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EDITORIAL COMMENT

Defining the Flow-Limiting Stenosis Noninvasively for Management of Patients With Coronary Artery Disease*

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Coronary artery disease (CAD) has become the number 1 pathological process responsible for disease burden in the world. Although traditionally the management of CAD was based on anatomic stenosis, more recently, better outcomes have been associated with revascularization of flow-limiting stenoses as opposed to indications on the basis of purely anatomic obstructions. The reference standard for defining ischemia-related coronary obstructions relies on the measurement of fractional flow reserve (FFR) in the catheterization laboratory during adenosine-induced vasodilation. Indeed, FFR-guided percutaneous coronary intervention (PCI) has become the standard of care for intermediate lesions, with a strong body of evidence now accumulated using this paradigm (1,2).

See page 72

In the past, the definition of flow-limiting stenoses was accomplished by combining the results of nuclear isotope perfusion studies with invasive coronary angiography performed on the basis of 3-dimensional vessel-perfusion territory models constructed mentally during or after coronary angiography, at the time of planning the revascularization procedure. In recent years, noninvasive assessment of functionally significant stenosis by computed tomography (CT) has become feasible by performing combined CT angiography and perfusion studies or by using mathematical models and fluid dynamics applied to coronary CT angiography (cCTA), and this technique was named "FFR-CT." Although the accuracy of FFR-CT was reported as only modest in a multicenter trial (3), this approach shows promise, particularly if combined with other methods recently developed in addition to pure pressure estimation, such as flow measurements of the large epicardial vessels made using CT images.

In this issue of *JACC: Cardiovascular Interventions*, Kim et al. (4) reported the application of pressure drop estimation by FFR-CT in 44 patients (48 lesions) to predict differences in intracoronary pressures before and after stent implantation (and, therefore, the success of stenting treatment), using invasive FFR as the reference. They found a good correlation between FFR and FFR-CT ($r = 0.60$ and 0.55 before and after stenting, respectively), and a diagnostic accuracy of 96% to predict residual ischemia after stenting. The new method correctly identified 44 treated lesions with no residual ischemia after stenting, and also 2 treated lesions with identifiable ischemia by invasive FFR. FFR-CT had only 2 false positives and no false negatives. Additionally, the investigators did not find differences between FFR and FFR-CT after stenting (0.024 [95% confidence interval: −0.08 to 0.13]). On the basis of these results, the authors emphasize that FFR-CT may be helpful for PCI planning and also for determination of revascularization strategies.

The data in the previous text provoke the following considerations: 1) Is FFR-CT indeed a robust noninvasive technique to identify absence of ischemia after stenting (high sensitivity); and 2) can we evaluate its performance to identify presence of ischemia after stenting (specificity), given the small number of true positives in the current analysis (2 FFR $\leq$0.8)? Nevertheless, it is important to mention that this is the first study, to our knowledge, evaluating FFR-CT for identification and planning of percutaneous revascularizations, and we congratulate the investigators for using it for this original purpose.

From a practical standpoint, the "virtual stenting" approach seems very attractive, especially when dealing with complex and sequential stenoses. Considering that different revascularization strategies can be simulated before the invasive procedure, in theory, it is possible to determine the obstruction(s) that lead to ischemia, and also predict the functional outcome of revascularizing such lesions. Pre-procedure FFR-CT might not only be convenient, but also cost effective, and can avoid unnecessary revascularizations as well.

On the other hand, there are some challenges to be overcome before making virtual stenting available in the clinical scenario. The first concern is related to the quality of the cCTA scans, the basis for FFR-CT calculations. The process involved in computational fluid dynamics requires a precise 3-dimensional model of the coronary tree, aorta, and myocardium to determine the pressures along the downstream circulation; and motion artifacts, presence of heavy calcifications, and/or poor signal-to-noise ratios can

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JANUARY 2014:79–80

interfere with the contours of the coronary tree and other structures. According to a recent meta-analysis (5), at least 1 coronary segment was nondiagnostic in 9.5% of the patients referred to cCTA for suspected CAD (6). In other words, for any the aforementioned reasons, and others that are less important in frequency and magnitude, we have a number of nondiagnostic segments in routine cCTA that can affect the diagnostic accuracy of FFR-CT. Even though previous data (7) showed the robustness of this methodology across different levels of image quality and artifacts, there is a consensus that an excellent quality scan should be the basis for a good FFR-CT study.

The second issue that should be addressed to improve this new approach is to carefully validate it using animal models. To date, there are no previous experimental studies unraveling the complex interactions between degree of stenosis, coronary blood flow, and computational fluid dynamics in stented lesions. As a result, the current methodology lacks a strong physiopathological foundation. Understanding these mechanisms will likely lead to consistent improvement in the noninvasive estimation of coronary blood flow.

Important advances in cardiovascular imaging of recent years have offered a wide range of tools to determine ischemic burden—one of the most important surrogate markers of CAD. Even though FFR is the current gold standard for identifying ischemia-producing obstructions, we cannot assess the coronary flow reserve using this technique. Both are important in the coronary physiology assessment, even being discordant sometimes because of the nature of the measurements (FFR relates to pressure drops, whereas coronary flow reserve relates to flow) (8). In this regard, myocardial blood flow estimations by other modalities are available, including by positron emission tomography (9), magnetic resonance (10), and most recently, by CT, using pharmacological stress (11). In the future, we should use a more physiological basis, combining pressure estimation by FFR-CT and also a measure of coronary flow, in the setting of a noninvasive revascularization procedure planning. If the matter is to use the "all-in-one" approach, CT methods are in the best position to provide this information.

About 35 years ago, we entered an era of minimally invasive coronary revascularization procedures after implementation of PCI (12). During this period, the diagnosis of obstructed CAD and its hemodynamic significance have been developing fast. Now we have a promising tool to verify the results of stenting using data from a CT scan. Cardiology is experiencing a shift from a minimally invasive approach to virtual-based, clinical decision making. The study by Kim et al. (4) is an important step in the new direction.

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Key Words: computational fluid dynamics ■ coronary CT angiography ■ fractional flow reserve.