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EDITORIAL COMMENT

Selecting the Right Fractional Flow Reserve in an Unsteady State

Keep It Simple*

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Fractional flow reserve (FFR) works. After 20 years and 3 landmark clinical trials, FFR is arguably the best standard for determining the significance of coronary artery disease. By revealing a specific coronary stenosis's ischemic potential, FFR often changes clinical decisions on the need for or method of revascularization, leading to demonstrably better clinical outcomes and cost-effectiveness.

Critical to ensuring continued implementation of any test is the operators' confidence in an accurate, reliable, and repeatable measurement. The original "instructions for use" from Dr. Pijls stated that FFR should be the distal coronary/arterial pressure ratio (Pd/Pa) during steady-state maximal hyperemia, because "a direct relation between coronary pressure and flow … may be presumed only if coronary resistances are constant (and minimal)" (1).

Using this succinct definition, selecting the FFR should be simple. Operators watch the pressures during adenosine infusion, track the Pd/Pa ratios, wait for stable signals, and select the lowest FFR value. However, sometimes the operators must resolve 2 conflicts before finalizing their FFR decision. The first issue is that the manually identified FFR may not always match the automated FFR software, which merely selects the simple minimum Pd/Pa value across the entire recording. This feature may accept a single artifactual beat from, say, a hiccup, and display an erroneous FFR.

The second conflict is selecting the right FFR during adenosine-associated hemodynamic variability and, at times, during a distinctly unsteady-state hyperemia (2–4). Two reports described that the minimum Pd/Pa commonly occurs during the onset of hyperemia, whereas the stable hyperemic value might be 0.03 to 0.04 units higher (2,3) (**Figure 1**). In accordance with the definition of FFR used in clinical trials, these reports recommended use of the "stable" value (2). Moreover, we recently noted that "steady-state" hyperemia was often not sustained during a single continuous infusion of adenosine, with attenuation of hyperemic effect or cyclical hyperemia a frequent occurrence (4). We recommended that the lowest value of Pd/Pa be used as the FFR because defining exactly when a "stable" hyperemic state occurred could be difficult, subjective, and variable. The investigators for the DEFER (Deferral of Percutaneous Coronary Intervention), FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation), and FAME2 trials validated the definition of FFR as the lowest Pd/Pa during the lowest "stable" hyperemic period. But without standardization and better rules from definitive data, when selecting the right FFR, we are often left in the position of Supreme Court Justice Potter Stewart, who famously defined obscenity by writing that "I know it when I see it" (5).

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Addressing this conundrum, in this issue of *JACC: Cardiovascular Interventions*, Johnson and 8 of the world's pre-eminent coronary physiologists (6), including Dr. Pijls, enter this debate with a reanalysis of digitized raw hemodynamic data from the 206 patients enrolled in the VERIFY (VERification of

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Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice) study (7). Hemodynamic tracings, obtained in duplicate, were previously analyzed by core lab technicians. This dataset enabled the authors to test the accuracy and repeatability of an automated FFR algorithm, the "smart FFR," and compare it to various FFR selection recommendations.

THE "SMART MINIMUM" FFR

Johnson et al. (6) applied a novel algorithm to automatically verify the quality of the pressure waveforms and select the minimal Pd/Pa value to define a "smart minimum" FFR (SMFFR). The SMFFR is "the lowest average Pd/Pa of 5 consecutive cardiac cycles of sufficient quality within a run of 9 consecutive quality beats" (6). Other components included high- and low-frequency signal filtering (to eliminate artifacts), a recentered Gaussian-weighted average (to smooth the curves and avoid step-ups and lag), and required reasonable physiologic values for Pd, Pa, pulse pressure, and heart rate. The specifics of the algorithm are less important than the desired goal, which was to replicate the human technician's ability to exclude artifacts and bad data and report the "simple minimum" FFR. With a perfect pressure measurement (without artifacts or errors), the SMFFR would equal the simple minimum FFR. Could the SMFFR equal the trained technician's pinpoint FFR during stable hyperemia? From the VERIFY and RESOLVE study's physiological core laboratory technician-selected FFR values, SMFFR was found to be highly correlated and reproducible, and it performed better than several other proposed algorithms, including empirically selecting the Pd/Pa value 1 or 2 min into an adenosine infusion.

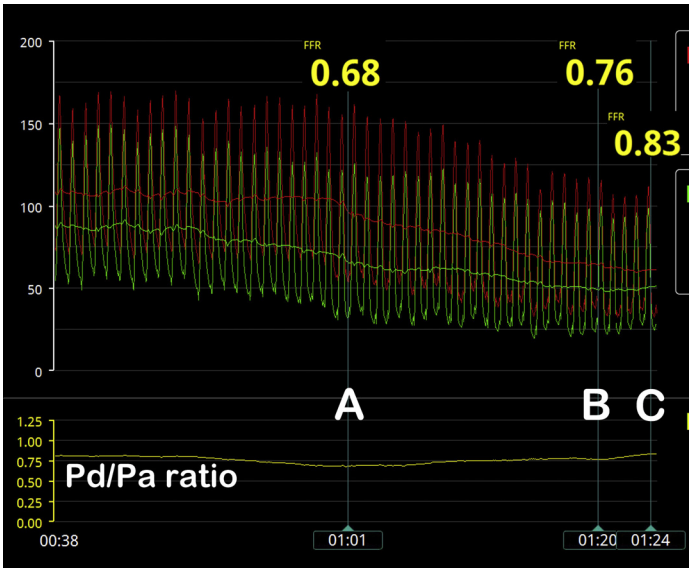
Is visual identification of the hyperemic phase, or a stable portion of that phase, superfluous when an automated algorithm is able to accurately seek out the minimal value of Pd/Pa across the entire recording? With only a few caveats, the short answer is yes, as the authors conclude "within reason, always take the minimum Pd/Pa value" (6). The rationale is that the minimum value of Pd/Pa will be selected as the largest gradient between Pd and Pa, which should only occur during maximal hyperemia.

ADENOSINE-INDUCED HEMODYNAMIC VARIABILITY AND FFR REPRODUCIBILITY

Johnson et al. (6) also confirm that a stable hyperemic state is frequently not created with intravenous adenosine (4). From the 190 complete data pairs during adenosine infusion, the authors visually grouped "sparkline" (data-intense, simple graphic display) curves of the moving average of the Pd/Pa ratio into 3 patterns: 1) "classic" stable pattern (sigmoid shape, 57% of responses); 2) "humped" pattern (sigmoid with superimposed bumps, 39%); and 3) "unusual" pattern (no particular shape, 4%). Strikingly, even in the same patient and lesion, the hemodynamic response to adenosine varied, with duplicate patterns occurring in only 41%, 24%, and 3% of the 3 patterns, respectively. The cause of adenosine-induced hemodynamic variation remains unknown, unpredictable, and of uncertain clinical importance. Cyclical hyperemia does complicate the measurement of FFR during pullback pressure measurements for serial lesions or in assessing multivessel disease (4), and a rapid pullback or multiple repeated measurements may be necessary.

The major feature of the SMFFR is that despite hemodynamic variability, it had excellent reproducibility (r^2 = 98.2%) on repeat testing and was not different from the VERIFY and RESOLVE study core lab analyses. In other words, a reproducible automated value comparable to core lab analysis only could be created by taking the minimal FFR

FIGURE 1 Typical Coronary Hemodynamic Response to Intravenous Adenosine



The lowest distal coronary/arterial pressure ratio (Pd/Pa; 0.68) occurs early in hyperemia, at point A. Values obtained at the earliest nadir of Pd (**point B,** 0.76) and during stable hyperemia (**point C**, 0.83 to 0.85) are significantly higher. Johnson et al. (6) recommend choosing the lowest 5-beat average Pd/Pa value (the lowest point on the Pd/Pa plot line, **point A**) as the fractional flow reserve (FFR).

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value across the entire recording, rather than attempting to divine when stable hyperemia had occurred. This value at maximal hyperemia would presumably be identical to values obtained with other hyperemic agents. Given the frequent instability of hyperemia with intravenous adenosine, a reconsideration of the advantages of intracoronary adenosine (more rapid onset with fewer systemic side effects despite being more operator-technique dependent) is appropriate.

Johnson et al. (6) are to be congratulated for addressing a thorny issue in a detailed and scientific manner, even as it partly upends conventional teaching on the subject. Selecting the right FFR depends on using the Pd/Pa at "maximal hyperemia" rather than waiting to achieve a "steady-state" FFR, which may not always be possible. At maximal hyperemia, resistance is minimized and sufficiently constant to satisfy the FFR derivation requirements to correlate with flow, at least for several seconds. As strong advocates of the FFR method, we welcome the clarity on this issue. Their results confirm the reproducibility of FFR when measured as the lowest value of Pd/Pa, the relative insensitivity of FFR to hemodynamic changes, and the ability of a simple automatic algorithm to match the best core lab values. Thanks to Johnson and colleagues' work (5), selecting the right FFR just became easier and simpler for the practicing interventionalist, which can only lead to better patient care.

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