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EDITORIAL COMMENT

Coronary Plaque Volume and Stenosis

Important Determinants of Myocardial Ischemia*

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It is now established that anatomical stenosis alone—whether by coronary computed tomographic angiography (CTA) or invasive angiography—is a limited predictor of myocardial ischemia (1,2). Conversely, the absence of myocardial ischemia, although helpful for identifying patients who are less likely to benefit from coronary revascularization, cannot be used to exclude the presence of prognostically significant coronary plaque. Given these limitations, it may seem appealing to combine anatomical data regarding coronary plaque with a functional test. Yet, in the current era of escalating health care costs, the common approach is to start with 1 test, and, only if needed, to then obtain a complementary test. Supporting this notion, the recent PACIFIC (Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CT Coronary Angiography with Invasive Coronary Angiography) trial found that the use of hybrid imaging did not improve the diagnostic accuracy to detect ischemia. However, in this well-conducted prospective study, coronary CTA used a threshold of having >50% stenosis to define a vessel as abnormal, and the prevalence of such disease was high. Consequently, although coronary CTA had high per-patient sensitivity (90%) to detect ischemia by invasive fractional flow reserve (FFR), the specificity was only 60%.

In this issue of the *Journal,* Driessen et al. (3) report a post hoc substudy from the PACIFIC trial evaluating the association of coronary plaque burden and morphology with both noninvasive and invasive measures of myocardial ischemia. This study was performed in the same population of 208 individuals with an intermediate pre-test likelihood of obstructive coronary artery disease who underwent CTA, cardiac positron emission tomography (PET), and invasive FFR as previously reported. PET-derived measures of hyperemic myocardial blood flow (MBF; in ml/g/min) during adenosine infusion was used to provide a noninvasive measure ischemia, whereas invasive FFR of ≤0.80 was considered to be hemodynamically significant.

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Results from a multivariable model adjusting for luminal stenosis revealed that noncalcified plaque volume and positive remodeling were strongly associated with impaired hyperemic blood flow by PET as well as reduced FFR. Low-attenuation plaque and spotty calcifications were also found to be associated with reduced FFR, but this relationship did not hold for hyperemic blood flow. When assessing the improvement in discrimination for ischemic lesions, the addition of noncalcified plaque volume and positive remodeling improved the area under the receiver-operating characteristic curve from 0.86 to 0.90 (this was driven mostly by the addition of noncalcified plaque volume).

Prior studies have shown that plaque characteristics on coronary CTA—such as positive remodeling, low attenuation plaque, and plaque volume—are not only associated with future acute coronary syndromes (4), but also that these features improve the identification of lesions that cause a reduction in FFR (5,6) in a manner that is incremental to coronary stenosis. The information from Driessen et al. from the PACIFIC trial extend these findings by providing a comprehensive assessment of various plaque features as part of a prospective study in which ischemia was assessed

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by both invasive (FFR) and noninvasive (MBF) techniques.

There are several important insights and lessons supported by the findings in this study.

1) FFR and MBF are influenced by both the severity of focal stenosis and diffuse atherosclerosis. In the present study (3), the severity of coronary stenosis (i.e., no stenosis, 50% to 70% stenosis, and >70% stenosis) had the strongest association with either abnormal MBF or FFR. When added to the severity of stenosis, noncalcified plaque volume provided a small but significant improvement in predicting abnormal FFR and MBF. This is not unexpected, because plaque volume (calcified or noncalcified) contributes to both focal stenosis severity and diffuse burden of atherosclerosis (7). Notably, the incremental value of adding plaque volume to stenosis severity was lower in this study than in prior investigations in which stenosis was modeled on a binary cutpoint of ≥50% stenosis. This difference may in part be due to using increasing categories of coronary stenosis—as defined by current multisociety consensus documents (8)—which results in a higher area under than the curve value than has been observed when evaluating stenosis on a single cutpoint of 50% stenosis, compared with invasive FFR (e.g., 0.86 in current study vs. 0.71 in Gaur et al. [6] or 0.72 in Park et al. [5]). When comparing these studies, it also is important to acknowledge that differences in reproducibility of various semiautomated plaque analysis techniques may contribute to some of these differences.

So why is the volume of noncalcified important? It is known that the burden of focal stenosis and diffuse atherosclerosis are important determinants of coronary pressure gradient and downstream flow, and, as shown in this study, a more robust discrimination for ischemia than positive remodeling or low attenuation plaque. On the other hand, the presence of low attenuation plaque was associated with impaired FFR but not with reduced MBF. The physiologic explanation for this apparent discrepancy is unclear. It may relate to an increased relative frequency of low attenuation features among plaques that contributed predominantly to focal plaque volume as opposed to diffuse atherosclerosis in this study.

2) Even when integrating multiple different variables of plaque extent, severity, and morphology, predicting physiology is, and will continue to be, imperfect. Certainly, trying to predict ischemia—whether assessed by invasive or noninvasive techniques—is always going to be imperfect when using anatomical measures. Although such studies are important for providing mechanistic insights into the determinants of myocardial ischemia, it is not clear that one can directly apply these findings to predict ischemia in an individual patient. In clinical practice, we must often ask about the objective of obtaining a cardiac imaging test and realize that, depending on the clinical question and patient characteristics, some tests will be better than others. Consequently, studies that try to compare anatomical approaches with functional ones, or functional approaches with coronary anatomy, will always reveal a certain level of discrepancy as they offer different insights into the pathophysiology of myocardial ischemia.

3) Clinical implications: we should routinely evaluate plaque morphology and extent, not just stenosis. This may be especially relevant in diagnostic patient cohorts that are less likely to have obstructive coronary artery disease. When coronary CTA studies are interpreted in clinical practice, a full quantitative assessment of noncalcified plaque may not always be possible or feasible. Nevertheless, when a large amount of diffuse plaque is present, even in the absence of focal stenosis, one should recognize that this finding has been associated with reduced FFR and MBF, angina, and adverse prognosis (9,10).

Interestingly, the amount of noncalcified plaque may be more responsive to some medical therapies—such as intense reduction in low-density lipoprotein cholesterol—and thus it is plausible that various interventions that may improve MBF may also, in part, mediate their effect via a reduction in plaque volume. Further research using both coronary CTA and MBF would be needed to substantiate these hypotheses further. For example, are patients with noncalcified plaque more likely to respond to various therapies (e.g., aggressive low-density lipoprotein cholesterol-lowering)? Or, are patients with impaired MBF the ones who will be more likely to benefit from certain therapies?

4) Both invasive and noninvasive measures of blood flow provided concordant results…are both needed in future studies? The current study by Driessen et al. (3) provides further support that noninvasive quantitative measures of MBF (or coronary flow reserve) by PET provide robust data that is comparable to assessing FFR invasively. In fact, there may be advantages to PET because it provides a measure of flow at the tissue level and thus may ultimately be more physiologic than assessing focal pressure gradient within the coronary artery. Given the cost and inherent risk of performing invasive FFR, future studies may benefit from greater adoption of MBF assessment by PET. Such studies also would have the advantage of not relying on patients who are referred to the catheterization laboratory, thus eliminating the inherent referral bias present when examining

high-risk populations. Finally, a noninvasive assessment by PET may facilitate serial testing of MBF and thus may enhance the ability to assess therapeutic response of various non-invasive interventions.

The authors of this PACIFIC substudy should be congratulated on providing a robust and well-conducted analysis comparing coronary plaque characteristics with both invasive and noninvasive measurements of ischemia. Although this study is limited in that it does not provide information on events—and would not have sufficient power for examining for differences in events across subgroups of interest—it does provide important insights regarding the relationship between coronary plaque characteristic and ischemia, as well as potential implications for clinical care and research.

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