MRI of Geometric and Compositional Features of Vulnerable Carotid Plaque

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Abstract—Noninvasive imaging of atherosclerotic disease provides a powerful opportunity to gain insight into the complex chain of events underlying atherogenesis, plaque progression, and ultimately those processes that result in atherothrombosis with accompanying clinical symptoms. MRI is particularly attractive because it is noninvasive and is capable of providing a rich array of information on vascular disease. MR methods have been demonstrated to provide information on important features of vascular disease, including the geometric morphology of the flow lumen and the vessel wall, the composition of atheroma, measurement of flow velocities through vessels independent of overlying structures, and more recently insights into the presence and activity of specific molecules that are considered to be important participants in the inflammatory processes and that might differentiate the stable plaque from the vulnerable plaque. 

Key Words: carotid artery ■ carotid stenosis ■ hemodynamics ■ MR angiography ■ MRI

In recent years, some of the capabilities of MRI for assessing vascular disease have been demonstrated in the clinical setting by evaluating the vascular lumen through the use of MR angiography (MRA). Traditional methods for evaluating vascular disease have focused on geometric features but have generally been applied in projection mode with 2-D visualization only.1,2 Steady improvements in hardware and software have enabled the implementation of robust MRA methods for delineating luminal contours with extensive coverage and fully 3-D assessment (Figure 1). These advances permit an improved appreciation of stenotic disease compared with conventional projection methods used in catheter-injected x-ray angiography which provides only limited views and are prone to incorrectly assessing irregular cross-sectional anatomy.3–5 MRA methods can be applied either with or without the use of contrast agents.6 Recent advances also provide the ability to evaluate dynamics of contrast passage, a valuable feature in the situation of tandem lesions.7,8 Studies have indicated the importance of ulceration and plaque irregularity as a risk factor for stroke. Lovett et al have shown that plaque surface morphology on angiography is strongly associated with the presence of rupture, plaque hemorrhage, lipid core size, and the proportion of fibrous tissue in carotid plaque,9 and like Eliasziw et al,10 conclude that angiographic appearances of ulceration and irregularity are strong predictors of overall carotid plaque instability. This points at an important potential role for 3-D imaging methods, such as MRA, which can assess ulcerations that might remain obscured on 2-D projection angiography.

Plaque Bulk

The unparalleled sensitivity of MRI to soft tissue signal has been exploited to examine not only the indirect manifestation of atherosclerosis as a narrowing of the vascular lumen but to assess its direct impact on remodeling of the vessel wall. Different settings of the MR scanner can be used to adjust the contrast between different tissue types, and in particular, to differentiate plaque from adjacent soft tissue.11 T1-weighted fast spin-echo images are generally the preferred method for defining the outer wall of the atheroma. Processes such as compensatory enlargement,12 where there is substantial formation of atheroma in the vessel wall without luminal narrowing, are only poorly recognized on other imaging modalities but can be clearly defined in vivo using MRI. High sensitivity signal detection is enabled by custom-designed radiofrequency coils permitting image acquisition from a 2-mm-thick slice with in-plane spatial resolution of 0.5×0.5 mm. Multicenter studies of measurement of atheroma volume indicate that these measurements can be made with an error of around 4%.

Plaque Composition

There have been extensive investigations directed at developing and validating MR methods that can essentially reproduce histological evaluation of plaque composition using in vivo methods. Ex vivo studies have demonstrated that a combination of sequences with different contrast-weighting is most effective in achieving that goal. However, some of these methods, such as diffusion-weighted sequences which are

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very powerful in delineating the location of the necrotic core of atheromatous plaque, are highly sensitive to motion and have reduced image quality when used for in vivo applications. The single sequence that has been most widely used in characterization of plaque composition is the T2-weighted fast spin-echo sequence (Figure 2). On these images, the lipid core appears as a hypointense region, fibrous cap appears relatively hyperintense, and calcification appears as a very dark region. The other principal component in the atheroma that can be readily defined is the location of fresh intraplaque hemorrhage consisting principally of met-hemoglobin. The development of a network of vasa vasorum that rupture and bleed into the plaque is associated with the inflammatory process. Methods of aging intraplaque hemorrhage on MR images is relatively imprecise, and increased signal intensity from methemoglobin is thought to persist for several months after a bleed. At a later stage, the blood will evolve into hemosiderin at which stage the blood products are associated with a focal signal loss associated with the iron components in the blood. Noninvasive imaging of carotid atheroma is particularly powerful in longitudinal studies designed to evaluate the natural history of disease progression or the response to pharmacological interventions.

Figure 1. MRA of a patient with moderate stenosis of the origin of the internal carotid artery. a, The anatomy of the bifurcation is well displayed in MIP images (4 different projection angles were selected for display here). b, Multiplanar reformats show complexity of the luminal shape at: level 1, distal common carotid artery with small invaginations; level 2, maximum stenosis showing internal carotid artery and external carotid artery; and level 3 mid–internal carotid artery with shape of a figure 8.

Figure 2. MRI of a patient with moderate stenosis of the left internal carotid artery. a, T1-weighted, fat-saturated black-blood fast spin-echo image, clearly shows inner and outer walls of atheroma (arrow). b, T2-weighted, fat-saturated black-blood fast spin-echo image, shows compositional variation with hyperintense fibrous cap and hypointense crescentic necrotic core (arrow). c, Postcontrast T1-weighted, fat-saturated black-blood fast-spin echo image, has greater signal variability in the atheroma than the precontrast image (a), but less than the T2-weighted image.
In a recent study, Takaya et al demonstrated the utility of using high-resolution MRI in a prospective study of the association between plaque composition and cerebrovascular events in 154 asymptomatic patients with ultrasonographically proven 50% to 79% carotid artery stenosis over a time period of at least 12 months. They found that the presence of a thin or ruptured fibrous cap, intraplaque hemorrhage, larger mean intraplaque hemorrhage area, larger maximum percentage of lipid-rich/necrotic core, and larger maximum wall thickness accounted for an increased risk of subsequent ipsilateral cerebrovascular events. Those findings are in agreement with retrospective trials showing a similar correlation. The presence of a lipid-rich/necrotic core without intraplaque hemorrhage was not found to be significantly associated with subsequent ischemic events in this study.

**Wall Shear Stress**

There is strong evidence that hemodynamic forces acting on cells of the endothelium are important in the initiation of the atherosclerotic process. This is often cited in the observation that atheroma forms preferentially in sites of recirculating flow where there is low wall shear stress, such as at locations of flow dividers. There are also more recent indications that increased wall shear stress in the presence of laminar flow can serve to promote the adhesion of rolling leukocytes and increase the synthesis of nitric oxide. An accurate assessment of wall shear stress requires a determination of the gradient of velocities immediately adjacent to the vessel wall. The spatial and temporal resolution requirements for this assessment cannot be achieved with any current in vivo imaging modality. It is, however, possible to numerically compute the value of wall shear stress for a specific vascular territory based on knowledge of the 3-D geometry of the flow lumen, and the inlet and outlet flows through the territory of interest. The luminal geometry can be determined using MRA, and boundary flow conditions can be determined using MR velocimetry methods. Detailed maps of wall shear stress can then be computed throughout space and at all points in the pulsatile cycle. MRI can thus be indirectly used to estimate the impact of these mechanisms on the inflammatory process.

**Molecular Contrast Agents**

In addition to the intrinsic contrast that can be generated in different plaque components using multicontrast MR methods, it is also possible, in principle, to examine the presence and activity of specific molecules involved in plaque inflammation. Developments in this regard have followed 2 paths: one using agents that are approved for use in humans, and the other where experimental formulations have been proposed and have been assessed in animal models.

Gadolinium chelates have been used for many years for a variety of applications in MRI. They have an extremely favorable safety profile. As indicated above, one application is in MRA where these agents provide a boost in magnetization strength and improved delineation of the vascular lumen. Studies have been directed at looking at the time-rate of signal increase into the vessel wall after contrast injection. Localized regions of increased signal strength have been shown to correlate with an increased density of neovascularization, with histological correlation of focal signal increase with regions of increased presence of vasa vasorum. Further, applications of kinetic modeling have been used to evaluate the relationship of rate constants that describe the uptake of these agents into plaque with macrophage density, and these studies show a strong linear relationship between those quantities.

Efforts are underway to explore the use of different molecular-imaging markers that would attach to specific targets after intravenous injection. One promising marker for this application is the use of iron oxides. A variety of different formulations containing iron oxides have been developed including the ultra-small super paramagnetic iron oxides (USPIOs). When injected, these contrast agents are phagocytosed by macrophages in plaques where there is an increased level of inflammation. Studies in white heritable hyperlipidemic rabbits have shown good correlation between the location of regions of signal decrease after administration of USPIOs and the presence of atherosclerotic lesions. Localization of one of these USPIOs, ferumoxtran-10, in macrophages associated with an area of atherosclerotic proliferation after balloon injury in a hyperlipidemic rabbit model has also been demonstrated. Those agents are also shown to generate signal voids or magnetic susceptibility artifacts on MRI.

Preclinical studies in humans have shown a similar signal decrease in the plaques of patients with symptomatic carotid plaques. Interestingly, decreased signal was also seen on the contralateral, asymptomatic artery but with a more narrow distribution, reflecting a systemic presence of inflammation with higher activity in the symptomatic artery. Examination of excised endarterectomy specimens revealed that the location of signal changes on MR images was confined to regions in the vessel wall containing macrophages.

Alternative carriers of contrast that home in on key constituents of the atherosclerotic process are attractive molecular-imaging tools. One interesting candidate has been reported that modifies a high density lipoprotein particle to incorporate a paramagnetic phospholipid, GdDTPA-DMPE. In addition, a fluorescent marker can also be attached to this particle so that colocalization of fluorescent signal in ex vivo studies with the observed hyperintensity on in vivo imaging could confirm the preferential uptake of this marker in regions of atherosclerosis. This marker was evaluated in application to an apolipoprotein E (apoE) knock-out mouse model of atherosclerosis, showing a pronounced time-course of signal enhancement into the intimal layer of the atherosclerotic aorta, with peak enhancement occurring 24 hours after injection of the modified HDL particles.

Targeted agents that carry a large gadolinium payload are well-suited for detecting atherosclerotic plaques. One candidate particle is liquid perfluorocarbon nanoparticles encapsulated in a lipid coating that have been designed to carry up to 90 000 gadolinium particles on the probe surface resulting in a pronounced contrast boost. The Washington University group have demonstrated that αvβ3 integrin could be attached to these probes and used to target the particle to sites of atherosclerosis. Greater enhancement was seen on MRI of the aorta of rabbits if the injected particles incorporated...
α(ν)β3 than if they did not. Rabbits without atherosclerosis showed no enhancement in either case. The matrix metalloproteinases (MMPs) are of major interest to investigators of vascular inflammation and the role of these enzymes in the degradation of the extracellular matrix has been extensively discussed.\textsuperscript{34} The expression and activity of MMPs is regulated by a variety of factors including hemodynamics and inflammation, and the ability to noninvasively monitor the activity level of these molecules could be extremely informative about the atherosclerotic process and the potential of a given plaque to erode and rupture. One candidate molecule for investigating MMP activity is P947, a short peptide ligand for MMPs. P947 has a gadolinium attached to it in order to generate MR visible signal. Again, studies in apoE knockout mice have shown strong uptake of this agent into regions of atherosclerosis after systemic injection through a tail vein.\textsuperscript{35} In these studies, preferential signal uptake was noted on the Adventitial side and Intimal side of the atheroma, locations where increased MMP activity is expected.

Similarly, recent studies have shown that an endogenous proteinase, cathepsin S, plays an important role in atherosclerotic plaque destabilization and rupture.\textsuperscript{36} There are reports that in apoE knockout mice, which otherwise develop unstable plaques, there are significant reductions in plaque size and an independent reduction in the incidence of plaque rupture after they were rendered insensitive to cysteine proteinase cathepsin S. They also found that human atherosclerotic plaques contain active cysteine proteinases supporting the idea that cathepsin S is a mediator of plaque destabilization and rupture. Weissleder’s group has suggested that a combined use of a fluorescence-imaging method together with MRI could be effective in identifying the location of molecularly active processes, such as the activity of cathepsin B, in vivo, and have demonstrated this in an animal model. Such methods are attractive in the potential they offer to identify biomolecular markers of vulnerable plaque but presently remain limited to animal investigations.\textsuperscript{37}

The importance of thrombus on the surface of ruptured plaques is well-recognized as an important risk factor for future events. Epix Medical have manufactured a fibrin-binding, clot-enhancing contrast agent EP-1873, composed of a gadolinium-labeled peptide derivative with 4 Gd molecules per peptide. This agent was used in a study of acute and subacute thrombosis after plaque rupture in an animal model of atherosclerosis.\textsuperscript{38} EP-1873 permitted imaging of large lumen-encroaching thrombi as well as submillimeter mural thrombi. Enhancement was seen throughout the thrombus and not in normal vessel wall.

Conclusions

MRI presents a broad spectrum of tools for imaging vascular disease. Techniques now exist for assessing geometric and compositional features of atheroma in the vessel wall. Advances in the development of contrast agents that are selectively taken up by target molecules that are considered to be important contributors to plaque inflammation offers the promise of being able to monitor the chain of events that lead a dormant plaque to manifest symptoms. Those methods must overcome the challenge that is presented by the relative low sensitivity of MRI to small concentrations of material. A new generation of high-field scanners with massively parallel array coils will provide important new capabilities for addressing this challenge.

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Disclosures

None.

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