resistance also depends on hemodynamic conditions.

Model for Hyperemic Perfusion Assuming Linear Pressure-Flow Relations

Pressure sensor–equipped guidewires were introduced, allowing measurement of pressure beyond a stenosis. It was assumed that the ratio between distal pressure (\( P_d \)) and aortic pressure (\( P_a \)) during maximal hyperemia can be translated to an estimate of relative (fractional) maximal flow. Because good pressure measurements are easier to obtain and the dependence on baseline conditions was eliminated, this ratio became favored to quantify the significance of a coronary stenosis. In particular, Pijls et al19 pioneered this field and established pressure-derived indices of stenosis severity in clinical practice.

\( \text{FFR}_{\text{myo}} \) was defined as the ratio of maximal myocardial blood flow distal to a stenotic artery to the theoretical maximal flow in the absence of the stenosis. The principles are illustrated by the model in Figure 1, with parallel normal and stenotic circuits that in this model are assumed to perfuse the same amount of tissue and may or may not be connected by collateral vessels proximal to the capillary bed. Even with collaterals, no collateral vessel flow will occur without a stenosis because no pressure difference is present across the collateral vessels, but collateral flow will occur with a stenosis because the distal pressure in the recipient vessel is lower than \( P_a \) in the donor vessel; the difference between the two is the driving pressure for collateral flow.

Pressure-based \( \text{FFR}_{\text{myo}} \) is obtained as \( (P_d - P_v)/(P_a - P_v) \), where \( P_a \) is proximal coronary arterial (= aortic) pressure, \( P_d \) is distal coronary pressure, and \( P_v \) is coronary venous pressure. A value for \( \text{FFR}_{\text{myo}} \) < 0.75 indicates that dilatation of the coronary stenosis is likely to relieve ischemia.

The physiological derivation for \( \text{FFR}_{\text{myo}} \) is as follows:

\[
\text{FFR}_{\text{myo}} = \frac{Q}{Q_n}
\]

where \( Q_n \) is myocardial flow without stenosis and \( Q \) is the myocardial flow when the artery is stenotic and represents the sum of flow through the stenotic vessels (\( Q_S \)) and collateral flow (\( Q_c \)).

\[
Q_n = \frac{P_a - P_v}{\text{Rmin}_n} \quad \text{and} \quad Q = \frac{P_d - P_v}{\text{Rmin}_s}.
\]

where \( \text{Rmin}_n \) and \( \text{Rmin}_s \) are the minimal resistances for the distal microcirculation without and with a stenosis in the supplying artery, respectively.

\[
\frac{Q}{Q_n} = \frac{P_d - P_v}{P_a - P_v} \times \frac{\text{Rmin}_n}{\text{Rmin}_s}
\]

Therefore, so that \( \text{FFR}_{\text{myo}} = (P_d - P_v)/(P_a - P_v) \) is true only if \( \text{Rmin}_n = \text{Rmin}_s \). If this were true, then minimal microvascular resistance would be independent of pressure because the respective perfusion pressures \( P_d \) and \( P_a \) are different. If \( \text{Rmin}_s \) were higher than \( \text{Rmin}_n \), then \( \text{FFR}_{\text{myo}} \) based on pressure measurements would underestimate the myocardial flow ratio \( Q/Q_n \). To test this assumption, Pijls et al19 compared \( (P_d - P_v)/(P_a - P_v) \) with the coronary flow ratio \( Q/Q_n \). Without collateral flow, the expected relation passes through the origin, as indicated by the dashed line in Figure 2. Their results showed that with increasing stenosis severity the coronary flow ratio progressively underestimated the pressure-based index. They assumed that this was because collateral flow was missed by measuring coronary flow proximal to the collateral connection. However, the magnitude of collateral flow was not verified by direct measurement. Moreover, in a PET study in humans, actual myocardial flow per gram of tissue was measured distal to a stenotic and reference vessel, and the myocardial flow ratio was plotted versus \( \text{FFR} \).20 In this setting, collateral flow was included in the measurements, but a similar underestimation was reported. Such underestimation would also follow if microvascular resistance increased as distal perfusion pressure fell. It is therefore important to
explore alternative explanations for the deviation between the dashed and solid lines in Figure 2.

Distensibility of Resistance Vessels as Rationale for Pressure Dependence of Coronary Resistance

At maximal vasodilation, the state at which $FFR_{\text{myo}}$ is defined, diameters of all vessels depend on distending pressure and more at lower than higher pressure. This fundamental property has been demonstrated in many studies on isolated and in situ vessels without tone. When normalized to the diameter at a pressure of 100 mm Hg, the pressure-diameter relations of blood vessels are independent of size. A compilation of such in vitro data is shown in Figure 3.21 The diameter change induced by a 10-mm Hg pressure change amounts to 1% at a mean pressure of 80 mm Hg, 4% at 40 mm Hg, and 10% at 20 mm Hg. These numbers seem small, but because pressure drop in tubes is inversely related to the fourth power of the diameter (Poiseuille’s law), these diameter changes correspond to 4%, 16%, and 40% resistance variations for 10-mm Hg pressure variations at the different mean pressures. The change in vessel diameter corresponding to a pressure increase from 50 to 100 mm Hg, as may occur when a stenosis is dilated by balloon angioplasty, is 8%, corresponding to a resistance change of 32%. Direct observations of resistance vessels at the subepicardium and subendocardium demonstrate a similar response to pressure changes of in situ vessels with diameter in the order of 100 μm.22 During hyperemia and at an arterial pressure of 100 mm Hg, ~25% of total coronary resistance is in venules and veins >200 μm.23 These vessels are rather distensible, and their resistance to flow will increase when Pd decreases as a result of flow limitation through a stenosis. When the effect of pressure changes on the diameter of dilated arterioles and other vessels constituting the microcirculation is considered, minimal microvascular resistance should decrease substantially in patients when a stenosis is dilated.

In vivo studies have demonstrated this fundamental relation between vascular diameters, volume, and resistance by investigating relationships between intramural vascular volume and resistance and the effect of arterial pressure on these relationships.24 Recent results from studies using ultrasound contrast showed a decrease of microvascular volume during hyperemia of >50% when arterial pressure was lowered from 80 to 40 mm Hg.25 This corresponds with earlier studies in which intramural blood volume was measured in different ways.26 Moreover, pressure dependence of coronary resistance was clearly demonstrated by experiments in which coronary flow increased when the arterial-venous pressure difference was kept constant by increasing both pressures by the same amount, which is only possible when resistance decreases with pressure.27 These findings are important because they imply that a stenosis not only adds resistance to flow in the epicardial arteries but additionally impedes myocardial perfusion by increasing microvascular resistance via the passive elastic behavior of the microvascular walls at vasodilation.

Coronary Pressure-Flow Relations and Microvascular Resistance

To translate results obtained in isolated vessels to an intact circulation, we make use of coronary pressure-flow relations at maximal vasodilation that are usually presented with pressure (independent variable) on the horizontal axis and flow (dependent variable) on the vertical axis. Many physiological studies show that these pressure-flow lines, even in the absence of collateral vessels, are straight at physiological pressures but follow a convex curve toward the pressure axis at lower pressures, and the zero flow intercept on the pressure axis $Pzf$ is higher than $Pv$ (solid line in Figure 4). When the
Diastolic Coronary Pressure-Flow Relations

Flow and pressure decrease during arrest or a long diastole, and flow near the origin of a major epicardial artery reaches zero when coronary pressure is ≈40 mm Hg during autoregulation and between 5 and 15 mm Hg during maximal vasodilation, ie, Pfz exceeds Pv. The pressure-flow lines can be remarkably straight, especially at physiological pressures. An elevated Pfz can be found because of capacitive flow from epicardial and particularly intramyocardial microcirculation. This interpretation is strongly supported by the observation that coronary venous outflow continues even when pressure has decayed to Pfz. This venous outflow at cessation of inflow has to come from a pool of blood within the microcirculation, which also constitutes the intramyocardial compliance. Pfz values above Pv could not be due to collateral flow in those experiments because pressure at the source of all epicardial vessels was essentially equal at all times.

Pfz and the whole pressure-flow line are shifted to the right (higher pressures) by left ventricular hypertrophy, elevated Pv caused by pericardial tamponade, or an increase in right or left ventricular diastolic pressures.

The effect of this shift is to decrease CFR and increase FFR independent of any associated stenosis.

A few studies in humans have examined long diastoles induced by intracoronary injections of high doses of adenosine or ATP and demonstrated the curvature at low pressure, although zero flow velocity was never reached. These clinical studies are consistent with the animal studies in that PfzE is high (30 to 40 mm Hg) when coronary autoregulation is present and <20 mm Hg at full vasodilation. The slope of the hyperemic diastolic coronary velocity–aortic pressure curve was proposed as an index for stenosis severity. However, interpretation of these diastolic aortic pressure–coronary flow relations is hampered by the superimposed hemodynamic effects of microcirculation and stenosis that can be overcome with modern guidewire technology measuring pressure and velocity distal to a stenosis simultaneously.

Back Pressure and Coronary Microvascular Resistance

The calculation of resistance requires knowledge of the pressure distal to the resistance; this is called the back pressure. It is commonly but erroneously assumed that coronary back pressure can be deduced from the arterial pressure-flow relation by measuring the intercept of this relationship with the pressure axis. Resistance must be calculated when blood is flowing, whereas the intercept is obtained at zero flow, when the reduced pressure has altered diameters in the coronary vascular bed sometimes even to the point of collapse.

Studies on microvascular diameters in subendocardium and subepicardium have not found such collapse in the presence of flow. When the heart is overfilled in diastole, pressure in epicardial veins may be uncoupled from and higher than right atrial pressure and correlate better with left ventricular diastolic pressure. In the examples discussed in relation to Figures 4 and 5, Pv has been taken as back pressure, assuming normal diastolic left ventricular filling.

Effect of Cardiac Contraction on Coronary Pressure-Flow Relations

Most studies of pressure-flow relations were done during diastole or cardiac arrest, and it is important to know how cardiac contraction affects these relations. More than 50 years ago, Sabiston and Gregg observed an increase in coronary flow at constant pressure when the heart was arrested by

![Image](http://circ.ahajournals.org/)

**Figure 4.** Interpretation of measured pressure-flow relations without collateral vessels. Solid curve represents a measured pressure flow relation. Dashed line indicates pressure-flow line when resistance is constant at RminN and dotted line indicates pressure-flow line when resistance is constant at RminS. PfzE indicates zero-flow pressure after linear extrapolation of the straight part of the pressure-flow curve.
vagal stimulation, thus demonstrating that cardiac contraction impeded coronary perfusion. The classic study of Downey and Kirk4 is highly relevant to this subject because it demonstrates the quantitative effect of cardiac contraction on the coronary pressure-flow relation (Figure 5). In their experiments, the left circumflex artery was perfused at constant flow, and the heart was arrested by vagal stimulation at different flow levels. Arterial perfusion pressure decreased during these periods of cardiac arrest. This pressure drop was rather constant at higher flows but decreased at lower flow rates, resulting in curved pressure-flow relationships at lower pressures. Linear extrapolation of the pressure-flow relations in the arrested and beating heart from physiological pressures to the pressure axis resulted in a shift of the pressure intercept, both above Pv. This shift in the extrapolated pressure-flow relation between the arrested and beating state has nothing to do with collateral flow, but also present at a flow rate at which pressure in the circumflex artery equals the Pa and a pressure difference to drive collateral flow is absent.43

The effect of cardiac contraction on coronary resistance can be described in a manner similar to the effect of perfusion pressure on the resistance in arrested hearts, and the 2 thin arrows in Figure 5 demonstrate the increased resistance. The slope of the line connecting Pv with the pressure-flow relations at the same flow rate is smaller for the beating than the arrested state. Hence, minimal coronary resistance has increased by contraction of the heart due to compression of intramural vessels. Microsphere studies have demonstrated that this increase in resistance takes place predominantly in the subendocardium and is related to diastolic time fraction.44 These observations agree well with direct in vivo observations of small-vessel diameters with a needle microscope.22,39,45,46

It is likely that mechanical forces will be altered in dyskinetic segments and therefore affect minimal resistance.

The linear fits through the measurements of Figure 2 and through the measurements of the beating heart in Figure 5 both have a non–zero pressure intercept. According to Figure 1 and assuming that Rmin is constant, this intercept must be caused exclusively by collateral flow. However, Figure 5 clearly demonstrates that such intercept is caused by cardiac contraction. The difference in the 2 curves in Figure 5 at higher pressures cannot be explained by collateral flow because of the absence of pressure gradient. Hence, the assumption that microvascular resistance is constant, which is thought to be supported by Figure 2, is not warranted.

The concept that heart contraction impedes myocardial perfusion particularly at the subendocardium is of great clinical importance. The beneficial effect of a β-blocker is frequently attributed to the reduction in oxygen consumption because of decreased heart rate. However, the induced increase in diastolic time fraction reduces the average time for compression of the subendocardial vasculature, which has a stronger effect in maintaining a positive balance between supply and demand.47

Collateral Flow and Coronary Pressure-Flow Relations
In the dog, well known for its naturally occurring collateral vessels in contrast to the pig, Messina et al48 cannulated the left main coronary artery and the left circumflex artery separately. Pressure in the left circumflex artery was varied to obtain the pressure-flow line, while pressure in the left main artery was set at different levels. A typical result is shown in Figure 6. When pressures were reduced simultaneously in the left circumflex and left anterior descending coronary arteries, there was no collateral flow, and the curve indicated by the open circles was obtained. When pressure was reduced in only 1 of the arteries there was collateral flow, and the curve indicated by the open triangles was obtained.

A deviation between the 2 relationships caused by collateral vessels appears only at low perfusion pressures (<40 mm Hg). At higher, clinically relevant pressures, the pressure-flow relations with and without collateral flow are indistinguishable, and the extrapolated pressure-flow relation with PzfE (curve 1 in Figure 6) is hardly affected. Although well-developed collateral vessels could induce a rightward shift in the pressure intercept, as suggested by curve 2 in Figure 6, the reason for such a shift should be distinguished from other possible effects.49

Wedge Pressure and Other Collateral Flow Indices
The pressure distal to an occlusion has been defined as peripheral coronary pressure. Peripheral coronary pressure falls gradually after an occlusion because of the loss of microvascular volume via the venous vessels32 and approaches a more or less stable pressure, referred to as wedge
diastolic stress levels and thereby higher Pw values.55,56

start to affect cardiac function regionally, leading to increased stable value. In this waiting time the cessation of flow will flow contribution.

absence of any collateral flow.51 Similar values of Pw in the amount of 25 mm Hg was found in patients with complete occlusion of an occluded vessel, a Pw of approximately the same pressure (Pw). In the absence of collateral vessels, Pw will fall to a lower level but will still exceed Pv.

A positive correlation was found between Pw/Pa and anterograde coronary flow velocity after coronary occlusion.50 However, without collateral flow Pw/Pa still equaled on average 0.2. Similarly, when collateral flow was scored by the degree of blush of contrast arriving in the perfusion area of an occluded vessel, a Pw of approximately the same amount of 25 mm Hg was found in patients with complete absence of any collateral flow.51 Similar values of Pw in the absence of detectable collateral flow were measured by our own group using a variety of techniques.52,53 These clinical studies corroborate the findings from animal studies that a Pw <25 mm Hg is not likely a measure of collateral flow. Therefore, using pressure alone as an index of collateral flow54 is likely to result in misinterpretation of the collateral flow contribution.

In the determination of Pw, it is important to wait for a stable value. In this waiting time the cessation of flow will start to affect cardiac function regionally, leading to increased diastolic stress levels and thereby higher Pw values.55,56 Obviously, this change in regional cardiac function is less with well-developed collateral vessels, which also results in higher values for Pw, and it is difficult to differentiate between collateral and wall stress effects on Pw without a direct measure of collateral flow.

**Effect of Stenosis on Hyperemic Microvascular Resistance in Humans**

The question related to constancy of coronary resistance has become relevant because conflicting conclusions have been published recently. In agreement with the aforementioned analysis, Verhoef et al calculated hyperemic microvascular resistance as \( R_d \) divided by flow velocity. They concluded that hyperemic microvascular resistance is elevated distal to a stenosis because of the lower perfusion pressure caused by the pressure loss across the stenosis and reported that it was reduced to a value even lower than in a nondiseased reference vessel of the same heart when perfusion pressure was restored after the lesion was treated. According to Aarnoudse et al and Fearon et al, such a conclusion is the result of an “improper” definition of minimal coronary resistance, and the effect of collateral flow as derived from Pw should be incorporated in the calculation of minimal microvascular resistance to render it constant regardless of perfusion pressure.

This argument can be refuted by pointing out that (1) there is no proof that Pw reflects collateral flow, as outlined above; (2) a constant hyperemic microvascular resistance is highly unlikely, as was shown by a large number of physiological studies with more direct measurements (eg, references 11,12,22,24,27,28,39,41,44, and 46); and (3) hyperemic microvascular resistance distal to a stenosis did not correlate with a collateral index, Pw/Pa, in the study of Verhoef et al. If the assertion of hyperemic microvascular resistance being independent of hemodynamic factors were correct, then many physiological concepts developed over the course of time would not apply in humans.

From the data of Aarnoudse et al, a pressure-flow relation can be derived demonstrating similarity with those represented in Figures 5 and 6. The 3 data points in Figure 7 are from Table 2 in the report of Aarnoudse et al and represent the uncorrected average surrogate flow values derived at 3 different distal pressures. The lowest measured pressure in this curve is 40 mm Hg, and, as shown in Figure 6, it was only below this pressure that collateral flow was effective in the dog study.48 In Figure 7, the extrapolated intercept with the pressure axis is \( \approx 25 \) mm Hg, which is similar to the studies of Messina et al (Figure 6) and Downey and Kirk (Figure 5). A curve with an arbitrary shift of 22 mm Hg (assuming a mean left ventricular pressure of 44 mm Hg) is included in this figure for comparison with Figure 5. This curve reflects the theoretical pressure-flow relation at cardiac arrest for this patient population. Hence, comparison between Figures 7 and 5 shows that the extrapolated intercept in Figure 7 may be to a large degree due to the effect of cardiac contraction on the intramural vessels rather than collateral flow, as discussed above.

We agree that a measurement of Pw of \( \approx 40 \) mm Hg, as some data points show in the study of Aarnoudse et al, is most likely related to collateral function. However, the aforementioned analysis suggests that values of Pw <25 mm Hg are related to factors determined by compression...
of the intramural vessels by cardiac contraction rather than to collateral flow.

Implications for Clinical Usefulness of Coronary Indices

The Table lists several indices that have been applied to assess the clinical severity of a coronary stenosis, ordered by the acquisition techniques. This table indicates some advantages and disadvantages of these techniques and of the respective derived indices. The threshold values for most of these indices as well as a further discussion of the merits of these indices can be found elsewhere.17,18

The usefulness of single-signal (pressure or velocity) indices is amply supported by clinical evidence and end points. They score much better than angiographic measurements in providing a basis for decision making during the catheterization procedure. However, clinical success is no proof of the underlying model, and despite their current usefulness, they hold limited promise for further advancement in clinical applications because stenosis and microvascular resistance cannot be differentiated. FFR and CFVR are affected in opposite directions by microvascular resistance, and in 27% of the patients with intermediate lesions, FFR and CFVR provided discordant advice with respect to treatment.57

It seems logical to have a measure of stenosis severity that can be separated from the effect of microvascular resistance.58 We introduced the hyperemic stenosis resistance index (HSR) for this purpose.59 HSR is calculated as the ratio between stenosis pressure drop and the distally measured flow velocity at maximal hyperemia. In a group of 151 patients, the accuracy of this index to predict inducible ischemia as determined by SPECT was significantly higher than that of FFR and CFVR. The prediction was particularly better in the subgroup in which CFVR and FFR produced discordant results.59 HSR is not completely independent of microvascular resistance because of the nonlinear relationship between pressure drop and flow velocity. However, because pressure drop and flow change in the same direction, the influence of altered hyperemic microvascular resistance on HSR is minimized compared with single-signal indices. It is therefore a pity that in the recent literature FFR is used as an independent variable, thereby obscuring the role of absolute pressure on microvascular resistance.

Combined Measurements of Pressure and Flow Velocity

Technical developments have produced a guidewire equipped with both a pressure and Doppler velocity sensor that allows simultaneous assessment of both stenosis and microvascular hemodynamics. In addition to the assessment of HSR as a hyperemic index of stenosis severity, combined measurements allow a more complete evaluation by the stenosis pressure drop–velocity relation throughout the hyperemic response. These relationships may demonstrate biomechanically induced variations in anatomic stenosis severity that cannot be detected by indices measured only by a single condition.3

Microvascular resistance is influenced not only by acute changes in hemodynamic conditions; long-term exposure to altered perfusion conditions will modify the structure of the vascular bed. Isolated microvessels adapt their structure rapidly to altered biophysical conditions,60 and evidence for outward remodeling has been found in patients in response to the decreased perfusion pressure induced by the stenosis.2 Assessment of microvascular resistance is an important tool for the evaluation of disease processes known to cause microvascular complications, such as diabetes, hypertrophy, or hypertension. Coronary flow and pressure are dynamic phasic signals, but the value of their time-dependent variation has scarcely been explored for clinical relevance. An example of using phasic flow velocity is detection of microvascular damage from the flow velocity waveform.61 Combined measurement of phasic pressure and flow velocity also enables coronary wave intensity analysis, a novel method allowing quantification of backward traveling waves originating in the coronary microcirculation by compression resulting from heart contraction.62

Conclusions

In this overview we have presented abundant physiological evidence based on coronary pressure-flow relations that minimal coronary microvascular resistance depends on hemodynamic factors such as heart rate and coronary pressure, which explains the vulnerability of the subendocardium to ischemia. These insights should be incorporated into the interpretation of indices describing the pathophysiological conditions of coronary lesions and of the microcirculation used for clinical decision making. It is important to realize that coronary pressure and flow are interdependent variables.
that vary with hemodynamic conditions. The simultaneous measurement of (phasic) flow and pressure will allow us to understand the human coronary pathophysiology in more detail and provide the basis for new clinically useful discoveries in relation to evaluation of coronary stenosis hemodynamics, quantification of collateral flow, and assessment of the coronary microcirculation in humans.

<table>
<thead>
<tr>
<th>Measured Variable</th>
<th>Advantages/Disadvantages of Acquisition Technique</th>
<th>Index of Stenosis Severity</th>
<th>Advantages/Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow velocity</td>
<td>+ Direct physiological measure of ability to increase flow at current hemodynamic conditions &lt;br&gt; + Phasic signal &lt;br&gt; - Velocity more difficult to measure than pressure &lt;br&gt; - Depends on stenosis and microvascular resistance</td>
<td>CFVR</td>
<td>- Depends on baseline flow</td>
</tr>
<tr>
<td></td>
<td>+ Pressure is measured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature by pressure guidewire</td>
<td>- $T_{mn}$ difficult to measure &lt;br&gt; - No phasic signal &lt;br&gt; - Time-consuming &lt;br&gt; - Depends on measurement location &lt;br&gt; - Depends on stenosis and microvascular resistance</td>
<td>CFRthermo</td>
<td>- Depends on baseline flow and hemodynamic conditions</td>
</tr>
<tr>
<td></td>
<td>+ Pressure is measured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal pressure</td>
<td>+ Easy to measure &lt;br&gt; + Phasic signal &lt;br&gt; + Pull-back to identify significant lesions in diffuse disease &lt;br&gt; - Depends on stenosis and microvascular resistance</td>
<td>FFR</td>
<td>+ Low variability &lt;br&gt; + Independent of baseline flow &lt;br&gt; + Well-defined normal value (1)</td>
</tr>
<tr>
<td></td>
<td>+ Pressure is measured</td>
<td></td>
<td>- Needs maximal vasodilation</td>
</tr>
<tr>
<td>Combined aortic pressure and distal flow velocity</td>
<td>+ Phasic signals &lt;br&gt; - Velocity more difficult to measure than pressure &lt;br&gt; - Time-consuming</td>
<td>IHDVPS</td>
<td>- Model-derived index of fractional maximal flow &lt;br&gt; - Assumes constant minimal microvascular resistance &lt;br&gt; - Model based on linearized coronary P-Q lines</td>
</tr>
<tr>
<td>Combined distal pressure and flow velocity</td>
<td>+ Direct physiological measure of stenosis severity &lt;br&gt; + Phasic signals &lt;br&gt; + Separate assessment of stenosis and microvascular resistance &lt;br&gt; + Yields stenosis pressure drop–velocity relation &lt;br&gt; - Velocity more difficult to measure than pressure</td>
<td>HSR</td>
<td>+ Stenosis-specific &lt;br&gt; + Less dependent on maximal vasodilatation &lt;br&gt; + Less dependent on hemodynamic conditions</td>
</tr>
<tr>
<td></td>
<td>+ Low variability &lt;br&gt; + Data also yield FFR and CFVR &lt;br&gt; - Needs more clinical validation</td>
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</tr>
</tbody>
</table>

$T_{mn}$ indicates mean transit time; +, advantage; -, disadvantage; RCFVR, relative coronary flow velocity reserve; CFRthermo, coronary flow reserve obtained by thermodilution; P-Q lines, pressure-flow lines; and IHDVPS, instantaneous hyperemic diastolic velocity pressure slope.

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Disclosures

Dr Hoffman has received honoraria for speaking to the California Academy of Medicine and is a member of the Circulation Research editorial board.
References


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