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EDITORIAL COMMENT

What Will Noninvasive Carotid Atherosclerosis Imaging Show Us About High-Risk Coronary Plaques?*

Chun Yuan, PHD,† Nayak L. Polissar, PHD,‡ Thomas S. Hatsukami, MD§

Seattle, Washington

With the advent of many noninvasive imaging techniques to characterize atherosclerotic plaques in vivo, it is time to investigate the relationships of high-risk lesions in different vascular beds as a systemic disease.

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The quest to noninvasively identify vulnerable atherosclerotic plaques that pose an increased risk of heart attack and stroke may have gained another tool in magnetic resonance imaging (MRI). Vulnerable plaque imaging remains a challenging field for many reasons: from the spatial resolution needed to identify thin cap fibroatheroma in the coronary arteries, to quantifying the amount of lipid content and inflammation in plaques (1). The technical challenges are further compounded by there perhaps being multiple vulnerable plaques in a single vascular bed (i.e., coronary arteries), and as a systemic disease, atherosclerosis may develop in multiple vascular beds (2). Direct noninvasive coronary vulnerable plaque imaging (with computed tomography) remains limited to the examination of calcium deposits and categorization of lesions as hard versus soft plaque rather than a direct characterization of thin cap fibroatheroma or other high-risk features (3). In this issue of the *Journal*, Noguchi et al. (4) suggest a direct plaque imaging approach to predict risk of future cardiovascular events. In this case, the direct plaque imaging technique is focused on bright T1 signals in MRI of the carotid arteries. The authors demonstrate that these "high-risk" signals in the carotids can help predict coronary events.

With a larger size, easy access by many imaging techniques, and less motion compared to the coronary arteries, it is natural that carotid artery atherosclerosis be considered as a surrogate for coronary artery disease. In particular, increased carotid intima media thickness (IMT) has been shown to be associated with increased risk of cardiovascular disease events (5), although the nature of this association is controversial. Carotid IMT, obtained from B-mode ultrasound, is not a direct measure of carotid plaque, and a recent summary of meta-analyses concludes that regression or slowed progression of carotid IMT does not reflect reduction in cardiovascular events (6). The true value of using the carotid artery as a surrogate of coronary artery disease may lie in linking the specific high-risk atherosclerotic lesions or lesion features in the 2 vascular beds. Indeed, in a large study of the histological features of plaques obtained from patients undergoing carotid endarterectomy, Hellings et al. (7) showed that presence of carotid plaque hemorrhage or marked intraplaque vessel formation predicted an increased risk for composite events (vascular death, nonfatal stroke, nonfatal myocardial infarction) during follow-up. While this study provides compelling evidence of a possible linkage between "high-risk" plaque features across vascular beds in patients requiring carotid surgery, the findings by Noguchi et al. (4) suggest that this association holds true among those with earlier stage, asymptomatic carotid atherosclerosis.

The bright T1 signal in MRI reported in this study is believed to be from intraplaque hemorrhage (IPH) and likely due to the degradation of hemorrhage into methemoglobin. Methemoglobin shortens the longitudinal relaxation time (T1) and gives the bright signals in T1-weighted images such as in the magnetization-prepared rapid acquisition gradient echo (MPRAGE) and time-of-flight and fast spin echo techniques. Each of these sequences has been validated with histology to detect IPH in the carotid atherosclerosis (8–13). More importantly, a series of prospective and cross-sectional studies have found a clear link between IPH and accelerated progression in carotid plaque burden, as well as associations between carotid IPH and the development of future ischemic neurological events (14–18).

The MRI studies of persons with asymptomatic, minimal carotid stenosis have demonstrated a surprisingly high prevalence of carotid plaques with IPH (19,20) and highlight the limitation of stenotic severity as the principal criterion for disease assessment. In the cohort reported by Noguchi et al. (4), >50% of the carotid plaques had MRI evidence of IPH, yet they had a mean stenosis of only 22.5%. Recently, a carotid atherosclerosis scoring system was introduced by Underhill et al. (21) to

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From the †Department of Radiology, University of Washington School of Medicine, Seattle, Washington; ‡The Mountain-Whisper-Light Statistical Consulting, Seattle, Washington; and the §Department of Surgery, University of Washington School of Medicine, Seattle, Washington. Dr. Yuan has received research grants from Philips Medical and VP Diagnostics, and has served as a consultant to Pfizer and Merck. All other authors have reported that they have no relationships to disclose.

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predict the presence of carotid IPH, and indicated that plaque burden and the size of plaque features such as the lipid-rich necrotic core were more strongly associated with IPH presence than with the severity of luminal narrowing.

The work of Noguchi et al. (4) is exciting and promising, but there are also several limitations associated with this study. Given the prominent role that high-intensity plaques (HIP) play in their report, there is no analysis with a continuous formulation of HIP that, in theory, reflects the size of intraplaque hemorrhage of a plaque and may enhance the statistical power of the study. It would also be useful to see if there is a dose-response relationship between continuous HIP and the risk of an event. Likewise, the reliability and robustness of HIP detection for general clinical application needs to be assessed.

The subjects selected for this study had confirmed carotid atherosclerosis and stable coronary artery disease. Translation of the main findings from this study to a more general high-risk population will be challenging. Interestingly, a recent MRI-based study (22) found that among subjects with confirmed CAD, only 9.7% had carotid plaques with intraplaque hemorrhage. It is clear that all these subjects belong to the high-risk population, but whether there is a better tailored diagnosis and treatment for a subset within this population remains to be seen.

Another observation from the study is the very abrupt decrease in risk of an event in the HIP group at about 18 to 20 months, with the curve leveling off considerably and a much weaker (and perhaps nonexistent) leveling off in the non-HIP group a little later (Fig. 2). That seems to suggest a statistically significant and approximately eightfold decrease in risk of an event per unit time comparing months 0 to 20 to months 20 to 40. That clearly needs further study and explanation.

Future work. The paper by Noguchi et al. (4) provides a strong start in the effort to test the hypothesis that high-risk plaque features are expressed systemically. Larger, multicenter studies are needed to confirm these promising initial findings. A key question is how plaque imaging should alter patient management. Ongoing studies such as the High-Risk Plaque Initiative (23) will provide valuable insight toward identifying persons who by current clinical guidelines are considered low to intermediate risk, and as such are currently not aggressively managed, and who may benefit from MRI plaque imaging.

Finally, what is even more exciting is that the study has been conducted through noninvasive imaging, and thus offers the potential to examine the changes in these lesions over time. Prospective, serial studies with MRI will result in a better understanding of the nature and etiology of IPH, may lead to the discovery of novel therapies to prevent its development, and will be needed to assess whether such therapies lead to a reduction in coronary and carotid events.

Reprint requests and correspondence: Dr. Chun Yuan, University of Washington, Radiology, Box 358050, 815 Mercer Street, Seattle, Washington 98109. E-mail: cyuan@u.washington.edu.

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