Editorial

Angiographically insignificant yet ischemia-causing coronary lesions: a case for routine use of invasive physiologic testing during diagnostic cardiac catheterization

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"To know what you know and what you do not know, that is true knowledge."—Confucius

Coronary angiography has been the gold standard for the diagnosis of obstructive coronary artery disease for more than 50 years. Despite its central role for diagnosing and treating coronary syndromes, coronary angiography has well-recognized and serious limitations, relying on a subjective interpretation of two-dimensional contrast "luminography" that is plagued by imprecision and wide interobserver variability (1). The frequent failure of angiographic severity to accurately reflect anatomic severity was highlighted very early in the history of coronary angiography by necropsy studies that commonly observed severe lesions at sites judged by experienced angiographers to have only mild narrowing at angiography, a phenomenon attributed most often to diffuse atherosclerotic disease (2). Multiple subsequent studies have concluded that coronary angiography has a limited ability to predict the physiologic significance of individual lesions, especially for intermediately severe narrowing in the 50% to 70% diameter stenosis range (3,4). Yet it remains our most commonly used tool for making clinical decisions for patients with chest pain syndromes and a wide variety of other clinical scenarios.

In the early 1990s, guide wire sensor technology advanced to the point that an accurate pressure sensor could be incorporated into a 0.014-inch guide wire, and carefully performed validation studies demonstrated that using such a pressure guide wire, measurement of myocardial fractional flow reserve (FFR), simplified as the ratio of pressure measured distal to a lesion to aortic pressure at peak hyperemia, was feasible and safe and provided a reproducible measure of stenosis severity where an FFR of ≤0.75 strongly correlated with rigorously determined ischemia by noninvasive testing (5,6). An FFR ≤0.75 was associated with inducible ischemia with a specificity of 100%, while an FFR of >0.80 correlated with absence of inducible ischemia with a sensitivity of 90%. Subsequent prospective clinical trials showed that: (I) measurement of FFR allowed safe deferral of PCI for lesions of >50% diameter stenosis that had been referred for PCI (based on visual interpretation of angiography) when the FFR was >0.75 (7); and (II) among patients with multivessel disease referred for PCI, when compared with angiographic guidance, selection of lesions for revascularization based on an FFR threshold of ≤0.80 provided improved clinical outcomes (8). A large body of evidence, therefore, shows that by enabling an objective measure of clinically relevant lesion physiologic significance, measurement of FFR can overcoming many of the limitations of angiography for diagnosing and treating coronary artery disease. The accumulated evidence from assessment of over 9,000 lesions with clinical follow-up shows that reduced FFR is a strong and independent predictor of adverse prognosis (9). On

the strength of the clinical data, use of FFR received a class IIa recommendation in the most recent 2011 ACCF/AHA/SCAI PCI guideline and a class I recommendation in the 2014 ESC/EACTS guideline for myocardial revascularization (10) for assessing angiographically intermediate coronary lesions to guide revascularization decisions in patients with stable ischemic heart disease (11). More recently, an index of physiologic lesion significance using resting translesional hemodynamics that may obviate the difficulties and cost associated with inducing coronary hyperemia, the instantaneous wave-free ratio or iFR, has also been validated as a method for objectively determining lesion physiology for selection of lesions for revascularization (12).

Nevertheless, the penetration of physiology-based decision-making into the management of coronary artery disease among diagnostic and interventional cardiologists has remained limited (13). In a recent prospective nationwide survey in Italy designed to assess reasons for use and non-use of invasive coronary physiology assessment among consecutive cases performed by 140 operators in 76 catheterization laboratories, the majority of decisions regarding stenosis management were still made based on visual assessment only, and the most common reason that operators chose to not perform physiologic lesion assessment was the operator's confidence that the clinical and angiographic data were sufficient to achieve the correct decision for the patient (14).

In that context, the recent publication by Lee *et al.* (15) regarding clinical outcomes of angiographically insignificant lesions with low FFR contributes novel observations with important clinical implications. In this study, patients undergoing coronary angiography underwent routine 3-vessel measurement of FFR. Among the 1,136 patients studied, there were 1,024 patients with 2,124 lesions where stenoses were judged to be angiographically insignificant (defined as percentage diameter stenosis by quantitative coronary angiography of <50%) and where revascularization was deferred. Perhaps surprisingly, despite a mean angiographic percent diameter stenosis of only about 30%, 185 of these lesions (8.7%) showed an FFR ≤0.80. Among the lesions with an increasing degree of diameter stenosis from <20% to 40–50%, the frequency of FFR ≤0.80 increased from 2.5% to 15.1%. The detection of the presence of physiologic obstruction also had prognostic value. Although that degree of angiographic disease might be typically dismissed and considered irrelevant for the patient's clinical syndrome, at 2-year follow-up, the group of patients with insignificant lesions but an FFR ≤0.80 showed a significantly higher risk of major adverse CV events compared with the high FFR group (3.3% *vs.* 1.2%, hazard ratio 3.37, P=0.009). In multivariable analysis, FFR ≤0.80 was the most powerful independent predictor of future adverse cardiac events for patients with deferred lesions and angiographically insignificant stenosis. Of note, and in support of those observations, another prospective study where FFR measurement was performed routinely in all coronary arteries (16) showed that among 81 cases where patients undergoing angiography were labeled by the operators as having no significant coronary artery disease, 18 cases (22%) were found to have at least one FFR <0.80, and among lesions graded by angiography as <30% and 30–50% diameter stenosis, 13% and 33%, respectively, were found to have an ischemic FFR of <0.80.

These results should be humbling for the community of physicians who perform diagnostic catheterization procedures and who continue to base the majority of clinical decisions on coronary angiography. The implications are significant: (I) among lesions considered insignificant by common angiographic standards, a significant minority can be shown to have an FFR associated with ischemia; and (II) as might be expected from the experience accumulated thus far with FFR, despite their misleadingly benign angiographic appearance, lesions with a diameter stenosis <50% but an FFR ≤0.80 are associated with increased adverse ischemic outcomes. The lesions described in the paper by Lee *et al.*—angiographically insignificant but ischemia-producing by FFR—likely represent flow-limiting lesions "hidden" by adjacent diffuse disease or by angiographic artifact, such as vessel overlap or foreshortening. The data further suggests that detecting these lesions has clinical value, and raises the intriguing possibility of a potential benefit of revascularization for such lesions, especially given evidence from a prospective randomized trial showing that, among patients with stable coronary artery disease and lesions with an FFR ≤0.80, revascularization as compared with medical therapy alone improved outcomes (17). From these observations it also seems possible that the hidden presence of ischemia-producing lesions within vessels with angiographically insignificant disease may, at least in part, help explain the adverse prognosis linked with so-called "nonobstructive" coronary artery disease (18).

What are the practical implications of these observations? To me they provide a compelling argument that use of invasive physiologic testing should be expanded widely

and current guideline recommendations revised to include endorsing the physiologic assessment of a much broader range of lesions. They even support a role for the addition of physiologic pressure-wire assessment to any diagnostic cardiac catheterization procedure when the disease encountered is considered angiographically "insignificant", and not just selectively but routinely and of all major vessels. In cases where an ischemic FFR or iFR is encountered, further assessment by, for instance, pressure sensor pullback and/or intravascular ultrasound imaging could be employed to localize the culprit vessel segment, characterize the lesion and reference vessel diameter, and determine the feasibility of revascularization. Prospective studies to test this strategy and the potential benefit of revascularization for such patients are needed. Nevertheless, it seems likely that such efforts would improve the sensitivity of cardiac catheterization for the identification of ischemia-producing coronary lesions, fill an important existing gap in the diagnosis of clinically important coronary artery disease, and hold promise for improving clinical outcomes among patients with a wider spectrum of coronary artery disease.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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