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EDITORIAL COMMENT

Carotid Atherosclerosis and Magnetic Resonance Imaging*

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In this issue of *JACC: Cardiovascular Imaging*, Raman et al. (1) illustrate the utility of magnetic resonance imaging (MRI) for the noninvasive evaluation of carotid atherosclerosis. The authors evaluate plaque T2* values from a single-vessel location where the lesion is of maximum size. They show that mean values of T2* are lower in symptom-producing plaques compared with asymptomatic lesions in patients with carotid atherosclerosis. The authors then evaluate ex vivo carotid endarterectomy specimens and suggest that these T2* differences are from characteristic changes in iron forms in the symptom-producing plaques. These findings demonstrate the capability of MRI to not only identify carotid lesion morphology and composition but also to evaluate signal patterns from particular molecules and elements within the tissue. In addition, this study highlights a unique advantage of carotid plaque imaging: to use intact surgical specimens as a gold standard for validation of in vivo imaging findings. Finally, this study illustrates the complexity of analyzing the multifaceted aspects of "culprit" lesions.

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Presently, there is much debate about the proper way to determine the vulnerability of atherosclerotic plaques both by histology and through in vivo imaging. Imaging methods have the potential to not only be used as a screening tool for the presence of atherosclerosis but also to help distinguish stable from vulnerable plaques and ultimately to distinguish patients with low versus high risk of cardiovascular complications. The model for vulnerable plaques comes from extensive accumulated knowledge about the structural and compositional features of culprit atherosclerotic lesions in the coronary arteries. A landmark study based on coronary autopsy specimens found that sudden cardiac death was highly associated with the presence of a ruptured fibrous cap, calcium nodule, or endothelial erosion (2). In a recent publication, Cheruvu et al. (3) emphasized the importance of determining the frequency and distribution of thin-cap fibroatheroma and ruptured plaques in coronary arteries.

These findings have helped diagnostic studies target specific areas where most rupture-prone lesions occur. Carotid arteries, the target of this publication, are larger than coronary arteries and have a very different hemodynamic environment. Studies have shown that ischemic cerebrovascular events are frequently the result of embolization, whereas cardiac events are often the result of plaque rupture followed by vessel thrombosis (3). Thus, it is also important to determine whether plaque features that are associated with coronary events are similar to those that cause carotid embolization.

On the basis of this background, the goals of carotid imaging might be summarized as: to establish and validate the capacity of imaging to detect the principal features believed to be associated with vulnerable plaques, to evaluate the association of these imaging findings with neurological symptoms in a cross-sectional study, and ultimately to assess whether the identification of these principal plaque features predicts future ischemic events in a prospective, longitudinal study.

In the last decade, significant progress has been made toward the noninvasive detection of vulnerable atherosclerotic plaque using MRI (4,5). Extensive technical development and validation studies have been conducted that have established the capability of MRI to noninvasively quantify plaque morphology, tissue composition,

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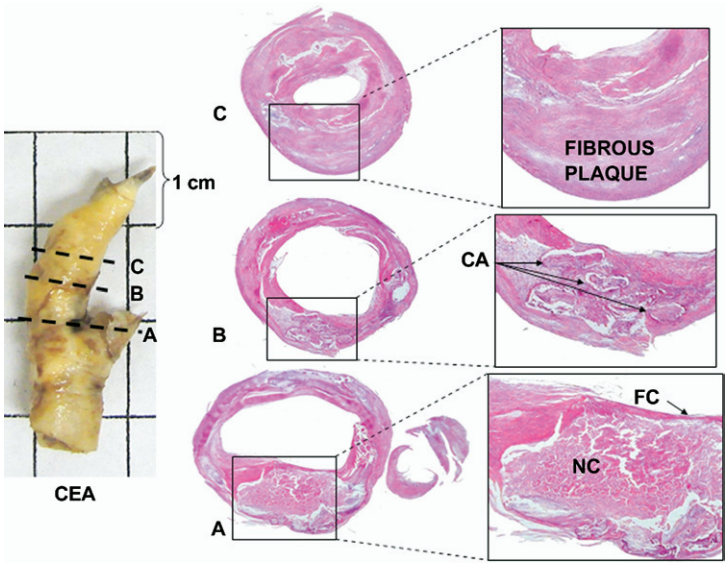

Figure 1. Three Histology Sections Taken From the Same Carotid Plaque Specimen

(A) A large necrotic core (NC) with a very thin fibrous cap (FC), **(B)** a heavily calcified (CA) plaque, and **(C)** the section with maximal plaque and maximal stenosis, composed of predominantly fibrous tissue. CEA = carotid endarterectomy.

and flow dynamic conditions. Cross-sectional studies have identified a series of MRI features associated with patient symptoms. These studies indicate that fibrous cap rupture (6,7), the presence of juxtaluminal (7) hemorrhage thrombus (8), and plaque stresses (9,10) are associated with patient symptoms. Several interesting studies compared bilateral carotid plaque features (morphology and tissue composition) (7,11) and contrast agent uptake (12,13) of symptomatic and asymptomatic plaques from the same subjects. In general, the key findings are that a greater incidence of fibrous cap rupture, juxtaluminal hemorrhage or thrombus, and complicated American Heart Association type VI lesions are associated with symptomatic plaques. Additionally, MRI studies that incorporate ultra-small, superparamagnetic iron oxide particles, which are believed to be taken up by activated macrophages, have shown an increased uptake (therefore, increased inflammation) in symptomatic plaques (12). Finally, initial results from prospective, longitudinal studies have demonstrated that identification, via MRI, of a thin or ruptured fibrous cap, intraplaque hemorrhage, and larger necrotic cores are associated with an increased hazard for future ischemic cerebrovascular events (14).

Findings from the study by Raman et al. (1), which uses an MRI technique to detect iron content, provide further corroborating evidence of the important role of hemorrhage in carotid plaque stability. The authors report that iron in plaques on histopathology occurred at sites of intraplaque hemorrhage and suggest that microhemorrhage into plaque with macrophage-mediated degradation of red blood cells leads to accumulation of iron. The authors acknowledge that the T2* measurement from a single slice at the point of maximal plaque is a limitation of their study and that development of 3-dimensional T2* acquisition techniques is needed.

The heterogeneity and complexity of human carotid atherosclerosis and the need for 3-dimensional analysis, not only of imaging data but also for histological findings, was highlighted in a critical review of the literature by Gao et al. (15). In their analysis of 31 observational studies that examined the role of intraplaque hemorrhage in the pathogenesis of ischemic neurological events, Gao et al. (15) found that the odds ratios varied widely. The authors suggested that a major contributing factor in this variability is the lack of a uniform method to analyze the size, number, and location of plaque features. Furthermore, some studies examined single cross sections, whereas others examined the entire lesion.

In our experience, the complex features of human carotid plaques vary substantially from location to location. Figure 1 shows 3 histology sections taken from the same carotid plaque specimen. There are a number of noticeable features: 1) the cross section obtained from the proximal internal carotid artery (label A in Fig. 1) demonstrates a large necrotic core with a very thin fibrous cap, but the section with maximal plaque and maximal stenosis (label C in Fig. 1) is predominantly fibrous tissue; and 2) the inter-

vening cross section (label B in Fig. 1) demonstrates a heavily calcified plaque, which would appear hypointense on T2-weighted imaging. For this particular plaque, images acquired only from the location with maximal plaque would have demonstrated a fibrotic plaque. This example highlights the need for comprehensive, 3-dimensional examination of lesions in histology and in imaging.

This article also points to the importance of a "multispectral" approach to plaque MRI, both in terms of multiple imaging techniques and multiple imaging targets. Reviewing the histology results of these authors, it is found that calcification emerges as the logical target, given that it has much greater volume overall and is strongly associated (negatively) with symptoms. For iron, on the other hand, only a weak association between symptoms and Fe(III) was found in the direction opposite that hypothesized. In other studies, equally compelling associations were found between symptoms and intraplaque hemorrhage, inflammation, and cap rupture. A logical conclusion is that many of these features are mutually dependent and that a very large study is needed to elucidate the most pertinent imaging target(s). The ideal technology for such a study would be MRI, given its extensive validation to noninvasively probe virtually all aspects of plaque structure.

In summary, substantial progress has been made in the in vivo characterization of human carotid atherosclerosis with MRI; MRI has been extensively validated with the use of a histological gold standard, and a number of cross-sectional studies that incorporate MRI have confirmed the association between specific plaque features such as fibrous cap status and intraplaque hemorrhage and clinical status. Furthermore, initial reports from prospective, longitudinal MRI studies are providing insights into the nature of the high-risk, vulnerable plaque. The challenge is to develop reproducible methods to evaluate these lesions 3-dimensionally to account for the variability in morphology and composition and to determine the combination of plaque features that best predicts risk for future ischemic events.

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