High resolution MRI of carotid atherosclerosis: looking beyond the arterial lumen

C Oppenheim (1), E Touzé (2), X Leclerc (3), E Schmitt (4), F Bonneville (5), P Vandermarcq (6), E Gerardin (7), JF Toussaint (8), JL Mas (2) and JF Méder (1)

Résumé
IRM haute résolution de l’athérosclérose carotidienne : au-delà de la lumière artérielle
J Radiol 2008;89:293-301


Abstract
Despite advances in diagnosis and treatment, atherosclerosis remains the second cause of death in the world. Due to technical advances, high resolution MRI (HR-MRI) allows depiction of the wall of cervical arteries, especially carotid atherosclerosis. HR-MRI allows visualization of the different components of atherosclerosis: necrotic lipid core, intraplaque hemorrhage, calcifications and fibrous cap. Global plaque volume as well as the volumes of individual plaque components can be calculated. Atherosclerotic plaque structure analysis, along with stenosis measurement, contribute to the stratification of the stroke risk. HR-MRI may also be used to assess treatment efficacy aimed at stabilizing or reducing plaque progression. Beyond the arterial lumen, direct evaluation of vessel wall should modify the management of atherosclerosis in the years to come.

Key words: Artery. Carotid. Prognosis. MRI. Atherosclerosis.

Apoplectic stroke is the sudden development of a neurological deficit due to a vascular disorder. This almost always involves an occluded artery and leads to cerebral ischemia, with ischemic stroke accounting for 80% of all apoplectic strokes. Some ischemic strokes associated with atherosclerotic carotid stenosis are due to a hemodynamic mechanism, but most are the result of a thromboembolic mechanism (embolism of thrombotic material derived from atherosclerotic plaque) or a thrombotic mechanism (occlusion of the internal carotid artery around the atherosclerotic plaque with distal thrombus extension) (1). Multicentre studies (NASCET, ECST) have revealed the major benefits of carotid surgery in cases of severe symptomatic atherosclerotic carotid stenosis (>70% NASCET) (1, 2). An analysis of pooled data from three large-scale randomised trials (n = 6092) recently confirmed that the 5-year risk of cerebral infarction is markedly reduced by surgery in >70% of stenosis cases (16% absolute risk reduction-ARR, p 0.001) (3). However, the extent of arterial stenosis is not the only premonitory sign of clinical carotid atherosclerosis (4, 5). The stroke risk increases with the extent of stenosis, but many ischemic strokes occur in patients with moderate stenosis (4, 6). This paradox, which has been noted in both coronary (7) and neurovascular pathologies, suggests that some moderately stenotic plaques could become complicated and give rise to thromboembolism (6). Many studies have shown that the composition of atherosclerotic plaque is likely a stroke risk factor, irrespective of the extent of stenosis (for review see Wasserman, et al. (6)). Different atherosclerotic plaque components can now be analysed as a result of recent advances in imaging techniques (7).

Atherosclerotic plaque
Atherosclerosis is a disease affecting large- and medium-sized arteries. The elementary lesion is atherosclerotic plaque, consisting of a lipid core (atheroma), a fibrous cap (sclerosis) and inflammatory cells (8). The respective proportions of lipid core and fibroed tissue vary in different plaques. Histopathological studies have shown that symptomatic plaques were more often ulcerated or ruptured,
Imaging and atherosclerosis

Several in vivo techniques are used to image atherosclerosis – they are invasive (X-ray angiography, intravascular ultrasound and angiography) or noninvasive (ultrasound, CT-scan, MRI and isotopic imaging) (10, 11). The three main noninvasive imaging techniques currently used for in vivo analysis of the structure of carotid atherosclerotic plaque are ultrasound, CT-scan and magnetic resonance imaging (MRI) (11).

Diagnostic ultrasound

Ultrasound examination is performed to distinguish between hypoechoic (echolucent) plaques with a large lipid core and hypechoic or fibrous plaques, with close histopathological correlations (12). Cross-sectional studies have revealed a link between the echolucency of plaque and the symptomatic nature of stenosis (11). These results were confirmed by those obtained in longitudinal studies of patients presenting with asymptomatic or symptomatic carotid stenosis, thus indicating a correlation between the echolucency of the plaque and the risk of ipsilateral ischemic stroke (threelfold higher risk) (13, 14). Other morphological features that have been studied are the presence of intraplaque hemorrhage, the aspect of the endolumenal surface (smooth, irregular or ulcerated) and the plaque motility. However, the agreement with histological findings does not seem as good and not enough studies have been conducted to determine correlations between these different echographic aspects and the ischemic stroke risk. The two main shortcomings of ultrasound analysis of plaques are the presence of calcifications, which induce acoustic shadowing, and interobserver variability. Post-treatment software could, however, be used to standardise the procedure and improve the reproducibility of morphological examinations of plaque.

CT-scan

CT-scan can help differentiate hypodense plaques (lipidic structure) from isodense plaques (fibrous structure). A multicentre cross-sectional study recently highlighted a correlation between the symptomatic nature of plaques (>50% stenosis) and the density measured in CT axial sections (15). Finally, calcified carotid plaque is a marker of atherosclerotic plaque stability. Calcified plaque is more often asymptomatic than noncalcified plaque (16). The calcification volume/total plaque volume ratio was found to be associated with greater plaque stability (17).

For further information on the advantages of ultrasound and scanning techniques for studying atherosclerotic plaque, readers should refer to papers (in French or English) by Lorenz, et al. (18), Gaúthier et al. (10), Gronholdt, et al. (12) and Serfaty et al. (15).

MRI

Spectroscopic techniques were used in initial MRI studies to analyse the lipidic constituent of plaque. These techniques were hard to apply in human studies because of the poor signal-to-noise ratio (SNR) due to the low lipid concentration relative to the highly prevalent water fraction. MRI – thanks to its high tissue analysis potential – is now the most promising technique for noninvasive imaging of atherosclerotic plaque (16).

Equipment

It is easier to image the carotid artery wall than the coronary artery walls because the carotid artery is not as mobile and is more superficially located. These anatomic features are adapted to surface coil MR systems. Coils designed for carotid artery imaging may be fitted around the patient’s neck, thus reducing discomfort. Phased-array coils consist of several small interfaced antennae and collect data simultaneously over a length of about 10 cm (fig. 1). These coils increase the SNR by around 40% as compared to conventional surface antennae while still ensuring good spatial resolution. High

Table I

Criteria of the American Heart Association used to identify vulnerable plaque on the basis of autopsy data (9).

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active inflammation (monocytes/macrophages, sometimes T-cells)</td>
<td>Superficial calcified nodules</td>
</tr>
<tr>
<td>Thin fibrous cap with a large lipid core</td>
<td>Intraplaque hemorrhage</td>
</tr>
<tr>
<td>Endothelial erosion with platelet aggregation and/or superficial fibrin deposits</td>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>Ruptured plaque</td>
<td>External remodelling*</td>
</tr>
<tr>
<td>Stenosis &gt;90%</td>
<td></td>
</tr>
</tbody>
</table>

*Nonstenotic plaque, generally with a thin fibrous cap and large lipid core, that has formed near the external side of the vessel (compensatory enlargement of the vessel).
resolution images (voxel = 250μm x 250μm x 2-3 mm) can be obtained with a satisfactory SNR and a reasonable acquisition time (≈ 5 min/sequence) with a 1.5 Tesla MRI scanner. The image quality may be improved by increasing the toroidal magnetic field. At 3 Tesla, the SNR, contrast-to-noise ratio and image quality in black-blood MRI sequences are thus improved without modifying the signal for the principal constituents, as indicated in the first studies published on this topic (19).

**Image quality**

Patient preparation is crucial for the examination, which lasts around 30 min. Excessive swallowing movements generate artefacts that are detrimental to the image quality (20). The carotid artery bifurcation should be accurately pinpointed (manually or via ultrasound with skin marking labels) so as to be able to suitably position the coils. In the detection sequence, the operator must check that the coil brightening is facing the bifurcation, and otherwise the coil should be repositioned (fig. 2). Finally, the image quality also depends on the patient’s neck morphology, i.e. optimal for slim patients since it is easier to position the coil facing the bifurcation. Similarly, it may be hard to obtain high quality images when the carotid artery bifurcation occurs in a high or deep location. According to the results of a multicentre study, around 10% of 1.5 Tesla MRI examinations are uninterpretable (21), but this is likely underestimated relative to examinations carried out in clinical conditions.

**Sequences**

MRI provides an excellent contrast between the arterial wall and lumen via so-called “white-blood” and “black-blood” sequences, so the technique can be used to image both the circulating lumen and the arterial wall, where the atherosclerosis process occurs.

**Black-blood sequence**

The aim of these sequences is to nullify the circulating blood signal to enhance the contrast between the arterial lumen (in black) and the arterial wall. Image acquisition is thus synchronised with the heartbeat and is preceded by a preliminary double-pulse sequence to nullify the circulating blood signal (22). This includes a preparation phase with two inversion pulse sequences (IR) prior to fast spin echo acquisition. The first pulse is nonselective and reverses magnetization of the whole body, including the blood. The second IR pulse, which is selective for the studied section, reverses the magnetization in the section plane. The magnetization outside the section (especially in the blood) is reversed whereas that within the section remains unchanged. A fast spin echo sequence starts after an inversion time (TI) at the end of which the blood in the section plane (which the spin has reversed) is forced out and is replaced by blood whose magnetization has been...
reversed, thus returning to equilibrium (fig. 3). This TI is a function of the blood T1 relaxation time and the repetition time (TR), as follows: $TI = -T1 \times (1 + e^{-TR/T1})/2$, where $TR = 2000$ ms, $T1 = 1200$ ms, and $TI = 625$ ms. The double inversion and fast spin echo sequences are repeated (at each 2xRR for T2 sequences) of the heartbeat synchronization until all FSE sequences have been acquired (fig. 4). A third IR pulse sequence may be added to obtain fat saturation. These black-blood sequences may be T1-weighted, proton-density-weighted or T2-weighted depending on the parameters used.

**White-blood sequence**

In white-blood or so-called time of flight (TOF) sequences, the arterial lumen has a high signal intensity (hypersignal). These sequences are generally used for angiographic analysis of intracranial arteries. Native sections are useful for analysis of artery walls. They have mixed T1 and proton density weighing.

Some representative acquisition parameters are given in table II.

**Image interpretation**

As atherosclerotic plaque is highly complex, several contrast levels are required to identify the different constituents (23): lipid core, calcium deposits, fibrous tissue and intraplaque hemorrhage. The fibrous constituent histologically corresponds to extracellular matrix that modifies protein-water interactions and induces shortening of the MRI T1 signal. It thus has a discrete high T1 signal intensity.

The lipid core contains cholesterol esters and nonesterified cholesterol which shorten the T2 relaxation time (24). Its signal decays with delayed T2-weighted echo sequences. T2-signal shortening is due to the micellar structure of lipoproteins, to their oxidation denaturation, or to exchanges between cholesterol esters and water. The signal differs from that of perivascular fat, which is mainly composed of triglycerides. Lipid core fat does not disappear when fat signal saturation techniques are applied, contrary to perivascular fat.

The calcium constituent consists of calcium hydroxyapatite. It has a hypersignal in all sequences because of its low proton density and a magnetic susceptibility effect.

Hemorrhagic constituent: Its MRI signal depends on the hemoglobin structure and its oxidative state. It is more complex than intracerebral bleeding, which occurs in a relatively uniform medium (whitish grey substance), whereas hemorrhage in atherosclerotic plaque mixes with the lipid and fibrous components. It is still possible to distinguish acute hemorrhages (<1 week), with a T1 hypersignal and T2 hyposignal, from relatively recent hemorrhages containing extracellular methemoglobin – which only generate a hypersignal in all sequences (25, 26).

As indicated in table III, a clearcut T1-weighted sequence hypersignal corresponds to a lipid constituent or hemorrhage constituent. Native sections of the 3D
TOF sequence differentiate these two constituents (23): the hypersignal disappears in the TOF sequence when lipidic lesions are mainly present without associated hemorrhage, whereas it remains in recent hemorrhage cases. T2- and T1-weighted sequences with a short echo time differentiate the lipid core from fibrous regions (27) (fig. 5). Based on these MRI criteria, the lipid core and intraplaque hemorrhage may be identified with good sensitivity and specificity. Measurements can be obtained from MRI images via manual or automatic contouring (28-30) of the plaque and constituents. These software programs have yet to be validated but are an interesting alternative to laborious manual contouring. It is quite easy to calculate the overall plaque volume. Once the different constituents are identified, they can be quantified with quite good interobserver reproducibility (21). This reproducibility is not perfect, however, and the variability should be taken into account when calculating the number of subjects to be included in therapeutic trials based on imaging assessment criteria.

The fibrous cap can be viewed on clinical 1.5 Tesla MRI images. 3D gradient echo TOF sequences in with a low tilt angle can highlight the circulating lumen, soft tissues and the fibrous cap. When thick and intact, the fibrous cap appears as a continuous low signal intensity band lodged between the arterial lumen (hypersignal) and the core of the plaque (intermediate signal) (31). It is also visible on T2-weighted sequences in the form of a periluminal hypersignal (32, 33). The interface between the cap and lumen is regular, especially in black-blood sequences. The gradient echo hypersignal of the cap is due to a layered structure that shortens the T2 relaxation time. The cap is thin when the arterial lumen surface is smooth on all sequences, but it is not visible (disappearance of the 3D TOF hypersignal band). Finally, a ruptured cap corresponds to a hypersignal interruption on native 3D TOF sections associated with an irregular artery wall/lumen interface, along with a hypersignal adjacent to the lumen. This juxtaluminal hypersignal region (relative to the lipid core) corresponds to an artery wall thrombus or recent intraplaque hemorrhage. It is also possible to analyse the cap on T2 sequences and its rupture is reflected by interruption of the juxtaluminal T2 hypersignal (fig. 6). There is quite good agreement between these MRI criteria and histological findings (34). However, some plaque constituents may generate a signal resembling that of the cap—calcifications that induce signal loss can be a source of error when they are juxtaluminal or located at the boundary between the lipid core and the cap. Chronic hemorrhage (hemosiderin) also has a signal resembling that of the cap. All of these factors could explain the low interobserver reproducibility in MRI analysis of the fibrous cap (21).

### Table II

<table>
<thead>
<tr>
<th>Parameters</th>
<th>3D TOF GRE</th>
<th>T1 BB-FSE</th>
<th>black-blood DP</th>
<th>black-blood T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR (msec)</td>
<td>30</td>
<td>1 RR</td>
<td>2 RR</td>
<td>2 RR</td>
</tr>
<tr>
<td>TE (msec)</td>
<td>6.9</td>
<td>9</td>
<td>16-20</td>
<td>50</td>
</tr>
<tr>
<td>FOV (mm)</td>
<td>130</td>
<td>130</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>Section thickness (mm)</td>
<td>2.2</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Matrix</td>
<td>288×224</td>
<td>352×256</td>
<td>256×512</td>
<td>256×512</td>
</tr>
<tr>
<td>NEX</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Synchronisation</td>
<td>-</td>
<td>Cardiac</td>
<td>Cardiac</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Number of sections</td>
<td>20</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Resolution (µm)</td>
<td>254×254</td>
<td>254×254</td>
<td>254×254</td>
<td>254×254</td>
</tr>
<tr>
<td>Scan time (min)</td>
<td>4</td>
<td>4-5*</td>
<td>4-6**</td>
<td>4-6**</td>
</tr>
</tbody>
</table>

* After zero-fill interpolation. ** Variable according to the heartbeat.

### Table III

<table>
<thead>
<tr>
<th>Plaque constituents</th>
<th>Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3D TOF</td>
</tr>
<tr>
<td>Lipid core</td>
<td>Isosignal</td>
</tr>
<tr>
<td>Fibrous constituent</td>
<td>Iso-discrete</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Hypersignal</td>
</tr>
<tr>
<td>acute &lt;1 week</td>
<td>Hypersignal</td>
</tr>
<tr>
<td>recent [1-6 weeks]</td>
<td>Hypersignal</td>
</tr>
<tr>
<td>Calcification</td>
<td>Hyposignal</td>
</tr>
</tbody>
</table>

Plaque vulnerability in MRI

Studies on histological validation of MRI measurements have generally been based on findings for a low number of patients and they raise methodological issues (35), but several suggest that MRI could be a useful prognostic tool for atherosclerotic plaque analysis. A cross-sectional study showed that the presence of a partially ruptured fibrous cap was associated with recent ischemic stroke: 70% of patients with a ruptured fibrous cap and 50% with a thin cap had a recent history of ischemic stroke, while the rate was only 9% in the group with a thick fibrous cap (31, 36). In a recent study of 154 patients presenting with asymptomatic stenosis (50-79% NASCET) followed up for a mean 3-year period, Takaya et al. showed that the ischemic cerebrovascular event risk (n = 12) was associated with the maximum plaque thickness, the presence of a thin or ruptured fibrous cap and intraplaque hemorrhage (fig. 7). This study did not, however, confirm the prognostic value of the lipid core size, irrespective of the hemorrhage constituent (37). Finally, intraplaque hemorrhage seems to stimulate plaque progression, as indicated in an 18-month longitudinal study (38). A French multicentre prognostic study that is currently under way should confirm the predictive value of MRI parameters with respect to the risk of stroke onset (HIRISC study) (21).

Molecular MRI

Atherosclerotic plaque evolution is marked by acute destabilisation phases associated with the inflammatory status of the lesion. Molecular magnetic resonance
imaging is still in its budding stage. The potential is considerable because it will enable functional noninvasive imaging, with high spatial resolution, of atheromatous lesions. Recent studies suggest that contrast agents could improve fine atherosclerotic plaque tissue analysis. Gadolinium injection can highlight neovascularisation in atherosclerotic plaque. When black-blood T1 sequences were compared before and after injection of this contrast agent, a barely vascularised lipid-rich necrotic core was revealed alongside highly vascularised fibrous tissues (39-41). High neovascularisation is associated with the presence of T-cell macrophages in relation with an inflammatory constituent, which is a key indication of plaque vulnerability. The extent of neovessels within atherosclerotic plaque in human subjects could be quantified through dynamic contrast enhancement assessments. Inflammation within plaque could be quantified by injecting other contrast agents with specific affinities (fibrin, macrophages, etc.) (42). USPIOs (ultrasmall super paramagnetic particles of iron oxide) are iron nanoparticles that have been stabilised by dextran particles (mean diameter 30 nm). They have a long half-life in blood (30 h), so they can be phagocytized by macrophages, especially those within atherosclerotic plaque. This accumulation of paramagnetic particles results in signal decay in the image. Two studies of carotid atherosclerotic plaque with histological verification revealed that USPIOs preferentially accumulated in so-called vulnerable plaque macrophages 24 h after i.v. injection, with signal decay in delayed T2* (gradient echo) sequences (43, 44). This contrast agent enhances the inflammatory constituent—a major indicator of plaque vulnerability (table I)—so it is a promising tool for differentiating low and high risk plaques. For instance, researchers recently documented substantial inflammatory burden in 95% of arteries controlateral to a symptomatic carotid artery, whereas stenosis was moderate. This is a further indication of the presence of systemic disease and underlines the fact that monitoring moderate stenosis controlateral to a symptomatic artery is warranted (45). Other contrast agents are also currently being assessed, e.g. myeloperoxidase for imaging enzymatic activity. Many projects, such as ATHIM (molecular imaging of atherothrombosis) involving joint...
teams of French academic and industrial stakeholders, are contributing to the development of a contrast agent that modifies the MRI signal at very high relaxivity and specificity, as well as determination of relevant targets that are highly present in atheromatous plaques.

Therapeutic follow-up

In animals (46) and humans (47), MRI can be used to monitor the progression or regression of atherosclerotic lesions (48). The size, composition and biological activity are three parameters that can be investigated in longitudinal studies. The size, or total wall thickening volume, is a more sensitive therapeutic efficacy criterion than maximum stenosis when considering the entire lesion, especially external remodelling. The plaque composition (calcium burden, lipid core) could be altered under treatment without modifying the extent of stenosis, thus transforming vulnerable plaque into more stable plaque. The biological activity, especially inflammation, is an emerging imaging target. These imaging parameters represent alternative assessment criteria for therapeutic studies (49). The number of subjects required for a relevant study is very important when only standard assessment criteria (myocardial infarction, stroke, etc.) are used, but this drawback could be overcome by including imaging criteria (49). For instance, MRI has been used to obtain objective therapeutic efficacy criteria such as regression of the lipid core volume under statin therapy. In untreated hypercholesterolemic patients (47), effects were noted 6 weeks after the beginning of treatment and became significant after 1 year of treatment. In MRI, statins induce remodelling, with reduction of the arterial wall thickness (~10%) but without lumen modification, thus supporting the hypothesis of plaque stabilisation via reduction of the lipid constituent. The use of MRI contrast agents that target inflammation could clarify the effects of statins, acetylsalicylic acid or angiotensin conversion enzyme inhibitors on stroke prevention through their anti-inflammatory activities.

From “vulnerable” plaque to “vulnerable” patient

Individual risk prediction is necessary to optimise vascular disease prevention. The term “vulnerable patient” has been proposed to designate stroke risk patients. It is clearly acknowledged that conventional prediction models (e.g. Framingham), based on standard risk factors, are inadequate for predicting individual risk, especially short-term risk (50). Identification of high risk atherosclerotic plaque and quantification of biological markers, especially inflammation, have considerably boosted the vascular risk prediction potential (50). In carotid stenosis patients, surgical treatment decisions are now...
High resolution MRI of carotid atherosclerosis: looking beyond the arterial lumen

Références

18. C Oppenheim et al.


