MRI for Plaque Assessment

An overview of the literature.

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Although assessment of atherosclerosis is routine in clinical practice, the standard-of-care approach to patient evaluation often leads to diagnosis in advanced stages, particularly when lesions have become symptomatic. Plaque imaging holds promise for the detection and characterization of atherosclerosis in early pathological stages and in the subclinical state. Also, the significance of atherosclerotic lesions can potentially be categorized into high-risk and low-risk subtypes. This concept of identifying the vulnerable plaque has been the topic of continuing research and has clinical implications for prevention of sudden cardiac death, stroke, and myocardial infarction, which collectively account for a great burden of morbidity and mortality worldwide. Ultimately, the expectation is that lesion assessment could guide therapy and early intervention by pharmacologic or mechanical means.

There are multiple standard imaging modalities that allow plaque assessment, including angiography, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Additionally, there are newer techniques, such as thermography, near-infrared spectroscopy, optical coherence tomography, and palpography that are primarily investigational. The task of plaque imaging is particularly challenging given the small size of vessels, inherent motion, and the complex composition of lesions. Thus, the ideal imaging modality has high spatial resolution, high temporal resolution for cardiac applications, and the ability to characterize tissue. Although it has its limitations, MRI fulfills this criteria, and the body of evidence describing its validation and application is the subject of this article.

MRI SOFTWARE AND HARDWARE

The MRI sequences or software used for vascular imaging are diverse and are utilized for both detection of stenosis and assessment of plaque composition. The hardware requirements are generally typical of most MRI; however, new techniques require specialized equipment.

Magnetic resonance angiography (MRA) is a technique employed in clinical practice for many years and is applied in various anatomic sites, including cerebral, carotid, aortic, renal, and lower extremity circulations. Gadolinium contrast is generally administered, and images are acquired during first pass and subsequently during the levo phase using a sequence known as *gradient echo*. Notable variations of MRA include ECG-gated sequences that reduce motion artifact in highly mobile vessels such as the aortic root and time-resolved imaging that allows multiple fast image acquisitions to visualize the wash-in and wash-out of contrast, much like conventional angiography. Because it provides primarily a luminogram, the purpose of MRA is usually for stenosis detection. Sensitivity and specificity are moderately high and vary according to anatomic site. Noncontrast methods have fallen out of favor due to technical limitations, with the exception of coronary MRA. However, since the recognition of nephrogenic systemic fibrosis in the renal failure population, noncontrast techniques for MRA have been the subject of great interest and may play a greater role in the future.[1] Although MRA is a clinically useful tool for evaluating the degree of stenosis, its role in plaque imaging is limited.

Black blood imaging utilizing spin echo or double inversion recovery fast spin echo techniques is the mainstay of plaque imaging.[2] Submillimeter, in-plane resolution is achieved, which is necessary to identify small plaque components, such as lipid core, vessel wall, hemorrhage, and calcium.[3] Studies have employed multicontrast approaches that incorporate proton-weight-

ed (PW), T1-weighted (T1W), and T2-weighted (T2W) imaging to distinguish the plaque components (Figure 1). The designations of PW, T1W, and T2W essentially refer to the contrast that is induced in tissues when protons are manipulated by radiofrequency and gradient pulses applied by the scanner. Thus, lipid, hemorrhage, and calcium can be identified by their specific characteristics under different weighting schemes. For example, lipid core is bright on T1W imaging, dark on T2W imaging, but grey on PW imaging; calcium is identified as being dark in all three weightings.[4] A summary of these weighting schemes is provided in Table 1.[5,6]

The hardware required for noninvasive plaque imaging is widely available. Either a 1.5-T or 3-T magnet with standard neck, chest, or extremity coils is utilized. Coils are devices that act as antennae to receive proton signals and are placed on the surface of the body part to be imaged. The more recently described intravascular MRI, which is predominantly investigational, entails placing a coil that is the caliber of standard catheterization equipment in the vessel lumen similar to intravascular ultrasound (IVUS).[7] The proximity of the coil to the tissue of interest increases the signal-to-noise ratio of the images. Although the technique as described appears somewhat cumbersome, requiring both fluoroscopic and MRI equipment, the advent of combined x-ray angiography and MRI scanners simplifies the procedure considerably. Interestingly, there are devices in development that provide a local magnetic field and a coil within the same catheter; however, it is too early to know how successful this strategy will be. Another notable hardware development in the literature involves a transesophageal coil.[8] The coil is 8 F in diameter and is combined with surface coils to enhance visualization of plaque in the thoracic aorta.

PERIPHERAL APPLICATIONS

Plaque imaging by MRI had its beginnings in 1983, as described by Herfkins et al and Kaufman et al.[10,11] Validation studies in animal models and explanted human tissue progressed to in vivo human studies and ultimately to population studies. MRI has been an ideal method for human studies because monitoring disease progression requires a noninvasive, reproducible, and nonionizing method. Most work has been performed in peripheral vessels for technical reasons and is summarized in this section.

The carotid arteries have provided a wealth of information due to their limited motion, proximity to surface coils, relatively large caliber, and most importantly, the ability to provide histological correlation through surgical endarterectomy. Explanted human tissue was utilized in early studies and demonstrated that MRI could discriminate lipid, fibrous cap, calcium, and hemorrhage in atherosclerotic lesions.[3] In vivo studies subsequently showed that MRI had high sensitivity and speci-

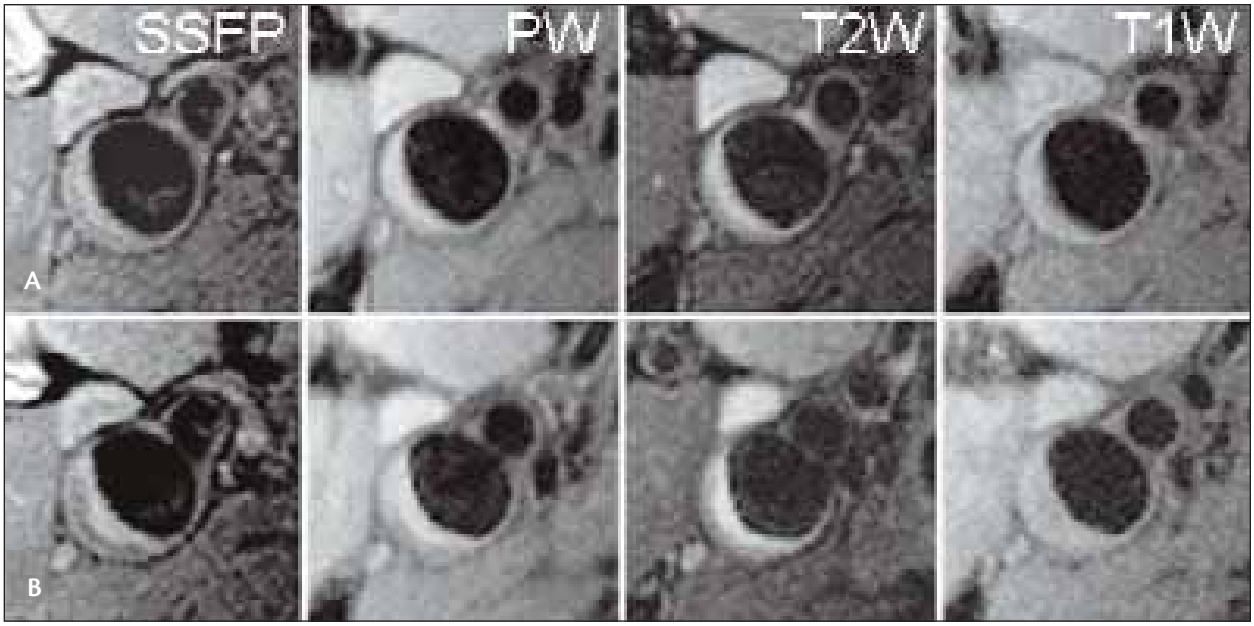

Figure 1. Multicontrast imaging of the carotid artery. Standard PW, T2W, and T1W images are shown depicting mild thickening of the carotid artery wall at two separate slice positions (rows A and B). A fourth sequence under development for plaque imaging, steady-state free precession (SSFP), is also shown.[9] Note the varied contrasts seen in the different weightings. Also, note the excellent agreement of carotid wall morphology in all images.

ficity for the evaluation of plaque components when multicontrast imaging was utilized.[12] This multicontrast method was also successful in categorizing plaque analogous to the American Heart Association histological classification in a comparison between in vivo imaging and explanted endarterectomy samples.[4] Another significant contribution involves gadolinium contrast imaging, which improves discrimination of the fibrous cap from the lipid core and further permits quantification of these structures, which has implications for identifying vulnerable plaques.[13,14]

Validation studies for emerging techniques have also used other peripheral vascular territories. For example, after initial testing in animal models and explanted tissue, the first in vivo application for intravascular coils was in the iliac arteries. In the primary study that describes in vivo human use, 25 patients underwent MRI with an intravascular coil (IVMRI) in addition to IVUS as a comparison. It was demonstrated that IVMRI was able to visualize the arterial wall in all vessels, even in calcified arteries that prevented adequate IVUS evaluation. IVMRI was also shown to be superior to IVUS in interobserver and intraobserver agreement.[15] This group applied the same technology in the iliac arteries to show that gadolinium contrast improves the characterization of plaque by enhancing the fibrous components.[16] The human coronary arteries have yet to be studied with this method in vivo.

Application of plaque imaging to clinically oriented research has been performed and continues to be an area that necessitates further investigation. One study that linked neurological symptoms with plaque morphology involved 28 symptomatic patients and 25 asymptomatic patients referred for carotid endarterectomy.[17] This study found that ruptured plaque was 23 times more likely to be associated with symptoms when compared to plaque with a thick fibrous cap. This technique has yet to be applied prospectively to understand its predictive value.

Some of the most noteworthy clinical investigations have been population studies documenting plaque regression with serial imaging. The first MRI study to demonstrate this process found regression of aortic and carotid plaque after 1 year of treatment with simvastatin.[18] Remarkably, response to simvastatin can be detected after 6 months of therapy in aortic plaques when transesophageal coils are utilized in addition to traditional surface coils.[19] More recently, it was shown that after 2 years of therapy with rosuvastatin, MRI detected a decrease in the proportion of lipid-rich necrotic core; however, it did not show a change in overall plaque volume.[20] This finding underscores the necessity for a modality that assesses plaque composition rather than just plaque volume to fully measure response to therapy. These types of surrogate outcomes will likely be important for pharmaceutical companies to test their prospective agents without large, expensive, time-consuming clinical trials in the future.

CORONARY APPLICATIONS

Imaging the coronary arteries has been an ongoing technical challenge due to their small size, distance from the surface of the body, tortuous course, and motion. Despite these limitations, significant advancements have been made in this field.

MRI was the initial means of noninvasive coronary imaging before the development of CT angiography.[21] MRI maintains advantages over CT, such as higher temporal resolution, no radiation exposure, and no contrast requirement. Its major disadvantage is poor visualization of small and distal vessels. Coronary MRA has been studied in a multicenter trial for detection of stenosis in proximal and midcoronary segments in which it showed high diagnostic accuracy for diagnosing left main or three-vessel disease.[22] It has also been applied in the evaluation of anomalous coronary arteries for which it continues to be useful.[23] More recent advances involve new sequences for improved signal-to-noise ratio, visualization of the entire coronary tree, and application of high field imaging at 3T.[24-27] Despite the data supporting its use, its application has largely been supplanted by CT angiography for evaluation of coronary atherosclerosis.

Plaque imaging in the coronary vessels is performed utilizing similar black blood sequences used in peripheral vessels; however, the level of detail obtained is less than typically seen in the carotid arteries, and assessment is limited to measuring the wall thickness of the proximal coronary artery tree.[28] There are newer black blood sequences that are acquired in a similar manner to coronary MRA in that they are three-dimensional volume acquisitions that can be manipulated in infinite angles and are obtained without breathholding. This technique demonstrated that positive remodeling can be detected by MRI in patients with minimal coronary plaques.[29] Also, it showed that diabetics with nephropathy had a higher plaque burden than diabetics without nephropathy.[30] Another approach is to use delayed enhancement imaging, similar to that used for infarct imaging, to visualize the vessel wall. In one study, presence of enhancement of the coronary vessel wall correlated to presence of plaque as compared to quantitative angiography.[31] Although significant gains have been made in recent years, technical issues have hampered

TABLE 1. APPEARANCE OF PLAQUE COMPONENTS BY MULTICONTRAST MRI

	Relative Signal Intensity*		
	T1W	PDW	T2W
Calcium	▽	▼	▼
Lipid	▲	△	▽
Fibrous	◁▷ to △	◁▷ to △	◁▷ to △
Thrombus†	▲▼	▲▼	▲▼
Hemorrhage†	▲▼	▲▼	▲▼

▽, hypointense; ▼, very hypointense.
△, hyperintense; ▲, very hyperintense.
◁▷, isointense; ▲▼, variable intensity.

**Relative to adjacent muscle tissue.*
†Dependent on thrombus/hemorrhage age.

the ability to characterize coronary plaque in the same manner as carotid plaque.

Imaging with intravascular coils has the theoretical safety issues of damaging the surrounding vessel and stimulating coagulation due to heating from radiofrequency energy that is emitted by the coil and by currents induced by the magnetic field. Due to their small size, it has been suggested that coronary vessels may not be able to dissipate the heat effectively. However, animal studies have shown that this does not occur experimentally based on coagulation factor analysis and histological vessel analysis.[32] At this point, there are explanted tissue studies that describe intravascular coils in human coronary arteries, but limited published data addressing their in vivo use are available.[33]

FUTURE DIRECTIONS

A compelling aspect of MRI with unknown clinical utility is the possibility of performing whole-body MRA. One study imaged all major arterial vessels from head to toe, in addition to infarct imaging of the heart, in a single 29-minute examination.[34] This technique utilizes total body surface coils and parallel imaging, which is a method that accelerates the acquisition process. Potentially, this could be used to screen individuals for vascular disease on a scale that has not been previously feasible. At the moment, this approach has unclear clinical implications.

With regard to contrast media, gadolinium-based compounds may continue to be the most practical agents in the near future because their use in humans is well established. One novel compound called *gadofluorine M* localizes to the extracellular matrix of plaque and potentially is a marker of high lipid content in animal models.[35]

Utilizing unique contrast agents is another frontier to be exploited in MRI for plaque imaging. One application is the use of ultra-small, superparamagnetic particles of iron oxide (USPIO). These particles are known to concentrate in activated macrophages and are, therefore, thought to be reflective of inflammation. The first human studies involved symptomatic patients in which USPIOs were more likely to localize to ruptured or rupture-prone lesions.[36] The technique of utilizing USPIOs provides a way for MRI to evaluate plaque activity, which is another increasingly important aspect of plaque assessment.

Molecular imaging conceptually involves the ability to target a cell or molecule with compounds that are tagged with an MR contrast agent for localization. Molecular targets related to plaque imaging that have been discussed in the literature include the LDL receptor, tissue factor, integrin subtypes, VCAM-1, and fibrin.[37-39] Nanoparticles are likely to play a major role in the development of this field. Although all imaging modalities can be potentially used for molecular imaging, MRI may have some advantage given its high spatial resolution, although it is likely not as sensitive as the nuclear imaging techniques.

CONCLUSION

MRI is well suited for vascular imaging, particularly of peripheral vessels. It can be used to assess both vessel patency and plaque composition. Studies have shown

the utility of MRI in documenting changes in plaque content as well as plaque volume. This application will continue to be important for research and especially for pharmaceutical development. Certainly, the armamentarium for plaque imaging continues to grow and be refined, and it is destined to be an area targeted for molecular imaging. The present challenge is to transform this remarkable research tool for population-based studies into a relevant clinical tool for patient-based risk assessment. ■

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