Computed Tomography Angiography for the Evaluation of Carotid Atherosclerotic Plaque
Correlation With Histopathology of Endarterectomy Specimens

Leighton J. Walker, MRCP; Azam Ismail, MD; William McMeekin, FIMBS; David Lambert, FRCS; A. David Mendelow, FRCS; Daniel Birchall, FRCR

Background and Purpose—The goal of this study was to determine the efficacy of CT angiography for the characterization of plaque morphology and composition in carotid atherosclerotic disease.

Methods—Fifty-five patients undergoing carotid endarterectomy were imaged preoperatively with single-slice spiral CT angiography. One hundred sixty-five endarterectomy sections were examined histologically at selected levels through the distal common and proximal internal carotid arteries. Plaque density was measured (in Hounsfield units) on axial CT sections, and the presence or absence of ulceration was noted. These observations were compared with the histological findings at corresponding levels. Data were analyzed with 2-sample t tests and 1-way analysis of variance (ANOVA).

Results—ANOVA testing showed a statistically significant decrease in CT attenuation values with increasing plaque lipid but with a very high standard deviation of values. No other histological factor showed a statistically significant link with CT attenuation. Plaque ulceration was detected by CT with a sensitivity of 60% and a specificity of 74%.

Conclusions—Analysis of plaque attenuation with single-slice spiral CT does not give useful information concerning plaque composition. The predictive value of CT for the detection of plaque ulceration was moderate. Single-slice CT angiography is insufficiently robust to be a useful tool for the characterization of carotid plaque composition and morphology. (Stroke. 2002;33:977-981.)

Key Words: angiography ■ carotid arteries ■ carotid artery plaque ■ computed tomography

Stroke is the third leading cause of severe disability and death in the Western world, creating an enormous health economic burden on society. Extracranial carotid atherosclerotic disease is well established as a major risk factor for cerebrovascular events, with increasing risk associated with increasing severity of stenosis. Several major multicenter studies have established carotid endarterectomy as an effective means of reducing risk in those patients with high-grade stenosis. However, high-grade stenoses may remain asymptomatic, and it is widely recognized that factors other than the degree of luminal narrowing are prognostically important.

Plaque morphology and composition have been proposed as important risk factors for thromboembolic events, giving rise to the concept of “unstable plaque.” It is suggested that embolic phenomena are associated with thinning and subsequent ulceration of the fibrous cap on the surface of atherosclerotic plaque, resulting in release into the parent vessel of necrotic lipid debris from the plaque substance. Several studies have established a correlation between plaque ulceration and irregularity with clinical presentation, outcome, and prognosis. For example, recent analysis of the European Carotid Surgery Trialists’ Collaborative Group data has shown that surface irregularity and ulceration seen on catheter angiography are associated with more frequent symptoms. Controversy exists regarding the importance of other pathological features. For example, no convincing evidence exists to firmly correlate intraplaque hemorrhage with symptoms. However, other workers have proposed a high plaque lipid content to correlate with clinical presentation, especially if located just beneath a thin fibrous cap.

In imaging carotid artery atherosclerotic disease, it is therefore increasingly important to identify factors other than the degree of angiographic stenosis. In particular, a large amount of work has been published on the imaging of plaque morphology and composition. Spiral CT angiography is a well-established technique for imaging atherosclerotic disease of the extracranial carotid artery and has been proposed as a possible means of evaluating plaque morphology and composition. We assessed the effectiveness of single-slice spiral CT angiography...
phy in characterizing carotid plaque in a series of patients undergoing carotid endarterectomy.

Methods
Fifty-five patients (34 male, 21 female; average age, 59 years) undergoing carotid endarterectomy were imaged preoperatively with CT angiography as part of a standard imaging protocol. Patients with a ≥70% stenosis (as defined by North American Symptomatic Carotid Endarterectomy Trial Collaborators criteria) previously identified on carotid duplex ultrasound were included in the study. CT angiography was performed on a single slice helical scanner (CTi, GE Medical Systems) with a standardized protocol. We injected 90 mL nonionic contrast medium (300 mg I/mL) at 4 mL/s with a predetermined time delay (typically 12 to 15 seconds) during a spiral acquisition from C6 to C2. We acquired 3-mm overlapping sections with a pitch of 1.5:1 using a 12-cm field of view, generating segmented axial images of 1.5-mm thickness. Images were transferred to an independent workstation (Advantage Windows, GE Medical Systems) for postprocessing.

Carotid endarterectomy was performed by experienced neurovascular surgeons (A.D.M., D.L.), and the surgical plaque specimen in each case was sent for histological analysis.

Specimens were received in 4% formaldehyde and fixed and decalcified in Gooding’s and Stewart’s solution. After washing, the specimens were dissected, and 5-µm-thick paraffin sections were obtained at 5-mm intervals. Sections were selected in each of the following 3 sites in each patient: through the distal common carotid artery 5 mm below the bifurcation, through the carotid bulb, and through the proximal internal carotid artery 5 mm above the bulb. These sections were stained with hematoxylin and eosin and with Martius scarlet blue. Each section was examined by a single experienced pathologist. The thickness of the lipid core and fibrosis was graded in thirds, from 0 (none present) to 3 (full thickness). Fibrous tissue was defined by the demonstration of connective tissue matrix, including collagen, elastic fiber, and proteoglycans. Lipid core was defined by the presence of a disorganized mass of lipid material, cholesterol clefts, cellular debris, and lipid-laden foam macrophages. Each section was also scored for the presence or absence of ulceration, defined by fissuring of the fibrous cap. This definition allowed the differentiation of ulceration from surgical or contamination by voxels containing calcium or contrast. Each section was also scored for the presence or absence of hemorrhage and inflammatory infiltrate. Representative samples are given in Figures 1 and 2. Calciﬁcation was not scored because the specimens were routinely decalcified during processing to optimize the standard of the sections obtained. All specimens included in the study had been removed in 1 piece. Fragmented specimens in which it was difficult to identify the carotid bifurcation were excluded from the study. A minor degree of longitudinal specimen shrinkage may have occurred as a result of processing, but this is unlikely to have been significant because of the poor state of hydration present within atheromatous material.

Axial CT images were subsequently analyzed on the independent workstation by an experienced radiologist blinded to the previous radiological report and clinical history. Axial sections were selected at 3 levels corresponding to the same levels chosen for histological analysis (5 mm below the bifurcation, through the carotid bulb, and 5 mm above the bulb). This process was performed with the radiologist blinded to the corresponding histological findings.

The attenuation in Hounsﬁeld units (HU) was measured by use of a circular or elliptical region of interest cursor in the predominant area of plaque at each level. In each case, the cursor was placed in the center of the atheromatous plaque, with care taken to avoid contamination by voxels containing calcium or contrast. Each section was also scored for the presence or otherwise of plaque ulceration, defined by the observation of extension of contrast beyond the vascular lumen into surrounding plaque. A representative section is shown in Figure 3.

Exploratory analysis of the HU data was performed for each histopathological factor, and 2-sample t tests were performed to determine the difference in HU level in the absence and presence of each factor. One-way analysis of variance (ANOVA) was performed to determine the link between the grading of each pathological factor and the HU level. An attempt was made to ﬁt a multiple linear regression model to the data.

The correlation between the identiﬁcation of ulceration on CT angiography and histopathological examination was determined with 2×2 contingency tables. Respective sensitivities, speciﬁcities, and negative and positive predictive values were calculated, with signiﬁcance determined with a Pearson χ² test statistic.

All analyses were performed with Minitab 12 for Windows (Minitab Inc).

Results
Two patients had staged bilateral endarterectomy. Two specimens were unsuitable for pathological analysis because of excessive fragility, resulting in 55 carotid specimens and 165 pathology sections available for pathological examination.
On 20 axial CT images, it was not possible to determine representative HU numbers because of the presence of excessive calcification or the absence of significant plaque, leaving 145 axial sections for exploratory analysis. Figure 4 shows the distribution of the HU data. The mean value was 60, with an SD of 26.6. No significant heterogeneity in HU number within individual plaques was found. One-way ANOVA testing demonstrated a significant decrease in the mean HU number as the amount of lipid increased, as demonstrated in Figure 5. However, the spread of data was very high. No relation between the HU number and the amount of fibrous tissue present was found.

The Table shows the results of multiple 2-sample t tests on the mean HU number for the absence and presence of each pathological factor. No entry is presented for the lipid core because all plaques had demonstrable lipid. Ulceration showed a significant difference between the mean values, with an increased incidence of ulceration associated with decreasing plaque density. No difference in the mean plaque density values was found for hemorrhage or inflammatory infiltrate. No significant multiple regression model could be fitted to the data.

The 2×2 contingency tables for the CT detection of plaque ulceration demonstrated a sensitivity of 60% and a specificity of 74%. The Pearson χ² test statistic for ulceration was 19.0 on 1 df, with significant probability (P<0.0001).

Discussion
It is widely recognized that plaque composition and surface morphology may have an important influence in determining the clinical significance of carotid atherosclerotic disease, and considerable work has been published in an attempt to characterize carotid plaque composition with a variety of imaging techniques. There is, however, no clear consensus regarding the optimal imaging strategy for the analysis of carotid plaque morphology.

Catheter angiography is widely accepted as the gold standard for the demonstration of carotid artery disease, but its ability to detect ulceration is relatively poor. For example, in one large series, catheter angiography had a sensitivity of 46% and a specificity of 74% for the detection of ulceration. No evaluation of plaque composition is possible with catheter angiography. In addition, catheter angiography has a well-established complication rate, is time and cost intensive, and is being widely supplanted by noninvasive imaging techniques.

Ultrasound has been used extensively for the analysis of plaque morphology. Several classification systems have been used to grade the composition of carotid plaque. However, there are several problems with this approach. For instance, the classification systems used are generally qualitative, without a defined objective standard. The computerized method described by El-Barghouty et al overcomes this problem to some extent but is not available outside large research centers. This subjectivity results in a large amount of interobserver and intraobserver error, which significantly impairs the reliability and reproducibility of ultrasound.

MR imaging has been described in the assessment of carotid plaque composition and morphology, and this is an...
Two-Sample t Tests for Each Histopathological Factor

<table>
<thead>
<tr>
<th>Factor</th>
<th>Present</th>
<th>HU</th>
<th>n</th>
<th>SD</th>
<th>SEM</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>Yes</td>
<td>61.7</td>
<td>88</td>
<td>29.2</td>
<td>3.1</td>
<td>-1.06</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>57.2</td>
<td>57</td>
<td>22.0</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Yes</td>
<td>59.7</td>
<td>133</td>
<td>27.0</td>
<td>2.3</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>62.4</td>
<td>12</td>
<td>22.6</td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td>Yes</td>
<td>54.0</td>
<td>53</td>
<td>18.6</td>
<td>2.5</td>
<td>2.33</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>63.4</td>
<td>92</td>
<td>29.8</td>
<td>3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>Yes</td>
<td>61.9</td>
<td>88</td>
<td>30.4</td>
<td>3.2</td>
<td>-1.22</td>
<td>NS</td>
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<tr>
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<td>56.9</td>
<td>57</td>
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</tr>
</tbody>
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active field of current research at many research centers.\textsuperscript{17,30–33} MR imaging of the coronary vessel wall and associated atheromatous plaque is relatively well established,\textsuperscript{31} and MR has subsequently been reported for the characterization of carotid plaque ex vivo\textsuperscript{32} and in vivo.\textsuperscript{33} The technology required for such imaging is becoming increasingly available outside major research centers. An important issue remains the lack of standardization between different centers in terms of scanner platform, sequence protocol, and coil design. In addition, there are significant difficulties in the definition of carotid plaque, including vessel wall pulsatility and limited patient toleration.

CT has been suggested as a possible means of characterizing carotid plaque.\textsuperscript{15,22,23} Spiral CT scanners are widely available, and CT angiography theoretically provides a semi-objective, quantitative, and potentially reproducible technique for the evaluation of carotid plaque. CT angiography has well-defined diagnostic accuracy in the detection of high-grade stenoses and is increasingly proposed as an alternative to MR angiography for the demonstration of carotid disease. The more widespread use of the technique has led to its proposal as a method for plaque evaluation, and a small number of preliminary studies have been performed to define its value in this area. For example, studies by Estes et al\textsuperscript{23} and Oliver et al\textsuperscript{22} in relatively small numbers of patients have suggested a role for CT in the differentiation of fibrous stroma and lipid-rich areas within plaques. Similarly, Cinat and coworkers\textsuperscript{15} have proposed a role for CT in the identification of plaque ulceration. The present article represents the largest study in world literature analyzing the efficacy of CT for the characterization of carotid plaque.

Our study confirms that there is a trend toward lower attenuation values as the amount of intraplaque lipid increases. This observation supports the suggestion that low-density plaques are more likely to be lipid rich. This result is not unexpected when we consider that fat has a much lower range of Hounsfield attenuation compared with fibrous tissue. However, the spread of data severely limits the reliability of individual Hounsfield readings as an indicator of plaque lipid. Our findings also indicate that plaque density on single-slice CT cannot be used to indicate the amount of fibrous tissue present.

The poor reliability of HU measurements for the prediction of the amount of lipid or fibrous tissue within an individual plaque may be explained at least partly by the great heterogeneity observed on histological examination of individual plaques. It became clear that the relatively homogeneous appearance of plaque on CT imaging did not adequately represent the plaque heterogeneity that was evident on microscopic analysis, as evident in Figure 1. As a result of these findings, we conclude that single-slice spiral CT angiography cannot be used to differentiate between fatty and fibrous plaques with any degree of certainty.

CT angiography did not prove useful in the detection of hemorrhage or inflammatory infiltrate. Interestingly, a correlation was demonstrated between the presence of ulceration at histopathological examination and low-density plaques. This observation may be explained by an increased incidence of fissured fibrous caps in plaques with a high lipid content.

Plaque ulceration was detected with an accuracy equivalent to that reported in other studies with catheter angiography.\textsuperscript{5,14} However, the predictive value of CT angiography for the detection of ulceration remains moderate, and this observation significantly limits the usefulness of this technique in this area. This probably relates to the slice thickness (1.5 mm) obtained with CT imaging at our institution, which will inevitably reduce the sensitivity for small fissures or areas of denuded or broken fibrous cap visible on the fine sections obtained with histopathological processing.

CT angiography is of known value in determining the degree of carotid stenosis. However, we believe that at present there are significant limitations to the application of single-slice spiral CT for the characterization of plaque morphology and composition. Studies using multidetector technology and thinner axial sections are necessary to further evaluate the role of CT angiography in the characterization of carotid atheromatous plaque.

References


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