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EDITORIAL COMMENT

FFR and Coronary Flow Reserve

Friends or Foes?*

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The FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study has re-emphasized the importance of assessing functional consequences of coronary stenoses (1,2). In that multicenter trial involving 1,005 patients with multivessel coronary artery disease (CAD), percutaneous coronary interventions (PCI) guided by functional assessments of coronary stenoses was associated with a significantly lower 2-year morbidity and

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mortality as compared to PCI guided only by coronary anatomy (1,2). The functional assessments were based on the fractional flow reserve (FFR), an invasive approach, which measures the stenosis-related decline in distal coronary pressure during maximum hyperemia. The normal coronary vessel exerts little if any resistance to flows even during hyperemia, so that the coronary pressure is fully maintained throughout the length of the epicardial coronary artery and the distal coronary pressure equals the central aortic pressure. In the presence of a focal coronary stenosis, however, the distal coronary pressure declines during hyperemia as a function of the stenosis severity; stenoses with FFRs <0.75 or <0.80 have been shown to induce ischemia and, hence, are defined as functionally significant. Methodologically, the FFR depends only on the distal to proximal pressure difference in the coronary vessel. The index is relatively independent of heart rate and blood pressure (3). It thus differs from other measures of functional significance of coronary stenosis like the coronary flow reserve (CFR) or stress-rest myocardial perfusion imaging (MPI), which compare hyperemic to resting flows or evaluate the effects of coronary stenosis on the relative distribution of myocardial blood flow.

Nevertheless, estimates of the functional significance of coronary stenoses by different techniques would be expected to be comparable. Indeed, initial comparison studies reported closely correlated values of FFR and MPI in patients with mostly single-vessel disease (4), yet, this agreement no longer holds for comparisons in patients with multivessel disease. For instance, FFR and MPI findings agreed in only about 40% of patients with 2- or 3-vessel disease (5,6), mostly because MPI was found to underestimate the extent of CAD. The lack of agreement was not necessarily surprising; values of FFR reflect the downstream pressure gradient in a given coronary artery whereas MPI compares the functional stenosis severity between coronary vessels; namely, stress-induced perfusion defects are related to the myocardial region with the highest perfusion, assuming that the upstream coronary artery is normal when in fact it is also frequently diseased although less severely than the comparison vessels.

In contrast, assessments of the stenosis severity by CFR do not depend on such intervessel comparison but on the maximum achievable flow relative to baseline flow in the very same vessel. Estimates by CFR would, therefore, be expected to agree well with those by FFR. Initial comparison studies again reported such close correlation (7). Yet, the findings in that study were based on patients with mostly single-vessel disease; subsequent investigations in patients with multivessel

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disease failed to confirm such close agreement; in fact, substantial disagreements between both measurements were noted (8,9). These disparities are at the center of the elegant studies by Johnson et al. (10) as reported in this issue of the *iJACC*.

The investigators seek to answer the question whether the disparity in measured indexes results from methodological shortcomings or is explained by disease-related disturbances of the coronary circulatory function. Collecting all reported intrapatient comparisons of CFR and FFR, they find a statistically significant, but only modest correlation between both measures of stenosis function, and thus reconfirm the limited concordance of the 2 functional parameters. In a second step, Johnson et al. (10) compare in 1,500 consecutive studies, performed in their own institution, qualitative Rb-82 positron emission tomography evaluations of stress-induced perfusion defects and CFRs. Again, they find a similarly modest although statistically significant correlation between both measures of coronary function. Two possible explanations for the observed disparities emerge: 1) disease of the "normal reference vessel" as would be expected for MPI; and 2) diffuse disease of the epicardial conduit vessel or isolated disease of the coronary microvasculature, or both. The potential implications of diffuse disease and of microvascular function on the CFR and the FFR are then tested in a theoretical model of varying degrees of diffuse conduit vessel disease with a single focal proximal left anterior descending coronary artery lesion superimposed. In addition to the actual stenosis severity, the model identifies diffuse conduit vessel disease and disease of the resistance vessels as significant contributors to observed FFR values. Importantly, although suspected previously (11) but now articulated more clearly by Johnson et al. (10), the fluid-dynamic effect of a discrete stenosis can only be fully appreciated if the resistance along the conduit vessel and of the microvessels is maximally reduced, or, in other words, if true maximum hyperemia can be achieved (12).

The investigators present compelling arguments for why maximum hyperemic flows are frequently not achieved so that FFRs often do not fully reflect the true functional impact of focal coronary lesions. Specifically, they point out that CFRs reported in the literature for angiographically "normal" vessels in patients with CAD are substantially lower than those in young normal volunteers, an observation the researchers attribute to diffuse epicardial coronary disease and/or microvascular disturbances that they assume to involve also those vessels with focal stenosis and that attenuate the hyperemic response to pharmacological vasodilation. Diffuse disease of the epicardial conduit vessel here refers to nonobstructive atherosclerotic disease with irregular luminal surfaces or mild stenoses that raise the resistance to high-velocity flows and attenuate the hyperemic response. This resistance to high-velocity flow causes a progressive fall in coronary pressure along the epicardial artery, which in 1 study averaged 10 mm Hg, that translates into an average FFR of 0.89 (13). In isolated microvessel disease, due to remodeling or rarefication, however, distal coronary pressure is presumably maintained so that the FFR approaches unity, yet responses to vasodilator stimuli are impaired and maximum hyperemia cannot be achieved (8). Immediate post-PCI measurements of the FFR lend support to the investigators' assumption of a coexistence of diffuse conduit vessel and microvessel disease with focal coronary stenosis. For example, the FFR measured immediately after successful PCI remained in about one-third of all patients <0.9 (14); that is, the average value found in diffusely diseased epicardial conduit vessels (13).

If the claim of these investigators is correct, then the widely employed FFR threshold of 0.75 to 0.80 for an ischemia-inducing lesion underestimates the true functional significance of a coronary stenosis, although they acknowledge its clinical value in "populations with sufficient (multivessel) diffuse disease." On the basis of findings obtained with their theoretical model, Johnson et al. (10) develop a conceptual framework that describes the interactions between estimates of the FFR and diffuse conduit and resistance vessel function as determinants of vascular resistance. Such conceptual framework has intriguing implications for image-based approaches for detecting and characterizing CAD, which the following examples in single-vessel and in balanced CAD serve to illustrate.

Stress-induced defects in "normal coronary arteries." The diagnostic performance of stress-rest MPI with single-positron emission computed tomography or positron emission tomography is typically judged against findings on invasive coronary angiography. Greater than 50% or 70% focal stenoses are considered "obstructive" and, thus, are defined as functionally significant. Accordingly, stress-induced perfusion defects without an angiographic correlate are defined as "false positives." Yet, diffuse conduit vessel disease without a focal stenosis but with a FFR of only 0.75 for example, namely, below the ischemia-inducing threshold (13), clearly can in-

duce a perfusion defect, especially when an adequate level of hyperemia can be achieved. Hence, stress-induced defects, even in the absence of obstructive stenoses, should be considered "true positive."

Normal MPI in advanced CAD. Balanced triple-vessel disease frequently serves as explanation for an apparently normal MPI in patients with advanced CAD. Such explanation assumes that obstructive CAD is of similar severity comparable in all coronary vessels. However, there may be another equally plausible explanation: diffuse but nonobstructive atherosclerosis and microvessel disease. Accordingly, even in the presence of an angiographic "obstructive stenosis," the vasodilator response is severely impaired and insufficient to produce a trans-stenotic pressure gradient, so that the FFR approaches unity while, paradoxically, the CFR is low as the hyperemic flow response is markedly diminished, and the relative distribution of myocardial blood flow remains unchanged from stress to rest.

As both scenarios suggest, even though values for CFR and FFR are at opposing ends of the normal to abnormal spectrum, when combined, they more adequately reflect the functional impact of advanced coronary atherosclerosis. Thus, as Johnson et al. (10) conclude, the disparity between different measures of stenoses significance cannot be explained by methodologies but reflects differences in the overall coronary pathophysiology. The disparity between FFR and CFR also has implications and offers opportunities for therapy targeting and for monitoring therapy responses. For example, decreases in stress perfusion defects associated with aggressive treatments are typically ascribed to improvements in stenosis severity. Yet, one could envision also an increase in perfusion defect size and severity as an indicator of treatment success; if, for example, the treatment strategy selectively improves the microvascular reactivity, allowing higher levels of pharmacologically stimulated hyperemia, then the trans-stenotic pressure gradient is likely to increase for the same focal stenosis and result in a lower FFRs. Therefore, as also suggested by the researchers, combining both measures of stenosis severity will result in a more comprehensive characterization of the pathophysiological state of a coronary artery. It would also offer an opportunity for defining and therapeutic targeting diffuse coronary atherosclerosis and microvessel disease, both highly prevalent in patients with advanced CAD (15,16).

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