Assessing Intermediate Coronary Lesions: More than Meets the Eye

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William F. Fearon, MD

Division of Cardiovascular Medicine, Stanford University Medical Center, Stanford, CA

Address for Correspondence:
William F. Fearon, MD
Director, Interventional Cardiology
Associate Professor of Medicine
Stanford University Medical Center
300 Pasteur Drive, H2013
Stanford, CA 94305
Phone: 650 725-2621
Fax: 650 725-6766
Email: wfearon@stanford.edu

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Although invasive coronary angiography traditionally has been considered the reference standard for diagnosing coronary artery disease, its limitations are being highlighted with increasing frequency.\textsuperscript{1} This is particularly evident in patients with intermediate or moderate coronary artery lesions. For this subset of narrowings, a number of adjunctive, invasive techniques have been proposed to improve the diagnostic accuracy of the coronary angiogram.

In landmark work by Lance Gould and colleagues, coronary flow reserve (CFR) defined as hyperemic coronary flow divided by resting coronary flow, was first proposed as a method for evaluating the functional significance of intermediate stenoses.\textsuperscript{2} However, CFR by definition interrogates the status of the entire coronary circulation, both the epicardial vessel and the microcirculation. In patients with microvascular dysfunction, for example from diabetes or a past myocardial infarction, CFR will be abnormal, thus limiting its application for identifying ischemia-producing epicardial disease. CFR is also limited by its lack of a normal value in any given patient or vessel. For example, in one patient a value of 3 may be normal, while in another patient a value of 5 is normal. A final limitation of CFR is its variability or lack of reproducibility; because resting flow is a component of its definition, changes in resting flow which occur with hemodynamic perturbations can dramatically affect CFR.\textsuperscript{3,4} For these reasons, CFR has fallen out of favor for invasively evaluating intermediate coronary lesions.\textsuperscript{5}

Others have proposed intracoronary anatomic evaluation with techniques such as intravascular ultrasound (IVUS).\textsuperscript{6} IVUS provides improved morphologic assessment of intermediate coronary disease, but its ability to predict future events\textsuperscript{7} or to correlate with other measures of myocardial ischemia has been disappointing\textsuperscript{8}, because it fails to account for one of the most important
determinants of the ischemic potential of an intermediate lesion, the maximum achievable flow across the stenosis.

Approximately 20 years ago, Nico Pijls and Bernard De Bruyne introduced a coronary pressure wire-derived index for interrogating intermediate coronary lesions termed fractional flow reserve (FFR).\textsuperscript{9,10} FFR is defined as the maximum myocardial flow down a vessel in the presence of a stenosis compared to the maximum flow in the hypothetical absence of the stenosis. By administering a vasodilator to induce maximal flow, myocardial resistance is minimized and flow becomes proportional to pressure. In a normal epicardial vessel there is very little loss of pressure along its course resulting in equal distal and proximal coronary pressures. Therefore, FFR can be determined by inducing maximal hyperemia and then comparing the mean distal coronary pressure (a reflection of the maximum myocardial flow in the presence of a stenosis) measured with a coronary pressure wire to the mean proximal coronary pressure (a reflection of the maximum myocardial flow in the hypothetical absence of the stenosis) measured with a guiding catheter at the ostium of the coronary artery.

FFR has a normal value of 1.0 in every patient and every vessel. It has a narrow ischemic threshold of 0.75-0.80, below which the potential for significant myocardial ischemia is extremely high and above which it is very unlikely. Because the measurement is made during maximal hyperemia, the effect of changes in resting hemodynamics is eliminated.\textsuperscript{3,4} FFR assumes that microvascular resistance is minimized during maximal hyperemia and constant in the presence and hypothetical absence of the stenosis; therefore, FFR is a specific measure of the contribution of the epicardial stenosis to the potential for myocardial ischemia and independent
of the microvasculature. FFR informs the operator about the expected gain in myocardial flow should the epicardial stenosis be relieved. For these reasons, FFR has become a very useful technique for identifying which epicardial lesions are responsible for producing myocardial ischemia, which are more likely to cause future cardiac events, and which are therefore most likely to result in a benefit for the patient if revascularized.\textsuperscript{11,12,13} A nonischemic FFR value in a particular vessel rules out significant epicardial atherosclerosis, but it does not rule out the potential for ischemia occurring in the microvasculature.

For many years it has been recognized that myocardial ischemia can result from other coronary circulatory pathology beyond epicardial artery stenosis. One of these mechanisms is microvascular dysfunction. To address the limitations of CFR and to complement FFR’s ability to assess the epicardial vessel, ten years ago the index of microcirculatory resistance (IMR) was introduced as a method specifically for evaluating the microvasculature.\textsuperscript{14} IMR is measured at the same time as FFR, with the same coronary pressure wire. With appropriate software, the pressure sensor acts as a distal thermistor and the shaft of the wire acts as a proximal thermistor allowing the calculation of the mean transit time of injected room temperature saline, which is inversely proportional to coronary flow. IMR is calculated by dividing distal coronary pressure by the inverse of the mean transit time during maximal hyperemia and represents the minimal achievable resistance in a particular myocardial territory. It correlates well with true microvascular resistance;\textsuperscript{14} it is reproducible and independent of hemodynamic perturbations;\textsuperscript{4} it is specific for the microvasculature and not affected by epicardial stenosis (as long as collateral flow is accounted for);\textsuperscript{15,16} and it has been found to be predictive of adverse outcomes in disease states affecting the microvasculature, such as acute myocardial infarction.\textsuperscript{17}
In this issue of *Circulation*, Echavarria-Pinto and colleagues measured FFR, CFR and IMR in 78 patients (91 vessels) with intermediate coronary lesions. One of their main findings was that in approximately one half of the lesions with an FFR above the ischemic threshold, CFR was abnormal, and in one third, IMR was abnormal. The meaning of the abnormal CFR is difficult to interpret because it is unclear to what extent epicardial disease and microvascular dysfunction combined to lead to the abnormal CFR. The abnormal IMR suggests that in one third of patients with intermediate epicardial disease, which is not physiologically significant, microvascular dysfunction is present. When considering this prevalence of microvascular dysfunction, it is important to note that the population studied had a high rate of predisposing factors (54% with previous myocardial infarction, 73% with hypertension, 69% with dyslipidemia and 26% with diabetes).

Another finding in this study was that an abnormal FFR, indicative of significant epicardial disease, did not imply abnormal microvascular function, as most of these vessels had a normal IMR. This is not too surprising given that the authors only studied intermediate coronary lesions. In order for an intermediate lesion to generate a significant pressure gradient and low FFR, the flow across the stenosis must be quite high. One would anticipate that if the authors also interrogated more severe stenoses, they might have found examples of lesions with both a low FFR and a high IMR, indicative of significant epicardial disease and microvascular dysfunction. A clinical scenario where this can be seen is in patients who receive fibrinolytic therapy for an acute myocardial infarction and subsequently undergo coronary angiography; the residual tight stenosis can have an abnormal FFR and the partially infarcted myocardium can
have a high IMR. The select population in the current study may also explain why a correlation was seen between FFR and IMR. A similar study by Melikian et al analyzed vessels with a broader range of stenosis severity (including true normal vessels without atherosclerosis and with a normal FFR and normal IMR), and did not find a correlation between FFR and IMR. Both findings argue against the hypothesis that atherosclerosis is a diffuse process involving both larger epicardial vessels and the microvasculature simultaneously.

Finally, the authors attempt to explain the reasons for unexpected findings between FFR and CFR in certain vessels. They argue that lesions with a low FFR and high CFR (>2.0) represent examples of a focal epicardial stenosis, in which case there is less effect on CFR because of the absence of diffuse epicardial disease and/or microvascular dysfunction. They suggest that revascularization may not be as beneficial in this group. Another explanation for this finding is that the CFR, although >2.0, is in fact abnormal. As mentioned previously, a CFR of 3.0 may be quite abnormal in a vessel which normally has a CFR of 5.0. This later hypothesis is supported by a recent prospective, randomized study including patients with focal disease and low FFR who did benefit from revascularization.

In the group of patients with a high FFR and low CFR, the authors attribute the findings to both diffuse epicardial atherosclerosis and microvascular dysfunction. Clearly patients with pure microvascular dysfunction will fall into this category, and indeed an abnormal IMR was found in many of these patients. However, some vessels did have a normal IMR, abnormal CFR and normal FFR. If diffuse atherosclerosis was the culprit, one would expect FFR to be abnormal as well. One of the advantages of FFR is that it interrogates the entire epicardial vessel and mild
diffuse atherosclerosis, which is not visible angiographically can still result in an abnormal FFR.\textsuperscript{20} Another explanation for the abnormal CFR despite the normal FFR and normal IMR relates to the dependence of the CFR calculation on resting flow. The authors found a significantly higher “resting” coronary flow (shorter mean transit time) in this cohort compared to the cohort with a high FFR and high CFR, while the hyperemic flow was similar; the higher “resting” flow, which can result from changes in heart rate, blood pressure and left ventricular contractility leads to the lower CFR, which may not be a reflection of pathology, but a limitation of the measurement.

In summary, when invasively assessing intermediate coronary disease, there is more to it than meets the eye; visual interpretation of the coronary angiogram is insufficient. Determining FFR provides information regarding the contribution of epicardial coronary disease to myocardial ischemia, while IMR and other measures of microvascular function provide further insight, particularly when FFR is in the nonischemic range.

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