Relationship of Carotid Plaque Echomorphology to Presenting Symptom

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KEYWORDS
Carotid stenosis; Echomorphology; Amaurosis fugax

Abstract  Background: Attempts to stratify carotid plaques according to clinical risk using single longitudinal view (SLV) echomorphology have not been uniformly successful. We compared SLV grey scale median measurements (SLV-GSM) with a newer technique of multiple cross-sectional view echomorphology (MCSV-GSM) in carotid plaques from 3 patient groups (asymptomatic, ocular, and hemispheric symptoms).

Methods: SLV and MCSV images were obtained from 109 carotid stenoses (70–99%; 41 hemispheric, 17 ocular, 51 asymptomatic). SLV-GSM and MCSV-GSM min (lowest plaque MCSV image GSM) were determined to assess echolucency whilst MCSV-GSM max−min (highest minus lowest MCSV-GSM) assessed heterogeneity.

Results: Echolucency was greater (lower GSM) in plaques causing hemispheric symptoms versus asymptomatic plaques (MCSV-GSM min, \( P = .002 \); SLV-GSM, \( P = .002 \)). Only MCSV imaging detected differences in echolucency between asymptomatic plaques and those causing ocular symptoms (SLV-GSM, \( P = .84 \); MCSV-GSM min, \( P = .003 \)). Symptomatic plaques showed greater heterogeneity versus asymptomatic plaques, significantly in those causing ocular symptoms (hemispheric \( P = .126 \); AF \( P = .011 \)).

Conclusions: Both SLV and MCSV echomorphology confirm increased echolucency in plaques causing hemispheric symptoms. Plaques causing ocular symptoms could only be distinguished from asymptomatic plaques with MCSV assessment (increased echolucency and heterogeneity). This suggests that amaurosis fugax may be associated with a more focal plaque instability that is best detected with MCSV imaging.

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Introduction

Stoke remains a leading cause of death and disability in the UK. Carotid endarterectomy (CEA) confers an advantage over best medical therapy in prevention of stroke for both high grade symptomatic and asymptomatic carotid stenoses. However, using severity of stenosis as the only criterion for selection of surgical candidates, the number needed to treat to prevent one stroke is 6 and 19 for symptomatic disease (at 5 years) and asymptomatic disease (at 4 years) respectively. Further, outcome from CEA or carotid stenting (CAS) may be influenced by plaque composition, as early CEA is associated with increased risk of peri-operative stroke and death and CAS for plaques with a low GSM appears more hazardous.

Identification of factors other than severity of stenosis which are markers for either reduced risk of stroke with best medical therapy or increased peri-operative risk would clearly improve the risk: benefit of CEA or CAS. Risk of stroke following transient ischaemic attack (TIA) is, in part, determined by the symptomatology of the event, with ocular symptoms carrying half the risk of hemispheric symptoms. This is supported by validation of the ABCD² score which grades reduced risk for ocular compared to hemispheric symptoms. Objective carotid plaque echomorphology as determined by grey scale median (GSM) assessment has been associated with symptomatic status and cerebral infarct on CT, microembolisation detected by transcranial Doppler and increased risk of stroke during CAS.

Studies assessing the relationship of carotid plaque echomorphology with presenting symptoms using a single longitudinal view (SLV) have produced varying results, perhaps because atheroma may be deposited in an eccentric manner and because the image selected for a single longitudinal view (providing global data on plaque echomorphology) may not be truly representative of the plaque as a whole. Multiple cross-sectional view GSM (MCSV-GSM) imaging assesses the whole plaque and allows a more focal assessment of plaque echomorphology. Thus it has been suggested that this technique is superior to SLV assessment. The aim of this study was to assess the relationship of both SLV and MCSV-GSM in high grade carotid stenoses to the presenting symptoms.

Materials and Methods

One hundred and fourteen carotid bifurcation plaques causing 70–99% stenosis were studied in 99 patients (64 males, 35 females) referred for consideration of carotid endarterectomy. Informed consent was obtained and the study was approved by the Ethics Committee of the Leeds Teaching Hospitals NHS Trust. A detailed neurological history and examination were recorded with symptoms classified as ocular (amaurosis fugax [sudden onset of partial or complete uniocular visual loss lasting less than 1 h], or retinal artery occlusion), transient ischaemic attack (TIA [sudden focal neurological deficit lasting less than 24 h with no other apparent cause]), or stroke (defined similarly to TIA but with symptoms lasting more than 24 h). Risk factors for vascular disease and medications were documented. Patients with potential cardioembolic sources for symptoms (concomitant cardiac arrhythmia on ECG or 24 h Holter monitoring; atrial thrombus or septal defect on cardiac ECHO) were excluded from the study. Plaques causing symptoms >3 months previously were excluded as we have previously reported GSM changes suggestive of remodelling in this group. Plaques with severe calcification precluding GSM assessment were also excluded. Cerebral haemorrhage and lacunar infarcts were excluded by cerebral computerized tomography in patients with stroke.

Ultrasound protocol

The % carotid stenosis was determined using duplex criteria for detecting more than 70% stenoses, validated within our unit (internal carotid artery [ICA] peak systolic velocity [PSV-ICA]>180 cm/s), end-diastolic velocity [EDV-ICA]>80 cm/s), ratio of peak systolic velocity in the ICA and common carotid artery [CCA] (PSV-ICA/CCA>4). A subgroup with 80–99% stenosis were also identified (PSV-ICA>250 cm/s; EDV-ICA>100 cm/s).

Grey scale median (GSM) assessment of each plaque was performed using a previously described method. Briefly, patients were scanned by one of two ultrasonographers (blinded to the clinical details) using a high resolution scanner (Acuson XP1200) and a 5–7 MHz multifrequency linear array probe. B-mode settings were fixed throughout the study. The most informative single longitudinal view (SLV; image with maximum plaque area) of the plaque was obtained using colour duplex and the image ‘frozen’. In order to determine plaque GSM by the technique of multiple cross-sectional imaging the carotid bifurcation was located with an axial sweep of the neck. The skin was marked at 5 mm intervals from this point and transverse colour flow images were obtained at each pre-marked site throughout the length of the plaque (5–8 multiple cross-sectional views [MCSV] per plaque). After ‘freezing’ each colour image, the colour-off facility of the scanner was used to obtain the grey scale image of each view. These images were captured, digitized in bitmap format by a commercially available videograbber (Matrox Marvel G400 AGP, Matrox Graphics Inc., Montreal, Canada) and downloaded to computer.

Images were normalized with computer software (MATLAB 5.3), using two reference points (blood and adventitia) to a set grey scale from 0 (black) to 255 (white). The GSM for each transverse and the single longitudinal image were then determined. Whilst the SLV-GSM provides a single, selected measure of global plaque echolucency, MCSV analysis allows identification of the transverse image with the lowest GSM (MCSV-GSMmin) reflecting maximal focal echolucency. Further, the difference in values between the transverse images with maximum and minimum GSM (MCSV-GSMmax–min) assesses plaque heterogeneity, which cannot be quantified with SLV imaging. We have previously published satisfactory correlations for intra- and inter-observer error for this technique having analysed 50 randomly picked images by one observer and repeated analysis one month later by the same person, plus one additional observer. Mean bias between two independent determinations of GSM was 0.538 (95%CI, −1.2 to +2.3), and mean bias for repeat measurements by the same observer was 0.469 (95% CI, −0.93 to +1.8). In addition, we have correlated low SLV-GSM and MCSV-GSMmin values with histological plaque instability.
Statistical analysis

Chi-squared test was used to determine differences in proportions. Kruskall Wallis test was used to compare age between groups. The one-sample Kolmogorov test determined that GSM data was nonparametric and thus the Mann–Whitney U test (2 groups) and Kruskall Wallis test (multiple groups) was used for comparative analysis. Multivariate logistic regression analysis was performed to assess the relative role of MCSV-GSM\textsubscript{min} and MCSV-GSM\textsubscript{max–min} in differentiating plaques causing amaurosis fugax from asymptomatic plaques. \(P < 0.05\) was considered significant. Statistical tests were performed using SPSS 17.0 computer software.

Results

Of the 114 70–99% internal carotid arteries stenoses, 5 were excluded due to excessive calcification precluding GSM assessment. Of the remaining 109, 58 had caused symptoms within 3 months (41 hemispheric symptoms within 3 months [15 stroke, 26 TIA], 17 ocular) and 51 were asymptomatic. The groups were well matched for age, sex, vascular risk factors, systemic atherosclerosis and medication (Table 1).

Plaques causing hemispheric symptoms had a significantly lower SLV-GSM than either plaques causing amaurosis fugax or asymptomatic plaques (12.7 [2.9–30.0] versus 38.9 [11.3–50.1]; \(P = 0.03\) and 31.5 [15.9–56.3]; \(P = 0.002\) respectively; Kruskall Wallis \(P = 0.006\)). There was no difference in SLV-GSM between plaques causing amaurosis fugax and asymptomatic plaques (\(P = 0.840\)). In contrast both groups of symptomatic plaques could be distinguished from asymptomatic plaques using MCSV-GSM\textsubscript{min} (hemispheric 2.0 [0.0–7.0], \(P = 0.002\) versus asymptomatic; amaurosis fugax 5.5 [1.2–9.9], \(P = 0.043\) versus asymptomatic; asymptomatic 11.0 [1.5–26.3]; Kruskall Wallis \(P = 0.004\)). Both groups of symptomatic plaques showed a tendency towards increased heterogeneity when compared to asymptomatic plaques (hemispheric 24.0 [11.0–38.0], \(P = 0.240\) versus asymptomatic; amaurosis fugax 32.7 [15.5–53.8], \(P = 0.011\) versus asymptomatic; asymptomatic 16.5 [7.5–29.3]; Kruskall Wallis \(P = 0.039\)). The tendency towards increased heterogeneity in plaques causing amaurosis fugax versus hemispheric symptoms did not reach significance (\(P = 0.126\) (Fig. 1).

A scatter plot of plaque MCSV-GSM\textsubscript{min} against MCSV-GSM\textsubscript{max–min} showed poor correlation between these variables in all plaque subgroups (Fig. 2). Multivariate logistic regression analysis confirmed MCSV-GSM\textsubscript{min} as an independent predictor of plaques causing amaurosis fugax versus asymptomatic plaques. MCSV-GSM\textsubscript{max–min} was not predictive in the multivariate model (Table 2).

Discussion

This is the first study to compare MCSV-GSM imaging in high grade carotid plaques with presenting symptom. Patients were well matched for demographics, vascular risk factors, medications and degree of stenosis. Plaques causing hemispheric symptoms demonstrated global echolucency on SLV-GSM assessment where as those causing ocular symptoms had a similar SLV-GSM to asymptomatic plaques. A previous study using subjective criteria identified similar results with 82% of 57 50–99% stenosis plaques causing amaurosis fugax as complex heterogenous (low echo pools in a lesion with high echo levels).\(^{19}\) This is in contrast to the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of patient demographics and risk factors with plaque symptomatology.</th>
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<tbody>
<tr>
<td></td>
<td>Hemispheric ((n = 41))</td>
</tr>
<tr>
<td>Age (range), years</td>
<td>73 (46–92)</td>
</tr>
<tr>
<td>Male sex</td>
<td>63%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63%</td>
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<tr>
<td>Diabetes mellitus</td>
<td>15%</td>
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<td>Hypercholesterolaemia</td>
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<tr>
<td>Ischaemic heart disease</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>23%</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>90%</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>10%</td>
</tr>
<tr>
<td>% stenosis (range)</td>
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findings of Holdsworth et al. who subjectively classified 71.8% of 39 carotid plaques causing amaurosis fugax as type I or II (predominantly echolucent) although the majority of these plaques were also causing higher severity stenoses (80–99%). In a previous objective GSV study of 295 plaques, those causing amaurosis fugax were associated with a lower SLV-GSM (and higher severity of stenosis) than those causing either hemispheric symptoms or asymptomatic plaques. Increasing levels of stenosis are associated with plaque echolucency, perhaps explaining the results of the latter 2 studies. In our study stenosis was not a confounding factor as groups were well matched for this variable. MCSV-GSM\textsubscript{min} was lower in both groups of symptomatic plaques, with increased heterogeneity (MCSV-GSM\textsubscript{max}−MCSV-GSM\textsubscript{min}) compared to asymptomatic plaques, significantly so in those plaques causing amaurosis fugax. This is in keeping with the findings of a recent study using complex measures to assess heterogeneity in plaque echotexture following SLV-GSM assessment which demonstrated higher rates of embolic cerebral infarction in homogenous, echolucent plaques.

These data suggest that plaques causing amaurosis fugax may be associated with only focal plaque echolucency, which cannot be identified on SLV imaging alone when compared with other plaque types of similar severity stenosis. Further, there appears to be a difference in plaque morphology between plaques causing ocular and cerebral symptoms which may explain the difference in clinical risk of future stroke, and the lower risk of peri-operative cerebral events in those plaques causing ocular symptoms. A histological study of 526 carotid plaques reported a trend towards increased fibrous tissue (36.1% versus 30.3%) and reduced haemorrhage (60.8% versus 69.7%) in plaques causing amaurosis fugax and hemispheric TIAs respectively although this failed to reach statistical significance. Another study of assessing 404 carotid endarterectomy specimens concluded that those plaques causing amaurosis fugax were phenotypically similar to asymptomatic plaques. However, only the 5 mm section of plaque with greatest plaque burden was analysed, potentially missing localised instability elsewhere in the plaque. We have previously published data comparing SLV-GSM and MCSV\textsubscript{min}.GSM to histological instability defined as cap rupture or thinning in any of multiple transverse sections taken at 4 mm intervals throughout the plaque. This showed a reduction in GSM in plaques defined as histologically unstable. It is therefore tempting to suggest that focal echolucency leads to smaller platelet emboli, rather than large emboli containing lipid and necrotic debris which may be released during plaque disruption in a plaque with more widespread instability.

One criticism of this study is that analysis of transverse images at 5 mm intervals may miss focal plaque instability in the regions between scanned images. Previous histological studies have determined that examination of the carotid bifurcation is most representative of plaque histology but sequential sections at 3 mm intervals from the bifurcation are required to avoid missing focal areas of instability. However, in that study this 3 mm interval was not compared to wider serial examinations throughout the plaque. The length of plaque interrogated by each transverse image on ultrasonography is greater than a 5 \mu m section examined histologically (1.7 mm ultrasound slice thickness at a depth of 1 cm increasing to 6 mm at 6 cm depth using the Acuson 128 XP10 and 5–7 MHz transducer). Therefore increased intervals between images is less likely to miss more focal variations in echomorphology.

Other methods assessing focal histology in plaques have been described. Pedro et al. described assessment of the percentage area of the plaque with echolucent pixels (P40) and demonstrated greater P40 values in symptomatic plaques. As yet this method has not been assessed in differentiating plaques causing amaurosis fugax specifically but one would expect P40 values intermediate to those of asymptomatic plaques and those leading to hemispheric symptoms. Evolution of 3D ultrasound may allow better resolution images for plaque characterisation in the future.

The results of this study provide a plausible explanation for differences in pre- and peri-operative stroke risk in symptomatic plaques presenting with different symptoms. Further, they support further trials of objective MCSV-GSM assessment to identify plaques which are at high risk of future symptoms, and perhaps to stratify risk associated with operative or endovascular intervention.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Beta</th>
<th>t</th>
<th>P value</th>
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<tbody>
<tr>
<td>MCSV-GSM\textsubscript{min}</td>
<td>−0.367</td>
<td>−4.016</td>
<td>&lt;0.001</td>
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<tr>
<td>MCSV-GSM\textsubscript{max}−MCSV-GSM\textsubscript{min}</td>
<td>0.111</td>
<td>1.211</td>
<td>0.229</td>
</tr>
</tbody>
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### Conflict of Interest

No conflicts of interest declared.

### Funding

None.
References


