

Physiological Assessment of Coronary Artery Disease in the Cardiac Catheterization Laboratory

A Scientific Statement From the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology

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Abstract—With advances in technology, the physiological assessment of coronary artery disease in patients in the catheterization laboratory has become increasingly important in both clinical and research applications, but this assessment has evolved without standard nomenclature or techniques of data acquisition and measurement. Some questions regarding the interpretation, application, and outcome related to the results also remain unanswered. Accordingly, this consensus statement was designed to provide the background and evidence about physiological measurements and to describe standard methods for data acquisition and interpretation. The most common uses and support data from numerous clinical studies for the physiological assessment of coronary artery disease in the cardiac catheterization laboratory are reviewed. The goal of this statement is to provide a logical approach to the use of coronary physiological measurements in the catheterization lab to assist both clinicians and investigators in improving patient care. (*Circulation*. 2006;114:1321-1341.)

Key Words: AHA Scientific Statements ■ angiography ■ catheterization

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Introduction

During the past decade, the physiological assessment of coronary artery disease (CAD) has become increasingly important in both clinical and research applications. It has evolved, however, in the absence of standards for the technology, acquisition of studies, measurement, and interpretation of the results. The lack of standards has undermined clinicians' confidence in their understanding of and ability to apply the current technology. Similarly, ambiguous terminology and alternative definitions exist for common physiological measurements. Therefore, the major tasks of this writing committee are to provide background and evidence with regard to nomenclature, standards for data acquisition and interpretation, and clinical studies for the physiological assessment of CAD in the cardiac catheterization laboratory. The goal is to provide a logical approach to the use of coronary physiological measurements to assist both clinicians and investigators in improving patient care. The need for this scientific statement arises from the extensive evidence about and practice-based experience with technologies for assessment of coronary physiology and the resulting integration of these technologies into clinical practice.

The writing committee consists of internationally recognized experts in coronary physiology. Both academic and private practice sectors are represented. The material contained herein is intended not only for the coronary angiographer and the interventional cardiologist but also referring cardiologists. The reader should view the experts' consensus opinions in this statement as the best attempt of the American Heart Association to guide clinical practice in those areas where evidence-based practice exists.

1. Fundamental Concepts and Techniques

1.1. Background and Rationale

Angiography alone cannot fully characterize the clinical significance of coronary stenosis. This well-recognized limitation has been documented repeatedly by intravascular ultrasound imaging and ischemia stress testing.^{1,2} Coronary angiography produces a silhouette image and cannot identify intraluminal detail or provide the angiographer with information about the characteristics of the vessel wall. Furthermore, accurate identification of both normal and diseased vessel segments is complicated by diffuse disease as well as by

angiographic artifacts of contrast streaming, image foreshortening, and calcification. Bifurcation or ostial lesion locations may be obscured by overlapping branch segments. Even with numerous angiographic angulations to reveal the lesion in its best view, the physiological significance of a coronary stenosis, especially for an intermediately severe luminal narrowing (approximately 40% to 70% diameter narrowing), cannot be accurately determined. This fact is demonstrated by the clinical uncertainty of the angiographer, with confirmatory ischemic stress testing frequently needed in patients with such "moderate" CAD. Like stress testing, measurements of coronary pressure and flow provide information complementary to the anatomic characterization of coronary disease obtained by both angiographic and intravascular ultrasound examinations. Such physiological data acquired during the angiographic procedure can facilitate timely and more objective decision-making about therapy. Thus, the rationale for using coronary physiological measurement is to overcome the limitations of coronary angiography and provide the angiographer with an objective indicator of clinically relevant lesion significance.

1.2. The Coronary Pressure-Flow Relationships

To appreciate the derivations of the commonly used physiology measurements, a brief review of coronary flow and pressure will be helpful. Myocardial ischemia results from an imbalance between myocardial oxygen supply and demand. Coronary blood flow provides the needed oxygen supply for any given myocardial oxygen demand and normally increases automatically from a resting level to a maximum level in response to increases in myocardial oxygen demand from exercise and neurohumoral or pharmacological hyperemic stimuli. This increase from baseline to maximal flow has been termed coronary flow reserve (CFR).^{3,4} Blood flow has 3 major resistance components: the epicardial vessel (R1), the small arteries and arterioles (R2), and the intramyocardial capillary system (R3). When coronary reserve is normal, these 3 resistances are assumed to be functioning normally. In patients without atherosclerosis, the large epicardial vessel resistance (R1) is trivial. Arteries with diameters >400 μm have only minimal resistance. Adjustment of coronary resistance occurs principally at the R2 resistance (vessels <400 μm in diameter) and is due to the integrated action of several control mechanisms.⁴⁻⁷ Across a normal epicardial artery, supplying normal myocardium, coronary blood flow can increase >3-fold in adults.^{3,8}

Autoregulation automatically maintains the basal flow at a constant level in response to changing pressure and oxygen demand. Atherosclerotic narrowings produce epicardial vessel resistance and, after a critical reduction in vessel lumen area, can abolish not only coronary reserve but also autoregulation, thus reducing resting coronary blood flow. Moreover, several conditions, including left ventricular hypertrophy, myocardial ischemia, and diabetes, can affect the microcirculation (R3 resistance), blunting the maximal increase in coronary blood flow in the absence of epicardial vessel narrowing.

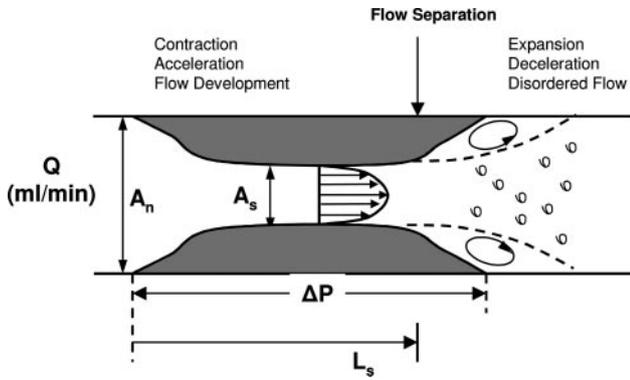


Figure 1. Total pressure loss is derived from 2 sources: frictional losses along the entrance and throat and inertial losses stemming from the sudden expansion, causing flow separation and eddies (exit losses). Frictional losses are linearly related to flow, Q (law of Poiseuille), and exit losses increase with the square of the flow caused by convective acceleration in the narrowed segment (law of Bernoulli). Total pressure gradient (ΔP) is the sum of the two: $\Delta P = (f_1 \times Q) + (f_2 \times Q^2)$. The loss coefficients f_1 and f_2 are a function of stenosis geometry and rheologic properties of blood (viscosity and density). The graphical representation of this equation results in a quadratic relationship, where the curvilinear shape demonstrates the presence of non-linear exit losses. When no stenosis is present, the second term is zero and the curve becomes a straight line (with a positive slope that depends on the diameter of the vessel; law of Poiseuille). A_s indicates area of the stenosis; A_n , area of the normal segment; and L_s , effective length of stenosis (up to the point of flow separation).

Coupled with reduced flow is the loss of pressure distal to a stenosis. The resistance to flow through a stenosis caused by viscous friction, flow separation, turbulence, and eddies at the site of the stenosis results in energy loss. Energy loss produces pressure loss distal to the stenosis and thus a pressure gradient across the narrowed segment (Figure 1). The pressure loss or gradient increases with increasing coronary flow along a quadratic pressure drop–flow relationship of the specific coronary stenosis, as illustrated in a patient shown in Figure 2.

In vessels without a stenosis, the pressure–flow curve of maximal vasodilation is linear in the physiological pressure range (Figure 3). However, when a stenosis is present, the maximal flow at any given arterial pressure is lower. In this setting, the coronary pressure–flow line at maximum vasodilation is no longer straight but curvilinear because stenosis resistance is flow dependent (Figure 3, dotted line, maximally dilated with stenosis). The clinical significance of these observations is that 2 nearly identical angiographic stenoses (eg, 60% diameter narrowing) can have a dramatically different clinical impact for the patient. One stenosis would limit flow for increasing demand and would produce angina, whereas the other would be angiographically apparent but would remain clinically unimportant.

1.3. Coronary Flow and Flow Reserve

As noted above, as stenosis severity increases, maximal coronary flow becomes attenuated and CFR decreases. CFR is a combined measure of the capacity of the major resistance components (the epicardial coronary artery and supplied vascular bed) to achieve maximal blood flow in response to

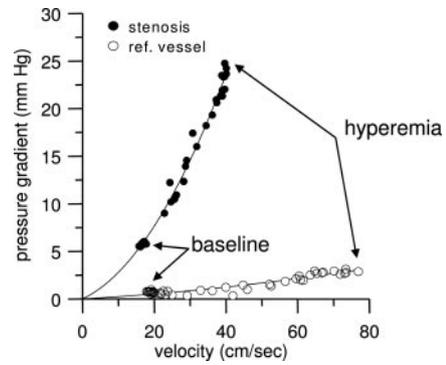


Figure 2. Measurements of the pressure drop (ΔP)–flow velocity relationship in a vessel with a 63% stenosis (closed circles) and in a normal reference vessel (open circles) of a 51-year-old patient, obtained by simultaneous measurement of distal pressure and flow velocity with a dual-sensor guidewire. Data points represent mean values of consecutive beats, from baseline to maximal hyperemia induced by an intracoronary injection of adenosine. Note the quadratic nature of the stenosis pressure drop–velocity relationship, $\Delta P = Av + Bv^2$, where A and B are constants of viscous and separation losses that are determined by the geometry of the stenosis and fluid properties of blood.²⁴

hyperemic stimulation (see Figure 3). A normal CFR implies that both the epicardial and minimally achievable microvascular bed resistances are low and normal. However, when abnormal, CFR does not indicate which component is affected, thus limiting the clinical applicability of this measurement. Although early studies in animals and patients suggested an absolute CFR of 3.5 to 5,^{8,9} in adult patients with chest pain syndromes and CAD risk factors undergoing cardiac catheterization with angiographically normal vessels, the normal CFR was 2.7 ± 0.6 ,¹⁰ which suggests a degree of patient variability and microvascular disease. In patients with essential hypertension and normal coronary arteries or in patients with aortic stenosis and normal coronary arteries, CFR may be reduced, in part because of myocardial hypertrophy and an abnormal microvasculature.

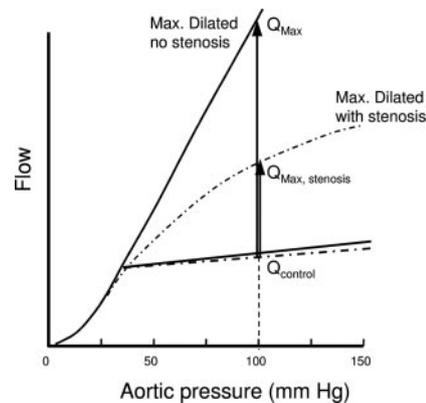


Figure 3. Effect of a stenosis on CFR. Solid lines represent the coronary pressure–flow relationship at baseline and maximal vasodilation (maximally dilated) without a stenosis. Changes in baseline and hyperemic flow affect coronary vasodilatory reserve (vertical arrows). CFR is represented by the ratio of flow at maximal dilation (Q_{Max}) to flow at baseline ($Q_{control}$). A stenosis progressively decreases the maximal flow (dashed lines) because the resistance of the stenosis is added to the resistance of the microcirculation. Flow reserve with a stenosis (the ratio of $Q_{Max, stenosis}$ to $Q_{control}$) is therefore markedly diminished.

CFR can be altered by changes in either basal or hyperemic flow, which are influenced by hemodynamics, loading conditions, and contractility. For example, tachycardia increases basal flow and decreases hyperemic flow, thus reducing CFR 10% for each 15-beat increase in heart rate.^{11,12}

Because CFR is a summed response of both the epicardial and microvascular flow, clinicians are reluctant to use CFR as the sole indicator of lesion significance except when it is normal. To increase confidence in CFR as a measure of lesion severity, the determination of relative CFR (rCFR) has been proposed by Gould et al,³ who defined rCFR as the ratio of maximal flow in a coronary artery with stenosis (Q^S) to maximal flow in a normal coronary artery without a stenosis (Q^N). It was shown that rCFR was independent of the aortic pressure and rate–pressure product and was well suited to assess the physiological significance of coronary stenoses when an adjacent nondiseased coronary artery was available. For invasive catheterization laboratory flow studies, rCFR was defined as the ratio of CFR_{target} to $CFR_{\text{normal reference vessel}}$:

$$rCFR = \frac{Q^S/Q_{\text{base}}}{Q^N/Q_{\text{base}}} = \frac{CFR_{\text{target}}}{CFR_{\text{reference}}}$$

The normal range for rCFR is 0.8 to 1.0.^{13,14} Because of the variability of CFR and limitations in patients with multivessel CAD, rCFR is not commonly used. Likewise, rCFR relies on the assumption that the microvascular circulatory response is uniformly distributed among the myocardial beds; thus, rCFR is of no value in patients with myocardial infarction (MI) or left ventricular regional dysfunction or in patients in whom the microcirculatory responses may be heterogeneous (eg, those with myocardial fibrosis or asymmetric hypertrophy).¹⁵

In clinical terms, CFR is best used to assess the microcirculation in the absence of epicardial artery narrowings. CFR is not used to assess stenosis significance because of the influence of hemodynamics and the unknown impact of the microcirculation.

1.4. Coronary Pressure and Fractional Flow Reserve

Myocardial perfusion pressure, normally the diastolic coronary pressure, equals aortic pressure minus the left ventricular diastolic pressure or central venous pressure. Across normal coronary arteries, aortic pressure is transmitted completely, without appreciable pressure loss even to the most distal regions. As noted earlier, the distal coronary pressure in arteries with an atherosclerotic narrowing is decreased in relationship to the degree of stenosis resistance. Pijls et al^{16,17} related the distal coronary pressure to the ischemic potential of a stenosis by calculating a value called the fractional flow reserve (FFR). By taking the ratio of the coronary pressure measured distal to the stenosis to aortic pressure as the normal perfusion pressure (distal coronary pressure/aortic pressure) and obtaining these measurements when the microvascular resistance was minimal and assumed to be constant (that is, at maximal hyperemia), the percentage of normal coronary flow, or a fraction of normal flow (ie, FFR), can be calculated. The FFR purportedly measures the maximum achievable myocardial blood flow in the presence of a coronary artery stenosis as a percentage of the maximum blood flow in the hypothetical case of a completely normal artery.^{16,17} The

FFR model assumes that under maximum arterial vasodilation, the resistance of the myocardium is minimal and constant across different myocardial vascular beds, and thus blood flow to the myocardium is proportional to the driving pressure (myocardial perfusion pressure).

FFR can be derived separately for the myocardium, for the epicardial coronary artery, and for the collateral supply. Calculations of myocardial, coronary, and collateral FFR from pressure measurements taken during maximal arterial vasodilation (ie, hyperemia) are as follows:

1. Myocardial FFR (FFR_{myo}) = $\frac{1 - \Delta P}{P_a - P_v} = \frac{P_d - P_v}{P_a - P_v}$
2. Coronary FFR (FFR_{cor}) = $\frac{1 - \Delta P}{P_a - P_w} = \frac{P_d - P_w}{P_a - P_w}$
3. Collateral FFR (FFR_{coll}) = $FFR_{\text{myo}} - FFR_{\text{cor}}$,

where P_a is mean aortic pressure; P_d , mean distal coronary pressure; ΔP , mean translesional pressure gradient; P_v , mean right atrial pressure; and P_w , mean coronary wedge pressure or distal coronary pressure during balloon inflation.¹⁸ Because FFR_{cor} uses P_w , it can be calculated only during balloon coronary angioplasty. For daily clinical practice, FFR can be easily calculated by a simplified ratio of pressures and expressed as:

$$FFR \approx \frac{P_d}{P_a}$$

The FFR is simplified to P_d/P_a given the assumption that P_v is negligible relative to P_a . An example of FFR measurement is shown in Figure 4. An FFR value of 0.6 means that the maximum myocardial flow across the stenosis is only 60% of what it should be without the stenosis (Figure 4). An FFR of 0.9 after percutaneous coronary intervention (PCI) means that the maximum flow to the myocardium is 90% that of a completely normal vessel. The concept of FFR has been thoroughly examined in both experimental and clinical studies.^{19,20}

Unlike most other physiological indices, FFR has a normal value of 1.0 for every patient and every coronary artery. Although findings in animal studies showed an effect on FFR from heart rate and arterial pressure, human studies did not show significant changes in FFR with changes in heart rate, blood pressure, or contractility.¹⁸ FFR has a high reproducibility and low intra-individual variability (Figure 5). Moreover, FFR, unlike CFR, is independent of gender and CAD risk factors such as hypertension and diabetes, and it varies less with common doses of adenosine than does CFR.²¹

A nonischemic threshold value has been prospectively confirmed¹⁹ and was compared with noninvasive stress testing.^{20,22} An $FFR < 0.75$ is associated with inducible ischemia (specificity, 100%), whereas a value > 0.80 indicates absence of inducible ischemia in the majority of patients (sensitivity, 90%).

In summary, for the assessment of an epicardial stenosis, the distal pressure–to–aortic pressure ratio at maximal hyperemia, or FFR, is a measurement of lesion significance that,

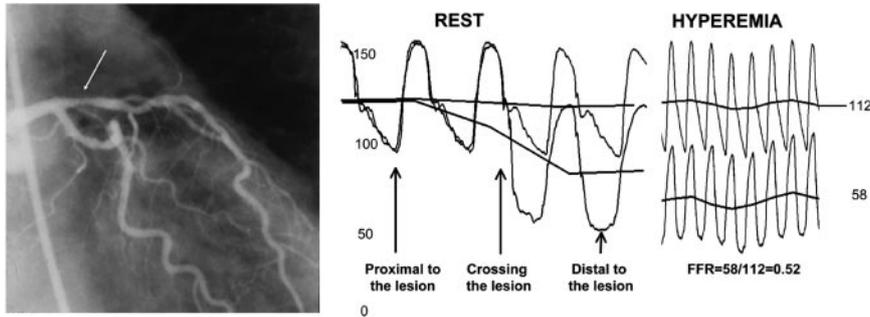


Figure 4. Illustration of the measurement of FFR in a 77-year-old patient with an intermediate coronary lesion in the proximal left anterior descending artery. Phasic and mean pressure signals are displayed as recorded by the guiding catheters and sensor-tip guidewire. At the left side of the pressure tracing, the pressure sensor is proximal to the stenosis with 2 identical pressures of the wire and guiding catheter. Distal pressure decreases as the pressure sensor crosses the stenosis. During maximal hyperemia (at the right side of the pressure tracing), the hyperemic distal pressure decreased to 58 mm Hg with aortic pressure of 112 mm Hg for an FFR of 0.52 (58/112). By FFR, maximal blood flow to the myocardium of the anterior wall of this patient is decreased to 52% of expected normal flow. Figure courtesy of N. Pijls.

unlike CFR, has low variability and high reproducibility and is relatively unaffected by changes in hemodynamics.

1.5. Combined Pressure and Flow Measurements

Recent advancements in sensor guidewire technology allow a more complete interrogation of the coronary circulation with a single wire (by pressure and velocity or by pressure and thermodilution). With combined distal measurements, a clinician has all the relevant hemodynamic information to make an informed decision about the physiological condition of the entire coronary circulation. Currently, 2 methods are used for these calculations. The first method combines simultaneous measurements of the phasic pressure and Doppler velocity distal to a stenosis. These measurements permit the calculation of stenosis and microvascular resistances and have been applied clinically. By using distal pressure and velocity during hyperemic conditions, a hyperemic stenosis resistance (HSR) index can be calculated as $HSR = \Delta P/v$, where ΔP represents the hyperemic pressure gradient ($P_a - P_d$) and v represents the average peak velocity at hyperemia.^{23,24} This index purportedly provides a refined physiological measurement quantifying the impediment to maximal flow caused exclusively by the stenosis. Like FFR, HSR has a normal reference value ($HSR=0$) and is independent of basal hemo-

dynamic conditions, with high reproducibility and low variability.^{23,24} Simultaneous measurement of distal pressure and flow velocity also allows the separate assessment of microvascular resistance^{25,26} and the construction of stenosis pressure gradient–velocity curves (Figure 2) that uniquely characterize the hemodynamics of any lesion and associated physiological responses.^{24,27} The pressure drop–velocity relations are also well suited to visualizing the effect of percutaneous intervention.²⁴ An HSR value $>0.8 \text{ mm Hg} \cdot \text{cm}^{-1} \cdot \text{s}$ is the threshold for prediction of reversible ischemia when compared with noninvasive stress testing.²³ HSR had a higher diagnostic accuracy than either pressure (FFR) or flow velocity (CFR) alone, especially in cases where outcomes of FFR and CFR do not agree.²⁸ HSR requires the use of both a distal pressure and flow velocity signal, which can be obtained with a dual-sensor (pressure and Doppler velocity) guidewire.^{24,26}

The second method uses distal pressure and thermodilution flow, as assessed by the inverse of the arrival (transit) time of a room-temperature saline bolus to the distal coronary artery segment.^{29–32} By measuring the mean transit time at rest and comparing it to the mean transit time at peak hyperemia, a thermodilution CFR can be calculated. Experimental animal and human studies have validated CFR_{thermo} against $CFR_{Doppler}$.^{30–32} The ability to measure distal pressure and

Reproducibility of FFR

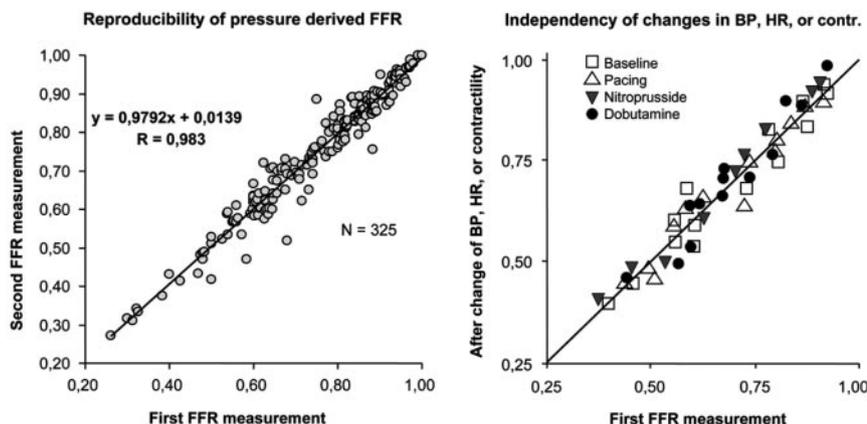


Figure 5. Left, Reproducibility of FFR by serial measurements in a multicenter study of 325 patients in whom FFR was measured twice within a 10-minute interval. Right, Changing heart rate, blood pressure, and contractility with pacing (Δ), nitroprusside (∇), and dobutamine (\bullet). Despite variations in heart rate of 40%, blood pressure of 35%, and contractility of 50%, FFR was unaffected by these changes.

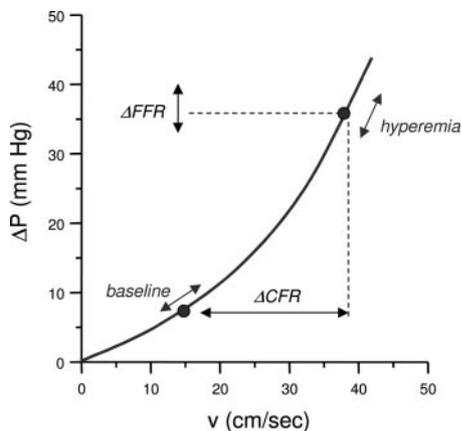


Figure 6. Schematic diagram of the curvilinear relationship between stenosis pressure gradient (ΔP) and flow velocity (v) illustrating the effect of changes in baseline or hyperemic flow velocity on physiological parameters for a given stenosis. Changes in baseline can affect CFR as much as changes in hyperemic flow velocity, whereas FFR and HSR are only affected by changes in hyperemic flow. Because pressure gradient and velocity change in the same direction, HSR ($=\Delta P/v$) is less sensitive to variations in maximal hyperemia.²³

estimate flow by using the thermodilution technique with a single wire also allows independent assessment of the microvasculature by calculating the index of microcirculatory resistance.³³ Although principally a research tool, the simultaneous measurement of FFR, CFR, and the index of microcirculatory resistance permits a unique characterization of the epicardial and microvascular resistances. The effect of changes in flow and pressure on the 3 parameters, FFR, CFR, and HSR, is illustrated in Figure 6. The significant features of available physiological measurements in the catheterization laboratory are listed in Table 1.

1.6. Techniques of Sensor-Wire Measurements

Relevant physiological data require accurate signal acquisition. Pressure and flow velocity signals are acquired with nearly identical methods. After diagnostic angiography or during angioplasty, a sensor guidewire is passed through an angioplasty Y-connector attached to a diagnostic or guiding catheter. Heparin (40 to 60 U/kg IV) and nitroglycerin (100 to 200 μ g IC) (to minimize vasomotion and measurement variability) are given several minutes before the measurements.

1.6.1. Flow Velocity

The flow velocity of red blood cells moving past the ultrasound emitter/receiver on the end of a guidewire is determined from the frequency shift, defined as the difference between the transmitted and returning frequency:

$$\text{Velocity (v)} = \frac{(f_1 - f_0) \cdot c}{(2f_0) \cdot \cos \theta}$$

where v represents velocity of blood flow; f_0 , transmitting (transducer) frequency; f_1 , returning frequency; c , constant for the speed of sound in blood; and θ , angle of incidence. If needed, volumetric flow can be calculated as the product of vessel area (in square centimeters) and mean cross-sectional

TABLE 1. Features of Measurements

Fractional flow reserve

- Nonischemic threshold range 0.75–0.80
- Normal value of 1.0
- Specific to epicardial lesions
- Linear relation with relative maximum blood flow
- Independent of hemodynamic alterations
- Value that accounts for total myocardial blood flow, including collaterals
- High reproducibility
- High spatial resolution (pressure pullback recording)

Coronary flow velocity

- Nonischemic threshold range of CFR >2.0
- CFR in nonobstructed vessels assesses microvascular integrity
- Complements invasive coronary studies of endothelial function
- Accurate estimation of volumetric flow when vessel cross-sectional area available
- Valuable for blood flow research studies

Combined pressure and flow velocity measurements

- Separate assessment of stenosis and microvascular resistances
- Allows construction of pressure drop–flow velocity curves (assessment of compliant lesions, hemodynamic gain after PCI)
- Stenosis resistance index:
 - Nonischemic threshold value <0.8 mm Hg/cm per second
 - Normal value of zero
 - Lesion specific
 - High reproducibility and sensitivity
 - Useful in cases of discordance between CFR and FFR

flow velocity: $\text{cm/s} \times \text{cm}^2 = \text{cm}^3/\text{s}$. Doppler flow velocities can be used to represent volumetric coronary flow when the vessel cross-sectional area remains constant over the measurement period. Compared with volumetric measurements, CFR by velocity alone may underestimate the volumetric CFR in vessels with intact endothelial function and flow-mediated vasodilation. For intermediately narrow lesions, sensor guidewires are considered to be nonobstructive to flow. The cross-sectional area of a 0.014-inch–(0.356-mm)–diameter sensor guidewire is 0.099 mm^2 , only 1.4% of the cross-sectional area of a 3-mm–diameter vessel and approximately 12% of the lumen area in a vessel with a diameter of 1 mm. Although it is true that a small guidewire does add cross-sectional area to a stenosis that is being interrogated, for intermediately severe lesions the addition of the small cross-sectional area is relatively negligible. However, if the cross-sectional area of the guidewire does reduce the true lumen area, this area is indeed already very small, and when FFR is abnormal the lesion is nearly always associated with abnormal stress imaging. For a scientist needing to know the precise effect of a stenosis on blood flow, a transstenotic measurement wire is not the most precise tool. However, in the clinical arena of the cardiac catheterization laboratory, the error contributed by the measurement wire in this system favors overestimating severity in the marginal cases over missing hemodynamically significant lesions.

To measure a flow velocity signal, the Doppler sensor at the tip of the wire is advanced ≥ 5 to 10 artery-diameter

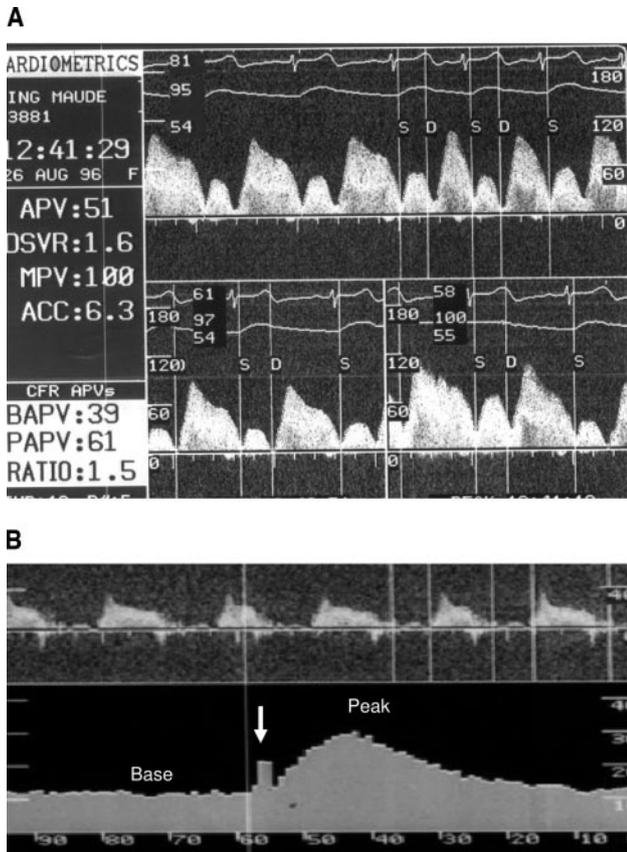


Figure 7. A, Coronary Doppler flow velocity tracings. The figure's upper section includes an ECG and aortic pressure and continuous flow velocity tracings displayed continuously. The coronary flow velocity phasic signals are demarcated by the systolic (s) and diastolic (D) lines. The velocity scale on the right is from 0 to 180 cm/s. The numbers in the box on the upper left represent heart rate and blood pressure. The lower section is divided into left and right panels. Left, Basal flow velocity recording. Right, Hyperemic velocity recording. In this example, the basal average peak velocity (BAPV) is 39 cm/s. The peak average peak velocity (PAPV) is 61 cm/s, and the coronary reserve (ratio) is 1.5. On the far left panel, the average peak velocity (APV) at the time shown is 51 cm/s, the diastolic-systolic velocity ratio (DSVR) is 1.6, and maximum peak velocity (MPV) is 100 cm/s. Acceleration time (ACC) is 6.3 cm/s. **B**, Continuous trend plot of average peak velocity showing the baseline and time course to peak hyperemia. An intracoronary bolus adenosine injection is seen by the square wave signal preceding the rapid increase in average peak velocity. The base and peak hyperemic phasic velocity signals are captured and displayed in the split screen shown in A. The trend plot scale is from 0 to 60 cm/s with a time base of 0 to 90 seconds. In this example, baseline flow is 13 cm/s, and peak hyperemic flow is 30 cm/s, for a CFR of 2.3.

lengths (>2 cm) beyond the stenosis, acquiring measurements in an area of reestablished laminar flow. Resting flow velocity data are recorded. Maximal coronary hyperemia is then induced by intracoronary or intravenous pharmacological stimulus (eg, adenosine), with average peak flow velocity (APV) continuously recorded. CFR is computed as the ratio of maximal hyperemic to basal APV (Figure 7). Poor Doppler signal acquisition may occur in 10% to 15% of patients. To optimize the velocity signal, the operator must adjust the guidewire position (sample volume). Several different tip orientations interrogating the maximal velocity spectra may

be tested. A full discussion of coronary Doppler flow measurement can be found elsewhere.²²

1.6.2. Pressure Measurements

For coronary pressure measurements, 2 pressure-wire systems are available at this time. Both wires can be used as angioplasty guidewires with mechanical properties close to those of standard clinical guidewires. For both wires, a pressure sensor is located 3 cm from the tip at the junction of the radioopaque and radiolucent portion of the wire. The pressure sensor therefore can be moved across a coronary artery stenosis and back again (showing a pressure drop) without recrossing the stenosis with the wire tip. An interface is available to record and analyze the pressure signals or to transfer the data to the regular catheterization laboratory physiological monitoring system.

Before inserting the guidewire into the patient, the sensor-wire and guide catheter pressure signals are calibrated and zeroed. The patient is given heparin and nitroglycerin as noted earlier. The sensor-wire is then introduced and positioned at the tip of the guiding catheter where the guiding catheter and wire pressures are equalized. The wire is then advanced across the stenosis or to the most distal part of the coronary artery for serial lesions or diffuse disease measurement.

Next, as described for CFR, a pharmacological hyperemic stimulus is administered via an intracoronary route (through the guide catheter) or intravenously. The mean and phasic pressure signals are continuously recorded. At peak hyperemia, represented by the nadir or lowest distal pressure, the FFR is then calculated as the ratio between the mean distal coronary pressure (measured by the pressure wire) and mean aortic pressure (measured by the guiding catheter).

1.6.2.1. Pressure Pullback Technique for Serial or Diffuse Stenoses

To study the distribution of abnormalities along a diseased coronary artery, the pressure wire can be pulled back slowly during hyperemia, precisely indicating at which particular locations hemodynamically significant abnormalities are present (Figure 8). To obtain a pullback recording, the sensor is placed in the distal segment of the coronary artery, and sustained maximum hyperemia is induced either by adenosine (140 μ g/kg per minute IV) or, in rare cases, by papaverine (10 to 15 mg intracoronary). The sensor is then pulled back slowly by hand under fluoroscopic guidance, with the pressure curves being recorded simultaneously. Pressure gradients and FFR at various segments over the length of the artery are calculated. Pressure loss due to diffuse atherosclerosis is gradual, whereas a focal stenosis can be differentiated by an abrupt increase in pressure proximal to the lesion. By moving the sensor back and forth, the exact location of a pressure drop representing a focal obstruction to flow can be determined.³⁴

After pressures are measured, the interface coupler is disconnected and a balloon catheter, stent, or other interventional equipment can be advanced over the pressure guidewire. Six-French guiding catheters are commonly used, but diagnostic catheters as small as 4F have been used as well,

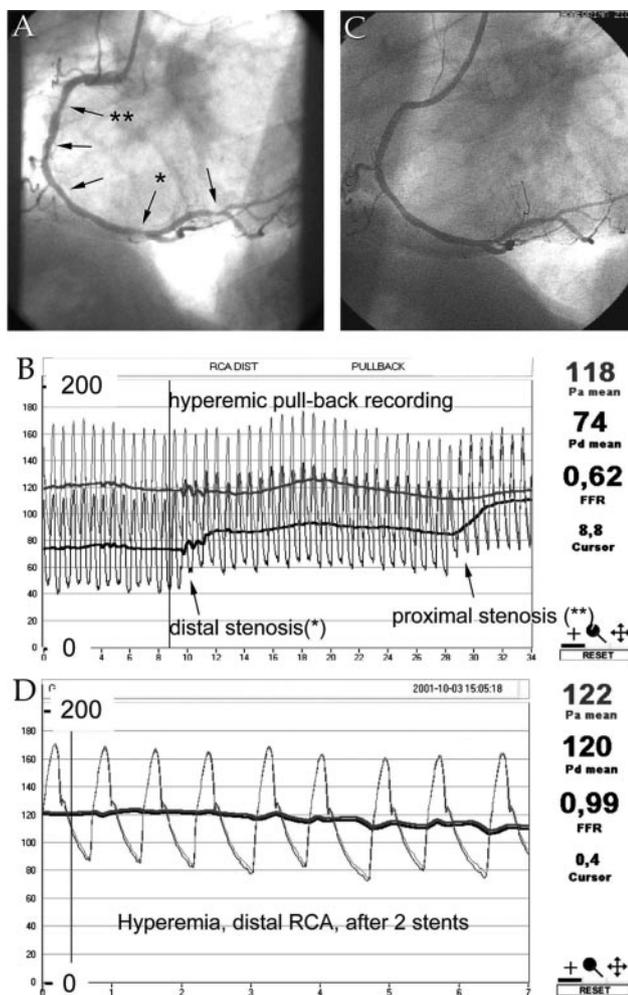


Figure 8. **A**, Right coronary artery of a 66-year-old man with recurrent angina who had stent implantation in the mid-right coronary artery 1 year previously and now has a positive nuclear scan in the inferior wall. The right coronary artery shows diffuse disease with ≥ 5 stenoses of intermediate severity (arrows). **B**, FFR of the distal myocardium obtained at the most distal point of the arrow was 0.62. The pressure pullback curve at hyperemia showed that 2 mild plaques (indicated by the asterisks) were hemodynamically significant. The other regions did not have hemodynamically significant stenoses. **C** and **D**, Two stents were placed with improved angiograms and normalization of FFR.

with appreciation for the limitations in the smaller-caliber catheters with regard to pressure damping.

At the end of the procedure, the wire is withdrawn, and the sensor is positioned again at the tip of guiding catheter to verify equal guiding catheter and guidewire pressures, thus ensuring that no pressure signal drift has occurred. A complete description of the application and pitfalls of coronary pressure measurements can be found elsewhere.³⁴

1.6.3. Pharmacological Agents for Coronary Hyperemia: Adenosine and Papaverine

The achievement of maximal hyperemia is critical to the physiological measurements as required by the underlying models. The measurement of the stenosis resistance index

appears to be somewhat less sensitive to this requirement.²³ The pharmacological agents most often used are intracoronary or intravenous adenosine and intracoronary papaverine (Table 2).

Adenosine is a naturally occurring nucleoside, formed within the myocytes from dephosphorylation of adenosine 5'-triphosphate (ATP) or cyclic adenosine monophosphate or from S-adenosyl homocysteine. It is rapidly removed from the blood by both a high-affinity red blood cell uptake mechanism and a direct deamination, with a half-life in human blood of <20 seconds. Adenosine interacts with purinergic subclass A2 receptors to increase cytosolic cyclic adenosine monophosphate as the second messenger for vasorelaxation. Because of its unique position in ATP metabolism, adenosine is thought to be an important endogenous regulator of coronary blood flow during both stress and ischemia.

The vasodilatory effects of adenosine are primarily on the microcirculation, with little effect on the epicardial conduit arteries. Both intracoronary and intravenous adenosine infusions produce maximal hyperemia in humans. To ensure maximal hyperemia, serial incremental intracoronary adenosine doses should be given until a plateau of response is achieved.^{21,35,36} However, in a small percentage of cases, coronary hyperemia has been suspected to be suboptimal with intracoronary adenosine, which suggests that a repeated higher intracoronary adenosine dose may be helpful. Adenosine is generally safe in the recommended intracoronary or intravenous dosages.

During intravenous adenosine administration, some patients may experience chest discomfort or dyspnea-like complaints that often resemble angina pectoris because of stimulation of free nerve fibers in the heart by the adenosine (which is also the intrinsic transmitter of angina pectoris), but these symptoms are not reflective of true ischemia. Such complaints should not be a reason to stop the infusion and should not be confused with bronchospasm, which has been infrequently reported in some patients with severe obstructive pulmonary disease. Asthma is a contraindication for intravenous adenosine administration.

During an intravenous adenosine infusion, the patient should avoid Valsalva maneuvers because straining interrupts continuous drug infusion and may produce fluctuations in both coronary blood flow and distal pressure. During exaggerated respiratory activity, FFR should always be taken as the lowest value of P_d/P_a during the respiratory cycle. When possible, intravenous adenosine should be infused through a large, preferably central, vein.

ATP, a precursor of adenosine, has the same effect in humans and, although less expensive than adenosine,^{37,38} is not available in the United States.

Intracoronary papaverine increases coronary blood flow velocity 4 to 6 times over resting values in patients with normal coronary arteries. Papaverine (10 to 15 mg) produces a response equal to that of an infusion of adenosine (140 $\mu\text{g}/\text{kg}$ per minute IV) or dipyridamole (0.56 to 0.84 mg/kg). The total duration of the hyperemic response to intracoronary papaverine is 60 to 90 seconds, or about 4 times longer than the response to intracoronary adenosine. Because papaverine

TABLE 2. Characteristics of Papaverine and Adenosine for Coronary Flow Studies

Drug	Dose	Plateau	T _{1/2}	Side Effect	Comments
Intracoronary papaverine	15 mg left coronary artery 10 mg right coronary artery	30–60 s	2 min	Transient QT prolongation T-wave abnormalities; very rarely, ventricular tachycardia or torsade de pointes	Do not use guiding catheter with side holes. Safety concerns make adenosine the preferred agent.
Intracoronary adenosine	30–60 μg left coronary artery; 20–30 μg right coronary artery	5–10 s	30–60 s	No side effects: sometimes atrioventricular block seconds after injection in right coronary artery	Stimulus is submaximum in some patients. Aortic pressure is interrupted during drug injection. Mean arterial pressure displayed is delayed relative to hyperemia in some cases. Maximum gradient is underestimated when calculated from mean signal, unless it is taken on beat-to-beat basis. No pullback curve is possible.
Intravenous adenosine (large vein)	140 μg/kg per minute	≤1–2 min	1–2 min	Decrease of blood pressure by 10% to 15% Burning or angina-like chest pain during infusion (harmless, not ischemia) Not to be used in patients with severe obstructive lung disease (bronchospasm)	If peripheral vein is used, avoid kinking. Avoid Valsalva maneuvers. Withdraw guiding catheter slightly out of ostium if any sign of obstruction of the ostium is present or if guiding catheter with side holes is used.

Modified with permission from Pijls et al.³⁴

can occasionally cause QT prolongation and ventricular tachycardia or fibrillation and has been reported to generate lactate and interact with ginkgo, adenosine is the preferred agent for induction of coronary hyperemia.

1.6.4. Safety of Intracoronary Sensor-Wire Measurements

Qian et al³⁹ examined the safety of intracoronary Doppler wire measurements in 906 patients. Complications with the procedure were rare: transient bradycardia (1.7%), coronary spasm (2%), and ventricular fibrillation (0.2%). The clinical practice of using sensor-wire measurements with pharmacologically induced hyperemia has been applied in thousands of patients in the past decade and is generally considered safe.

1.6.5. Limitations of Physiological Measurements

Several potential pitfalls and confounding conditions can complicate or produce erroneous coronary physiological measurements (Table 3). The 3 most common major technical problems are guiding catheter obstruction to flow, poor zeroing/calibration, and signal drift (pressure) or signal loss (Doppler). Additionally, for both pressure and flow measurements, suboptimal guide catheter engagement may result in inadequate delivery of bolus adenosine, producing submaximal hyperemia and thus limiting the accuracy of the FFR and CFR.

Guiding catheter obstruction of the coronary ostium will limit hyperemic blood flow and is generally indicated by arterial pressure wave deformity (eg, damping). Although guiding catheter side holes permit better flow and pressure transmission into the artery, some degree of obstruction may remain. This issue is avoided by not seating the guiding catheter and by using intravenous adenosine rather than

intracoronary bolus. A smaller caliber guide catheter may also obviate this problem. An artificial difference between aortic and distal coronary pressures may appear because of a damped guiding catheter pressure signal (often in association with small caliber catheters caused by contrast media in the catheter) and can be recognized by the shape of the pressure waveform. Flushing the guiding catheter with saline will restore a reliable aortic pressure.

Although uncommon, pressure signal drift may occur during a procedure. In such cases, true coronary wire pressure can be verified by pulling the sensor back to the tip of the

TABLE 3. Pitfalls, Artifacts, and Limitations of Physiology Measurements

Insufficient hyperemia

- Check infusion, pump system, and lines.
- Infuse through central vein.
- Avoid Valsalva maneuver during infusion.
- Guiding catheter may fail to seat for drug delivery or may obstruct flow.

Hemodynamic artifacts

- Avoid damped pressure waveforms. Flush guiding catheter.
- Large guiding catheter may obstruct coronary inflow.
- Guiding catheters with side holes may create ostial pseudostenosis.
- Identify pressure wire signal drift or erroneous zero.
- Poor velocity envelope requires tip manipulation to recapture signal.

Safety considerations

- Guiding catheter or wire may cause vessel trauma (not different from regular angioplasty wires).
- Thrombus and vasospasm are possible.

guiding catheter. In addition, the preservation of the dirotic notch of distal pressure is a marker of adequate distal pressure transmission and is always associated with FFR >0.80 .⁴⁰

For the coronary Doppler flow, technical artifacts of signal acquisition also must be recognized and then minimized to obtain reliable flow data.²²

In summary, the technique for sensor-wire pressure and flow measurements is identical to angioplasty guidewire placement. The induction of maximal hyperemia with intracoronary or intravenous adenosine is important for obtaining accurate data. When used by trained operators, sensor-wire measurement is generally considered safe and valuable for the important clinical data obtained.

2. Clinical Applications of Coronary Physiology

A summary of physiological thresholds for common clinical applications is provided in Table 4. The PCI Guideline Recommendations for use of physiologic measurements are summarized at the end of this section (Table 8). The important clinical applications not yet recommended by the Guidelines and under study are discussed in the following sections.

2.1. Ischemic Thresholds of Coronary Physiological Measurements

Testing modalities for myocardial ischemia have been compared with all of the physiological indices described above. Studies attempting to limit false-positive and false-negative results provide the best correlative data. Whether radionuclide perfusion abnormalities represent true ischemia is controversial, but this method is among the most commonly used for decision-making about lesion severity and indications for intervention and thus has served as a common standard against which the physiological measurements have been assessed.

An FFR <0.75 identified coronary stenoses in patients with inducible myocardial ischemia with high sensitivity (88%), specificity (100%), positive predictive value (100%), and overall accuracy (93%). A CFR of <2.0 corresponded to reversible myocardial perfusion imaging defects with high sensitivity (86% to 92%), specificity (89% to 100%), predictive accuracy (89% to 96%), and positive and negative predictive values (84% to 100% and 77% to 95%, respectively). For intermediate lesions, the sensitivity and specificity of HSR (>0.8 mm Hg \cdot cm⁻¹ \cdot s) were 79% and 90%, respectively, with a predictive accuracy of 87%.²³

TABLE 4. Criteria Associated With Clinical Applications

Indication	CFR	rCFR	HSR, mm Hg \cdot cm ⁻¹ \cdot s	FFR
Ischemia detection	<2.0	<0.8	>0.8	<0.75
Deferred angioplasty	>2.0	>0.80
End point of angioplasty	>2.0 – 2.5^*	>0.90
End point of stenting	>0.90

Modified from Kern²² with permission from the American Heart Association. Copyright 2000.

*With $<35\%$ diameter stenosis.

A summary of studies of the correlations between stress imaging and coronary physiological measurements is provided in Table 5.

2.2. Angiographic Subsets

2.2.1. The Intermediate Stenosis

The intermediate lesion, usually reported in the range of 40% to 70% narrowing, is the most frequently encountered stenosis in patients with CAD and has been associated with a large interobserver and intraobserver variability in the reported angiographic interpretation. When FFR is <0.75 or CFR is <2.0 , the stenosis is considered to be hemodynamically significant and a PCI can be supported. If FFR is >0.80 or CFR >2.5 , the clinical benefit of PCI can be questioned. The FFR range 0.75 to 0.80 can be considered a gray zone in which clinical judgment must complement quantitative assessments in forming the final treatment decision. Although most studies identify a distinct threshold, this value varies slightly depending on multiple study design and patient factors. For this reason, deferral of intervention can be confidently considered with FFR values >0.80 . A number of studies^{41–44} have shown that for a given intermediate coronary stenosis and FFR >0.75 , the combined risk for death or acute MI is only 1% per year with medical treatment alone. In the DEFER (Deferral versus Performance of PTCA in patients without Documented Ischemia)⁴¹ study, the risk of an adverse event increased if a vessel with an intermediate lesion and an FFR >0.75 was treated percutaneously with a bare-metal stent (Figure 9). In a similar fashion, the ILIAS (Intermediate Lesion: Intracoronary flow ASsessment versus 99mTc-MIBI SPECT) study,⁴⁵ using CFR and technetium ^{99m}Tc sestamibi single-photon emission computed tomography (MIBI SPECT), examined intermediate lesions in 191 patients with multivessel CAD. PCI was performed when both CFR and SPECT were indicative of myocardial ischemia. PCI was deferred when both CFR and SPECT were normal. When disparity existed between CFR and SPECT, PCI was deferred (deferred patients n=182). At the end of 1-year follow-up, 19 events had occurred. CFR was a more accurate predictor of events than was SPECT (relative risk: 3.9).^{26–30} The risk for death and acute MI exceeded the risk of medical treatment compared with PCI for nonhemodynamically significant lesions.

At this time, implantation of stents in nonsignificant plaques, even drug-eluting stents, is not supported by evidence-based studies. For an asymptomatic patient with mild stenosis and an FFR >0.75 (or CFR >2.5), one would consider noncardiac causes of the chest pain.

Despite excellent safety, some patients with deferred procedures may still have recurrent angina requiring continued medical therapy. Nonetheless, when a lesion is physiologically normal, the clinical impact of deferring intervention is associated with a satisfactory clinical outcome.^{41–44} Like other medical tests obtained at a single point in time, in-laboratory translesional physiology may not reflect the episodic, dynamic ischemia-producing conditions of daily life, particularly those related to vasomotor changes during exercise or emotional stress, conditions often highly respon-

TABLE 5. Physiological Measurements and Noninvasive Stress Test Results

Reference	Reference No.	n	Ischemic Test	BCV	Accuracy, %
FFR					
Pijls	16	60	X-ECG	0.74	97
De Bruyne	20	60	X-ECG/SPECT	0.66	87
Pijls	19	45	X-ECG/SPECT/pacing/DSE	0.75	93
Bartunek	79	37	DSE	0.67	90
Abe	80	46	SPECT	0.75	91
Chamuleau*	47	127	SPECT	0.74	77
Caymaz	81	40	SPECT	0.75	95
Fearon	82	10	SPECT	0.75	95
De Bruyne†	57	57	SPECT	0.78	85
Jimenez-Navarro	83	21	DSE	0.75	90
Meuwissen	23	151	SPECT	0.74	75
Usui†	84	167	SPECT	0.75	79
Yanagisawa	85	165	SPECT	0.75	76
CFR					
Joye	86	30	SPECT	2.0	94
Miller	87	33	SPECT	2.0	89
Deychak	88	17	SPECT	1.8	96
Tron	89	62	SPECT	2.0	84
Donohue	90	50	SPECT	2.0	88
Heller	91	55	SPECT	1.7	92
Schulman	92	35	X-ECG	2.0	86
Danzi	93	30	DSE	2.0	87
Verberne	94	37	SPECT	1.9	85
Piek	95	225	X-ECG	2.1	76
Abe	80	46	SPECT	2.0	92
Chamuleau*	47	127	SPECT	1.7	76
Duffy	96	28	DSE	2.0	88
El-Shafei	14	48	SPECT	1.9	77
Meuwissen	23	151	SPECT	1.7	75
Voudris	97	48	SPECT	1.7	75
rCFR					
Verberne	94	37	SPECT	0.65	85
Chamuleau*	47	127	SPECT	0.60	78
Duffy	96	28	DSE	0.75	81
El-Shafei	14	48	SPECT	0.75	75
Voudris	97	48	SPECT	0.64	92
HSR					
Meuwissen	23	151	SPECT	0.80	87

n indicates number of patients; BCV, best cutoff value (defined as the value with the highest sum of sensitivity and specificity); X-ECG, exercise ECG; DSE, dobutamine stress echocardiography.

*Multivessel disease.

†MI.

sive to medical therapy. Physiological thresholds, validated by stress imaging modalities and clinical outcomes, support decisions to defer intervention while continuing medical therapy for endothelial dysfunction, hypertension, hyperlipidemia, and episodic coronary vasoconstriction. Despite normal physiological measurements at one point in time, mild

hemodynamically nonsignificant lesions may progress and become significant, leading to new cardiac events. Continued surveillance and medical therapy for atherosclerosis are recommended in all such patients.

Table 6 summarizes results of studies deferring PCI of intermediate lesions on the basis of physiological endpoints.

TABLE 6. Outcomes After Deferral of Coronary Intervention in Intermediate Coronary Lesions

Reference	Reference No.	n	Defer Value	MACE	Follow-Up, mo
FFR					
Bech	98	100	0.75	8%	18
Bech	41	150	0.75	8%	24
Hernandez Garcia	99	43	0.75	12%	11
Bech†	42	24	0.75	21%	29
Rieber	43	47	0.75	13%	12
Chamuleau	48	92	0.75	9%	12
Rieber	44	24	0.75	8%	12
Leesar‡	100	34	0.75	9%	12
CFR					
Kern	101	88	2.0	7%	9
Ferrari	102	22	2.0	9%	15
Chamuleau*	45	143	2.0	6%	12

n indicates number of patients. MACE refers principally to rates of PCI; rates of death/MI were not significant.

*Multivessel disease.

†Left main stenosis.

‡Unstable angina pectoris.

2.2.2. Multivessel Disease

With the increasing use of coronary stents in an ever more complex patient population, a frequent application of physiological assessment involves lesion selection in patients with multivessel disease. Accurate lesion selection is important because noninvasive studies have demonstrated that MIBI SPECT fails to correctly indicate all ischemic areas in 90% of patients.⁴⁶ In 35% of such patients, no perfusion defect was present, possibly because of balanced ischemia. Often, one ischemic area was masked by another, more severely underperfused area. Furthermore, when several stenoses or diffuse disease is present within one coronary artery, an abnormal MIBI SPECT hypoperfusion image cannot discriminate among the different stenoses along the length of that vessel. For clinical practice, these observations highlight that regions that are not responsible for ischemia may contain significant-appearing narrowings, whereas other, more severe-appearing lesions may not be hemodynamically important. Coronary pressure measurements are particularly useful for localizing regions of suspected ischemia.

Several small nonrandomized studies have reported the use of coronary physiology in multivessel disease.^{45,47,48} Recently, in patients with multivessel disease referred for bypass surgery, patients who underwent selective PCI of hemodynamically significant stenoses had a prognosis similar to that of patients who had coronary artery bypass surgery of all angiographic diseased vessels.⁴⁶

2.2.3. Left Main and Ostial Lesions

Angiography cannot reliably characterize many ostial lesions, an especially critical problem when the left main coronary artery (LMCA) is involved. Furthermore, in patients with multivessel disease, uncertainty about the contribution of the LMCA to the clinical syndrome may confuse the issue of whether to perform PCI or surgery.

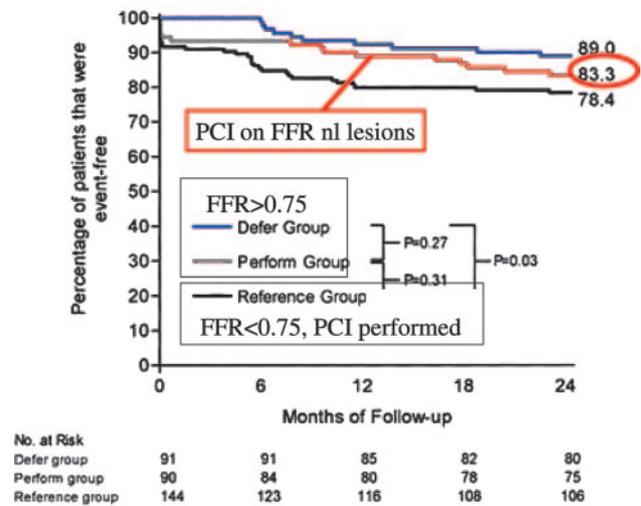


Figure 9. Kaplan-Meier survival curves for freedom from adverse cardiac events during 24 months of follow-up. Reproduced from Bech et al⁴² with permission from the American Heart Association. Copyright 1999.

FFR is used to assess LMCA narrowings, with specific technical considerations for guiding catheter seating and intravenous adenosine. Because of the potential for the guiding catheter to obstruct blood flow across an ostial narrowing, FFR measurements should be performed with the guiding catheter disengaged from the coronary ostium and with hyperemia induced by intravenous adenosine. Initially, the guiding catheter and wire pressures should be matched (equalized) before the guiding catheter is seated. Then, the guiding catheter is seated, and the pressure wire is advanced into the left anterior descending or left circumflex artery. The guiding catheter is then disengaged and the intravenous adenosine infusion initiated. After 1 to 2 minutes, FFR is calculated, and thereafter the wire can be pulled back slowly to identify the exact location of the pressure drop. In case of a distal left main narrowing, this procedure may be performed twice, once with the pressure wire in the left anterior descending artery and again with the wire in the circumflex artery. Figure 10 illustrates FFR in a patient with an ostial LMCA narrowing.

The use of FFR in an LMCA stenosis has been examined in 54 patients.⁴⁹ In those 30 patients with an FFR < 0.75, surgery was performed, and in those 24 patients with an FFR ≥ 0.75, medical therapy was chosen. After a follow-up of 3 years, no differences in event-free survival rate or functional class were seen between the groups. None of the patients in the medical group experienced MI or died.

2.2.4. Serial Stenosis and Diffuse Disease

When ≥ 2 discrete stenoses are present in the same vessel, the hyperemic flow and pressure gradient through the first one will be attenuated by the presence of the second one and vice versa. One stenosis will mask the true effect of its serial counterpart by limiting the maximum hyperemia that can be achieved. This fluid, dynamic interaction between 2 serial stenoses depends on the sequence, severity, and distance between the lesions, as well as on the flow rate. When the distance between 2 lesions is > 6 times the vessel diameter,

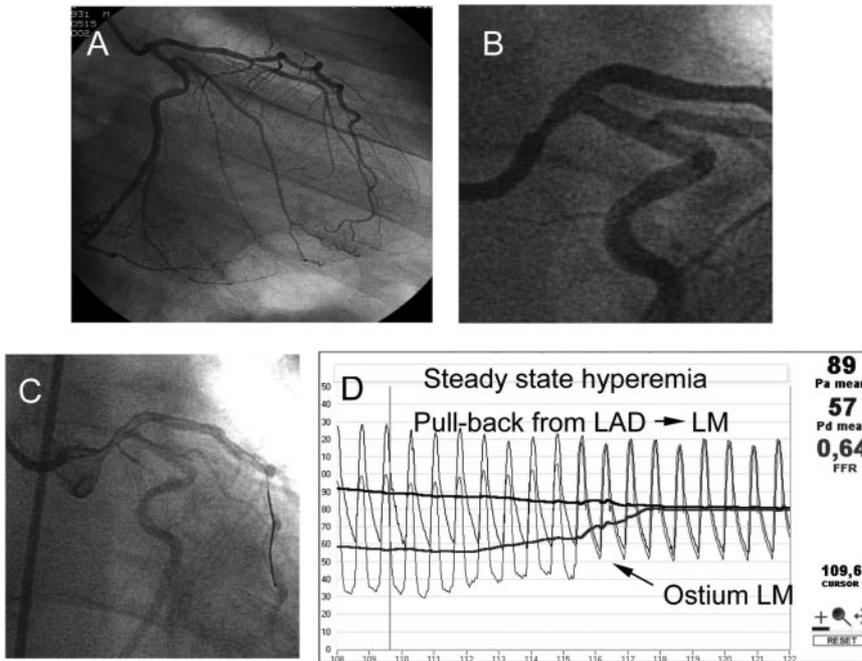


Figure 10. A, Seventy-one-year-old patient was referred for PCI of the diagonal artery. The pressure wire was used as a routine angioplasty guidewire. When the pressure wire crossed the left main, a pressure gradient was observed, which gave rise to the suspicion of a left main narrowing. B, C, and D, Additional angiograms demonstrated this finding and prompted the pressure pullback recording to assess the ostial left main lesion. In D, there is a pressure gradient in the body of the left main artery, and a further sudden pressure drop is observed when the sensor crosses the aortal ostium. Note that for the interrogation of an ostial stenosis, intravenous adenosine is used and the guiding catheter is withdrawn from the ostium during the measurement. Figure courtesy of N. Pijls.

the stenoses generally behave independently, and the overall pressure gradient is the sum of the individual pressure losses at any given flow rate.

The calculation of the exact FFR of each lesion separately is possible but remains academic, as the coronary wedge pressure (during coronary balloon occlusion) is needed to perform these calculations.^{50,51} In clinical practice, the use of the pressure pullback recording is particularly well suited for identifying the several regions of a vessel with large pressure gradients that may benefit from treatment. The stenosis with the largest gradient can be treated first, and the FFR can be remeasured for the remaining stenoses to determine the need for further treatment.

In arteries with diffuse atherosclerotic disease, unlike in normal vessels, coronary pressure noticeably declines along the length of the artery, indicating an increase in resistance caused by diffuse diameter changes. De Bruyne et al⁵² demonstrated that in 37 strictly normal coronary arteries, FFR was 0.97 ± 0.02 , whereas in 106 nonstenotic arteries in patients with atherosclerosis elsewhere in the coronary circulation, FFR was 0.89 ± 0.08 , with frank ischemic values < 0.75 in 8% of them (Figure 11).

2.2.5. Diffuse Disease and Long Lesions

Considerations similar to those for patients with several discrete stenoses in 1 coronary artery can be applied to patients with diffuse CAD or long lesions. The pressure pullback recording at maximal hyperemia will provide the information that is needed to decide if and where stent implantation may be useful. The location of a focal pressure drop superimposed on the diffuse disease can be identified as an appropriate location for treatment. In some cases, the gradual decline of pressure along the vessel occurs over a very long segment, such that interventional treatment is not possible. Medical treatment (or bypass surgery) can then be elected.

2.3. Prognostic Value of Physiological Parameters

2.3.1. Percutaneous Coronary Interventions

Because of the limitations of the angiogram for precisely identifying luminal abnormalities, the angiographic criteria before and after balloon angioplasty are poor predictors of immediate and long-term prognosis. However, when coupled with a satisfactory angiographic result, coronary physiological indices were predictive of the short-term and long-term clinical outcomes after balloon angioplasty.^{42,53,54,54a,54b} For example, in patients with single-vessel disease, a CFR ≥ 2.5 in combination with diameter stenosis $\leq 35\%$ after balloon angioplasty alone was associated with a favorable long-term outcome (major adverse cardiac event [MACE] rates $< 20\%$).⁵³ When compared with coronary stent implantation, physiologically guided balloon angioplasty (with $< 35\%$ diameter stenosis) had similar event-free survival rates at 1 year: 86.6% and 85.6% for primary stent implantation and optimal balloon angioplasty, respectively.^{54c} As expected,

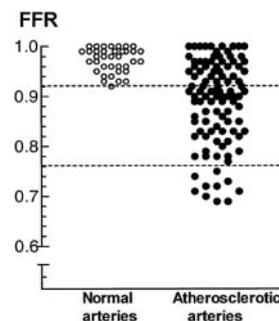


Figure 11. Graphs of individual values of FFR in normal arteries and in atherosclerotic coronary arteries without focal stenosis on arteriogram. The upper dotted line indicates the lowest value of FFR in normal coronary arteries. The lower dotted line indicates the 0.75 threshold level. Reproduced from De Bruyne et al⁵² with permission from the American Heart Association. Copyright 2001.

coronary stent implantation after a suboptimal balloon angioplasty was associated with a significantly improved outcome, decreasing the MACE rate from 26.7% to 10.7% (odds ratio [OR]: 3.0, $P=0.005$).^{54d} Interestingly, coronary stent implantation after an optimal balloon angioplasty also improved outcome, decreasing the MACE rate from 15.9% to 6.5% (OR: 2.7, $P=0.066$). Although use of physiological information for guidance of balloon angioplasty has been clinically valuable, this approach has yielded to near-universal stent implantation as the treatment of choice.^{54c,55}

For the practice of stent implantation, physiological measurements, specifically FFR, do not address adequacy of implantation but do provide prognostic information about the patient's long-term results. In a multicenter trial, Pijls et al⁵⁶ examined 750 patients with poststenting FFR data and found that the FFR immediately after stent implantation was an independent variable related to all MACE (Figure 12). The lowest MACE rates occurred in patients with the highest FFR values. FFR normalized (>0.95) in 36% of patients, a finding associated with an event rate of 5%. For patients with FFRs between 0.90 and 0.95 (32% of patients), the event rate was 6%. In the 32% of patients with FFRs <0.90 , event rates were 20%. In the 6% of patients with FFRs <0.80 , the event rate was 30%. The lower the FFR, the more likely the patient would have late events (>6 months after the procedure), which suggests that both procedurally related problems (eg, dissections) and untreated diffuse disease were associated with worse long-term outcomes. The use of FFR after stent implantation, although not routine, can provide insight into the patient's prognosis.

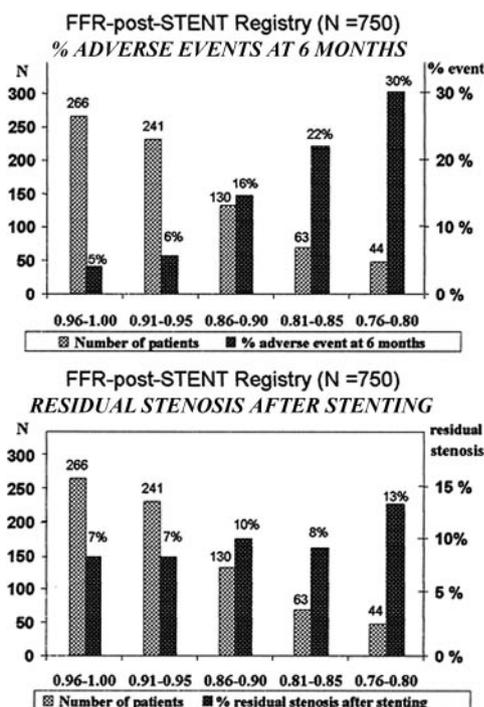


Figure 12. **Top**, Distribution of the study population over the 5 FFR categories. A strong inverse correlation was present between FFR after stenting and event rate at 6-month follow-up. **Bottom**, Distribution of percentage residual stenosis in the 5 FFR categories. Reproduced from Pijls et al⁵⁶ with permission from the American Heart Association. Copyright 2002.

2.3.2. Acute Coronary Syndromes

2.3.2.1. Acute Myocardial Infarction

Because acute coronary syndromes involve dynamic changes in both the active lesion and the supplied myocardial bed, the clinical validity of applying physiological measurements in such a setting remains uncertain.

However, the use of FFR in patients with a previous MI has been studied. De Bruyne et al⁵⁷ compared SPECT imaging and FFR in 57 patients >6 days after acute MI. FFR was measured before and after the PCI. The sensitivity and specificity of FFR >0.75 for detecting normal SPECT imaging were 82% and 87%, respectively (Figure 13), with a concordance between FFR and SPECT imaging of 85% ($P<0.001$). When only true positive and true negative SPECT imaging studies were used, the corresponding values increased to 87%, 100%, and 94%, respectively. It was also of interest that patients with higher FFRs had higher left ventricular ejection fractions despite similar stenosis diameters. FFR could distinguish patients with positive SPECT imaging ≥ 6 days after acute MI who could benefit from revascularization.

CFR has been used to study the microvascular responses to an acutely infarcted myocardial bed. Because microvascular injury is also a dynamic process that partially resolves over time, highly variable short-term results might be anticipated. In one study, immediate (<1 hour after reperfusion) postinfarction CFR >1.3 was associated with preservation of the microcirculation.⁵⁸ However, others found no relationship between CFR and myocardial viability and concluded that CFR did not differentiate patients with extensive infarctions from those with small ones.⁵⁹

Unlike CFR, phasic coronary flow velocity patterns and trends in APV are predictive of myocardial viability. Kawamoto et al⁶⁰ measured systolic APV and diastolic flow velocity deceleration time in 23 patients with acute anterior MI and found improved left ventricular wall motion recovery, which was sustained on subsequent follow-up when the systolic APV was >6.5 cm/s or the diastolic flow velocity deceleration time >600 ms. In addition, early systolic flow reversal and a continuous declining 24-hour trend of APV were associated with worse regional wall motion abnormalities and lower ejection fractions at follow-up after acute MI.^{61,62}

2.3.2.2. Unstable Angina and Non-ST-Segment-Elevation Myocardial Infarction

After stabilization of patients with unstable angina or non-ST-segment-elevation MI, traditional management involves instituting maximal medical therapy and performing risk stratification by stress testing before coronary angiography and intervention based on the results. As an alternative approach, Leesar et al⁶³ used FFR to risk-stratify acute coronary syndrome patients in the laboratory at the time of catheterization after medical stabilization. The 70 patients were randomly assigned to either early in-hospital invasive evaluation ($n=35$) with FFR or noninvasive evaluation by perfusion scintigraphy ($n=35$). The decision to revascularize was based on abnormal FFR or MIBI SPECT scans. The effectiveness of the early invasive FFR-guided approach was

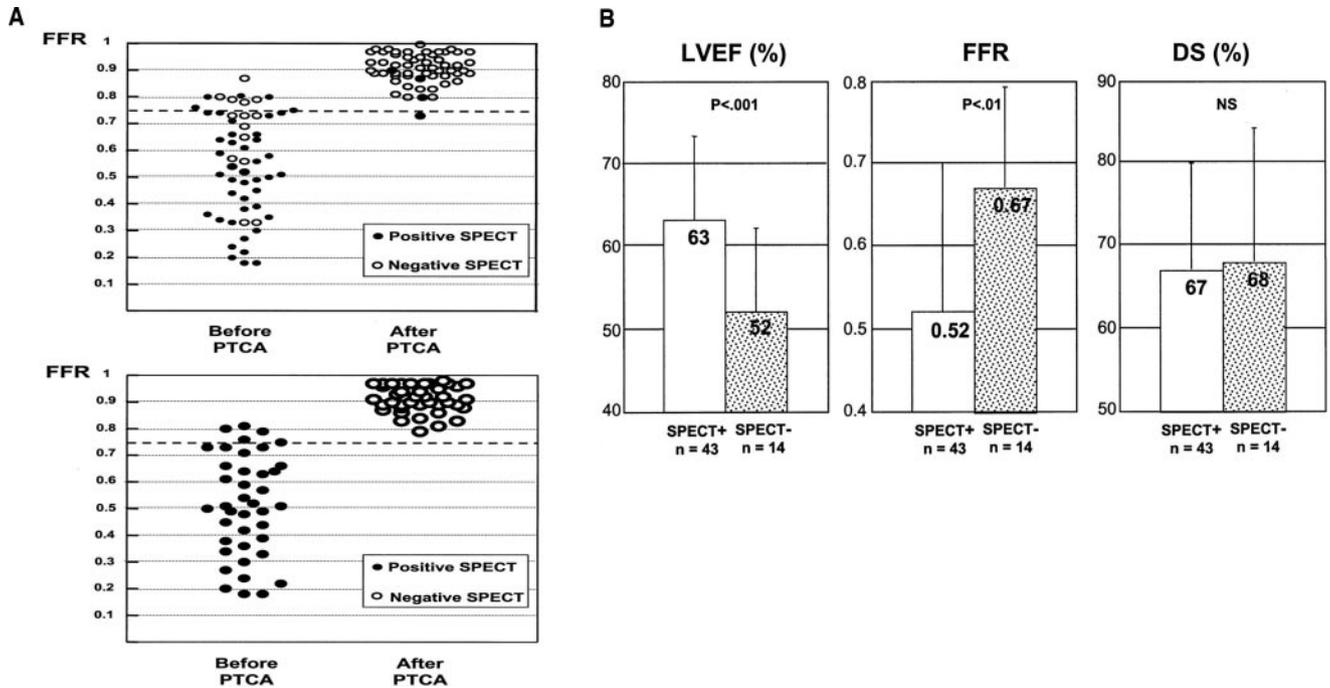


Figure 13. A, Values of FFR before and after PCI according to results of MIBI SPECT myocardial perfusion imaging in patient population as a whole (top) and in patients with truly positive and truly negative SPECT imaging (bottom). B, Values of left ventricular ejection fraction (LVEF), FFR, and diameter stenosis (DS) according to results of SPECT imaging. At a similar degree of stenosis, patients with positive SPECT imaging have better preserved LVEF and lower FFR than patients with negative SPECT imaging, which suggests a larger amount of viable tissue. Both panels reproduced from De Bruyne et al⁵⁷ with permission from the American Heart Association. Copyright 2001.

equal to standard care with noninvasive risk stratification. MACE rates at 1-year follow-up were similar between the groups. The FFR-guided approach was also associated with a shorter hospital stay and a significant decrease in the total cost of hospitalization. In patients who cannot be medically stabilized, current guidelines recommend urgent angiography with appropriate revascularization as indicated without FFR. Nonetheless, FFR could be useful in assessing other intermediately severe nonculprit lesions for consideration of complete revascularization.

TABLE 7. Pathologies Impairing the Microcirculation

Abnormal vascular reactivity
Abnormal myocardial metabolism
Abnormal sensitivity toward vasoactive substances
Coronary vasospasm
Myocardial infarction
Hypertrophy
Vasculitis syndromes
Hypertension
Diabetes
Recurrent ischemia

Adapted from Baumgart et al.⁸

2.4. Assessment of Endothelial Function in Patients With Chest Pain and Nonobstructive Coronary Artery Disease

The treatment and diagnosis of chest pain in patients with nonobstructive CAD (NOCAD) remain a challenge in contemporary cardiology, with ≥20% of patients referred for cardiac catheterization having no significant angiographic CAD. Currently, few existing algorithms provide NOCAD

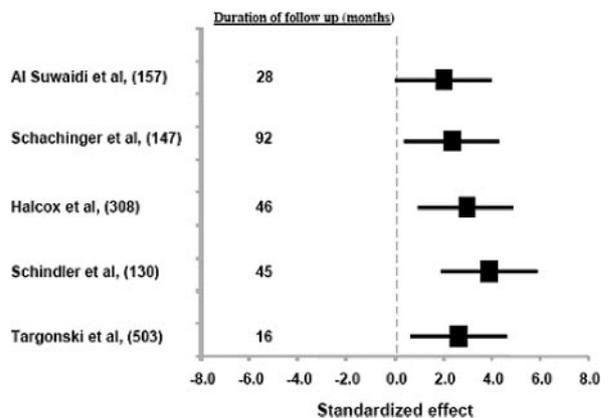


Figure 14. A multivariate analysis of the hazard ratio of current studies reporting the association between coronary endothelial function and cardiovascular events. The figure depicts individual studies and the number of patients included in the study. Reproduced from Lerman and Zeiher⁶⁷ with permission from the American Heart Association. Copyright 2005.

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patients with appropriate diagnosis and treatment while limiting unnecessary testing and expense. Patients with chest pain and NOCAD generally can be categorized into one of 3 main groups: (1) patients with chest pain and a flow-limiting coronary lesion that is not apparently severe by angiography but may be detected during physiological evaluation; (2) patients with epicardial or microvascular reactivity abnormalities (eg, Prinzmetal's angina with coronary vasospasm) that are associated with myocardial ischemia; and (3) patients with noncardiac cause of chest pain, a diagnosis of exclusion from the other 2 groups.

When the patient with NOCAD is assessed, several pathological entities that are known to affect the coronary microcirculation should be considered (Table 7). It has been proposed that patients with refractory, recurrent, or disabling chest pain and NOCAD may have endothelial-dependent and endothelial-independent abnormalities of the microcirculation that can be tested by invasive and noninvasive methods and have been reviewed elsewhere.⁶⁴ To date, these evaluations remain research tools for gauging responses to therapies directed at improving endothelial function. In the catheterization laboratory, endothelial function is assessed by both flow and vascular reactivity (vasodilation and constriction).⁶⁵ A Doppler-tipped angioplasty guidewire with simultaneous angiography can be used to measure the response to graded intracoronary infusions of acetylcholine. In coronary arteries with normal endothelium, intracoronary acetylcholine dilates epicardial and microvascular circulation, increasing coronary blood flow. However, when the endothelium is damaged or disrupted, intracoronary acetylcholine induces vasoconstriction and a decrease in coronary blood flow. Moreover, several studies have demonstrated that endothelial dysfunction is associated with inducible ischemia. Invasive assessment of coronary endothelial function with acetylcholine infusions should only be performed in specialized laboratories by highly experienced personnel. Most importantly from a clinical point of view, endothelial dysfunction is an early stage of atherosclerosis⁶⁶ and is associated with poor prognosis^{67,78} (Figure 14).

2.5. Collateral Circulation

The study of collateral function and physiology has been greatly enhanced by direct measurements of coronary pressure and flow.^{68–72} Measurement of collateral flow responses can be obtained from either ipsilateral or contralateral coronary arterial flow velocity. These responses can characterize collateral stimulation, recruitment, and behavior during maneuvers to examine mechanisms, function, and clinical significance of various patterns of collateral flow in patients before and during coronary interventions.

For example, Seiler et al⁷⁰ examined simultaneous coronary pressure and flow data in 51 patients with coronary artery stenosis treated by percutaneous transluminal coronary angioplasty (PTCA). The calculated collateral flow indices (CFI) using velocity (CFIv) or pressure (CFIp) demonstrated that in 11 patients without ECG signs of ischemia during coronary occlusion, relative CFI amounted to 46%, whereas in patients with ischemic ST changes (n=40), CFI values were only 18%. With a CFI of 30%, patients with sufficient and insufficient collaterals

TABLE 8. Applications of Physiologic Measurements in the Catheterization Laboratory

A. PCI Guideline recommended uses*	
1.	Assessment of the effects of intermediate coronary stenoses (30% to 70% luminal narrowing) in patients with anginal symptoms. Coronary pressure or Doppler velocimetry may also be useful as an alternative to performing noninvasive functional testing (e.g., when the functional study is absent or ambiguous) to determine whether an intervention is warranted. (Class IIa, Level of Evidence: B)
2.	Assessment of the success of PCI in restoring flow reserve and to predict the risk of restenosis (Class IIb, Level of Evidence: C)
3.	Evaluation of patients with anginal symptoms without an apparent angiographic culprit lesion (Class IIb, Level of Evidence: C)
4.	Routine assessment of the severity of angiographic disease in patients with a positive, unequivocal noninvasive functional study is not recommended. (Class III, Level of Evidence: C)
B. Applications of coronary pressure under study†	
1.	Determination of 1 or more culprit stenoses (either serially or in separate vessels) in patients with multivessel disease
2.	Evaluation of ostial or distal left main and ostial right lesions, especially when these regions cannot be well visualized by angiography
3.	Guidance for treatment of serial stenoses in a coronary artery
4.	Determination of significance of focal treatable region in vessel with diffuse coronary artery disease
5.	Determination of prognosis after stent deployment
6.	Assessment of stenosis in patients with previous (nonacute, lasting >6 days) myocardial infarction
7.	Assessment of lesions in patients with treated unstable angina pectoris
8.	Assessment of the collateral circulation
C. Applications of coronary Doppler flow velocity under study†	
1.	Assessment of microcirculation
2.	Endothelial function testing
3.	Assessment of myocardial viability in acute myocardial infarction
D. Applications of combined coronary pressure and Doppler flow velocity under study†	
1.	Assessment of intermediate stenosis
2.	Assessment of the microcirculation
3.	Identification of lesion compliance (change of pressure drop–velocity relationship)

* Adapted from Smith SC Jr et al.¹⁰³

†Not yet recommended by PCI Guidelines.

could be differentiated with 100% sensitivity and 93% specificity by intracoronary flow velocity and with 75% sensitivity and 92% specificity by intracoronary pressure measurements. There was good agreement between the 2 techniques. In coronary arteries without a stenosis, Wustman et al⁷² measured CFI values averaging 18% (range 4% to 36%) and concluded that functional collateral vessels are also present in humans with angiographically normal coronary arteries. Further investigation of collateral flow and function in patients with acute MI has demonstrated persistent microvascular dysfunction despite a satisfactory collateral supply in 55% of patients after recanalization of chronically totally occluded coronary arteries.^{73–75}

In summary, intracoronary flow velocity and/or pressure measurements during routine coronary occlusion represent a quantitative method for assessing the collateral coronary artery circulation in humans.

2.6. Economics of Physiologically Guided Interventions

The use of physiological lesion assessment is associated with favorable medical economics for the strategy of risk assessment in the catheterization laboratory.^{63,76,77} In one study,⁷⁷ a decision model was generated comparing the long-term costs and benefits of 3 strategies: (1) deferring the decision for PCI to obtain a nuclear stress imaging study (the NUC strategy), (2) measuring FFR at the time of angiography to help guide the decision for PCI (the FFR strategy), and (3) stent implantation for all intermediate lesions without measuring FFR (the STENT strategy). The investigators found that the FFR strategy saved \$1795 per patient as compared with the NUC strategy and \$3830 per patient as compared with the STENT strategy. Quality-adjusted life expectancy was similar among the 3 strategies. Comparable results were obtained for patients admitted with unstable angina/non-ST-segment-elevation MI who, after stabilization, were randomized either to angiography with measurement of FFR and interventional or medical treatment as indicated by FFR, or to nuclear stress imaging with angiography if results were abnormal. The investigators found that the FFR strategy significantly reduced both the duration and cost of hospitalization, with identical cardiac event rates in the 2 groups at 1-year follow-up.⁶³

Although the cost of the physiological information translates into an operational expense for the catheterization

laboratory, the in-laboratory physiology can provide a significant overall savings to the healthcare delivery system and clinical benefit to the patient for objective and timely decision-making.

2.7. Future Applications of Coronary Physiology

The future use of physiological measurements will likely focus on combined distal pressure and velocity data acquired for the direct assessment of both conduit and microvascular resistances, exploring the role of pressure-dependency of the microcirculation and its adaptations.¹⁰⁴ Using both pressure and flow, researchers can establish the role that collateral dependant blood flow can play in the evaluation of the subtle effects of vascular growth factors in patients with end-stage CAD. The role of flow velocity and pressure, the 2 most basic physiological signals, will continue to be explored to reveal their contributions to important clinical syndromes involving vulnerable plaques, microvascular disease, and endothelial dysfunction. Understanding the coronary circulation in patients with atherosclerosis and ischemic and nonischemic cardiomyopathies will assist clinicians in enhancing long-term outcomes.

2.8. Recommendations and Summary

The present scientific statement summarizes the current knowledge and understanding of the use of coronary physiology in the cardiac catheterization laboratory. Best clinical practice suggests that the addition of coronary physiological measurements complements traditional angiographic information and is essential for accurate clinical decision-making. The current applications of coronary physiology and the ACC/AHA/SCAI guidelines for use are shown in Table 8.

Disclosures

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