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Contemporary coronary imaging from patient to plaque: part 4 magnetic resonance imaging

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In recent years a large amount of research has focused on developing both invasive and non-invasive methods of assessing atherosclerosis. In this regard, magnetic resonance imaging (MRI) is safe, non-invasive, requires no ionising radiation, and is capable of giving high-resolution images of atherosclerotic plaque. As a result, MRI has been extensively applied to imaging of the vascular system – in particular, the carotid arteries – where it has been shown to have the ability to not only accurately quantify the extent of atherosclerotic plaque disease, but also to identify several compositional features suggestive of plaque vulnerability. Imaging of the relatively small coronary arteries has, until now, been limited by the problems of cardiac and respiratory motion, however, more recently, technological advancements have allowed more detailed plaque information to be acquired. This article will review the origins of MRI imaging of atherosclerotic disease, its current status, and its potential future applications.

Background: carotid/vascular MRI

Magnetic resonance arteriography (MRA) has for many years been used as a non-invasive means of producing an arterial lumenogram, an image of flow down the arterial lumen, from which the presence of significant stenosis could often be detected, if needed, by comparison to the comparatively normal flow in the contralateral vessel. However, the first description of the use of magnetic resonance imaging (MRI) to describe direct imaging of atherosclerotic plaque itself was by Gold in 1993.[1] The authors used *ex vivo* human aorta specimens containing atheroma to correlate MRI signal changes with the presence of specific histological features, including lipid-rich necrotic core, calcification, and fibrous plaque. Following this, the first *in vivo* description of MRI plaque imaging was performed in 1996 on six patients prior to carotid endarterectomy.[2] Histological verification of these images with the carotid endarterectomy specimens clarified that MRI was capable of distinguishing a number of plaque features, including lipid cores, fibrous caps, calcification, haemorrhage and acute thrombosis, in addition to the normal media and adventitia of the vessel wall (**figure 1**). This discovery stimulated a large amount of subsequent research into carotid plaque MRI,[3-6] ultimately leading to a modification of the American Heart Association (AHA) plaque classification system to allow MRI grading of carotid atherosclerotic plaque.[7] More recent work has begun to move towards potential clinical uses of carotid MRI imaging. For example, Yuan *et al.* have described the positive association between identification of a ruptured fibrous cap on MRI, and a recent history of transient ischaemic attack (TIA) or stroke.[3] In prospective studies, the presence of intraplaque haemorrhage on carotid MRI has been shown to predict the short-term combined risk of ipsilateral TIA and stroke,[8] and, in addition, the chances of cerebral embolisation during surgery.[8] Although larger long-term clinical studies are required,

Figure 1. 3T magnetic resonance imaging (MRI) of atherosclerotic plaque in a right common carotid artery. The vessel wall is lined with complicated, lipid-rich plaque, which has a necrotic core (solid arrow). A thin fibrous cap can be seen in the bottom-left of the image (dashed arrow)

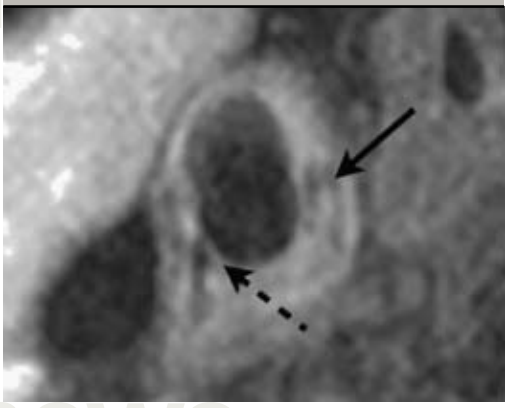

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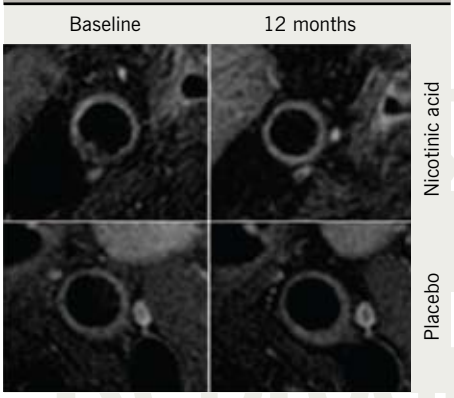
Figure 2. Effect of nicotinic acid on the carotid artery. Nicotinic acid is seen to prevent progression of carotid arterial wall thickening, while patients treated with placebo show clear progression of wall thickness



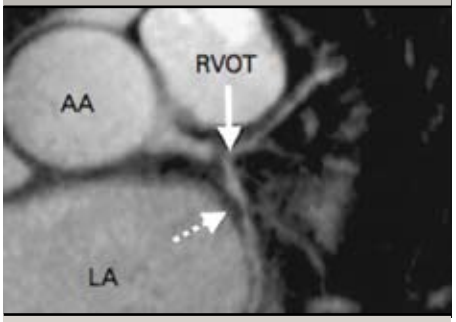
these studies indicate that carotid plaque MRI may have an important future role in the assessment and treatment of TIA and stroke.

In addition to its potential clinical applications, the ability of MRI to provide highly accurate information on plaque burden and morphology has been used to examine the effect of both established and novel pharmacotherapies on the vasculature in the research and clinical trial domains. Corti *et al.* were the first to demonstrate a reduction in carotid and aortic atherosclerosis using serial MRI after 12 months of statin treatment.[9] Subsequently, it was demonstrated that more intensive lipid lowering, to low-density lipoprotein (LDL)-cholesterol <100 mg/dL, was associated with a larger decrease in plaque size, also over 12 months.[10] MRI has also been used to provide further mechanistic insights into how atherosclerotic plaque responds to cholesterol-altering medications. Lee *et al.* used MRI to demonstrate, in the carotid arteries and aorta, reduction in the plaque index (normalised vessel wall area) as early as three months after statin initiation. In the same patients, early changes in atherosclerosis (within three months) were significantly correlated with later change at 12 months.[11] More recently, MRI has been used to investigate the effects of various treatment strategies, including the use of niacin to increase levels of high-density lipoprotein (HDL) (**figure 2**).[12] As a result of these successes, MRI of atherosclerotic plaque is currently being used in phase III trials of novel therapeutic agents.

Coronary MRI

MRI of the coronary arteries has progressed relatively more slowly. Not only are the coronary arteries small, but they are in constant motion and have similar characteristics to the surrounding myocardium and cardiac veins. Nonetheless, MRA of the coronary arteries, allowing the detection of stenotic plaque disease, has now been performed for over a decade, and was originally shown to be able to reliably detect patients with left main coronary or three-vessel disease (**figure 3**).[13] Subsequently, in an attempt to improve acquisition times, whole heart magnetic resonance (MR) coronary angiography has been developed.[14] This allows free-breathing images to be taken during a patient-specific time window of the cardiac cycle during which coronary artery motion is minimal. In a manner analogous to coronary computed tomography (CT), the upper and lower boundaries of the heart are defined in order to allow imaging over a single volume that covers both coronary arteries. As a result, images are simpler to acquire, and the scan can be performed in a much shorter time period. Using this technique, Sakuma *et al.* demonstrated that significant narrowing of coronary arterial segments with a diameter >2 mm could be detected with moderate sensitivity (82%) and high specificity (90%).[15] However, despite technological advances such as this, the overall acquisition speed of 3D MRA remains considerably slower (>2 minutes) than that of multi-slice CT (<2 seconds). Nonetheless, it should be noted that MR coronary imaging does hold several advantages over CT plaque imaging: the ability to safely perform serial imaging, the lack of need for an injected contrast agent in image acquisition, and the ability to characterise heavily calcified areas of the coronary tree.[16] Currently, however, clinical guidelines only recommend the use of coronary MRA for determining the proximal course of anomalous coronary arteries.

Figure 3. Magnetic resonance arteriography (MRA) of the left main stem, showing two separate plaques, which are seen as dark areas on the bright-blood signal (arrows). Adapted from Kim *et al.*[13]



Key: AA = ascending aorta; LA = left atrium; RVOT = right ventricle outflow tract

More recent work has suggested a brighter future for MRI imaging of coronary atherosclerotic plaque. In addition to coronary MRA, black-blood imaging of the coronary artery wall is now possible, which allows detection of increased wall thickness in patients with angiographically documented coronary artery disease with high reproducibility.[17,18] In a recent sub-study of the Multi-Ethnic Study of Atherosclerosis (MESA) trial, 179 asymptomatic patients with subclinical atherosclerosis underwent coronary wall MRI.[19] Although no significant coronary artery narrowing was detected by MRA, direct wall imaging noted that as the arterial wall became thicker, the luminal diameter remained relatively constant; in contrast, the outer vessel wall was seen to expand with the thickened arterial wall. This phenomenon, termed 'positive remodelling' and first described by Glagov,[20] highlights the need to develop accurate methods of direct coronary plaque imaging using MRI, in a similar manner to those methods currently used for carotid plaque. Currently, non-contrast T_1-weighted imaging of coronary plaque can identify high-intensity signal (HIP) (**figure 4**), which has recently been associated with positive coronary remodelling and low CT signal density.[21] However, the prognostic significance of HIP lesions is currently unknown.[22] Compared with carotid imaging, MRI of coronary atherosclerotic plaque is currently unable to identify individual plaque features with the same sensitivity and specificity.

Future directions

Ongoing improvements in imaging sequences, combined with higher field strength imaging, are likely to enhance the ability of MRI to provide high-resolution plaque images while simultaneously decreasing scan acquisition times. In addition, several novel contrast agents are under investigation that may permit MRI to simultaneously provide information on both vascular biology and morphology. For example, McAteer *et al.* constructed a dual-ligand microparticle of iron-oxide (4.5 μm

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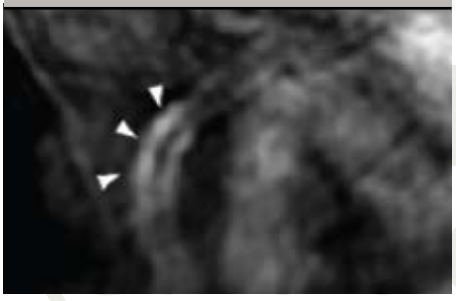
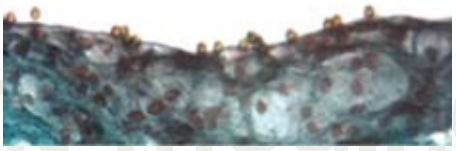
Figure 4. T_1-weighted imaging of the right coronary artery wall. Arrows show bright signal from a recently symptomatic plaque in the right coronary artery. Adapted from Tanaka *et al.*[22]



diameter) to target endothelial P-selectin and vascular cell adhesion molecule (VCAM)-1 (**figure 5**).[23] Binding of the microparticles to inflamed mouse endothelium was subsequently shown by high resolution *ex vivo* MRI (9.4 T). In human work, Tang *et al.* have demonstrated the use of ultrasmall particles of iron oxide (USPIO) to provide information on carotid plaque macrophage content using 1.5 T MRI.[24]

Figure 5. Microparticles of iron oxide (MPIO) bound to the aortic root of apolipoprotein E knockout mice. These particles have a paramagnetic effect, which leads to signal dropout when imaged using MRI



Conclusions

MRI is emerging as a leading non-invasive modality for the assessment of atherosclerotic plaque disease. While MRI of atherosclerotic plaque in the coronary arteries awaits further technical developments, imaging of plaque in the carotid arteries has already shown that MRI is capable of giving detailed information both on vessel wall thickness and plaque composition. With the ongoing development of novel contrast agents, MRI is likely to play a major role in the future development of imaging strategies to aid risk stratification and treatment in ischaemic vascular disease

Conflict of interest

None declared.

Key messages

- Magnetic resonance imaging (MRI) is one of the leading non-invasive plaque imaging modalities
- Detailed images are available for carotid artery plaque and there is excellent promise for tissue characterisation
- The absence of radiation exposure permits serial studies of plaque over time
- There is the potential for a 'one-stop shop' able to provide every facet of cardiovascular imaging in one scan
- Routine coronary imaging will require further improvements in technology and resolution

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