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EDITORIAL COMMENT

Atherosclerosis, Stenosis, and Ischemia

One Primary, One Secondary, and One Tertiary*

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Many invasive imaging modalities have been validated for assessing coronary artery disease (CAD). In general, each of these methods has been developed to target specific features of the CAD process, such as characterization of stenosis severity by invasive coronary angiography (ICA), determination of translesional pressure differences by fractional flow reserve (FFR), plaque quantification and characterization by intravascular ultrasound, classification of lipid-laden atherosclerotic lesions by near-field infrared spectroscopy, and representation of coronary luminal geometry and surface plaque features by optical coherence tomography (1). Despite these advances, coronary artery stenosis severity by ICA remains the predominant arbiter of a decision to proceed to revascularization in most clinical practices. Even in patients with a noninvasive functional imaging test showing inducible ischemia, it is still the coronary anatomy that determined subsequent decision-making. Discordance between them (e.g., ischemia in a vessel without significant stenosis with ICA) is most often passed off as a "false positive" result of noninvasive testing. The limitation of such a stenosis-focused approach has become more apparent recently; the advent of FFR most clearly demonstrated this lack of a good correlation between visual stenosis on ICA and a functional stenosis with FFR—that is, causing reduced blood flow, ischemia (presumably the underlying factor for a positive noninvasive stress imaging test), and adverse outcomes. Post hoc analyses of the multicenter randomized controlled FAME (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) trial emphasized the discordance between FFR and ICA findings, with coronary stenoses of 50% to 70% diameter luminal narrowing exhibiting ischemia only 35% of the time, and those of 71% to 90% diameter luminal narrowing causing no ischemia 20% of the time (2).

The apparent discordances between ICA and FFR to identify coronary stenoses that are suitable for performance of or deferral from revascularization and the ability of FFR to encourage therapeutic decision making in a manner that results in improved event-free survival better than ICA alone leads to interesting questions: Is FFR better because it triages a given stenosis severity better, or because it predicts inducible ischemia better? Even more intriguing is whether a given FFR, apart from better describing the severity of the stenosis, also reflects some crucial element of the plaque composition itself that is predicting outcomes while both causing the stenosis and also influencing blood flow across it.

In the last decade, coronary computed tomographic angiography (CTA) has emerged as a powerful noninvasive option that allows for direct visualization of angiographic coronary artery stenoses (3). While its diagnostic performance in the detection of CAD has been well studied in large observational studies as well as in a few randomized controlled trials, its strength appears in its ability to evaluate the vessel wall in addition allowing information not only about plaque presence and extent but also about finer details of plaque composition itself. This raises a number of issues of great practical utility: 1) visualizing plaque allows for focused use of preventive therapies such as statins—not surprisingly, despite its moderate diagnostic specificity, coronary CTA use has proven effective for informing clinical decision making of patients with suspected CAD, with the recently reported randomized controlled SCOT-Heart (Scottish Computed Tomography of the HEART) trial showing improved

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event-free survival in patients evaluated with coronary CTA versus those treated with standard of care techniques (4). 2) With its unique ability to estimate FFR noninvasively and with sufficient accuracy compared to invasive FFR, computed tomography might help unravel the complex relationship between stenosis appearance, plaque composition, its physiologic severity, inducible ischemia and possibly in future, hard events; it is important to remember the continued presence of hard events, albeit few, in the invasive FFR negative group of the FAME studies.

Notwithstanding its lesser spatial and temporal resolution compared to its counterpart invasive imaging modalities, coronary CTA allows for quantification and characterization of atherosclerotic plaque burden and type, lipid-rich coronary plaques, and surface plaque features similar to intravascular ultrasound, near-field infrared spectroscopy, and optical coherence tomography, respectively. These noninvasive coronary CTA findings have been demonstrated to yield important, independent, and incremental diagnostic and prognostic information in patients with suspected CAD. There is already evidence that plaque composition influences inducible ischemia in addition to measures of stenosis severity. Diagnostically, coronary CTA-derived atherosclerotic plaque features improve identification of ischemia through quantitative determination of aggregate plaque volume, low attenuation (hypodense) plaques (LAPs), positive arterial remodeling and spotty calcifications (5,6). These features also portend poor prognosis, and the presence of LAP and positive arterial remodeling are associated with poor near- and intermediate-term outcomes (7,8).

In this issue of *iJACC*, Ahmadi et al. (9) present the results of a sub-analysis of the NXT (HeartFlow Analysis of Coronary Blood Flow Using Coronary CT Angiography) study, a prospective multicenter evaluation of 254 patients undergoing coronary CTA, ICA, and FFR to carefully examine the relationship of atherosclerosis, stenosis, and ischemia. Atherosclerosis was quantified semiautomatically by computer software, and LAP—a coronary CTA surrogate marker of necrotic intraplaque core—was evaluated in volumetric fashion (mm^3). High-grade stenosis by ICA and ischemia by FFR was defined as >50% and ≤0.80, respectively. The authors evaluated the relationship of LAP, stenosis, and ischemia by 2 different approaches: 1) in coronary vessels in which only a single atherosclerotic lesion was present; and 2) in all vessels. The purpose of the former was to evaluate the direct relationship of atherosclerotic plaque characteristics to stenosis severity and ischemia. Among these 128 vessels, in addition to percent stenosis severity, LAP volume and presence of atherosclerosis in the left anterior descending artery were predictors of ischemia. In the model that included all vessels, these relationships remained consistent, but were further strengthened by the improved ability to diagnosis ischemia through identification of atherosclerosis in the proximal portion of a vessel as well as the number of atherosclerotic lesions. As expected, classification of coronary stenosis as <50%, 50% to 70%, and >70% improved categorization of lesions that were ischemic by FFR. Yet, within these 3 categories, coronary stenoses were sometimes variably associated with ischemia. In these groups, LAP atherosclerotic volume successfully discriminated ischemic versus nonischemic lesions. Combined together, these results emphasize the importance of evaluating both the atherosclerotic plaque features as well as the secondary consequences of the atherosclerosis on the vessel geometry (i.e., stenosis severity). Indeed, among the 300 lesions considered nonischemic (FFR >0.80), 98% were absent of high-grade stenosis and highest LAP volume. In contrast, among ischemic lesions (FFR <0.80), 88% of lesions showed either high-grade coronary stenosis or moderate-large LAP volume. Further, independent of stenosis severity, moderate or large LAP volume accounted for 72% of the ischemic lesions by FFR. Among categorizations of stenosis severity, the differences in LAP volume between ischemic and nonischemic coronary lesions were both statistically significant as well as remarkably consistent for <50% stenosis (17 mm^3 vs. 11 mm^3), 50% to 70% stenosis (19 mm^3 vs. 14 mm^3), and >70% stenosis (21 mm^3 vs. 14 mm^3), and suggest a binary cutpoint >15 mm^3 LAP as a potentially highly useful marker of atherosclerosis-defined ischemia.

The authors should be congratulated for the successful performance of this very interesting and provocative study, and for advancing the concept of ischemia determination beyond simply accounting for measures of coronary luminal narrowing and, instead, to also include quantitative atherosclerotic plaque assessment in a manner that better identifies and excludes ischemia. These present study findings offer novel insights to support previous work discussing some possible ways an atheromatous plaque can mediate ischemia over and above a given anatomical flow limitation (10). The hypodense nature of LAP atherosclerotic lesions on coronary CTA seem to be important surrogate markers of local metabolic processes that may influence endothelial function, vasoconstriction, and coronary flow. Numerous other atherosclerotic plaque features visualized by coronary CTA have been validated

for their diagnostic and prognostic significance-including measures of plaque burden, volume, diffuseness, spotty calcifications, and arterial remodeling—and it will be interesting if the authors would consider examining the additive effects of these quantitative atherosclerotic findings to LAP in their cohort. At present, coronary CTA is unique in its ability to enable comprehensive noninvasive characterization of coronary atherosclerosis and arterial geometry. The present study findings remind us that that atherosclerosis, not stenosis or ischemia, is the primary disease process. Instead, stenosis severity represents a secondary anatomic consequence of atherosclerosis on coronary lumen size, whereas ischemia is a tertiary physiologic consequence of atherosclerosis and luminal narrowing on intracoronary flow. Although atherosclerosis, stenosis, and ischemia are all well-accepted predictors of outcome, it has remained generally unknown to date their relationship to each other. These present study results represent a large step forward towards improving our understanding of these relationships, and strongly establish a novel concept of atherosclerosis-defined ischemia that does not necessarily have to be dependent on and defined by only on a given cut off value of stenosis severity alone. By this approach, atherosclerosis burden and type may be considered the primary variables of interest, and may serve to identify the highest-risk coronary artery lesions that cause luminal narrowing, ischemia, and downstream adverse events. Lord Kelvin once said, "If you cannot measure it, you cannot improve it." By recent advances in quantitative coronary CTA imaging, it is now feasible to comprehensively characterize patient-specific atherosclerotic processes, as well as determine their secondary consequences on coronary lumen geometry and tertiary consequences on coronary flow. Future studies evaluating atherosclerosis burden and its features as the primary measure of CAD severity may hearken a paradigm shift in what coronary measures are most appropriate and most effective for diagnosis, prognostication and therapeutic decision-making in patients with suspected CAD.

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