Noninvasive Imaging of Atherosclerotic Plaques Using MRI and CT

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ABSTRACT

Noninvasive, high-resolution MRI has shown its efficacy in the visualization of carotid atherosclerotic plaque characteristics. MRI is the only noninvasive option for thin plaque cap, active inflammation, fissured/injured plaque and intraplaque hemorrhage, is also useful in monitoring the response after statin therapy, and has the potential to image a coronary plaque and to determine its composition. New contrast agents and targeted molecular imaging open a window for MRI detection of thrombi and assessment of atherosclerotic activity and plaque vulnerability. Currently, multidetector CT is capable of the noninvasive detection of coronary stenosis and coronary calcifications. High resolution CT may be beneficial in the detection of noncalcified vulnerable coronary plaques, and more reliable with the use of newer high-speed volume CT scanners.

KEY WORDS: Atherosclerosis; Tomography, spiral computed; Magnetic resonance imaging.

Introduction

Conventional angiography has been regarded as the gold standard technique for the detection and diagnosis of arterial stenosis and occlusion. Recently, noninvasive techniques have advanced very rapidly. Fast multidetector-row CT (MDCT) and MRI enable rapid screening of the whole body vascular tree for atherosclerosis. These imaging modalities demonstrate an angiographic display of the vasculature using three-dimensional image reconstruction techniques.\(^1\)\(^\text{4}\) CT and MRI also provide cross-sectional images of atherosclerotic vessels.\(^1\)\(^2\)\(^3\)\(^5\) High-resolution CT and unique tissue contrast of MRI, combined with contrast agent application, may be useful in the characterization of atherosclerotic plaques. It is very important to detect coronary and carotid atherosclerosis before the fatal outcomes of the process appear clinically.

The concept of ‘vulnerable plaque’ implies that detection of unstable plaques is important in the prevention of future cardiovascular events, because vulnerable plaques may rupture and cause sudden arterial occlusion or distal embolization. Naghavi et al.\(^6\) proposed criteria for defining a vulnerable plaque based on the study of culprit plaques. In their proposal, the major criteria for vulnerable plaque were active inflammation, a thin cap with a large lipid core, endothelial denudation with superficial platelet aggregation, fissured plaque and stenosis >90%, and the minor criteria were a superficial calcified nodule, glistening yellow on angioscopy, intraplaque hemorrhage, endothelial dysfunction and outward remodeling. Therefore, we were urged to find ideal noninvasive methods for atherosclerosis imaging. In this context, MDCT and MRI are most suited for this purpose.

For the detection of most major and minor criteria for plaque vulnerability, MRI and MDCT are noninvasive options. MRI is the only noninvasive option for a thin plaque cap, active inflammation, fissured/injured plaques and an intraplaque hemorrhage.\(^6\) MDCT and MRI are very rapidly evolving, and the future applications of these techniques are promising. The resultant, timely and appropriate intervention of the atherosclerotic process may benefit patients by stabilizing atherosclerotic plaques or restoring the luminal diameter by angioplasty/stenting.

Noninvasive Modalities for Atherosclerosis Imaging

The carotid artery is a major source of cerebral embolism, and atherosclerosis of the carotid artery reflects the degree of
systemic atherosclerosis. Noninvasive imaging modalities are clinically useful for screening carotid diseases and assessment of the degree of stenosis. Recent developments in ultrasonography (US), MRI and CT have much improved the image quality and diagnostic reliability of each modality. US has been utilized for the noninvasive assessment of carotid stenosis and measurement of the carotid wall thickness. Focal ulceration and change in the echogenicity of the plaque can be visualized with using US. The Doppler technique is useful in the measurement of flow velocity through the stenotic lumen. The Doppler US threshold and criteria for significant carotid stenosis vary according to individual laboratories.7)

High resolution and contrast of the images are achieved by high frequency transducers (7–13 MHz) and recent developments in imaging techniques, such as tissue harmonic US. The intimomedial thickness is easily measurable by US. However, US has limitations in characterizing the plaque. US has limited anatomical coverage of the internal carotid artery and is more operator-dependent than other techniques.

### MRI of Atherosclerosis

Time-of-flight (TOF) MR angiography has been useful in the luminal depiction of intracranial and extracranial carotid arteries. The recently-introduced contrast-enhanced MR angiography is more advantageous in eliminating flow-related artifact and in obtaining 3-dimensional angiographic images with high contrast. High-resolution MRI techniques enable reliable characterization of the plaque, especially in carotid arteries.8) High-resolution carotid MRI is performed using 3-inch bilateral surface coils (FOV, 10 × 10 cm; slice thickness, 2–3 mm). Image acquisition includes 3-dimensional TOF MR angiography; T1-weighted pre- and post-contrast spin echo (T1WI) or a double inversion recovery technique, T2-weighted spin echo imaging (T2WI) and T1-weighted fatsaturated spin echo imaging. The components of the plaque can be intracellular lipid and extracellular lipid core, loose connective tissue/collagen matrix/fibrocellular, calcifications and hemorrhagic components.9) High-resolution MRI can visualize fibrous cap and focal ulcers, and differentiate fibrocellular components from the lipid core or hemorrhagic components using a multi-spectral approach (Table 1) (Fig. 1-5).10-12)

Fibrocellular components and loose connective tissue show modestly high signal intensities (SI) on T2WI (Fig. 1).9) The lipid core typically shows low SI on T2WI and high SI on T1WI. Hemorrhagic components or thrombi are of variable SI on T2WI (low SI, mostly) and high SI on T1WI with fat saturation (Fig. 2). Infrequently, hydrophilic necrosis shows very high SI on T2WI and low SI on T1WI (Fig. 5). Plaques with friable, gel-like state component may be prone to rupture and embolization. Peculiar findings of this plaque component distinguish it from the fibrocellular component or lipid-rich area.

### MRI classification and characterization of atherosclerotic lesions

According to the study of Cai et al,13) in vivo high-resolution multicontrast MRI was capable of classifying intermediate to advanced atherosclerotic lesions in the human carotid artery and was also capable of distinguishing advanced lesions from early and intermediate atherosclerotic plaques. Using 4 different contrast-weighted images (time of flight and T1-, PD- and T2-weighted), the classification obtained by MRI and the American Heart Association classifications showed good agreement, with a Cohen’s kappa value (95% CI) of 0.74 (0.67 to 0.82) and a weighted kappa of 0.79. The sensitivities and specificities of MRI classification were as follows: type I-II lesions, 67 and 100%; type III lesions, 81 and 98%; type IV-V lesions, 84 and 90%; type VI lesions, 82 and 91%; type VII lesions, 80 and 94% and type VIII lesions, 56 and 100%, respectively.

### Table 1. MRI appearance of plaque components on various imaging sequences

<table>
<thead>
<tr>
<th>Plaque components</th>
<th>T2WI</th>
<th>T1WI</th>
<th>Intermediate weighted</th>
<th>TOF</th>
<th>Enhancement on T1WI, postcontrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent hemorrhage</td>
<td>Variable</td>
<td>High to moderate</td>
<td>Variable</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>Lipid-rich core</td>
<td>Variable (low, typically)</td>
<td>High (low with FS)</td>
<td>High</td>
<td>Moderate</td>
<td>No</td>
</tr>
<tr>
<td>Hydrophilic necrosis</td>
<td>Very high</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>Fibrous tissue</td>
<td>Variable (moderate, typically)</td>
<td>Moderate</td>
<td>High</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>Calcification</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>No</td>
</tr>
</tbody>
</table>

*Enhancement on T1WI, postcontrast.*

Tissue contrast is relative to SI of muscle, FS: fat-saturation, TOF: time-of-flight MR angiography.
Evaluation of fibrous cap

The TOF technique can show the fibrous cap of the plaque as a low signal band along the plaque surface (Fig. 2, 3). Multisequence MRI can accurately characterize the in vivo state of the fibrous cap. Hatsukami et al. first described the use of the TOF sequence for fibrous cap imaging in vivo. They studied 22 patients with a 3-dimensional multiple overlapping thin slab angiography protocol before carotid endarterectomy. There was a high level of agreement between the MRI and histological findings in 36 sites available for comparison: 89% agreement, kappa (95% CI=0.83 (0.67 to 1.0) and weighted kappa=0.87 and a Spearman’s correlation coefficient of 0.88 (significant to the 0.01 level). Using the TOF MRI technique, they distinguished intact, thick fibrous caps from intact thin and disrupted caps in atherosclerotic carotid arteries in vivo. Mitsumori et al. examined pre-surgical MR images using four contrast weightings (3D time of flight, T1, proton density, and T2) to evidence an unstable fibrous cap in 18 patients. Assessment of the preoperative appearance of the fibrous cap had a high sensitivity (0.81) and specificity (0.90) for identifying an unstable cap in vivo. The availability of different contrast weightings facilitated image interpretation when intimal calcifications or flow artifacts obscured the lumen surface.

Trivedi et al. quantified the fibrous cap and lipid core contents proportional to the overall plaque area in 25 symptomatic patients. The intra-class correlation coefficients between two MR readers were 0.94 and 0.88 for quantifying fibrous cap and lipid core components, respectively. There was good agreement between MR and histology derived quantification of both the fibrous cap and lipid core content.

Yuan et al. correlated the state of the fibrous caps with the symptoms of the patients, and showed a strong and significant trend showing a higher percentage of symptomatic patients for ruptured caps (70%) compared with thick caps (9%) (p=0.001). Patients with ruptured fibrous caps were 23 times more likely to have a recent transient ischemic attack or stroke (95% CI=3,210) compared with patients with thick caps.

Fig. 1. Fibrous component-dominant plaque in the internal carotid artery. A: high-resolution T2-weighted spin echo MR image, showing a high signal intensity area (arrow) in the inner part of the plaque. B: photomicrograph showing a fibrous component (arrow) in the corresponding area (H & E).

Fig. 2. High-resolution MRI of a hemorrhagic carotid plaque, with an intact fibrous cap. A: source image of TOF MR angiography showing a thick fibrous cap (arrowhead) as a dark signal intensity band. High signal intensity area in the plaque (arrow) suggests intraplaque hemorrhage. B: T1-weighted spin echo image, with fat-saturation, showing high signal intensity (arrow) of the plaque due to hemorrhage. C: photomicrograph showing a thick fibrous cap (arrowheads) and intraplaque hemorrhage (arrow) (H & E).
Intraplaque hemorrhage

High SI in the plaque may suggest a focal area of fresh hemorrhage on TOF images (Fig. 2).\textsuperscript{16-18} The presence of an intraplaque hemorrhage may imply increased risk of plaque rupture and distal embolization. According to Chu et al.,\textsuperscript{16} MRI detected carotid intraplaque hemorrhage in 27 patients with high sensitivity (90%), but only moderate specificity (74%). Using the sequences of 3-dimensional TOF, double-inversion recovery, T1WI, PDW and T2WI, two readers grouped hemorrhages into fresh, recent and old categories. A hemorrhage was histologically identified and staged in 145/189 (77%) of carotid artery plaque locations.

\textit{In vivo} high-resolution MRI can detect and differentiate an intraplaque hemorrhage from a juxtaluminal hemorrhage/thrombus with good accuracy. According to Kampschulte et al.,\textsuperscript{17} the sensitivity and specificity for MRI to correctly identify cross sections containing a hemorrhage were 96 and 82%, respectively, in 26 patients. MRI was able to distinguish a juxtaluminal hemorrhage/thrombus from an intraplaque hemorrhage, with an accuracy of 96%. The distribution of lesion types underlying hemorrhages differed significantly ($p=0.004$). Intraplaque hemorrhages had an underlying lipid-rich type IV/V lesion in 55% of histological sections, whereas juxtaluminal hemorrhages/thrombi had an underlying calcified lesion type VII in 70% of sections. The association of a hemorrhage and lesion types suggests potential differences in origin.

Cappendijk et al.\textsuperscript{18} also investigated the performance of high-resolution T1-weighted (T1w) turbo field echo (TFE) magnetic resonance imaging (MRI) for the identification of intraplaque hemorrhages in 11 patients. More than 80% of the histologically proven intraplaque hemorrhages could be...
detected using the TFE sequence, with high interobserver agreement (Kappa=0.73).

**Gd-DTPA-enhanced imaging**

Gd-DTPA-enhanced MRI may differentiate necrotic or lipid-rich components from fibrous components, as the former do not show enhancement, but the latter do (Fig. 4).\(^{19}\) Enhancement after injection of a conventional contrast agent, Gd-DTPA, indicates increased vascularity in the plaque. Paradoxically, increased vascularity may mean an increased degree of inflammation and ongoing active atherosclerosis. Plaques with increased vascularity are subject to increased risk of an intraplaque hemorrhage. According to Yuan et al.,\(^ {19}\) there were statistically significant differences in the mean intensity change between tissues before and after contrast injection, with the largest increase for the fibrous tissue (79.5%) and the smallest for a necrotic core (28.6%). Additionally, histological analysis showed that a subset of fibrous regions, rich in plaque neovascularization, could be identified using a threshold of 80% enhancement (sensitivity, 76%; specificity, 79%).

Kerwin et al.\(^ {20}\) measured the neovasculature volume in carotid atherosclerotic plaques using a kinetic model. Dynamic contrast-enhanced MRI provided an indication of the extent of the neovascularization within carotid atherosclerotic plaques. They estimated the fractional blood volume and compared it with fractional microvascular area on histological staining with ULEX and CD-31. The correlation coefficient for the two measurement was 0.80 (\( p<0.001 \)).

The MRI characteristics of the aorta and carotid arteries may be associated with elevated serum markers of inflammation, frequently in the absence of a definite atheroma. Weiss et al.\(^ {21}\) compared the MRI findings with serum markers for systemic inflammation. Double inversion recovery, fast spin-echo images of the common carotid arteries and infrarenal aorta were obtained at 1.5 T, both before and after gadolinium-DTPA, in 52 subjects \( \geq 40 \) years of age. Twenty-two study participants had increases in wall thicknesses (\( n=14 \)), T2-weighted signal intensities (\( n=11 \)) and/or contrast enhancement values (\( n=7 \)) \( > 2 \) standard deviations of the control group mean values. Ten subjects in this group had evidence of focal plaques in the carotids (\( n=5 \)) and/or aorta (\( n=6 \)). Compared with the remaining 30 subjects, these 22 had significantly higher levels of interleukin-6, C-reactive protein, vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, but no significant differences in the levels of E-selectin.

**Accuracy of MRI plaque imaging**

Multispectral MRI can identify the lipid-rich necrotic core in human carotid atherosclerosis *in vivo*, with high sensitivity and specificity. Yuan et al.\(^ {12}\) compared 90 *in vivo* MRI cross sections with matched histological sections of the endarterectomy specimen in 18 patients. Using 4 contrast weightings (T1, T2, proton density, and 3D TOF), the MR images of the vessel wall were examined for the presence of a lipid-rich necrotic core and/or intraplaque hemorrhage. The overall accuracy (95% CI) of multispectral MRI was 87% (80 to 94%), with sensitivity and specificity of 85% (78 to 92%) and 92% (86 to 98%), respectively. There was good agreement between the MRI and histological findings, with a value of kappa=0.69 (0.53 to 0.85).

*Fig. 5.* Gel-like, hydrophilic necrosis of the carotid plaque. A: T1-weighted spin echo image showing a low signal intensity of the plaque. B: T2-weighted spin echo image showing a bright signal intensity of the plaque, suggestive of the high water content of this plaque. C: carotid endarterectomy specimen showing the gel-like state of the plaque content.
MRI monitoring of the response after statin therapy

High-resolution carotid MRI can provide useful information on the therapeutic response to lipid-lowering drugs. Measurements of the plaque thickness, area, volume, stenosis degrees and characters of plaque components can be compared before and after medical treatment. The treatment plan can be decided from the initial plaque MRI findings. Vulnerability of the plaques, rather than the degree of stenosis, may count more toward the surgical/interventional treatment of carotid stenosis.

McConnell et al. observed regression of atherosclerosis 12 to 20 months after withdrawal of a cholesterol diet and the progression of the atherosclerosis in rabbits with a continued high cholesterol diet by T2WI. The plaque thickness decreased significantly in the low-cholesterol group \((0.60 \pm 0.05 \text{ mm at 20 months versus } 0.85 \pm 0.06 \text{ mm at 4 months, } p<0.006)\), with a trend toward an increase in the high-cholesterol group \((1.02 \pm 0.08 \text{ mm at 20 months versus } 0.85 \pm 0.06 \text{ mm at 4 months, } p=0.1)\). Helft et al. observed regression or progression of lipid components in the plaque on serial MRI. MRI of the aorta was performed 3 times: baseline, after atherosclerosis induction (9 months old), and after atherosclerosis regression or progression (15 months old). There was a significant \((p<0.001)\) reduction in the lipidic component of plaques in the regression group, an increase in the progression group, and a significant decrease in the fibrotic composition of lesions in the progression group. A significant correlation \((p<0.001)\) was found between the MRI and histopathology for the atherosclerotic burden and plaque composition.

Corti et al. observed regression of carotid and aortic atherosclerotic lesions (44 aortic and 32 carotid artery plaques) in 21 asymptomatic hypercholesterolemic patients after maintained lipid-lowering therapy with Simvastatin for 24 months. The effects of statin on these atherosclerotic lesions were evaluated as changes versus the baseline lumen area (LA), vessel wall thickness (VWT) and vessel wall area (VWA) by MRI. Maximal reductions in the plasma total and LDL cholesterol by Simvastatin (23% and 38% respectively; \(p<0.01\) versus baseline) were achieved after approximately 6 weeks of therapy, and maintained thereafter throughout the study. Significant \((p<0.001)\) reductions in the maximal VWT and VWA at 12 months (10 and 11% for aortic and 8 and 11% for carotid plaques, respectively), without changes in the LA, have been reported. Further decreases in the VWT and VWA, ranging from 12 to 20%, were observed at 18 and 24 months. A slight, but significant, increase (ranging from 4 to 6%) in the LA was seen in both carotid and aortic lesions at these later time points.

According to Corti et al., the anti-atherogenic effects of a selective peroxisomal proliferator-activated receptor-gamma (PPAR-gamma) agonist and Simvastatin, as well as their combination, were demonstrated in cholesterol-fed rabbits by MRI after treatment for 6 months. In rabbits treated with Simvastatin or Simvastatin plus a PPAR-gamma agonist showed significant plaque regression \((-12 \pm 4\% \ [p<0.05] \text{ and } -22 \pm 4\% \ [p<0.01], \text{ respectively})\) by MRI plaque area measurements. The regression was independent of the plasma lipid levels. Histopathological analysis showed decreased macrophage content and matrix metalloproteinase activity, but an increased smooth muscle cell/collagen content of lesions.

Lima et al. measured atherosclerotic plaques in the thoracic aorta by combined surface/transesophageal MRI in 27 patients, both before and after 6 months of Simvastatin therapy (20 to 80 mg daily). The plaque volume and luminal dimensions were measured in 6 cross sections used to construct a 2.4-cm 3D volume of the aorta, including the plaque and lumen. The plaque volume was reduced from \(3.3 \pm 1.4 \text{ to } 2.9 \pm 1.4 \text{ cm}^3\) at 6 months \((p<0.02)\). The plaque regression (plaque volume/area reduction) was significantly related to the LDL cholesterol reduction \((p<0.02 \text{ and } p<0.005, \text{ respectively})\).

In our institution, 45 patients with 30–70% sonographic carotid stenosis were treated daily with 20 mg of Simvastatin. They were followed up for 19 ± 7.5 months. In 7 patients (16%), increased fibrous content or plaque cap thickness on multispectral MRI suggested plaque stabilization. There was significant change in the plaque thickness after medical treatment \(4.2 \text{ mm} \pm 1.0 \text{ vs. } 3.4 \text{ mm} \pm 1.3, \text{ p}<0.001\) (unpublished data) (Fig. 6).

Coronary artery wall imaging

Contrast arteriography can not directly image plaques. Noninvasive, high-resolution magnetic resonance has the potential to image coronary plaques. Fayad et al. used a black-blood MRI (BB-MR) method, free of motion and blood-flow artifacts, for high-resolution (down to 0.46 mm in-plane resolution and 3-mm slice thickness) imaging of the coronary artery lumen and wall. The difference in the maximum wall thickness between the 8 normal subjects \(0.75 \pm 0.17 \text{ mm (range, 0.55 to 1.0 mm)}\) and 5 patients with
≥40% stenosis [localized wall thickness of 4.38 ± 0.71 mm (range, 3.30 to 5.73 mm)] was statistically significant (p < 0.0001).

Free-breathing 3D black-blood coronary MRI, with isotropic resolution, identified an increased coronary vessel wall thickness, with preservation of the lumen size, in patients with nonsignificant coronary artery disease. This approach showed potential to quantify subclinical diseases. Botnar et al.30) used a 3D approach, together with a novel local inversion technique, to facilitate more extensive coverage. The combination of a nonselective inversion prepulse with a 2D selective local inversion prepulse allowed for the suppression of an unwanted signal outside a user-defined region of interest. Among 10 subjects evaluated using 3D-spiral readout, the local inversion pulse effectively suppressed the signal from ventricular blood, myocardium and chest wall tissue in all cases. The coronary vessel wall could be visualized within the entire imaging volume.

Kim et al.31) evaluated high-resolution black-blood 3D MRI on a 1.5 T scanner for in vivo visualization of the proximal coronary artery vessel wall in 6 clinically healthy subjects and 6 patients with nonsignificant coronary artery disease. Free-breathing 3D coronary vessel wall imaging was performed along the major axis of the right coronary artery, with isotropic spatial resolution (1.0 × 1.0 × 1.0 mm²), using black-blood spiral image acquisition. MRI visualized the contiguous proximal right coronary artery in all subjects. Both the mean vessel wall thickness (1.7 ± 0.3 versus 1.0 ± 0.2 mm) and wall area (25.4 ± 6.9 versus 11.5 ± 5.2 mm²) were significantly increased in the patients compared with the healthy subjects (both p < 0.01).

Differentiation of fibrocellular, lipid-rich and calcific regions is feasible using MRI, as shown in a study on ex vivo coronary arteries.32) The findings of each component of coronary arteries were similar to those found for the carotid arteries in the previous literature.

Botnar et al.33) demonstrated the feasibility of intravascular free-breathing black blood coronary vessel wall imaging using a double inversion fast spin echo technique after x-ray guided placement of an internal receiver coil in, or in close proximity to, the target vessel, with reproducible image quality. With internal coil placement in the left circumflex coronary artery, images of the left anterior descending vessel wall appeared similar or superior to those of commercially available phased array surface coil images.

Recently, clinical 3 T scanners have become available. With higher field strengths, coronary vessel wall imaging is likely to benefit from the remarkable gain in signal-to-noise ratio. Botnar et al.34) demonstrated the feasibility of in vivo human high field (3 T) coronary vessel wall imaging, using a free-breathing black blood fast gradient echo technique, with respiratory navigator gating and real-time motion correction.

Contrast agents and molecular MRI approach

Ultrasmall superparamagnetic particles of iron oxide (USPIO: Sinerem, Laboratoire Guerbet, Paris, France) can migrate through the interendothelial junctions and capillary pores, because of the small size of the agent and its long half-life in the blood. Ruehm et al.35) demonstrated iron uptake in the macrophages embedded in atherosclerotic plaque of hyperlipidemic rabbits using MR angiography 5 days after a USPIO injection. The USPIO contrast agent caused marked
susceptibility effects (spotty signal voids) in the aortic wall. USPIO in the actively phagocytosing cells signifies the presence of active inflammation in the plaque. Therefore, the agent is expected to be useful in the detection of atherosclerosis before luminal stenosis becomes evident.

Kooi et al.\(^{36}\) observed significant signal decrease in the regions of interest on T2*-weighted MR images 24 hours after administration of Sinerem (2.6 mg Fe/kg) in patients with carotid atheromas. On histopathological and electron microscopic examinations, the USPIO was located primarily in the macrophages within the plaques in 10 of 11 patients, and was found in 75% (27/36) of ruptured or rupture-prone lesions and 7% (1/14) of stable lesions. Signal changes on post-USPIO MRI T2*-weighted gradient echo images were seen in 54% (67/123) of quadrants after 24 hours and 35% (19/55) of quadrants after 72 hours. Schmitz et al.\(^{37}\) also observed USPIO uptake in human atherosclerotic walls. They found areas of profound signal loss in abdominal aorta and iliac arteries in 7 of 19 elderly patients 24 hour after an intravenous injection of Sinerem (2.6 mg Fe/kg). The optimal time window for imaging of USPIO-induced SI reductions was between 24 and 36 hours, decreasing after 48 hours, but SI reduction was still evident up to 96 hours after infusion.\(^{37}\) According to Trivedi et al.,\(^{38}\) areas of signal intensity reduction, corresponding to USPIO/macrophage-positive histological sections, were visualized in 7 of 8 patients given Sinerem (2.6 mg/kg).

Litovsky et al.\(^{39}\) demonstrated cytokine-induced recruitment of monocyte into aortic atherosclerotic plaques using superparamagnetic iron oxide particles (SPIO, Feridex, Berlex Laboratories) (1 mmol/kg iron injected over 3 min). Feridex was injected into female apo E knockout mice after intraperitoneal injections of cytokines (tissue necrosis factor-\(\alpha\), interleukin-1\(\beta\), interferon-\(\gamma\)). Histological studies were performed 6 days later. The atherosclerotic plaques in cytokine-treated mice contained more iron-positive macrophages per cross-section than sham-treated apo E knockout mice (42 ± 11.8 vs. 11.6 ± 5.9, p < 0.0001). The authors believed that iron-laded macrophages in the cytokine-treated mice were newly recruited monocytes, and that initiation of new atherosclerotic plaques may be apparent microscopically. Therefore, USPIO- or SPIO-enhanced MRI may be considered to have potential for detecting active atherosclerosis.

Another experimental contrast material, Gadofluorine M (Schering AG, Berlin, Germany), is a lipophilic, macrocyclic gadolinium-based contrast agent with a perfluorinated side chain. Gadofluorine creates its own interface by forming very small aggregates or micelles in dilute solution. The fluorinated side chain is hydrophobic. Gadofluorine showed specific delayed enhancement in the atheroma of Watanabe heritable hyperlipidemic rabbits (WHHL). According to Barkhausen et al.,\(^{40}\) delayed enhancement occurred in the aortic wall of WHHL examined with Gadofluorine, but not in the vessel wall of animals with Magnevist (Gd-DTPA; Schering AG, Berlin, Germany) or the control group. The gadolinium concentration was 368 ± 30 nmol/g in aortic walls with plaques in WHHL and 7 ± 5 nmol/g in normal aortic walls. Siroi et al.\(^{41}\) developed a new pulse sequence for early imaging, instead of a 48 hour delay. A combination of inversion-recovery and diffusion flow-nulling preparatory pulse gradient echo sequence (IR-DIFF-TFL) suppressed the aortic luminal signal, with higher signal intensity 1 hour after injection than with conventional IR-TFL. They also found Gadofluorine to have high affinity for lipid-rich areas.

The mechanism of accumulation of Gadofluorine in the atheroma is unclear, but explanations include; slow leakage of contrast agent into the plaque, with altered endothelial permeability, accumulation in the enlarged interstitial space, necrotic areas and lipid plaque components, and phagocytosis by macrophages or other active transport.\(^{40,41}\) Binding of the contrast material with denatured protein is also speculated. The advantage of Gadofluorine enhancement is that of positive contrast with visualization on T1WI and a high signal-to-noise ratio (Fig. 7). The clinical benefit of this agent is its ability to detect atherosclerotic plaques very early.

Recently, fibrin-targeted paramagnetic lipid-encapsulated perfluoro-carbon nanoparticles were introduced.\(^{42}\) This agent targets fibrin in the thrombi overlying the vulnerable plaque, not the plaque itself. Fibrin clots targeted in vitro with paramagnetic nanoparticles showed highly detectable T1-weighted enhancement. Botnar et al.\(^{43}\) demonstrated that Gd-DTPA-labeled fibrinogen clots appeared as bright hot spots on the black-blood inversion-recovery TFE sequence. A coronary in-stent thrombus was also visible as high signal intensity on the black-blood inversion-recovery TFE sequence after an intracoronary injection of 60 \(\mu\) mol EP-2104R (EPIX Medical, Inc) over 3 min in swine. In their earlier experiment, Botnar et al.,\(^{44}\) found that fibrin-targeted agent is useful in noninvasive in vivo MRI of acute and subacute thrombosis following a plaque rupture in an animal model of atherosclerosis. In the early stage of coronary thrombosis, thrombi are rich in platelets and fibrin. Therefore, detection of acute
coronary thrombosis is feasible with the fibrin-targeted agent. According to Johansson et al., the ability to visualize clots was highly dependent on the spatial resolution of the images. An in-plane resolution of at least 0.2 × 0.2 mm² was required for in vivo clot visualization after contrast enhancement.

Myeloperoxidase (MPO), which is secreted by activated neutrophils and macrophages, is a potential MRI target for atheroma imaging, as MPO secretion correlates well with a plaque rupture. Chen et al. demonstrated MPO activity in enzyme solutions and in a model tissue system, using a lead compound consisting of a covalent conjugate of GdDOTA and serotonin.

Integrin αβ₃ is a marker for angiogenesis and; therefore, represents an attractive target for molecular imaging aimed at the early identification of vulnerable plaques. Winter et al. developed a nanoparticle targeted against integrin αβ₃ by incorporating peptide-like particles into its lipid outer layer, which was linked to gadolinium-DTPA. By intravenous injection of a nanoparticle-Gd-DTPA targeted against integrin αβ₃ in atherosclerotic cholesterol-fed rabbits they detected increased angiogenesis as a 47 ± 5% enhancement in the MRI signal averaged throughout the wall of an abdominal aorta. Pretreatment of atherosclerotic rabbits with αβ₃-targeted nonparamagnetic nanoparticles competitively blocked specific contrast enhancement of the αβ₃-targeted paramagnetic nanoparticles. Histology and immuno-histochemistry confirmed marked proliferation of angiogenic vessels within the aortic adventitia, coincident with prominent, neointimal proliferation among cholesterol-fed, atherosclerotic rabbits compared with the sparse incidence of neovascularure in the control animals. The detection of integrin αβ₃ by MRI may serve as a useful signature of early atherosclerosis, although the role of integrin αβ₃ is unclear in the expansion of the vasa vasorum. With the clinical adoption of 3 T MRI, higher resolution of images should improve neovascular localization.

Ligand-targeted nanoparticles may be useful in site-specific drug delivery for early atherosclerotic lesions, as well as in monitoring the changes in the lesions after medical treatment. Lanza et al. used tissue factor-targeted nanoparticles, containing doxorubicin or paclitaxel, targeted to vascular smooth muscle cells (VSMC), which significantly inhibited their proliferation in cultures over the subsequent 3 days. Targeting of the nanoparticles to VSMC surface epitopes significantly increased the nanoparticle antiproliferative effectiveness, particularly that of paclitaxel. In vitro dissolution studies revealed that nanoparticle drug release persisted for over a week. The targeted antiproliferative results were dependent on the hydrophobic nature of the drug and the noncovalent interactions with other surfactant components. Molecular imaging of the nanoparticles adherent to the VSMC was demonstrated with high-resolution T1-weighted MRI at 4.7T. They concluded that targeted paramagnetic nanoparticles might provide a quantifiable drug delivery system for the prevention of restenosis after angioplasty.

**Multidetector CT**

The recently developed high speed CT technique (multidetector-row CT) provides improved z-direction spatial and
time resolutions. Stenotic lesions and adjacent anatomic landmarks (e.g., cervical bones) are visualized simultaneously on reconstructed images. MDCT has the capability of noninvasive detection and characterization of coronary artery plaques and thrombi (Fig. 8-10) (Table 2). The lipid core of the plaque is easily characterized, with a dark density in the plaque (Fig. 8).

**CT detection and measurement of coronary artery calcium**

Without injection of a contrast agent, CT clearly visualizes calcifications and coronary calcifications can be quantified.\(^{49}\) Their presence and extent correlates to the presence and amount of coronary atherosclerotic plaques. Prospective studies have demonstrated a high predictive value concerning the occurrence of coronary artery disease events and overall mortality.\(^{50}\) Calcium scoring by CT may be clinically useful in patients at intermediate risk for coronary artery disease events.

Shaw et al.\(^{51}\) followed up a cohort of 10,377 asymptomatic individuals undergoing cardiac risk factor evaluation and coronary calcium screening with electron-beam CT. The risk-adjusted relative risk values for coronary calcium were 1.64, 1.74, 2.54 and 4.03 for scores of 11–100, 101–400, 401–1,000 and greater than 1,000, respectively (\(p<0.001\) for all values), compared with that for a score of 10 or less. Five-year risk-adjusted survivals were 99.0 and 95.0% for calcium scores of 10 or less and of greater than 1,000 (\(p<0.001\) respectively. This study shows that coronary calcium provides

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**Fig. 8.** MDCT demonstrates a fatty plaque (arrow), seen as an area of very low attenuation, along with calcification (arrowhead) distal to a stent in the left anterior descending branch. A: volume-rendered image of the heart. B: axial MDCT image (0.625 mm slice thickness).

**Fig. 9.** MDCT and intravascular ultrasound (IVUS) demonstration of coronary artery noncalcified plaque. A: volume-rendered MDCT image, showing mild focal narrowing in the distal segment of the left circumflex artery (crossed by a line). B: reformatted CT image, corresponding to the line on the volume-rendered image, showing an eccentric noncalcified plaque in the coronary arterial wall. The measured CT number of the central low density area (arrow) of the plaque was about 20 HU, suggestive of the presence of a lipid-rich core. C: IVUS image obtained in the same area showing an anechoic area in the wall, confirming the lipid-rich component of the plaque. Courtesy of Joon Beom Seo, MD, Asan Medical Center.
independent incremental information in the prediction of all causes of mortality.

MDCT versus MRI in the detection and measurement of atherosclerosis

MDCT correlated well with MRI for the detection and measurement of atherosclerotic lesions. According to an experimental study, in 6 cholesterol-fed rabbits, there was excellent agreement between 3-mm axial reconstructions of 16-slice MDCT and MRI for measurements of vessel wall areas and diameters. The sensitivities and specificities of MDCT and MRI were 89 and 77% and 97 and 94%, respectively, in the detection of atherosclerosis. The interobserver agreements, as determined by $\kappa$, were 0.81 and 0.87 for MDCT and MRI, respectively. There was a significant difference in the CT densities between the two components ($p<0.01$) (Table 2). However, it was difficult to distinguish the lipid-rich from the fibrous areas within the same atherosclerotic lesion on the CT images.

Nikolaou et al. compared MDCT and MRI in human ex vivo coronary arteries. MDCT was performed with an isotropic voxel size of 0.6 mm$^3$, and the MRI with an in-plane resolution of 195 $\mu$m, with a 3 mm thickness. Of 28 atherosclerotic lesions, 21 and 23 lesions were found by MDCT and MRI, respectively. There were 4 and 3 false positive cases on MDCT and MRI, respectively, with sensitivities of 75 and 82% for MDCT and MRI. Although the differentiation of AHA type III, IV and V a plaques was difficult using MDCT, there was a significant difference between the mean CT density of predominantly lipid-rich ($n=10$, HU=47±13) and predominantly fibrous plaques ($n=11$, HU=87±29) ($p<0.01$). Using MRI, lipid-rich or fibrocellular regions could be well distinguished. Thus, both MDCT and MRI were able to differentiate the typical morphologic features of fatty, fibrous or calcified plaque components.

**MDCT detection and characterization of plaque components**

Contrast-enhanced MDCT permits the accurate identification of coronary plaques, with the CT density values measured within plaques reflecting the plaque composition. In vivo and ex vivo MDCT show significantly different attenuation values among the plaque components (Table 2).
Schoenhagen et al.\textsuperscript{39} compared the \textit{ex vivo} 16-slice CT and histological findings in 9 human popliteal artery specimens. Although calcified and non-calcified lesions could be differentiated, the diagnostic accuracy by further subclassifying non-calcified plaques as lipid rich and fibrotic was low. In another \textit{ex vivo} study,\textsuperscript{55} the mean attenuation was 47 ± 9 HU for lipid-rich plaques and 104 ± 28 HU for fibrous plaques. Leber et al.\textsuperscript{38} compared MDCT with intracoronary ultrasound for the detection and characterization of coronary atherosclerotic plaques in 68 vessels of 37 patients. The MDCT-derived density measurements within coronary lesions revealed significantly different values for hypoechoic, hypechoic and calcified plaques (Table 2). MDCT correctly classified 62 of 80 (78\%) sections containing hypoechoic plaque areas, 87 of 112 (78\%) sections containing hypechoic plaque areas and 150 of 158 (95\%) sections containing calcified plaque tissue. In 484 of 525 (92\%) sections, atherosclerotic lesions were correctly excluded.

Achenbach et al.\textsuperscript{59} compared MDCT with invavascular ultrasound in 22 patients. For the detection of segments with any plaque, MDCT had sensitivity and specificity of 82 (41 of 50) and 88\% (29 of 33), respectively. For calcified plaques, the sensitivity and specificity were 94 (33 of 36) and 94\% (45 of 47), respectively. Coronary segments containing noncalcified plaques were detected with a sensitivity and specificity of 78 (35 of 45) and 87\% (33 of 38), respectively, but the presence of exclusively noncalcified plaques was detected with a 53\% sensitivity (8 of 15) only.

According to an \textit{ex vivo} study,\textsuperscript{59} micro CT is feasible for analysis of the human coronary artery wall. The remarkably high spatial resolution (pixel size, 2 μm) with very thin sections (6 μm section thickness) of 80-kV micro CT (Sky-Scan, 1072; Sky-Scan, Aartselaar, Belgium) enabled calculations of the vessel wall perimeter, and plaque, calcified, lumen and media areas. Micro CT provided quantitative information about the plaque morphology, equivalent to that provided by histomorphometric analysis. Micro CT was able to visualize and characterize areas with different histological predominance. Using gray-scale differences, lesions could be classified as plaque areas with and without smooth muscle cells, and lipid-rich and calcified areas. Thus, micro CT should be considered as an additional tool for \textit{ex vivo} analysis of atherosclerosis.

Data on the accuracy of MDCT plaque detection, quantification of plaque volume and discrimination of lipid-rich from fibrous plaques are still limited. The prognostic significance of noncalcified coronary atherosclerotic plaque detection is unclear. Furthermore, there is significantly high radiation exposure with coronary angiography using the current MDCT technique. The effective dose using a 16-slice CT is 8.8 mSv (120 kVP, 370 mA, 0.42 sec exposure time)\textsuperscript{61}, while that of diagnostic coronary angiography ranges from 3 to 6 mSv.\textsuperscript{62} However, high-resolution CT is advantageous for the noninvasive detection and characterization of early coronary atherosclerosis. Future development of flat-panel detector CT will lead to more reliable detection of noncalcified, vulnerable plaques in proximal coronary arteries and significant stenosis in distal segments.

**Summary**

High-resolution MRI can noninvasively help to identify a vulnerable carotid plaque. Changes in the plaque burden or characteristics of its components can be quantitatively monitored using this technique. The detection and characterization of coronary artery plaques and calculation of the coronary artery plaque volume may be feasible using high-field (3 T) MRI equipment. With the aid of molecular imaging techniques, including newer contrast agents, MRI will be able to visualize vulnerable atherosclerotic lesions more specifically and sensitively in the future. The current MDCT technique reliably shows calcified coronary lesions, and has the potential to detect noncalcified, vulnerable lesions.

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