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EDITORIAL COMMENT

Noninvasive Imaging of Plaque Inflammation

Role of Contrast-Enhanced MRI*

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In recent years, great strides have been made in noninvasive imaging of atherosclerotic plaque, motivated by the potential to identify specific plaque characteristics associated with clinical sequelae or disease progression. In this endeavor, inflammation has been a prominent imaging target because of its importance in all stages of plaque development. Intimal infiltration of inflammatory cells is one of

See page 1127

the first steps in the development of an atherosclerotic lesion (1). Development of a necrotic core is driven by apoptosis of macrophage-derived foam cells and the entry of blood cells through leaky neovessels stimulated by proinflammatory mediators (2). Disruption of the overlying fibrous cap leads to clinical thromboembolic events and may be precipitated by degradation of the fibrous matrix via matrix metalloproteinases released from inflammatory cells (3). Thus, imaging plaque inflammation may play a role in diagnosing high-risk plaque, identifying therapeutic targets, or evaluating novel anti-inflammatory therapies.

Within the atherosclerosis imaging community, inflammation largely has been synonymous with macrophages. It is important to recognize, however, that inflammation is a multifaceted entity characterized not only by macrophage infiltration, but also by the presence of other immune cells, stimulation of neovasculature, the presence of edema, and changes in temperature and pH. All of these aspects present opportunities for imaging inflammation.

In the case of neovasculature and edema, magnetic resonance imaging (MRI) with clinically used gadolinium contrast agents can be remarkably powerful. The entry and retention of these contrast agents within atherosclerotic plaques is determined by the extent and permeability of the neovasculature. The resulting variations in contrast agent uptake and patterns of enhancement are analogous to the results of delayed enhancement and perfusion MRI of the myocardium, which have become powerful tools in the detection of fibrosis and ischemia in the heart (4).

In this issue of *iJACC*, Hur et al. (5) explore the use of contrast-enhanced MRI in a rabbit model of atherosclerosis. They report a correlation between vessel wall enhancement and density of neovessels within the plaque. This corroborates previous reports of a link between enhancement and neovessels in a similar rabbit model (6) of atherosclerosis and in human atherosclerotic disease (7,8).

Hur et al. (5) also demonstrate the relevance of this finding to inflammation by demonstrating strong relationships of both contrast enhancement and neovessel density with macrophage content. Again, this finding is supported in the prior literature on contrast-enhanced plaque MRI. In our own work, we have used dynamic contrast-enhanced MRI and kinetic modeling to probe plaque physiology quantitatively in terms of fractional plasma volume and contrast agent transfer constant (8–10). These efforts have demonstrated correlations between these parameters and a variety of markers of inflammation, including macrophages, neovessels, and serum C-reactive protein.

A drawback of the study of Hur et al. (5) is that their use of enhancement ratio to measure uptake is affected by a variety of imaging and physiological parameters, such as the volume of contrast agent relative to the total volume of blood plasma or the

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amount of signal void resulting from calcification. Outside the highly controlled rabbit model, the impact of physiological variability in a diverse human population is uncertain. Nevertheless, this study is important in further establishing the link between contrast agent uptake and plaque inflammation.

One point that distinguishes the work of Hur et al. (5) from past studies is that the lesions studied in the rabbit model are quite small in comparison with the advanced carotid artery lesions evaluated in prior human studies. Thin walls with small plaque deposits present a technical challenge for many of the past approaches to measuring enhancement, which are sensitive to partial volume effects from the large contrast agent concentration in the vessel lumen. Hur et al. (5) address this problem with a novel 3-dimensional (3D) black-blood acquisition that effectively suppresses the lumen signal. The use of 3D imaging also boosts the signal-to-noise ratio compared with 2-dimensional imaging techniques, allowing high-resolution imaging. Thus, this result serves as evidence of the feasibility and validity of contrast-enhanced MRI for the assessment of inflammation in small or early lesions of atherosclerosis. Technical advancement leading to robust 3D imaging with efficient blood suppression is an ongoing development goal in vessel-wall MRI (11).

Although these findings emphasize the role that contrast-enhanced MRI can play in assessing plaque inflammation, the approach must be placed into context with the many other assessment tools for plaque inflammation. Atherosclerosis has been one of the predominant targets in the emerging field of molecular imaging. Targeted contrast agents for atherosclerosis have been proposed for MRI, positron emission tomography (PET), computed tomography, and ultrasound imaging (12–15). Molecular targets of the contrast agents have included numerous inflammatory markers, such as $\alpha_v\beta_3$ integrin, matrix metalloproteinases, and the macrophage scavenger receptor B (16–18). These agents likely represent a bright future for imaging of plaque inflammation, but they face a long road before they are considered safe and effective for large-scale human use.

In the nearer term, imaging of plaque inflammation in humans will require the adaptation of existing technologies, such as contrast-enhanced MRI. Because inflammatory components, such as macrophages, account for small fractions of the total plaque volume and exhibit no exogenous contrast, imaging of plaque inflammation requires the use of injected agents. In addition to gadolinium-based MRI agents, studies have successfully linked inflammation to uptake of [18F]-fluorodeoxyglucose (FDG) in PET, ultrasmall superparamagnetic iron oxides (USPIOs) in MRI, and microbubbles in ultrasound (19–21).

Each of these agents works on different, but interrelated, aspects of inflammation. For instance, FDG PET uses the fact that macrophages are the predominant metabolically active cell in atherosclerotic plaque to identify inflamed regions with high activity on subsequent PET images. USPIOs have been shown to be ingested by macrophages residing within atherosclerotic plaque, yielding signal voids on MRI approximately 24 h after administration. Microbubble contrast-enhanced ultrasound is most analogous to contrast-enhanced MRI, relying on free distribution of the agent into the plaque via neovasculature. Nevertheless, given the importance of the neovasculature in delivery of FDG or USPIOs into the plaque, all of these strategies for imaging of plaque inflammation are likely to elicit closely interdependent measurements.

In deciding among these approaches, a strong case can be made for contrast-enhanced MRI. First, the absence of ionizing radiation makes MRI ideal for serial research studies. Also, despite the risk of nephrogenic systemic fibrosis in populations with impaired kidney function, gadolinium contrast agents have an excellent safety profile. From a practical standpoint, contrast-enhanced MRI can be performed in a single session lasting only minutes, whereas USPIOs require 2 imaging sessions separated by 24 h or more. Also, MRI is already leading the field for comprehensive plaque analysis in large arteries, such as the carotid (22). Therefore, contrast-enhanced MRI can be a minor add-on to an existing MRI examination. In fact, the use of gadolinium contrast agents for MRI of atherosclerosis is already advocated for accurate detection of plaque components (23). Finally, MRI permits high-resolution imaging of plaque, with pixel dimensions of $\leq$500 μm. This permits localized measurements of enhancement, limited, for example, to fibrous regions of the plaque (24). With regard to disadvantages of contrast-enhanced MRI, an important distinction is the nonspecific nature of contrast agent uptake. Enhancement does not directly measure macrophages or other inflammatory cells, but signifies an increase in plaque perfusion that is strongly associated with inflammatory cells.

Ultimately, imaging of inflammation in atherosclerosis is intended as a clinical tool for identifying individual plaques at risk of rupture. For this

JACC: CARDIOVASCULAR IMAGING, VOL. 3, NO. 11, 2010
NOVEMBER 2010:1136–8

purpose, studies are needed that prospectively link imaging assessments of plaque inflammation to outcomes. Another application where inflammation imaging is already in use is the evaluation of drug therapies in clinical trials. Already, reports of statin effects on FDG uptake have been reported using PET (25). Similar studies are under way using contrast-enhanced MRI.

Overall, contrast-enhanced MRI is a strong contender for an imaging technique that is sensitive to plaque inflammation. The next challenge is to determine to what extent it adds value to either clinical risk assessment or evaluation of therapeutic effects.

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