A Black and White Response to the “Gray Zone” for Fractional Flow Reserve Measurements

Petraco et al. (1) raise a universal issue that affects all clinical tests. Every binary cutoff produces cases just on either side of the threshold for whom a repeat measurement might alter the decision, no matter how accurate the test or how small its variability. By analogy to a Gaussian distribution of observations about the true value, the critical measure for any diagnostic test remains the “width” of that curve. Indeed, the topic predates the concept of fractional flow reserve (FFR). Measurement repeatability came to attention almost 25 years ago when thresholds were proposed for total cholesterol (2). Therefore, although the core statistical issue also applies to FFR by definition, we have fundamental concerns regarding Petraco and colleagues’ (1) method and conclusions in this specific case.

First, Petraco et al. (1) extracted repeated FFR measurements from a digitized figure instead of using the raw data or its published, analyzed results. Given overlap and clustering in the scatter plot, we suspect they could extract at most one-half to two-thirds of the data points. As a result, they incorrectly estimate the SD of the difference between repeated FFR measurements as 0.032 when the original publication stated ±0.02 using the raw data (3). Furthermore, those FFR measurements obtained at least 15 years ago used prior-generation pressure wires, including fiber-optic technology with more drift, all technically inferior to modern FFR wires.

Second, the recent VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in Every day Practice) study (4) also found the SD between repeated FFR measurements to be ±0.02. Therefore, it is very unlikely that a lesion’s FFR measurement will change from <0.75 (definitely ischemic) to >0.80 (definitely not ischemic) or vice versa upon repeat measurement. Such a change would be >3 SD (0.81 – 0.74 = 0.07, which is larger than 3 SD, or 3 × 0.02), which would occur <0.3% of the time. For example, in the VERIFY trial, no subject (0%) crossed between FFR <0.75 and FFR >0.80—indeed, no subject crossed between ≤0.75 and ≥0.80.

Finally, the universal considerations regarding measurement variability apply even more to the instantaneous wave-free ratio (iFR). The VERIFY study demonstrated 95% limits of agreement for repeated FFR measurements of ±0.04—much narrower than the wider ±0.07 variability in iFR (4). Similarly, in the VERIFY trial, FFR ≤0.80 agreed with itself 95% of the time, whereas iFR ≤0.89 agreed with itself only 92% of the time.

To account for both biological variability and measurement uncertainty, we have never advocated a single cutoff, but have rather clearly stated that FFR possesses “a narrow cut-off value discriminating ischaemic stenoses” but “in the grey zone, between 0.76 and 0.80, decision making should be based upon sound clinical judgement, typicality of complaints, presence of other test results” (5), and myocardial mass at risk.

In conclusion, Table 1 demonstrates that FFR offers one of the most reproducible numbers in cardiology practice, as quantified by its coefficient of variation (extent of variability around the typical value) for repeated measurements (4,6–11). If only every test we rely on daily for clinical decisions would have the narrow “gray zone” offered by FFR, our lives would be far more black and white.

Nils P. Johnson, MD, MS
Nico H. J. Pijs, MD, PhD
Bernard De Bruyne, MD, PhD
G. Jan Willem Bech, MD, PhD
Richard L. Kirkeeide, PhD
*K. Lance Gould, MD

*Weatherhead P.E.T. Center for Preventing and Reversing Atherosclerosis
University of Texas Medical School at Houston
6431 Fannin Street, Room 4.256 MSB
Houston, Texas 77030
E-mail: K.Lance.Gould@uth.tmc.edu

Table 1. Coefficients of Variation in Cardiology Practice

<table>
<thead>
<tr>
<th>Measurement</th>
<th>First Author (Ref. #)</th>
<th>Coefficient of Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR</td>
<td>Berry et al. (4)</td>
<td>3%</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>Mooy et al. (6)</td>
<td>9%</td>
</tr>
<tr>
<td>Ambulatory systolic blood pressure</td>
<td>Eguchi et al. (7)</td>
<td>11%</td>
</tr>
<tr>
<td>LDL</td>
<td>Miller et al. (8)</td>
<td>6%–14%</td>
</tr>
<tr>
<td>Ejection fraction by MRI</td>
<td>Grothues et al. (9)</td>
<td>12%</td>
</tr>
<tr>
<td>Percent diameter stenosis by QCA</td>
<td>Reiber et al. (10)</td>
<td>17%–18%</td>
</tr>
<tr>
<td>CRP</td>
<td>Bower et al. (11)</td>
<td>46%</td>
</tr>
</tbody>
</table>

CRP = C-reactive protein; FFR = fractional-flow reserve; LDL = low-density lipoprotein; MRI = magnetic resonance imaging; QCA = quantitative coronary angiography.

Please note: Dr. Johnson, Kirkeeide, and Gould have received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis; and have signed non-financial, mutual nondisclosure agreements to discuss coronary physiology with Volcano Corporation, maker of invasive pressure wires. Dr. Pijs has received institutional research grants from St. Jude Medical, Abbott, and Maquet; and is a consultant for St. Jude Medical and Heartflow. Dr. De Bruyne is a consultant for St. Jude Medical. Dr. Bech has reported that he has no relationships relevant to the contents of this paper to disclose.

REFERENCES


---

**Reply**

**Fractional Flow Reserve: A Good or a Gold Standard?**

“Coronary pressure NEVER lies.”
—Koolen and Pijls (1)

“...the authors took the responsibility and consequences of their actions by STRICTLY adhering to treating patients with FFR < 0.80 and deferring patients with FFR > 0.80.”
—Pijls and Tonino (2)

We thank Dr. Johnson and colleagues and Dr. Fan and colleagues for their interest in our work (3).

Fractional flow reserve (FFR) has come a long way over the last 20 years, from an upstart to what is now commonly proposed as an infallible gold standard for the detection of myocardial ischemia. The brilliance of the pioneer clinical scientists who forged their way forward against skepticism may understandably have moved them to exceptional heights of eloquence and may explain why the inherent limitations of this valuable technique have never been openly discussed. Our reflections on FFR variability (3) do not question the value of FFR, a tool that we use every day in our laboratory as a guide to treatment decisions. We simply addressed the potential limitations of a dichotomous interpretation of FFR results. Our aim was to help clinicians see that FFR, like all other measurements in medicine, does not carry strict dichotomous implications for which treatment is best, and this is especially true close to the cutoff.

Dr. Johnson and colleagues point out that we used only the data salvaged from oblivion through publication by Kern et al. (4), because the original DEFER study data seem to have been mislaid, unfortunately—an increasingly common problem with pivotal FFR datasets. They are also right that our methodology perhaps influenced our results. However, may we correct them: we underestimated FFR variability (SD of difference) at only 3.2%. The DEFER study reported only mean absolute difference, from which SD of difference can be derived as 3.7%. We have explored this issue in more details in a recent publication (5), from which readers can test the FFR intrinsic variability in their own samples.

Dr. Johnson and colleagues and Dr. Fan and colleagues also cast doubts on our analysis because of the old pressure guidewire technology used in the DEFER study. Do they suggest that the positive results of the DEFER study should be re-examined? Also, should these concerns be extended to the validity of other early pivotal FFR studies? We should recall that the most important piece of evidence on the diagnostic efficiency of FFR in identifying ischemia-generating stenoses comes from a study of 46 patients, investigated nearly 20 years ago with even older pressure wires (6). Reassuringly, using state-of-the-art wire technology, Ntalianis et al. (7) recently reported the test–retest variability of FFR to be 5% when taken more than 24 h apart, demonstrating elegantly that FFR measurement variability is a true biological phenomenon.

We do agree with Dr. Fan and colleagues that clinicians should assess test–retest reproducibility of FFR in their own hands and make repeated measurements of FFR when facing intermediate values. We merely recommend parsimony, both with adenosine and with references to golden infallibility. Clinicians must integrate many aspects of lesion and patient characteristics into their decisions. If clinicians sometimes stent stenoses with an FFR < 0.81, or indeed defer some with an FFR > 0.74, they are not automatically irresponsible or careless.

*Ricardo Petraco, MD
Javier Escaned, MD, PhD
Sukhjinder Nijjer, MB ChB
Mauro Echavarria-Pinto, MD
Darrel P. Francis, MB BChir, MA, MD
Justin E. Davies, MB BS, PhD

*International Centre of Circulatory Health
National Heart and Lung Institute
St Mary’s Hospital, Imperial College London
59-61 North Wharf Road
London W2 1LA
United Kingdom
E-mail: rpetraco@imperial.ac.uk

http://dx.doi.org/10.1016/j.jcin.2013.11.005

**REFERENCES**


