

EDITORIAL COMMENT

# Resting Versus Hyperemic Coronary Pressure Measurements for Stenosis Evaluation

## The New Kids Have Come to Stay\*

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The physiological assessment of coronary stenosis using fractional flow reserve (FFR) is considered standard practice in the setting of stable ischemic heart disease with epicardial stenosis of equivocal angiographic severity. Despite strong guideline recommendations, however, the use of this index is limited to <10% of eligible procedures (1). Obviously, this represents a drastic underuse of the technology, intuitively leading to frequent misinformed revascularization decisions in daily practice (2). Resting coronary pressure-derived physiological indexes were introduced with the aim of simplifying physiological stenosis assessment and increasing the feasibility of routine physiological assessment in daily practice. These indexes include the instantaneous wave-free ratio (iFR) and the resting distal coronary-to-aortic pressure ratio (Pd/Pa) (3,4). Direct comparisons with FFR as the reference standard have documented 80% overall agreement for these resting indexes with FFR (3-5). Although, considering its position in clinical guidelines, it is conceivable that FFR is applied as a first diagnostic reference standard, there are many reasons why it should not be considered a gold standard reference test (6). FFR was introduced as a

pressure-derived estimate of relative flow reserve (RFR) and is not the same as direct measures of maximal coronary flow or flow reserve that are the critical determinants of myocardial ischemia (7). Discordance of FFR with direct measures of flow occurs in 30% to 40% of cases (8). Because the myocardium thrives on coronary flow and not on perfusion pressure, such discordance illustrates that FFR frequently does not accurately reflect the true impact of the stenosis on coronary perfusion (8-10). Concordantly, the FAME 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2) study documented that the majority of stenoses with abnormal FFR values have uneventful clinical follow-up when managed with medical therapy alone instead of undergoing revascularization (11). Hence, despite the unequivocal clinical benefit of FFR guidance over angiographic guidance of revascularization, it becomes clear that FFR is not a gold standard reference test, neither physiologically nor in terms of prognostic value, and should therefore not be the only reference test used to evaluate novel diagnostic approaches. Comparisons with independent reference tests are crucial to identify the true comparative diagnostic efficiency of iFR and/or Pd/Pa versus FFR. Several investigators have performed such studies, using invasive reference standards such as coronary flow reserve (CFR) and the hyperemic stenosis resistance index, noninvasive reference tests such as myocardial perfusion imaging, and even combinations of both (12-14). These investigations have been unable to identify a diagnostic advantage of using FFR over iFR or Pd/Pa for the identification of functionally relevant coronary

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stenosis, and some studies have even suggested superior diagnostic efficiency of iFR (5,13). However, these studies have been scrutinized for small sample sizes and, in the absence of a true gold standard for myocardial ischemia, for the use of reference standards that themselves are associated with diagnostic uncertainty. In this issue of *JACC: Cardiovascular Interventions*, Hwang et al. (15) report a comparison of FFR, iFR, and Pd/Pa with what many may refer to as the gold standard for myocardial perfusion: positron emission tomography (PET). From PET, the investigators applied several flow-based indexes as reference standard: stress maximal myocardial blood flow (MBF) in target segments, CFR (the ratio of stress to rest MBF in target segments), and RFR (the ratio of stress MBF in target segments distal to a stenosis to stress MBF in a normally perfused area). In 115 patients, the investigators documented no difference in diagnostic efficiency between resting and hyperemic pressure-derived indexes for the identification of stenosis associated with impaired CFR, regardless of whether they used data-derived or clinically validated cutoff values for comparison.

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Also, correlations between FFR, iFR, or Pd/Pa and stress MBF were similar. In contrast, FFR provided slightly higher diagnostic efficiency for the presence of abnormal RFR compared with iFR and Pd/Pa. A purported benefit of RFR is that it would be more stenosis specific than CFR. This follows from the fact that RFR “normalizes” perfusion in the target segments for perfusion abnormalities in reference segments, aiming to correct for the presence of microvascular dysfunction throughout the myocardium and to provide a more stenosis-specific metric of myocardial perfusion. However, this assumption is invalidated by the well-documented heterogeneity of microvascular function between normally perfused territories (16). Hence, the correction in RFR is suboptimal because microvascular function is intrinsically different for each perfusion territory. Direct studies of RFR have focused mainly on its ability to identify FFR-defined functionally significant coronary disease, which has led to equivocal results on the added value of RFR over CFR or MBF for the identification of abnormal FFR (17,18). As mentioned by the investigators, a prognostic value is inferred from studies on FFR, which is a pressure-derived estimate of RFR. In sharp contrast, impaired stress MBF and CFR are unequivocally related to manifestations of myocardial ischemia (19). Similarly, the prognostic value of stress MBF and CFR is undisputable (6-8,10). Taking into consideration the robust data on stress

MBF and CFR and the limitations of RFR as an index, the data from Hwang et al. (15) importantly confirm previous studies showing no clinically relevant difference in diagnostic efficiency among FFR, iFR, and resting Pd/Pa. At least as important, however, is the finding that discordance among all coronary pressure-derived indexes versus PET-derived direct measurements of perfusion occurred in approximately 30% of cases. Because the aim of these indexes is to identify stenosis that pertinently impairs myocardial perfusion, such discordance seems clinically relevant, as it suggests frequent misidentification of true stenosis functional significance by coronary pressure measurements. However, even though diagnostic efficiency of coronary pressure measurements may be lower than direct assessment of coronary flow, clinical benefit of coronary pressure-guided revascularization over angiographic guidance has been well documented (2). Hence, the crux remains that direct measurement of coronary flow is difficult, because PET is scarcely available and invasive flow measurements remain technically challenging. Therefore, coronary pressure measurements are crucial to facilitate widespread adoption of physiology-guided interventions and thereby to benefit as many patients as possible. It is also in this light that iFR and Pd/Pa can have a disruptive added value in clinical practice by providing access to physiological guidance of revascularization to at least part of the 90% of patients still undergoing angiography-guided revascularization despite the strong body of evidence confirming its inferiority to physiological guidance. The findings of Hwang et al. (15) help ease the minds of the critics: as far as we can now appreciate, no diagnostic difference exists between resting and hyperemic coronary pressure-derived indexes, even when using PET as the reference standard. Whether this equivalence in diagnostic efficiency culminates into equivalent outcomes after FFR-guided or iFR-guided intervention will be elucidated in short order, as the results of the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR SWEDEHEART (Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome) trials are expected soon. After strong debate, it seems the time has come to embrace the use of these emerging technologies in clinical practice. There are new kids on the block, and they have come to stay.

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