Determination of Carotid Artery Atherosclerotic Lesion Type and Distribution in Hypercholesterolemic Patients With Moderate Carotid Stenosis Using Noninvasive Magnetic Resonance Imaging

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Background and Purpose—The aims of this study were to noninvasively determine carotid atherosclerotic lesion type and distribution and to evaluate the reproducibility of determining lesion types in asymptomatic patients with moderate hypercholesterolemia and moderate carotid artery (CA) stenosis using MRI.

Methods—Forty-two asymptomatic patients with moderate CA stenosis underwent bilateral carotid MRI in a 1.5-T scanner using a protocol that generated 4 contrast weightings (T1, T2, proton density, and 3D time of flight). MRI-modified American Heart Association criteria were used to evaluate lesion types at 3 locations (common and internal CA [CCA and ICA, respectively] and CA bifurcation) and at the minimum lumen area. Two identical MR scans were conducted to evaluate reproducibility of lesion types.

Results—Lesion types were obtained from 230 locations. Type III (39%) occurred most commonly, followed by types IV–V (25%), I–II (20%), VI (12%), and VII (4%). Type III was more commonly distributed in the CCA (n=110, 35%) and ICA (n=112, 36%). Type IV–V was more commonly distributed in the CCA (n=94, 41%) and at the bifurcation (n=38, 36%). Forty-two lesions were available at the site of minimum lumen area: type III (33%), IV–V (33%), VI (29%), and VII (5%). There was good agreement of lesion types between both MRI scans (Cohen’s κ=0.73; 95% CI: 0.65 to 0.81).

Conclusions—MRI can determine lesion types reproducibly as well as the distribution of lesions in hypercholesterolemic patients with moderate CA stenosis. A wide range of lesion types, including advanced lesions, were found in these patients. (Stroke. 2004;35:2444-2448.)

Key Words: atherosclerosis • carotid artery • carotid stenosis • MRI

Atherosclerosis is an inflammatory process that begins relatively early in life. Early detection of carotid atherosclerosis may allow for selection of subjects at risk for future cerebrovascular events at a time when dietary and lifestyle modification may have its greatest impact, and when medical intervention may be useful for those who are refractory to such treatment or who are at greater risk for an event. Recent studies of the relationship between lesion type progression and clinical events, particularly in coronary artery disease, have led to efforts to characterize the types of lesions present, not just in terms of luminal narrowing but also with regard to morphology and composition. New emphasis on prevention of complicated lesions, such as those with fibrous cap rupture or intraplaque hemorrhage or both, has made early detection of lesions and assessment of lesion extent and composition important clinical goals.1

Early detection relies on knowledge of the distribution of atherosclerotic lesion types. However, early lesions may be accompanied by compensatory (expansive) remodeling that normalizes the area of the vessel lumen, making detection of these lesion types impossible by digital subtraction angiography.2 In addition, digital subtraction angiography carries a permanent neurological deficit risk of 1%, with a mortality rate of 0.1%.3 This risk is compounded in patients undergoing repeated studies, making serial examination with angiography undesirable. Transcutaneous ultrasound techniques are noninvasive, making it ideally suited for serial studies of atherosclerosis progression. However, ultrasound is an operator-
dependent modality, and the restricted imaging plane of ultrasound can lead to over- or underestimation of disease severity. Computed tomographic angiography has the disadvantages of ionizing radiation exposure and the need for iodinated contrast agents.

Studies have demonstrated that MRI not only can quantify the luminal and diseased arterial wall area but also can characterize the composition of human carotid atherosclerotic plaque, such as fibrous tissue, lipid and necrotic core, calcium, hemorrhage, thrombus, and the status of the fibrous cap. Furthermore, a recent study has demonstrated that classification of human carotid atherosclerotic lesions is possible with in vivo multicontrast MRI that used modified American Heart Association (AHA) criteria. Therefore, noninvasive MRI is an ideal method for studying early lesions of carotid atherosclerosis.

As part of the ongoing ORION (Outcome of Rosuvastatin treatment on CA atheroma: a magnetic resonance Imaging Observation) trial, we determined atherosclerotic lesion types and their distribution in the carotid arteries, using MRI-modified AHA criteria in asymptomatic patients with moderate hypercholesterolemia and moderate carotid artery stenosis. We also assessed the reproducibility of these lesion types by using 2 independent MR scans from the same patients.

Methods

Ethical Considerations

This trial was designed and conducted in accordance with the Declaration of Helsinki (version amended in October 2000) and in compliance with the ethical principles of good clinical practice. Institutional Review Boards at the University of Washington (UW), Seattle, Wash, USA, and the University of Utah (UU), Salt Lake City, Utah, USA, approved the research protocol and consent forms, and all patients gave their written, informed consent before initiation of any trial procedure.

Trial Design

The 2-year ORION trial was a randomized, double-blind, parallel-group trial designed to assess the effect of low and high (5- and 40-mg) doses of the highly effective HMG-CoA reductase inhibitor rosuvastatin (Crestor, AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK; licensed from Shionogi & Co Ltd, Osaka, Japan) on progression of atherosclerosis, using multicontrast, high-resolution MRI. Patients with moderate hypercholesterolemia (fasting low-density lipoprotein cholesterol levels ≥2.6 and <6.5 mmol/L) and either moderate CA stenosis (16% to 79%) of one or more carotid arteries or an atherosclerotic plaque with a lipid/necrotic core, as assessed by baseline duplex ultrasonography and MRI, were enrolled in this trial.

MRI Protocol

MR scans were performed with two 1.5T whole-body scanners (Signa Horizon EchoSpeed, General Electric Medical Systems). One scanner had software release version 5.8 (UW) and the other had version 8.4 (UU). A custom-built, phased-array carotid coil was used to improve signal-to-noise performance as well as a head holder to keep patients in a consistent, comfortable position.

A standardized protocol was used to obtain 4 different contrast-weighted images of bilateral carotid arteries in the transverse plane: T1-weighted (T1W), proton-density weighted (PDW), T2-weighted (T2W), and 3-dimensional time-of-flight MR angiography (3D TOF). Parameters for the imaging sequences were as follows: (a) T1W: double inversion-recovery, black-blood, 2D fast spin-echo, repetition time (TR)/echo time (TE) = 800/10 ms, echo train length (ETL) = 8; (b) PDW and T2W: double echo, cardiac-gated, TR = 3 or 4 cardiac R-R intervals, effective TE = 20 ms for PDW and 40 ms for T2W, ETL = 8; and (c) 3D TOF: TR/TE 23/3.8 ms, flip angle 25°. All images were obtained with a field of view of 16 cm, matrix size of 256, slice thickness of 2 mm, and 2 signal averages. Interslice spacing was 0 mm for T1W, PDW, and T2W, and –1 mm for 3D TOF (1 mm overlapping between adjacent slices). Fat suppression was used for T1W, PDW, and T2W images to reduce signals from subcutaneous fat. A pixel size of 0.25×0.25 mm was achieved after zero-filled Fourier transformation. The longitudinal coverage of each carotid artery was 24 mm (12 slices) for T1W, 30 mm (15 slices) for PDW and T2W, and 40 mm (40 slices) for 3D TOF.

MRI was centered on the carotid bifurcation on the index side. The index side was defined to be the side of carotid artery with the higher degree of lumen area reduction compared with the contralateral side by MRI. Both MR scans from the same patients used the carotid bifurcation as a landmark to assure registration for comparison of results.

MRI Image Review and Criteria

Image quality was rated per location for each contrast weighting on a previously established 5-point scale (1 = poor and 5 = excellent), depending on the overall signal-to-noise ratio and the clarity of the artery wall. Images with a quality score of ≤2 (indicating significant degradation of image quality due to patient motion or low signal-to-noise ratio) were excluded from the study.

Lesion types at 3 discrete locations 8 mm apart (common carotid artery [CCA], internal carotid artery [ICA], and carotid bifurcation) of each artery were evaluated by 1 reviewer (C.Y.). As carotid bifurcations of bilateral arteries may not be in the same level, ICA or CCA locations (8 mm from CA bifurcation) on the nonindex side were not available in some cases, precluding evaluation of lesion types.

In addition, lesion type at the site of the minimum lumen area on the index side was evaluated. Minimum lumen area was defined to be the smallest lumen area among all the cross-sectional MR images on the index side of the carotid artery. Therefore, each patient had only 1 lesion type determined at the site of the minimum lumen area.

The following modified AHA classification of lesion types for MRI was used: type I–II represents near-normal wall thickness without calcification; type III represents diffuse intimal thickening or small eccentric plaque without calcification; type IV–V represents plaque with a lipid or necrotic core surrounded by fibrous tissue with possible calcification; type VI represents complex plaque with a possible surface defect, hemorrhage, or thrombus; type VII represents calcified plaque; and type VIII represents fibrotic plaque without a lipid core and with possible small calcifications. Each cross-sectional location was ascribed 1 of these 6 classifications.

Data Analysis

Percentage of lesion types was computed for each of the 4 locations: CCA, ICA, carotid bifurcation, and the location with minimum lumen area on the index side. The patients from UW had 2 carotid MRI scans, with an interval of 1 to 21 days, whereas the patients from UU had only 1 MR scan available. For the patients with 2 MR scans, the same reviewer (C.Y.), who was blind to subject name and temporal order, evaluated the lesion types in both MR scans. Locations from the MR scan with the best image quality were chosen to determine the distribution of lesion type found. If image quality was equal across both scans, locations from the first MR scan were chosen to determine lesion type distribution. For the patients with 1 MR scan, locations with image quality scores ≥3 were used to determine the distribution of lesion types.

Cohen’s k with a 95% CI was computed to quantify the agreement of lesion types in the corresponding locations between right and left carotid arteries, and between 2 MR scans.

Previous research has shown that Cohen’s k analysis of lesion types, comparing adjacent locations 4 mm apart, was less than 0.20 for a very similar AHA classification scheme, which indicates very little dependence in lesion types between sections that are 4 mm
Because the 3 locations from each carotid artery were 8 mm apart in this study, the lesion types obtained were considered to be independent of each other. A value of $\kappa = 0.75$ was used to indicate excellent agreement, and $0.40 \leq \kappa < 0.75$ denotes good agreement. All calculations were made with SPSS for Windows (version 10.1).

### Results

Forty-two hypercholesterolemic patients (29 men and 13 women; mean age 65 years) were enrolled in this study. Among them, 40 were from UW and 2 from UU. These patients had 16% to 79% CA stenosis and no recent neurological symptoms (within the past 90 days before MRI examinations). As summarized in Table 1, the major risk factors included current smoker (n=9, 21%), type II diabetes (n=8, 19%), prior myocardial infarction (n=7, 17%), coronary artery stenosis $\geq 50\%$ (n=8, 19%), and other peripheral artery stenosis $\geq 50\%$ (n=3, 7%). The mean value of total cholesterol, LDL-C, and HDL-C was 6.2, 4.0, and 1.2 mmol/L, respectively.

Of the 252 possible locations (42 patients × 2 sides × 3 locations), 22 ICA or CCA locations (8 mm proximal or distal to the carotid bifurcation) on the nonindex side were not available for review on cross-sectional MR images. The remaining 230 locations were assessed for lesion types, with all 230 locations having good image quality (scores, $\geq 3$; mean, 3.8).

The minimum lumen area on the index side was able to be identified in all 42 patients. In 240 possible discrete locations (40 patients × 2 sides × 3 locations), 22 ICA or CCA locations on the nonindex side were not available and 31 were excluded because of poor image quality on either of the 2 MR scans, resulting in 187 locations with matched images between 2 MR scans for assessment of interscan reproducibility.

### Lesion Type Distribution at CCA, ICA, and Carotid Bifurcation

Lesion types obtained from 230 locations were distributed as follows: type III (39%), IV–V (25%), I–II (20%), VI (12%), and VII (4%) (Figures 1 to 3 and Table 2).

#### Comparisons of Lesion Types Between 2 Sides of Carotid Arteries

Among 230 bilateral locations, 104 left CA locations had corresponding right-side locations. Cohen’s $\kappa$ showed weak correspondence of lesion types between matched left and right CA locations ($\kappa = 0.20$; 95% CI: 0.07 to 0.32).
Lesion Types at Minimum Lumen Area on the Index Side

Forty-two lesions were distributed as follows: type III (n=14, 33%), IV–V (n=14, 33%), VI (n=12, 29%), and VII (n=2, 5%). No type I–II or type VIII lesions were found at the sites of the minimum lumen area (Table 2).

Interscan Reproducibility of Lesion Types

One hundred eighty-seven locations with matched images generated good agreement of lesion types between both MR scans (Cohen’s $\kappa=0.73$; 95% CI: 0.65 to 0.81) (Table 3).

Discussion

For the first time in a clinical trial, the current study establishes the atherosclerotic lesion type profile in asymptomatic patients with moderate hypercholesterolemia and moderate CA stenosis or atherosclerotic plaque, using MRI-modified AHA criteria. This study demonstrates that MRI is capable of characterizing lesion types with a high degree of reproducibility. Thus, MRI may be a reliable tool for assessing lesion progression or regression following lipid-lowering therapy.

Table 2: Lesion Types in the 3 Discrete Locations and at the Minimum Lumen Location

<table>
<thead>
<tr>
<th>Type</th>
<th>3 locations</th>
<th>Minimum lumen locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I–II</td>
<td>13</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Type III</td>
<td>35</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Type IV–V</td>
<td>24</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Type VI</td>
<td>3</td>
<td>12 (29%)</td>
</tr>
<tr>
<td>Type VII</td>
<td>2</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Type VIII</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>230 (100%)</td>
</tr>
</tbody>
</table>

Percentage in the parentheses indicates percentage of each lesion type.

Table 3: Interscan Reproducibility of Lesion Types

<table>
<thead>
<tr>
<th>Lesion type: Scan 2</th>
<th>I–II</th>
<th>III</th>
<th>IV–V</th>
<th>VI</th>
<th>VII</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>25</td>
<td>13</td>
<td>1</td>
<td></td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>58</td>
<td>7</td>
<td>1</td>
<td></td>
<td>71</td>
</tr>
<tr>
<td>IV–V</td>
<td>4</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>VI</td>
<td>3</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>VII</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>75</td>
<td>54</td>
<td>23</td>
<td>5</td>
<td>187</td>
</tr>
</tbody>
</table>

Cohen’s $\kappa=0.73$ (95% CI: 0.65–0.81).

In this study, the lesion profile describes a spectrum of lesion types ranging from type I–II to type VII in 3 specific locations: CCA, carotid bifurcation, and ICA. It is not surprising that type VIII lesions were not found because the patients in this study had only moderate CA stenosis, whereas type VIII lesions are highly fibrotic lesions that often result in severe CA stenosis.1

In the current study, type III lesions were found to be the most common (39%). These lesions demonstrate diffuse intimal thickening or small eccentric plaque, representing intermediate lesions that are the morphological bridge between type II and advanced lesions.16,17 The intimal thickening is considered to be an adaptive response to the mechanical stresses on the arterial wall. Such small eccentric lesions could result from the lipoprotein deposition driven by the same mechanical forces when atherogenic lipoproteins exceed certain critical levels. Therefore, type III lesions represent atherosclerosis-prone lesions.16,17

Type VI lesions represent complex lesions that are considered to be highly associated with a recent history of transient ischemic attack or stroke.18–23 However, we found such lesions in 12% of our asymptomatic patients. These results suggest that the production of neurological symptoms is not inevitable when complex plaque is present. Our results are consistent with histological findings that demonstrate silent plaque rupture is a frequent finding in the presence of severe coronary atherosclerosis.24

Type VII lesions represent calcified atherosclerotic plaques, which were present in 4% of our patients. These lesions are different from the calcified nodules that are associated with luminal surface disruption and mural thrombi (type VI),19 and the early “stippling” calcifications that are associated with type III lesions.25 These lesions most likely...
represent the calcifications seen on the CA walls on computed tomography.26

The distribution pattern of lesion types by location is noteworthy in this study. Our results demonstrated weak correspondence of lesion types between matched left and right CA locations, indicating asymmetry of local plaque lesion characteristics. This is in contradistinction to the symmetry of human CA atherosclerosis that has been observed in terms of total wall volume and plaque calcification.27 Moreover, the MRI-based lesion profile results in this study may provide insight into atherosclerotic lesion progression. In particular, type IV–V (33%) and type VI (29%) lesions found in the minimum lumen locations on the index side of the carotid artery were more common than type IV–V (25%) and type VI (12%) lesions found in the 3 specific locations. These results suggest that type IV–V and type VI lesions may be associated with the compromised CA lumen.

Summary
This study is the first to use MRI-modified AHA criteria to define the atherosclerotic lesion profile in hypercholesterolemic patients with moderate CA stenosis or atherosclerotic plaque. As atherosclerotic lesion types can be reproducibly characterized with MRI, this technique should be valuable for assessing lesion progression or regression following lipid-lowering therapy.

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References
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