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An Adenosine-Independent Index of Stenosis Severity From Coronary Wave–Intensity Analysis

A New Paradigm in Coronary Physiology for the Cath Lab?*

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More than 15 years ago, Nico Pijls, from Eindhoven, the Netherlands, conceived, and, along with Bernard De Bruyne from Aalst, Belgium and others, developed and tested the fractional flow reserve (FFR) concept (1–3). They are to be credited for one of the most important advances in the diagnosis and treatment of coronary artery disease in the percutaneous coronary intervention (PCI) era. The current paradigm of FFR revolutionized coronary physiology and translated directly to the practical in-lab functional assessment of coronary stenosis in patients before and during PCI.

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The working theory of FFR is derived from the fact that coronary pressure is linearly related to flow only if the coronary microcirculatory resistance is constant and minimal. FFR is thus computed from the ratio of absolute translesional pressures measured during pharmacologically induced (usually adenosine) hyperemia required to achieve the necessary resistance condition. The validation studies and the studies of associated beneficial clinical outcomes have finally placed FFR on strong bedrock for daily use in the cath lab (4–7).

However, despite demonstrating better outcomes with FFR guidance for PCI treatment decisions (6,7) and the recent FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) economic study showing the lower cost of achieving such outcomes (8), the use of FFR in the interventional community at large is <10% of PCI procedures performed in the absence of appropriate clinical evidence and at times in contravention to guideline recommendations (9,10). Why is the use of FFR less than what one would expect for such a strongly supported in-lab measure of ischemia, a measurement that is particularly helpful, if not critical, when uncertainty exists regarding the "treat/not treat" decision? The barriers to FFR adoption, as discussed previously (11), involve concerns regarding the perceived increased procedure time and cost, physician reimbursement, uncertainty about the technique or data, and the cumbersome requirement of adenosine with complaints about dose, route of administration, femoral venous access, and achievement of maximal hyperemia.

Motivated by both science and practicality, Sen et al. (12) now present a novel concept, the instantaneous wave-free pressure ratio (iFR), using and expanding on the tenets of FFR. iFR, an index of stenosis severity, is based on the instantaneous ratio of translesional pressures acquired during a specific period of diastole in which the coronary microcirculatory resistance is constant and minimal, fulfilling the FFR resistance criteria without the need for adenosine hyperemia.

In their most recent and perhaps the most clinically relevant work, Sen et al. (12) identified through their earlier studies of coronary wave–intensity analysis (13) a period of diastole in which an equilibrium or balance between pressure waves from the aorta and distal microcirculatory wave reflections is established; that is, a wave-free period beginning just after the onset of diastole. Importantly, during the wave-free period, the calculated coronary microcirculatory resistance is constant and minimal. This insight alone would not be enough to move their concept forward were it not for an equally important observation about adenosine. Adenosine has its greatest effect on the systolic component of resistance, resulting in a significant reduction in the mean resistance during adenosine-induced hyperemia. This series of observations logically led the investigators to address 2 key questions. 1) Is the wave-free period resistance similar or identical to the adenosine-induced reduction in resistance? 2) If so, would the iFR match the FFR?

Sen et al. (12) addressed these questions in a 2-part pilot study of 157 patients in the cath lab. In answer to the first question, the investigators found that resistance during the wave-free period was nearly the same as resistance during pharmacologic adenosine hyperemia. In the second part, the investigators compared iFR with FFR in 118 stenoses and found a very strong ($r = 0.9$) correlation with high (>85%) sensitivity, specificity, and positive and negative predictive

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values. iFR reproducibility was also very high. From the data, iFR appears comparable to FFR without the need for pharmacologic vasodilation. Given the barriers to FFR adoption, the implications for an easier, adenosine-independent lesion assessment tool are obvious.

Like all new science, we need to look more closely at the intricacies and possible limitations of iFR. The identification of the wave-free period is derived from the complex wave–intensity analysis as used in previous studies (13). The wave-free period began 25% of the way into diastole (its beginning denoted by the dicrotic notch) and ended 5 ms before the end of diastole (approximately 75% of the diastolic period). The algorithm for the beat-to-beat calculation must account for varying R-R intervals of arrhythmias. Indeed, an example of such a problem is shown in the paper. Although the correlation of iFR with FFR was very strong with very small mean differences (-0.05 ± 0.19), there were some measurements that varied >10%. Might the variation be due to the individual's responsiveness to adenosine itself, a factor not in play for iFR? It is interesting that the intrinsic variability of FFR (5%) and iFR (2%) differed only slightly but favored iFR. Or could the wave-free period resistances vary due to hemodynamic factors yet to be tested? Although provocative, these concerns are tempered by the appreciation that the coefficients of variation of 2 resistance measurements were in fact identical.

How should iFR be validated for ischemia? In the study of human coronary physiology, a true clinical gold standard of ischemia is difficult, if not impossible, to be easily identified, let alone tested. In the landmark 1996 FFR validation study reported in the *New England Journal of Medicine*, Pijls et al. (4) used a model of 3 outpatient ischemia stress tests in the same patient and required at least 1 of the 3 tests to convert from positive to negative after PCI to indicate that the lesion was ischemia related. This validation protocol has never been repeated and likely never will. The highly variable false-negative and -positive rates of different stress test modalities used in subsequent studies account for currently accepted FFR values wherein a positive ischemic FFR is <0.75 and a negative ischemic FFR is >0.80, with a zone of mixed results (uncertainly) between them. Recent clinical outcome studies used >0.80 as a dichotomous cut point to test treatment strategies (6,7,14).

Although the iFR value of 0.83 provided optimal agreement with an FFR of 0.80, it is unlikely that the same arduous "3-test" ischemia standard could be repeated for iFR or any lesion assessment index (e.g., intravascular ultrasound minimal lumen area). Given the very strong initial correlation, FFR alone could act as the standard against which iFR could be tested in a larger population.

Critical to the acceptance of iFR is knowing whether the wave-free resistance is truly constant and minimal during hemodynamic perturbations including pharmacologically or even exercise-induced hyperemia. Like FFR, it remains to be seen whether a correction for elevated right heart pressure will improve accuracy and is at all necessary for most coronary artery disease patients. Should hyperemic wave-free resistance be significantly different under changing hemodynamic states, the close approximation of iFR to FFR would need to be reconsidered.

Finally, just as was done with FFR, there will be numerous clinical conditions, such as assessment of diffuse disease, serial lesions, severe left ventricular hypertrophy, and acute coronary syndromes, that will require study of the iFR behavior. One immediately relevant scenario is that of serial lesion assessment. FFR cannot assess individual lesions in the series without hyperemia and a distal coronary occlusion pressure, a highly impractical approach. Because it does not require hyperemia, iFR may be useful to examine individual serial lesions including those involving the left main coronary artery, a clinical scenario yet to be tested. We should also remember that iFR will be subject to all the technical limitations of FFR regarding pressure-measurement techniques involving guide catheter placement, zero and equilibration, and identification of signal damping and drift.

The iFR concept has great appeal. It would make lesion assessment quicker, easier, less expensive, and more widely used, but it must be carefully vetted before wholesale implementation. Each new paradigm rewrites the history of its predecessor. Old theories are discarded and then reconstructed, emerging under a new paradigm. Such was the case with FFR compared with earlier physiology methods. Should large-scale validation studies meet positive expectations, iFR may take its place among cath lab lesion assessment methods, providing critical information for the treatment of our PCI patients.

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