JACC: CARDIOVASCULAR INTERVENTIONS VOL. 6, NO. 3, 2013

ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

http://dx.doi.org/10.1016/j.jcin.2012.10.014

CLINICAL RESEARCH

Fractional Flow Reserve–Guided Revascularization

Practical Implications of a Diagnostic Gray Zone and Measurement Variability on Clinical Decisions

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Objectives This study sought to evaluate the effects of fractional flow reserve (FFR) measurement variability on FFR-guided treatment strategy.

Background Current appropriateness guidelines recommend the utilization of FFR to guide coronary revascularization based on a fixed cut-off of 0.8. This rigid approach does not take into account the intrinsic biological variability of a single FFR result and the clinical judgment of experienced interventionists.

Methods FFR reproducibility data from the landmark Deferral Versus Performance of PTCA in Patients Without Documented Ischemia (DEFER) trial was analyzed (two repeated FFR measurements in the same lesion, 10 min apart) and the standard deviation of the difference (SDD) between repeated measurements was calculated. The measurement certainty (probability that the FFR-guided revascularization strategy will not change if the test is repeated 10 min later) was subsequently established across the whole range of FFR values, from 0.2 to 1.

Results Outside the [0.75 to 0.85] FFR range, measurement certainty of a single FFR result is >95%. However, closer to its cut-off, certainty falls to less than 80% within 0.77 to 0.83, reaching a nadir of 50% around 0.8. In clinical practice, that means that each time a single FFR value falls between 0.75 and 0.85, there is a chance that the FFR-derived revascularization recommendation will change if the measurement is repeated 10 min later, with this chance increasing the closer the FFR result is to 0.8.

Conclusions A measurement FFR gray-zone is found between 0.75 and 0.85]. Therefore, clinicians should make revascularization decisions based on broadened clinical judgment when a single FFR result falls within this uncertainty zone, particularly between 0.77 and 0.83, when measurement certainty falls to less than 80%. (J Am Coll Cardiol Intv 2013;6:222–5) © 2013 by the American College of Cardiology Foundation

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Manuscript received August 23, 2012; revised manuscript received October 1, 2012, accepted October 26, 2012.

Over the last 20 years, the development of fractional flow reserve (FFR) has promoted a major shift in paradigm in assessing coronary stenosis severity in the cardiac catheterization laboratory. Supported by clinical data (1–4), invasive coronary physiology has been shown to improve patient

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outcomes by selecting patients for percutaneous coronary interventions. At times of increased scientific (5) and public (6) concerns about the appropriateness of coronary revascularization, it is essential that the behavior of FFR is discussed and clearly understood, to focus its application on patients in whom measurements can be interpreted confidently.

The idea of making a strict dichotomous revascularization decision based on a fixed FFR cutoff with nearly absolute diagnostic power was initially received with some skepticism. However, it was subsequently accepted by most cardiologists following demonstration of how physiological stenosis assessment can overcome the limitations of a purely anatomical angiographic approach and improve patient outcomes. This has led to the incorporation of FFR into coronary revascularization guidelines, which currently recommend its clinical use based on a fixed 0.8 cutoff (7–9). But application of a rigid dichotomy may neglect important physiological aspects of FFR, which have implications for its clinical interpretation.

First, it should be remembered that the current evidence on the value of FFR as a clinical decision tool is based on studies that have used 2 different FFR cutoff values. The DEFER (Deferral Versus Performance of PTCA in Patients Without Documented Ischemia) trial (1) demonstrated the safety of a deferral strategy in stenoses with an FFR $\geq$0.75, whereas the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) (3) and FAME II (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2) (4) studies used an 0.80 FFR cutoff to investigate its value in guiding angioplasty. This different choice of dichotomous cutoffs has its origin in early validation studies, which demonstrated that an FFR $<$0.75 has 100% specificity to identify stenoses with inducible ischemia in noninvasive tests, whereas an FFR of $>$0.80 has a sensitivity of more than 90% to exclude stenoses that generate myocardial ischemia (10). Because both studies yielded positive results, the most reasonable explanation is that the main determinant of improved patient outcome in the physiology-guided arms was the substitution of angiography by FFR in the decision-making process, not the strict application of either 0.75 or 0.80 FFR cutoffs. Yet, in the post-FAME era, this diagnostic FFR gray zone is not currently incorporated in clinical guidelines (8).

Second, the DEFER-FAME gray zone (0.75 to 0.80) does not take into account the intrinsic variability of FFR measurements, which is important to bear in mind when mandating a strict 0.8 cutoff to guide clinical decisions. For instance, the current approach implies that a difference in FFR as low as 0.01 is enough to mandate a physician to intervene on 1 lesion and forbid a physician from intervening on another. This observation is of particular importance in the context of the current recommendations in clinical practice guidelines, which is the use of FFR in patients with angiographic intermediate coronary lesions of unclear physiological significance (7–9). In contrast to early validation studies of FFR (11–13), which were designed to evaluate the performance of the index across a broad spectrum of coronary stenoses, clinical populations are formed predominantly by physiologically intermediate lesions with unimodally distributed FFR values that straddle the treatment threshold, and a median FFR close to 0.80 (14,15). Therefore, small variations in FFR results could potentially influence clinical decisions in such populations.

To investigate the effects of FFR intrinsic variability on treatment decisions in this clinically relevant zone, we calculated how much the test-retest variability in FFR measurements could affect the certainty of its results, by analyzing the landmark FFR reproducibility data from DEFER (2 repeated FFR measurements, 10 min apart) using a cutoff of 0.80 (1) (Fig. 1A).

Abbreviations and Acronyms

FFR = **fractional flow reserve**

We found that, at the extremes of the disease spectrum, the diagnostic agreement between repeated FFR measurements is 100%. Every time cardiologists face a single FFR measurement of $<$0.75 or $>$0.85, they can be confident that stenosis classification (and therefore revascularization strategy) is very unlikely to change if FFR is repeated.

Within the region of physiologically intermediate values (0.75 to 0.85), however, the agreement between repeated FFR measurements falls, reaching a nadir of approximately 50% around its 0.80 established clinical cutpoint. In practice, this means that when repeating a measurement that is within 0.01 of the cutoff, the chance of the repeated measure being on the same side of the cutoff is only about a one-half. The further away a single FFR value falls from the 0.80 cutoff, the greater the certainty that the recommended treatment strategy will not be reversed when the test is repeated. Outside the 0.77 to 0.83 range, measurement certainty is approximately 80% and outside the 0.76 to 0.84 range, it is approximately 90%. Measurement certainty only reaches 95% when FFR falls outside the 0.75 to 0.85 range (Fig. 1B). This measurement uncertainty creates a second type of FFR gray zone—a measurement gray zone—which has several important implications, both to the interpretation of available FFR studies and to its application in clinical

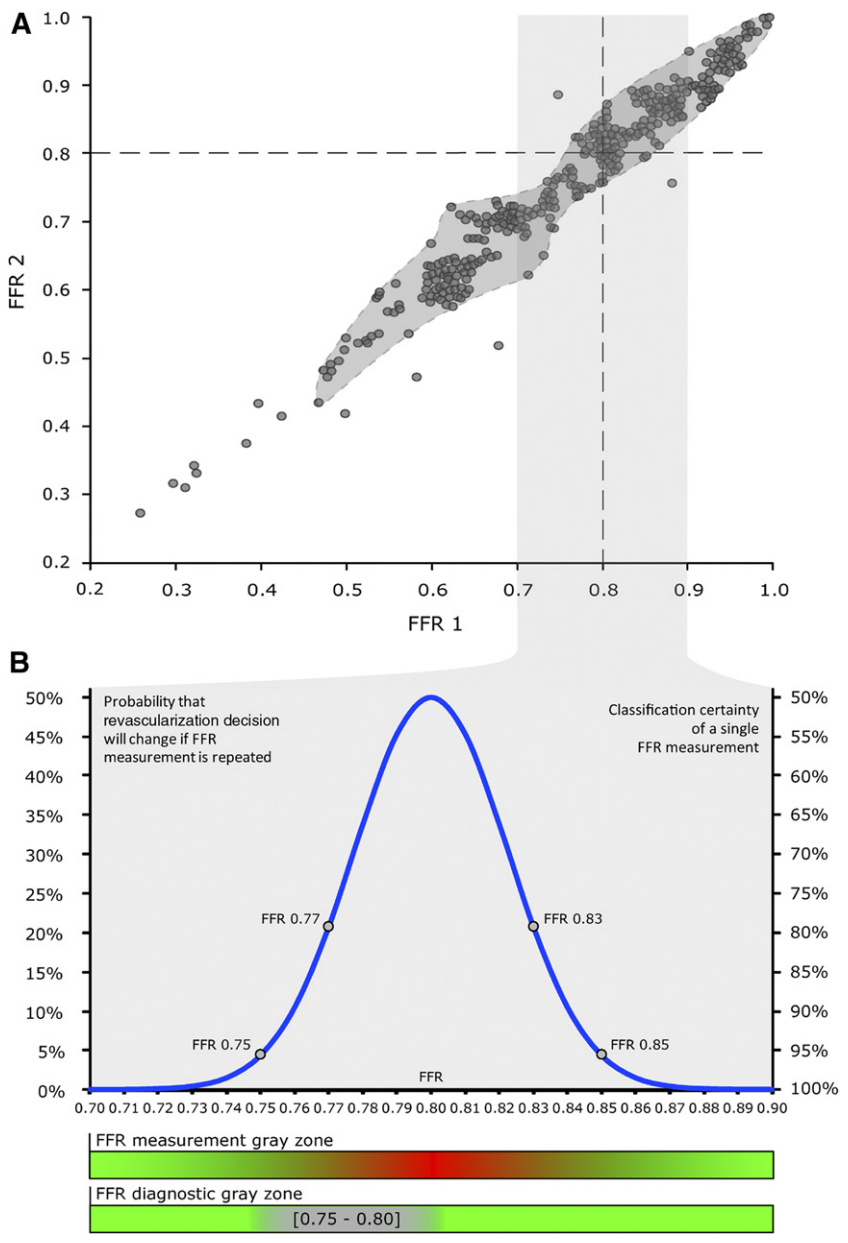

Figure 1. Biological Variability of FFR

Test-retest reproducibility of 2 repeated measurements of fractional flow reserve (FFR) taken 10 min apart is shown as a scatter plot (**A, gray dashed envelope** demarcates 99% of the data points from 0.5 to 1 and **dotted lines** show the 0.8 cutoffs). The classification certainty of a single FFR measurement is presented for FFR values from 0.70 to 0.90 (**B,** right vertical axis). Outside the 0.75 to 0.85 range, measurement certainty is higher than 95%. However, closer to its cutpoint, this certainty falls, reaching a nadir of approximately 50% around 0.8. In clinical practice, that means each time a single FFR value falls between 0.75 and 0.85, there is a chance that the dichotomous classification of a stenosis (and therefore the FFR-guided revascularization decision) will change if the test is repeated 10 min later. Within 0.77 to 0.83 this measurement certainty falls to <80%. The FFR diagnostic gray zone (0.75 to 0.85) is also displayed in **B** for comparison. FFR reproducibility data are from the landmark study DEFER (1) and data were obtained and digitized, from Kern et al. (7). Classification certainty (**B,** right vertical axis) was calculated using the standard formula:

$$1-\left(\frac{1}{2}e^{-\left(\frac{x-0.80}{0.032}\right)^2}\right)$$

With **x** representing each FFR value. Constant e is the base of the natural logarithm and equals 2.718. 0.8 is the currently established cutoff for FFR and 0.032 is the standard deviation of the difference (SDD) between repeated FFR measurements, obtained from the digitized DEFER (Deferral Versus Performance of PTCA in Patients Without Documented Ischemia) reproducibility data. As this analysis was performed using the SDD of the *overall* population, it could be applied to any FFR cutoff. The chosen FFR cutoff of 0.8 follows current recommendations from clinical guidelines (1) and is in line with the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) (3) and FAME II (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2) trials (4).

practice. The causes for this variability are multifactorial and include the variable response of the microcirculation to adenosine (16,17), the systemic vasodilator effects of adenosine influencing aortic blood pressure (18,19), and a possible direct effect of adenosine on myocardial function (20).

Clinicians interpreting the appropriateness criteria for FFR-guided revascularization should be aware of the consequence of natural biological variability of FFR on diagnostic classification of stenoses (Fig. 1). We suggest that when FFR is <0.75 or >0.85, they can use a strict dichotomous approach based solely on the FFR result, confident that a repeat FFR will recommend the same strategy in >95% of occasions. The lower limit (FFR = 0.75) coincides with the initially proposed cutoff from early validation studies and the value above which the safety to defer revascularization has been demonstrated in DEFER. For patients with FFR between 0.75 and 0.85, however, a repeat FFR might allocate the patient to the opposite treatment category, with the chance of change in strategy increasing as FFR approximates to 0.80. Between 0.77 and 0.83, the chance of this happening is as high as 1 in every 5 patients (20%).

In our view, therefore, it would be rational for clinicians to make revascularization decisions based on broadened clinical judgment when FFR values fall in this 0.75 to 0.85 biological variability zone, particularly between 0.77 and 0.83. Within this range, it would be particularly relevant to use all available information (including other perfusion imaging modalities, considering anatomical features and risk-benefit profile) to deliver safe and suitable care for individual patients.

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Key Words: adenosine ■ coronary physiology ■ coronary revascularization ■ fractional flow reserve.