JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN
COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 70, NO. 17, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.08.069

EDITORIAL COMMENT

Agreement and Differences Among Resting Coronary Physiological Indices

Are All Things Equal?*

Morton J. Kern, MD,[a,b] Arnold H. Seto, MD, MPA[a,b]

In the universe of ischemic stress testing and coronary physiological measurements (**Figure 1**), fractional flow reserve (FFR) emerged as a simple, practical, and validated ischemic index with proven value in daily practice. FFR has, over the years, been compared with other physiological indices, and, depending on the statistical method, these comparisons seemed to indicate either diagnostic equivalency or high agreement among resting pressure indices and to some degree hyperemic flow (coronary flow reserve [CFR] and hyperemic stenosis resistance [HSR]). More recently, outcomes with instantaneous wave-free pressure ratio (iFR) were found to be noninferior to those of FFR in 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) studies (1,2).

SEE PAGES 2105 AND 2114

In this issue of the *Journal*, 2 independent studies, by Kobayashi et al. (3) and Lee et al. (4), demonstrate that the resting translesional-distal-coronary-pressure-to-aortic pressure ratio (P_d/P_a) and iFR are very similar measurements. Kobayashi et al. (3) found that in 763 patients from the CONTRAST (Can Contrast Injection Better Approximate FFR Compared to Pure Resting Physiology?) study (5), the median iFR and P_d/P_a were 0.90 and 0.92, respectively, with a high correlation ($r^2 = 0.93$; $p < 0.001$). From the receiver-operating characteristic (ROC) curve analysis, P_d/P_a had a high accuracy for predicting iFR (area under the curve [AUC]: 0.98; 95% confidence interval: 0.97 to 0.99; $p < 0.001$) with a best cutoff value of $P_d/P_a \leq 0.91$. Although iFR does not equal P_d/P_a on a 1:1 basis, there is a linear relationship with $iFR = (1 + k) \times P_d/P_a - k$, where k was derived using a 1-parameter regression. The diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were all >91% and were similar in patients with acute coronary syndromes as well as in patients with stable angina.

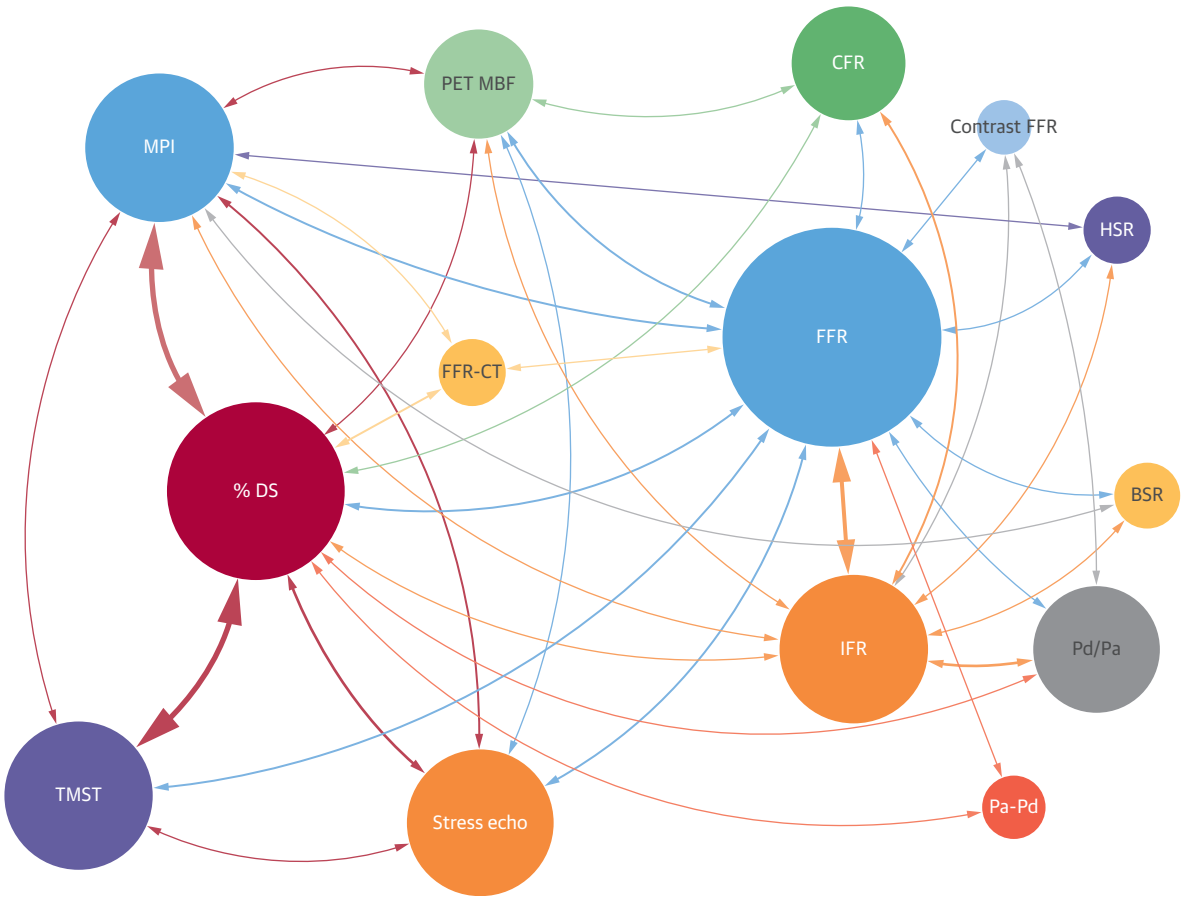
Lee et al. (4) compared pre-intervention resting P_d/P_a and iFR with diameter stenosis (%DS) in 1,024 vessels. These investigators found a linear correlation between P_d/P_a and iFR that was nearly identical to that observed by Kobayashi et al. (3) ($R = 0.970$; $p < 0.001$; $iFR = 1.370 \times \text{resting } P_d/P_a - 0.370$). A subset of 115 patients who had absolute myocardial blood flow measured by nitrogen-13 (^{13}N)-ammonia positron emission tomography (PET) allowed further stratification of the resting indices according to basal stenosis resistance (BSR) and HSR. For each increase in anatomic and hemodynamic severity, the investigators noted that the percent change in iFR (%Δ iFR) was higher than that of the resting P_d/P_a, thus indicating that iFR was more sensitive to the difference of stenosis severity. Despite higher measurement variability than resting P_d/P_a, iFR had lower variability in estimated risk of major adverse cardiac events because of this larger response to increasing stenosis severity.

Differences between P_d/P_a and iFR are small but worth noting. P_d/P_a is measured from the mean

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the [a]Department of Medicine, Veterans Administration Long Beach Health Care System, Long Beach, California; and the [b]Division of Cardiology, Department of Medicine, University of California, Irvine, California. Dr. Kern is a consultant and speaker for Abbott/St. Jude, Philips Volcano, Acist Medical Inc., Opsens Inc., and Heartflow Inc. Dr. Seto has received research grants and honoraria from Philips Volcano and Acist Medical Inc.

FIGURE 1 **The Universe of Ischemic Clinical Testing**



Network diagram of noninvasive and anatomic tests for ischemia **(left side)**, invasive hemodynamic indices **(right side)**, and hyperemic tests **(top half)**. The **size of the circle** represents the number of studies using the parameter as comparators with other modalities. The **thickness of the connectors** reflects the number and strength of comparative studies. The **circles** are illustrative and not to scale—most studies use the percent diameter stenosis (%DS) as a comparator. BSR = basal stenosis resistance (ΔP/flow at rests); CFR = coronary flow reserve; CT = computed tomography; echo = echocardiography; FFR = fractional flow reserve; HSR = hyperemic stenosis resistance (ΔP/flow at hyperemia); IFR = instantaneous wave-free ratio; MPI = myocardial perfusion imaging; Pd/Pa = ratio of distal pressure to proximal aortic pressure; PET MBF = positron emission tomography myocardial blood flow; TMST = treadmill stress electrocardiography.

pressures over several cardiac cycles, whereas iFR is derived from a pressure ratio over the cardiac cycle's diastolic "wave-free" period, by averaging individual values over 5 beats of data collection. iFR requires proprietary software, thus limiting real-time application to a specific pressure system and sensor wire (Verrata, Philips Volcano, San Diego, California). The original iFR software required electrocardiographic gating and was susceptible to poor electrocardiographic signals, whereas P_d/P_a is displayed continuously in real time and has fewer unacceptable artifacts. Both iFR and P_d/P_a are susceptible to transient hyperemia of contrast media, nitroglycerin, or saline flush and thus require some time before measurement to ensure a resting state. An iFR pullback recording can be co-registered with the angiogram, a feature yet to be developed for P_d/P_a.

The near equivalency of P_d/P_a with iFR leads us to this question: If P_d/P_a is equal (or nearly so) to iFR, and iFR is equal to FFR (or at least noninferior), then by extension, would P_d/P_a also be noninferior to FFR for outcomes? As another index joins the club of high agreement, we must ask, "Coronary physiologically speaking, are all things equal?"