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Multicenter Core Laboratory Comparison of the Instantaneous Wave-Free Ratio and Resting P_d/P_a With Fractional Flow Reserve

The RESOLVE Study

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Objectives This study sought to examine the diagnostic accuracy of the instantaneous wave-free ratio (iFR) and resting distal coronary artery pressure/aortic pressure (P_d/P_a) with respect to hyperemic fractional flow reserve (FFR) in a core laboratory–based multicenter collaborative study.

Background FFR is an index of the severity of coronary stenosis that has been clinically validated in 3 prospective randomized trials. iFR and P_d/P_a are nonhyperemic pressure-derived indices of the severity of stenosis with discordant reports regarding their accuracy with respect to FFR.

Methods iFR, resting P_d/P_a, and FFR were measured in 1,768 patients from 15 clinical sites. An independent physiology core laboratory performed blinded off-line analysis of all raw data. The primary objectives were to determine specific iFR and P_d/P_a thresholds with ≥90% accuracy in predicting ischemic versus nonischemic FFR (on the basis of an FFR cut point of 0.80) and the proportion of patients falling beyond those thresholds.

Results Of 1,974 submitted lesions, 381 (19.3%) were excluded because of suboptimal acquisition, leaving 1,593 for final analysis. On receiver-operating characteristic analysis, the optimal iFR cut point for FFR ≤0.80 was 0.90 (C statistic: 0.81 [95% confidence interval: 0.79 to 0.83]; overall accuracy: 80.4%) and for P_d/P_a was 0.92 (C statistic: 0.82 [95% confidence interval: 0.80 to 0.84]; overall accuracy: 81.5%), with no significant difference between these resting measures. iFR and P_d/P_a had ≥90% accuracy to predict a positive or negative FFR in 64.9% (62.6% to 67.3%) and 48.3% (45.6% to 50.5%) of lesions, respectively.

Conclusions This comprehensive core laboratory analysis comparing iFR and P_d/P_a with FFR demonstrated an overall accuracy of ~80% for both nonhyperemic indices, which can be improved to ≥90% in a subset of lesions. Clinical outcome studies are required to determine whether the use of iFR or P_d/P_a might obviate the need for hyperemia in selected patients. (J Am Coll Cardiol 2014;63:1253–61) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CI = confidence interval
ECG = electrocardiographic
FFR = fractional flow reserve (hyperemic by definition)
iFR = instantaneous wave-free ratio (nonhyperemic)
LAD = left anterior descending
NPV = negative predictive value
P_d/P_a = distal coronary artery pressure/aortic pressure (nonhyperemic)
PPV = positive predictive value
ROC = receiver-operating characteristic

Fractional flow reserve (FFR) is an index of the hemodynamic significance of a coronary stenosis that is calculated directly from measurements of hyperemic pressure (1,2). The physiological basis of FFR has been extensively validated in animal and human studies, and FFR shows good correlation to noninvasive ischemia testing with perfusion scintigraphy (3) and positron emission tomography (4).

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FFR has been shown in 3 randomized trials to identify coronary stenoses that will benefit from early revascularization (those with a positive FFR) (5) and conversely those lesions with a negative FFR for which revascularization may be safely deferred (6,7). To measure FFR, a vasodilator (most commonly intravenous or intracoronary adenosine) is administered to minimize microvascular resistance and the effect of resting hemodynamics such that coronary pressure becomes proportional to myocardial flow.

Interest has recently emerged as to whether 2 nonhyperemic measures of pressure might be useful to assess the severity of coronary stenosis. P_d/P_a is the ratio of distal coronary artery pressure to aortic pressure over the entire cardiac cycle. Conversely, the instantaneous wave-free ratio (iFR) measures coronary pressure during a specific period of diastole when resting resistance is the lowest (8). By reducing procedural time and cost, avoiding patient-related discomfort from pharmacological hyperemia, and allowing continuous online measurements (thereby facilitating multivessel interrogation), assessment of the severity of coronary stenosis without induction of hyperemia is intuitively appealing, provided diagnostic accuracy is preserved. However, in prior reports, the diagnostic accuracy of iFR compared with FFR has ranged widely from 60% to 91% (8–11), and its relative accuracy compared with P_d/P_a has been debated. Previous comparative studies to date have been limited by different study methodologies, modest sample sizes, and the use of different algorithms to calculate iFR. Given these conflicting reports, we formed a collaborative group of investigators to perform a large-scale, physiology core laboratory–based analysis with standardized methods to compare the diagnostic accuracy of iFR and P_d/P_a with respect to FFR as the reference standard and to determine the proportion of patients in whom the accuracy of iFR and P_d/P_a is at least 90%.

Methods

Patient population and study inclusion criteria. The present investigation was an international, multicenter, nonrandomized, retrospective, core laboratory–based analysis in patients with coronary artery disease undergoing physiological lesion assessment by FFR, iFR, and P_d/P_a. The principal investigators representing all of the published iFR/FFR comparative studies agreed to collaboratively participate in this effort, including the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study and registry (8,11), VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice) (9), and Johnson et al. (10). In addition, 6 other study sites contributed unpublished data to the analysis. All studies included in this analysis were approved by the institutional review boards of the individual sites. Original raw phasic pressure waveforms from each patient were submitted digitally to the Physiology Core Laboratory at the Cardiovascular Research Foundation (New York, New York) for independent off-line analysis. In addition, selected baseline patient demographic and procedural data were supplied to the core laboratory. This study was an investigator-sponsored study by the Cardiovascular Research Foundation and was supported by funding from Volcano Corp. (San Diego, California). The funding source was uninvolved with the design of the protocol and the analysis and interpretation of the study results.

Patients with stable angina, unstable angina, or non–ST-segment elevation myocardial infarction undergoing

Netherlands; ##Departments of Cardiology and Biomedical Engineering and Physics, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; and the ***Department of Cardiology, Catharina Ziekenhuis, Eindhoven, the Netherlands. Dr. Jeremias has served as a consultant and member of the Speakers' Bureau for Volcano Corp. Dr. Berry has served as a consultant for and received a research grant from St. Jude Medical. Dr. De Bruyne has received institutional consulting fees from St. Jude Medical. Dr. Davies has received study support from and served as a consultant with licensed intellectual property for Volcano Corp. Dr. Escaned has served as a member of the Speakers' Bureau for St. Jude Medical and Volcano Corp. Dr. Fearon has received research support from St. Jude Medical. Dr. Gould holds a nonfinancial, mutual nondisclosure agreement with Volcano Corp. and is a 510(k) applicant for cfrQuant, a software package for quantifying absolute flow using cardiac PET; all royalties will go to a University of Texas scholarship fund and the University of Texas has a commercial, nonexclusive agreement with Positron Corporation to distribute and market cfrQuant in exchange for royalties; however, Dr. Gould retains the ability to distribute cost-free versions to selected collaborators for research. Dr. Johnson holds a nonfinancial, mutual nondisclosure agreement with Volcano Corp. Dr. Koo has received honorarium and a research grant from St. Jude Medical. Dr. Oldroyd has served as a member of the Speaker's Bureau for St. Jude Medical and Volcano Corp. Dr. Piek has served as a consultant for MAB Abbott Vascular and Miracor. Dr. Pijls has served as a consultant for St. Jude Medical; received institutional research grants from St. Jude Medical; and served as an advisory board member for Heart Flow. Dr. Mintz has served as a consultant and received grant support from Volcano Corp. Dr. Stone has served as a consultant for Volcano Corp., InfraReDx, and Boston Scientific. This study was an investigator-sponsored study by the Cardiovascular Research Foundation and was supported by funding from Volcano Corp. (San Diego, California). The funding source was uninvolved with the design of the protocol and the analysis and interpretation of the study results. All other authors have reported that they have no relationships relevant to the content of this paper to disclose.

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