Clinical Imaging of the High-Risk or Vulnerable Atherosclerotic Plaque

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Abstract—The study of atherosclerotic disease during its natural history and after therapeutic intervention will enhance our understanding of disease progression and regression and aid in selecting appropriate treatments. Several invasive and noninvasive imaging techniques are available to assess atherosclerotic vessels. Most of the standard techniques identify luminal diameter, stenosis, wall thickness, and plaque volume; however, none can characterize plaque composition and therefore identify the high-risk plaques. We will present the different imaging modalities that have been used for the direct assessment of the carotid, aortic, and coronary atherosclerotic plaques. We will review in detail the use of high-resolution, multicontrast magnetic resonance for the noninvasive imaging of vulnerable plaques and the characterization of plaques in terms of their various components (ie, lipid, fibrous, calcium, or thrombus). (Circ Res. 2001;89:305-316.)

Key Words: atherosclerosis ■ magnetic resonance imaging ■ ultrasound ■ computed tomography ■ lipid-lowering

Atherosclerosis is a systemic disease of the vessel wall that occurs in the aorta and in the carotid, coronary, and peripheral arteries.1 The main components of the atherosclerotic plaques are (1) connective tissue extracellular matrix, including collagen, proteoglycans, and fibronectin elastic fibers; (2) crystalline cholesterol, cholesteryl esters, and phospholipids; and (3) cells such as monocyte-derived macrophages, T lymphocytes, and smooth muscle cells.2 Varying proportions of these components occur in different plaques, thus giving rise to a spectrum of lesions.1,3,4

Atherosclerotic Plaques and Need for Imaging
The high-risk or vulnerable plaque has different characteristics depending on the arterial regions (ie, coronaries, carotids, or aorta).

Coronary Artery Vulnerable Plaques
Rupture-prone plaques in the coronary arteries, the so-called “vulnerable plaques,” tend to have a thin fibrous cap (cap thickness <65 to 150 μm) and a large lipid core. Acute coronary syndromes (ACSs) often result from rupture of a modestly stenotic vulnerable plaque,3,4 not visible by x-ray angiography.1

According to the criteria of the American Heart Association Committee on Vascular Lesions, lesion types depend in part on the phase of progression as shown schematically in Figure 1.1,4 Coronary “vulnerable” type IV and type Va lesions (phase 2) and the “complicated” type VI lesions (phase 4) are the most relevant to ACS. Type IV and Va lesions, although not necessarily stenotic at angiography, are prone to disruption (see the Figure in the online data supplement available at http://www.circresaha.org), with
macrophage-dependent release of proteolytic enzymes such as metalloproteinases.\textsuperscript{2,5} Type IV lesions consist of extracellular lipid intermixed with fibrous tissue covered by a fibrous cap, whereas type Va lesions possess a predominant extracellular lipid core covered by a thin fibrous cap. Disruption of a type IV or Va lesion leads to the formation of a thrombus or “complicated” type VI lesion. The lipid core is highly thrombogenic as a result of the presence of tissue factor.\textsuperscript{1,6} The type VI lesion associated in ACS, rather than being characterized by a small mural thrombus, consists of an occlusive thrombus.

Relatively small type IV and Va coronary lesions may account for as many as two-thirds of cases of unstable angina or other ACSs.\textsuperscript{3} These relatively nonstenotic plaques with large lipid cores are more vulnerable and at higher risk of rupture and thrombosis; the caps are often thinnest at the shoulder region where macrophages\textsuperscript{7} and mast cells\textsuperscript{8} accumulate and disruption tends to occur.\textsuperscript{5} In contrast, the most severely stenotic plaques at angiography, which have a high content of smooth muscle cells and collagen, and little lipid, are less susceptible to rupture.

**Carotid Artery High-Risk Plaques**

In contrast to coronary artery vulnerable plaques characterized by high lipid content and a thin fibrous cap, high-risk plaques in carotid arteries are severely stenotic. The term “high-risk” is used rather than the classic term “vulnerable,” which only implies the presence of a lipid-rich core. High-risk carotid plaques are heterogeneous, very fibrous, and not necessarily lipid-rich. Rupture often represents an intramural hematoma or dissection, probably related to the impact of blood during systole against the resistance of such stenotic lesion.\textsuperscript{9} Imaging and plaque characterization of carotid arteries are simpler than those of coronary arteries because the former are superficial and not subject to significant motion.\textsuperscript{10} This is also true for the assessment of lower-extremity atherosclerotic disease, in which the pathobiology is similar to that of carotid disease. However, compared with peripheral vascular lesions, more information about carotid plaques and their imaging is available.

**Aortic Vulnerable Plaques**

Postmortem\textsuperscript{11} and transesophageal echocardiography (TEE)\textsuperscript{12} studies have shown that thoracic aortic atherosclerosis is a significant marker for coronary artery disease (CAD).\textsuperscript{13} Parameters such as aortic wall thickness, luminal irregularities, and plaque composition are strong predictors of future vascular events.\textsuperscript{14,15} Using TEE, the French Aortic Plaque in Stroke investigators determined increased risk of all vascular events (stroke, myocardial infarction, peripheral embolism, and cardiovascular death) for patients who had noncalcified aortic plaques >4 mm thick.\textsuperscript{14,15} Such noncalcified plaques, relatively easy to assess and characterize by imaging methods, are thought to be lipid-laden plaques (types IV/Va),\textsuperscript{15} which are prone to rupture and thrombosis in coronary arteries.

**Imaging of Atherosclerotic Plaques**

Direct visualization of plaques may enhance understanding of the natural history of atherosclerotic disease. Currently, a number of invasive and noninvasive imaging modalities are used to study atherosclerosis (Table 1); most identify luminal diameter or stenosis, wall thickness, and plaque volume.

**Invasive Imaging**

**X-Ray Angiography**

The x-ray angiogram reflects luminal diameter and provides a measure of stenosis with excellent resolution or irregular luminal surface implying the presence of atherosclerotic disease. But this imaging method does not image the vessel wall or provide information about the composition of the atherosclerotic plaque such as the vulnerable lipid-rich plaques or other histopathological features.\textsuperscript{16} This technique, however, has become the gold standard for diagnosis of coronary, carotid, and peripheral artery lesions. Nevertheless, angiography may reveal advanced lesions, plaque disruption,
TABLE 1. Clinical Imaging of the High-Risk or Vulnerable Plaque

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Luminal Stenosis</th>
<th>Wall Lipid</th>
<th>Fibrous</th>
<th>Thrombus</th>
<th>Calcium</th>
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<tr>
<td>X-ray angiography</td>
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<td>IVUS*</td>
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<td>Angioscopy</td>
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<tr>
<td>Thermography/OCT†/Raman spectroscopy/NIR</td>
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<td>US‡</td>
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<td>UFCT</td>
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● indicates coronary artery; ○, carotid artery; and ○, aorta.
*IVUS in carotid arteries or aorta is theoretically feasible.
†Optical coherence tomography (OCT) is able to image the vessel in very high resolution.
‡TEE may identify some of the plaque components in the aorta.

IVUS may be useful in selecting the most appropriate option of transcatheter therapy (rotational atherectomy, stents, etc). Invasive imaging can be performed in the catheterization lab (usually under local anaesthesia). If necessary, the procedure can be repeated after 6 months to assess treatment response. However, IVUS may not be able to detect calcified plaques or those with a high lipid content. A combination of IVUS and functional testing (e.g., IVUS elastography) may be needed to assess the risk of rupture and determine the optimal therapy.

Intravascular Ultrasound (IVUS)
Ultrasound (US) imaging is based on transmitting and receiving high-frequency sound waves. The time between transmission and reception of the wave is directly related to the distance between the source and reflector. Catheter-based US is a new approach to the arterial vascular wall imaging. This invasive modality permits direct and real-time imaging of atheroma and provides a cross-sectional, tomographic perspective of the vessel and atherosclerotic disease. Diagnostic applications of IVUS include detection of angiographically unrecognized disease, detection of lesions of uncertain severity (40% to 75% stenosis), and risk stratification of atherosclerotic lesions in interventional practice.

Current-generation catheters (incorporating a transducer) range in diameter from 0.96 to 1.17 mm and provide high-quality images. The spatial resolution is approximately 100 to 250 μm (depending on the US probe frequency). On the basis of plaque echogenicity, coronary atheroma can be differentiated into three categories, as follows: (1) highly echoreflective regions with acoustic shadows, often corresponding to calcified tissue; (2) hyperechoic areas representing fibrosis or microcalcifications; or (3) hypoechoic regions corresponding to thombothrombotic or lipid-rich tissue or a mixture of these elements. IVUS can delineate the thickness and echogenicity of vessel wall structures; however, histopathological information is limited. Spectral information of the radiofrequency signal may facilitate the discrimination of atheroma. Angioscopy (described below) and histological studies generally report low sensitivity to IVUS in detection of thrombus and lipid-rich lesions.

Angioscopy
Intracoronary angioscopy allows direct visualization of the plaque surface, color of the luminal surface (red, white, or luminal thrombosis, and calcification. The degree of stenosis measures blood flow obstruction. Calculation of the stenosis depends on proper designation of a normal reference segment. One of the major limitations of angiography is that diffuse atherosclerotic disease may narrow the entire lumen of the artery, and as a result underestimate the degree of local stenosis. In addition, because some of the plaques may be displaced outward, the luminal diameter may appear normal despite significant disease. IVUS elastography may be useful in selecting the most appropriate option of transcatheter therapy (rotational atherectomy, stents, etc). For example, lesions with calcification would be expected to be more rigid and, therefore, prone to rupture in response to the mechanical stress of balloon dilation, whereas softer, lipid-rich, noncalcified plaques may stretch but not fracture. Studies aimed at sensitivity and specificity involving large numbers of patients are required to determine the use of IVUS for the detection of atherosclerotic disease. Methods such as IVUS elastography have been introduced to assess mechanical properties of the vessel wall, which may relate indirectly to the histopathological composition of the atherosclerotic plaque. Intravascular elastography is obtained from cardiac-gated IVUS images coupled with intraluminal pressures during the cardiac cycle. The images provide vessel wall strain information and reflect mechanical properties of the tissue. Figure 2 shows an example of an elastographic image of a diseased human femoral artery.

Figure 2. Intravascular US image (left) and elastogram (right) of diseased human femoral artery. Elastogram reveals low strain in plaque (0.24%; I), similar strain in nondiseased vessel wall between 3 and 7 o’clock positions (0.32%; II), and high strain in vessel wall between 7 and 9 o’clock positions (0.96%; III). Region with high strain contains fatty foam cells at lumen–vessel wall boundary and increased macrophage activity. Modified from de Korte et al.
yellow), presence of thrombus, and macroscopic features (tears, ulcerations, and fissures). A recent clinical trial suggested a potential application of this invasive technique. In patients with various coronary syndromes, angiographic findings were directly compared with histomorphology and ex vivo angioscopy of atherectomy material. This study concluded that yellow (lipid-rich) plaques are associated with the development of ACSs. Another study concluded that angiographic identification of plaque rupture and thrombus was independently associated with adverse outcome in patients with complex lesions after interventional procedures. These features were not identified by either angiography or IVUS. However, like IVUS, this technique is invasive. Angioscopy thus remains a research tool because of the inability to examine small-caliber vessels or cross-stenotic lesions, and the different layers within the arterial wall.

Thermography, Optical Coherence Tomography, Raman Spectroscopy, and Near-Infrared (NIR) Spectroscopy
Several new technologies for invasive atherosclerotic plaque detection may have diagnostic and therapeutic implications.

In vitro and in vivo studies illustrate that detection of heat released by activated inflammatory cells of atherosclerotic plaques may predict plaque disruption and thrombosis. A study using carotid endarterectomy specimens and a needle thermistor demonstrated that atherosclerotic plaques exhibit thermal heterogeneity on their luminal surface. Temperature differences correlated positively with cell (macrophage) density. A catheter-based technique for the temperature measurement of human coronary arteries in vivo has been developed. The system consists of a 3F catheter, with 0.05°C accuracy and a spatial resolution of 500 μm. Using this catheter, thermal heterogeneity was found to be larger in patients with unstable angina compared with those with acute myocard infarction. Thermal techniques could conceivably be combined with IVUS or optical coherence tomography (see below) to provide both functional and anatomic information.

Optical coherence tomography is analogous to IVUS, but measures the intensity of reflected infrared light rather than acoustic waves. A Michelson interferometer is used as a gate to detect unscattered photons and thus generates high-resolution images. Although penetration is generally 1 to 2 mm, the use of light allows a resolutions of 10 to 30 μm. Initial in vitro imaging (resolution of 16 μm) of human aortic plaques demonstrated a strong correlation with the corresponding histopathology. In vitro optical coherence tomography exhibited superior delineation of structural detail when compared with IVUS. In vivo optical coherence tomography imaging, using a laser as light source, at four frames per second has been obtained in the rabbit esophagus. Potential limitations of optical coherence tomography for in vivo intravascular imaging are the possible reduction of image quality when imaging through blood or large volumes of tissue, relatively slow data acquisition rate, lack of an adequate portable source for in vivo imaging, and multiple scattering. Like IVUS, this technique is invasive, which may restrict its use in patients.

Raman spectroscopy is an optical technique that characterizes the chemical composition of biological tissue. Raman spectra can be obtained by processing the collected light that is scattered by a tissue as it is illuminated with a laser. Raman spectroscopy can be combined with other catheter-based imaging techniques, such as IVUS, to localize and quantify cholesterol and calcium salts in atherosclerotic plaques. Current limitations of Raman spectroscopy are the strong background fluorescence, the absorbance by blood of the laser light, and the relatively long acquisition time. Because this is a 1-dimensional technique (no depth information), it may be more powerful when combined with other imaging techniques.

Infrared spectroscopy also yields information on the chemical composition of tissue. NIR spectroscopy (750 to 2500 nm) has the advantage of deep penetration. Recently, the use of NIR spectroscopy has been explored for the characterization of the composition of atherosclerotic lesions. A study showed a good correlation between NIR spectra and plaque composition by histology for formalin-fixed human atherosclerotic plaques. Another study used a small (2.5-mm diameter) fiberoptic catheter combined with NIR reflectance spectroscopy and detected cholesterol in the rabbit aorta. Similar to Raman spectroscopy, NIR may be combined with other catheter-based imaging techniques.

Noninvasive Imaging

Surface and Transesophageal US
Measurements of carotid and aortic wall thickness as well as qualitative and quantitative analysis of plaque can be determined by surface and transesophageal US. Echogenicity of the plaque reflects its characteristics. Hypoechoic heterogeneous plaque is associated with both intraplaque hemorrhage and lipids, whereas hyperechoic homogeneous plaque is mostly fibrous. The North American Symptomatic Carotid Endarterectomy Trial and the Asymptomatic Carotid Artery Stenosis Study have shown that the degree of stenosis and its hemodynamic consequences play a significant role in producing stroke. High-resolution (<0.4 mm axial), real-time B-mode US with Doppler flow imaging has emerged as the modality of choice for examining the carotid arteries.

Using ≥8-MHz transducers, B-mode US can be used for measuring intima-media thickness (IMT) of large- and medium-size peripheral arteries such as the carotid, femoral, or radial. Because of the physical principles of a diagnostic US, the measurement is reliable only at the far arterial wall and does not indicate whether the thickening is due to intima or media infiltration and/or hyperplasty. As with other US methods, this technique is operator-dependent and has low reproducibility.

Several studies have found that carotid and aortic atherosclerosis are markers for coronary atherosclerosis. Patients with symptomatic CAD have increased IMT compared with asymptomatic controls. Carotid wall thickening was also found in patients with silent ischemia. The relationship between IMT and CAD severity is constant but rather weak. Nevertheless, large prospective studies have demonstrated that IMT may be a useful marker of CAD progression. For
example, the Cardiovascular Health Study found associations between carotid IMT and the incidence of new myocardial infarction or stroke in patients ≥65 years of age. Prevention trials of lipid-lowering treatments using IMT as a surrogate end point have shown that retardation in the progress of IMT correlates with a reduction of clinical end points.

Studies also have shown an association between aortic plaque seen on chest x-ray and the subsequent development of clinical CAD. Examinations of the aorta by B-mode US and TEE have been used as predictors of CAD and cardiovascular risk. Using TEE, the French Aortic Plaque in Stroke group found a significantly increased risk of all vascular events for patients who had noncalcified aortic plaques >4 mm in thickness. TEE-detected aortic plaque has been correlated with a higher prevalence of CAD and the presence of significant angiographic coronary artery stenosis. In addition, the lack of aortic plaque on TEE has been shown to be predictive of the absence of CAD.

Ultrasonic contrast agents have been introduced to improve image resolution and specificity. For example, acoustic liposomes conjugated with monoclonal antibodies can be used for plaque component–targeted imaging. The liposome formulation also has been modified to allow site-specific drug or gene delivery.

**Ultrafast Computed Tomography (UFCT)**

UFCT allows image acquisition at a faster rate than conventional computed tomography (CT). Fast imaging is essential elimination of cardiac and respiratory motion artifacts. Atherosclerotic calcification is found more frequently in advanced lesions, and may occur in small amounts in early lesions.

Magnetic resonance imaging (MRI), x-ray angiography, and US can identify calcified deposits in blood vessels; however, only electron-beam CT (EBCT) and fast-gated helical or spiral CT can measure the amount or volume of calcium. In EBCT, x-ray radiation passes through the patient and is detected by two 240° detector rings. To measure coronary calcium, 30 to 40 contiguous, 3-mm-thick slices are obtained from the aortic root to the apex of the heart. The scans are usually acquired during one or two separate breath holds. Non-EBCT systems use a continuously rotating x-ray source. Recently, non-EBCT systems have been introduced, using multidetector arrays for short rotation times that improve imaging speed.

Histological and UFCT studies support the association of tissue densities ≥130 Hounsfield units with calcified plaques. However, high-risk plaques often lack calcium. There is an association between coronary calcium and obstructive CAD, and it has been suggested that the amount of coronary calcium is a predictor of risk of coronary events. However, the predictive value of coronary calcification, at least in high-risk subjects, may not be superior to that of standard coronary risk factors. In addition, a high calcium score is sensitive but not a specific marker for coronary stenosis. The greatest potential for coronary calcium scores appears to be in the detection of advanced coronary atherosclerosis in patients who are apparently at intermediate risk. The new volumetric method for calcium detected the effect of lipid-lowering on coronary calcification. Nevertheless, there is no evidence to support that changes in coronary calcification may correspond to changes in cardiovascular events.

UFCT angiography with intravenous injection of a contrast medium is widely used for detection of stenosis in peripheral vessels. With the advent of faster and higher-resolution imaging and soft-tissue delineation with UFCT, assessment of coronary stenosis and the detection of noncalcified coronary plaques are being explored.

**Nuclear Scintigraphy**

Many radiotracers have been developed on the basis of molecules and cells involved in atherogenesis. The potential diagnostic utility of such radiotracers for imaging atherosclerotic lesions has been examined in animal models and in humans. Many proteins labeled with radioidine, 99m Tc, 111In, or 125In were evaluated. These include lipoproteins (native LDL and oxidized LDL), immunoglobulins against macrophages, smooth muscle cells, and endothelial adhesion molecules. These tracers showed significant uptake in experimental atherosclerotic lesions, although the limited clinical trials could not demonstrate utility because of slower clearance of radiotracers from circulation and poor target/background ratios. Radiolabeled peptides and metabolic tracers such as fluorodeoxyglucose, which show faster clearance from circulation and appear to provide higher contrast than radiolabeled proteins, were recently introduced. Similarly, radiolabeled antifibrin antibody fragments and peptides (which bind to glycoprotein IIb/IIIa receptors on activated platelets) clear faster from circulation compared with radiolabeled platelets. A new glycoprotein IIb/IIIa platelet inhibitor, DMP-44, labeled with 99m Tc accurately identifies the platelet-rich thrombus in a canine model. We recently illustrated that in vivo fluorodeoxyglucose positron emission tomography may detect and quantify macrophage content in rabbits with aortic plaques. However, no single radiotracer is ideally suited to image atherosclerosis and to provide the prognostic and clinical indicators necessary for medical and surgical interventions.

**Magnetic Resonance Imaging**

High-resolution magnetic resonance (MR) has emerged as the potential leading noninvasive in vivo imaging modality for atherosclerotic plaque characterization. MR differentiates plaque components on the basis of biophysical and biochemical parameters such as chemical composition and concentration, water content, physical state, molecular motion, or diffusion. MR provides imaging without ionizing radiation and can be repeated sequentially over time.

High-resolution MR relies on the same principles as other MR techniques. During the examination, the patient is subjected to a high local magnetic field, usually 1.5 T, which aligns the protons in the body. These protons (or spins) are excited by a radiofrequency pulse and subsequently detected by receiver coils. Detected signals are influenced by the
relaxation times (T1 and T2), proton density, motion and flow, molecular diffusion, magnetization transfer, changes in susceptibility, etc. Three additional magnetic fields (gradient fields) are applied during MRI; one selects the slice and two encodes spatial information. The timing of the excitation pulses and the successive magnetic field gradients determine the image contrast. The ability to obtain images of the atherosclerotic vessels is dependent on the amount of available signal, contrast, and the lack of noise.

The MR images can be “weighted” to the T1, T2, or proton density values through manipulation of the MR parameters (ie, repetition time and echo time). In a T1-weighted (T1W) image, tissues with low T1 values will be displayed as hyperintense picture elements or pixels (high signal intensity) and, conversely, high T1 values will be displayed as hypointense pixels (low signal intensity). In a T2-weighted (T2W) image, tissues with high T2 values will be portrayed as hyperintense pixels, and those with low T2 values as hypointense pixels. Thus, a T1W and a T2W image for the same anatomy can appear quite different because an MR image is not a photograph, but a computerized map of radio signals emitted by the human body. Finally, a proton density–weighted (PDW) image is an image in which the differences in contrast are proportional to the density of water and fat protons within the tissue. It is also referred to as an intermediate-weighted image because the contrast in the image is a combination of mild T1 and T2 contrast.

Ex Vivo MR Plaque Studies

Early work on applying MR techniques to characterizing plaque focused on lipid assessment with nuclear MR spectroscopy and chemical-shift imaging. These techniques suffer from poor signal-to-noise (SNR) ratio, because the concentration of the lipid present in the plaque is very low in comparison with water. Therefore, it has been difficult to extend these methods to an in vivo setting. Current studies are focused on MRI of water protons.

MR Multicontrast Plaque Imaging

After an ex vivo study, Herfkens et al performed the first in vivo patient imaging study of aortic atherosclerosis. Only the anatomic or morphological features such as wall thickening and luminal narrowing were assessed.

Improvements in MR techniques (eg, faster imaging and detection coils), conducive to high resolution and contrast imaging, have permitted the study of the different plaque components using multicontrast MR, generated by T1, T2, and PDW imaging. Atherosclerotic plaque characterization by MR is based on the signal intensities (Table 2) and morphological appearance of the plaque on T1W, PDW, and T2W images as previously validated.

<table>
<thead>
<tr>
<th>TABLE 2. Plaque Characterization With MR</th>
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<tr>
<td>Relative MR Signal Intensity*</td>
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<tr>
<td>Calcium</td>
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<tr>
<td>Hypointense</td>
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<tr>
<td>Very hypointense</td>
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<tr>
<td>Hyperintense</td>
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<tr>
<td>Very hypointense</td>
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<tr>
<td>Lipid</td>
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<td>Very hyperintense</td>
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<tr>
<td>Hyperintense</td>
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<tr>
<td>Very hypointense</td>
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<tr>
<td>Fibrous</td>
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<tr>
<td>Isointense to slightly hyperintense</td>
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<td>Isointense to slightly hyperintense</td>
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<td>Hyperintense</td>
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<td>Hyperintense</td>
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<td>Thrombus†</td>
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<td>Variable</td>
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*Relative to that of immediately adjacent muscle tissue.

†In some cases, surface irregularities; the variable signal intensity may be due to the thrombus age.

The plaque fibrous tissues consisting mainly of extracellular matrix elaborated by smooth muscle cells are associated with a short T1. The origin of the T1 shortening (increased signal intensity on T1W images) is specific to protein-water interactions. The plaque lipids consist primarily of unesterified cholesterol and cholesteryl esters and are associated with a short T2. The short T2 (decreased signal intensity of T2W images) of the lipid components is in part due to the micellar structure of lipoproteins, their denaturation by oxidation, or the exchange between cholesteryl esters and water molecules (both from the fatty chain or from the cholesterol ring), with a further interchange between free and bound water. Perivascular fat, mainly composed of triglycerides, has a different appearance on MR than atherosclerotic plaque lipids. The plaque-calcified regions consist primarily of calcium hydroxylapatite and are associated with low signal intensities on the MR images because of their low proton density and because of diffusion-mediated susceptibility effects. The MR appearance and evolution of thrombus or hemorrhage have been investigated in the central nervous system, pelvis, and aorta. These studies showed that the different MR signal intensities of hemorrhage depend on the structure of hemoglobin and its oxidation state. Additional studies in the context of arterial thrombus and atherosclerosis are necessary.

In a recent study, we analyzed 22 human carotid endarterectomy specimens with ex vivo MR and histopathological examination. Cross-sections were matched between the multicontrast MR images and histopathology. The overall sensitivity and specificity for each component were very high. Calcification, fibrous tissue, lipid core, and thrombus were readily identified. Diffusion imaging, which probes the motion of the water molecules, facilitated thrombus detection.

In Vivo MRI Experimental Studies

MR has been used in the study of plaques in several animal models. Skinner et al induced aortic plaque in the rabbit through a combination of atherogenic diet and double-balloon denudation, which showed in vivo aortic plaque progression. In a similar rabbit model, we validated the ability of MRI to...
quantify lipid-rich and fibrous components of lesions.\textsuperscript{89} Fast-spin echo multicontrast sequences with in-plane resolution of 0.35 mm and slice thickness of 3 mm were obtained. We have asserted that aortic MR atherosclerotic imaging can be used as a tool for documentation of arterial remodeling in the rabbit model.\textsuperscript{100} Two separate MRI serial studies\textsuperscript{101,102} have shown a significant regression of the aortic plaque in vivo in atherosclerotic rabbits undergoing cholesterol lowering. A significant correlation was found between MR and histopathology for atherosclerotic burden and plaque composition.\textsuperscript{102}

Another serial MRI study on the effect of lipid-lowering therapy with 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) and a novel class of agents, acyl-CoA:cholesterol O-acyltransferase (ACAT) inhibitors showed the beneficial effects in a Watanabe rabbit.\textsuperscript{103} The combination of statins and ACAT inhibitors induced a significant regression of previously established atherosclerotic lesions.

Using conventional MR systems (ie, 1.5 T), an in-plane spatial resolution $\approx 300 \mu m$ can be achieved with a high SNR and contrast-to-noise ratio for in vivo vessel wall imaging. To study small structures, such as the abdominal aorta of mice ($\approx <1$ mm in luminal diameter), it is necessary to increase the SNR by using high magnetic field scanners with small radiofrequency coils and strong magnetic field gradients.\textsuperscript{104} Using a 9.4-T (89-mm-bore system), we studied in vivo atherosclerosis in live animals.\textsuperscript{104} The achieved spatial resolution with MR microscopy (MRM) was $\approx 50$ to 97 $\mu m$ in-plane and 500 $\mu m$ in slice thickness. Using transgenic apolipoprotein E knockout mice, we showed an excellent agreement between MRM and histological findings for aortic plaque size, shape, and characteristics (Figure 3). We also followed the rapid progression of atherosclerosis in animals with lesions of varying severity.\textsuperscript{105} Therefore, high-resolution MRI and MRM may allow convenient and noninvasive quantitative assessment of serial changes in atherosclerosis in different animal models of disease progression and regression.\textsuperscript{98}

### In Vivo MRI Studies on Human Carotid Artery Plaque

MR has been used for the study of atherosclerotic plaque in the human carotid,\textsuperscript{10,106} aortic,\textsuperscript{107} peripheral,\textsuperscript{108} and coronary\textsuperscript{109} arterial disease. In vivo images of advanced lesions in carotid arteries have been obtained from patients referred for endarterectomy.\textsuperscript{10} The superficial location and relative absence of motion of carotid arteries present less of a technical challenge for imaging than does the aorta or coronary arteries. Short T2 components were quantified in vivo before surgery and correlated with values obtained in vitro after surgery.\textsuperscript{10} Some of the MR studies of carotid arterial plaques include the imaging and characterization of normal and pathological arterial walls,\textsuperscript{10} the quantification of plaque size,\textsuperscript{106} and the detection of fibrous cap "integrity."\textsuperscript{7,10} Typically the images are acquired with resolution of $0.4 \times 0.4 \times 3$ mm$^3$ using a carotid phased-array coil.

Most of the in vivo MR plaque imaging and characterization have been performed using a multicontrast approach with high-resolution black-blood spin echo– and fast spin echo–based MR sequences. The signal from the blood flow is rendered black by the use of preparatory pulses (eg, radiofrequency spatial saturation or inversion recovery pulses) to better visualize the adjacent vessel wall. Hatsukami et al\textsuperscript{110} introduced the use of bright blood imaging (ie, 3-dimensional fast time-of-flight imaging) for the visualization of the fibrous cap thickness and morphological integrity. This sequence provides enhancement of the signal from flowing blood and a mixture of T1 and proton density contrast weighting that highlights the fibrous cap.

MR angiography (MRA) and high-resolution black-blood imaging of the vessel wall can be combined (Figure 4). Comparison studies of MRA and contrast angiography have shown good sensitivity and specificity in the aorta and in the carotid, renal, and other peripheral vessels.\textsuperscript{111} MRA demonstrates the severity of stenotic lesions and their spatial distribution, whereas the high-resolution black-blood wall characterization technique may show the composition of the plaques and may facilitate the risk stratification and selection of the treatment modality. Improvements in spatial resolution ($\geq 250 \mu m$) have been possible with the design of new phased-array coils\textsuperscript{112,113} tailored for carotid imaging\textsuperscript{114} and new imaging sequences such as long echo train fast spin echo imaging with “velocity-selective” flow suppression or double-inversion recovery preparatory pulses (black-blood imaging).\textsuperscript{107,109}
In Vivo MRI Studies on Human Aortic Plaque

In vivo black-blood MR atherosclerotic plaque characterization of the human aorta has been reported recently. The principal challenges associated with MRI of the thoracic aorta are obtaining sufficient sensitivity for submillimeter imaging and exclusion of artifacts caused by respiratory motion and blood flow. Summers et al. showed by MRI that the wall thickness of the ascending aorta is increased in patients with homozygous familial hypercholesterolemia. However, conventional T1W spin echo images were obtained and no plaque composition analysis was performed. Fayad et al. assessed thoracic aorta plaque composition and size using T1W, T2W, and PDW images. The acquired images had a resolution of 0.8×0.8×5 mm³ using a torso phased-array coil. Rapid high-resolution imaging was performed with a fast spin echo sequence in conjunction with velocity-selective flow suppression preparatory pulses. Matched cross-sectional aortic imaging with MR and TEE showed a strong correlation for plaque composition and mean maximum plaque thickness. A patient with a lipid-rich plaque in the descending aorta is shown in Figure 5.

A recent study using MR in asymptomatic subjects from the Framingham Heart Study demonstrated that aortic plaque burden (ie, plaque volume/aortic volume) increased significantly with age, and was higher in the abdominal aorta compared with the thoracic aorta. Results ascertained that long-term measures of risk factors and Framingham Heart Study coronary risk score are strongly associated with asymptomatic aortic atherosclerosis as detected by MR.

In Vivo MRI Studies on Coronary Artery Plaque

Preliminary studies in a pig model proclaimed that the difficulties of coronary wall imaging are due to the combination of cardiac and respiratory motion artifacts, nonlinear course, small size, and location of the coronary arteries. We extended the black-blood MR methods used in the human carotid artery and aorta for imaging of the coronary arterial lumen and wall. The intraobserver and interobserver variability assessment by intraclass correlation for both MRI and histopathology showed good reproducibility, with the intraclass correlation coefficients ranging from 0.96 to 0.99. MRI was also able to visualize intralesion hematoma (sensitivity 82%, specificity 84%).

High-resolution black-blood MR of both normal and atherosclerotic human coronary arteries was performed. The difference in maximum wall thickness between the normal
restenosis after angioplasty.

Peripheral vasculature and demonstrate the remodeling and MR can define the extent of atherosclerotic plaque in the detected and serial changes in lumen diameter, blood flow, angioplasty, plaque fissuring, and local dissection were easily 49% to 76% of potential lumen area were identified. After erosclerotic lesions with cross-sectional areas ranging from segments of vessel that were angiographically normal, ath-

plaque (arrow) in left anterior descending artery (LAD). Inset represents magnified view of LAD plaque. MR images are 4 mm thick with an in-plane spatial resolution of 750 μm acquired during suspended respiration (<16 seconds) using long-echo train fast spin echo imaging with “velocity-selective” flow suppression. RV indicates right ventricle; LV, left ventricle. Modified from Fayad et al.109

In Vivo Monitoring of Therapy With MRI

As shown in experimental studies, MR is a powerful tool to investigate serially and noninvasively the progression and regression of atherosclerotic lesions in vivo. We have shown recently that MR can be used to measure the effect of lipid-lowering therapy (statins) in asymptomatic untreated hypercholesterolemic patients with carotid and aortic atherosclerosis.120 Atherosclerotic plaques were assessed with MR at different time points after initiation of lipid-lowering therapy. Significant regression of atherosclerotic lesions was observed. Despite the early and expected hypolipidemic effect of the statins, a minimum of 12 months was needed to observe changes in the vessel wall. No changes were detected at 6 months. In agreement with previous experimental studies, there was a decrease in the vessel wall area and no change in the lumen area at 12 months.301,103

MR of the popliteal artery and its response to balloon angioplasty has been reported by Coulden et al.108 The extent of plaque could be defined in all patients, such that even in segments of vessel that were angiographically normal, atherosclerotic lesions with cross-sectional areas ranging from 49% to 76% of potential lumen area were identified. After angioplasty, plaque fissuring, and local dissection were easily detected and serial changes in lumen diameter, blood flow, and lesion size were documented. This study illustrated that MR can define the extent of atherosclerotic plaque in the peripheral vasculature and demonstrate the remodeling and restenosis after angioplasty.

Limitations and Potential Improvements of MRI

Thinner slices such as those obtained with 3-dimensional acquisition techniques could further improve artery wall imaging.121 Tailored coil designs, such as smaller anterior 4-element phased-array coils, may enhance the spatial resolution and may allow the identification of the substructures within coronary atherosclerotic lesions.113 Additional MR techniques such as water diffusion weighting,96,97 magnetization transfer weighting,122 and contrast enhancement123,124 may provide complementary structural information and allow more detailed plaque characterization. Slowly flowing blood near the vessel walls is another phenomenon that may potentially improve the accuracy of vessel wall imaging with black-blood techniques. Preliminary results in our study and with a similar black blood–MR sequence in the coronary arteries and the brain109,118 suggest that this effect is minimal. However, new and more robust blood-suppression methods are needed for accurate plaque imaging especially in the carotid artery bifurcation.125

Conclusions

Assessment of atherosclerotic plaques by imaging techniques is essential for in vivo identification of vulnerable plaques. Several invasive and noninvasive imaging techniques are available. Most techniques identify luminal diameter or stenosis, wall thickness, and plaque volume, and are ineffective in identifying the high-risk plaques that are vulnerable to rupture and thrombosis. In vivo, high-resolution, multicontrast MRI holds the best promise of noninvasively imaging high-risk plaques. MR allows serial assessment of progression and regression of atherosclerosis. Application of MRI opens new areas for diagnosis, prevention, and treatment (eg, lipid-lowering drug regimens) of atherosclerosis in all arterial locations.

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Figure I: Macroscopic view of a cross-sectioned coronary artery containing a large lipid-rich core (left panel), the core, which is separated from the arterial by the fibrous cap of the plaque, is very large occupying most of the area of the plaque cross-section. A cross-sectioned coronary artery contained a disrupted plaque is shown in the right panel. The fibrous cap is torn and a thrombus projects into but does not occlude the lumen.