Atherothrombosis and High-Risk Plaque
Part II: Approaches by Noninvasive Computed Tomographic/Magnetic Resonance Imaging

Valentin Fuster, MD, PhD, FACC,* Zahi A. Fayad, PhD, FACC,* Pedro R. Moreno, MD, FACC,* Michael Poon, MD, FACC,† Roberto Corti, MD, FACC,‡ Juan J. Badimon, PhD, FACC* New York, New York; and Zurich, Switzerland

This second part of the review on atherothrombosis highlights the diffuse nature of the disease analyzing the feasibility and potential of the noninvasive imaging modalities, including computed tomography (electron-beam computed and multi-detector computed tomography) and magnetic resonance imaging for its detection and monitoring. These imaging modalities are being established as promising tools in high-risk cardiovascular patients for identification and/or management of coronary calcification, stenotic or obstructive disease, high-risk plaques (not necessarily stenotic), and overall burden of the disease. In addition, such technology facilitates the understanding of the processes involved in the development and progression of atherothrombosis responsible for coronary, cerebral, and peripheral ischemic events. (J Am Coll Cardiol 2005;46:1209–18) © 2005 by the American College of Cardiology Foundation

ATHEROTHROMBOSIS AS A SYSTEMIC DISEASE: CLINICAL IMPACT
Atherothrombotic cardiovascular disease is a diffuse condition involving the coronary arteries, carotid arteries, aorta and peripheral arteries. However, the pathobiology of the disease and clinical consequences vary in the four regions. In patients with atherothrombotic disease, myocardial ischemia or infarction causes as much as 70% of deaths (1,2). Cerebrovascular disease causes approximately 10% to 17% of deaths in these patients, and another 10% are caused by ruptured aneurysms or visceral infarctions. Peripheral arterial disease may be viewed as benign because it does not cause direct mortality. However, it is an ominous manifestation of underlying disseminated atherosclerosis and, therefore, of mortality related to coronary disease and cerebrovascular disease (1). Thus, symptomatic individuals (i.e., those presenting with claudication) have a history of myocardial infarction or stroke in 20% to 30% of cases and evidence of underlying coronary disease in 50% to 70% of cases (1–5); an abnormal ankle-brachial index (≤0.9) without symptoms is 90% sensitive and 95% specific for peripheral artery disease and may also indicate underlying disseminated atherosclerosis (4,5). Most importantly, on long-term follow-up, patients with peripheral arterial disease, symptomatic or not, have a two- to three-fold increase in their rate of mortality related to myocardial infarction and stroke compared with age-matched control subjects (6,7). In atherothrombotic disease, the rate of mortality proportionally increases with the number of regions involved and degree of distribution of the disease (4,8,9).

The concept of multi-territory atherothrombosis has been recently addressed by the Trans-Atlantic Inter-Society Consensus (TASC) (10,11) by pooling the data from available studies of 1,886 patients older than 62 years of age with symptomatic atherothrombotic disease and by the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial of ~20,000 patients (12). In these two large populations, the data showed that 3% to 8% had symptomatic atherosclerotic disease in all three main arterial territories and 23% to 32% in two (Fig. 1).

NONINVASIVE CT/MR IMAGING OF “HIGH-RISK PLAQUES” AND DISEASE “BURDEN”
Because the composition of “high-risk plaques” varies depending on the arterial region and because striking heterogeneity exists in the composition of human atherothrombotic plaques even within the same individual, reliable noninvasive imaging modalities are needed that can detect atherothrombotic disease in various stages and regions, characterize the composition of the plaques, measure the extent of plaque “burden,” further study the mechanisms of plaque progression, assess the response to therapy, and allow for assessment of subclinical disease (13). We will focus on two most promising noninvasive techniques—computed tomography (CT) and magnetic resonance imaging (MRI) (14)—since, eventually, these techniques are likely to be more widely used.
Today, two different modes of CT are available. One uses the non-mechanical movement of the X-ray source (i.e., electron-beam computed tomography [EBCT]) and the other involves the motion of the X-ray source and table, combined with multiple detectors to acquire the data in spiral or helical fashion (i.e., multi-detector-row computed tomography [MDCT]) (14). Atherosclerotic coronary calcifications (15,16) most frequently are found as lumps of calcium in advanced atherosclerotic lesions (American Heart Association [AHA] plaque type Vb) but may occur as small deposits of calcium earlier in the course of lesion development (16). Both EBCT and MDCT are able to accurately quantify the coronary calcium plaque burden. Although EBCT has been considered the gold standard for the assessment of calcified plaques (17,18), MDCT usually includes an initial non-enhanced scan for the screening and quantification of coronary artery calcium (CAC) followed by CT angiography for direct visualization of coronary stenosis.

**Coronary calcium scoring by EBCT and non-enhanced MDCT.** Coronary calcification is a frequent phenomenon that does not necessarily indicate significant obstructive disease (15) (Fig. 2). It reflects “chronic plaque burden” as it relates to healed plaque ruptures and/or compensatory remodeling rather than “vulnerable or high-risk lipid-rich plaques” (16,19). However, increased chronic plaque burden is associated with increased vulnerable or high-risk plaques and, therefore with coronary events (20). Thus, it is only indirectly that calcium measurements may reflect underlying plaque biology and propensity for future plaque rupture (19).

There are various methods used to determine the amount of CAC. The standard parameter is the Agatston score based slice-by-slice analysis, maximum X-ray attenuation coefficient, and the area of calcium deposit. The Agatston score calculates the calcium burden by multiplying the area of the calcified lesion by a weighting factor dependent on the peak signal of the lesion (17). Individual scores are separately accumulated for the left main, left anterior descending, left circumflex, and right coronary artery. The sum of these separate scores yields a total coronary score. However, Agatston score is susceptible to noise artifact as well as to scan protocol variations, primarily regarding slice thickness parameters. A calcium volume score that interpolates sections to determine the isotropic volume of the lesion has been more recently developed (21). The most promising approach is to expand volumetric quantification of coronary calcium score (CS) to absolute mass quantification using a phantom calibration method of hydroxy apatite independent of different scanner properties and protocol variations (22). Thus, measurements of calcium volume and calibrated calcium mass instead of the conventional Agatston score yield improved reproducibility and consistency.

According to the American College of Cardiology (ACC) and AHA consensus on coronary calcium (18) and competence in training (23), the clinical indications that may be considered are the detection of coronary calcium as a surrogate marker in patients with atypical chest pain and for quantification and follow-up of the coronary calcium
plaque load in asymptomatic patients with cardiovascular risk factors. However, although the 34th Bethesda Conference provides an encouraging document about the diagnostic and prognostic future of noninvasive imaging (24), an outline of clear clinical indications of CAC is still considered to be premature until ongoing prospective studies provide more definitive answers (25). Thus far, it appears that the presence of CAC is a sensitive marker of patients with significant obstructive disease but that only a significant extent of CAC is reliable regarding specificity (18). In other words, patients with no or a low calcium CAC score have lower probabilities of developing clinical events than those of high scores (26–28). Nevertheless, although established as an indicator of overall disease extent, its percentile ranking adjusted to age and gender is more powerful for predicting coronary events (29). As a general guideline and, based on the CS, plaque burden interpretation has been graded as minimal (CS 0 to 10), mild (CS 11 to 100), moderate (CS 101 to 400), or extensive (CS >400) (30). Nevertheless, a CS of 45 in a 45-year-old man, which would represent above the 95th percentile, would exceed the risk of cardiac events of a 75-year-old with similar CS, who would rank at less than the 10th percentile (29).

Whether coronary calcium is an independent and superior marker of risk to conventional (28) or emerging risk factors (31) as a predictor for future cardiac events is not yet well established. In terms of risk stratification, the algorithms that combine the conventional major risk factors, such as those of the Framingham Heart Study or Prospective Cardiovascular Munster (PROCAM) study, remain the most widely used methods to estimate absolute risk for major coronary events (24). The AHA Prevention V Conference (32) established the use of CS assessment, among other noninvasive tests, as a potential tool for further stratification in selected groups of asymptomatic patients. For example, in patients with a pretest coronary event risk estimated between 6% and 20% in 10 years (intermediate risk patient) a positive CS of more than 300 to 400 would be useful in further stratification toward a high-risk status and assist in decisions regarding the need for preventive therapies (Fig. 3) (33). Indeed, there is recent supporting evidence that a promising approach to further estimate risk results from this combination of CS with conventional risk factor profile (34–36). Moreover, added to a high CS and risk factor profile, a stress test with perfusion and/or function can provide further diagnostic and prognostic information (Table 1). The coronary calcium measurement from non-enhanced MDCT appears to correlate well with EBCT (37,38). Although further comparative studies are needed, particularly at lower CS levels (39), acquisition time and radiation are less with EBCT (40), but non-enhanced MDCT yields greater reproducibility (38).

Whole-body EBCT has been performed to evaluate coronary, carotid, and aorto-iliac arteries for atherosclerotic calcifications. Age and hypertension were the dominant risk factors for systemic calcified atherosclerosis. Thus, in regard to age, approximately one-third of subjects younger than 50 years of age were free of calcified disease, whereas all subjects older than 70 years of age were found to have some calcium (41). This study suggests that there are significant correlations and risk factor associations for calcified atherosclerosis in different vascular beds.

For clinical purposes, the specific patient who may benefit the most from calcium scores is the patient with an estimated 10-year risk of 10% to 20% (two or more risk factors) according to the most recent national cholesterol education program adult treatment panel (National Cholesterol Education Program-Adult Treatment Panel III) executive summary (42). The rationale to perform a CS in this patient is supported by the significant increase in the actual risk if the test is positive, and the dramatic reduction in risk if the test is negative, as shown in Table 1 (34).

**Coronary non-calcified components of plaque imaging by contrast-enhanced MDCT.** Recently, it has been shown that CT has the potential to identify non-calcified plaques in the coronary arteries in vivo (Fig. 4) (23,43,44). Various components of atherosclerotic plaque may be distinguished and characterized by contrast-enhanced MDCT, which holds the promise of identifying vulnerable or high-risk plaques (45). In an ex vivo study on human coronary arteries, it has been shown that various imaging features of non-calcified and calcified plaques depicted with CT correlate well with histopathologic stages of atherosclerosis defined by the AHA (46). As groups, lipid-rich, fibrous and calcified plaques display different Hounsfield units (HU), and could be differentiated reliably. However, the HU units may overlap when differentiating individual plaques. Table 2 gives an overview of the typical morphologic appearance with contrast-enhanced MDCT attenuation (HU), for various plaque components. Overall, for assessment of the non-calcified (47) components of the atherosclerotic plaque, (including coronary, carotid, and aorta), the limited spatial resolution of contrast-enhanced MDCT will need to be improved for better sensitivity and accuracy; in addition, radiation dose will need to be reduced (35,40).
Coronary artery disease visualization by contrast-enhanced MDCT. Results of a number of promising studies concerning the use of contrast-enhanced MDCT for noninvasive coronary angiography (computed tomography angiography) have been published. It appears that the diagnostic accuracy is reasonable (Fig. 5), but complete assessment can be hindered by calcium deposits in the vessel wall and by motion artifacts, particularly in patients with high heart rates (23,48–51). In case the heart rate of a patient is significantly greater than 60 beats/min, the administration of beta-blocker medication to slow down the heart is commonly used. Contrast-induced nephropathy could be a risk for some patients.

Studies with 16-slice scanners showed improved accuracy as compared with previous reports with four-slice scanners (52–54). These studies reported sensitivity of 73% to 95% and specificity of 86% to 93%, for detection of obstructive disease (Table 3). However, some of the contrast-enhanced MDCT coronary angiography studies excluded approximately 30% of coronary segments mainly because of image degradation from cardiac motion. The image artifacts and the number of excluded coronary segments may be significantly reduced (to approximately 10%) by the use of beta-blockers to minimize cardiac motion and careful patient selection, which allows the imaging of the entire coronary tree within one breath hold. Improvements in MDCT using the 64-slice systems equipped with more and thinner detector rows and increased rotation speed have a potential to allow a more reliable coronary stenosis detection with a very short scan time (55,56).

Table 1. Changes in 10-Year Risk According to Calcium Scores and Exercise Testing

<table>
<thead>
<tr>
<th>Pre-test Probability of a Coronary Event Within 10 yrs (%)</th>
<th>Probability Within 10 yrs According to Results of Electron Beam CT (%)</th>
<th>Probability Within 10 yrs According to Results of Exercise Electrocardiography (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calcium Score &gt;80</td>
<td>Calcium Score &lt;80</td>
</tr>
<tr>
<td>1.0</td>
<td>3.0</td>
<td>0.2</td>
</tr>
<tr>
<td>2.0</td>
<td>6.5</td>
<td>0.4</td>
</tr>
<tr>
<td>3.0</td>
<td>9.5</td>
<td>0.6</td>
</tr>
<tr>
<td>4.0</td>
<td>12.5</td>
<td>0.9</td>
</tr>
<tr>
<td>5.0</td>
<td>15.0</td>
<td>1.0</td>
</tr>
<tr>
<td>6.0</td>
<td>18.0</td>
<td>1.2</td>
</tr>
<tr>
<td>7.0</td>
<td>20.0</td>
<td>1.4</td>
</tr>
<tr>
<td>10.0</td>
<td>27.0</td>
<td>2.2</td>
</tr>
<tr>
<td>15.0</td>
<td>38.0</td>
<td>3.4</td>
</tr>
<tr>
<td>20.0</td>
<td>46.0</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Pre-test probability of a coronary event within 10 years is derived from the data on coronary risk factors. Other probabilities of coronary event were calculated on the basis of the results of electron-beam computed tomography (CT) or exercise electrocardiography. Please note that a 10% probability is increased to 27% if a calcium score is >80 and reduced to 2.2% if the score is <80. Reproduced with permission from Greenland P et al. (34).

Figure 4. Contrast-enhanced, 16 detector-row computed tomography angiography of the coronary arteries in a 65-year-old patient. (A) Maximum-intensity projection along the course of the proximal left coronary artery shows a large non-calcified coronary artery plaque in the distal left main coronary artery (arrow). (B) A cross-sectional image reconstruction of the corresponding vessel region proves significant lumen obstruction due to the concentric plaque. (C) Using dedicated post-processing tools, the vessel can be stretched longitudinally and rotated in any direction for improved visualization of the plaque.

MAGNETIC RESONANCE IMAGING

Because atherothrombotic disease affects the entire arterial system, simultaneous assessment of coronary and peripheral arteries to the distal runoff vessels has been proposed using contrast-enhanced whole-body magnetic resonance angiography (MRA) (23,57). Most important, high-resolution MRI has emerged as the potential leading noninvasive in vivo imaging modality for atherosclerotic plaque characterization (13,14).
Whole-body contrast-enhanced MRA and coronary MRA. Magnetic resonance angiography was found to have high specificity and sensitivity compared with X-ray angiography for the detection of luminal narrowing >50% (57). Today, whole-body MRA excludes the intracranial and coronary arteries, for which a dedicated examination is still required. Several coronary MRA techniques have been proposed for the assessment of stenosis, anomalies, and patency of bypass grafts. T2-weighted navigator-gated fat-suppressed free-breathing gradient-echo sequences usually are used for coronary MRA (57). Navigator-gated free-breathing steady-state free precession (SSFP) techniques also have been proved effective for bright-blood coronary MRA (58,59). Recently, radial SSFP sequences, spiral SSFP sequences, and other improvements to SSFP navigator also have been developed for coronary MRA (60–62). Spuentrup et al. (63) recently have compared Cartesian and non-Cartesian MRA acquisition methods. Thus far, the

Table 2. Contrast at CT and MRI of Main Components of Atherothrombotic Plaque

<table>
<thead>
<tr>
<th>Sequence</th>
<th>CT (HU)</th>
<th>MRI (SI*)</th>
<th>T1W</th>
<th>PDW</th>
<th>T2W</th>
<th>TOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent thrombus</td>
<td>20</td>
<td>+ to ±</td>
<td>- to ±</td>
<td>- to ±</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lipid</td>
<td>50</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td></td>
</tr>
<tr>
<td>Fibrous</td>
<td>100</td>
<td>±</td>
<td>± to +</td>
<td>± to -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>&gt;300</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Signal intensity (SI) relative to adjacent muscle. †Vessel contrast enhancement. + = hyperintense; ± = isointense; − = hypointense. CT = computed tomography; HU = Hounsfield unit; MRI = magnetic resonance imaging; PDW = proton density-weighted; TOF = time-of-flight; T1W = T1-weighted; T2W = T2-weighted.

Table 3. Multidetector CT Angiography of the Coronary Arteries

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-slice CT (segments &gt;2.0 mm)</td>
<td>Nieman et al. (50) 38</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Achenbach et al. (48) 64</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>Knez et al. (49) 44</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>Leber et al. (82) 98</td>
<td>82</td>
</tr>
<tr>
<td>16-slice CT (segments &gt;2.0 mm)</td>
<td>Nieman et al. (52) 58</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Ropers et al. (53) 78</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Mollet et al. (83) 128</td>
<td>92</td>
</tr>
<tr>
<td>16-slice CT (all segments)</td>
<td>Kuettner et al. (54) 60</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Hoffman et al. (47) 33</td>
<td>63</td>
</tr>
</tbody>
</table>

Five confirmatory studies of 2005 were just published (55). CT = computed tomography.

Figure 5. A 38-year-old man presenting with atypical chest pain. The calcium screening examination revealed no calcifications within the coronary arterial tree (A). After administration of contrast agent, using a three-dimensional volume-rendering reconstruction technique, all epicardial vessels, including major side branches, could be depicted with sufficient image quality, allowing reliable exclusion of significant coronary artery lesions or the presence of extensive non-calcified atherosclerotic vessel wall changes (B, C, D). Ao = aorta; CV = cardiac vein; DBs = diagonal branches; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; OM = obtuse marginal branch; PA = pulmonary artery; RCA = right coronary artery.
sensitivity and specificity are quite promising (14,57,64). Overall, it is likely that in the near future, and just for diagnostic purposes, MRA will provide complete assessment of the systemic arterial tree, whereas noninvasive CT with intravenous injection of contrast medium may, in part, replace conventional diagnostic coronary angiography (14).

Regional high-spatial resolution MRI for plaque characterization. Magnetic resonance differentiates plaque components on the basis of biophysical and biochemical parameters, such as chemical composition, water content, physical state, molecular motion, or diffusion (57). Specifically, recent improvements in MR techniques (e.g., black-blood MRI, faster imaging, and detection coils), conducive to high-resolution and contrast imaging, have permitted the study of the different plaque components using multi-contrast MR, generated by T1- and T2-weighted, proton-density-weighted, and time-of-flight imaging (Table 2) (13,14,65,66). Moreover, MR provides imaging without ionizing radiation and can be repeated over time.

Recent developments in MR imaging sequences have improved the speed of acquisition, enabling rapid extended coverage of aorta and carotid arteries (67). This development was accomplished by modifying existing double inversion recovery black blood MRI. Improvements in receiver coil design (such as 8-channel carotid array) also have enabled high-resolution imaging of carotid arteries (68). Multi-contrast imaging coupled with spatially enhanced cluster analysis has allowed the quantitative evaluation of various plaque components (69). New, targeted contrast agents that are being developed to selectively image atherosclerotic plaques (70) and are currently being tested in animal models with new methods for nulling the blood with very short T1 relaxation time (71). In vivo characterization of aortic arch atherosclerosis in apolipoprotein E knockout mice transplant model has also been recently shown (72).

MRI studies of carotid artery plaques. Carotid arteries’ superficial location and relative absence of motion present less of a technical challenge. Some carotid plaque MR studies (Fig. 6) showed the imaging and characterization of normal and pathological arterial walls (66,73), the quantification of plaque size (74,75), and the assessment of fibrous cap integrity (76). A strong association between fibrous cap thinning or rupture, as determined by MR vessel wall imaging, and the history of recent transient ischemic attack or stroke was recently demonstrated (77). The MRA demonstrates the severity of stenotic lesions and their spatial distribution, whereas the high-resolution wall characterization technique may show the composition of the plaques. MRA and high-resolution MR imaging of the vessel wall can be combined (14).

Using a T1-weighted method, MR-direct thrombus imaging sensitive to thrombus and methemoglobin, Moody et al. (78,79) studied patients suffering acute cerebral infarction or transient ischemic attacks and showed that a significant number of them had a complicated carotid plaque ipsilateral to the side of their cerebral event that was corroborated in the carotid endarterectomy specimens. Interestingly, in a significant minority this occurred in vessels with stenoses <50% to 70%. The occurrence of high signal material was also found in the contralateral side in 30% of these patients (80).

MRI studies of aortic plaques. 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. Thoracic aorta plaque composition and size have been assessed using high-resolution multi-contrast images (Fig. 7). Matched MRI and transesophageal echocardiography cross-sectional aortic segments showed a strong correlation for plaque thickness, whereas MRI was better for plaque characterization (81). In a recent study of asymptomatic subjects, the Framingham Heart Study showed by MRI that aortic plaque prevalence and burden (i.e., plaque volume/aortic volume) significantly increased with age and were

Figure 6. In vivo black-blood magnetic resonance imaging cross-sectional T2-weighted image of a patient with a significant plaque in the right carotid artery (arrow). The magnified image (bottom left) shows a complex lipid-rich plaque.

Figure 7. In vivo black-blood magnetic resonance images of a patient with a large plaque in the aortic arch (right panel) at the level of the descending aorta (left panel). The arrows indicate plaque. The asterisk indicates the areas of most prominent ulcerations.
higher in the abdominal aorta than in the thoracic aorta (82). It also was found that long-term measures of risk factors and Framingham Heart Study coronary risk score are strongly associated with asymptomatic aortic plaques as detected by MRI. Other approaches for the noninvasive detection of plaque in aorta are gadolinium-enhanced three-dimensional MRA (83) or new semi-invasive procedures like transesophageal MRI (84). In conclusion, MR may be a powerful noninvasive imaging tool for direct noninvasive assessment of aortic atherosclerotic plaque thickness, extent, and composition and may thereby allow the serial evaluation of progression and therapy-induced regression of atherosclerotic plaques.

MRI studies of peripheral arteries. High-resolution MRI of the femoral and popliteal artery and the response to balloon angioplasty have been documented (84,85). The extent of the plaques could be defined such that even in angiographically “normal” segments of vessel, lesions with cross-sectional areas ranging from 49% to 76% of potential lumen area were identified (85). After angioplasty, plaque fissuring and local dissection were easily identified, and serial changes in lumen diameter, blood flow, and lesion size were documented.

MRI studies of coronary artery plaques. The ultimate goal is noninvasive imaging of plaque in the coronary arteries. By using a combination of multi-contrast MRI sequences, differentiation of fibrocellular, lipid-rich, and calcified regions of the atherosclerotic coronary plaque is feasible, as shown in an ex vivo study on human coronary arteries correlated to histopathology (86). Our group adapted the black blood MR method used in the human carotid artery and aorta to the imaging of the coronary arterial lumen and wall. The method was validated in swine coronary lesions induced by balloon angioplasty (87). High-resolution, black-blood MR of both normal and atherosclerotic human coronary arteries was performed for direct assessment of coronary wall thickness and the visualization of focal atherosclerotic plaque in the wall (Fig. 8) (88). To alleviate the need for breath holding, real-time navigator for respiratory gating and real-time slice-position correction has been reported (89). Near isotropic spatial resolution black-blood imaging may provide a quick way to image a long segment of the coronary artery wall and may be useful for rapid coronary plaque burden measurements (90).

In vivo monitoring of therapy with MRI. It has been shown that in vivo MRI can be used to measure the effect of lipid-lowering therapy (statins) in asymptomatic, hypercholesterolemic patients with carotid and aortic atherosclerosis (74). Atherosclerotic plaques were visualized and measured with MRI at different time points after initiation of lipid-lowering therapy. Significant regression of atherosclerotic lesions was observed. There was a decrease in the vessel wall area but no change in the lumen area at 12 months. A longer follow-up showed a continued reduction on vessel wall area and even a small, but significant, increase in the arterial lumen at 24 months (Fig. 9) (75). Similar findings were obtained with atorvastatin. A case-control study demonstrated substantially reduced carotid plaque lipid content in patients treated for 10 years with an aggressive lipid-lowering regimen (76,91). We have just demonstrated the beneficial effects of statins on experimental atherosclerosis followed by MRI, and additional anti-atherogenic benefits of combining a peroxisome proliferator-activated receptor-
gamma agonist with simvastatin (92). Overall, such role of MRI on the in vivo monitoring of therapies can be pivotal for the better understanding of new pharmacological agents before undergoing clinical trials. It also can serve as a guide to assess the vascular wall response by individual patients to proven beneficial therapies.

A clear distinction between imaging the coronary arteries, which move, and the larger arteries, which have less motion, is important when considering CT/MRI for research or clinical purposes. Evaluation of plaque composition by either technique is superior in larger arteries, including carotids and the aorta. Despite of great advances with the coronaries, plaque characterization in the epicardial vessels of the heart remains a challenge that requires further work for complete clinical application.

**INTEGRATION OF NONINVASIVE CT AND MRI**

Together, CT and MRI may provide unique information, thus allowing the assessment of subclinical disease, atherosclerotic progression, and its response to therapy (14,57). Computed tomography may first be used to localize suspicious atherosclerotic lesions in the coronary arteries within a short scan time. Magnetic resonance angiography does the same in the systemic arteries, but within a much longer scan time. Magnetic resonance imaging can then proceed with tissue characterization of the problem sites.

Reprint requests and correspondence: Dr. Pedro R. Moreno and Dr. Zahi A. Fayad, Mount Sinai School of Medicine, Box 1030, New York, New York 10029. E-mail: Pedro.Moreno@msnyuhealth.org.

**REFERENCES**


