Atherosclerotic Plaque Imaging

Contemporary Role in Preventive Cardiology

Paolo Raggi, MD; Allen Taylor, MD; Zahi Fayad, PhD; Daniel O’Leary, MD; Steven Nissen, MD; Daniel Rader, MD; Leslee J. Shaw, PhD

Coronary artery disease imaging has traditionally been based on luminal angiography, but it has become evident that this tool, although extremely useful in diagnosing obstructive disease, is insufficient to define the presence and extent of atherosclerotic disease in the vessel wall. Progression of coronary artery disease was also initially evaluated using quantitative coronary angiography, and evidence soon accumulated that minor regression or nonprogression of luminal disease was associated with a favorable cardiovascular outcome. In recent years, however, several other techniques have been developed to image atherosclerosis and are emerging as useful tools in preventive cardiovascular medicine. These techniques provide new methods to assess the burden of atherosclerosis, gauge the risk of cardiovascular events, and offer a means to test the efficacy of therapeutic approaches to atherosclerosis. Furthermore, non-invasive coronary angiography can be performed with some of the new imaging modalities, potentially reducing the number of unnecessary invasive tests. This review focuses on techniques such as cardiac computed tomography, carotid artery intima-media thickness, cardiovascular magnetic resonance imaging, and intravascular ultrasonography as emerging tools in cardiovascular disease prevention.
Figure 1. A calcium deposit in the proximal portion of the left anterior descending coronary artery (arrow) is shown. Calcium accumulates in the context of the atherosclerotic plaque as the plaque grows, and this accumulation is dependent on active mechanisms similar to bone formation.

Table 1. Studies Using CAC Measurement as a Marker of Cardiovascular Event Risk

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Type</th>
<th>No. of Patients</th>
<th>Mean Follow-up, y</th>
<th>Type of Cardiovascular Event</th>
<th>No. of Events</th>
<th>Incremental Prognostic Value of CAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arad et al,7 1996</td>
<td>Prospective</td>
<td>1173</td>
<td>1.5</td>
<td>Stroke, MI, death, revascularization</td>
<td>26</td>
<td>Yes</td>
</tr>
<tr>
<td>Detrano et al,a 1999</td>
<td>Prospective</td>
<td>1196</td>
<td>3.4</td>
<td>MI, death</td>
<td>46</td>
<td>No</td>
</tr>
<tr>
<td>Arad et al,4 2000</td>
<td>Prospective</td>
<td>1172</td>
<td>3.6</td>
<td>MI, death, revascularization</td>
<td>39</td>
<td>Yes</td>
</tr>
<tr>
<td>Raggi et al,9 2001</td>
<td>Observational</td>
<td>676</td>
<td>2.5</td>
<td>MI, death</td>
<td>30</td>
<td>Yes</td>
</tr>
<tr>
<td>Wong et al,10 2000</td>
<td>Observational</td>
<td>926</td>
<td>5.0</td>
<td>Stroke, MI, death, revascularization</td>
<td>41</td>
<td>NA</td>
</tr>
<tr>
<td>Shaw et al,11 2003</td>
<td>Observational</td>
<td>10377</td>
<td>5.0</td>
<td>MI, death, revascularization</td>
<td>249</td>
<td>NA</td>
</tr>
<tr>
<td>Kordos et al,12 2003</td>
<td>Observational</td>
<td>5635</td>
<td>3.0</td>
<td>MI, death, revascularization</td>
<td>224</td>
<td>NA</td>
</tr>
<tr>
<td>Greenland et al,14 2004</td>
<td>Prospective</td>
<td>1029</td>
<td>7.0</td>
<td>MI, death</td>
<td>84</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: CAC, coronary artery calcium; MI, myocardial infarction; NA, not assessed.

Table 2. Studies Investigating Calcium Deposition Reduction in Patients at Risk for Cardiovascular Events

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Type</th>
<th>No. of Patients</th>
<th>Type of Treatment</th>
<th>Calcium Score Change per Year, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Callister et al,20 1998</td>
<td>Observational</td>
<td>149</td>
<td>Statins (unspecified) vs usual care</td>
<td>52 ± 36 (Mean ± SD)</td>
</tr>
<tr>
<td>Budoff et al,21 2000</td>
<td>Observational</td>
<td>299</td>
<td>Statins (unspecified) vs usual care</td>
<td>35-40 (Mean), varying according to baseline risk factor</td>
</tr>
<tr>
<td>Achenbach et al,22 2002</td>
<td>Prospective crossover design</td>
<td>66</td>
<td>Cerivastatin sodium, 0.3 mg/d, vs placebo Statins (unspecified) vs usual care</td>
<td>25 (Median)</td>
</tr>
<tr>
<td>Hecht and Harman,23 2003</td>
<td>Observational</td>
<td>230</td>
<td>8.9 (Mean) vs 10.4 (Mean)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.
axiom should be tested against the ability of traditional algorithms to estimate risk. The incremental prognostic value of atherosclerosis imaging should come at an affordable cost such that the advantage of an expanded diagnosis and therapy can be justifiable.

If accurate atherosclerosis imaging techniques were implemented, a proposed strategy to track an individual patient’s risk would be to use intermediate end points that carry prognostic relevance and can be identified before the occurrence of a definite end point. Intermediate end points should possess pathobiologic relevance to the inferred outcome and should be present in study subjects to a degree sufficient for accurate detection and serial measurement. In addition, a change in the end point should demonstrate a shift in clinical risk. Once these requirements were satisfied, intermediate end points would permit a marked reduction in sample size of future research studies compared with the current large clinical trials. This approach would also shorten trials, leading to a more rapid dissemination of research findings into clinical practice or halting the expensive development of ineffective pharmacologic agents. Obviously, the widespread availability of imaging modalities would be germane to making this shift in risk assessment and management a clinically fruitful and acceptable tool for most practicing physicians. To date, there is a large body of evidence surrounding the use of numerous atherosclerosis imaging modalities, and a few of them will be discussed in this review.

**COMPUTED TOMOGRAPHY**

As a marker of atherosclerosis burden, coronary artery calcium (CAC) as measured with computed tomography (CT) (Figure 1) has been used in several studies to predict outcome in patients at risk of cardiovascular events. Table 1 summarizes the most relevant studies in this field. Elevated CAC scores add incremental prognostic information in individuals with an intermediate pretest likelihood of disease based on traditional risk factors. In addition, the absence of CAC shows a high negative predictive value for the occurrence of future events.

Because calcification of the vessel wall occurs via active enzymatic and cellular processes resembling bone formation, researchers have investigated whether calcium deposition can be reduced with medical intervention. Table 2 summarizes the most relevant publications in this field. Although the preponderance of data show that CAC progression can be slowed with lipid-lowering therapy, some investigators have disputed this view. However, CAC progression seems related to cardiovascular outcome. In 2 observational studies, subjects who experienced a myocardial infarction had a 3-fold greater yearly increase in CAC score than did event-free survivors (P < .001), and in the presence of CAC score progression, the relative risk of myocardial infarction increased 11- to 17-fold compared with no progression. Hence, CAC progression appears to be an indicator of risk and an intermediate end point worth being measured. Nonetheless, these preliminary data will need to be confirmed in larger prospective studies.

Noninvasive coronary angiography was made possible by the introduction of electron-beam CT (EBCT) with a temporal resolution (imaging time) as short as 50 milliseconds per tomographic image. While the first generation of mechanical CT scanners were too slow to perform noninvasive coronary angiography, current multidetector CT (MDCT) scanners provide adequate temporal and excellent spatial resolution. Although invasive coronary angiography will retain its role in guiding surgical interventions and catheter-based revascularization, noninvasive CT angiography will likely become of great value in excluding the presence of obstructive lesions in patients with a low pretest probability of disease, patients unwilling to undergo invasive angiography, and patients experiencing chest discomfort after coronary artery bypass surgery.

In a landmark study published by Achenbach et al, EBCT angiography was performed in 125 patients and demonstrated a sensitivity and specificity of 92% and 94%, respectively, compared with invasive coronary angiography for the detection of a luminal obstruction greater than 50%. However, these results were based on the assessment of 75% of all coronary segments, because 25% of the segments were not properly visualized owing to various technical limitations (excessive motion, calcium overlay, low signal-noise ratio, etc). Similar angiographic results were obtained with 4-slice MDCT scanners, with a sensitivity and specificity of 82% and 96%, respectively. Furthermore, the limitation noted in the report of Achenbach et al, that is, the inability of EBCT to evaluate approximately 25% to 30% of the coronary segments, was seen with 4-slice MDCT scanners as well. Nonetheless, MDCT angiography has improved substantially since the introduction of 16-slice MDCT scanners with higher temporal resolution, a higher signal-noise ratio, and better spatial resolution than the preceding 4-slice MDCT scanners. With the arrival on the market of 32- and 64-slice MDCT scanners, it is hoped that the quality of CT angiography will approach that of invasive coronary angiography. The earlier MDCT scanners provided a much larger radiation dose than did EBCT scanners (8.2 vs 2.7 mSv, respectively, for angiographic studies). This problem was largely solved with the more modern MDCT scanners, in which a “pulsatile” output of radiation (reduced output during systole and increased output during diastole, when most of the diagnostic images are acquired) allows the radiation dose to be reduced to levels similar to those of EBCT.

Finally, plaque characterization, with identification of both hard and soft plaque components (Figure 3) during CT angiography, has been reported by several investigators. Although this is potentially useful information, it is still awaiting a viable clinical application. Nonetheless, it is an important extension of CT’s ability to merely detect calcified plaque, potentially affording the opportunity to detect unstable and high-risk plaques.
CAROTID INTIMA-MEDIA THICKNESS

Measurement of the arterial intima-media thickness (IMT), achieved with high-resolution B-mode ultrasonographic imaging, was first presented as a means of assessing atherosclerosis of the aorta in 1986 and was soon applied to the carotid arteries. Large observational studies established that carotid IMT correlates with levels of cardiovascular risk factors and is an independent marker of risk for the occurrence of cardiovascular events. Nonetheless, IMT has never been shown to provide incremental prognostic information over traditional risk factors for the prediction of events.

Serial measurements of carotid IMT have been used in several longitudinal studies that have explored the effect of lipid-lowering therapies, as well as beta-blockade, calcium antagonists, and treatment of hyperglycemia on progression of carotid IMT. Most of the studies showed a slowing of carotid IMT progression with active therapy. Despite these favorable results, however, no study has yet conclusively linked slowing of carotid IMT progression to reduction in cardiovascular events, and this remains an area of active research.

MAGNETIC RESONANCE

Cardiovascular magnetic resonance can be used to image atherosclerotic plaques of large vessels and to characterize plaque composition. Cardiovascular magnetic resonance differentiates plaque components on the basis of biophysical and biochemical factors such as water content, physical state, and molecular motion and diffusion.

Most cardiovascular magnetic resonance (CMR) plaque imaging is currently being performed on whole-body 1.5-T magnetic resonance (MR) systems, although future work may be carried out on 3.0-T whole-body MR systems. In vivo CMR plaque imaging and characterization have been performed by using a multicontrast approach with high-resolution black-blood spin-echo and fast spin-echo–based MR and bright-blood sequences. In the black-blood sequence, the signal from the flowing blood is suppressed and turned black to better image the adjacent vessel wall. On the other hand, bright-blood imaging can be used to assess the thickness of the fibrous cap and the morphological integrity of atherosclerotic plaques.

Using in vivo multicontrast CMR, Yuan et al detected the presence of a lipid core and acute intraplaque hemorrhage in human carotid arteries with a sensitivity of 85% and a specificity of 92%. In a recent study, 53 consecutive patients (49 of them men; mean age, 71 years) scheduled for carotid endarterectomy were submitted to CMR of the carotid arteries prior to surgery. Twenty-eight patients had a recent history of transient ischemic attack or stroke on the side ipsilateral to the index carotid lesion, and 25 were asymptomatic. The fibrous cap was categorized as intact-thick, intact-thin, or ruptured on the basis of...
CMR images. Ruptured caps were significantly more frequent than intact-thick caps in symptomatic patients (70% vs 9%, P = .001).

Direct MR thrombus imaging, a technique sensitive to methemoglobin in the plaque, has been used to detect complex carotid disease with intraplaque hemorrhage.55-57 Moody et al56 compared direct MR thrombus imaging findings with endarterectomy specimens and reported this imaging technique to have a sensitivity and specificity of 84% for the detection of complex plaque in the carotid artery ipsilateral to an old transient ischemic attack or stroke. Murphy et al59 described a high prevalence of complex carotid plaques with direct MR thrombus imaging ipsilateral to a recent transient ischemic attack or stroke, but a significantly lower prevalence in the contralateral carotid artery and complete absence of such findings in healthy control subjects.

Human aortic plaque can also be accurately visualized with CMR. In asymptomatic Framingham study subjects, the prevalence of aortic atherosclerosis imaged by CMR increased significantly with patient age and was higher in the abdominal aorta than in the thoracic aorta.58 In 102 symptomatic patients undergoing coronary angiography,60 plaques were seen by means of CMR more frequently in the abdominal (90%) than in the thoracic (61%) aorta and were more prevalent in patients with established coronary artery disease. In addition, low-density lipoprotein cholesterol (LDL-C) level was correlated with thoracic aorta disease and smoking was correlated with abdominal aorta atherosclerosis.

Elevated serum levels of inflammatory markers such as fibrinogen and C-reactive protein60 or interleukin 6, intercellular adhesion molecule 1, and vascular cell adhesion molecule 161 have been correlated with increased wall thickness of the aorta and carotid arteries.

Cardiovascular MR imaging has been used serially to investigate the progression of atherosclerotic lesions of the aorta and carotid arteries in small in vivo studies. Corti...
et al62 studied the effect of statins on carotid and aortic plaques in 51 asymptomatic, untreated, hypercholesterolemic subjects. The treatment effect was assessed as the change in lumen area, vessel wall thickness, and vessel wall area compared with baseline measurements. Significant ($P=0.01$) reductions in maximal vessel wall thickness and area (10% and 11%, respectively, for aortic and 8% and 11%, respectively, for carotid plaques), without changes in lumen area, were reported at 12 months.61 Further decreases in vessel wall thickness and area ranging from 12% to 20% were observed at 18 and 24 months, along with a slight but significant increase (ranging from 4% to 6%) in lumen area.63

In a case-control study, Zhao et al64 demonstrated that carotid plaques in patients treated for 10 years with an aggressive lipid-lowering regimen contained a lower amount of lipids and a greater amount of calcium, with no substantial overall plaque area reduction, compared with untreated controls. The effects of moderate and aggressive lipid-lowering therapy on plaque regression were addressed in a prospective study by Lima et al.65 The investigators used a combination of surface and transesophageal CMR to enhance the detection of thoracic aorta plaque regression in 27 asymptomatic subjects treated with either a moderate (20 mg/d) or high (80 mg/d) dosage of simvastatin. Both plaque volume and plaque area regressed significantly ($P<0.02$ for both measurements) during a follow-up period of merely 6 months, whereas the vessel lumen area did not change. The response of plaque to medical therapy appeared directly related to the LDL-C-lowering effect of statins.

Finally, in an experimental rabbit model, Corti et al66 demonstrated that the addition of peroxisome proliferator-activated receptor $\gamma$ agonists enhanced the treatment effect of statins on atherosclerotic plaque regression and composition change.

Despite these exciting results, prospective studies are still needed to ascertain the predictive value of subclinical atherosclerosis detected by means of CMR for future cardiovascular events. Furthermore, CMR still lacks sufficient technological accuracy to image smaller vessels such as the coronary arteries, where motion and spatial resolution remain challenging. Nonetheless, small preliminary human studies67 using the black-blood technique have shown promise and will need further pursuit. Future studies should also concentrate on establishing a correlation between the imaging of plaque progression by CMR and cardiovascular events.

**INTRAVASCULAR ULTRASONOGRAPHY**

The high spatial resolution of intravascular ultrasonography (IVUS) has been exploited to image atheroscle-
atherosclerotic plaque and its components and to assess vascular remodeling (Figure 6). Outward vascular remodelling prevents encroachment of the vessel lumen by the growing atherosclerotic plaque and is responsible for apparently patent coronary arteries in the presence of extensive atherosclerosis of the arterial wall. Inward vascular remodelling has been reported in patients with unstable coronary syndromes. Intravascular ultrasonography has been used extensively as a supportive technique during the performance of catheter-based interventions, but it has more recently been used to follow the progression of atherosclerotic plaques in patients exposed to treatment. With IVUS it is possible to accurately quantify plaque volume in a coronary artery segment of interest. The plaque area in each section is derived by carefully outlining the perimeter of the luminal endothelium, as well as that of the external elastic lamina. The sum of all areas, computed at multiple contiguous levels, amounts to the total plaque volume. Reference points, such as vessel branches, are used to orient the operator to the starting and ending points for intravascular imaging.

Jensen et al implemented a lipid-lowering diet for 3 months followed by therapy with simvastatin, 40 mg daily, for 12 additional months in 40 hypercholesterolemic men with ischemic heart disease. Intravascular ultrasonography was performed at 3 and 15 months. The study showed no substantial plaque volume change at 3 months, but demonstrated a significant reduction (P=.002) in volume in the absence of a change in lumen diameter after the additional 12 months of therapy with simvastatin.

Okazaki et al performed percutaneous angioplasty of the culprit vessel in 70 patients with an acute myocardial infarction and randomized the subjects to therapy with atorvastatin calcium, 20 mg/d, or placebo. Six months after randomization, the plaque volume in the nonculprit vessel increased significantly with placebo (8.7%) and decreased significantly with therapy (-13%).

Nissen et al were recently able to show the beneficial effects on coronary atherosclerotic plaque of 2 different treatment regimens aimed at modifying the lipid milieu of an individual patient. In animal experiments, recombinant apolipoprotein A 1 (ApoA-1) Milano has been shown to rapidly shrink atherosclerotic plaques. In a 5-week randomized study, a weekly intravenous treatment with recombinant ApoA-1 Milano–phospholipid complexes or placebo was administered to 47 patients within 14 days of experiencing an acute coronary event. The active treatment group showed a 1.06% reduction in atheroma volume (P=.02), corresponding to an average 14.1-mm³ loss in absolute plaque volume. Conversely, the placebo group showed a 0.14% increase in absolute plaque volume (P=.97). Regression was seen with both low and high doses of recombinant ApoA-1 Milano (P<.001).

The effects of intensive LDL-C lowering with atorvastatin calcium, 80 mg/d, on atherosclerotic plaque volume were compared by means of IVUS with those obtained with a moderate regimen of pravastatin sodium, 40 mg/d, in 502 patients undergoing coronary angiography. Subjects exposed to moderate therapy (average LDL-C level with treatment, 110 mg/dL [2.85 mmol/L]; 25% reduction) demonstrated progression of atheroma volume (2.7% progression, P<.001 compared with baseline), whereas subjects exposed to intensive therapy (average LDL-C level with treatment, 79 mg/dL [2.05 mmol/L]; 46% reduction) showed stabilization of increase in atheroma volume (-0.4%, P=.98).

These studies clearly demonstrated the high accuracy of IVUS for detecting even minimal changes in atherosclerotic plaque burden and represent an important emerging trend in research. The precision and reproducibility of IVUS renders it an especially desirable imaging tool, albeit invasive, because it may allow for the design and conduction of short-duration studies and studies with small patient cohorts. As with several other imaging techniques, these promising results will require confirmation that surrogate end points translate into substantial reduction in morbidity and mortality.

CONCLUSIONS

The material presented in this summary represents a synopsis of the extensive work conducted to date in the field of atherosclerosis imaging with just a few of the technologies currently available. Tools such as vasoactivity to assess endothelial function, palpography, carotid plaque volume measurement by means of 3-dimensional ultrasonography, radioactive imaging of inflamed plaques, plaque thermography, and others have not been covered owing to space considerations. Responsible application of the current technologies and structured research must continue to foster the growth of the field of plaque imaging. Our goal should be to educate physicians, third-party payers, and the public about the proper indications for atherosclerosis imaging. Avoiding inappropriate uses of these technologies will reduce costs and increase overall gain for the individual patient and society.

Accepted for Publication: May 19, 2005.
Correspondence: Paolo Raggi, MD, Section of Cardiology, Department of Internal Medicine, Tulane University, 1430 Tulane Ave, SL-48, New Orleans, LA 70112 (praggi@excite.com).
Financial Disclosure: None.

REFERENCES


