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EDITORIAL COMMENT

The Game Changer?*

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Aside from its inability to accurately triage patients with obstructive disease to the interventional laboratory (1), the noninvasive evaluation of coronary artery disease has been plagued from its inception by a poorly appreciated, fundamental paradox that renders its application to individual patients problematic. All the technologies used to measure the significance of an angiographic coronary stenosis have been validated by using the coronary stenosis itself as the gold standard and have then used the technology to judge

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the gold standard from which it was derived (2). For instance, the sensitivity and specificity of myocardial perfusion imaging were defined by its ability to identify a >50% diameter stenosis on coronary angiography. Thus, a normal scan in the setting of an 80% stenosis is by definition a false-negative finding. However, current clinical practice concludes that the 80% stenosis being evaluated is incapable of producing ischemia. Which is it: a false-negative result on myocardial perfusion imaging or a misleading 80% stenosis? Is an abnormal scan in the setting of apparently normal coronary arteries a false-positive finding or evidence of microvascular ischemia? We cannot have it both ways. This critique applies as well to electrocardiographic stress testing, stress echocardiography, positron emission tomography, magnetic resonance imaging, coronary computed tomography angiography (CTA), and CTA perfusion, all of which were validated by using angiographic stenosis as the gold standard. The argument of whether function trumps anatomy is irrelevant if all are fundamentally flawed.

Critics of this logic would point to the very large databases demonstrating the prognostic value of each of these technologies as confirmation of their utility and validity. This argument reflects the viewpoint of "lumpers," who regard patients as representatives of a large database, rather than "splitters," who appropriately treat them as unique subjects. For example, the benign prognosis of a normal stress echocardiogram or myocardial perfusion test in large databases is assumed to apply to all patients who have had a normal study, irrationally equating those with normal coronary arteries to those with left main or triple-vessel disease.

What then is to be used as the gold standard to evaluate individual patients? Two invasive technologies have been used: intravascular ultrasound and fractional flow reserve (FFR). Intravascular ultrasound is subject to the same criticism as the noninvasive technologies: it was validated by myocardial perfusion imaging and stress echocardiography, which, as noted earlier, were validated by angiographic coronary stenosis. FFR, conversely, has become the accepted gold standard (3,4). Although initially validated by using myocardial perfusion imaging and stress echocardiography, it has emerged from the bonds of the paradox to be the first technology to use clinical outcomes, most notably in the DEFER (A Multicenter Randomized Study to Compare Deferral Versus Performance of PCI of Non-Ischemia-Producing Stenoses) and FAME (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) studies (5–7), as its gold standard. Decisions based on specific FFR values significantly affected patient morbidity and mortality, resulting in the incorporation of FFR-guided intervention for intermediate stenoses into the interventional guidelines with a recommendation of Class IIa, Level of Evidence: A (3). However, it is even more invasive than coronary angiography and is clearly not suitable for routine patient evaluation.

FFR_{CT}, FFR derived from standard acquired CTA datasets (HeartFlow, Inc., Redwood City, California), is the first noninvasive test to be validated from its inception by an outcome-based gold standard; that is, invasive FFR, rather than one ultimately based on coronary stenosis measurement. The application of computational fluid dynamics allows for derivation of FFR, based on projected adenosine-induced vasodilation at any point in the vascular tree, from a CTA of at least moderate quality acquired at rest, without adenosine infusion (8). The brief history of FFR_{CT} trials is summarized in Table 1.

The initial report (DISCOVER-FLOW [Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve]) was nothing short of spectacular, with remarkable improvements in specificity, positive predictive value, and accuracy with the addition of FFR_{CT} to CT alone by using invasive FFR as the gold standard, but it was a single-center study with only 103 patients (9). The first multicenter study (DeFACTO [Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography]) was eagerly awaited but proved to be a disappointment; the addition of FFR_{CT} yielded no significant increases in any parameter (10). Consequently, for the multicenter study (NXT [Analysis of Coronary Blood Flow Using CT Angiography: Next Steps]) presented in this issue of the *Journal* by Nørgaard et al. (11), the investigators went to great lengths to correct the perceived shortcomings of the DeFACTO trial. Improved automated

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Table 1 Summary of FFR_{CT} Trials for Detection of Invasive FFR ≤0.80

	DISCOVER-FLOW (9)		DeFACTO (10)		NXT (11)	
Year	2011		2012		2013	
No.	103		252		251	
Design	Single-center		Multicenter		Multicenter	
	CT	FFR_{CT}	CT	FFR_{CT}	CT	FFR_{CT}
Sensitivity	94%	93%	84%	90%	94%	86%
Specificity	25%	82%	42%	54%	34%	79%
PPV	58%	85%	61%	67%	40%	65%
NPV	80%	91%	72%	84%	92%	93%
Accuracy	61%	81%	64%	73%	53%	81%

CT = computed tomography; DeFACTO = Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography; DISCOVER-FLOW = Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve; FFR_{CT} = fractional flow reserve (FFR) derived from standard acquired computed tomography angiography datasets; NPV = negative predictive value; NXT = Analysis of Coronary Blood Flow Using CT Angiography: Next Steps; PPV = positive predictive value.

image processing methods were implemented for better lumen boundary identification; physiological models of microcirculatory resistance that yielded better diagnostic performance than the previous studies were used; and strict adherence to the best practices for image acquisition (in particular, rate control and nitroglycerin administration) was mandated. The results reflect the remedies: in 484 vessels in 251 patients, the addition of FFR_{CT} to CT dramatically and significantly improved the per-patient specificity, positive predictive value, and accuracy for invasive FFR ≤0.80 (Table 1), and the area under the receiver-operating characteristic curve increased from 0.81 to 0.90 ($p = 0.0008$). Similar results were obtained for per-vessel analysis, 30% to 70% stenosis, and for patients with coronary artery calcium Agatston scores >400. Thus, FFR_{CT} seems poised to assume the role of gatekeeper to the interventional laboratory for patients with CTA-defined intermediate stenoses, a role initially envisioned for—but not fulfilled by—CTA alone.

There are numerous issues to be considered:

1. Are there sufficient data to warrant implementation of this new technology? There have been a total of only 606 patients reported in the literature using FFR_{CT}, and only the current study (11) of 251 patients used the latest physiological modeling and improved automated image processing. As the authors acknowledge, additional appropriately designed prospective trials are needed. Is it correct to demand randomized controlled trials (RCTs), similar to FAME and DEFER (5–7), to prove that FFR_{CT} improves outcomes, or is a strong correlation with invasive FFR sufficient? Ironically, there has never been an RCT demonstrating that any form of noninvasive testing improves outcomes, yet the absence of RCTs has been a constant criticism of coronary CTA and coronary artery calcium scanning.
2. Demonstration of superior cost-effectiveness compared with other noninvasive testing, as well as superior accuracy, will be a prerequisite. Such analyses (12) may already have been or will be presented to payers, and they will also be instrumental in determining the level of reimbursement.
3. Will an FFR_{CT} ≤0.8 be sufficient to proceed with intervention or will confirmation by invasive FFR be necessary? The positive predictive value of 65% is not high enough to preclude the need for confirmation by invasive FFR. Further improvements in the HeartFlow technology or new algorithms from other vendors may render confirmation unnecessary. The negative predictive value of CTA alone (92%) is high enough to defer catheterization and is not augmented by FFR_{CT}.
4. If future studies lend convincing additional support for FFR_{CT} as the preferred modality, there is likely to be a devastating impact on all the noninvasive functional technologies, with expensive, high technology myocardial perfusion imaging bearing the brunt. As long as invasive FFR reigns supreme, the correlations with FFR_{CT} remain excellent, and CTA technology continues to improve as radiation exposure decreases, why would other tests be used except in those cases not suitable for CTA (e.g., renal dysfunction, very excessive calcification)? In turn, the resulting decreased income from noninvasive testing will accelerate the rapidly ongoing hospital acquisition of private practices with all the implications thereof.
5. Succession of invasive FFR to the throne of functional evaluation is based on several reports in a limited number of patients. If further studies cast doubt on its supremacy, CT FFR will suffer accordingly.
6. Logistical issues (i.e., offsite data analysis by HeartFlow and the attendant turnaround time) are unlikely to be problematic for patients in stable condition.
7. There will always be skeptics who will not accept the derivation of vasodilator parameters without applying vasodilation itself. However, the data, although counterintuitively derived, will speak for themselves.

Time will tell whether FFR_{CT} will emerge as the gold standard of noninvasive functional testing. The initial experience, however, is promising, and wide acceptance would indeed be a major "game changer."

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