Editorial

Instant Wave-Free Ratio or Fractional Flow Reserve for Hemodynamic Coronary Lesion Assessment?

Yes, Just Do It!

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When you come to a fork in the road, take it.
—Yogi Berra[1]

Since the introduction of the instant wave-free ratio (iFR) in 2012,[2] the field of coronary physiology has undergone a quantum leap in scientific progress, vigorous debate, and multitude of scientific publications. Although fractional flow reserve (FFR) is based on a plethora of data and well-conduced randomized trials demonstrating substantial clinical benefit,[3] its uptake in daily practice has been limited. A potential reason for this may be the somewhat cumbersome technical aspects of the procedure, including the need for hyperemia. Interestingly, although much of the physiological information is present in the resting gradient, the use of that data point has been largely ignored, predominantly because hyperemia was considered a sine qua non for the proper assessment of a coronary stenosis.[4]

See Article by De Rosa et al

iFR represents a diastolic resting index that allows the assessment of coronary lesions during the phase in the cardiac cycle where microvascular resistance is at its lowest, allowing for increased myocardial perfusion and coronary flow.[2] Although microvascular resistance during resting conditions is not as low and coronary flow not as high as during pharmacological hyperemia, iFR may still be sufficient for clinical decision-making under most circumstances. Initial studies comparing iFR against FFR as a reference standard demonstrated good correlation between the 2 indices,[2] although subsequent analyses varied with respect to iFR diagnostic accuracy.[5] A pooled analysis showed a ≈80% overall diagnostic accuracy of iFR[6] which has been widely accepted as an accurate estimate (although the actual correlation can vary based on the patient population studied). The present meta-analysis by De Rosa et al in this issue of *Circulation: Cardiovascular Interventions* demonstrates excellent correlation of iFR with FFR of 0.798 (0.78–0.82; $P<0.001$) and a good diagnostic performance of iFR to identify FFR-positive coronary stenoses with an area under the curve of 0.88 (0.86–0.90; $P<0.001$).[7]

Even though most analyses demonstrate a relatively good diagnostic accuracy for iFR, almost all of the debate surrounding the diagnostic performance of iFR has focused on discrepant iFR/FFR values and associated patient outcomes. Initial sentiment suggested that iFR discordance naturally implied inferiority of that index to FFR which has been backed by a large body of literature and clinical experience and some proposed the concept of a pyramid of accuracy in which FFR is placed on top and above all resting indices.[8] More recent evidence, including the present study, indicates that the diagnostic accuracy of iFR and FFR is very similar and statistically not different when compared with an independent ischemia test such as positron emission tomography. This may be partially related to the difficulty of defining true myocardial ischemia with any diagnostic test but also to the fact that many discordant iFR/FFR pairs are not really discordant. Both FFR and iFR are physiological markers of myocardial ischemia which is not a binary measure but a biological variable with a risk continuum across its spectrum.[9] Therefore, both FFR and iFR are most useful when clearly positive or negative. Around their respective cutoff values, the reproducibility of each measurement may be as low as 50%,[10] similar to a coin toss. In other words, when the first measurement is within a few points of the cutoff value and the test is repeated, there is as much as a 50% chance of the opposite finding. Similarly, when iFR and FFR disagree close to their cutoff values, there may not be true discordance but just a misclassification in a binary test because of the proximity to the cutoff point. Although the implementation of a cutoff value is of great importance in the conduct of clinical trials and subsequent guideline recommendations, its use in clinical practice has to incorporate the concept of the ischemic risk continuum and revascularization decisions should be based on clinical circumstances, including the degree of ischemia.

This meta-analysis elegantly demonstrates that truly discordant iFR/FFR results (where one index is clearly abnormal and the other clearly normal) are relatively uncommon circumstance. When it happens, it is most often in the setting of an abnormal FFR in the absence of a significant resting gradient, that is, iFR is nonischemic. This may be because of a mild-to-moderate coronary stenosis in the setting of a healthy microcirculation that is capable of a substantial increase in coronary flow, creating a significant pressure gradient and therefore resulting in a low FFR value. Whether coronary revascularization is beneficial in this setting remains an unanswered question, although patients with preserved coronary flow reserve (CFR) have been shown to have a good clinical prognosis despite the presence

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(*Circ Cardiovasc Interv*. 2018;11:e006284.
DOI: 10.1161/CIRCINTERVENTIONS.117.006284.)

***Circ Cardiovasc Interv* is available at**
http://circinterventions.ahajournals.org
DOI: 10.1161/CIRCINTERVENTIONS.117.006284

of coronary artery disease.[11] A recent clinical study among patients with mild-to-moderate coronary stenoses undergoing both flow and pressure measurements focused on the patient population with discrepant iFR/FFR values.[12] There was an excellent correlation between iFR and CFR such that patients with abnormal FFR and normal iFR typically had a preserved CFR that was numerically similar to CFRs among healthy controls. These findings suggest that in the presence of an iFR/FFR discordance, the true ischemia-producing potential of a stenosis may be better characterized by iFR.

In a recent study of 374 patients with 821 lesions with available iFR and FFR data in whom revascularization was deferred and the cohort followed for 2 years, both FFR and iFR showed a significant nonlinear association with major adverse cardiac events.[13] Deferred lesions with abnormal FFR or iFR values showed an exponentially increased risk of major adverse cardiac events when compared with nonischemic FFR and iFR values. FFR and iFR had a comparable discriminant ability in the prediction of major adverse cardiac events. Among patients with discordant iFR/FFR measurements, the prognosis was generally good and similar to the patient population with nonischemic FFR and iFR values, indicating that the decision-making process is similarly safe with FFR and iFR. Patients with concordant low iFR and FFR values had a 3-fold higher major adverse cardiac events rate, predominantly because of ischemia-driven revascularization. Two large randomized trials demonstrate noninferiority and similar clinical outcomes with iFR when compared with FFR.[14,15] However, both the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization) and iFR SWEDEHEART trials (The Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome) adopted exclusive randomization into FFR- or iFR-guided strategy groups and did not permit the simultaneous measurement of both indices to avoid bias. Thus, no information can be discerned from these data sets with respect to iFR/FFR discordant patients. Assuming that most of the discordance would occur close to the ischemic cutoff points where clinical event rates are relatively low, it has been estimated that as many as 290 000 patients would be required to demonstrate a significant difference between iFR and FFR if such a difference exists.[16]

From a practical standpoint, the question remains what the clinical consequence of these discrepant indices means for patient care and whether there is value in measuring both iFR and FFR. For most clinical scenarios, measuring one or the other index should be sufficient for adequate guideline-based decision-making based on one individual's comfort level for each test. However, in some clinical circumstances, the argument can be made to obtain both measurements (which is very simple and fast from a technical standpoint) to get a rough estimate of coronary flow. This concept is called pressure-bounded CFR[17] and may aid in our understanding of microcirculatory function and the underlying physiological principles of coronary pressure and flow measurements. The available clinical evidence strongly supports the current practice of an ischemia-guided revascularization strategy, in which lesions with abnormal invasive physiology benefit from revascularization, whereas lesions with negative physiology can be safely deferred. It seems that this basic principle holds true regardless of whether FFR or iFR is used for clinical decision-making. So when you get to the fork in the road, take it—any physiological assessment of intermediate lesions among patients with stable angina is preferable to sole angiographic guidance.

Sources of Funding

Dr Jeremias received institutional funding (unrestricted education grant) and serves as a consultant for Volcano/Philips and Abbott Vascular; and serves on the speaker's bureau and as a consultant to Opsens Medical and Boston Scientific.

Disclosures

None.

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KEY WORDS: Editorials ■ area under the curve ■ coronary artery disease ■ myocardial ischemia ■ percutaneous coronary intervention ■ prognosis

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Circ Cardiovasc Interv. 2018;11:e006284
doi: 10.1161/CIRCINTERVENTIONS.117.006284
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7640. Online ISSN: 1941-7632