Published in final edited form as:

Expert Rev Cardiovasc Ther. 2007 January ; 5(1): 69–80. doi:10.1586/14779072.5.1.69.

MRI of Atherosclerosis: Diagnosis and Monitoring Therapy

Justin D. Anderson, MD and Christopher M. Kramer, MD

Departments of Medicine and Radiology, University of Virginia Health System

Summary

Atherosclerosis is a prevalent disease affecting millions of Americans. Despite our advances in diagnosis and treatment, atherosclerosis is the leading cause of death in America. High resolution MRI has overcome the limitations of current angiographic techniques and has emerged as a leading noninvasive imaging modality of atherosclerotic disease. Atherosclerosis of the arterial wall of human carotid, aortic, peripheral, and coronary arteries have all been successfully evaluated. In addition, the power of MRI to differentiate the major components of atherosclerotic plaque has been validated. The ability to image the vessel wall and risk stratify atherosclerotic plaque will create management decisions not previously faced and has the potential to change the way atherosclerosis is treated.

Background

Atherosclerosis is a systemic disease that may silently affect the entire arterial tree. Frequently the initial clinical manifestation is stroke, myocardial infarction, or sudden death. According to the latest American Heart Association statistics over 71 million Americans suffer from cardiovascular disease (CVD), and atherosclerosis is the underlying etiology in the vast majority of cases [1]. Despite the advances in the diagnosis and treatment of atherosclerosis, the cause of death in 1 out of 2.7 American adults is attributed to CVD [1]. Over the past two decades our understanding of the pathological mechanism of atherosclerosis has rapidly advanced. Two important concepts "positive remodeling" and "vulnerable plaque," coupled with technological advances have catapulted magnetic resonance imaging (MRI) to the forefront of atherosclerosis imaging.

Traditionally, identifying atherosclerotic disease has relied heavily on techniques that evaluate the arterial lumen. However, a significant portion of the arterial wall can be involved with atherosclerotic plaque before the lumen is compromised. Glagov et al [2] observed that in the early stages of atherosclerosis, the response of the arterial wall to plaque formation is to expand outwardly, preserving the lumen and increasing only the external diameter, a phenomenon commonly referred to as outward or "positive" arterial remodeling (figure 1). In fact, luminal encroachment typically does not occur until 40% of the area circumscribed by the internal elastic lamina is occupied by plaque. Thus, a significant atherosclerotic burden could be underestimated or missed entirely with lumenographic techniques such as x-ray, MRI, or computed tomography (CT) angiography.

Furthering our understanding of the atherosclerotic disease process, histopathological studies have shown that the majority of myocardial infarctions and stroke are due to an atherosclerotic plaque that erodes or ruptures generating a thromboembolic event at the site or downstream of the disrupted plaque. Interestingly, the majority of coronary plaques that had ruptured and caused the acute clinical syndrome were only mildly to moderately

stenosed [3, 4, 5, 6]. Histological studies have focused on identifying and characterizing plaques that are prone to rupture. In the coronary arteries, mild to moderately stenotic plaque with a thick lipid-rich core and a thin fibrous cap with intraplaque inflammation is most prone to disruption and thrombosis, and thus result in an acute coronary syndrome. This is in contrast to the stable plaque which is typically severely stenotic (>70% stenosed) with a thick fibrous cap and little lipid content or inflammation that usually presents as stable angina [7, 8, 9, 10, 11] (figure 1). In the carotid vasculature, high risk or symptomatic plaques are those with a thin fibrous cap, intraplaque inflammation or hemorrhage, and a lipid-rich necrotic core. [12, 13, 5] (figure 2). The reader is referred to the consensus statement by Naghavi et al [14] for a detailed description of the components of vulnerable plaque.

Current Approaches to the Diagnosis of Atherosclerosis and Their Limitations

Currently the diagnosis of atherosclerosis relies heavily on lumenographic techniques such as x-ray angiography, magnetic resonance angiography (MRA), or CTA. X-ray angiography is limited by the invasive nature of the procedure and by the use of potentially harmful radiation and contrast dye. CTA has the benefit of being noninvasive; however, like x-ray angiography the patient is exposed to radiation and iodinated contrast agents. Recent studies have suggested that CTA can image the coronary artery wall and give a generalized description of plaque components, distinguishing calcified from noncalcified plaque. However, CTA is unable to provide further detailed differentiation of soft plaque such as the fibrous cap or lipid core. [15, 16]. MRA is noninvasive and does not expose the patient to radiation and uses a non-iodinated, well-tolerated contrast agent, gadolinium which is used in a chelated form. However, like all angiographic techniques, it is limited in its ability to image the vessel wall. The inability to adequately image the vessel wall limits the success of angiographic techniques to diagnosis early atherosclerotic disease and to estimate total plaque burden. In addition current lumenographic techniques are unable to differentiate plaque components and thus are unable to detect vulnerable plaque [17, 18].

The importance of this limitation is highlighted as clinical research has shown that the activity of coronary plaque is disproportional to the degree of coronary stenosis detected by angiography. Ambrose et al [19] compared angiograms of patients who had one before and after a myocardial infarction and found the median stenosis of the culprit lesion on the initial angiogram was 48%. Only 22% of the lesions that lead to an infarction were >70% stenosed. In a similar study, Little et al [20] found that two thirds of the culprit lesions on the initial angiogram were less than 50% stenosed at the time of the initial angiogram and only one of the 29 patients studied was the initial lesion greater than 70% stenosed.

Duplex ultrasonography is widely used in the diagnosis of atherosclerosis of the carotid and peripheral arteries. Ultrasound techniques do not solely rely on visualizing the lumen to determine the degree of stenosis. They also provide information on the changes in the velocity of blood flow through the vessel of interest [21]. Ultrasound has the advantage of being portable, noninvasive, and harmless to the patient. The major limitations are the lack of standardization, operator dependence, inability to image the vessel of interest due to patient body habitus or vessel course, and acoustic shadowing from calcifications. Ultrasound like CTA can provide a general assessment of plaque composition, calcified and soft plaque, but both are yet to provide the detailed characterization necessary to determine plaque vulnerability [22, 23, 24, 25].

The need to visual the vessel wall for early detection of atherosclerosis and to characterize plaque components has led to the development of several new diagnostic techniques. The

most utilized today is intravascular ultrasound (IVUS). IVUS has been shown to be able to accurately image the vessel wall and characterize tissue when compared to ex vivo specimens [26, 27, 28]. IVUS has been used to distinguish plaque characteristics in patients presenting with acute coronary syndromes [29, 30]. IVUS is limited due to the invasive nature and intrinsic and extrinsic artifacts that interfere with image interpretation. Other techniques such as optical coherence, plaque thermography, and angioscopy are not widely used as they are still under development, are not FDA-approved, and remain invasive [31].

MRI and Diagnosis of Atherosclerosis

The concepts of positive remodeling and vulnerable plaque have enhanced our understanding of atherosclerosis and further illuminated the limitations of lumenographic techniques. They also suggest that a diagnostic technique capable of visualizing the vessel wall and characterizing atherosclerotic plaque would be most accurate for the assessment of plaque burden and perhaps determining the patient at highest risk. High resolution MRI has thus emerged as a leading noninvasive imaging modality of atherosclerotic disease due to its ability to assess the lumen while also assessing plaque burden and differentiating plaque components in an accurate and noninvasive manner [13]. High resolution MRI has been used in the research setting to evaluate atherosclerotic plaque in human carotid [32, 33, 34], aortic [35, 36], peripheral [37], and coronary arteries [38, 39]. Several in vitro and in vivo studies have validated the ability of MRI to differentiate the major components of atherosclerotic plaque including fibrous cap, lipid core, calcium, and hemorrhage. In addition, MRI can accurately and reproducibly measure arterial wall dimensions [40, 41].

Carotid atherosclerosis

The carotid artery is an excellent target for MRI of atherosclerosis because of its large size, superficial location, and minimal motion. In addition, the available tissue pathology from carotid endarterectomy specimens provides a mean of validation. Toussaint et al [33] were among the first to demonstrate that MRI could accurately measure and differentiate carotid plaque in vivo. A substantial amount of subsequent work has further refined and validated the ability to detect and characterize carotid plaque morphology. Yuan and colleagues [42, 43, 34] have shown that in vivo high resolution MRI can identify the lipid rich necrotic core, plaque hemorrhage, and fibrous cap, as well as categorize carotid plaque lesion according to the AHA classification system, with a high degree of sensitivity and specificity when compared to histopathological specimens. Furthermore, they have validated against histopathology that high resolution MRI can correctly evaluate the thickness and integrity of the fibrous cap [44]. Subsequently, they have shown that the identification of a ruptured fibrous cap is correlated with a recent history of a transient ischemic attack or stroke [45]. Moody et al [46, 47] have used direct thrombus imaging to identify complicated plaques in patients with cerebral ischemia. These two latter results are important in that they suggest that a patient could be potentially risk stratified based on the recognition of high risk plaque morphology. However, it is necessary to bear in mind that high resolution MRI is currently a research tool and the clinical implications are still unknown.

Aortic atherosclerosis

Several investigators have demonstrated the ability to quantify and determine plaque composition in the aorta. Fayad et al [35] analyzed aortic plaque composition and size and showed a high correlation with transesophageal echocardiogram (TEE). Chan et al [48] demonstrated the excellent reproducibility of MRI techniques when measuring aortic luminal area as well as plaque area. Our group has demonstrated the ability of MRI to differentiate fibrous cap, lipid core, and thrombus components of plaque within abdominal aortic aneurysms in patients prior to surgery [36] (figure 3).

Peripheral artery atherosclerosis

Peripheral arterial disease, like aortic disease, is a marker for atherosclerosis in other vascular territories. Although the peripheral arteries are ideal for vessel wall imaging due to their superficial location, long length, straight course, and lack of motion, they have not been extensively investigated. Choulden et al [49] successfully used high resolution MRI to define the extent of atherosclerotic plaque and characterize the changes that occur with remodeling and restenosis following angioplasty of the popliteal artery. Our group has demonstrated the feasibility and reproducibility of MRI to assess plaque volume in the superficial femoral artery [37] (figure 4). Based on the reliability of the techniques used, sample sizes for clinical trials of atherosclerosis regression could be reduced using this approach [37]. These two studies highlight the tremendous potential MRI has to survey the effects of treatment whether it is invasive or medical on the progression or regression of atherosclerosis.

Coronary atherosclerosis

An ultimate goal of MRI is to accurately and rapidly image the coronary artery lumen and vessel wall, and thus provide a noninvasive alternative to x-ray or CT angiography while also providing more robust information on plaque burden and composition. However, the coronary arteries have proven difficult to image due to respiratory and cardiac motion, small size, deep course, and vessel tortuosity. Initial attempts aimed at imaging solely the coronary lumen with MRA have met with modest success. In a recent meta-analysis of the diagnostic performance of coronary MRA (CMRA) versus conventional x-ray angiography in patients with moderate to high probability of CAD, CMRA was able to detect about 75% of significant proximal stenoses in evaluable segments with a specificity of 86% [50]. Thus, at the present, CMRA has limited clinical use in diagnosing CAD due to the inability to evaluate distal coronary segments and the high rate of unevaluable segments as well as longer acquisition times. Furthermore, it has the same shortcomings as conventional lumenographic techniques discussed above.

More recently, investigators have attempted to image the coronary wall in humans. Fayad et al [39] and Botnar et al [38] used black blood imaging techniques to demonstrate that coronary wall thickness is increased in patients with coronary artery disease (CAD) (figure 5). Coronary vessel wall imaging has been shown to be accurate and has the ability to detect increased coronary wall thickness in patients with essentially normal lumens by x-ray angiography [51]. Using 3D free-breathing MRI and semi-automated analysis software, Desai et al [52] have measure the coronary vessel wall thickness with excellent reproducibility. Maintz and colleagues [53] recently demonstrated that contrast enhanced coronary plaque imaging is feasible and may aid in differentiating plaque composition. However, despite these encouraging studies, it is not yet possible to adequately determine plaque composition, mainly due to limited spatial resolution of current MRI techniques [54]. It should also be noted that due to size and tortuosity of much of the coronary artery tree, high resolution MRI has not been shown to reliably evaluate the distal coronary arteries or their branches.

MRI and Monitoring Therapy

The ideal imaging modality for monitoring treatment of atherosclerotic disease must be non-invasive, rapid, and reproducible. In addition, it should be able to image the vessel wall without radiation exposure or iodinated contrast. Traditionally, x-ray angiography was used in studies evaluating the effects of therapy on atherosclerosis. However, therapies such as lipid lowering agents have shown robust reduction in clinical endpoints but very minimal improvement in lumen expansion [55, 56, 57]. This phenomenon likely represents changes

in plaque composition and plaque stabilization, underscoring the need to visualize not only the lumen but also the vessel wall. Nevertheless, these studies provide the foundation for plaque regression as an acceptable surrogate endpoint for treatment effect [58]. In recent years, IVUS been used to evaluate plaque burden and vascular remodeling as a surrogate efficacy endpoint in randomized clinical trials [59, 60, 61]. Although IVUS is somewhat limited by acoustic shadowing from calcium and intrinsic artifacts, it is still effective at measuring plaque burden and discriminating plaque components. However, its invasive nature and its attendant risks make IVUS less appealing for the serial studies that are necessary for plaque regression trials.

On the other hand, enthusiasm for MRI as the imaging efficacy endpoint in therapeutic trials of plaque regression is on the rise due to its ability to image the vessel wall reliably, reproducibly, and without potential risk to the patient as long as the patient has no contraindication to MRI. Furthermore, because plaque volume measured by MRI is highly reproducible, the sample sizes needed to adequately power clinical studies could be dramatically reduced [37]. Excitement over using MRI for this purpose has already spawned several small clinical studies in which MRI has demonstrated significant carotid and aortic plaque regression after treatment with lipid lowering therapy.

Zhao et al [62] were among the first to show in a small cross-sectional case-controlled study that carotid artery plaque in patients with known CAD who had been successfully treated for hyperlipidemia for the previous 10 years, versus matched controls who had never been on lipid therapy, had significantly decreased lipid core area when measured by MRI. Corti et al [63, 64] used MRI to detect carotid and aortic plaque in 21 asymptomatic hypercholesterolemic patients. These patients were then placed on lipid lowering therapy (simvastatin) and followed with serial MRI every 6 months for 2 years. They found a significant reduction in total vessel area (TVA), a surrogate of atherosclerotic plaque burden, but not luminal area (LA), at one year in both the carotid and aortic plaques. Interestingly, at two years they found a further reduction in TVA and a small but significant increase in LA in both carotid and aortic lesions (figure 6). The same group compared results between 20mg versus 80mg of simvastatin. A significant reduction in TVA by MRI after 12 months of treatment with simvastatin was seen regardless of the dose [65]. Lima et al [66] used a slightly different technique which combined surface and transesophageal MRI to show a significant reduction in thoracic aortic plaque after only 6 months of treatment. Finally, a recent Japanese study of 40 hyperlipidemic patients used MRI to assess plaque regression in the thoracic and abdominal aorta after atorvastatin therapy for 12 months. They found a significant reduction in vessel wall area in the thoracic but not in the abdominal aorta [67]. These studies illustrate the power of MRI to serially monitor the effects of atherosclerotic therapy accurately and reproducibly without risk to the patient.

Limitations of MRI

Despite the excitement over the potential utilization of MRI for clinical trials, it has several limitations to overcome before it is ready for routine clinical use in atherosclerotic plaque imaging. In order to achieve the high spatial resolution that is essential for the differentiation of plaque components, a high signal to noise ratio is required; this necessitates longer imaging times. While not prohibitively long, scan times are longer relative to other modalities. To analyze the vessel wall, cross sectional images ranging from several hundred microns to a few millimeters are used. Each section may take anywhere from 20 seconds to several minutes depending on the MRI sequence used and the vessel being imaged. This can be burdensome when broader coverage is needed or when multiple sequences are needed as is necessary for plaque differentiation. Also, high resolution MRI for plaque morphology assessment is typically limited to a single plaque or vascular segment, making plaque

morphology assessment problematic over large segments of arterial systems. Unique to MRI in general is that patients who have claustrophobia, pacemakers, defibrillators, and certain aneurysm clips are unable to enter the MRI environment. Cardiac imaging quality can be severely limited by arrhythmias. Carotid imaging can be limited by motion due to patient swallowing. Finally and perhaps most importantly, the clinical applicability and implications of diagnosing atherosclerosis early before it compromises the lumen, as well as determining plaque burden, and characterizing plaque composition, are yet to be determined.

Five Year View

Currently a significant amount of research time and dollars are being spent on development of atherosclerotic plaque imaging with MRI. Over the next five years, due to advances in technology and contrast agents, the current drawbacks of MRI will likely be overcome or at least become less relevant. In order to overcome the longer scan times and the inability to cover multiple vascular territories, newer sequences are being developed to allow broader coverage in less time. Higher field strength magnets such as 3.0 T and 7.0T along with advances in receiver coils will likely improve the signal to noise ratio and thus improve the spatial resolution that is necessary to readily differentiate plaque composition in the coronary artery [68, 69]. The development of new contrast agents will improve contrast to noise ratio and thus allow for improved plaque differentiation[54]. Further experience with newer noniodinated contrast agents such as ultra small superparamagnetic particles of iron oxide (USPIO) and vascular cell adhesion molecules [70] will enable visualization of inflamed plaques which are considered vulnerable or at high risk of rupture. Already, USPIO's which are ingested by macrophages, have been used to identify macrophage activity, hence inflammation, in atherosclerotic plaque in in vivo animal models [71] as well as humans [72, 73, 74]. In addition, there has been excitement over the development of contrast agents that specifically target plaque components such as the lipid core, or intraplaque thrombus [75, 76, 77]. Finally, newer targeted contrast agents aimed at specific cell surface receptors or proteins will be developed which undoubtedly allow for earlier more sensitive detection of atherosclerotic plaque while also enhancing plaque imaging.

Further advances in technology not directly related to the acquisition of MRI images will also broaden the use of MRI. The limitation of pacemakers, defibrillators and other implantable metallic devices entering the MRI will likely be overcome in the near future as manufacturers are currently researching MRI compatible products. With our current standard technology, Nazarian et al [78] and Sommer et al [79] have demonstrated that MRI can be safely performed under controlled conditions in selected patients who have an implantable defibrillator or pacemaker. However, at present the pacemaker and ICD's are still considered a relative contraindication to MRI.

As high resolution MRI becomes ready for routine clinical practice, image analysis and post processing software will be necessary to increase throughput of a large volume of patients. A number of semiautomated image processing tools have been proposed to quantify plaque volume. On the other hand, automated identification of plaque composition remains problematic with many obstacles to overcome. However, there is still optimism that computer based platforms for the analysis of atherosclerosis will be a reality [80].

In addition to the advances in technology and contrast agents that will widen the use of MRI in atherosclerotic disease, the clinical importance and application of detecting atherosclerosis earlier than ever before and identifying vulnerable atherosclerotic plaque will likely be unveiled. As mentioned previously, MRI is well suited for therapeutic efficacy trials. Undoubtedly, MRI will continue to be utilized to study the effects of current and novel drugs used in the treatment of atherosclerosis. In the near future, population based

studies will likely be undertaken in attempts to determine the significance of the MRI features of atherosclerotic plaque for assessing risk of future cardiovascular event. Takaya et al [81] have recently shown that patients with asymptomatic moderate carotid stenosis and high risk plaque characteristics had an increased risk of having a subsequent cerebral vascular event. These studies will be essential for helping the patient and physician understand the clinical implications of this unprecedented data.

Intravascular MRI (IVMR) and transesophageal MRI may have a future role in imaging human atherosclerosis. These two techniques, while being invasive, overcome some of the limitations of conventional MRI such as signal to noise ratio and lower spatial resolution by placing the imaging coil in close proximity to the vessel wall. However, catheter motion in vivo can lead to artifacts. Plaque imaging has been achieved using animal models with excellent spatial resolution in a variety of vascular territories and has been validated against histopathology [82]. Schneiderman et al [83] showed proof of concept in ex vivo human aortas and ex vivo hearts with in situ coronary arteries. They found a strong correlation between the IVMRI characterization of plaque components with histology. Rogers et al [84] successfully used IVMRI on ex vivo human carotid endarterectomy specimens to identify histologically verified plaque components. Larose et al [85] validated IVMRI against histopathological specimens ex vivo for the quantification and differentiation of iliac plaque. They then applied the same approach to evaluate human iliac arteries in vivo, and the results were compared to IVUS. They were able to reliably differentiate plaque composition with a high degree of interobserver and intraobserver agreement, which was not the case with IVUS. In regards to in vivo coronary artery imaging, early results of clinical studies indicate that the evaluation of coronary artery lipid content by IVMRI is feasible and safe [86]. Finally, Hillenbrand et al [87] have demonstrated in a porcine model improvement in imaging efficiency for IVMRI using fast high resolution sequences that have traditionally been reserved for noninvasive MRI. This has the potential to replace the more cumbersome conventional IVMRI sequences and streamline further investigations.

Expert Opinion

Insights into the pathogenesis of atherosclerosis and technological improvements have moved high resolution MRI to the forefront of atherosclerotic imaging. It can now be considered the new gold standard for vessel wall imaging and plaque characterization in the carotid and peripheral arteries as well as the aorta. While the current spatial resolution hinders the ability of MRI to evaluate the vessel wall of coronary arteries, newer technology is already beginning to overcome this limitation. IVMRI may play an important role in plaque imaging of the coronary arteries. Clinically, MRI has created the unique opportunity to noninvasively monitor plaque modification over time. This provides an unprecedented platform for efficacy trials of current and novel drugs used in atherosclerosis as well as interventional therapy. The ability to image the vessel wall and thus characterize plaque lesions that would have previously been unrecognized or underappreciated by current techniques has the potential to fundamentally change the way atherosclerosis is managed. By diagnosing atherosclerosis earlier and by identifying high risk vulnerable plaque, MRI of atherosclerosis will likely provide better risk stratification than current angiographic techniques and potentially risk stratify patients beyond traditional clinical markers. Ultimately, high resolution MRI might be the key to identifying the vulnerable patient in whom focal or systemic intervention could be started to prevent cardiovascular events.

Summary

Atherosclerosis is a prevalent disease affecting millions of Americans. Despite our advances in diagnosis and treatment, atherosclerosis is the leading cause of death in America. High

resolution MRI has overcome the limitations of current angiographic techniques and has emerged as the leading noninvasive imaging modality of atherosclerotic disease due to its ability to assess plaque burden and differentiate plaque components in an accurate manner. The arterial wall of human carotid, aortic, peripheral, and coronary arteries have all been successfully evaluated. The ability of MRI to differentiate the major components of atherosclerotic plaque has been validated in the carotid artery as well as the aorta. While current limits on spatial resolution hinder the ability of MRI to evaluate the coronary vessel wall and plaque, newer technologies, such as high strength magnets and contrast agents, are already overcoming this limitation. Novel contrast and molecular agents that target high risk features within atherosclerotic plaque, like inflammation and thrombus, are being developed. IVMRI may play an important role in plaque imaging of the coronary arteries due to its superior spatial resolution. MRI is the ideal imaging modality for monitoring treatment of atherosclerotic disease over time. In addition, the ability to image the vessel wall and risk stratify plaque lesions will create management decisions not previously faced and has the potential to change the way atherosclerosis is managed. MRI of atherosclerosis is progressing towards its ultimate goal, the identification of the vulnerable patient in whom medical or interventional treatment could be initiated to prevent cardiovascular events.

Reference List

1. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006; 113:e85–151. [PubMed: 16407573]
2. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N. Engl. J. Med.* 1987; 316:1371–1375. [PubMed: 3574413]
3. Bassiouny HS, Sakaguchi Y, Mikucki SA, et al. Juxtalumenal location of plaque necrosis and neoformation in symptomatic carotid stenosis. *J Vasc. Surg.* 1997; 26:585–594. [PubMed: 9357458]
4. Davies MJ. Anatomic features in victims of sudden coronary death. *Coronary artery pathology. Circulation*. 1992; 85:I19–I24. [PubMed: 1728500]
5. Hatsukami TS, Ferguson MS, Beach KW, et al. Carotid plaque morphology and clinical events. *Stroke*. 1997; 28:95–100. [PubMed: 8996496]
6. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler. Thromb. Vasc. Biol.* 2000; 20:1262–1275. [PubMed: 10807742]
7. Casscells W, Naghavi M, Willerson JT. Vulnerable atherosclerotic plaque: a multifocal disease. *Circulation*. 2003; 107:2072–2075. [PubMed: 12719287]
8. Libby P. Inflammation in atherosclerosis. *Nature*. 2002; 420:868–874. [PubMed: 12490960]
9. Shah PK. Pathophysiology of coronary thrombosis: role of plaque rupture and plaque erosion. *Prog. Cardiovasc Dis.* 2002; 44:357–368. [PubMed: 12024334]
10. Shah PK. Mechanisms of plaque vulnerability and rupture. *J. Am. Coll. Cardiol.* 2003; 41:15S–22S. [PubMed: 12644336]
11. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation*. 1995; 92:1355–1374. [PubMed: 7648691]
12. Carr S, Farb A, Pearce WH, Virmani R, Yao JS. Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. *J Vasc. Surg.* 1996; 23:755–765. [PubMed: 8667496]
13. Corti R, Fuster V, Badimon JJ, Hutter R, Fayad ZA. New understanding of atherosclerosis (clinically and experimentally) with evolving MRI technology in vivo. *Ann. N.Y. Acad. Sci.* 2001; 947:181–195. [PubMed: 11795266]

14. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation*. 2003; 108:1664–1672. [PubMed: 14530185]
15. Becker CR, Nikolaou K, Muders M, et al. Ex vivo coronary atherosclerotic plaque characterization with multi-detector-row CT. *Eur. Radiol*. 2003; 13:2094–2098. [PubMed: 12692681]
16. Hausleiter J, Meyer T, Hadamitzky M, et al. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. *J. Am. Coll. Cardiol*. 2006; 48:312–318. [PubMed: 16843181]
17. Pasterkamp G, Falk E, Woutman H, Borst C. Techniques characterizing the coronary atherosclerotic plaque: influence on clinical decision making? *J. Am. Coll. Cardiol*. 2000; 36:13–21. [PubMed: 10898406]
18. Yuan C, Kerwin WS. MRI of atherosclerosis. *J Magn Reson Imaging*. 2004; 19:710–719. [PubMed: 15170778]
19. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J. Am. Coll. Cardiol*. 1988; 12:56–62. [PubMed: 3379219]
20. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation*. 1988; 78:1157–1166. [PubMed: 3180375]
21. Rose SC, Nelson TR. Ultrasonographic modalities to assess vascular anatomy and disease. *J Vasc. Interv. Radiol*. 2004; 15:25–38. [PubMed: 14709684]
22. Fosse E, Johnsen SH, Stensland-Bugge E, et al. Repeated visual and computer-assisted carotid plaque characterization in a longitudinal population-based ultrasound study: the Tromso study. *Ultrasound Med Biol*. 2006; 32:3–11. [PubMed: 16364791]
23. Gronholdt ML, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. *Circulation*. 2001; 104:68–73. [PubMed: 11435340]
24. Schminke U, Hilker L, Motsch L, Griewing B, Kessler C. Volumetric assessment of plaque progression with 3-dimensional ultrasonography under statin therapy. *J Neuroimaging*. 2002; 12:245–251. [PubMed: 12116743]
25. Spagnoli LG, Mauriello A, Sangiorgi G, et al. Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke. *JAMA*. 2004; 292:1845–1852. [PubMed: 15494582]
26. Komiyama N, Berry GJ, Kolz ML, et al. Tissue characterization of atherosclerotic plaques by intravascular ultrasound radiofrequency signal analysis: an in vitro study of human coronary arteries. *Am. Heart. J*. 2000; 140:565–574. [PubMed: 11011329]
27. Nair A, Kuban BD, Tuzcu EM, et al. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation*. 2002; 106:2200–2206. [PubMed: 12390948]
28. Nissen SE, Yock P. Intravascular ultrasound: novel pathophysiological insights and current clinical applications. *Circulation*. 2001; 103:604–616. [PubMed: 11157729]
29. Rodriguez-Granillo GA, Garcia-Garcia HM, Mc Fadden EP, et al. In vivo intravascular ultrasound-derived thin-cap fibroatheroma detection using ultrasound radiofrequency data analysis. *J. Am. Coll. Cardiol*. 2005; 46:2038–2042. [PubMed: 16325038]
30. Rodriguez-Granillo GA, Garcia-Garcia HM, Valgimigli M, et al. Global characterization of coronary plaque rupture phenotype using three-vessel intravascular ultrasound radiofrequency data analysis. *Eur. Heart J*. 2006; 27:1921–1927. [PubMed: 16840496]
31. MacNeill BD, Lowe HC, Takano M, Fuster V, Jang IK. Intravascular modalities for detection of vulnerable plaque: current status. *Arterioscler. Thromb. Vasc. Biol*. 2003; 23:1333–1342. [PubMed: 12805071]
32. Toussaint JF, Southern JF, Fuster V, Kantor HL. T2-weighted contrast for NMR characterization of human atherosclerosis. *Arterioscler. Thromb. Vasc. Biol*. 1995; 15:1533–1542. [PubMed: 7583524]
33. Toussaint JF, LaMuraglia GM, Southern JF, Fuster V, Kantor HL. Magnetic resonance images lipid, fibrous, calcified, hemorrhagic, and thrombotic components of human atherosclerosis in vivo. *Circulation*. 1996; 94:932–938. [PubMed: 8790028]

34. Yuan C, Mitsumori LM, Ferguson MS, et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. *Circulation*. 2001; 104:2051–2056. [PubMed: 11673345]
35. Fayad ZA, Nahar T, Fallon JT, et al. In vivo magnetic resonance evaluation of atherosclerotic plaques in the human thoracic aorta: a comparison with transesophageal echocardiography. *Circulation*. 2000; 101:2503–2509. [PubMed: 10831525]
36. Kramer CM, Cerilli LA, Hagspiel K, et al. Magnetic resonance imaging identifies the fibrous cap in atherosclerotic abdominal aortic aneurysm. *Circulation*. 2004; 109:1016–1021. [PubMed: 14967731]
37. Isbell DC, Meyer CH, Rogers WJ, et al. Reproducibility and reliability of atherosclerotic plaque volume measurements in peripheral arterial disease with magnetic resonance imaging. *J Cardiovasc Magn Reson*. 2007
38. Botnar RM, Stuber M, Kissinger KV, et al. Noninvasive coronary vessel wall and plaque imaging with magnetic resonance imaging. *Circulation*. 2000; 102:2582–2587. [PubMed: 11085960]
39. Fayad ZA, Fuster V, Fallon JT, et al. Noninvasive in vivo human coronary artery lumen and wall imaging using black-blood magnetic resonance imaging. *Circulation*. 2000; 102:506–510. [PubMed: 10920061]
40. Kang X, Polissar NL, Han C, Lin E, Yuan C. Analysis of the measurement precision of arterial lumen and wall areas using high-resolution MRI. *Magn Reson Med*. 2000; 44:968–972. [PubMed: 11108636]
41. Yuan C, Beach KW, Smith LH Jr, Hatsukami TS. Measurement of atherosclerotic carotid plaque size in vivo using high resolution magnetic resonance imaging. *Circulation*. 1998; 98:2666–2671. [PubMed: 9851951]
42. Cai J, Hatsukami TS, Ferguson MS, et al. In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. *Circulation*. 2005; 112:3437–3444. [PubMed: 16301346]
43. Mitsumori LM, Hatsukami TS, Ferguson MS, et al. In vivo accuracy of multisequence MR imaging for identifying unstable fibrous caps in advanced human carotid plaques. *J Magn Reson Imaging*. 2003; 17:410–420. [PubMed: 12655579]
44. Hatsukami TS, Ross R, Polissar NL, Yuan C. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. *Circulation*. 2000; 102:959–964. [PubMed: 10961958]
45. Yuan C, Zhang SX, Polissar NL, et al. Identification of fibrous cap rupture with magnetic resonance imaging is highly associated with recent transient ischemic attack or stroke. *Circulation*. 2002; 105:181–185. [PubMed: 11790698]
46. Moody AR, Murphy RE, Morgan PS, et al. Characterization of complicated carotid plaque with magnetic resonance direct thrombus imaging in patients with cerebral ischemia. *Circulation*. 2003; 107:3047–3052. [PubMed: 12796133]
47. Murphy RE, Moody AR, Morgan PS, et al. Prevalence of complicated carotid atheroma as detected by magnetic resonance direct thrombus imaging in patients with suspected carotid artery stenosis and previous acute cerebral ischemia. *Circulation*. 2003; 107:3053–3058. [PubMed: 12796136]
48. Chan SK, Jaffer FA, Botnar RM, et al. Scan reproducibility of magnetic resonance imaging assessment of aortic atherosclerosis burden. *J Cardiovasc Magn Reson*. 2001; 3:331–338. [PubMed: 11777225]
49. Coulden RA, Moss H, Graves MJ, et al. High resolution magnetic resonance imaging of atherosclerosis and the response to balloon angioplasty. *Heart*. 2000; 83:188–191. [PubMed: 10648495]
50. Dianas PG, Roussakis A, Ioannidis JP. Diagnostic performance of coronary magnetic resonance angiography as compared against conventional X-ray angiography: a meta-analysis. *J. Am. Coll. Cardiol*. 2004; 44:1867–1876. [PubMed: 15519021]
51. Kim WY, Stuber M, Bornert P, et al. Three-dimensional black-blood cardiac magnetic resonance coronary vessel wall imaging detects positive arterial remodeling in patients with nonsignificant coronary artery disease. *Circulation*. 2002; 106:296–299. [PubMed: 12119242]

52. Desai MY, Lai S, Barmet C, Weiss RG, Stuber M. Reproducibility of 3D free-breathing magnetic resonance coronary vessel wall imaging. *Eur. Heart J.* 2005; 26:2320–2324. [PubMed: 15972291]
53. Maintz D, Ozgun M, Hoffmeier A, et al. Selective coronary artery plaque visualization and differentiation by contrast-enhanced inversion prepared MRI. *Eur. Heart J.* 2006; 27:1732–1736. [PubMed: 16787955]
54. Leiner T, Gerretsen S, Botnar R, et al. Magnetic resonance imaging of atherosclerosis. *Eur. Radiol.* 2005; 15:1087–1099. [PubMed: 15723215]
55. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N. Engl. J. Med.* 2001; 345:1583–1592. [PubMed: 11757504]
56. Cashin-Hemphill L, Mack WJ, Pogoda JM, et al. Beneficial effects of colestipol-niacin on coronary atherosclerosis. A 4-year follow-up. *JAMA.* 1990; 264:3013–3017. [PubMed: 2243429]
57. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA.* 1998; 280:2001–2007. [PubMed: 9863851]
58. Taylor A, Shaw LJ, Fayad Z, et al. Tracking atherosclerosis regression: a clinical tool in preventive cardiology. *Atherosclerosis.* 2005; 180:1–10. [PubMed: 15823269]
59. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA.* 2004; 292:2217–2225. [PubMed: 15536108]
60. Nissen SE. Effect of intensive lipid lowering on progression of coronary atherosclerosis: evidence for an early benefit from the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial. *Am. J. Cardiol.* 2005; 96:61F–68F. [PubMed: 15979434]
61. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA.* 2006; 295:1556–1565. [PubMed: 16533939]
62. Zhao XQ, Yuan C, Hatsukami TS, et al. Effects of prolonged intensive lipid-lowering therapy on the characteristics of carotid atherosclerotic plaques in vivo by MRI: a case-control study. *Arterioscler. Thromb. Vasc. Biol.* 2001; 21:1623–1629. [PubMed: 11597936]
63. Corti R, Fayad ZA, Fuster V, et al. Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging. *Circulation.* 2001; 104:249–252. [PubMed: 11457739]
64. Corti R, Fuster V, Fayad ZA, et al. Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years' follow-up by high-resolution noninvasive magnetic resonance imaging. *Circulation.* 2002; 106:2884–2887. [PubMed: 12460866]
65. Corti R, Fuster V, Fayad ZA, et al. Effects of aggressive versus conventional lipid-lowering therapy by simvastatin on human atherosclerotic lesions: a prospective, randomized, double-blind trial with high-resolution magnetic resonance imaging. *J. Am. Coll. Cardiol.* 2005; 46:106–112. [PubMed: 15992643]
66. Lima JA, Desai MY, Steen H, et al. Statin-induced cholesterol lowering and plaque regression after 6 months of magnetic resonance imaging-monitored therapy. *Circulation.* 2004; 110:2336–2341. [PubMed: 15477398]
67. Yonemura A, Momiyama Y, Fayad ZA, et al. Effect of lipid-lowering therapy with atorvastatin on atherosclerotic aortic plaques detected by noninvasive magnetic resonance imaging. *J. Am. Coll. Cardiol.* 2005; 45:733–742. [PubMed: 15734619]
68. Berg A, Sailer J, Rand T, Moser E. Diffusivity- and T2 imaging at 3 Tesla for the detection of degenerative changes in human-excised tissue with high resolution: atherosclerotic arteries. *Invest Radiol.* 2003; 38:452–459. [PubMed: 12821860]
69. Botnar RM, Stuber M, Lamerichs R, et al. Initial experiences with in vivo right coronary artery human MR vessel wall imaging at 3 tesla. *J Cardiovasc Magn Reson.* 2003; 5:589–594. [PubMed: 14664136]
70. Nahrendorf M, Jaffer FA, Kelly KA, et al. Noninvasive vascular cell adhesion molecule-1 imaging identifies inflammatory activation of cells in atherosclerosis. *Circulation.* 2006; 114:1504–1511. [PubMed: 17000904]

71. Ruehm SG, Corot C, Vogt P, Kolb S, Debatin JF. Magnetic resonance imaging of atherosclerotic plaque with ultrasmall superparamagnetic particles of iron oxide in hyperlipidemic rabbits. *Circulation*. 2001; 103:415–422. [PubMed: 11157694]
72. Kooi ME, Cappendijk VC, Cleutjens KB, et al. Accumulation of ultrasmall superparamagnetic particles of iron oxide in human atherosclerotic plaques can be detected by in vivo magnetic resonance imaging. *Circulation*. 2003; 107:2453–2458. [PubMed: 12719280]
73. Tang T, Howarth SP, Miller SR, et al. Assessment of inflammatory burden contralateral to the symptomatic carotid stenosis using high-resolution ultrasmall, superparamagnetic iron oxide-enhanced MRI. *Stroke*. 2006; 37:2266–2270. [PubMed: 16917091]
74. Trivedi RA, Mallawarachi C, King-Im JM, et al. Identifying inflamed carotid plaques using in vivo USPIO-enhanced MR imaging to label plaque macrophages. *Arterioscler. Thromb. Vasc. Biol*. 2006; 26:1601–1606. [PubMed: 16627809]
75. Botnar RM, Perez AS, Witte S, et al. In vivo molecular imaging of acute and subacute thrombosis using a fibrin-binding magnetic resonance imaging contrast agent. *Circulation*. 2004; 109:2023–2029. [PubMed: 15066940]
76. Botnar RM, Buecker A, Wiethoff AJ, et al. In vivo magnetic resonance imaging of coronary thrombosis using a fibrin-binding molecular magnetic resonance contrast agent. *Circulation*. 2004; 110:1463–1466. [PubMed: 15238457]
77. Sirol M, Itskovich VV, Mani V, et al. Lipid-rich atherosclerotic plaques detected by gadofluorine-enhanced in vivo magnetic resonance imaging. *Circulation*. 2004; 109:2890–2896. [PubMed: 15184290]
78. Nazarian S, Roguin A, Zviman MM, et al. Clinical utility and safety of a protocol for noncardiac and cardiac magnetic resonance imaging of patients with permanent pacemakers and implantable-cardioverter defibrillators at 1.5 tesla. *Circulation*. 2006; 114:1277–1284. [PubMed: 16966586]
79. Sommer T, Naehle CP, Yang A, et al. Strategy for safe performance of extrathoracic magnetic resonance imaging at 1.5 tesla in the presence of cardiac pacemakers in non-pacemaker-dependent patients: a prospective study with 115 examinations. *Circulation*. 2006; 114:1285–1292. [PubMed: 16966587]
80. Liu F, Xu D, Ferguson MS, et al. Automated in vivo segmentation of carotid plaque MRI with Morphology-Enhanced probability maps. *Magn Reson Med*. 2006; 55:659–668. [PubMed: 16470594]
81. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI--initial results. *Stroke*. 2006; 37:818–823. [PubMed: 16469957]
82. Choi CJ, Kramer CM. MR imaging of atherosclerotic plaque. *Radiol. Clin. North. Am*. 2002; 40:887–898. [PubMed: 12171190]
83. Schneiderman J, Wilensky RL, Weiss A, et al. Diagnosis of thin-cap fibroatheromas by a self-contained intravascular magnetic resonance imaging probe in ex vivo human aortas and in situ coronary arteries. *J. Am. Coll. Cardiol*. 2005; 45:1961–1969. [PubMed: 15963393]
84. Rogers WJ, Prichard JW, Hu YL, et al. Characterization of signal properties in atherosclerotic plaque components by intravascular MRI. *Arterioscler. Thromb. Vasc. Biol*. 2000; 20:1824–1830. [PubMed: 10894824]
85. Larose E, Yeghiazarians Y, Libby P, et al. Characterization of human atherosclerotic plaques by intravascular magnetic resonance imaging. *Circulation*. 2005; 112:2324–2331. [PubMed: 16203910]
86. Wilensky RL, Song HK, Ferrari VA. Role of magnetic resonance and intravascular magnetic resonance in the detection of vulnerable plaques. *J. Am. Coll. Cardiol*. 2006; 47:C48–C56. [PubMed: 16631510]
87. Hillenbrand CM, Jesberger JA, Wong EY, et al. Toward rapid high resolution in vivo intravascular MRI: evaluation of vessel wall conspicuity in a porcine model using multiple imaging protocols. *J Magn Reson Imaging*. 2006; 23:135–144. [PubMed: 16416441]

Key Issues

- High resolution MRI has emerged as a leading noninvasive imaging modality of atherosclerosis
- Quantification of plaque volume within the vessel wall of human aortic, carotid, and peripheral arteries is accurate and reproducible with MRI
- Differentiation of atherosclerotic plaque morphology by MRI has been validated
- The current spatial resolution of MRI has limited the evaluation of coronary plaque and vessel wall
- MRI is the ideal imaging modality for monitoring atherosclerotic therapy
- The clinical importance and application of diagnosing atherosclerosis with high resolution MRI is yet to be determined.

Figure 1.

Progression of atherosclerotic plaque depicted in the cross section of a coronary artery. In the initial phase of atherosclerotic development there is no compromise in the arterial lumen as the plaque expands the vessel wall outward (positive remodeling). As the plaque progresses the lumen is encroached upon. If a large lipid core develops in conjunction with a thin fibrous cap, the plaque is considered at increased risk to rupture (vulnerable plaque). On the other hand, if the lipid core remains small and a thick fibrous cap develops, the plaque is thought to be at low risk to rupture (stable plaque). If a vulnerable plaque ruptures a subsequent thrombus forms potentially causing an acute coronary syndrome. Not all plaque ruptures are clinically evident. Many heal which results in further luminal compromise.

(Adapted from Libby P. *Nature* 2002; 420, 868–874.)

Figure 2. Transverse MR images of a high risk plaque in the left common carotid artery. A surface irregularity and a hyperintense juxtaluminal signal (black arrow) visible on the time-of-flight (TOF) angiogram (carotid lumen appears bright) indicate a fibrous cap rupture or ulcer. On T1-weighted (*T1W*) the rupture or ulcer appears as a filling defect on the luminal border (white arrow). A hyperintense area (chevron) visible on TOF, T1W, intermediate-weighted (*IMW*) and T2-weighted (*T2W*) images indicates a necrotic core with hemorrhage. (Adapted from Saam T. *Radiology* 2006;240, 464–472.)

Figure 3. Top left, The plaque components within an abdominal aortic aneurysm are established by T2-weighted MRI. Top right, T1-weighted MRI after Gd-DTPA infusion with very high signal intensity seen in luminal layer, signifying fibrous cap. Bottom left, Histopathology showing fibrous cap, thrombus, and lipid corresponding to components visualized by MRI. Bottom right, High power magnification of fibrous cap demonstrating dense infiltration of polymorphonuclear leukocytes. (Adapted from Kramer CM. *Circulation* 2004;109, 1016–21.)

Figure 4. Sequential axial, black blood images of the superficial femoral artery. Note the thickened arterial wall. Also note the heterogeneous signal within the vessel wall, suggesting complex plaque morphology.

Figure 5.

X-ray angiography in 2 patients with (A) a focal 40% stenosis (white arrow) and (C) minor ($\approx 10\%$ stenoses) luminal irregularities (white arrows) of the proximal RCA. The corresponding black-blood 3D CMR vessel wall scans (B, D) demonstrate an irregularly thickened RCA wall (>2 mm) indicative of an increased atherosclerotic plaque burden. The inner and outer RCA walls are indicated by the white dotted arrows. (Adapted from Kim WY. *Circulation* 2002;106, 296–299.)

Figure 6. Changes in atherosclerotic vessel wall dimensions after statin treatment. Data on VWA (top) and LA (bottom) at baseline, 6, 12, 18, and 24 months on simvastatin for aorta (left) and carotid arteries (right). Data are given as mean $\pm$ SEM. (Adapted from Corti R. *Circulation* 2002; 106, 2884–2887.)