Carotid plaque vulnerability: the correlation of plaque components as quantified based on Computed Tomography Angiography with neurologic symptoms.

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Aims and objectives

Carotid atherosclerotic disease is a well-known cause of transient ischemic attack (TIA) and stroke and its diagnosis and grading primarily relies on imaging, including virtually every imaging modality from ultrasound (US) to cross-sectional imaging with computed tomography angiography (CTA) or magnetic resonance angiography (MRA). The degree of internal carotid artery stenosis has been traditionally regarded as the primary determinant for the risk of neurovascular symptoms and the main criterion for defining optimal treatment of patients with carotid disease. Nevertheless, the recent literature has made it clear that features of the plaque other than the degree of stenosis also contribute to the plaque's potential for symptoms, thus introducing the term "vulnerable plaque" to describe these plaques. Such features include surface morphology, intraplaque neovascularization and plaque composition [1-5].

In terms of composition, atherosclerotic plaques contain different components such as fatty tissue, calcification, intraplaque hemorrhage, and fibrous tissue. This feature has been found to be associated with the risk for stroke and can be studied with every imaging modality. CTA has the capability to assess plaque composition using density analysis and measurements in Hounsfield Units (HU). Based on this method, plaques can be characterized as fatty when their density is lower than 60 HU, mixed if density is between 60 and 130 HU and calcified if density is higher than 130 HU. Studies have shown that fatty plaques are characterized by increased risk for stroke while calcified ones are associated with a lower risk [4, 6, 7, 8]. Nevertheless, it is known that plaque characterization with CTA can be limited by technical artifacts such as blooming artifact. As a result, new technological advances have been introduced into applications commercially available in an attempt to overcome these limitations. The application used in this study has been previously used in publications and has already provided promising results in the characterization of carotid plaque components [9, 10].

The purpose of this study was to investigate the correlation of carotid plaque composition as evaluated and quantified with computed tomography angiography (CTA) and the use of a specialized commercially available software with the occurrence of neurologic symptoms in patients with carotid atherosclerotic disease.
Methods and materials

Patient population

The present study was observational and the patients studied were recruited on a prospective and consecutive pattern from the Radiology and Neurology Department of the Hospital. Institutional ethics review board approval and written informed consent from every patient were obtained. Patients who were considered candidates for inclusion in the study were all those referred for carotid CTA after being diagnosed with carotid atherosclerotic disease on US, either being symptomatic or asymptomatic based on clinical examination and brain imaging. The cause of referral could either be the occurrence of transient ischemic attack or stroke (symptomatic patients) or other unrelated conditions (such as pre-operative work-up in asymptomatic patients). Both carotid systems of every patient were included in the study and analyzed separately. A plaque was considered symptomatic if ipsilateral to a stroke occurring during the last six-month period or asymptomatic if located on the contralateral side or ipsilateral to the side of stroke but after the six-month period. For a plaque to be considered symptomatic, a stroke needed to be diagnosed on brain imaging with magnetic resonance imaging (MRI). The primary inclusion criterion was the identification of an internal carotid artery plaque with moderate (50-69%) or severe (70-99%) stenosis as CTA is only performed if such a plaque is detected on US, based on the Radiology Department's standard of care. Exclusion criteria used in this study included any contra-indication to the use of CTA contrast agents like history of allergy as well as presence of other diseases mimicking stroke or comorbidities that could cause stroke (including arrhythmias, cardiac anatomic abnormalities, thrombophilia and immunologic diseases like antiphospholipid syndrome). These comorbidities were excluded in an attempt to accurately associate the stroke with carotid disease. If a patient fulfilled the inclusion criteria and had no exclusion criteria, his CTA examination was exported in digital imaging and communications in medicine (DICOM) format and was used for quantitative analysis with the specialized software in a computer.

Imaging technique

CTA examinations were performed with a 128-slice multi-detector CT system (GE Optima CT660, GE Healthcare), both with an unenhanced scan and an angiographic scan. The scan range covered the area from the ascending aorta and up to the intracranial arteries, at the level of the frontal sinuses. Eighty milliliters of contrast agent (37% iodine, iopromide, Ultravist, Bayer) were intravenously administered in a bolus followed by 50 ml of saline bolus chaser, both administered at an injection rate of 4 ml/s. Real-time bolus tracking was performed at the level of the ascending aorta and used in order to
synchronize contrast passage with the angiographic data acquisition. The slice thickness of the images reviewed was 0.625 mm for optimal isotropic imaging.

**Image analysis**

Commercially available imaging analysis software (vascuCAP™, Elucid Bioimaging) has been used for the quantification of carotid plaque components. One board-certified radiologist with 10 years of experience on carotid CTA was specifically trained for the use of this software and performed the quantitative analysis. The reader initially defined the common, internal and external carotid artery. A center-line was then computed by the software and lumen and outer wall segmentation were performed. Blooming artifact, blurring of the image and partial volume effects are well-established factors limiting the accuracy of CTA measurements of plaque density. The process is further complicated by the fact that density may vary even within areas of the same tissue type, also depending on contrast agent uptake. The software used in this study makes use of previously described and tested algorithms which are histology-validated and mitigate known limitations of blurring, calcium blooming, partial volume effects of routine CTA acquisitions and overly strict dependence on HU thresholds. These algorithms have been previously described in detail [9, 10]. After computation of vessel center-line and segmentation of lumen and wall, the software determines the scanner blur based on the lumen boundary and can thus optimize component densities evaluated at subvoxel boundaries in an attempt to best fit the presented image. After initial segmentation of wall and plaque components, the reader had the opportunity to manually edit the automated results using the software’s interactive tools, if necessary. The plaque components whose volume was quantified using this software included: lipid core, fibrous matrix and calcification. Both absolute and relative volumes were calculated, with the latter being calculated by dividing absolute values by the sum of all absolute values. The ratio of lipid and calcification (plus one) volume (L/C) was also calculated. The degree of diametric internal carotid artery stenosis was manually measured using the European Carotid Surgery Trial (ECST) method.

**Statistical analysis**

The IBM SPSS Statistics version 23.0 was used for statistical analysis. Descriptive statistics included mean and standard deviation (SD) for normally distributed variables and median and inter-quartile range (IQR) for non-normally distributed variables. The Kolmogorov-Smirnov test was used to test the normal distribution of variables. Mann-Whitney U test and t-test were used to compare means between groups depending on the normality of distribution. Receiver Operating Characteristic (ROC) analysis was
used for diagnostic accuracy analysis for the detection of symptomatic plaque. Statistical significance level was set at 0.05.
Results

In total 54 patients (67.7% male, 32.3% female, median age of patients: 61 years) and 65 internal carotid artery plaques were included in this study. Diametric stenosis of the internal carotid artery (based on ECST criteria) was significantly higher in symptomatic plaques (median 74.8% vs 66.6%, p<0.01). Regarding plaque composition analysis, symptomatic plaques were found to have significantly higher lipid volume (median \( \text{mm}^3 \) 124.3 vs 64.4, p<0.01), relative lipid volume (median 10.87 vs 7, p=0.001), lower relative calcification volume (median 4.9 vs 8.2, p<0.05) and higher L/C ratio (1.7 vs 0.6, p=0.001) compared with asymptomatic. On the contrary, no statistically significant difference was detected between symptomatic and asymptomatic plaques for fibrous matrix and calcification volume, the sum of three components volume (lipid, fibrous matrix and calcification) and relative fibrous volume. The exact values of every variable and the statistical tests results can be found in Table 1 on page 9. The boxplots of these comparisons are presented in Fig. 1 on page 9. Based on these results, it appears that some plaque components are significantly associated with the occurrence of stroke, while others not.

On ROC analysis, the areas under the curve (AUC) of all these parameters were assessed and were as follows: stenosis (ECST) 0.724, lipid volume 0.697, calcification volume 0.379, fibrous matrix volume 0.533, total plaque volume 0.535, relative lipid volume 0.749, relative calcification volume 0.335, relative fibrous volume 0.432, ratio of lipid volume divided by calcification volume plus one 0.733. The three variables with the greatest AUC were: i) the relative lipid volume (0.749), followed by ii) L/C ratio (0.733) and iii) lipid volume (0.697). The 95% confidence intervals of ROC analysis can be found in Table 2 on page 10. The AUC of the variables can be found in Fig. 2 on page 11. Screening, optimal and diagnostic cut-off values were defined for the relative lipid volume, L/C ratio and lipid volume to achieve superior sensitivity, balanced sensitivity and specificity and superior specificity respectively. For lipid volume, the screening cut-off value was 19.75 \( \text{mm}^3 \) and the resulting sensitivity and specificity was 96.7% and 21.2% respectively. The optimal cut off value was 76.25 \( \text{mm}^3 \) and the respective values were 70% and 63.6%. The diagnostic cut-off value was 264.35 \( \text{mm}^3 \) and the respective measures were 16.7% and 97%. For relative lipid volume the screening, optimal and diagnostic cut-off values were 2.67 \( \text{mm}^3 \), 8.02 \( \text{mm}^3 \) and 15.65 \( \text{mm}^3 \) respectively. The respective resulting sensitivities and specificities are 96.7% and 21.2%, 70% and 72.7%, 33.3% and 97%. For L/C ratio the screening, optimal and diagnostic cut-off values were 0.36, 1.18 and 12.5 respectively. The respective resulting sensitivities and specificities are 96.7% and 27.3%, 70% and 69.7%, 20% and 97%.
Examples of cases analyzed with the software can be found in Fig. 3 on page 12, Fig. 4 on page 13, Fig. 5 on page 14, Fig. 6 on page 15.

The limitations of the study include the relatively small number of patients and carotid plaques examined as well as a potential spectrum bias as only plaques with moderate or severe stenosis have been recruited. Further studies are needed to confirm the value of this technology and investigate the implications of these results in terms of patient management.
**Table 1:** Descriptive statistics of variables and comparison between symptomatic and asymptomatic plaques.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* (years)</td>
<td>66.3 (9.7)</td>
<td>61.3 (9.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Stenosis (ECST)**</td>
<td>66.6% (19%)</td>
<td>74.8% (14%)</td>
<td>0.005***</td>
</tr>
<tr>
<td>Lipid volume**</td>
<td>64.4 (94.5)</td>
<td>124.3 (127.3)</td>
<td>0.007***</td>
</tr>
<tr>
<td>Matrix volume*</td>
<td>941.8 (487)</td>
<td>910 (330.9)</td>
<td>0.76</td>
</tr>
<tr>
<td>Calcification volume**</td>
<td>78.5 (168.7)</td>
<td>44.4 (129)</td>
<td>0.099</td>
</tr>
<tr>
<td>Total plaque volume**</td>
<td>962.1 (817.6)</td>
<td>1140 (906.8)</td>
<td>0.63</td>
</tr>
<tr>
<td>Relative lipid volume**</td>
<td>7 (4.7)</td>
<td>10.8 (12.3)</td>
<td>0.001***</td>
</tr>
<tr>
<td>Relative fibrous volume*</td>
<td>83 (8.7)</td>
<td>81.5 (8.2)</td>
<td>0.495</td>
</tr>
<tr>
<td>Relative calcification volume**</td>
<td>8.2 (10.7)</td>
<td>4.9 (8.7)</td>
<td>0.025***</td>
</tr>
<tr>
<td>Lipid / (calcification + 1) volume ratio**</td>
<td>0.6 (1.5)</td>
<td>1.7 (4.3)</td>
<td>0.001***</td>
</tr>
</tbody>
</table>

* Normally distributed variable: mean and standard deviation presented
** Non-normally distributed variable: median and inter-quartile range presented
*** Statistically significant difference
Volumes are presented in mm³
T-test used for normally distributed variables and Mann-Whitney U test used for non-normally distributed variables

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Fig. 1: Boxplots comparing ECST stenosis (A), lipid volume (B), relative lipid volume (C), relative calcification volume (D) and ratio L/C (E) in asymptomatic and symptomatic plaques.

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<table>
<thead>
<tr>
<th>Test examined</th>
<th>AUC</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis (ECST)</td>
<td>0.724</td>
<td>0.595</td>
<td>0.853</td>
</tr>
<tr>
<td>Lipid volume</td>
<td>0.697*</td>
<td>0.566</td>
<td>0.828</td>
</tr>
<tr>
<td>Matrix volume</td>
<td>0.535</td>
<td>0.389</td>
<td>0.677</td>
</tr>
<tr>
<td>Calcification volume</td>
<td>0.379</td>
<td>0.238</td>
<td>0.519</td>
</tr>
<tr>
<td>Total plaque volume</td>
<td>0.535</td>
<td>0.391</td>
<td>0.68</td>
</tr>
<tr>
<td>Relative lipid volume</td>
<td>0.749*</td>
<td>0.627</td>
<td>0.872</td>
</tr>
<tr>
<td>Relative fibrous volume</td>
<td>0.432</td>
<td>0.289</td>
<td>0.576</td>
</tr>
<tr>
<td>Relative calcification volume</td>
<td>0.335</td>
<td>0.201</td>
<td>0.47</td>
</tr>
<tr>
<td>Lipid / (calcification volume + 1) ratio</td>
<td>0.733*</td>
<td>0.587</td>
<td>0.841</td>
</tr>
</tbody>
</table>

AUC: Area under the curve, CI: Confidence Intervals

* The three plaque composition variables with the greatest AUC

**Table 2:** ROC analysis for the detection of symptomatic carotid plaque.
Fig. 2: ROC curves for the detection of symptomatic carotid plaque. The blue line represents lipid volume, the green line corresponds to relative lipid volume and the yellow line to L/C ratio.

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Fig. 3: Curved multi-planar reconstruction image of a CTA showing an internal carotid artery plaque. Using the software investigated, different components of the plaque are detected and quantified. The plaque examined is extensively calcified (green colour) while lower quantity of lipid component (yellow colour) has been detected.

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Fig. 4: Same patient as in previous figure. A screenshot of the software is shown. The volumes of the components quantified are presented in detail. The plaque examined is extensively calcified (green colour), while lower quantity of lipid component (yellow colour) has been detected.

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**Fig. 5:** An axial CTA image showing an internal carotid artery plaque affected by a plaque containing a large lipid rich necrotic core (yellow colour).

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Fig. 6: Same patient as in previous figure. Screenshot of the software analyzing an internal carotid artery plaque showing a large lipid rich necrotic core (yellow colour), a small calcification (green colour) and fibrous matrix. The exact volumes quantified are presented in detail by the software.

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Conclusion

Based on the findings of this study it can be concluded that CTA quantification of carotid atherosclerotic plaque components is feasible using existing commercially available specialized software. Features quantified include lipid, fibrous matrix and calcification. The volume of lipid tissue both in absolute and relative value, the relative calcification volume and the ratio of lipid and calcification volume have been found to be associated with the occurrence of stroke, with the symptomatic carotid plaques exhibiting higher absolute lipid volume, higher relative lipid volume, lower relative calcification volume and higher lipid/calcification volume ratio.

These findings are in keeping with those of previous studies in the literature. The novelty though of this study is that it employed software quantifying the volumes of plaque components using software algorithms able to mitigate the blurring and partial volume effects of routine CT angiography acquisitions in order to produce more accurate quantification so as to enhance current clinical practice [9, 10]. This improved technique of plaque composition quantification with CTA provided results which were able to correlate with the occurrence of stroke and are thus clinically significant.
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