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EDITORIAL COMMENT

Progress in the Noninvasive Detection of High-Risk Coronary Plaques*

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Pathologists have known for almost a half century that disruption of coronary plaque is responsible for coronary thrombosis (1), leading to acute coronary syndromes (ACS), including sudden cardiac death (1,2). Clinicians, understandably, want to detect these plaques before they rupture so that they can undertake preventive measures. In their classic 1992 article on the pathogenesis of coronary artery disease and ACS, Fuster et al. (3) predicted, correctly, that "It may soon be possible to detect fatty plaques in the vascular system by several techniques, such as intravascular ultrasound (IVUS) or noninvasive magnetic resonance imaging, ultrafast computed tomography, spectroscopy, or radioisotope imaging."

Six years ago, I was invited to prepare an editorial comment on an important paper on this subject published in the *Journal*. Motoyama et al. (4) carried out contrast-enhanced computed tomographic angiography (CTA) in 1,059 patients with known or suspected coronary artery disease (CAD) who were followed for an average of 27 months (2,383 patient-years). Only 15 (1.5%) of these patients experienced an ACS, but 10 of these occurred among the 45 patients who showed positive coronary artery remodeling and exhibited plaques with low attenuation ("soft plaques") on CTA (4). This pivotal paper opened the door to a *noninvasive* approach to the detection of atherosclerotic plaques at high risk of rupture, so-called "vulnerable plaques." I suggested that before widespread adoption of this interesting use of CTA, the study of additional patients was in order, as were further refinements of the technology and more potent therapies designed to prevent the rupture of such plaques (5).

LESSONS LEARNED SINCE 2009

Not surprisingly, characterization of and efforts to identify and treat such coronary plaques has remained a subject of intense interest, and we have learned much in the interim. Narula et al. (6) returned to the pathology laboratory and characterized the histopathological features of 295 coronary plaques obtained postmortem from patients who died suddenly. They reported that thinning of the fibrous cap is a very important indicator of plaque vulnerability. Although it is possible to make measurements of the thickness of a cap overlying a lipid-filled necrotic core in vivo using optimal coherence tomography or gray-scale and radiofrequency IVUS (virtual histology), these techniques obviously require coronary artery catheterization. However, they also noted that greater plaque burden and severe stenosis, both of which can be assessed noninvasively by CTA, can be helpful in determining the risk of plaque rupture. Stone et al. (7) used IVUS to study 697 patients with ACS who had undergone percutaneous coronary intervention (PCI). The 3-year cumulative event rate of recurrent ACS or cardiac death was 20.4%. Interestingly, only about one-half of these events resulted from recurrences at the site of the culprit lesion and the other one-half to nonculprit lesions characterized by thin cap fibroatheroma, extensive plaque burden, and small luminal area. As stated in the preceding text, the 2 latter characteristics can be assessed noninvasively by CTA.

During the past 6 years, CTA has certainly become an important diagnostic tool in cardiology. In one study, 34 of 368 patients who presented to an emergency department with acute chest pain, but no

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other signs of ischemia, had significant coronary stenosis on CTA, and 21 of these 34 had ACS. Morphological characteristics predictive of ACS included plaque length, plaque volume, and arterial remodeling (8). Normal coronary arteries on CTA in these patients essentially ruled out ACS (i.e., the technique had a high negative predictive value). In another analysis of CAD patients who underwent CTA for diagnostic purposes and who were then followed for an average of 3.6 years, Bittencourt et al. (9) reported that patients with plaques that were extensive and/or accompanied by severe obstruction had a higher risk of cardiovascular death or myocardial infarction than did patients whose plaques did not have these features.

For many years, it has been accepted that atherosclerotic CAD is usually a generalized rather than a focal disorder, and there is increased evidence of the dynamic nature of the morphology of coronary arterial lesion morphology. Serial studies, using largely invasive techniques, have demonstrated that some thin-cap, fibrous, atheromatous lesions, the hallmark of high-risk plaques, may increase in size and number, whereas other plaques may develop thicker caps or even become frankly fibrotic (10,11).

Important refinements of noninvasive assessment of plaques are ongoing. The uptake of ^{18}F-2-deoxyglucose (FDG) detected by positron emission tomography (PET) occurs in metabolically active, macrophage-rich regions, reflecting the inflammatory changes in the plaque and neighboring arterial wall that appear to be predictive of future vascular events (12). The coupling of the morphology of plaques as assessed by CTA to their metabolism ascertained by FDG-PET, although complex and expensive, may in the future permit more accurate noninvasive recognition of high-risk plaques.

From a therapeutic perspective, although no new anti-inflammatory drugs have been shown convincingly to reduce the risk of plaque rupture in the past 6 years, some such agents are now in phase III trials. However, it is reassuring that high-dose statin therapy, which is safe and now inexpensive, appears to reduce atherosclerotic plaque volume and increase fibrous cap thickness. This action is likely to be the result of resolution of inflammation secondary to lowering of the plaque's lipid content by the statin (13). Although the issue has not been settled definitively, it does appear that in patients with ST-segment elevation myocardial infarction who have undergone PCI of their culprit artery, preventive PCI of stenotic nonculprit arteries improves clinical outcome. Whether this applies to other forms of ACS is unclear (14).

THE PRESENT STUDY

In this issue of the *Journal,* Motoyama et al. (15) now have extended their earlier assessment of coronary arteries by CTA to 3,158 patients and have followed them over an average of 3.9 years, providing an observation period of 12,316 patient-years, a more

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than 5-fold greater experience than in their 2009 paper (4). During this period, 88 (2.8%) developed an ACS. High-risk plaques were defined as showing a remodeling index (lesion diameter/reference diameter) ≥1.1 and/or low plaque attenuation. They also observed that when entered into a multivariable Cox hazard analysis that included clinical variables, the presence of high-risk plaques detected by CTA was an independent predictor of subsequent ACS. Two CTAs were carried out in 449 of their patients an average of 1 year apart. Both progression and stabilization of coronary plaques were observed; the subsequent risks of ACS were higher in patients in the former group. Not surprisingly, ACS occurred 10 times more frequently in patients with than in those without high-risk plaques. Because the former were present in only 9.3% of the patients, the actual number of patients developing ACS from these 2 groups was almost identical: 45 in patients with and 43 in patients without high-risk plaques, respectively. Therefore, if a therapeutic intervention were carried out in only the patients with high-risk plaques, the incidence of the development or recurrence of ACS could, at best, be reduced by one-half.

TAKE-HOME POINTS

There are several takeaways from this study:

1. Although patients with coronary artery plaques having thin-walled fibrous caps and large lipid-filled necrotic cores are at the highest risk of future ACS, cap thickness and plaque composition cannot now be identified by any noninvasive technique, including CTA.
2. Nevertheless, coronary anatomy can be ascertained noninvasively and with reasonable accuracy using contrast-enhanced CTA in patients with known or suspected CAD.
3. CTA may be useful clinically to rule out ACS in patients with chest pain of unclear etiology presenting to emergency departments.
4. In patients with chronic CAD, the number of vessels with significant obstruction on CTA correlates directly with mortality. In symptomatic patients with suspected CAD, the negative

predictive value of a normal coronary CTA is high and may be useful to rule out epicardial CAD.

5. Clinically apparent CAD usually involves more than a single plaque; it is often a diffuse disease, and it is dynamic, with several plaques in various stages of formation, evolution, and regression at any time.
6. CTA can detect high-risk plaques, characterized by positive remodeling of the vessel and low attenuation, and is often accompanied by significant stenosis of the artery in the region of the plaque.
7. The detection of multiple high-risk plaques by CTA identifies patients at high risk of adverse outcome and is an independent predictor of subsequent ACS.
8. There is increasing interest in and emphasis on the identification of high-risk *patients* rather than high-risk *plaques* (11,16).
9. High-dose statin therapy reduces the number of high-risk plaques and the patient's risk of adverse coronary events. New anti-inflammatory agents are under active investigation. The use of prolonged antiplatelet therapy and the revascularization of nonculprit arteries with high-risk plaques should be handled on a case-by-case basis.
10. Combining metabolic with anatomic imaging, such as the combination of PET with CTA, may enhance the noninvasive characterization of arterial plaques, thereby further improving risk stratification and management.

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