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EDITORIAL

Nonhyperemic Pressure Ratios Versus Fractional Flow Reserve: What to Do With Discordant Results?

Timir K. Paul, MD, PhD; Arnold H. Seto, MD; Christopher J. White, MD

Invasive physiologic indices for the assessment of intermediate coronary lesions have become the standard of care as per guideline recommendations. Hyperemic fractional flow reserve (FFR) is the established physiologic index based on favorable long-term prognostic data.[1–4] Recently, nonhyperemic diastolic pressure ratios (NHPRs) such as instantaneous wave-free ratio (iFR) have emerged as resting physiologic indices that perform comparably to FFR for clinical decision making.[5–8] When the FFR and NHPRs measurements are concordant (NHPRs+/FFR+ or NHPRs–/FFR–), the decision to revascularize is straightforward. However, when the measurements of FFR and NHPR are discordant (NHPRs+/FFR– or NHPRs–/FFR+) (as in ≈20% of cases),[9] the operator is left with a dilemma, as the clinical outcomes of discordant lesions are unclear.

See Article by Lee et al.

Several randomized clinical trials have compared FFR versus angiography and FFR versus iFR for long-term outcomes.[1–4,7,8] The results of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation), FAME-2, and DEFER (Deferral Versus Performance of Percutaneous Coronary Intervention of Functionally Nonsignificant Coronary Stenosis) trials demonstrated the clinical benefit of using FFR to guide revascularization decisions and the safety of deferring revascularization when FFR is negative in intermediate coronary stenoses.[1–4] The DEFINE-FLAIR trial (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization) and the iFR-SWEDEHEART trial (Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome) demonstrated that iFR was noninferior to FFR in clinical outcomes in lesions deferred for revascularization.[7,8] Based on these outcome studies, the 2018 European Society of Cardiology guidelines on myocardial revascularization gave Class IA recommendations for both FFR and iFR to assess the hemodynamic significance of intermediate coronary lesions.[10] Resting indices have become increasingly popular because of more rapid measurement compared with FFR and freedom from adenosine-related costs, symptoms, and heart block. Despite these advantages, the equivalency in clinical outcomes with iFR (and by extension, other NHPRs) has been questioned given the frequent discordance between FFR and NHPRs.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Lee et al investigated the long-term prognostic implications of NHPRs compared with FFR on 5-year clinical outcomes of coronary lesions deferred for revascularization.[11] From the 3VFFR-FRIENDS (3-Vessel Fractional Flow Reserve

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Correspondence to: Timir K. Paul, MD, PhD, MPH, FACC, FSCAI, FAHA, East Tennessee State University, 329 N State of Franklin Rd, Johnson City, TN 37604. E-mail: timirpaul@yahoo.com

For Disclosures, see page 3.

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Nonstandard Abbreviations and Acronyms

FFR	fractional flow reserve
iFR	instantaneous wave-free ratio
NHPR	nonhyperemic diastolic pressure ratio

for the Assessment of Total Stenosis Burden and Its Clinical Impact in Patients With Coronary Artery Disease) registry, the authors analyzed 1024 vessels from 435 patients who had FFR measured, using off-line analysis to derive the various NHPRs at a core laboratory. Of these 1024 vessels, 160 vessels were revascularized based primarily on abnormal FFR values. The primary end point was a 5-year vessel-oriented composite outcome measure, defined as a composite of cardiac death, target vessel-related myocardial infarction, and ischemia-driven revascularization. The outcomes were compared among 3 groups: revascularized with positive FFR ≤0.80 (n=124), deferred lesions with concurrent negative NHPR and FFR values (n=688), and deferred vessels with discordant results (n=57). Among the 3 groups, the cumulative incidence of vessel-oriented composite outcomes at 5 years was 14.8%, 7.5%, and 14.4%, respectively for the revascularized, deferred negative concordant and deferred discordant groups. Despite a prior study from the same registry[12] indicating nearly numerical equivalence among all of the diastolic NHPRs, the present study surprisingly found and excluded 74 vessels (7.2%) with NHPR values that were not consistently classified across the modalities (iFR, resting full-cycle ratio, diastolic pressure ratio), indicating many of these were in the borderline range around 0.89.

The results indicate that the prognostic implications of NHPRs and FFR were similar if the values were concordant positive (measured as ≤0.89 and ≤0.80 respectively) as both would have classified a lesion as requiring revascularization. The discriminant function for 5-year vessel-oriented composite outcomes were similar among NHPRs and FFR (C-index: 0.623–0.641, *P* for comparison=0.215). Deferred lesions with discordant results between NHPRs and FFR demonstrated a significantly higher risk of 5-year vessel-oriented composite outcomes than those with concordant negative results but had no excess risk compared with revascularized lesions. This suggests that deferral of revascularization may be a reasonable option for lesions with discordant results between NHPRs and FFR. The further implication is that measurement of both NHPR and FFR would provide better risk stratification of patients than either measurement alone (as one might be a false positive or negative), though such an inference ignores the continuous nature of the indices and that discordance is more likely within the borderline range.

This study provides a relatively large data set to compare NHPRs and FFR with long-term follow-up.[11] Several inherent if minor limitations to this study are present including (1) nonrandomized design, (2) off-line post hoc calculation of NHPRs, (3) the revascularization decision was mainly based on the FFR value, and (4) lack of blinding. More important, the patient population in this study was anatomically and clinically low risk including mostly stable angina (93.2%) patients with an average SYNTAX score of 15 in revascularized vessels. This resulted in low event and revascularization rates, which might tend to bias toward the null hypothesis that FFR and NHPRs are equivalent. The results of this study may not be generalizable to higher risk patients, such as those with diffuse disease, calcified vessels, or acute coronary syndrome. Further reducing power are the small number of patients with discordant results between NHPRs and FFR (n=57, 6.6%), which is smaller than the 20% seen in several studies including the VERIFY (Verification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in Everyday Practice) study.[9] This may reflect again the lower risk cohort of patients studied. Finally, as revascularization decisions were left to the operator, 53 vessels were not revascularized despite concordant abnormal results in both NHPRs and FFR, and 17 vessels were revascularized despite FFR >0.80, all of which were excluded from the analysis. This may pose significant selection bias especially with the low event rates. As the investigators were not blinded, there was a possibility that investigators chose not to revascularize these subsets of patients anticipating a higher probability of complications with more complex anatomy.

The prognostic importance of discordant results between FFR and NHPRs in patients with deferred revascularization is controversial. A post hoc analysis of DEFINE-FLAIR trial showed that in patients with left anterior descending artery lesions, iFR-guided deferral of revascularization had significantly reduced event rates compared with FFR-guided deferral.[13] Additionally, the results of the combined DEFINE-FLAIR trial and the iFR-SWEDEHEART trial revealed more lesions were deferred for revascularization based on iFR as compared with FFR without increasing the risk of coronary events.[14] The difference in prognostic implications between these 2 indices may be because of better agreement of iFR with coronary flow reserve.[15] Individual cases where coronary flow reserve is normal and high and FFR is abnormal reflect high flow states in response to adenosine, which pathophysiologically may imply normal

microvascular function and a benign prognosis. The study by Lee et al suggests similar safety outcomes of FFR and all of the diastolic NHPRs in guiding the deferral of revascularization, extending the results of DEFINE-FLAIR and iFR-SWEDEHEART to the resting full-cycle ratio and diastolic pressure ratio.[11] Without measurement error, resting full-cycle ratio and diastolic pressure ratio can be used interchangeably with iFR for deferral of revascularization, and extending the clinical recommendations of FFR and iFR to other diastolic NHPRs would be reasonable in daily clinical practice.

Where does this study leave us? Even if the outcomes are similar between NHPRs and FFR, this study is unable to distinguish whether NHPR or FFR should be used for a clinical decision making in cases with discordant results. The following algorithm could be considered when evaluating intermediate coronary lesions in the catheterization laboratory.

1. Start with either FFR or any one of the NHPRs (preferably iFR as it has prognostic data from randomized clinical trials, but whatever commercial system you have available). Which to choose first depends on the availability, local set-up, and relative contraindication of using adenosine (ie, chronic obstructive pulmonary disease, asthma, heart block, caffeine use).
2. Perform second index if:
   a the clinical suspicion for symptoms related to the lesion is high but either FFR or NHPR is negative.
   b or the initial measurement is borderline (0.75–0.85 FFR, 0.85–0.93 NHPR).
3. If the second index is negative, defer revascularization (concordant negative).
4. If the second index is positive, (discordant) then you have the option to defer revascularization, particularly if the risks of revascularization are high (lesions that are calcified, bifurcation, complex). Performing intravascular imaging with ultrasound or optical coherence tomography to assess plaque morphology and percent diameter or minimal lumen area may be considered both to assess lesion complexity and provide a third measure of potential significance.

Although this study suggests that simultaneous measurement of both NHPRs and FFR would provide better risk stratification of patients when revascularization is deferred, this would not be necessary in all or even most cases. Given the similar safety outcomes of FFR and NHPRs in guiding the deferral of revascularization, this study supports the use of NHPR potentially alone. The choice of selecting 1 physiologic index in the case of discordant results remains uncertain and further studies with a larger sample and longer-term follow-up are needed. To date, there remains no safety signal to argue against using just an NHPR, which will be a relief to the many operators who prefer a faster and simpler measurement.

ARTICLE INFORMATION

Affiliations

From the Division of Cardiovascular Medicine, East Tennessee State University, Johnson City, TN (T.K.P.); University of California Irvine, Irvine, CA (A.H.S.); and Department of Cardiovascular Diseases, The Ochsner Clinical School, University of Queensland, AU and the John Ochsner Heart & Vascular Institute, Ochsner Medical Center, New Orleans, LA (C.J.W.).

Disclosures

None.

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