Stroke due to atherosclerotic disease is a major cause of disability and death all over the world. Atherosclerotic plaque rupture in the internal carotid arteries and subsequent thrombosis and/or embolism is believed to be the major factor in stroke or transient ischemic attack (TIA).

Carotid atherosclerosis is marked by plaque deposition, mainly at the bifurcation of the common carotid artery into the internal and external carotid arteries. Increased sequestration of circulating cholesterol into the vessel wall leads to the development of lipid pools and eventually large lipid cores. Ensuing inflammation and angiogenesis cause intraplaque hemorrhage and necrosis to form a thrombogenic necrotic core separated from the lumen by a well-defined fibrous cap. Identification of the plaque that is vulnerable to rupture at this stage is of primary importance if thrombosis or embolism is to be prevented. The steps involved in the progression to possible stroke are shown in Figure 1.

Traditionally, luminal stenosis has been used as a measure of carotid atherosclerotic disease. Recent studies have shown that luminal stenosis may not be the only causation of symptoms, but that plaque composition may also impact disease outcome. Although angiography is still used to decide whether patients will receive surgical treatment (endarterectomy) or other interventions, it is increasingly recognized that a large proportion of vulnerable plaques cannot be seen by angiography. Non-invasive high-resolution MRI can identify these angiographically silent but potentially vulnerable plaques.

Components such as lipid/necrotic core and hemorrhage, along with inflammation, are currently considered vulnerability markers regardless of plaque size. MRI can easily visualize and quantify these components. These are valuable capabilities, not only in diagnosis but also in the study of atherosclerosis progression and in pharmaceutical clinical trials.

This article reviews the currently established procedure for plaque characterization by MRI. It addresses the technical advances in coils, sequences, imaging protocols and post-processing methods for quantification, followed by examples of the MR appearance of plaque components. The article concludes with a discussion of the current state of the art imaging as implemented on a Philips Achieva 3T scanner.

MRI of the carotid atherosclerotic plaque

The widely accepted AHA classification of atherosclerotic plaques is based on plaque composition [1]. A modified AHA classification [2] based on the MR appearance of plaque components was shown to have good correlation...
with the traditional AHA classification, suggesting that MRI is a reliable way to characterize plaque composition.

The detection of the vulnerable plaque \textit{in vivo} is considered to be the primary purpose of atherosclerotic plaque imaging. Histological studies of vulnerable plaques indicate that plaque composition is a primary determinant of plaque vulnerability [3, 4]. Histological criteria for the vulnerable plaque are known from cross-sectional studies. Imaging markers corresponding to many of those criteria have been identified in the last decade [5-8]. MRI possesses unique features which can reveal a wide range of information, including excellent soft tissue contrast, ability to visualize plaque morphology and tissue constituents, and the ability to quantify those components [9]. Several markers of plaque vulnerability can be identified by MRI [10]:

- Large lipid-rich necrotic core
- Intra-plaque hemorrhage
- Surface disruption
- Inflammation
- Surface calcific nodules

**Technical advances**

Plaque characterization requires high spatial resolution with good blood-suppression and enhancement. MR plaque characterization has been made possible by recent advances in the design of coils, sequences and post-processing algorithms targeted to these needs.

**Coils**

Quantification of plaque components requires both high resolution and good signal-to-noise ratio (SNR). Therefore, receiver coils need to be tailored specifically to the needs of carotid imaging. Small field-of-view surface phased array coils have been shown to be ideally suited for this purpose. Array coils for carotid imaging are designed to provide good SNR at a depth of about 4 cm from the surface. Hayes et al. demonstrated a four-channel phased array coil construction that performs well for carotid imaging [11]. This has continued to be a standard setting design. A suitable head retractor and positioner is an integral part of the coil design to ensure patient comfort and reproducible patient positioning for serial studies.

**Sequences**

A comprehensive assessment of plaque morphology and composition requires a multi-contrast time-efficient protocol with good blood-suppression and enhancement, high resolution and high SNR. Currently established multi-contrast protocols use a combination of bright blood (Time-of-Flight (TOF) MRA), black-blood and contrast-enhanced imaging. The vessel wall and plaque components are best characterized on high-resolution black-blood sequences while TOF provides complimentary angiography. Contrast-enhanced MRI improves delineation of plaque components. Dynamic contrast-enhanced MRI (DCE) provides information about functional characteristics such as inflammation and neovascularization. Sequences targeted at specific plaque components may also be added to the protocol.

**Blood-suppression techniques**

Excellent blood suppression is mandatory for plaque characterization. Several new time-efficient techniques have been developed for black-blood imaging:

- Multi-slice double inversion recovery (MDIR)
- Quadruple inversion recovery (QIR)
- Motion-sensitized driven equilibrium (MSDE)

**Multi-slice double inversion recovery (MDIR)**

Double inversion recovery (DIR), in which a non-selective inversion followed by a slice-selective re-inversion nulls the blood signal after an inversion delay, provides adequate blood-suppression. However, the DIR preparation was initially developed as a single-slice technique and is time-inefficient. Several multi-slice DIR mechanisms have been recently proposed to improve scan time. The technique proposed by Yarnykh et al., which uses a slab-selective re-inversion pulse to acquire up to eight slices per TR interval with good blood suppression [12], has been found to be SAR efficient and is thus desirable for high-field imaging.

**Quadruple inversion recovery (QIR)**

The DIR inversion time (TI) is blood T1 dependent. The TI therefore changes when T1 shortening contrast agents such as gadolinium are injected. This requires separate sequence parameter optimization for pre- and post-contrast scans. In this case, the image contrast will be a function of both sequence parameters and contrast enhancement. The QIR technique solves this problem by employing two DIR blocks with two different TIs [13]. By adjusting the TIs, nulling of the blood signal can be achieved over a wide range of T1, covering both pre- and post-contrast blood T1. Thus the same sequence parameters can be used for pre- and post-contrast scans allowing quantitative measurements of contrast enhancement in the vessel wall.

**Motion-sensitized driven equilibrium (MSDE)**

Slow and re-circulating blood flows produce plaque-mimicking artifacts near the carotid
bifurcation, sometimes even with DIR and MDIR preparation, because blood in the imaging slab is not completely replaced by fresh blood inflow. Recently a new black-blood preparation referred to as Driven-Equilibrium Fourier Transform (DEFT) [14] or Motion-Sensitized Driven Equilibrium (MSDE) [15] has been introduced to surmount this problem. The MSDE preparation refocuses stationary spins while destroying moving spins, and has been shown to provide better suppression of slow flowing blood when compared with DIR [15] (Figure 2).

**Contrast-enhanced MRI**

Contrast-enhanced MRI improves plaque tissue contrast and provides additional information about the presence of macrophages [16] and neovascularature [17]. This information is obtained from modeling the transfer kinetics of contrast into the plaque and is otherwise not obtainable from standard contrast weightings. Thus both a post-contrast T1 weighted sequence and dynamic CE-MRI (DCE) can be included in a standardized protocol. This use of contrast agents is for research purposes only and not for the purposes of diagnoses.

**Image processing**

Image processing methods and software are for research purposes only and not FDA approved. They are used for investigational studies and are not commercially available. Quantitative plaque analysis is important for identification of vulnerable plaque. Vessel wall and plaque components have to be identified and segmented from multi-contrast images before quantification is possible. Furthermore, precision and reproducibility of measurements is important where small treatment effects have to be discerned in limited study populations. Image misregistration is a major impediment to reproducible measurements, especially in clinical trials or natural history studies that contain several imaging sessions spanning months or years. Specialized algorithms to overcome these problems have been collected into a plaque analysis package (CASCADE) [17]. Efficient workflow and semi-automated image review help reviewers translate their findings into precise repeatable quantitative plaque measurements for clinical trials involving multiple image readings.

The image review process starts with matching all contrast weightings by using the carotid bifurcation as the landmark. Lumen and outer wall contours are drawn by semi-automated algorithms [18]. After the lumen is identified on one contrast weighting, image locations are accurately registered by an active contour map method. A morphology-based probabilistic segmentation algorithm [19] can segment these registered multi-contrast images into plaque components. A rendering of the 3D distribution of plaque components (Figure 3) helps in comprehensive review and correction of contours. The radiologist reviews the results and corrects the contours if necessary. The final plaque measurements are derived from the radiologist’s contours. Derived measurements may vary according to the study design. For example, a carotid risk score may be derived for each patient in a patient risk stratification study.
Figure 3. 3D distribution of carotid atherosclerotic plaque components segmented from axial multi-contrast high-resolution MRI at 3T. Two 3D views (A, B) show the complex structure of plaque as visualized by MRI. The plane (green) on (B) corresponds to the level of the axial slices shown (C, D). Contours drawn on the axial images are shown in (C) with the corresponding post-contrast image (D).

Figure 4. Example of histological validation of MRI at four consecutive locations spanning the bifurcation. Multiple histological sections (at 0.5 to 1.0 mm separation) generally correspond to each 2 mm thick MR image. Contours have been drawn for:
- lumen (red)
- outer wall (cyan)
- LR/NC (yellow)
- calcification (black)
- loose matrix (pink/white)
- hemorrhage (orange).

H&E indicates hematoxylin-eosin.

Dynamic contrast information requires separate processing algorithms. DCE requires accurate registration of the dynamic series for obtaining contrast enhancement curves. A targeted registration algorithm (KFRS) has been implemented for this purpose [20]. By modeling the exchange kinetics between the blood and tissue compartments, Kerwin et al. obtained a quantitative index of fractional plasma volume ($V_p$) and transfer constant ($K_{trans}$) of contrast into the extracellular space, from the contrast enhancement curves. $V_p$ correlates well with plaque neovasculature [17] while $K_{trans}$ is indicative of plaque inflammation [21].

Plaque characterization by MRI

Drawing on a decade of experience obtained from reviewing hundreds of subjects, Yuan et al. developed an MRI classification of carotid atherosclerotic plaque [3]. This classification has been validated against histology (Figure 4) and is being further refined with new technological advances. The currently accepted signal characteristics of plaque morphology and components are discussed below.

Vessel morphology

Vessel wall boundaries are used to measure the volume and extent of atherosclerotic plaque burden. Black-blood imaging is important for the identification of the lumen boundary. Outer wall boundaries are best visualized on T1W and PDW images and are dependent on adequate fat suppression and the signal-to-noise ratio (SNR). Wall thickness measurements can be calculated once the lumen and outer wall boundaries are identified, and have been shown to correlate well with ultrasound intima media thickness measurements [18].

The change in plaque burden is often used as the endpoint in clinical trials. Accurate and reproducible measurement of vessel wall boundaries are therefore crucial. Use of semi-automated tools for plaque burden assessment has not only reduced the effort required by the radiologist but also improved the reproducibility of measurement.

Detection of lipid/necrotic core

The lipid pools of early plaques change with increased hemorrhage and inflammation into a necrotic core filled with blood and necrotic debris. Consequently the appearance of the necrotic core on MRI is often variable. A pure lipid core with no hemorrhage is generally hyper-intense on T1W and PDW and iso-intense on T2W and TOF. In the presence of hemorrhage the signal characteristics of hemorrhage (hyper-intense on TOF) predominate.

The margins of the lipid core are best appreciated by comparing the pre- and post-CE images, because the lipid core and hemorrhage are slow to enhance in post-contrast. Since lipid cores tend to be large, MRI can measure them with reasonable precision. Thus they are good candidate parameters in clinical studies since they are the direct targets of lipid-lowering drugs used in attempts to stabilize the plaque. A representative case is shown in Figure 5.

Figure 5. Multi-contrast weighted high-resolution 3T MR shows the presence of a lipid-rich necrotic core (arrow) at the left carotid bifurcation. The core produces iso-intense signals on TOF, T1W, and a slightly hyper-intense signal on T2W. However, the CE T1W image has a clear demarcation of the core boundary due to the absence of neovasculature or loose matrix into the necrotic core.
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Detection of hemorrhage
Hemorrhage can be identified by using multiple contrast weightings. Methemoglobin content varies depending on the age of hemorrhage, thereby altering signal intensities. Type-I (fresh) hemorrhages are bright on TOF and T1W but iso-intense or hypo-intense on PDW and T2W images. Type-II (recent) hemorrhages are bright on all pre-contrast weightings [6]. Recently, direct thrombus imaging (MP-RAGE) has been shown to be sensitive for hemorrhage/thrombus detection [22]. A representative case is shown in Figure 6.

Figure 6. Multi-contrast weighted high-resolution 3T MR shows the presence of intraplaque hemorrhage in the common carotid artery. Intraplaque hemorrhage at 3T is characterized by a slight hyper-intense signal on 3D TOF; hyper-intensity on T1W and PDW; and hypo-intensity on T2W, depending on the age of the hemorrhage. However MPRAGE gives a striking hyper-intense signal that corresponds well with areas of hemorrhage on the matching histology.

Detection of rupture
Rupture of the fibrous cap can be detected on MRI [23] and is often associated with symptomatic status [24]. The thickness of the cap can be measured using post-contrast images [5]. Ulceration after rupture can be identified on TOF as a bright indentation into the lumen surface indicative of blood flow into the ulcer. A representative case is shown in Figure 7.

Figure 7. Multi-contrast weighted high-resolution MR readily shows the presence of a large ulceration in the atherosclerotic plaque of the right internal carotid (long arrow). The lower signal inside the ulcer on TOF, when compared to the signal in the parent internal and external carotid arteries, indicates turbulent flow. The turbulence is also visualized as a thin irregular line in the four black blood images (short arrows). The oblique black blood MRA (OB BB MRA) confirms the presence of the large ulceration.

Detection of inflammation
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Detection of inflammation

Unlike other plaque components, inflammation is an active biological process. DCE can be used to measure the permeability of tissues by visualizing the diffusion of contrast out of vascular spaces and into the surrounding tissues (Figure 8). Ktrans measured from kinetic modeling of DCE images correlates well with plaque inflammation [21]. In addition, ultrasmall superparamagnetic iron oxide particles (USPIOs) have been shown to produce hypo-intense signals in areas of macrophage density [25]. The use of contrast agents is for research purposes only and not for the purposes of diagnoses.

Detection of calcification

Calcification appears hypo-intense on all image weightings (Figure 9). Highly calcified plaques have historically been thought to be more stable than non-calcific plaques. However, calcified plaques containing calcium nodules protruding into the lumen can trigger coagulative pathways leading to thrombosis and/or embolism [26].

State of the art

An optimized high-resolution carotid imaging protocol implemented on the Philips Achieva 3T platform is currently being used in several research studies. The protocol, based on the latest advances in black-blood imaging, is described below:

- A standard three-plane survey is followed by a 2D MRA to locate the A/P coordinates of the carotid bifurcation.
- An oblique MSDE black-blood Turbo spin-echo (TSE) sequence is used to find the exact S/I coordinates of the bifurcation.
- An axial geometry centered on the bifurcation and covering both arteries is then determined.
- PDW MDIR TSE, T2W MDIR TSE, T1W QIR TSE, 3D TOF (3D T1-Fast Field Echo (FFE) MRA), 3D MP-RAGE (3D T1-FFE with IR preparation and ProSet) are acquired.
• A dynamic T1-FFE with 12 slices, 20 phases per slice is acquired within 4.5 min immediately after a single-dose gadolinium-based contrast agent injection (2 phases pre-contrast).
• A post-contrast T1W QIR TSE is also obtained with the same parameters as pre-contrast.

The total scan time for this comprehensive carotid imaging protocol with 0.63 mm in-plane acquired resolution (0.25 mm interpolated), 2 mm slice thickness and 20 slices is less than 35 minutes for bilateral arteries on a Philips Achieva 3T scanner. All axial images are obtained with the same geometry so that they can be used for multi-contrast analysis. Carotid plaque measurements are not influenced by cardiac gating [27]. Thus, gating is generally not required for carotid plaque imaging. An example of using this protocol can be found in Figure 5.

Quantitative plaque measurements derived from these images using custom-built software implementing the segmentation and registration algorithms described earlier, are currently being used in pharmaceutical trials and natural history studies. A carotid artery risk score describing the vulnerable plaque components derived from plaque analysis is being assessed for its efficacy to identify high-risk subjects. The custom-built software is not an FDA approved device, and is used for research and investigational purposes only.

Future of plaque imaging

Reduction of plaque burden, as detected by MRI, has been used as the primary endpoint in clinical trials involving lipid-lowering drugs [28]. Reduction in plaque burden as well as lipid content [29] of atherosclerotic plaque has been reported in clinical trials. Large-scale multi-center clinical trials using carotid MRI are feasible based on current technology. The move towards this goal can be seen by the concerted efforts to standardize imaging protocols in trials involving multiple imaging centers and the increased participation by equipment vendors in coil and sequence development for carotid MRI.

If vulnerable plaques can be identified and treated appropriately before they become symptomatic, morbidity and mortality associated with stroke could be significantly reduced. Selection of patients for treatment based on plaque vulnerability has the potential to lower health care costs by reducing unnecessary interventions or the subsequent devastating cost of stroke. Identifying new imaging markers for the vulnerable atherosclerotic plaque is an area of active research and carotid MRI is quickly establishing itself as the best non-invasive imaging modality used to identify vulnerable carotid plaque.

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References


