

Physiologic Lesion Assessment

Fractional flow reserve has become an indispensable tool in guiding the decision for PCI in intermediate lesions and likely improves outcomes in patients undergoing multivessel PCI.

BY WILLIAM F. FEARON, MD

Despite advances in the noninvasive evaluation of coronary artery disease and improvements in invasive coronary imaging, interventional cardiologists are commonly forced to determine the need for percutaneous coronary intervention (PCI) on coronary artery lesions of uncertain physiologic significance. Measurement of fractional flow reserve (FFR) using a coronary pressure wire in the catheterization laboratory has become the gold standard for identifying ischemia-producing lesions that might benefit from PCI. This article provides a review of the role of the coronary pressure wire and FFR in the daily practice of the interventional cardiologist.

THE CONCEPT OF FFR

FFR is defined as the maximum achievable flow down a coronary artery in the presence of a stenosis compared to the maximum flow in the hypothetical absence of the stenosis.¹ During maximal hyperemia, both the epicardial artery and microvascular resistance are minimized, and

coronary flow becomes proportional to coronary pressure. Thus, FFR can also be defined as the coronary pressure in the presence of a stenosis compared to the coronary pressure in the theoretical absence of the stenosis. In a completely normal coronary artery, the distal epicardial pressure is equal to the proximal coronary or aortic pressure. Because of this, FFR can be calculated by measuring the mean distal coronary pressure with a pressure wire and dividing it by the mean proximal coronary or aortic pressure, as measured with the guiding catheter. This proximal pressure is a reflection of what the distal pressure or flow would be in the theoretical absence of the coronary stenosis. To be perfectly accurate, the central venous pressure should be subtracted from both the distal pressure and the proximal pressure, but because the venous pressure is usually negligible compared to the coronary pressure, it is generally neglected.

FFR is unique compared to other physiologic indices, such as coronary flow reserve (CFR), in that it has an absolute normal value of 1. In addition, because it is measured during

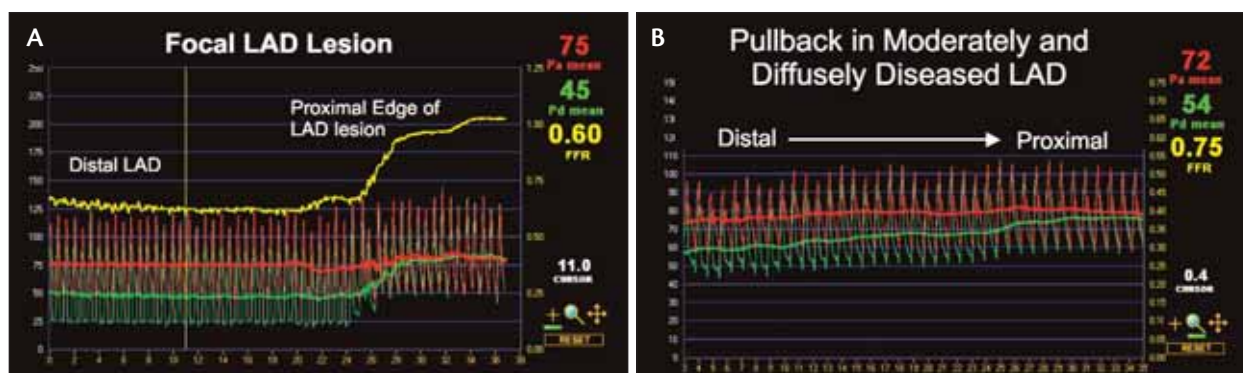


Figure 1. Pressure tracing displaying the aortic or proximal coronary pressure recording from the guide catheter in red and the coronary pressure wire recording in green. On the left side of the figure, the pressure sensor is in the distal vessel. It is pulled back slowly during maximal hyperemia and is positioned at the ostium of the guide catheter on the right side of the figure. The sudden loss of the pressure gradient indicates a focal proximal stenosis. The FFR is 0.6 (A). Pressure tracing displaying the aortic or proximal coronary pressure recording from the guide catheter in red and the coronary pressure wire recording in green. On the left side of the figure, the pressure sensor is in the distal vessel. It is pulled back slowly during maximal hyperemia and is positioned at the ostium of the guide catheter on the right side of the figure. The gradual loss of the pressure gradient indicates moderate diffuse disease. The FFR is 0.75 (B).

maximal hyperemia, FFR is independent of hemodynamic perturbations, making it extremely reproducible. FFR also takes into account collateral flow. FFR informs the operator of the fraction of myocardial flow achieved in the presence of coronary disease. For example, an FFR of 0.6 implies that only 60% of the maximum flow that should be reaching the myocardium actually is reaching the myocardium.²

HOW TO MEASURE FFR

FFR is readily measured in the cardiac catheterization laboratory using standard interventional techniques. Currently, two companies manufacture pressure wires (Radi Medical Systems, Wilmington, MA; and Volcano Corporation, Rancho Cordova, CA). Both have analyzers that connect to the catheterization laboratory hemodynamic system. The analyzers display the pressure recordings from the wire and the guiding catheter and automatically calculate and record FFR.

Before measuring FFR, 100 to 200 μ g of intracoronary nitroglycerin is administered to maximally dilate the epicardial vessel, and 50 to 70 units of intravenous heparin is given. The pressure wire is then connected to the analyzer via its interface connector, which is attached to the distal end of the wire. The wire is calibrated and advanced via the guiding catheter so that the pressure sensor, which is located 3 cm from the tip of the wire (at the junction of the radiopaque and radiolucent segments), sits at the ostium of the coronary vessel. In this position, the pressure wire and the guiding catheter should record the same pressure. If this is not the case, the pressure reading from the pressure wire can be equalized to the guiding catheter's pressure reading. The wire is then advanced to the distal part of the coronary artery and FFR is measured after inducing maximal hyperemia. If there is difficulty passing the wire because of vessel tortuosity or side branches, the wire can be disconnected from its interface connector, which will facilitate maneuvering the wire. It is then reconnected once the wire is properly positioned.

The induction of maximal hyperemia is integral for accurately measuring FFR. The most reliable method is to administer intravenous adenosine at 140 μ g/kg per minute via the femoral vein. An antecubital vein can be used; however, maximal hyperemia may not be achieved as reliably, and higher doses may be necessary because of the short half-life of adenosine. Hyperemia reliably occurs after 1 minute of central venous infusion and continues as long the infusion continues, which allows the operator to disengage the guiding catheter in case ostial disease is present or in case the catheter is impairing flow down the vessel. In this manner, very accurate determination of FFR is possible. The operator is also able to slowly pull back the pressure sensor and identify exactly which part of the vessel is contributing most to

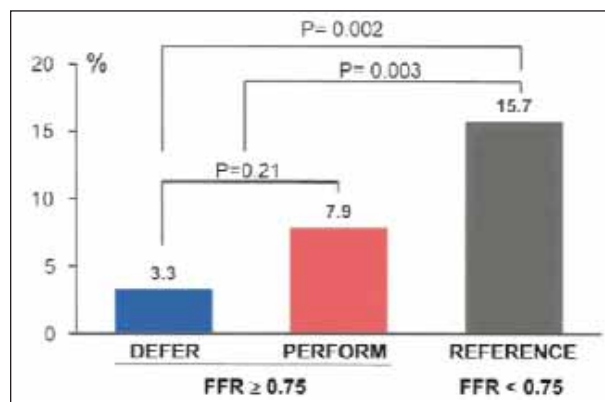


Figure 2. Chart depicting the cardiac death and myocardial infarction rates at 5 years in patients with intermediate lesions and an $\text{FFR} \geq 0.75$ randomized to deferral of PCI (red bar) or performance of PCI (blue bar) and in those with an $\text{FFR} < 0.75$ treated with PCI (gray bar). The higher event rate in the reference group is likely a reflection of greater atherosclerotic burden as detected by the lower FFR (Reprinted with permission from J Am Coll Cardiol. 2007;49:2105-2111⁸).

the pressure gradient. In this way, FFR is not only a vessel-specific index but also a lesion-specific index with superior spatial resolution (Figure 1).²

Patients often feel a sensation of chest pressure or shortness of breath with intravenous adenosine, but as long as they are forewarned, they tolerate it quite well. Rarely, transient heart block occurs, which does not require discontinuation of the infusion. Very rarely, a patient with severe obstructive lung disease develops bronchospasm with intravenous adenosine, which does require discontinuation of the infusion.

Intracoronary adenosine is also commonly used to measure FFR because it is less expensive and easier to administer. To start, doses of 40 to 60 μ g are given in the left coronary artery and 20 to 40 μ g in the right coronary artery. Transient heart block is the only side effect. If one is concerned that maximal hyperemia has not been achieved, higher doses of up to 150 μ g or higher have been administered safely.³ The downside to using intracoronary adenosine is that the peak effect lasts only 5 to 10 seconds, making it more difficult to accurately measure FFR and impossible to do a pullback of the pressure wire. Another drawback is that one is never entirely sure that all of the adenosine is reaching the microcirculation as opposed to entering the aorta. Finally, in the presence of ostial coronary disease, in which it is important to disengage the guiding catheter, the use of intracoronary adenosine makes FFR measurement more difficult and less reliable.

Intracoronary papaverine is another agent occasionally used to measure FFR. Papaverine has a longer hyperemic

TABLE 1. CHARACTERISTICS OF FFR

- Specific for epicardial artery
- Normal value of 1 in all patients
- Narrow ischemic threshold value of 0.75–0.8
- Value >0.9 after PCI suggests optimal result
- Reproducible
- Independent of hemodynamic changes
- Not only vessel specific but also lesion specific

TABLE 2. LIMITATIONS AND PITFALLS OF FFR

- Inadequate hyperemia
- Guide catheter issues
 - Deep-seating obstructing flow
 - Side holes allowing adenosine to spill into aorta
 - Artifactual drift secondary to contrast in guide
- Drift in pressure wire signal
- Left ventricular hypertrophy

effect, lasting 40 to 60 seconds, but it can rarely cause ventricular arrhythmias, which limits its clinical use.⁴

After FFR has been measured, if the decision is made to perform PCI, the pressure wire can serve as a regular guidewire. The interface connector is disconnected, and a balloon catheter or stent can be passed over the wire in the usual fashion. FFR can be remeasured after PCI to assess the success of the intervention.⁵ Before removing the wire entirely, it is useful to reposition the sensor at the coronary ostium to assess whether any pressure drift occurred (Table 1).

The main potential pitfall of FFR measurement is achieving inadequate hyperemia. One should be aware of this possibility, particularly if using intracoronary adenosine, and consider switching to intravenous adenosine administered via the femoral vein. FFR has not been well validated in patients with cardiomyopathy or significant left ventricular hypertrophy. In the case of significant left ventricular hypertrophy, the mass of myocardium outgrows the vasculature, and ischemia may occur at a lower threshold, meaning a higher FFR cutoff value might be warranted. Another potential reason for a false-negative FFR measurement can occur in a patient with a moderate stenosis and exercise-induced vasoconstriction at the site of the stenosis, leading to reversible myocardial ischemia during exercise testing. During FFR measurement in the catheterization laboratory with adenosine, exercise-induced vasoconstriction does not occur, and the same moderate stenosis may not affect blood flow to as great a degree (Table 2).

FFR FOR ASSESSING INTERMEDIATE LESIONS

FFR has been validated against a number of noninvasive tests for ischemia, and a cutoff value of 0.75 best distin-

guishes ischemia-producing lesions from nonischemia-producing lesions.^{2,6} The specificity of FFR is very high—if the FFR is <0.75, ischemia is present. The sensitivity of FFR is in the 90% range at a cutoff of 0.75 and can be improved somewhat by extending the cutoff to <0.8 if a patient has classic symptoms and focal disease.² An FFR >0.8 means significant ischemia is not present.

A number of retrospective studies and one large randomized study have shown that deferring PCI in patients with chest pain, an intermediate lesion, and FFR ≥ 0.75 is at least as safe, if not safer than, performing PCI.^{2,7} The 5-year rate of cardiac death and myocardial infarction in 91 patients with intermediate lesions and FFR ≥ 0.75 who were randomized to deferral of PCI was 3.3%, compared to 7.9% in the 90 patients with an FFR ≥ 0.75 who were randomized to PCI with bare-metal stents ($P=.2$) (Figure 2).⁸ Studies also suggest that patients with FFR <0.75 who are treated medically have worse outcomes than those with FFR ≥ 0.75 and that these patients may benefit from PCI.^{9,10} Measuring FFR in patients with intermediate lesions appears to be cost-effective compared to a noninvasive imaging or a routine stenting strategy.^{11,12}

FFR IN PATIENTS WITH MULTIVESSEL CORONARY DISEASE

Interventional cardiologists are performing PCI in patients with increasingly complex coronary disease. Determining the culprit lesion(s) in a patient with multivessel coronary disease can be challenging because of the limitations of coronary angiography and because noninvasive stress imaging studies are less reliable in this setting.¹³ Deferring PCI in a second vessel because the FFR is ≥ 0.75 in patients with multivessel coronary disease in whom PCI was performed in another vessel has been shown to be safe and results in low event rates during follow-up.¹⁴ A retrospective study comparing an FFR-guided strategy to PCI to an angiography-guided strategy in patients with multivessel coronary disease resulted in significantly improved outcomes and reduced costs.¹⁵

The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study is a large, randomized, multicenter, international study comparing outcomes in patients with multivessel coronary disease randomized to PCI with drug-eluting stents guided by FFR measurement versus angiography.¹⁶ Enrollment of 1,000 patients was completed in September of 2007, and the primary endpoint of major adverse cardiac events at 1 year will be reported in late 2008. This study will provide important data regarding the role of routine FFR measurement in patients with multivessel coronary disease. It will also explore the cost-effectiveness of this approach.

FFR IN PARTICULAR PATIENT SUBSETS

Acute Coronary Syndromes

During and shortly after an ST-segment elevation myocardial infarction, there may be some degree of reversible myocardial damage. Measuring FFR in this setting may be unreliable because maximum hyperemia is blunted, flow across a given stenosis will be less, the pressure gradient will be less, and FFR will be higher than expected. With time, stunning of the myocardium may resolve and maximum hyperemia will be greater, resulting in higher flow across the same stenosis, a larger pressure gradient, and a lower FFR.

In the setting of chronic myocardial infarction, the microvascular damage is irreversible, and, although the peak flow across a stenosis is blunted and the pressure gradient is less with a higher FFR than one would expect, the higher FFR is not falsely elevated, but it reflects the smaller amount of viable myocardium supplied by the vessel and still provides information about the expected gain in flow after PCI.

Two important studies have evaluated FFR after myocardial infarction and demonstrate that 3 to 6 days after a myocardial infarction, FFR can be reliably measured, and a cutoff value between 0.75 and 0.8 still applies for determining ischemia-producing lesions.^{17,18} FFR has also been measured in the setting of non-ST-elevation acute coronary syndromes, and its use has been shown to be reliable and safe.¹²

Intermediate Left Main Disease

Angiographic assessment of left main coronary disease can be particularly challenging. Multiple small studies have demonstrated that deferring revascularization in patients with left main disease and FFR ≥ 0.75 is safe.^{19,20} Intravascular ultrasound has been the preferred method for evaluating left main disease; it evaluates the anatomic characteristics of the coronary stenosis, whereas FFR provides the functional significance. More recently, FFR has been the reference standard to which intravascular ultrasound was compared to identify optimal anatomic cutoffs in the setting of left main disease.²⁰

Serial Lesions

FFR is useful for assessing serial coronary lesions in the same vessel. Practically speaking, when faced with tandem lesions of uncertain significance, FFR is first measured, as defined, with the pressure sensor in the distal vessel. If the FFR is >0.75 to 0.8, neither stenosis is significant, and medical therapy can be prescribed. If the FFR is below this threshold, a slow pullback of the pressure wire during continuous hyperemia should be performed. The stenosis with the greater pressure gradient and/or the one that angiographically appears most significant should be stented first. If both appear equally significant, and the pressure gradient appears to be equally divided between both, stenting the distal

lesion first makes the most sense from a technical standpoint. It is critical to remeasure FFR after treating the first lesion because flow across the second stenosis may now be augmented, and the FFR may remain abnormal. It is possible to determine the exact FFR of each stenosis, but it requires balloon occlusion of the vessel to measure the coronary wedge pressure, and, from a practical standpoint, this is optimal.²¹

Other Subsets

FFR is also useful for assessing “jailed” side branches after stenting and ostial lesions.^{22,23} Myocardial bridges are a unique subset in which FFR may not be reliable because of the dynamic changes in the severity of the stenosis.²⁴ FFR in bypass grafts has not been well studied, but with the sensor positioned in the native vessel beyond the anastomosis of the bypass graft, in theory, FFR should remain accurate.

PHYSIOLOGIC ASSESSMENT OF THE CORONARY MICROCIRCULATION

The coronary microcirculation plays an important role in determining patient outcomes in a number of settings. Although there are a number of noninvasive techniques for evaluating the microvasculature, patients often undergo coronary angiography without any previous noninvasive evaluation. For this reason, it would be advantageous to have a relatively simple, invasive method for assessing microvascular function. CFR has been the traditional method for assessment of microvascular function, but it has a number of limitations, including poor reproducibility and the fact that it interrogates both the epicardial artery and the microcirculation.²

Recently, we introduced the index of microcirculatory resistance (IMR), which can be measured with a coronary pressure wire.²⁵ IMR is defined as the distal coronary pressure divided by coronary flow. Flow can be estimated using a validated thermodilution technique, which allows measurement of the mean transit time.²⁶ With commercially available software, the pressure sensor can act as a distal thermistor, while the shaft of the wire acts as a proximal thermistor. After injecting room temperature saline, the mean transit time is calculated and is inversely proportional to coronary flow.^{27,28}

IMR has been validated in an animal model and found to be more reproducible in humans than CFR.^{25,29} As long as the collateral contribution to myocardial flow is accounted for, IMR has been shown in an animal model and in humans to be independent of epicardial stenosis.^{30,31} When measured after primary PCI for acute myocardial infarction, IMR is a better predictor of acute myocardial damage and longer-term recovery of left ventricular function compared to traditional measures of microvascular function, such as

CFR, myocardial perfusion grade, and ST-segment resolution.³² IMR may also be useful for following patients after cardiac transplantation or after experimental regimens, such as stem cell therapy.^{33,34} IMR has been used as an endpoint when comparing different PCI treatment strategies in both unstable and stable patients.^{35,36}

CONCLUSION

Measurement of FFR is an indispensable tool in the cardiac catheterization laboratory that not only guides the decision for PCI in intermediate lesions but also likely improves outcomes in patients undergoing multivessel PCI. FFR is applicable in a broad range of clinical settings and has been shown to be cost effective. The large, randomized FAME study should provide important data regarding the role of FFR in patients with multivessel coronary disease undergoing PCI with drug-eluting stents. ■

William F. Fearon, MD, is Assistant Professor, Division of Cardiovascular Medicine Stanford University Medical Center, in Stanford, California. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Fearon may be reached at (650) 725-2621; wfearon@stanford.edu.

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