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EDITORIAL COMMENT

From Newton to the Coronaries

Computational Fluid Dynamics Has Entered the Clinical Scene*

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More than 3 centuries have passed since Sir Isaac Newton published his laws of motion and more than 150 years ago Euler, Bernoulli, Navier, and Stokes, by generalizing Newton's laws, formed the equations upon which the modern theory of fluid dynamics was founded (1). Based on this scientific framework and more than 60 years of technology development behind computational fluid dynamics (CFD), today well-validated and proven applications of CFD are found in many scientific and engineering domains, such as modern aircraft, automobile, and, more recently, cardiovascular device design. During the last decade, emerging evidence of the value of CFD in clinical medicine has been established, in particular with regard to noninvasive coronary computed tomography angiography (CTA)-based computation of fractional flow reserve (FFR) (2–7). Although the naysayers have been abound referring to this method as a "black box technology," questioning its scientific validity and its value beyond visual stenosis assessment, coronary CTA-derived FFR recently has seen remarkable advancements in technology and its support in the clinical community challenging conventional coronary CTA and ischemia testing.

The most rigorously validated method for noninvasive assessment of FFR is based on a patient-specific 3-dimensional model of the aortic root, epicardial coronary arteries, and the myocardial mass obtained from a standard acquired coronary CTA dataset (FFR_{CT}) (1). The computation is founded on CFD under conditions simulating maximal hyperemia providing FFR_{CT} values throughout the coronary tree (1). The methodology requires a precise and comprehensive analysis of all arteries visible in the coronary CTA image, and the 3-dimensional CFD modeling requirements are significant, thus the analyses need to be performed centrally (HeartFlow Inc., Redwood City, California). Since 2010, we have seen 3 large-scale prospective multicenter trials validating the diagnostic performance of FFR_{CT} for the adjudication of lesion-specific ischemia, all of which documented high and significantly greater diagnostic performance as compared with both invasive angiography and coronary CTA using FFR as the reference standard (2–4). More recently, we have seen the technology advance beyond diagnostic validation to the realm of clinical utility. In a multicenter prospective setting, the use of FFR_{CT}, when compared with traditional testing, demonstrated a drastic reduction in the overall use of invasive angiography and fewer patients with normal or nonobstructive findings at the time of invasive angiography (7). Despite these advancements, many in the field of cardiovascular medicine continue to question its role clinically, debating the viability of off-site post processing and analysis, driven by concerns of modest turnaround times and likely to some extent the perceived loss of control of image analysis. These concerns have driven renewed interest in past generations of reduced order CFD that are less computationally intense and when coupled with less comprehensive anatomic modeling enables the possibility of on-site analysis with resultant significantly reduced analysis times. To date, the feasibility of on-site coronary CTA-derived FFR computation has been demonstrated in a few small single-center retrospective studies (5,6).

The single-center study by Kruk et al. (8) in this issue of *iJACC* sought to evaluate the proportion of symptomatic patients (N = 90) with intermediate coronary stenosis (50% to 90% by visual assessment)

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who could be saved from further testing through the use of an on-site CT-derived FFR solution (CT-FFR).

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The evaluation of intermediate lesions is noteworthy because such lesions represent those in whom coronary CTA interpretation is most challenging and where additional ischemia testing often is necessary. In agreement with previous studies, CT-FFR showed higher diagnostic performance in identifying lesion-specific ischemia than stenosis assessment by coronary CTA. Because "black and white" decision-making based on a specific FFR threshold does not always fit into the reality of clinical practice, the investigators should be praised for their attempt to identify a CT-FFR "gray-zone" within which further diagnostic testing is needed. The importance of an awareness of a gray-zone in clinical practice is supported by previous studies that have highlighted the variability of both repeated FFR measurements (9) and FFR_{CT} calculations (10) having the greatest impact on interpretation around the clinical threshold of 0.80. Moreover, it should be acknowledged that there is a continuous relationship between the FFR numerical value and clinical outcome with the largest benefit of revascularization being obtained at lower FFR values (11). The gray-zone in this study was established in a simple fashion by defining the CT-FFR thresholds (<0.74 and >0.87) for which both the positive and negative predictive values exceeded 90% (FFR threshold of 0.80). The width of this gray-zone depends on the overlap between distributions of CT-FFR values in patients (vessels) with and without FFR ≤ 0.80, or simply the dispersion of values shown in Figure 5 of the report by Kruk et al. (8), and thus is dependent on disease prevalence and the diagnostic performance related to the test setting (including "test" and "operator" performance, as well as the reliability of the reference standard for exclusion or inclusion of ischemia). By a "hybrid" diagnostic approach with "no-further-testing" outside and additional invasive FFR measurement inside the CT-FFR gray-zone, the investigators reported 95% agreement with the FFR-only strategy. However, the clinical value of a quantitative test whose gray-zone width includes one-half of the patients (as in the present study), and thus CT-FFR per se being good enough only for the other one-half of the patients seems limited. Moreover, it is important to acknowledge that in the gray-zone group, the CT-FFR hybrid diagnostic approach was commonly followed by a nonischemic FFR measurement (Figure 5 of Kruk et al. [8]). It may be speculated that integration of patient symptoms and/or CT measures related to coronary plaque characteristics and burden would have added valuable information to the assessment of patients in the CT-FFR gray-zone as gatekeepers to the catheterization lab. Although further investigation is needed, the introduction of a coronary CTA-derived FFR gray-zone group is highly appealing.

Complex questions usually require sophisticated solutions. A reduced order CFD solution used for the on-site CT-FFR algorithm cannot fully characterize the 3-dimensional geometry of the circulation, or the complexity of pulsatile or turbulent flow. The study by Kruk et al. (8) builds further on other single-center studies growing the global experience with CT-FFR. Though additive, there remain important unanswered questions including whether this method has the capacity of computing flow and pressure in relation to bifurcations and its diagnostic accuracy in the setting of severe lesions. Moreover, issues related to observer minimum requirements for CT-FFR analysis in a busy real-world clinical setting need to be addressed. For the on-site CT-FFR computation algorithm, the clinical cardiovascular imaging community now needs information regarding its diagnostic performance based on large prospective multicenter settings.

Sir Isaac Newton is often quoted as saying, "If I have seen further, it is by standing on the shoulders of giants" (12). Coronary CTA-derived FFR is in essence doing this exactly by leveraging CFD providing a deeper understanding of coronary artery disease than ever before by standing on the shoulders of the giants that have come before in the fields of fluid dynamics, coronary physiology, and cardiovascular imaging.

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