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EDITORIAL COMMENT

Is FFR_{CT} Ready to Assume the Crown Jewels of Invasive FFR?*

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Supported by an evidence base unrivalled in many medical and surgical specialties, interventional cardiology is continually evolving to improve patient outcomes, minimize patient risk, and decrease burgeoning health care costs. A prime example of this is the paradigm shift in revascularization decision making being guided by fractional flow reserve (FFR) (i.e., ischemic surrogate) rather than the oculostenotic reflex (i.e., anatomy). Through the endeavors of pioneers in the field of coronary physiology extolling the virtues of an FFR-guided approach to percutaneous coronary intervention, we are now implanting fewer stents with less risk and better results for our patients with stable angina (1,2). However, given the dependence of FFR on invasive coronary angiography and pressure wire assessment, innovators in the field have tried to develop new techniques aimed at combining the prognostic benefits of FFR assessment with the reduced risks of a noninvasive approach.

Fractional flow reserve derived from coronary computed tomography angiography (FFR_{CT}) is such a technique. As the name suggests, this approach derives functional data (FFR) from a purely anatomical, noninvasive dataset: coronary computed tomography angiogram images (3). This avoids the limitations of other noninvasive tests such as stress echocardiography and perfusion-dependent modalities that are currently unable to combine high-resolution coronary anatomical data with the detection of myocardial ischemia on a per-vessel basis (4). Enthusiasm for FFR_{CT} has therefore been high and it has been widely tipped as a potential "game changer" in the field (5). Since the initial introduction of the concept of a noninvasive measure of FFR, a series of diagnostic performance studies have been performed, comparing the performance of FFR_{CT} to invasive FFR as the gold standard. The first of these—the DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenosis Obtained via Non-invasive Fractional Flow Reserve) study reported per-vessel diagnostic accuracy of FFR_{CT} of 84.3% (6). Subsequently, the DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) study (7) and, most recently, the NXT Trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) (8) reported diagnostic accuracy ranging from 73% to 86%, respectively. In 2009, the propriety software algorithm for FFR_{CT} gained U.S. Food and Drug Administration approval (9), and in 2015, Douglas et al. (10) published the first prospective FFR_{CT} study, demonstrating a 60% reduction in the primary endpoint of the rate of invasive coronary angiography, which did not show obstructive coronary artery disease in the FFR_{CT} arm versus the usual care arm. Therefore, evolution of FFR_{CT} has been impressive and rapid, with a widespread expectation that the technique will enter mainstream clinical practice soon. However, enthusiasm for FFR_{CT} must be tempered by an appreciation of some of the limitations intrinsic to the technique. Before we embark on a journey, we must be confident of our route and final destination.

FFR is calculated as the ratio of distal intracoronary pressure to aortic pressure, during stable hyperemia. During conventional invasive FFR measurement, aortic pressure and distal intracoronary pressure are both measured directly using a fluid-filled guiding catheter and intracoronary pressure wire, respectively. However, to derive an FFR value noninvasively, without any measure of coronary hemodynamic parameters, complex mathematical modeling is required. To determine the rest and

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hyperemic coronary flow and pressure fields, the governing equations of fluid dynamics known as the Navier-Stokes equations must be solved. This requires a series of assumptions to satisfy the mathematical model, assumptions that are themselves based on estimations of cardiac output, aortic pressure, and microcirculatory resistance (4). As with any mathematical equation, the output value is only as reliable as the input variables and herein lays the major limitation of FFR_{CT}—uniform and constant values of microvascular resistance and coronary flow do not exist. A recent study providing the largest experience of coronary pressure flow in humans has once again shown that the relations between microvascular resistance and anatomy is nonlinear (11). The complex interplay between epicardial anatomy and microcirculatory function unique to each individual patient guarantees this.

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The unlikelihood of finding any such mathematical constants in biology explains the failure of the study by Gaur et al. (12) in this issue of *iJACC* to demonstrate high diagnostic accuracy of FFR_{CT} to diagnose lesion-specific ischemia in nonculprit vessels of patients with recent ST-segment elevation myocardial infarction (STEMI). When performed at a median of 38 days post-STEMI, FFR_{CT} demonstrated only moderate diagnostic accuracy that was surprisingly lower than previously shown in patients with stable angina (6–8). Post hoc analysis revealed that the recent STEMI cohort had a substantially lower total coronary vessel lumen volume relative to left ventricular mass volume-to-mass ratio when compared with patients with stable angina from the NXT trial (8). This could account for the observed difference in diagnostic performance, but more importantly, it also exposes the vulnerability of FFR_{CT} in different disease states where altered assumptions to fulfill the mathematical model (as yet undefined) seem to be needed. The investigators conclude that currently there is no evidence to support the use of FFR_{CT} in the post-STEMI setting to guide complete revascularization and that further investigation is required to better define the clinical benefit and safety of noninvasive anatomical-functional assessment of nonculprit lesions by FFR_{CT}. If we accept that more investigation is required and the FFR_{CT} technique will never fully replicate invasive measures of coronary physiology, the final question becomes how much error are we (and our patients) willing to accept?

Refinement to the computational fluid dynamics model may yet yield further improvement in FFR_{CT}, as was noted between the DeFACTO software version 1.1 (HeartFlow Inc., Redwood City, California) and NXT software version 1.4 (HeartFlow Inc.,) studies. This may increase diagnostic accuracy as assessed within the confines of a trial setting; however, we must be clear about the intended clinical applications of FFR_{CT}—our "final destination." Of note, the major conclusion of all of the diagnostic accuracy studies was that FFR_{CT} was superior to plain computed tomography angiogram for the detection of ischemic stenoses arbitrated by follow-on invasive FFR assessment (6–8). This more subdued message is often lost in the enthusiasm that surrounds FFR_{CT}, which has not yet been assessed in direct comparison with invasive FFR in any prospectively designed patient outcome study. Perhaps it is through clever marketing that with a shared name and mutual cut-point we already hold FFR_{CT} in such high regard. However, the demonstrated clinical applicability of invasive FFR determined over 20 years of research cannot simply be transplanted to its noninvasive counterpart. That privilege must be earned.

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