Evaluating Intermediate Coronary Lesions in the Cardiac Catheterization Laboratory

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Angiography is notoriously poor at distinguishing ischemia-producing from non–ischemia-producing intermediate coronary lesions. Here, three invasive modalities for evaluating the physiologic significance of moderate coronary stenoses are reviewed: Doppler wire–derived measurement of coronary flow reserve (CFR), coronary pressure wire–derived fractional flow reserve (FFR), and intravascular ultrasound (IVUS) imaging. Studies investigating the correlation between each of these modalities and various noninvasive tests (eg, nuclear perfusion imaging or stress echocardiography) are discussed. Each of these invasive modalities has its limitations: CFR is limited by its dependence on heart rate and blood pressure, calling into question its reproducibility; both FFR and CFR are limited by their reliance upon achieving maximal hyperemia; and IVUS is limited by the fact that it provides anatomic information only. Ultimately, FFR appears to be the ideal method for interrogating intermediate coronary lesions.

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Many patients who undergo coronary angiography for evaluation of chest pain syndromes do so prior to a noninvasive evaluation for myocardial ischemia.[1] When an intermediate or indeterminate coronary lesion is discovered, the interventional cardiologist is faced with the challenge of determining the functional importance of the stenosis. Angiography is notoriously poor at distinguishing ischemia-producing intermediate coronary lesions from non–ischemia-producing ones.[2] For this reason, a number of invasive modalities have been introduced as means for evaluating the physiologic significance

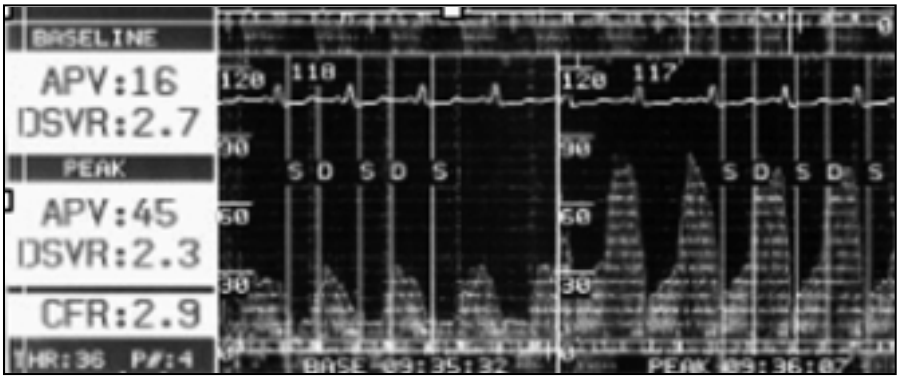

Figure 1. *An example of a normal Doppler wire–derived coronary flow reserve. The left panel represents the resting Doppler velocity, and the right panel shows the peak Doppler velocity. APV, average peak velocity; DSVR, diastolic systolic velocity ratio; S, systole; D, diastole.*

of moderate coronary stenoses. We will review and compare the three most commonly employed methods: Doppler wire–derived measurement of coronary flow reserve (CFR), coronary pressure wire–derived fractional flow reserve (FFR), and intravascular ultrasound (IVUS) imaging.

Doppler Wire–Derived Coronary Flow Reserve

CFR is defined as the ratio between the maximum achievable coronary flow during hyperemia and the resting coronary flow. Because coronary velocity is proportional to coronary flow, CFR can be estimated by measuring the coronary velocity at rest and during maximal vasodilation. This can be performed in the catheterization laboratory by using a standard angioplasty guidewire, with a Doppler transducer mounted at its tip, and by administering a vasodilatory agent, such as adenosine or papaverine (Figure 1).

CFR in a patient with normal coronary structure and function should be greater than 2 and can be up to 5. In a patient with a functionally significant coronary stenosis, CFR will be less than 2. Miller and colleagues compared CFR measured in this manner with nuclear perfusion imaging in 27 patients with intermediate coronary stenoses (30%–70% diameter stenosis).[3] They found that among the 14 patients with a CFR of 2 or lower, all had nuclear perfusion imaging studies showing reversible myocardial ischemia. Ten of the 13 patients with a CFR greater than 2 had normal myocardial perfusion studies. The concordance between the two techniques was 89%.

Joye and coworkers added to these findings by comparing Doppler wire-derived CFR with nuclear perfusion imaging in 30 patients with intermediate coronary stenoses.[4] They also found an excellent agreement between the noninvasive and invasive evaluations for ischemia, reporting a sensitivity of 94%, specificity of 95%, and diagnostic accuracy or concordance of 94%. These investigators concluded that the invasive assessment of CFR in a coronary artery with an intermediate lesion can reliably predict the presence of ischemia on nuclear perfusion imaging.

Subsequently, the ability of Doppler wire–derived CFR to detect ischemia-producing intermediate coronary lesions has been tested in larger cohorts of patients, as well as in comparison with stress echocardiography.[5–7] Unfortunately, these studies have found lower values for concordance between Doppler wire-derived CFR and the noninvasive modality tested: 84%, 79%, and 72%, respectively, for the three studies.

Pressure Wire–Derived Fractional Flow Reserve

FFR is defined as the maximum blood flow to the myocardium achieved in the presence of a narrowing compared with the maximum blood flow possible in the theoretical absence of the narrowing.[8] At maximal hyperemia, coronary pressure is proportional to coronary flow, and FFR can be calculated by comparing the distal coronary pressure in the presence of a stenosis with the distal coronary pressure in the theoretical absence of the stenosis.[9] Because resistance in a normal epicardial artery is minimal at peak hyperemia, the distal coronary pressure will be the same as the proximal coronary pressure. Therefore, in a diseased coronary artery, the distal coronary pressure that would be present if there were no disease can be estimated by measuring the proximal coronary pressure with a guide catheter. FFR is thus derived by comparing the mean coronary pressure distal to a stenosis, as measured by a coronary pressure wire, with the mean proximal coronary pressure, as measured by a guide catheter, at

In a diseased coronary artery, the distal coronary pressure that would be present if there were no disease can be estimated by measuring the proximal coronary pressure with a guide catheter.

maximal hyperemia.[10]

The correlation between FFR and a variety of noninvasive tests for ischemia in patients with intermediate coronary lesions has been extensively investigated.[11–18] In a landmark study, Pijls and colleagues compared FFR measured in 45 patients with intermediate coronary lesions with bicycle exercise testing, nuclear perfusion imaging, and stress echocardiography.[14] In all 21 patients in whom the FFR was less than 0.75, at least one noninvasive test demonstrated inducible ischemia. In 21 of the 24 patients in whom the FFR was 0.75 or greater, there was no inducible ischemia on any of the noninvasive tests. The sensitivity, specificity, and concordance of FFR were 88%, 100%, and 93%, respectively. Based on this study, the cut-off FFR value of 0.75 for detecting ischemia-producing lesions was established.

In a smaller study, we compared FFR with nuclear perfusion imaging in patients with intermediate coronary lesions before and after angioplasty of the lesion. We found the sensitivity, specificity, and concordance of an FFR less than 0.75 for predicting ischemia on the noninvasive test to be 90%, 100%, and 95%.[15] Similar results have been shown when comparing FFR with stress echocardiography and when measuring FFR in patients with multivessel disease or after myocardial infarction.[13,16,18]

Intravascular Ultrasound Imaging

IVUS provides superior anatomic definition of the coronary arterial dimensions compared with coronary angiography. For this reason, it has been performed in cases of intermediate coronary lesions to provide a better assessment of the degree of narrowing and the clinical significance of a narrowing. Abizaid and colleagues performed IVUS in a group of 73 patients, including patients with intermediate lesions, and compared various anatomic parameters measured by IVUS with Doppler wire-derived CFR.[19] They found a linear relation between CFR and the minimum lumen cross-sectional area ($r = 0.77$, $P < .0001$). The authors defined an abnormal minimum lumen cross-sectional area as less than 4 mm^2 and demonstrated a concordance of 89% with CFR, when defining an abnormal CFR as less than 2.

Nishioka and coworkers extended these findings by comparing IVUS parameters measured in 70 *de novo* coronary lesions (the majority classified as intermediate) with the results of nuclear perfusion imaging.[20] The authors found that a minimum lumen cross-sectional area defined as 4 mm^2 or less had a sensitivity of 88% and specificity of 90% for predicting a reversible perfusion defect on the nuclear perfusion imaging study. Other IVUS parameters, such as percent area stenosis, performed less well, with sensitivities and specificities in the 80% range.

More recently IVUS parameters have been compared with FFR for determining the functional significance of moderate stenoses.[21,22] Takagi and colleagues performed IVUS in 51 coronary lesions (approximately half were considered intermediate) and compared the IVUS-derived minimum lumen cross-sectional area and percent area stenosis with the FFR result.[21] They found a strong positive correlation between the minimum lumen cross-sectional area and FFR ($r = .79$, $P < .0001$) and negative correlation between percent area stenosis and FFR ($r = -0.77$, $P < .0001$). Using a cut-off point of less than 3 mm^2 to define an abnormal minimum lumen cross-sectional area and less than 0.75 to define an abnormal FFR, the investigators found that IVUS had a sensitivity of 83% and a specificity of 92% for detecting ischemia-producing lesions based on FFR. Defining an abnormal percent area stenosis based on IVUS as greater than 60% resulted in a sensitivity of 92% and a specificity of 89% for predicting an abnormal FFR. In every lesion in which either the minimum lumen cross-sectional area or the percent area stenosis was abnormal, the FFR was less than 0.75.

Another group compared IVUS with FFR only in patients with intermediate coronary lesions.[22] The correlation between the IVUS-derived minimum lumen cross-sectional area and FFR was significant, but weaker ($r = 0.41$, $P < .004$). In addition, the sensitivity and specificity of a minimum lumen cross-sectional area of 4 mm^2 or less for predicting an FFR less than 0.75 were 92% and 56%, respectively. Presumably the weaker correlation and concordance in this study compared with the study by Takagi and colleagues can be explained by the inclusion of only intermediate lesions in this study. Figure 2 shows an example of a patient with two intermediate lesions evaluated at Stanford University Medical Center with FFR and IVUS.

Limitations and Comparison of the Three Techniques

CFR is limited by its dependence on heart rate and blood pressure, calling into question its reproducibility.[23] In addition, CFR does not have a clear normal value: in general, a CFR greater than 2 is "normal," but this may vary from patient to patient. Measuring CFR with a Doppler wire can be technically challenging because centering the transducer in the coronary artery is critical to

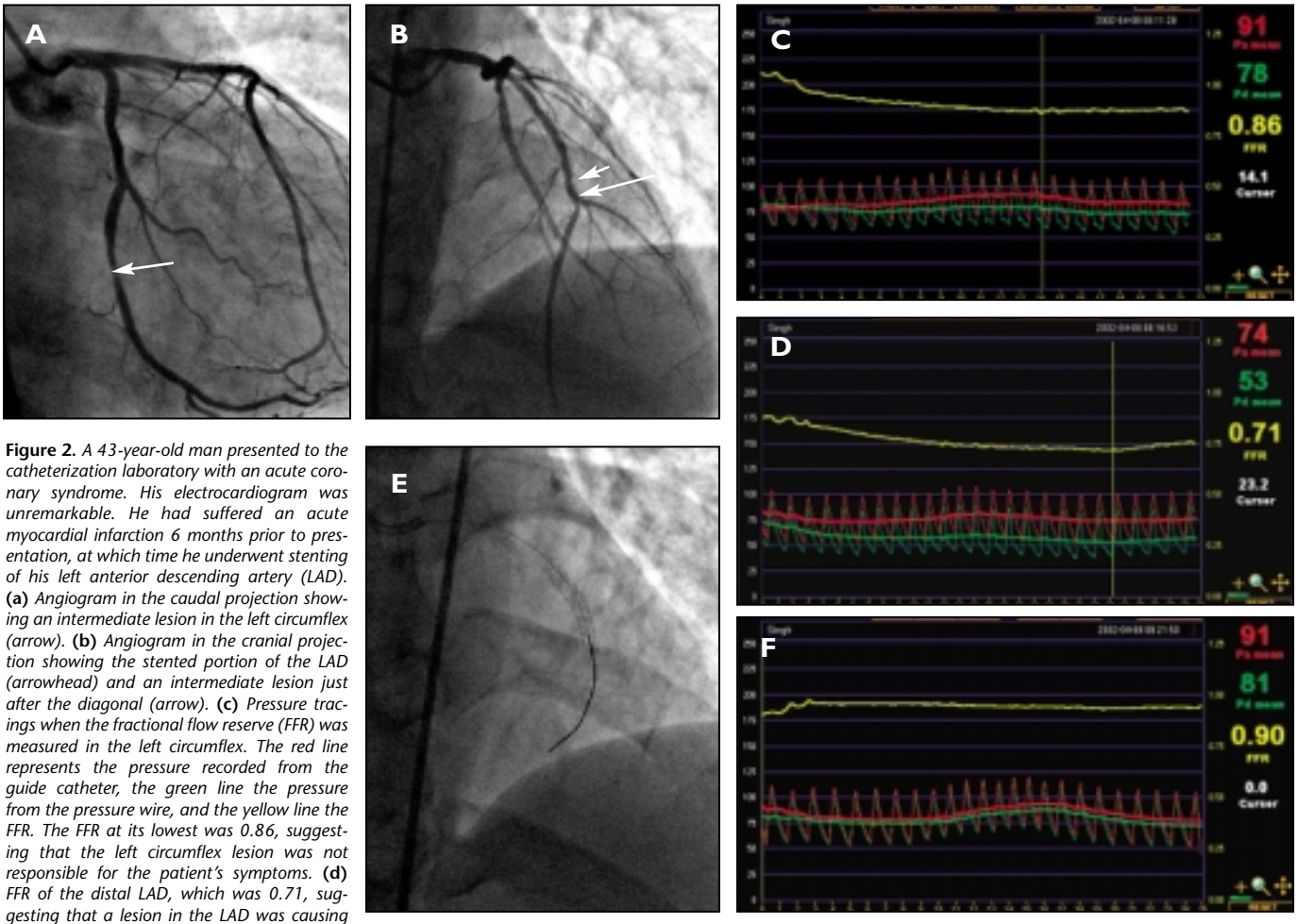

Figure 2. *A 43-year-old man presented to the catheterization laboratory with an acute coronary syndrome. His electrocardiogram was unremarkable. He had suffered an acute myocardial infarction 6 months prior to presentation, at which time he underwent stenting of his left anterior descending artery (LAD).* **(a)** *Angiogram in the caudal projection showing an intermediate lesion in the left circumflex (arrow).* **(b)** *Angiogram in the cranial projection showing the stented portion of the LAD (arrowhead) and an intermediate lesion just after the diagonal (arrow).* **(c)** *Pressure tracings when the fractional flow reserve (FFR) was measured in the left circumflex. The red line represents the pressure recorded from the guide catheter, the green line the pressure from the pressure wire, and the yellow line the FFR. The FFR at its lowest was 0.86, suggesting that the left circumflex lesion was not responsible for the patient's symptoms.* **(d)** *FFR of the distal LAD, which was 0.71, suggesting that a lesion in the LAD was causing ischemia.* **(e)** *Angiogram showing the pressure wire pulled back, just proximal to the diagonal and distal to the stent.* **(f)** *FFR with the pressure sensor just distal to the stent was 0.90, suggesting that the ischemia-producing lesion was after the diagonal and not due to in-stent restenosis.* **(g)** *Intravascular ultrasound image of the LAD just after the diagonal. This was the region of the minimum lumen area, which was 2.2 mm^2. The diagonal can be seen coming in the upper right quadrant. The patient had successful stenting of this region of the LAD, and his symptoms resolved.*

maximize the signal.

CFR interrogates the entire coronary system, including the epicardial artery as well as the microcirculation. For this reason, a patient without epicardial disease but with abnormal microcirculatory function can have an abnormal CFR, potentially limiting the applicability of CFR when assessing an intermediate epicardial stenosis in patients with microvascular disease. Because most abnormal microvascular function (eg, due to diabetes or left ventricular hypertrophy) occurs diffusely throughout the myocardium, investigators have introduced the *relative* CFR index (rCFR) as a way of isolating the contribution of the epicardial disease to the abnormal CFR.[24] rCFR is defined as the CFR in the artery with epicardial disease divided by the CFR in an adjacent vessel without epicardial disease. By definition, rCFR cannot be calculated in patients with three-vessel disease.

Baumgart and colleagues recently compared CFR and rCFR with FFR determined in 24 vessels with moderate-to-severe lesions.[25] They found no correlation between CFR and FFR (r = 0.33, P = ns), whereas rCFR had a strong correlation with FFR (r = 0.91,

$P < .0001$). Furthermore, rCFR is advantageous compared with CFR alone because there is a defined normal value of 1. Thus it appears that rCFR may be a more useful method of evaluating intermediate coronary stenoses than CFR, although it does mandate the presence of a normal adjacent artery and the need to measure CFR in two separate vessels.

IVUS is limited by the fact that it provides anatomic information only. The physiologic or functional significance of a lesion does not always appear to correlate with the anatomic severity, as described above. The time required for performing a careful IVUS examination, the expense of the catheters, and the expertise required to interpret the images represent practical barriers for many operators. Finally, based on the studies discussed above, a clear cut-off value for an abnormal minimum lumen cross-sectional area has not been established.

Both FFR and CFR are limited by their reliance upon achieving maximal hyperemia. If maximal hyperemia does not occur, the pressure gradient across a stenosis will be underestimated and the FFR overestimated. Conversely, CFR will be underestimated in the absence of maximal hyperemia. For these reasons, careful and adequate administration of the vasodilating agent, particularly when using the intracoronary route, is critical. Intravenous adenosine is considered the reference standard for inducing hyperemia; however, administration requires a large-bore intravenous line and, in the United States, the added expense for the medication can be prohibitive. For that reason, most operators in the United States use intracoronary adenosine. Recent data suggest that larger doses (30–50 μg) of intracoronary adenosine than previously used are necessary to achieve peak vasodilatation.[26]

Also like CFR, FFR will be affected by significant microvascular disease. Because achieving maximal hyperemia when measuring the pressure gradient across a stenosis is critical to accurately assess FFR, a dysfunctional microcirculation secondary to, for example, myocardial infarction, can impair the microvascular vasodilatory capacity. This can result in a decrease in the transstenotic pressure gradient and in what one initially might consider an overestimation of the FFR. Furthermore, the mass of viable myocardium supplied by a coronary artery is reduced in the setting of a previous myocardial infarction, which will also decrease maximum flow and increase FFR for a similar degree of stenosis, compared with before infarction. Unlike CFR, however, the FFR measurement continues to provide useful information about the epicardial lesion in this setting: an FFR greater than 0.75 implies the absence of myocardial ischemia and the lack of need for revascularization.

FFR appears to be the ideal method for interrogating intermediate coronary lesions. Unlike CFR, FFR is independent of the systemic blood pressure and heart rate and is very reproducible.[27] FFR has a clear normal value, 1.0, and a well-established abnormal value, less than 0.75. It is relatively easy to perform and interpret. FFR can be accurately measured in patients with multivessel disease and is advantageous because it takes into account the contribution of collateral circulation (Table 1).

Recently, software has been developed that makes possible the calculation of both FFR and CFR simultaneously with a single standard coronary pressure wire. CFR is calculated using a novel coronary thermodilution technique, which early studies suggest correlates with Doppler wire–derived CFR.[28,29] This technique may facilitate a more thorough physiologic evaluation of

Table 1
Comparison of CFR, rCFR, FFR and IVUS for Evaluating Intermediate Stenoses.

Method	Absolute Normal Value	Abnormal Cut-Off Value	Use in Multivessel Disease	Independent of Microcirculation	Independent of Hemodynamics
CFR	No	~ 2	Yes	No	No
rCFR	Yes (1.0)	~ 0.65	No	Yes	No
FFR	Yes (1.0)	0.75	Yes	Yes	Yes
IVUS	No	MLA 3-4 mm^2	Yes	Yes	Yes

CFR, coronary flow reserve; rCFR, relative CFR; FFR, fractional flow reserve; IVUS, intravascular ultrasound; MLA, minimum lumen cross-sectional area.
Adapted from Kern et al.[23]

The time required for performing a careful IVUS examination, the expense of the catheters, and the expertise required to interpret the images represent practical barriers for many operators.

patients with intermediate coronary lesions. ■

References

1. Topol EJ, Ellis SG, Cosgrove DM, et al. Analysis of coronary angioplasty practice in the United States with an insurance-claims data base. *Circulation*. 1993;87:1489–1497.
2. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *New Engl J Med*. 1984;310:819–824.
3. Miller DD, Donohue TJ, Younis LT, et al. Correlation of pharmacological ^{99m}Tc-sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenoses. *Circulation*. 1994;89:2150–2160.
4. Joye JD, Schulman DS, Lasorda D, et al. Intracoronary Doppler guide wire versus stress single-photon emission computed tomographic thallium-201 imaging in assessment of intermediate coronary stenoses. *J Am Coll Cardiol*. 1994;24:940–947.
5. Heller LI, Cates C, Popma J, et al. Intracoronary Doppler assessment of moderate coronary artery disease: comparison with 201Tl imaging and coronary angiography. FACTS Study Group. *Circulation*. 1997;96:484–490.
6. Verberne HJ, Piek JJ, van Liebergen RA, et al. Functional assessment of coronary artery stenosis by Doppler-derived absolute and relative coronary blood flow velocity reserve in comparison with (99m)Tc MIBI SPECT. *Heart*. 1999;82:509–514.
7. Duffy SJ, Gelman JS, Peverill RE, et al. Agreement between coronary flow velocity reserve and stress echocardiography in intermediate-severity coronary stenoses. *Catheter Cardiovasc Interv*. 2001;53:29–38.
8. Pijls NHJ, van Son JAM, Kirkeeide RL, et al. Experimental basis of determining maximum coronary, myocardial and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*. 1993;86:1354–1367.
9. Pijls NHJ, De Bruyne B. Fractional flow reserve. In: Pijls NHJ, De Bruyne B, eds. *Coronary Pressure*. Dordrecht: Kluwer Academic Publishers; 2000:51–82.
10. Pijls NHJ, Kern MJ, Yock PG, De Bruyne B. Practice and potential pitfalls of coronary pressure measurement. *Catheter Cardiovas Interv*. 2000;49:1–16.
11. De Bruyne B, Bartunek J, Sys SU, Heyndrickx GR. Relation between myocardial fractional flow reserve calculated from coronary pressure measurements and exercise-induced myocardial ischemia. *Circulation*. 1995;92:3183–3193.
12. Pijls NHJ, Van Gelder B, Van de Voort P, et al. Fractional flow reserve a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation*. 1995;92:3183–3193.
13. Bartunek J, Marwick TH, Rodrigues ACT, et al. Dobutamine-induced wall motion abnormalities: correlation with fractional flow reserve and quantitative coronary angiography. *J Am Coll Cardiol*. 1996;27:1429–1436.
14. Pijls NHJ, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334:1703–1708.
15. Fearon WF, Takagi A, Jeremias A, et al. Use of fractional myocardial flow reserve to assess the functional significance of intermediate coronary stenoses. *Am J Cardiol*. 2000;86:1013–1014.
16. Chamuleau SAJ, Mewissen M, van Eck-Smit BLF, et al. Fractional flow reserve: absolute and relative coronary blood flow velocity reserve in relation to the results of technetium-99m sestamibi single-photon emission computed tomography in patients with two-vessel coronary artery disease. *J Am Coll Cardiol*. 2001;37:1316–1322.
17. Abe M, Tomiyama H, Yoshida H, et al. Diastolic fractional flow reserve to assess the functional severity of moderate coronary artery stenoses comparison with fractional flow reserve and coronary flow velocity reserve. *Circulation*. 2000;102:2365–2370.
18. De Bruyne B, Pijls NHJ, Bartunek J, et al. Fractional flow reserve in patients with prior myocardial infarction. *Circulation*. 2001;104:157–162.
19. Abizaid A, Mintz GS, Pichard AD, et al. Clinical, intravascular ultrasound, and quantitative angiographic determinants of the coronary flow reserve before and after percutaneous transluminal coronary angioplasty. *Am J Cardiol*. 1998;82:423–428.
20. Nishioka T, Amanullah AM, Luo H, et al. Clinical validation of intravascular ultrasound imaging for assessment of coronary stenosis severity: comparison with stress myocardial perfusion imaging. *J Am Coll Cardiol*. 1999;33:1870–1878.
21. Takagi A, Tsurumi Y, Ishii Y, et al. Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis: relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. *Circulation*. 1999;100:250–255.
22. Briguori C, Anzuini A, Airoldi F, et al. Intravascular ultrasound criteria for the assessment of the functional significance of intermediate coronary artery stenoses and comparison with fractional flow reserve. *Am J Cardiol*. 2001;87:136–141.
23. Kern MJ. Coronary physiology revisited prac-

Main Points

- The three most commonly employed methods for evaluating the physiologic significance of moderate coronary stenoses are Doppler wire–derived measurement of coronary flow reserve (CFR), coronary pressure wire–derived fractional flow reserve (FFR), and intravascular ultrasound (IVUS) imaging.
- CFR is defined as the ratio between the maximum achievable coronary flow during hyperemia and the resting coronary flow. It can be estimated in the catheterization laboratory by measuring the coronary velocity at rest and during maximal vasodilation, using a standard angioplasty guidewire, with a Doppler transducer mounted at its tip and by administering a vasodilatory agent.
- FFR is derived by comparing the mean coronary pressure distal to a stenosis, as measured by a coronary pressure wire, with the mean proximal coronary pressure, as measured by a guide catheter, at maximal hyperemia.
- IVUS provides superior anatomic definition of the coronary arterial dimensions compared with coronary angiography, and so has been performed in cases of intermediate coronary lesions to provide a better assessment of the degree of narrowing and its clinical significance.
- CFR is limited by its dependence on heart rate and blood pressure, calling into question its reproducibility; both FFR and CFR are limited by their reliance upon achieving maximal hyperemia; and IVUS is limited by the fact that it provides anatomic information only.
- Each of these three invasive modalities has been compared with noninvasive modalities (eg, nuclear perfusion imaging) in its ability to detect ischemia-producing intermediate coronary lesions; FFR has performed the best, showing a concordance of 93% with the noninvasive modality.

tical insights from the cardiac catheterization laboratory. *Circulation*. 2000;101:1344–1351.
24. Gould KL, Kirkeeide RL, Buchi M. Coronary flow reserve as a physiologic measure of stenosis severity. *J Am Coll Cardiol*. 1990;15:459–474.
25. Baumgart D, Haude M, Goerge G, et al. Improved assessment of coronary stenosis severity using the relative flow velocity reserve. *Circulation*. 1998;98:40–46.
26. Fearon WF, Luna J, Samady H, et al. Fractional flow reserve compared to intravascular ultrasound guidance for optimal stent deployment. *Circulation*. 2001;104:1917–1922.
27. de Bruyne B, Bartunek J, Sys SU, et al. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. *Circulation*. 1996;94:1842–1849.
28. De Bruyne B, Pijls NH, Smith L, et al. Coronary thermodilution to assess flow reserve: experimental validation. *Circulation*. 2001;104:2003–2006.
29. Pijls NH, De Bruyne B, Smith L, et al. Coronary thermodilution to assess flow reserve: validation in humans. *Circulation*. 2002;105:2482–2486.