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EDITORIAL COMMENT

Fractional Flow Reserve From 3-Dimensional Quantitative Coronary Angiography

Fresh Light Through an Old Window*

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In this issue of *JACC: Cardiovascular Interventions*, Tu et al. (1) report on an initial validation study for a less-invasive approach to derive fractional flow reserve (FFR) based on the coronary angiogram. The investigators should be congratulated on developing an innovative means to expand the diagnostic value of angiography by including physiological ischemic assessment, potentially broadening access FFR data to every patient undergoing cardiac catheterization.

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Clinical Relevance of FFR Derived From Quantitative Coronary Angiography

Revascularization of coronary artery disease should be based on objective evidence of ischemia. The clinical utility of invasive FFR-guided percutaneous coronary intervention (PCI) to selectively treat patients with stable ischemic heart disease using an FFR threshold of ≤0.8 to define ischemia is well established (2,3). FFR-guided therapy was shown to reduce major adverse cardiac events (death, myocardial infarction, repeat revascularization) by approximately 28% compared with angiography-guided PCI (2), and by 68% compared with optimal medical therapy alone (3). Ischemia-guided PCI based on FFR is not only cost effective but also net cost saving compared with PCI based on anatomy alone (4).

The ability of FFR to identify patients who will benefit most from revascularization represents a major advance in the field of interventional cardiology, and has contributed to the very low short-term and long-term event rates now achievable with PCI. Accordingly, FFR has become an integral part of the ischemic evaluation, finding its way into PCI guidelines as Class IA recommendation from the European Society of Cardiology and Class IIa (Level of Evidence: A) in the U.S. joint guidelines (5,6).

In addition, FFR has become an important diagnostic safety net for interventionalists in the evaluation of intermediate coronary lesions, particularly in the current climate of intense scrutiny of perceived overuse of PCI. Increasing governmental oversight of PCI utilization is planned in the United States, including by the Center for Medicare & Medicaid Services as a condition of payment (7). The methodology for such ascertainment has not been specified; however, the burden of proof that an intervention was appropriate will ultimately lie with the operator, and the clear linkage between FFR and clinically significant disease provides the evidence necessary, as outlined in the guidance on appropriate use criteria for coronary revascularization (8).

In this context, FFR derived from quantitative coronary angiography (FFR_{QCA}) described by Tu et al. (1) is a timely addition to our diagnostic armamentarium, and is clearly relevant to daily clinical practice. With a fully integrated and automated software solution, the processing time is expected to be <2 min for complete longitudinal FFR computation of each coronary vessel and its major side branches; in other words, FFR of the entire coronary tree would be obtained in <10 min at the time of angiography. Based on the reported validation against invasive FFR, the high diagnostic accuracy of FFR_{QCA} (88%) relative to the traditional anatomic angiographic measures of minimal lumen area (64%) and percent diameter stenosis (68%) offers better discrimination of the clinical significance of intermediate lesions. In contrast with invasive FFR, which selectively interrogates a single lesion at a time, FFR_{QCA} permits longitudinal assessment of the entire coronary vessel, and if necessary the entire coronary tree, and can assist in identifying additional ischemia-producing lesions that would otherwise be missed. FFR_{QCA} also eliminates the risks associated with intracoronary pressure wire placement through a guiding catheter and systemic heparin administration. Ultimately, these advantages could enable more appropriate, more complete ischemic revascularization for our patients.

Methodology of FFR_{QCA}

The unique feature of FFR_{QCA} that likely explains the high reported accuracy is its derivation from computational fluid dynamics applied to reconstruction of the individual's

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coronary tree (coronary vessel *including* side branches). This is accomplished using validated 3-dimensional (3D) quantitative coronary angiography (QCA) and hyperemic volumetric flow rates derived from Thrombolysis In Myocardial Infarction frame count, adjusted to parent and daughter vessel flow distribution in side branches. The inclusion of major side branches allows better adjustment for differences in myocardial mass subtended by the interrogated vessel, and the use of individual hyperemic flow better accounts for distal microvascular disease, providing a better approximation of invasive measures overall. This is also the primary difference between FFR_{QCA} and FFR derived from computed tomography, which uses empiric flow derivation based on average population–based physiological model assumptions under rest conditions, rather than individual hyperemia—likely contributing to the lower observed accuracy of FFR derived from computed tomography compared with the pressure wire technique (9).

Acquisition Implications and Requirements

The current FFR_{QCA} application is simple and can be applied to standard diagnostic angiography technique with minimal impact on acquisition. 3D QCA requires 2 angiographic projections of each coronary artery with minimal overlap and foreshortening, obtained at least 25° apart; larger angles do not improve 3D accuracy (10). In addition to using intracoronary nitroglycerin, at least 1 projection should be obtained during either intracoronary or intravenous adenosine-induced hyperemia. A mean arterial pressure from the guiding catheter and a hematocrit are the only additional inputs necessary to obtain FFR_{QCA}. These requirements are minimal compared with invasive FFR, and should be straightforward to incorporate into routine clinical practice. Therefore, FFR_{QCA} has the potential to reduce the barrier to physiological assessment in the catheterization laboratory, and expand its clinical utility by reducing unnecessary revascularization of insignificant lesions and enabling identification of additional clinically significant lesions.

Validity of FFR_{QCA}

The diagnostic accuracy of FFR_{QCA} reported by Tu et al. (1) is very good (88%), with an area under the receiver-operating characteristic curve of 0.93, a negative predictive value of 91%, and a positive predictive value of 82% compared with invasive FFR. The study population was derived from 4 separate centers and appropriately reflects the target patient population with intermediate lesions (diameter stenosis 46.6 ± 7.3%) most relevant for FFR interrogation. The narrow standard deviation points to the homogeneity of intermediate lesions included in the study, minimizing outliers (extremes of stenosis) that would otherwise bias the validation results. In addition, this first validation study demonstrated reproducible and accurate results of FFR_{QCA} in a range of relevant clinical scenarios including: 1) a spectrum of challenging lesions (including 64% bifurcations); 2) acquisition at different frame counts (15 and 30 frames/s); 3) use of different angiographic systems (Siemens, Philips, GE); and 4) different routes of adenosine administration (intravenous and intracoronary). Although this validation represents an exciting first step toward a new technology, additional evidence will be required to confirm these results and the feasibility of implementation in real-world clinical practice. Validation in more complex lesion subsets (e.g., eccentric, angulated, tortuous, or calcified lesions), along with confirmation that the reported accuracy is generalizable to calculations based on angiograms obtained outside the clinical trial environment, will be critical. The clinical relevance of this method in defining significant nonculprit lesions in patients with acute coronary syndromes will also require verification.

Conclusions

As a new technology, FFR_{QCA} should be received as a welcome addition to our diagnostic tool kit in the catheterization laboratory. We eagerly await confirmation of these results in a fully integrated, low-latency system that will be necessary to enable widespread application of FFR-guided PCI, improving the risk stratification and, ultimately, the outcomes of patients with ischemic heart disease.

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Key Words: diagnostic angiography ■ fractional flow reserve ■ percutaneous coronary intervention.