Journal of the American Heart Association

EDITORIAL

Understanding Fractional Flow Reserve/ Instantaneous Wave-Free Ratio Discordance Can Provide Coronary Clarity

David M. Tehrani, MD, MS; Arnold H. Seto, MD, MPA

Functional evaluation of coronary artery stenoses using fractional flow reserve (FFR) is considered the gold standard given its relation to clinical outcomes. More recently, nonhyperemic pressure-derived ratios are increasingly used preferentially over FFR as they eliminate the time, cost, and adverse effects of pharmacologic hyperemia. The best validated index is the resting instantaneous wave-free ratio (iFR), which measures the pressure ratio during a specified period of diastole when the coronary resistance is relatively minimized and stable. Two large randomized clinical outcome trials, DEFINE-FLAIR (functional lesion assessment of intermediate stenosis to guide revascularisation) and IFR-SWEDEHEART (spontaneous wave-free ratio versus fractional flow reserve to guide PCI),[1,2] demonstrated that percutaneous coronary intervention guided by iFR ≤0.89 was noninferior to percutaneous coronary intervention guided by FFR ≤0.80 in major adverse cardiac events at 1, 2, and now 5 years.

See Article by Kovarnik et al.

On average, 20% of patients will have discordant iFR and FFR values, leading some to question whether they can rely on iFR alone for clinical decision making. The observational outcome studies of iFR/FFR discordance to date have all suggested that clinical outcomes are only impaired when both FFR and iFR are abnormal, reinforcing that one test is enough for clinical decision making.[3] However, measuring both FFR and a nonhyperemic pressure-derived ratio may provide additional information about a stenosis and its subtended myocardium.

Not until recently have the reasons for discordance between FFR and iFR been evaluated with large prospective data sets. Dérimay et al performed a post hoc analysis using data from the CONTRAST (Can cONTrast Injection Better Approximate FFR compAred to Pure reSTing Physiology?) study, where they found iFR and FFR agreement in 79.4% of patients.[4] iFR was more frequently negative than FFR, with FFR+/iFR– measurements in 11.8% compared with FFR–/iFR+ measurements in 8.9%. Unsurprisingly, discordance was more frequently found immediately on either side of 0.80 FFR cut point. Multivariable analysis suggested that proximal stenosis, increased stenosis severity, younger age, and slower heart rate were associated with FFR+/iFR– discordance, whereas lack of β blockade, older age, and less severe stenosis were predictors of FFR–/iFR+.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Tomas et al evaluate the predictors of FFR/iFR discordance in the large prospective

Key Words: Editorials ■ discordance ■ fractional flow reserve ■ hemodynamics ■ instantaneous wave-free ratio ■ instantaneous wave-free ratio pull back

Correspondence to: Arnold H. Seto, MD, MPA, Long Beach Veterans Administration Medical Center, 5901 E 7th St, 111C, Long Beach, CA 90822. Email: arnold.seto@va.gov
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international FiGARO (FFR versus iFR in assessment of lesion hemodynamic significance and explanation of their discrepancies) study.[5] The authors measured FFR and iFR in 1884 nonculprit acute coronary syndrome vessels or from patients with chronic stable angina. The study population was then divided into 3 groups based on hemodynamically positive and negative FFR and iFR values: FFR/iFR concordant, FFR+/iFR– discordant, and FFR–/iFR+ discordant. In a subset of patients, coronary flow reserve (CFR) was measured, whereas another subset was evaluated for polymorphisms in endothelial NO synthetase and heooxygenase-1 at-risk patients ($ENOS_r$ and $HO\text{-}1_r$, respectively). The authors hypothesized that such polymorphisms could predict FFR/iFR discordance given their role in causing variable or submaximal hyperemic responses after adenosine administration, potentially leading to a false-negative FFR.

The results of the present study affirmed that FFR/iFR discordance occurs in ≈20% of evaluations, with the largest discordance occurring around the FFR threshold of 0.80 (R=0.33; P<0.0001). CFR was only evaluated in 343 lesions (of 1884 FFR/iFR pairs), but was found to be better associated with iFR (R=0.56; P<0.0001) than FFR (R=0.36; P<0.0001). Multivariable logistic regression analysis found sex, age, and right coronary artery lesion location as predictors for FFR+/iFR– discordance, whereas hemoglobin level, smoking, and renal insufficiency were predictors for FFR–/iFR+ discordance. Among the 219 patients who had ENOS or HO-1 polymorphisms evaluated, 67 (30.6%) had FFR/iFR discordance. The FFR–/iFR+ type of discordance was significantly more frequent in patients with both at-risk types of polymorphisms ($ENOS_r$+$HO\text{-}1_r$) compared with FFR+/iFR– discordance (8 patients or 24.2% versus 2 patients or 5.9%; P=0.03).

What are the important findings from these data? First, it is important to state that these findings are not meant to suggest any difference in clinical outcomes based on FFR/iFR discordance or the presence of polymorphisms. With that said, these data reaffirm the work by others that FFR/iFR discordance occurs ≈20% of the time and that CFR correlates better with iFR than FFR.[6,7] The present study found that right coronary artery lesions are correlated to FFR+/iFR– discordance, whereas prior studies found that left main or proximal left anterior descending coronary artery lesions were more correlated with this type of discordance.[3,8] In fact, left main or proximal left anterior descending coronary artery lesions were one of the strongest predictors for FFR+/iFR– discordance in prior studies, presumably because such stenoses are associated with higher coronary flow reserve given the large amount of myocardium supplied. Why right coronary artery stenoses were instead correlated to FFR+/iFR– discordance in the current study is unclear.

Higher CFR values were seen in the present study for those with FFR+/iFR– discordance compared with FFR+/iFR+ and FFR–/iFR– concordant groups. In contrast, Cook et al showed high CFR values were similar in the FFR+/iFR– and FFR–/iFR– discordant groups. The authors of the present study suggest that this is related to the lower CFR values in their FFR–/iFR– group given their older population, increased diabetes prevalence, and higher proportion of nonculprit patients with acute coronary syndrome compared with the study by Cook et al.[6]

The FFR–/iFR+ type of discordance appears to be largely related to increased microcirculatory resistance. Predictors in this study, including smoking and decreased renal function, are well known to be related to endothelial dysfunction, leading to basal coronary flow that does not augment adequately with hyperemia. The most novel component of this study was the evaluation of the polymorphisms of endothelial NO synthetase and heooxygenase-1 in at-risk patients for predicting discordance. However, the rate of FFR/iFR discordance did not differ based on the risk profile of either the ENOS or HO-1 genes. The authors did find the FFR–/iFR+ discordance type was significantly more frequent in patients with both risk type of polymorphisms ($ENOS_r$+$HO\text{-}1_r$) compared with the FFR+/iFR– discordance. Although this mechanistically is logical given the inability to create sufficient hyperemia in the presence of these polymorphisms, the number of patients evaluated for the polymorphisms and the numbers included in the discordance groups are small. As the authors suggest, no clinical implications can be assumed at this time even as this result remains thought provoking.

There are multiple limitations to this study, which the authors describe. The first is that the data on genetic polymorphisms are limited and are only hypothesis generating. Similarly, the number of lesions with concomitant CFR data is also limited, which would have been helpful in understanding why right coronary artery rather than proximal left lesions were associated with FFR+/iFR– discordance. To this end, this study also included a relatively high number of patients with acute coronary syndrome (≈13%), which can affect the evaluation of nonculprit lesions in terms of coronary flow.[9]

Most of the suggested predictors for why patients have FFR/iFR discordance are not easily modified. Although it becomes important to understand that the factors of older age, smoking, and chronic kidney disease may be complicating the interpretation of FFR and iFR values, it would be ideal if identifying discordance helped in making clinical decisions. Patients

with concomitant abnormal FFR and iFR have a significantly increased risk of major adverse cardiac events compared with those with normal FFR and iFR values (hazard ratio, 7.7; $P<0.001$) based on data from the 3V FFR-FRIENDS (3-vessel fractional flow reserve for the assessment of total stenosis burden and its clinical impact in patients with coronary artery disease) study.[3] In this study, lesions with FFR and iFR discordance were not associated with increased major adverse cardiac events compared with those with normal values for both. Future prospective studies should evaluate how discordance between FFR and iFR predicts clinical outcomes, but also consider whether the incremental addition of a positive iFR to a positive FFR or a negative iFR to a negative FFR would lead to better revascularization decisions.

So, how can FFR/iFR discordance actually improve our understanding rather than add confusion? Discordance can help distinguish between diffuse and focal coronary artery disease. Warisawa et al compared FFR/iFR discordance with the pattern of coronary artery disease based on iFR pull back.[10] They found that diffuse disease was more likely to be related to FFR–/iFR+ discordant results (81.6% [31 of 38 lesions with this pattern of disease]). This finding may be explained by the pressure loss across a stenosis being related to both separation and frictional components. For diffuse disease, the pressure losses predominately arise from the frictional component and are directly proportional to coronary flow. For focal lesions, separation forces (where flow is squared) dominate. The result is that a hyperemic index, like FFR, is more likely to be positive for focal lesions, which are easier to relieve with stenting, whereas iFR is more likely to be positive in diffuse disease. The focal versus diffuse pattern of disease can more easily be assessed with pressure wire pull back, but FFR/iFR discordance has a reassuring clinical outcome, as previously discussed.

Should we measure both FFR and iFR? Whether using FFR or NPHR first, if a value is clearly normal or abnormal, there is likely little additional clinical utility of testing with another modality. If near the threshold of significance (on either side), though, one can consider measuring with the other modality for confirmation or reassurance. Additional information can aid the operator by providing either justification for revascularization for simple lesions or reassurance that deferral will be safe in lesions that are more complex or risky (eg, bifurcations and calcified lesions). In other words, measuring both lets the operators pick the result that best fits their clinical judgment.

ARTICLE INFORMATION

Affiliations

Ronald Reagan UCLA Medical Center, Los Angeles, CA (D.M.T.); and Long Beach Veterans Administration Medical Center, , Long Beach, CA (A.H.S.).

Disclosures

Dr Seto has received research grants from Philips and Acist, has received consulting fees from Medtronic and Medicure, and is a speaker for Terumo, General Electric, and Janssen. Dr Tehrani has no disclosures to report.

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