Atherosclerosis and thrombotic complications are the first cause of mortality and morbidity in industrialized countries. Furthermore, despite pharmacological intervention and lifestyle changes, cardiovascular disease (CVD) continues to be the principal cause of death in the US. Despite great advances in the understanding of the initiation and progression of atherosclerosis and its risk factors, to make a strong clinical impact, patients who have lesions that are vulnerable to rupture and thrombosis must be focused on.

Atherosclerosis is a systemic disease that mainly affects medium- and large-sized arteries, is characterized by a thickening of the arterial intima, and is typically composed of a lipid core with an overlying fibrous cap. Angiography remains the gold standard for diagnosis and quantification of atherosclerotic plaques resulting in flow-limiting arterial stenoses, but only offers an indirect view of atherosclerosis burden. Positive remodeling of the arterial wall, a process in which the vessel dilates to limit the narrowing of the lumen in the presence of atherosclerotic plaques, leads to a clear underestimation of the true extension of atherosclerosis disease with angiography. Moreover, studies have shown that plaque vulnerability is related to plaque composition rather than to the degree of stenosis.

**Atherosclerosis Plaque Composition and Feature of Plaque Vulnerability**

The main components of atherosclerotic plaques are:

- fibrous elements such as connective tissue, extracellular matrix, including collagen, proteoglycans, and fibronectin elastic fibers;
- lipids such as crystalline cholesterol, cholesteryl esters, and phospholipids;
- smooth muscle cells, which are intimately associated with atherosclerotic plaque; and
- inflammatory cells, such as monocyte-derived macrophages and T-lymphocytes, which contribute to the inflammatory pathogenesis of atherosclerosis.

The occurrence of these components in varying proportions in different plaques gives rise to a spectrum of lesions with varying stabilities, depending on the arterial region in which it is located (i.e. coronary arteries, carotids, or aorta). Acute coronary syndromes and stroke are mainly caused by the endothelial disruption of atherosclerotic plaques (superficial intimal erosion or fibrous cap rupture), triggering the formation of an intraluminal thrombus. These atherosclerotic plaques are typically described as containing a large lipid core representing more than half of the plaque volume, a thin fibrous cap (less than 65um) and a heavy infiltrate of inflammatory cells (macrophages and lymphocytes). In contrast to vulnerable plaques in the coronary arteries, high-risk plaques in the carotid arteries are severely stenotic. Indeed, high-risk carotid plaques are not necessarily lipid-rich but rather heterogeneous, and they are very rich in fibrous tissue. These plaques often become symptomatic due to an intramural hematoma or dissection that likely develops secondary to the impact of blood during systole against a resistant area of stenosis.

Based on the postulate that early identification of atherosclerosis lesions could preclude ischemic events by applying aggressive primary prevention therapies, a reliable imaging modality able to identify high-risk or vulnerable plaques in vivo that might be at risk for rupture/erosion, would greatly help for both diagnosis and improvement of therapy. Since all luminographic techniques such as X-ray, multislice computed tomography (MSCT), and magnetic resonance angiography (MRA) are limited to the diagnosis of stenotic plaques, the most interesting imaging modality would combine imaging of the vessel wall itself, with a high spatial resolution, and the detection of a specific biological activity within the atherosclerotic plaques.

**Magnetic Resonance Imaging for Atherosclerosis Plaque Characterization**

High-resolution magnetic resonance imaging (MRI) has emerged as a very promising imaging modality not only to detect but to characterize atherosclerotic plaques. Due to advances in both hardware and software, MRI now offers an infra-millimetric resolution of the arterial wall allowing direct evaluation...
MRI does not expose patients to ionizing radiation and therefore seems well suited to monitor the extension of atherosclerotic disease and follow its evolution under anti-atherosclerotic treatments.

**Imaging Considerations**

There are several main factors to consider for non-invasive imaging of atherosclerosis. Due to the small size of the vessels and adjacent lumen, imaging of atherosclerosis requires the acquisition of high spatial and contrast resolutions. Adequate spatial resolution to visualize lesion components is therefore necessary and in good contrast between various components of lesions. Furthermore, techniques must be able to effectively remove potential signal interference from motion and flowing blood.

**Spatial Resolution**

Depending on the severity of atherosclerosis, a plaque can form a slight increase in wall thickness, to several millimeters in thickness. Critical tissue components to be identified include fibrous tissue (especially the presence and condition of the fibrous cap), calcifications, lipid rich necrotic core, and intraplaque hemorrhage. In addition, the condition of the plaque/lumen interface is important for the identification of any forms of disruption such as fibrous cap rupture and/or ulceration. Currently, screening large segments of the arterial system during a free-breathing, fast scan has become feasible. Using clinical magnets (1.5 Tesla), spatial resolutions in the order of 200–300 µm are possible with surface coils for non-moving, superficial structures, such as the carotid arteries. Sub-millimeter in-plane resolution can also be achieved for the aorta and coronary arteries (0.8mm and 0.5mm, respectively).

**Tissue Contrast**

The signal characteristics originating from a particular tissue partly depend on the amount of water and intrinsic magnetic properties within the tissue. These can be characterized by two parameters—the T1 (longitudinal relaxation time) and T2 (transverse relaxation time). In so-called T1-weighted (T1W) images, tissues with short T1 times will have high signal intensity and appear bright on the image. Conversely, in T2-weighted (T2W) images, tissues with short T2 times will have low signal intensity in comparison with those with high T2. In proton density-weighted (PDW) images, the amount of signal depends on the concentration of water (or fat) molecules. The use of ‘multi-contrast’ imaging (the combination of different weightings and sequences, usually three to four) improves the ability to characterize atherosclerotic plaques with MRI. The most commonly employed approaches include T1W, T2W, and PDW spin-echo sequences (see Figure 1).

Spin-echo (or black-blood) sequences are commonly employed because they render the moving blood invisible. Black-blood sequences improve the contrast between atherosclerotic plaques and the lumen, and therefore offer a better delineation of the contours of the plaque. Fast spin-echo sequences allow for clinical application of the technique within reasonable scanning times. Special radiofrequency (RF) pulses can similarly eliminate the signal from adipose tissue, which consists mainly of triglycerides. Conversely, the plaque lipid core is composed of phospholipids and unsterified/sterified cholesterol, and has different magnetic properties. Using black-blood techniques, clinical studies demonstrated that cardiovascular magnetic resonance (CMR) provides excellent quantitative capabilities for the measurement of total plaque volume with an error in vessel wall area measurement as low as 2.6% for the aorta, and 3.5% in the carotids. Similar low measurement errors in plaque area and volume (4% to 6%) were reported by others, proving that plaque area and volume can be accurately assessed with MRI. Frequently, bright-blood techniques such as 3-D time-of-flight are used to depict specific plaque characteristics. Additional sequences include diffusion weighting, magnetization transfer weighting or steady state free precession (SSFP).

Subsequent technical developments have enabled the simultaneous acquisition of multiple slices, resulting in a...
significant shortening of imaging times. Using a recently described sequence, imaging time can be sped up 17 times with adequate blood nulling, and it is feasible to acquire up to 20 sections in less than one minute.

In the future, 3.0 Tesla whole-body MR systems could further increase the spatial resolution and provide a higher signal-to-noise ratio, indirectly reducing acquisition time of these techniques.

**Contrast Agent Application**

Multicontrast MRI is needed to accurately identify the lipid core, fibrous cap, and other plaque components. T2-weighted images are used to provide the greatest contrast for distinguishing between the fibrous cap and the lipid core. However, T2-weighted images have inherently low signals, making plaque component delineation difficult. Wasserman et al. showed that the use of a gadolinium (Gd)-based contrast agent helped discriminate the fibrous cap from the lipid core with a contrast-to-noise ratio as good as or better than that with T2-weighted MR images, but with approximately twice the signal-to-noise ratio. Yuan et al. reported similar results. Although the contrast agent penetrated both the fibrous cap and the lipid core, both studies found that there was preferential uptake of the contrast agent into the fibrous tissue. The preferential uptake into the cap improved its conspicuity against the adjacent lipid core. Kerwin et al. showed a high correlation between the fractional blood volume of plaque determined by dynamic contrast-enhanced MRI and the fractional vessel area determined by micovessel density on the corresponding histologic section, reflecting the plaque neovascularity.

Gd-based contrast agents in atherosclerotic plaque imaging were first investigated in an animal model study by Lin et al. and first explored in humans by Aoki et al. Most studies have revolved around commercially available Gd chelates in conjunction with double inversion recovery (IR) gradient recalled echo sequences, to investigate enhancement patterns within the lesions. One problem with the double IR approach is that suppression of blood may be compromised as the contrast agent alters its T1. This difficulty has been overcome by a quadruple IR technique that leads to T1 insensitive flow suppression. Similar results are also provided by the use of a diffusion module that has the ability to strongly null blood flow signal after contrast injection.

However, complete characterization and assessment of atherosclerotic plaque activity by conventional Gd chelates is limited. Novel contrast agents, such as ultra-small superparamagnetic particles of iron oxide (USPIOs), have been successfully used to image inflammation within the atherosclerotic lesion. USPIOs accumulate in the macrophages present in atherosclerotic plaques and can be detected as a focal decrease of the MR signal on T2*-weighted sequences. Iron oxide contrast agents have superparamagnetic properties, i.e. they decrease T2* relaxation time by generating heterogeneities in the local magnetic field, and can be detected on MRI as signal voids, called susceptibility artifacts, with T2*-weighted sequences. Kooi et al. studied symptomatic patients scheduled for carotid endarterectomy with USPIO-enhanced MRI, and found a 24% decrease in signal intensity on corresponding T2*-weighted sequences, and uptake of USPIO on histology in 75% of ruptured or rupture-prone lesions. Several contrast agents have been found to accumulate in atherosclerotic plaques and are detected with MRI, either by a decrease (iron-oxide-based contrast agents) or by an increase (Gd-based...
Recent advances in biochemistry have led to the development of contrast agents that selectively enhance plaque constituents. This emerging area, known as 'molecular imaging', allows the targeting of molecules directly to the atherosclerotic lesion itself. These new contrast agents are mostly Gd-based, and consist either of nanoparticles, liposomes, or micelles that are linked to specific peptides or antibodies conjugated with molecules of Gd chelates. The recent advances in the knowledge of the pathophysiology of atherosclerotic disease have led to the identification of a number of targets that might play a critical role in plaque instability or vulnerability.\textsuperscript{17–20} Targets such as fibrin (see Figure 3), α\textsubscript{v}β\textsubscript{3} integrins, or vascular cell adhesion molecules (VCAM) are one example of recent applications of MR molecular imaging.\textsuperscript{17–20}

In the future, the development of MR contrast agents specific for atherosclerotic plaque components will allow in vivo imaging of biological activities present in human atherosclerotic plaques and will improve understanding of the pathophysiology of atherosclerotic plaque rupture and subsequent intra luminal thrombosis.

References
