Association Between Carotid Artery Plaque Ulceration and Plaque Composition Evaluated With Multidetector CT Angiography

Philip J. Homburg, MD*; Sietske Rozie, MD*; Marjon J. van Gils, MD; Quirijn J.A. van den Bouwhuijsen, MD; Wiro J. Niessen, PhD; Diederik W.J. Dippel, MD, PhD; Aad van der Lugt, MD, PhD

Background and Purpose—Symptomatic carotid artery plaque ulceration is associated with distinct plaque components such as a large lipid-rich necrotic core (LR-NC) in ischemic stroke patients with a ≥50% carotid stenosis. We evaluated the associations between carotid artery plaque ulceration and plaque characteristics in ischemic stroke patients with ≥50% stenosis, as well as in those with a low degree of stenosis (0% to 49%).

Methods—Consecutive patients (n=346) with symptoms in the anterior circulation were evaluated with multidetector CT angiography (MDCTA) for the presence of atherosclerotic plaque, degree of stenosis, and plaque ulceration in the symptomatic carotid artery. Plaque volume and plaque component proportions of LR-NC, fibrous tissue, and calcification were measured. The associations between plaque ulceration and plaque characteristics were analyzed using logistic regression.

Results—Atherosclerotic plaque was present in 185 patients. Plaque ulcerations were present in 38 (21%) patients, of which half had a low degree stenosis (0% to 49%). Plaque volume was significantly larger in ulcerated plaques. After adjustment for age, sex, and degree of stenosis, LR-NC proportion was strongly associated with plaque ulceration (odds ratio, 2.21; 95% CI, 1.49 to 3.27), whereas calcification proportion was inversely associated with plaque ulceration (odds ratio, 0.60; 95% CI, 0.40 to 0.89). These associations remained significant in patients with a low degree stenosis (0% to 49%).

Conclusion—Plaque volume, degree of stenosis, and LR-NC proportion evaluated noninvasively with MDCTA are associated with carotid artery plaque ulceration, even in patients with a low degree stenosis (0% to 49%). Plaque volume and composition analysis with MDCTA may identify rupture prone plaques and improve risk stratification in ischemic stroke patients. (Stroke. 2011;42:367-372.)

Key Words: atherosclerosis ■ atherosclerotic plaque composition ■ carotid artery ■ CT ■ ulceration

Atherosclerotic carotid plaque ulceration is an independent marker of previous plaque rupture and an influential predictor of ischemic stroke.1,2 Thus far, histological and noninvasive imaging assessment of the relationship of carotid plaque characteristics with plaque surface disruption has been limited to patients with a ≥50% carotid stenosis.3,4 In patients with severe symptomatic stenosis, carotid plaque ulceration has been associated with the presence of fibrous cap rupture and distinct plaque components such as intraplaque hemorrhage, large lipid core, and less fibrous tissue.3 However, a ≥50% carotid stenosis is present in only ~10% of patients with amaurosis fugax, transient ischemic attack, or minor ischemic stroke.5 Whereas two-thirds of carotid plaque ulcerations is observed in carotid arteries with a low degree stenosis (0% to 49%),6 little is known about the relation between carotid plaque characteristics with plaque ulceration in these patients. Also, limited data are available on the association between plaque volume and carotid plaque surface disruption.4

Analysis of atherosclerotic plaque volume and plaque composition using noninvasive imaging could be useful to identify rupture prone plaques. However, concomitant assessment of carotid plaque characteristics associated with plaque rupture cannot be advocated in the general population of ischemic stroke patients without knowledge of the relationship between plaque characteristics and plaque surface disruption.

In the present study, we analyzed the relationship between the symptomatic carotid plaque characteristics, comprising of plaque component proportions and plaque volume, with plaque ulceration in consecutive patients with amaurosis fugax, transient ischemic attack, or ischemic stroke using multidetector CT angiography (MDCTA). The analysis included and compared the associations of plaque characteris-
tics with plaque ulceration in symptomatic carotid arteries with significant stenosis (≥50%), as well as in those with a low degree stenosis (0% to 49%).

Methods

Study Population
From a prospective registry of 911 consenting patients with amaurosis fugax, transient ischemic attack, or ischemic stroke (Rankin score, <4) who underwent MDCTA of the carotid arteries, we selected a 2-year cohort of consecutive patients (n=346) with symptoms in the anterior circulation. Patients were enrolled from a specialized transient ischemic attack/stroke outpatient clinic or the neurology ward. All patients underwent an interview, neurological examination, electrocardiography, laboratory analysis, and MDCTA on admission. Medical history and cardiovascular risk factors, as defined previously,7 were recorded. Patients without atherosclerotic plaque (n=137), with carotid occlusion (n=20), and with an MDCTA of insufficient quality (n=4) were excluded from the analysis.

MDCTA Data Acquisition and Data Analysis
Imaging was performed with a 16-slice MDCT scanner (Sensation 16, Siemens, Erlangen, Germany) or a 64-slice MDCT scanner (Sensation 64, Siemens, Erlangen, Germany) with a standardized optimized contrast-enhanced protocol (120 kVp, 180 mAs, collimation 16×0.75 mm or 64×0.6 mm, pitch ≤1).8 Details of the MDCTA scan protocol have been described previously.7,9 MDCTA images were sent to a stand-alone workstation (Leonardo, Siemens Medical Solutions, Forchheim, Germany) with dedicated 3D analysis software. The symptomatic carotid bifurcation was evaluated by 2 experienced investigators blinded to clinical data with multiplanar reformatting software, which allows reconstruction of sagittal, coronal, and oblique views from axial sections. Discrepancies were solved by consensus.

Symptomatic carotid arteries were evaluated for the presence of atherosclerotic plaque, defined as thickening of the vessel wall or the presence of calcification. Plaque ulceration was defined as extension of contrast media beyond the vascular lumen into the surrounding plaque. Degree of stenosis in the symptomatic carotid artery was determined according to the NASCET criteria10 on multiplanar reformating images perpendicular to the central lumen line.

Plaque volume and plaque component proportions were measured with custom-made software, programmed in MeVisLab (MeVis Medical Solutions, Bremen, Germany). Using this software, the components of the atherosclerotic plaque within regions of interest drawn on axial MDCTA images can be determined from their corresponding Hounsfield values using thresholds determined previously.11 The threshold for the distinction between fibrous tissue and lipid-rich necrotic core (LR-NC) was set at 60 Hounsfield units. The threshold for distinguishing calcifications from fibrous tissue was set at 130 Hounsfield units; the value currently used for calcium scoring. Based on previous studies, it may be assumed that intraplaque hemorrhage, if present, would be classified as LR-NC11 or fibrous tissue.12 Plaque volume and plaque component volumes were automatically calculated from the number and dimensions of voxels for different ranges of Hounsfield unit values within the regions of interest (Figure 1). Plaque component proportions were calculated from plaque component volumes as a percentage of the plaque volume.

Statistical Analysis
Baseline population and plaque characteristics are presented as means±SD or number of patients (%). Differences were tested with χ² tests, Fisher exact tests, or Mann–Whitney tests when appropriate. For logistic regression analysis, continuous data were divided by 10 or 100, as indicated in the relevant tables. The correlation between degree of stenosis and plaque volume was evaluated by calculation of the Spearman rank correlation coefficient. The associations between carotid plaque ulceration and degree of stenosis, plaque volume, and plaque component proportions were evaluated using logistic regression analysis. Two models were constructed. In model I, plaque characteristics were adjusted for age and sex. In model II, adjustments were made for age, sex, and degree of stenosis. Finally, in a stratified analysis, the associations between carotid plaque ulceration and plaque characteristics were evaluated in patients with low (0% to 49%), and with significant (≥50%) carotid stenosis, with adjustment for age, sex, and degree of stenosis. Probability values of ≤0.05 were considered statistically significant. All analyses were performed using SPSS 15.0 statistical package for Windows (SPSS Inc, Chicago, IL).

Results

Patients Characteristics
From the 346 evaluated patients, 185 patients with atherosclerotic plaque were included in all further analyses. Baseline characteristics of patients with and without atherosclerotic plaque ulceration in the symptomatic carotid artery are illustrated in Table 1. Atherosclerotic plaque ulceration in the symptomatic carotid artery was present in 38 (21%) patients. The prevalence of cardiovascular risk factors was not significantly different between the 2 groups.

Plaque Characteristics on MDCTA
Atherosclerotic plaque characteristics of patients with and without atherosclerotic plaque ulceration in the symptomatic carotid artery are illustrated in Table 2. Degree of stenosis was significantly higher in patients with plaque ulceration. In patients with carotid artery ulcerations, 19 had 0% to 49% stenosis, whereas the remaining 19 patients had ≥50% stenosis (Figure 2).

Plaque volume of ulcerated plaques was significantly larger as compared with nonulcerated plaques. A moderate correlation was observed between degree of stenosis and plaque volume (r=0.57; P=0.01). Ulcerated plaques contained a significantly larger LR-NC volume, fibrous tissue
volume, and LR-NC proportion. Fibrous tissue proportion was significantly lower in ulcerated plaques as compared with nonulcerated plaques.

### Plaque Characteristics Associated With Plaque Ulceration on MDCTA

Results of multivariable analyses relating plaque characteristics and plaque ulceration are provided in Tables 3 and 4. After adjustment for age and sex (model I), degree of stenosis, plaque volume, and the LR-NC proportion were associated with plaque ulceration, whereas fibrous proportion was inversely associated with plaque ulceration. After adjustment for age, sex, and degree of stenosis (model II), plaque volume and the LR-NC proportion remained significantly associated with plaque ulceration, whereas the calcification proportion was inversely associated with plaque ulceration. In a stratified analysis of patients with a low degree stenosis of 0% to 49% (n=144), the LR-NC proportion remained strongly associated with plaque ulceration, whereas the calcification proportion remained inversely associated with plaque ulceration. In patients with significant stenosis of ≥50% (n=41), plaque volume was associated with plaque ulceration, whereas a trend toward a significant association between the LR-NC proportion and plaque ulceration was observed.

### Discussion

In the present study of patients with amaurosis fugax, transient ischemic attack, or ischemic stroke, half of the plaque ulcerations were identified in symptomatic carotid arteries with a low degree stenosis of 0% to 49%. Noninvasive carotid artery plaque analysis with MDCTA revealed that degree of stenosis, plaque volume, and the LR-NC proportion were associated with plaque ulceration in the symptomatic carotid artery. Of these plaque characteristics, the LR-NC proportion was most strongly associated with plaque ulceration. In contrast, the calcification proportion was inversely associated with plaque ulceration. The observed associations remained significant in patients with a low degree carotid stenosis of 0% to 49%. The present study

### Table 1. Characteristics of Patients With and Without Symptomatic Carotid Artery Plaque Ulceration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Plaque Ulceration (n=38; 21%)</th>
<th>Patients Without Plaque Ulceration (n=147; 79%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67±10</td>
<td>67±11</td>
<td>0.74</td>
</tr>
<tr>
<td>Male sex</td>
<td>28 (74%)</td>
<td>93 (63%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>28 (74%)</td>
<td>124 (84%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (71%)</td>
<td>120 (82%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (11%)</td>
<td>30 (20%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Smoking</td>
<td>17 (45%)</td>
<td>45 (31%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>4 (11%)</td>
<td>15 (10%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>7 (18%)</td>
<td>19 (13%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Previous transient ischemic attack</td>
<td>8 (21%)</td>
<td>27 (18%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Previous intracerebral hematoma</td>
<td>2 (5%)</td>
<td>2 (1%)</td>
<td>0.19</td>
</tr>
<tr>
<td>History of ischemic heart disease</td>
<td>7 (18%)</td>
<td>42 (29%)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Data are nos. (percentage) or means±SD.

### Table 2. Plaque Characteristics of Patients With and Without Symptomatic Carotid Artery Plaque Ulceration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Plaque Ulceration (n=38; 21%)</th>
<th>Patients Without Plaque Ulceration (n=147; 79%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of stenosis</td>
<td>44±29%</td>
<td>18±27%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque volume</td>
<td>1320±708 mm³</td>
<td>765±588 mm³</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LR-NC volume</td>
<td>416±283 mm³</td>
<td>168±197 mm³</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrous volume</td>
<td>736±333 mm³</td>
<td>468±306 mm³</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcification volume</td>
<td>163±178 mm³</td>
<td>129±180 mm³</td>
<td>0.196</td>
</tr>
<tr>
<td>LR-NC proportion</td>
<td>29±10%</td>
<td>18±10%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrous proportion</td>
<td>60±11%</td>
<td>67±13%</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcification proportion</td>
<td>10±9%</td>
<td>15±14%</td>
<td>0.152</td>
</tr>
</tbody>
</table>

Data are means±SD.
is the first to evaluate the associations between plaque ulceration and plaque characteristics irrespective of the degree of stenosis.

**Association of Atherosclerotic Plaque Characteristics With Ischemic Stroke**

Several studies have evaluated the relationship of carotid artery plaque characteristics with ischemic stroke. In general, imaging studies with magnetic resonance and CT have identified positive associations between fibrous cap thickness, the size of the LR-NC, intraplaque hemorrhage and the presence of carotid plaque surface disruption with ischemic stroke in cross-sectional and follow-up studies. Accordingly, in ultrasound studies, echolucent carotid plaques were associated with increased risk of cerebrovascular events. Echolucent plaques are known to have higher levels of lipid and hemorrhage compared with echogenic plaques, which contain more calcification and fibrous tissue. On the contrary, proportion of carotid plaque calcification is shown to be inversely associated with the occurrence of ischemic stroke. However, results of histological analyses have been less consistent. A review by Golledge et al demonstrated the lack of an association between histologically defined LR-NC and intraplaque hemorrhage with ischemic stroke.

The observed discrepancy may be a consequence of disparate etiology of ischemic stroke. Nevertheless, plaque rupture and subsequent thromboembolism are considered crucial elements in the pathophysiological cascade between the development of a heterogeneous plaque and thromboembolic stroke. As a result, in the present study, we evaluated the direct associations between plaque characteristics comprising plaque stenosis, plaque volume, and composition with plaque ulceration in patients with ischemic stroke.

**Table 3. Multivariable Analysis for the Associations Between Symptomatic Carotid Artery Plaque Ulceration and Plaque Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of stenosis (/10%)</td>
<td>1.33 (1.18–1.50)</td>
<td>&lt;0.001</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Plaque volume (/100 mm³)</td>
<td>1.14 (1.07–1.21)</td>
<td>&lt;0.001</td>
<td>1.09 (1.02–1.16)</td>
<td>0.01</td>
</tr>
<tr>
<td>LR-NC proportion (/10%)</td>
<td>2.58 (1.77–3.78)</td>
<td>&lt;0.001</td>
<td>2.21 (1.49–3.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrous proportion (/10%)</td>
<td>0.64 (0.48–0.87)</td>
<td>0.004</td>
<td>0.85 (0.60–1.20)</td>
<td>0.35</td>
</tr>
<tr>
<td>Calcification proportion (/10%)</td>
<td>0.75 (0.54–1.04)</td>
<td>0.08</td>
<td>0.60 (0.40–0.89)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

NA indicates not available; OR, odds ratio.

**Association of Atherosclerotic Plaque Characteristics With Carotid Plaque Surface Disruption**

Previous research relating atherosclerotic carotid plaque characteristics with plaque surface disruption has focused on stenotic plaques corresponding with luminal narrowing of ≥50%. In a magnetic resonance study, the LR-NC proportion of carotid plaques of ≥50% stenosis was the strongest predictor of new surface disruption, in form of an ulceration or a fibrous cap rupture. In that particular study, the calcification proportion was inversely related with plaque surface disruption. In addition, the presence of intraplaque hemorrhage as assessed with magnetic resonance is significantly associated with the presence of plaque ulceration on MDCTA. Plaque ulceration on conventional angiography in symptomatic carotid arteries with ≥50% stenosis was associated with the presence of intraplaque hemorrhage, large lipid core, and less fibrous tissue in carotid endarterectomy specimens. Similarly, ultrasonographic examination of carotid arteries demonstrated a relationship between echolucency of stenotic plaques and plaque ulceration. However, conventional angiography and ultrasound provide no quantitative information on plaque volume. Therefore, only limited data are available on the relationship of plaque volume with plaque surface disruption as assessed using magnetic resonance.

MDCTA allows for fast and reliable evaluation of stenotic disease in extracranial and intracranial arteries and is widely available. The technique is effective in the detection of carotid plaque ulceration with a sensitivity and specificity of 94% and 99%, respectively. Furthermore, distinct plaque components, as well as plaque volume, can be quantified in good correlation with histology. In the present study, using MDCTA, the relationship between

**Table 4. Stratified Multivariable Analysis for the Associations Between Symptomatic Carotid Artery Plaque Ulceration and Plaque Characteristics in Patients With Low (0–49%) and With Significant (≥50%) Carotid Stenosis**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque volume (/100 mm³)</td>
<td>1.06 (0.98–1.14)</td>
<td>0.15</td>
<td>1.23 (1.04–1.46)</td>
<td>0.02</td>
</tr>
<tr>
<td>LR-NC proportion (/10%)</td>
<td>3.04 (1.70–5.45)</td>
<td>&lt;0.001</td>
<td>1.82 (0.98–3.40)</td>
<td>0.06</td>
</tr>
<tr>
<td>Fibrous proportion (/10%)</td>
<td>0.88 (0.57–1.36)</td>
<td>0.56</td>
<td>1.05 (0.53–2.08)</td>
<td>0.89</td>
</tr>
<tr>
<td>Calcification proportion (/10%)</td>
<td>0.34 (0.16–0.69)</td>
<td>0.003</td>
<td>0.68 (0.40–1.15)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.
plaque composition and plaque volume with plaque ulceration was evaluated in patients with a symptomatic carotid stenosis of ≥50% as well as in patients with a low degree of stenosis (0% to 49%). Interestingly, in line with previous reports, a substantial proportion of the plaque ulcerations were located in symptomatic carotid arteries with a low degree of stenosis. The association between the LR-NC proportion with plaque ulceration was significant in ischemic stroke patients with a low degree of stenosis (0% to 49%), whereas a trend toward significance was observed in patients with a stenosis of ≥50%. The inverse association observed between the calcification proportion and plaque ulceration was significant in patients with a low degree stenosis. Furthermore, only a weak correlation was observed between the degree of carotid artery stenosis and plaque volume on MDCTA. Importantly, plaque volume was associated with plaque ulceration, even after adjustment for the severity of stenosis. Overall, these findings demonstrate that the associations between plaque composition and volume with plaque ulcerations are present in ischemic stroke patients irrespective of the degree of the carotid plaque stenosis. In addition, an etiologic explanation is provided for the previously observed correlation of plaque characteristics with ischemic stroke events. Herein, a key role is suggested for plaque ulceration in the pathophysiologic cascade between the development of a heterogeneous plaque and thromboembolic stroke. As a consequence, apart from degree of stenosis, assessment of carotid plaque composition and volume that predisposes ulceration could contribute to risk stratification for plaque instability or stroke recurrence.

Study Limitations
First, the study has a cross-sectional design. Indeed, the prognostic value of plaque composition analysis with MDCTA and, more specifically, of the LR-NC proportion for the development of plaque ulceration and subsequent thromboembolic ischemic stroke should be confirmed in longitudinal serial imaging studies. Second, in the present study, the presence of intraplaque hemorrhage was not evaluated because plaque composition analysis software used in the present study has not been validated for differentiation of intraplaque hemorrhage. As a result, both LR-NC and fibrous tissue assessed with MDCTA may contain intraplaque hemorrhage if present in the plaque. Finally, plaque composition analysis can be performed on routine MDCTA scans used for carotid stenosis evaluation. Nevertheless, every MDCTA leads to ionizing radiation exposure. Therefore, repeated examinations should not be advocated.

Clinical and Research Implications
To our knowledge, the present study is the first to examine the associations between carotid plaque characteristics and carotid plaque ulceration in ischemic stroke patients with a ≥50% stenosis, as well as in those with a low degree stenosis of 0% to 49%. The LR-NC proportion was identified as the strongest determinant for plaque ulceration. The association between the LR-NC proportion and carotid plaque ulceration was independent of the degree of stenosis. Plaque composition analysis with MDCTA may prove useful for detection of rupture-prone plaques and could potentially improve risk stratification in ischemic stroke patients.

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Disclosures
None.

References


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Abstract

多発出血性CT血管造影によって評価した頭動脈プラック隆発形とプラック組成との関連

Association Between Carotid Artery Plaque Ulceration and Plaque Composition Evaluated With Multidetector CT Angiography

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背景および目的：複数の頭動脈プラック隆発形は、頭動脈硬化症を50%以上の虚血性脳卒中患者にみられる脳卒中と深い関係にある。今回は、頭動脈プラック隆発形の有無とその程度を評価できるCT血管造影（MDCTA）を用いて、頭動脈内の大動脈硬化性プラックの有無、形状、広がり、形状によるプラック隆発形の評価を行った。結果：プラック隆発形とグラックの形状、広がり、形状によるプラックの特徴と関連性を検討した。結果：186例に動脈硬化性プラックが認められた。22例（21%）にプラック隆発形が認められ、このうち半分は狭窄度が低かった（0～49%）。隆発形化したプラックはプラック体積が有意に大きかった。性別、統計のため補正を行った結果、L.R.-NCの比率とプラック隆発形は強い関連性が認められた（オッズ比=2.21, 95% CI: 1.49 ～ 3.37）。一方で、石灰化の比率とプラック隆発形の間には負の関連が認められた（オッズ比=0.60, 95% CI: 0.40 ～ 0.89）。これらの関連は統計的に有意であった。

結論：MDCTAを用いて非侵襲的に評価したプラック体積、形状、L.R.-NCの比率と、頭動脈プラック隆発形の間には関連があり、この関連は統計的に有意（0～49%）患者でも変わらない。MDCTAを用いてプラック体積およびプラック隆発形を評価すれば、頭動脈プラックの脈絡を改善することが可能であり、虚血性脳卒中患者のリスク要因が向上する可能性がある。