Coronary Physiology Revisited
Practical Insights From the Cardiac Catheterization Laboratory

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Abstract—Various coronary physiological measurements can be made in the cardiac catheterization laboratory using sensor-tipped guidewires; they include the measurement of poststenotic absolute coronary flow reserve, the relative coronary flow reserve, and the pressure-derived fractional flow reserve of the myocardium. Ambiguity regarding abnormal microcirculation has been reduced or eliminated with measurements of relative coronary flow reserve and fractional flow reserve. The role of microvascular flow impairment can be separately determined with coronary flow velocity reserve measurements. In addition to lesion assessment before and after intervention, emerging applications of coronary physiology include the determination of physiological responses to new pharmacological agents, such as glycoprotein IIb/IIIa blockers, in patients with acute myocardial infarction. Measurements of coronary physiology in the catheterization laboratory provide objective data that complement angiography for clinical decision-making. (Circulation. 2000;101:1344-1351.)

Key Words: physiology ■ catheterization ■ heart ■ coronary blood flow

An appreciation of coronary physiology is an integral part of clinical decision-making for cardiologists treating patients with coronary artery disease. The pioneering research efforts of Dr Lance Gould, who explored the relationship between the anatomic severity of a stenosis and its flow resistance,1,2 have been transferred to clinical practice.3,4 Within the last few years, technology has advanced such that, in patients undergoing coronary angiography, the influence of a coronary stenosis on the distal arterial pressure-flow relationship can now be easily and safely determined with sensor-tipped angioplasty guidewires that measure the poststenotic absolute coronary flow velocity reserve (CVR), the relative CVR (rCVR), and the pressure-derived fractional flow reserve of the myocardium (FFR). However, theoretical concerns regarding the translation of basic physiology from experimental animal models has given some clinicians pause in applying the available techniques for patient care.5,6 This review will discuss the current concepts, methods, and clinical outcomes of these techniques and provide practical insights for patient management.

Before applying these physiological measurements, a brief review of several fundamental principles is in order. Recall that when an epicardial stenosis produces an increased resistance to flow, the distant microvascular resistance vessels dilate to maintain regional basal flow at a level appropriate for concurrent myocardial oxygen demand. The increased dilation reduces the potential maximal flow reserve available. Because the distal microcirculation has compensated for the potential reduction in regional flow, the resting poststenotic epicardial conduit blood flow, depending on the severity of the stenosis, may be somewhat diminished; however, this epicardial flow usually satisfactorily maintains myocardial function and metabolism. Under these conditions, any increase in myocardial oxygen demand or other hyperemic stimuli now results in a smaller increment in poststenotic flow relative to the coronary flow increase that would be elicited in the same (or another) myocardial region without a stenosis (ie, diminished CVR and rCVR).

A significant stenosis also produces distal artery pressure loss (ie, a translesional pressure gradient) because of a loss of kinetic (flow) energy to viscous friction, turbulence, and flow separation. The reduction of the distal distending arterial pressure results in a pressure differential or gradient between the driving aortic pressure and the poststenotic coronary pressure. The degree of pressure loss is directly related to the flow rate as described by the curvilinear pressure-flow relationship of the particular lesion resistance (Figure 1).1,2

Beyond Coronary Pressure Gradients
For clinical coronary artery lesion assessment, resting pressure gradients measured during the early experience with coronary angioplasty were unsatisfactory because of (1) inadequate devices (ie, balloon catheters), (2) data being used in an incompletely understood manner (ie, only at rest and not during maximal blood flow),7,8 and (3) a weak correlation to ischemic testing and clinical outcomes.7,8,10 Pijls et al11-13 demonstrated that the hyperemic absolute distal coronary pressure, but not the resting pressure gradient, is related to the ischemic potential of a stenosis. Moreover, they derived a new concept of a pressure-derived estimate of coronary blood...
Lesion-Specific Physiological Measurements

A normal absolute CVR, the ratio of hyperemic to basal mean flow (velocity), indicates a normal 2-component system, with a patent epicardial conduit supplying a normal myocardial bed. In the absence of epicardial conduit obstruction, the CVR may be abnormal when the microvascular circulation is compromised by left ventricular hypertrophy, chronic or acute ischemia, diabetes mellitus, or other diseased rheological conditions. An abnormal CVR cannot differentiate which of the 2 components is responsible for flow impairment. In this setting, an additional measurement of CVR in an adjacent, normal vessel as a reference value (CVRreference) can confirm the significance of the coronary lesion and compute the rCVR (rCVR=CVRsignal/CVRreference). Assuming that systemic hemodynamic and microcirculatory abnormalities affect the different regions of the myocardium to the same degree, the rCVR should nullify the influence of the variables and provide an enhanced discrimination of flow impairment due to a stenosis. The CVR in angiographically normal vessels from adult patients with coronary artery disease risk factors is $2.7 \pm 0.6$ and, in most studies, it seems to have little regional variation ($<15\%$) in both cardiac transplant patients and patients with chest pain syndromes. The normal value of the rCVR is $>0.8$. Unlike absolute CVR, both rCVR and the FFR are considered more lesion-specific physiological measurements. Baumgart et al compared FFR to both absolute CVR and rCVR in 24 vessels that had stenoses ranging from 40% to 95% (average, $74 \pm 15\%$). Target and reference vessel CVR were $2.1 \pm 0.5$ and $2.6 \pm 0.7$, respectively; the rCVR was $0.82 \pm 0.13$ (range, $0.53$ to $1.0$), and the FFR was $0.81 \pm 0.15$ (range, $0.49$ to $0.99$). FFR and rCVR, but not CVR, showed a strong curvilinear relationship to percent area stenosis ($r=0.89$ and $r=0.79$; $P<0.0001$), with a close linear relationship between FFR and rCVR ($r=0.95$; $P<0.0001$) that supported the lesion-specific nature of these 2 measurements.

Limitations of Coronary Flow Reserve

Microcirculatory impairment is the major limitation in assessing a stenosis using absolute CVR; this issue is addressed by rCVR or FFR. In patients in whom the target vessel supplies an area of myocardial infarction, neither CVR nor rCVR can confidently identify flow impairment due solely to a stenosis because the assumption that the microvascular circulation is uniform no longer applies. In patients with 3-vessel coronary disease, no suitable reference vessel may exist, which compromises the use of rCVR. A lesion in these situations may be best assessed by FFR.

Advantages and Limitations of FFR

Although FFR seems to be independent of microvascular responses or changing hemodynamics, which is a significant advantage over CVR, the magnitude of the flow increase during maximal vasodilatation still influences FFR. A limited increase in flow across a stenosis could minimize the true FFR value. However, because the FFR reflects the extent to which the epicardial resistance reduces myocardial perfusion, it can be argued that in the setting of microvascular disease, a normal FFR indicates that the conduit resistance (ie, the stenosis in question) is not a major contributing factor to perfusion impairment and that the enlargement of such a conduit obstruction would not restore normal perfusion. In such diagnostic dilemmas, FFR and Doppler velocimetry are complementary; they describe the physiology of both the epicardial stenosis and the microvascular disease (if present) as potential contributors to inducible myocardial ischemia.

It should be recognized that the normal threshold of FFR ($<0.75$) for ischemia was derived from a selected, stable patient population with single-vessel coronary disease and normal left ventricular function. The data are limited for patients with microvascular disease, acute or remote myocardial...
dial infarction, and unstable angina. Caution should be applied in extending the current physiological criteria to such patients. The advantages and limitations of the 3 physiological measurements for patients with coronary artery disease are summarized in Table 1.

**Concerns Regarding the Practical Application of Physiological Measurements in Patients**

Although the discussed techniques are particularly well suited for both diagnostic and interventional therapy, several investigators have expressed concerns over the potential technical and biological limitations of in-laboratory physiological measurements.5,6,20 Technical or operator-related artifacts, such as variability in Doppler velocity envelopes, pressure signal drift, or malalignment, should be avoided as previously described.11,18 Similarly, the cross-sectional area of a sensor guidewire (0.16 mm²) is negligible relative to all but the most critical stenoses.21 Although a potentially false-negative physiological evaluation could occur in the setting of transient vasoconstriction of a stenotic lesion or the microcirculation, episodic or dynamic ischemia that is not detectable by measurements at the time of investigation can be attenuated or eliminated by concomitant antianginal therapies. Dynamic stenotic resistance with inducible variations may occur both at rest and during maximal hyperemia22 in response to a variety of intrinsic and extrinsic stimuli.22–24 A false-negative CVR could also be obtained if the ischemic myocardium was confined to only a small region, such as the subendocardium or papillary muscle. Like any diagnostic modality, the results must be considered in the dynamic course of the clinical presentation.

The pharmacological hyperemic agents used to identify impaired flow are thought to be equivalent to exercise stress hyperemia. These agents may be unsatisfactory in rare individuals with increased susceptibility to myocardial ischemia that is not reflected solely in the flow-limiting nature of the stenosis. Figure 2 illustrates the physiological assessment of difficult intermediate coronary stenoses.

**Clinical Validation**

Although some of the theoretical concerns regarding the limitations of direct physiological measurements cannot be completely satisfied, the clinical validation and outcomes strongly support the practical value of in-laboratory measurements. Many of the above-noted concerns and potential complexities of using coronary physiological measurements for clinical decisions arise from the failure of suitable experimental animal and clinical studies to define unambiguous criteria of myocardial ischemia. In patients, the valida-

| **TABLE 1**. Comparison of Absolute and Relative CVR and FFR |
|--------------------|----------------|---------------|-----------------|-----------------|
| Hemodynamic Independence | Independent of Microcirculation Abnormalities | Unequivocal Normal Values | Use in Multivessel CAD | Assessment of Collateral Flow During Angioplasty |
| CVR | – | – | Range > 2.0 | + | + |
| rCVR | + | + | 1.0 | – | – |
| FFR | + | + | 1.0 | + | + |

CAD indicates coronary artery disease, and +, applicable to conditions.

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**Figure 2.** Measurements of absolute CVR and rCVR were used to assess long 60% stenosis in mid-left anterior descending (LAD) coronary artery in a patient (J.M.; top right). Left anterior descending CVR target is 2.9. CVR reference in circumflex (CFX) artery is 3.0. rCVR is 0.9. FFR, also measured but not shown, was 0.96. Angioplasty was deferred.
tion of coronary physiological criteria has been established by population correlations with clinically accepted norms of several types of ischemic stress provocation.\textsuperscript{13,25–33}

For poststenotic coronary flow velocity reserve, several single-center studies\textsuperscript{26–28} and one multicenter trial\textsuperscript{29} have reported strong correlations with myocardial stress perfusion; one study using 2D echocardiographic stress imaging\textsuperscript{32} reported strong correlations with myocardial stress perfusion; these studies had high sensitivity (86% to 92%), specificity (89% to 100%), predictive accuracy (89% to 96%), and positive and negative predictive values (94% to 100% and 77% to 95%, respectively; Table 2).

Similarly, for FFR, Pijs et al\textsuperscript{13} and De Bruyne et al\textsuperscript{14} also report high correlations for identifying reversible ischemia with an FFR<0.75. In the study by Pijs et al,\textsuperscript{13} sensitivity was 88%, specificity was 100%, and positive and negative predictive values were 100% and 88%, respectively; the study had a predictive accuracy of 93%.

The clinical outcomes of deferring coronary intervention for intermediate stenoses with normal physiology that are now reported in \( \geq 5 \) studies\textsuperscript{13,34–38} are remarkably consistent, with clinical event rates of \(<10\%\) over a 2-year follow-up period. In these studies, because of clinical requirements, it was not feasible to defer treatment in symptomatic patients with abnormal translesional physiology. It is highly likely that these individuals would, at the least, continue to be symptomatic or have higher event rates. It should also be noted that although the safety of deferring angioplasty on the basis of a normal CVR can be demonstrated, some patients with deferred procedures had a lower rate of angina-free follow-up compared with patients who underwent angioplasty.\textsuperscript{39} Nonetheless, when physiologically normal, the functional and clinical impact of medically-treated, angiographically intermediate-severe stenoses is associated with an excellent clinical outcome. Physiological criteria support decisions to defer intervention in such situations while continuing medical therapy for endothelial dysfunction, hypertension, hyperlipidemia, and episodic coronary vasoconstriction.

### Comparison With Intravascular Ultrasound Imaging

Despite sophisticated quantitative modeling, neither intravascular ultrasound imaging (IVUS) nor coronary angiography can predict the resistance to flow through intermediately-narrowed epicardial coronary conduits. This is due to factors such as stenosis length, entrance and exit angles, coefficients of viscous friction and separation, and the status of the distal microvascular bed.

Moses et al\textsuperscript{39} studied 42 patients with coronary stenoses ranging from 18% to 95%; they reported that in those patients with a CVR<1.8, the IVUS reference segment area, IVUS lumen area, and angiographic percent diameter stenosis were higher (17.7±0.3 versus 12.9±4.4 mm\textsuperscript{2}, \( P<0.05; \) 6.2±3.76 versus 4.34±2.0 mm\textsuperscript{2}, \( P<0.05; \) and 60±14 versus 46±17%, \( P<0.01, \) respectively) compared with patients with a CVR≥1.8. However, the IVUS minimal luminal diameter and angiographic percent stenosis were only weakly correlated with poststenotic CVR (\( r=0.312, P=0.047; \) and \( r=0.305, P=0.052, \) respectively).

In contrast, Abizaid et al\textsuperscript{40} found that before intervention, the CVR and IVUS minimal luminal cross-sectional areas were correlated (\( r=0.83, P<0.0001 \); after the procedure, this relationship was attenuated (\( r=0.514, P=0.006; \) and, after stent placement, \( r=0.62, P=0.031 \). An IVUS minimal luminal cross-sectional area \( \geq 4 \) mm\textsuperscript{2} had a diagnostic accuracy of 89% for a CVR\textsuperscript{41} ≥2.0. Recently, Takagi et al\textsuperscript{41} demonstrated that an IVUS minimal lumen area <3.0 mm\textsuperscript{2} and an area stenosis <60% had 100% predictive accuracy for a FFR<0.75. Despite a precise dimensional measurement, a single tomographic IVUS image (except in the extremes) correlated weakly with measured coronary physiological responses.

Conversely, FFR may be equivalent to IVUS in the assessment of optimal stent deployment. Hanekamp et al\textsuperscript{42} found IVUS and FFR>0.94 had 91% concordance in the identification of optimal stent apposition and deployment.

### TABLE 2. Stress Testing and Directly Measured Coronary Blood Physiology

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>No. of</th>
<th>Ischemic Test</th>
<th>CVR</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PV+</th>
<th>PV−</th>
<th>Accuracy</th>
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Adeno indicates adenosine; dipy, dipyridamole; MIBI, sestamibi scan; dobu, dobutamine; PV+/PV−, predictive value positive/ negative; and echo, echocardiogram.
Figure 3. A, Physiological measurements during coronary angioplasty in 78-year-old woman (78yW; E.E.) with severe circumflex (CFX) coronary artery lesion and positive ischemic testing. Top left, Cineangiogram in shallow right anterior oblique projection showing 90% midcircumflex stenosis. Top right, CVR was measured in circumflex (1.1) and left anterior descending (LAD, 2.0) arteries. rCVR was 0.5. Bottom, Distal coronary pressure during maximal hyperemia was 32 mm Hg, and aortic pressure was 96 mm Hg. FFR was 0.33. B, Top left, Angiographic appearance of coronary artery after balloon angioplasty was satisfactory. However, CVR was 1.5. Because of impaired CVR despite satisfactory angiographic appearance, stent was positioned in circumflex artery (bottom left). CVR then normalized to 2.0, with rCVR of 1.0 and FFR of 1.0.
Physiological End Points for Coronary Interventions

It is now known that the failure of coronary blood flow reserve to improve after balloon angioplasty in ≥50% of patients is principally due to 2 mechanisms: impairment of microcirculatory responses (either preexisting or induced after vessel trauma) and/or inadequate epicardial lumen expansion not readily appreciated by angiography. Microvascular circulatory impairment, which was initially thought to be the predominant mechanism, is likely the less common condition because stenting, compared with angioplasty alone, achieves a larger and more uniformly cylindrical lumen by IVUS and normalizes CVR in most (≈80%) patients. In the 20% of patients with a poststent CVR < 2.0, rCVR or FFR may be useful in identifying persistent conduit abnormalities. A typical example of pressure and flow measurements after coronary angioplasty and stenting is illustrated in Figure 3.

A physiological end point associated with improved late outcomes after coronary angioplasty was identified in the Doppler End point Ballon Angioplasty Trial, Europe (DEBATE I), trial. A CVR > 2.5 coupled with an acceptable quantitative coronary angiographic result (≥35% diameter stenosis) identified a subset of patients after single- vessel balloon angioplasty in whom there was a 16% angiographic restenosis rate and a 16% target lesion revascularization rate at the 6-month follow-up. Using FFR after angioplasty without stenting, Bech et al found that when a FFR > 0.9 was achieved, repeat interventions at 6, 12, and 24 months were 12%, 12%, and 15%, respectively, compared with patients who had a FFR ≤ 0.9 after angioplasty, with restenosis rates of 24%, 28%, and 30% at 2 years.

A physiologically-guided angioplasty approach is being prospectively evaluated in 3 multicenter trials: DESTINI-CFR (Doppler Endpoint Stent International Investigation of Coronary Flow Reserve), DEBATE II, and FROST (French Optimal Stent Trial). These studies will confirm whether a provisional, physiologically-guided approach will produce clinical outcomes equivalent to a mandatory or primary stent approach without the adverse effects of stenting.

Preliminary data from studies in >1000 patients indicate that although crossover to stenting was required in ≈40% to 50% of patients, the major adverse in-hospital and 6-month clinical cardiac event rates were similar in both provisional and primary stent strategies. The physiologically-guided approach to balloon angioplasty, although clinically supported and economically attractive, limits the operator preferences and advances in stent technology that have reduced stent-related complications and restenosis.

Emerging Developments in Catheterization Laboratory-Based Coronary Physiology

The coronary physiology after acute myocardial infarction and reperfusion strongly influences clinical outcomes. In patients with acute infarction, the microcirculatory responses to pharmacological and mechanical interventions that release or remove thrombus or particulate matter can be quantitated in physiological terms and, using FFR, discriminated from epicardial flow impairment.

For example, Claeys et al reported that for similar angiographic stenoses, the CVR measured 13 ± 7 days after acute myocardial infarction in 36 patients was lower both before and after angioplasty compared with the 38 patients without myocardial infarctions (1.22 ± 0.26 versus 1.50 ± 0.45 and 1.72 ± 0.43 versus 2.21 ± 0.74, respectively). Although CVR increased after angioplasty in both patient groups, a persistently impaired CVR was present in 80% of patients with acute myocardial infarctions and in only 44% of patients without myocardial infarctions, which suggests that CVR was related more to conduit narrowing than myocardial viability and that increasing the residual lumen by stenting may improve myocardial recovery.

Similarly, Neumann et al examined acute and 14-day coronary flow and left ventricular wall motion in 102 patients with acute myocardial infarction who received abciximab and in 98 patients who received standard care with heparin. With similar degrees of residual stenosis, the change in peak (but not resting) flow velocity was greater (P < 0.024) and wall motion index improved more (P < 0.007) in the patients receiving abciximab. Coronary physiological responses correlated with left ventricular functional recovery, which suggests that mechanisms involving microvascular perfusion may identify new therapeutic avenues in these patients.

Summary

Recent advances in our understanding of human coronary circulation and clinically-validated physiological relationships to ischemic stress testing in patients have enhanced the conceptual applications of and overcome most technical limitations surrounding the usefulness of in-laboratory coronary physiological measurements to facilitate clinical decisions to treat or defer intervention. Although current clinical practice favors primary stenting, when considering strategies for optimal balloon angioplasty compared with obligatory stenting, multicenter preliminary reports indicate that a physiologically-guided approach can identify ≈50% of patients who will have equivalent clinical outcomes without the additional cost of stents and the potential for in-stent restenosis.

The practical application of physiological concepts in patients strongly complements coronary lumenology and has important clinical and economic implications for the care of patients with coronary artery disease.

Acknowledgment

The author thanks the J.G. Mudd Cardiac Catheterization Laboratory team and Donna Sander for help with manuscript preparation.

References


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Circulation. 2000;101:1344-1351
doi: 10.1161/01.CIR.101.11.1344

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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