Effects of Prolonged Intensive Lipid-Lowering Therapy on the Characteristics of Carotid Atherosclerotic Plaques In Vivo by MRI
A Case-Control Study

Xue-Qiao Zhao, Chun Yuan, Thomas S. Hatsukami, Ellen Huss Frechette, Xiao-Jian Kang, Kenneth R. Maravilla, B. Greg Brown

Abstract—High-resolution magnetic resonance imaging (MRI) with flow suppression not only provides useful information on luminal and wall areas of the carotid artery but also can identify the principal tissue components of the carotid atherosclerotic plaque. The effects of intensive lipid-lowering therapy on these MRI tissue characteristics were examined in patients with coronary disease (CAD). Eight CAD patients who have been receiving intensive lipid-lowering treatment (niacin 2.5 g/d, lovastatin 40 mg/d, and colestipol 20 g/d) for 10 years in the Familial Atherosclerosis Treatment Study (FATS) follow-up were randomly selected from among 60 such treated patients. Eight CAD patients who were matched to the treated patients for age (±3 years), baseline low density lipoprotein (±5 mg/dL), and triglycerides (±50 mg/dL) but who had never been treated with lipid-lowering drugs were selected as controls. For each of these 32 carotid arteries, luminal and plaque areas were measured by planimetry, in a blinded protocol, from the magnetic resonance image that showed most plaque. Fibrous tissue, calcium, and lipid deposits were identified on the basis of established criteria. Plaque composition was estimated as a fraction of total planimetered area. Patients treated with 10-year intensive lipid-lowering therapy, compared with control subjects, had significantly lower low density lipoprotein cholesterol levels (84 versus 158 mg/dL, respectively; \( P < 0.001 \)) and higher high density lipoprotein cholesterol levels (51 versus 37 mg/dL, respectively; \( P < 0.001 \)). As a group, treated patients, compared with untreated control subjects, had a smaller core lipid area (0.7 versus 10.2 mm\(^2\), respectively; \( P = 0.01 \)) and lipid composition (1% versus 17%, respectively). Group differences in luminal area (55 [treated] versus 44 [control] mm\(^2\), \( P = \text{NS} \)) and plaque area (58 [treated] versus 64 [control] mm\(^2\), \( P = \text{NS} \)) tended to favor treatment. MRI appears useful for estimating carotid plaque size and composition. Hyperlipidemic CAD patients frequently (97%) have at least moderate (≥40% area stenosis) carotid plaque. In this case-control study, prolonged intensive lipid-lowering therapy is associated with a markedly decreased lipid content, a characteristic of clinically stable plaques. (Arterioscler Thromb Vasc Biol. 2001; 21:1623-1629.)

Key Words: MRI ■ atherosclerotic plaque ■ lipid-lowering therapy

Pathological studies\(^1,2\) of acute coronary syndromes have shown that erosion or rupture of a single coronary plaque, with superimposed thrombosis and vasospasm, is the principal mechanism precipitating ischemia. Histological studies of these culprit lesions have shown that the majority of ruptured plaques contain a soft lipid-rich core that is covered by a thin cap of fibrous tissue infiltrated by foam cells.\(^1,4\) In the past 2 decades, numerous clinical\(^5-7\) and angiographic\(^5\) studies have demonstrated that lipid-lowering therapy is effective in the primary and secondary prevention of cardiovascular events and induces angiographic regression in ≈12% of coronary lesions.\(^8\) The reduction in clinical events in these trials appears to be best explained by the effects of lipid-lowering therapy on the above high-risk features of plaque morphology. A hypothesis has been proposed: Lipid-lowering therapy selectively lipid-depletes (regresses) a relatively small but dangerous subgroup of vulnerable lesions containing a large lipid core and dense clusters of intimal macrophages. These lesions are thereby effectively stabilized, and the clinical event rate is accordingly decreased.\(^9\) Although shown in experimental models, plaque lipid depletion remains to be confirmed in humans.

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Recent human and animal studies have suggested that MRI of atherosclerosis may provide information on plaque com-
Table 1. MRI Parameters Used in the Present Study

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Time-of-Flight</th>
<th>T1W</th>
<th>PDW</th>
<th>T2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image mode</td>
<td>3D</td>
<td>2D</td>
<td>2D</td>
<td>2D</td>
</tr>
<tr>
<td>TR, ms</td>
<td>22</td>
<td>550</td>
<td>3RR (gated)*</td>
<td>3RR (gated)*</td>
</tr>
<tr>
<td>TE, ms</td>
<td>3.4</td>
<td>14</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>Field of view, cm</td>
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<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Matrix size</td>
<td>256×160</td>
<td>256×256</td>
<td>256×256</td>
<td>256×256</td>
</tr>
<tr>
<td>No. of excitations</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Slice thickness, mm</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Echo train length</td>
<td>...</td>
<td>...</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

T1W, PDW, and T2W indicate T1-weighted, proton density–weighted, and T2-weighted images, respectively; TR, repetition time; and TE, echo time.

*Peripheral gating was used to suppress flow and motion artifacts in these relatively long TR/TE scans.

position as well as on plaque volume.10–15 The development of high-resolution MRI technique holds great promise for the evaluation of carotid atherosclerosis in vivo.11,15 In this cross-sectional case-control study, we sought to determine, by using MRI, whether hyperlipidemic patients with coronary artery disease (CAD) treated according to the recommendations of the National Cholesterol Education Program (NCEP)16 over an extended period would have carotid plaque characteristics different from those of a comparable group of untreated CAD patients. Our findings support a major lipid-depleting effect of such therapy on the carotid plaque.

Methods

Patients

Eight male CAD patients who had been receiving intensive lipid-lowering treatment (niacin 2.5 g/d, lovastatin 40 mg/d, and colestipol 20 g/d) for an average of 10 years in the Familial Atherosclerosis Treatment Study (FATS) follow-up17 were selected at random from a group of 60 such patients and designated the treated group. All 8 patients had completed 10 years and were still active in treatment; as a group, their LDL averaged <100 mg/dL during the intensive treatment. Eight male CAD patients who were matched to the treated patients for age (±3 years), off-treatment LDL (±5 mg/dL), and triglycerides (±50 mg/dL) and who had never been treated with lipid-lowering drugs were selected as controls. The diagnosis of CAD was based on coronary angiography demonstrating at least one 50% stenosis or three 30% lesions. The 2 groups were identified before any MRI was performed.

MRI Scanning

Thirty-two carotid arteries in these 16 patients were examined. All of the images were obtained with a 1.5-T imager (SIGNA, Horizon Echo Speed 5.7, General Electric Medical Systems) with custom-made bilateral carotid phased-array coils.18 MRI time was 30 to 40 minutes per patient.

Fourteen consecutive levels (per artery) that were centered at the carotid bifurcation with 3-mm section thickness and no intersection gap and that covered ~4-cm portions of the common carotid, bifurcation, and internal and external carotid arteries were scanned by using time-of-flight, T1, proton-density, and T2 weightings.

The MRI parameters used in the present study are listed in Table 1.

Image Analysis

The image analyses were performed with the observers blinded to patient identity, treatment group, and clinical details. Images from 5 consecutive levels centered at carotid bifurcation, at 4 magnetic resonance (MR) weightings (see Table 1), were selected for detailed image analysis because plaque is more likely to develop near the carotid bifurcation.

Visual Assessment of Disease Severity and Complexity

Lesion morphology in these 20 images was visually classified into 5 types: (1) normal, (2) diffuse concentric thickening, (3) eccentric with luminal area greater than plaque area, (4) eccentric with luminal area smaller than plaque area, and (5) total occlusion. From the series of sections in each artery, the image showing the largest plaque was selected for quantitative assessment of the luminal and plaque areas and the subregions of various plaque morphological features.

Identification of Carotid Atherosclerotic Plaque Components

The selected image from each carotid artery was traced, including the outer wall, lumen, and plaque morphological features. The latter were identified as subregions of the plaque with a relatively homogeneous gray scale for each weighting. See Figure 1 for an example of this process. MR signal intensity from 4 different MR weightings was visually identified by direct comparison with a 16-level gray scale stanard along the border of each image and recorded for each feature and lumen. Carotid plaque components, including fibrous tissue, calcium, and lipid deposits, were identified on the basis of previous studies that used signal intensity variation from 4 different weightings.10,19–22 Figure 2 presents an example of histological confirmation of carotid plaque tissue components, luminal, and wall area by MRI. A detailed qualitative comparison of the relative contrast from the 4 different image weightings for 4 possible plaque tissue types is given in Table 2. Prior analyses19,22 of the tissue contrast features of human atherosclerotic plaque have shown that 4 important plaque components, ie, (1) lipid, (2) calcium, (3) fibrous tissue, and (4) lipid mixed with calcium, have statistically significant differences in their pattern of imaging contrast for the 4 weightings. However, none of the contrast weighting techniques alone can differentiate all of the tissue types; a combination of different weightings is required.
therapy, compared with matched but untreated patients, would demonstrate different carotid plaque composition, as identified by MRI. Unpaired 2-tailed t tests were used to compare measurements from the 2 study groups, with level of $P<0.05$ considered significant.

**Results**

**Patient Clinical and Lipid Characteristics**

As shown in Table 3, control and treated patients were comparable in terms of CAD risk and concomitant medication. However, compared with the control group lipid profile that was obtained before the MRI study, treated patients had significantly lower average on-treatment total cholesterol levels (228 ± 14 [control] versus 163 ± 19 [treated] mg/dL, $P<0.001$) and LDL levels (157 ± 14 [control] versus 84 ± 14 mg/dL [treated], $P<0.001$) and significantly higher HDL levels (37 ± 10 [control] versus 51 ± 10 [treated] mg/dL, $P<0.001$). Triglyceride levels did not differ significantly (174 ± 74 [control] versus 184 ± 62 mg/dL [treated], $P=0.6$).

**Interobserver Variability**

Thirty-two images selected for greatest plaque size were analyzed by 2 independent observers (X.-Q.Z. and B.G.B.) for measurements of the outer arterial and luminal areas and plaque morphological composition. These measurements between the 2 observers were highly concordant. The correlation coefficients were $r=0.84$ ($P<0.001$) for the outer area measurement and $0.88$ ($P<0.001$) for the luminal area. Estimates of lipid area were most concordant ($r=0.93$, $P<0.001$), with $r=0.90$ ($P<0.001$) for calcium. Because of its relative small proportion of plaque area, estimates for lipid mixed with calcium were not as well correlated ($r=0.59$).

**Statistical Analysis**

The primary question addressed in this cross-sectional study was whether CAD patients exposed to prolonged intensive lipid-lowering

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**TABLE 2. Signal Intensities of Plaque Components With Use of a 16-Level Gray Scale**

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Time-of-Flight</th>
<th>T1W</th>
<th>PDW</th>
<th>T2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen</td>
<td>Very high (1–2)</td>
<td>Very low (14–16)</td>
<td>Very low (14–16)</td>
<td>Very low (14–16)</td>
</tr>
<tr>
<td>Fibrous tissue</td>
<td>Low (14–16)</td>
<td>High (2–3)</td>
<td>Very high (1–3)</td>
<td>Very high (1–3)</td>
</tr>
<tr>
<td>Calcium</td>
<td>Very low (14–16)</td>
<td>Very low (13–16)</td>
<td>Very low (14–16)</td>
<td>Very low (14–16)</td>
</tr>
<tr>
<td>Lipid deposits</td>
<td>...</td>
<td>Very high (1–3)</td>
<td>Medium (8–11)</td>
<td>Low (10–14)</td>
</tr>
<tr>
<td>Lignins + calcium</td>
<td>...</td>
<td>Medium (8–11)</td>
<td>Low (9–13)</td>
<td>Low to very low (10–16)</td>
</tr>
</tbody>
</table>

*The range of 1 to 16 represents the Gray scale, the range of signal intensity of tissues and lumen in the carotid artery image. A value of 1 indicates very high (brightest), and a value of 16 indicates very low (darkest). By using the pattern of densities for each tissue over the set of specified weightings, the 5 principle morphological features of the atherosclerotic artery may be identified. (Please refer to Figure 2 for more detail).*

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**Figure 2.** An eccentric and advanced plaque in the right common carotid artery from a patient who underwent carotid endarterectomy. The matching in vivo MR images were obtained before surgery. The histological specimen showed that this complex plaque with a large lipid core contains extracellular lipid, amorphous debris, cholesterol monohydrate crystals, calcifications, and hemorrhage (red). The matching MR images showed that the area of hyperintense signal on T1 weighting correlates well in size and appearance with the large lipid-rich region on the histological slide. *Luminal area.*

**Figure 3.** A diseased right common carotid artery from the matched control patient shown in Figure 1. Images from left to right are T1W, PDW, and T2 weighting (T2W). The arrowheads point to the calcification, which appears dark on all 3 contrast weightings. The arrows point to the lipid-rich region that appears very bright on T1W, dark on PDW, and darker on T2W.
Effects of Stenosis Severity on Plaque Tissue Characteristics
The sections selected for greatest plaque size in each carotid artery were classified into approximate tertiles of measured cross-sectional luminal area reduction: 26% to 50% (n = 11), 51% to 65% (n = 9), and 66% to 83% (n = 12). There were no significant between–treatment group differences in this distribution.

As shown in Table 4, the carotid wall area increased significantly when luminal area reduction became more severe. A trend of decreased fibrous tissue composition and of increased calcium and lipid mixed with calcium was observed with increasing luminal area reduction. Nonsignificant difference in lipid content was seen among the 3 tertiles of luminal area reduction; however, there was substantially less lipid among treated arteries in all 3 categories.

Between-Group Differences in Carotid Plaque Location and Obstruction
The carotid arteries from patients treated with intensive triple lipid-lowering therapy, compared with those from the matched controls, had a nonsignificant larger luminal area (55 [treated] versus 44 [control] mm², \( P = 0.27 \)), a smaller wall area (58 [treated] versus 64 [control] mm², \( P = 0.34 \)), and a greater lumen/wall ratio (1.0 [treated] versus 0.7 [control], \( P = 0.19 \)), as presented in Table 5. The most prominent carotid lesions were located in the common carotid in 53% of cases, at the bifurcation in 34%, and in the internal carotid arteries in 13%. There was no difference between the 2 groups.

Between-Group Differences in Carotid Plaque Composition
Table 5 and Figure 5 demonstrate that intensive triple lipid-lowering therapy was significantly associated with less plaque lipid content (0.7 [treated] versus 10.2 [control] mm², \( P = 0.01 \)) and lipid composition (1% [treated] versus 17% [control], \( P = 0.01 \)). The treated arteries tended to have more calcium (6.4 [treated] versus 1.8 [control] mm², \( P = 0.07 \)). Fibrous tissue content, per plaque, was not significantly different between the treated and control groups (46.3 versus 49.2 mm², respectively; \( P = 0.57 \)), however, its composition tended to be greater in treated than in control plaques (84% versus 77%, respectively).

Discussion
Our understanding of atherosclerotic plaque development and regression is derived largely from animal experiments. Studies of the nonhuman primate by Armstrong and Megan, Clarkson at al., Small et al., and Wissler and Vesselino-vitch have demonstrated convincing evidence that atherosclerotic plaque lipid content is depleted with plasma cholesterol reduction. When cholesterol-fed animals are changed to a vegetarian diet, plasma lipids fall quickly to 140 mg/dL, and the greatly increased arterial lipid content (principally cholesterol ester) decreases by 60% over 24 to 48 months. However, collagen content is only modestly (20%) reduced. In our case-control study, prolonged intensive lipid-lowering therapy is associated with strikingly reduced plaque lipid content (1% in treated versus 17% in control patients) and with only minor difference in fibrous tissue. Thus, the MRI-measured treatment group differences in human carotid plaque composition appear consistent with the known effects of therapy on plaque composition in nonhuman primates.

Atherosclerotic plaque characteristics play an important role in plaque instability and the risk of plaque disruption with superimposed thrombosis is predicted by its lipid-related features, such as the area of the core lipid region as a percentage of total plaque area and foam cell cluster size in the fibrous cap and shoulder regions. The fibrous cap is also weakened by macrophage-associated stromelysin, one of a family of inflammatory matrix metalloproteinases.

The extremely low plaque lipid composition (1%) among 8 CAD patients treated with intensive lipid-lowering therapy...
for 10 years was associated with a low rate (5%) of the composite end point: cardiac death or nonfatal myocardial infarction over 10 years of follow-up among the larger group of 60 patients, from whom these 8 were randomly chosen.17 This encouraging result supports the idea that prolonged intensive lipid-lowering therapy will significantly decrease lipid composition in the plaque, an effect that would predict greater plaque stability and would thus reduce clinical ischemic events. Prospective studies are presently under way in randomized controlled trials to further test the hypothesis that intensive lipid-lowering therapy depletes plaque lipid and to examine the time course of such depletion and the relationship between plaque lipid depletion and change in other plaque components or plaque size (regression).

Our understanding of human plaque composition is mainly from histological studies. The Roberts group36–40 has studied human coronary plaque composition in the spectrum of clinical atherosclerosis. Others31,41,42 have studied aortic and carotid plaques. Our assessments of carotid fibrous tissue and calcium and lipid deposits with the use of MRI in vivo are consistent with previously reported histological findings.41,42 In a coronary plaque study, 37 91%, 82%, and 73% of coronary plaque area was fibrous tissue identified by histology for plaque with postmortem luminal narrowing of 26% to 50%, 51% to 75%, and 76% to 95%, respectively. In the

| TABLE 4. Tissue Characteristics of 32 Carotid Atherosclerotic Plaques In Vivo by MRI |
| Lucinal Area Reduction | 26%–50% | 51%–65% | 66%–83% |
| No. of carotid arteries | 11 | 9 | 12 |
| Carotid wall area, mm² | 48±10 | 66±12 | 70±22* |
| Carotid luminal area, mm² | 75±28 | 45±10 | 30±14* |
| Fibrous tissue area mm² | 40.7±13.0 | 53.1±8.2 | 50.2±15.4† |
| Percentage of total plaque area | 86±23% | 82±11% | 74±17% |
| Calcium tissue area mm² | 1.4±2.8 | 6.4±8.9 | 4.8±8.3‡ |
| Percentage of total plaque area | 3±5% | 9±12% | 7±12% |
| Calcium+lipid area mm² | 0.6±2.0 | 2.9±4.4 | 7.5±17.7‡ |
| Percentage of total plaque area | 1±5% | 4±6% | 7±17% |

Treated arteries (N=16) n 6 5 5
Lipid deposit area, mm² 0.6±1.6 1.6±3.6 0
Percentage of total plaque area 1±3% 3±6% 0
Control arteries (N=16) n 5 4 7
Lipid deposit area, mm² 10.1±17.6 4.9±9.8 13.0±15.3
Percentage of total plaque area 20±34% 7±14% 20±20%

Values are group mean±SD. Data on lipid content are presented for treated and control groups; other characteristics do not differ between groups and are combined.

*P<0.01, †P<0.05, and ‡ P<0.01 for differences among the 3 luminal area reduction categories.

| TABLE 5. Comparisons of Carotid Artery Lumen, Wall Area, Plaque Tissue Components, and Composition Between Patients Treated With Intensive Lipid-Lowering Therapy and Matched Control Subjects |
| Treated (n=16) | Control (n=16) | P |
| Carotid outer area, mm² | 113±35 | 108±27 | 0.69 |
| Carotid luminal area, mm² | 55±33 | 44±20 | 0.27 |
| Carotid artery lumen/wall ratio | 1.0±0.8 | 0.7±0.4 | 0.19 |
| Carotid wall area, mm² | 58±19 | 64±18 | 0.34 |
| Fibrous tissue area, mm² | 46.3±6.8 | 49.2±18 | 0.57 |
| Percentage of total plaque area | 84±14% | 77±22% |
| Calcium cluster area, mm² | 6.4±7.8 | 1.8±5.9 | 0.07 |
| Percentage of total plaque area | 10±11% | 3±7% |
| Lipid deposit area, mm² | 0.7±2.2 | 10.2±14.4 | 0.01 |
| Percentage of total plaque area | 1±4% | 17±23% |
| Lipid plus calcium area, mm² | 4.5±12.5 | 3.2±10.2 | 0.74 |
| Percentage of total plaque area | 5±12% | 3±11% |

Values are mean±SD.
present study, 86%, 82%, and 74% of the carotid plaque area was identified by MRI as fibrous tissue for plaques with in vivo luminal area reduction of 26% to 50%, 51% to 65%, and 66% to 83% stenosis, respectively. We saw a trend of increased calcium content with increasing luminal narrowing in carotid plaques, and the Roberts group (Kragel and colleagues66,67) has demonstrated the same phenomena in the coronary plaques. Furthermore, our measured lipid content, 17% by MRI, from the control patients was also similar to pultaceous debris plus foam cells and foam cells with lymphocytes (12% to 14% in coronary plaques by histology).67 Ex vivo MRI was recently found to identify lipid-rich core and fibrocellular lipid with a high level of sensitivity and specificity.43 These data suggest that carotid plaque composition may have important potential to serve as a surrogate marker for coronary plaque composition.

To study the effects of lipid-lowering therapy on human atherosclerotic plaque size and composition in vivo, an imaging technique is needed that can characterize the cross-sectional morphology and composition of the atherosclerotic arterial wall. MRI is ideal for longitudinal studies of atherosclerotic arteries because it is noninvasive and is superior to other imaging modalities in discriminating soft tissue content.10–14,19,20,44–46 With current technology, the carotid application illustrated in the present study appears most promising. For widespread use, the speed of these measurements and their variability must be improved. Currently under development in our laboratory is an automated MRI analysis system that should provide accurate and more reproducible quantification of arterial luminal and wall areas and of the various tissue components and that will make image analysis more objective and less tedious.

In summary, the noninvasive analysis of carotid plaque in vivo by MRI provides an opportunity for longitudinally assessing changes in atherosclerotic lesions and, in particular, their tissue composition. Such studies appear to have great potential for more meaningful subclassification of atherosclerotic plaque pathology, for risk stratification, and for elucidation of certain of the mechanisms by which effective therapies prevent ischemic events.

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