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iVIEW

EDITOR'S PAGE

Would an FFR by Any Technique Perform as Sweet?

Harvey S. Hecht, MD,[a] Y. Chandrashekhar, MD,[b] Jagat Narula, MD, PhD[a]

Two thousand sixteen marks the 400th anniversary of William Shakespeare's death, and his legacy of famous quotations has gained relevance in almost all aspects of our lives. "A rose by any other name would smell as sweet," from *Romeo and Juliet* (1), has long been used to imply that names do not affect what things really are. Is this true in medicine? Does changing the name change the nature of the entity? Does assigning the same name to different object make them interchangeable?

This is particularly relevant when we are discussing diagnostic testing, which is often validated against a *gold standard*. A gold standard classically implies an immutable truth. Yet the constant ebb and flow of new information in medicine often results in a change in the gold standard, for example, migrating to fractional flow reserve (FFR) for detecting coronary lesions that would benefit from revascularization. What is even more difficult is that sometimes even the goal area itself changes, and what was once precious and true often becomes seriously questionable. For instance, the paradigm to fix lesions subtending ischemia on nuclear perfusion imaging is itself finding new equipoise for questioning and is being tested in latest generation clinical trials. All this ferment is good in the long run to develop evidence-based practice. However, the rapid development of technology providing solutions to questions that may become less relevant makes finding gold standards to confidently anchor one's clinical decision making more and more difficult.

From the [a]Icahn School of Medicine at Mount Sinai, New York, New York; and the [b]University of Minnesota & VA Medical Center, Minneapolis, Minnesota. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Invasive coronary angiography (ICA) has served as the gold standard for validating all the functional testing. However, ICA has been replaced by invasive fractional flow reserve (iFFR) as the unequivocal *new* gold standard for flow-limiting lesions that are better served with percutaneous coronary intervention. Does this invalidate the use of functional testing? Logic dictates that it does, but then iFFR *itself* was *originally* validated against a panel of noninvasive functional tests of ischemia. However, before the widespread use of iFFR, functional testing to assess the significance of an *anatomic stenosis* was based on the paradox of the functional test determining the accuracy of the gold standard from which it was derived. For example, a negative result on a functional test in the setting of a 90% proximal stenosis could be interpreted as evidence for that stenosis not being capable of producing ischemia (*if ischemia is the gold standard*), whereas, by definition, the test result is a false negative (*if stenosis is the gold standard*). Thus, the enormous database of sensitivity, specificity, predictive value, and accuracy of functional testing may need to be reassessed with changing times of changing gold standards.

The advent of iFFR as the gold standard for stenosis that needs revascularization by percutaneous coronary intervention probably imposes the need to amass an extensive database afresh of functional testing compared with iFFR. A recent meta-analysis showed that single-photon emission computed tomographic myocardial perfusion imaging (area under the curve [AUC] = 0.82) and stress echocardiography (AUC = 0.83) were less effective than positron emission tomography (AUC = 0.93), magnetic resonance imaging (AUC = 0.94), and rest computed tomography angiography (CTA) (AUC = 0.93) for the detection of iFFR <0.80 (2). Whereas the negative

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likelihood ratio (the main endpoint) was better for CTA, magnetic resonance imaging, or positron emission tomography, the post-test likelihood curves for computed tomography (CT) were not much different from stress echocardiography or myocardial perfusion imaging. Clearly, as the rose (or gold standard) itself changes, the tests derived from it may not smell as sweet or, at the very least, will have a different aroma. We also need to be judicious about what a test is expected to do. A test that is strong for *ruling out* a disease might have as good a role to play as a test that is strong for *ruling in* the disease, except that the population in which it will be crucial will be different in each situation. A less robust standard also does not mean that it is worthless! It just means that we have a better standard (which may or may not be easy to use), and the less precious one—20-karat rather than 24-karat gold—may still have a role or value depending on its ease of use, the pre-test probability of the disease, and, most important, the clinical question.

In the same vein, given the superior performance of rest CTA for excluding significant disease but some limitation in its positive predictive value, the notion of adding a functional component is attractive and has helped develop 3 distinct approaches: CT FFR (HeartFlow; HeartFlow, Redwood City, California), myocardial CT perfusion, and transluminal attenuation gradient. Of these, CT FFR has generated much excitement on the basis of accumulated data (3) and the intrinsic appeal of providing the same parameter as the *current* gold standard, iFFR, for stenosis that needs intervention. One limitation for its widespread use so far is the requirement to outsource the data for analysis and receive the results at a later time. Newer methods, albeit less computationally robust, that allow on-site analysis are becoming available. Here Shakespeare, once again, becomes relevant. Should iFFR, outsourced CT FFR, and in-house CT FFR smell equally sweet simply because they share part of the same name? Similarly, are different CT FFR methods equivalent because they provide the same parameter?

As Kruk et al. (4) and Norgaard and Leipsic (5) point out in this issue of *iJACC*, Shakespeare might have been out of his league on this one (not that he tried), and his quotation clearly does not apply to CT FFR versus iFFR. The newer methods, although promising, have some ways to go. The *gray zone* of CT FFR values from 0.74 to 0.87 (4), accompanied by the use of reduced-order computational fluid dynamics and anatomic modeling, emphasizes the importance of not painting all CT-derived FFR with the same brush. Although iFFR does show a similar gray zone of uncertainty, single-value FFR cutoffs have worked well in clinical trials such as DEFER, FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation), and FAME 2. The report of the prospective studies of CT FFR assessment with the latter strategy, and that of consequent effect on reducing referral for invasive assessment and cost containment (6–9), have generated considerable buzz, and we need to show similar progress with the desktop strategies. However, the effects on outcomes and superiority over conventional functional testing, as shown with iFFR, remain to be demonstrated with either technique.

The FAME family of studies have demonstrated the superiority of an iFFR-based revascularization strategy over angiography-driven revascularization (10) and optimal medical therapy (11). It has been proposed that abnormal iFFR, in addition to identifying anatomically severe stenosis, is also able to identify lesions with high-risk morphology on CTA (characterized by positive remodeling and low-attenuation plaque) that is known to be associated with hard cardiac events (12) independent of the degree of stenosis (13). More important, normal iFFR also correctly identifies CTA-verified benign lesions regardless of luminal stenosis (12). It is probably why there is no perfect agreement between ICA (the old gold standard) and iFFR (the new gold standard) or events (12). For instance, 20% lesions with <50% stenosis on ICA have abnormal iFFR (*ischemia without stenosis*), and 50% of lesions with 50% to 70% luminal stenosis have normal IFFR (*stenosis without ischemia*) (12,14). The high-risk lesions, in fact, may result in abnormal iFFR, presumably by their inability to respond to vasodilators (nitroglycerin and adenosine) at the site of large low-attenuation plaque (12), and benign lesions may vasodilate adequately to result in a higher iFFR occasionally, even sometimes in presence of significant luminal stenosis. Because vasodilators are not (or are inconsistently) used, CT FFR might not be able to reproduce these results. The desktop versions, although desirable, may have more limitations. Therefore, methods using CT to obtain FFR would not always *perform* as sweet unless the resting CTA protocols are completely overhauled and technology improves further. Shakespeare obviously was not aware of the pending conflicts that would happen 4 centuries later.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Jagat Narula, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, New York 10029. E-mail: narula@mountsinai.org.

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