Texture Analysis of Ultrasonic Images of Symptomatic Carotid Plaques can Identify Those Plaques Associated with Ipsilateral Embolic Brain Infarction

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Objectives. The aim of our study was to determine the association between objective, computerised texture analysis of carotid plaque ultrasonic images and embolic CT-brain infarction in patients presenting with hemispheric neurological symptoms.

Design. Cross-sectional study in patients with 50%–99% (ECST) carotid stenosis.

Patients and Methods. Carotid plaque ultrasonic images (n = 54, 26 with TIAs and 28 with stroke) obtained during carotid ultrasound were normalised and standardised for resolution and subsequently assessed visually for the presence of discrete echogenic or juxtaluminal echolucent components and overall echogenicity (plaque type). Using computer software, 51 histogram/textural features of the plaque outlines were calculated. Factor analysis was subsequently applied to eliminate redundant variables. Small cortical, large cortical and discrete subcortical infarcts on CT-brain scan were considered as being embolic.

Results. Twenty-five cases (46%) had embolic infarcts. On logistic regression, grey-scale median (GSM), a measure of echolucency, spatial grey level dependence matrices (SGLDM) correlation and SGLDM information measure of correlation-1, measures of homogeneity were significant (p < 0.05), but not grey level runlength statistics (RUNL) Run Percentage (RP), stenosis severity, type of symptoms or echolucent juxtaluminal components. Using ROC curves methodology, SGLDM information measure of correlation-1 improved the value of GSM in distinguishing embolic from non-embolic CT-brain infarction.

Conclusion. Computerised texture analysis of ultrasonic images of symptomatic carotid plaques can identify those that are associated with brain infarction, improving the results achieved by GSM alone. This methodology could be applied to prospective natural history studies of symptomatic patients not operated on or randomised trials of patients undergoing carotid angioplasty and stenting in order to identify high-risk subgroups for cerebral infarction.

Keywords: Carotid arteries; Cerebral infarction; Texture; Ultrasound.

Introduction

It has been shown that specific ultrasonic characteristics of carotid plaque atheroma are associated with the presence of ipsilateral embolic brain infarcts on CT scan. Echolucent and homogeneous carotid plaques are more frequently identified in patients with ipsilateral hemisphere infarcts.1,2 Recent advances in plaque imaging include grey scale and resolution standardisation,3,4 and has enabled objective computer-assisted plaque characterisation.5–7 Improved brain infarct classification into embolic infarcts (discrete subcortical and cortical infarctions in the distribution area of the anterior and middle cerebral artery) and non-embolic pathology (haemodynamic infarctions, diffuse widespread white matter lesions, lacunar and basal ganglia infarctions) has also improved our understanding of the unstable carotid plaque.5

The aim of the present study was to determine the relationship between embolic pattern of brain infarcts and unstable plaque echomorphology, using computer-assisted histogram and texture assessment of carotid plaque images.
Patients and Methods

One hundred and two patients with internal carotid artery stenosis 50%–99% in 106 carotid arteries participated in this study. Stenosis was graded using velocity ratios, as previously described. Each plaque was treated as an independent case and defined the side of interest in each patient. To avoid possible systemic effects related to plaque instability, contralateral (asymptomatic) sides of symptomatic patients were not included. Symptomatic patients with cardioembolism were excluded from this study, while only neurovascular symptoms within the last 6 months on the side of interest were considered. Carotid plaques were associated with ipsilateral amaurosis fugax in 19 cases and ipsilateral hemispheric symptoms (26 TIA's and 28 strokes) in 54 cases. For 33 carotid stenoses (29 patients) no symptoms were reported.

Carotid ultrasound scanning and off-line image analysis was performed as previously described. Briefly, ultrasound (duplex) scans were performed using duplex scanning and colour flow imaging. Duplex scans and longitudinal plaque images were recorded on S-VHS videotapes and transferred to a computer, using a S-VHS “Panasonic” videocassette recorder (model AG-7350-B, Matsushita Electric Ind. Co. Ltd, Japan) and an external capturing device-frame grabber (Snappy v2, Play Inc., Ca, USA). Following image digitisation, in Tag Image File Format (Aldus TIFF), a manual standardising procedure (brightness normalisation), developed by our group, was applied, with the use of commercially available software (Adobe Photoshop version 5.5, Adobe Systems Inc., Palo Alto, Ca, USA). Bicubic interpolation was subsequently employed to resize all images at a fixed resolution (pixel density) of 20 pixels/mm, before texture analysis was performed, as previously described. Subsequently, subjective and objective plaque analysis was performed.

Subjective (visual) plaque classification

Plaques were classified into 5 types, according to the Geroulakos classification: type 1 completely echolucent lesions, sometimes a thin fibrous cap is visible, type 2 predominantly echolucent lesions having less than 50% echogenic components, type 3 predominately echogenic with less than 50% echolucent components, type 4 uniformly dense echogenic lesions (with less than 10% echolucent components) and type 5 plaques, that could not be accurately classified due to excessive plaque calcification and acoustic shadowing. The presence of a substantial (15% or more of the total plaque area) echolucent plaque component near the lumen (juxtaluminal), or discrete echogenic plaque components was also noted.

Objective plaque classification

Using commercially available and appropriately programmed software (texture tools of Matlab, MathWorks Inc.), carotid plaques were manually outlined, by one of the authors (SKK), with the aid of the corresponding colour coded image. The region of interest - carotid plaque - was saved as a separate file, which was used for subsequent analysis. It is imperative texture analysis is done after standardisation of the overall image brightness (normalisation), as previously suggested. Fifty-one histogram and texture features (Appendix I) of the grey tones produced within the outlined plaque area were extracted using the following algorithm methods:

(i) Histogram measures. These are novel features introduced by the authors.
(ii) First order grey level parameters, including grey scale median (GSM).
(iii) The Spatial Gray Level Dependence Matrices (SGLDM).
(iv) Gray level difference statistics (GLDS).
(v) Gray level run length statistics (RUNL).
(vi) The Fourier power spectrum (FPS).

Methods (iii)–(vi) are established texture analysis algorithms, traditionally used to study heterogeneity. Ischaemic infarction was defined as a low attenuation area on CT brain scan that was usually confined to one vascular territory or was located in the border zone between two vascular territories. Ischaemic brain infarction was classified as follows, using the Stevens’ classification:

1. Discrete subcortical: well-circumscribed hypodense lesions greater than 1 cm in size, adjacent to apparently non-involved cerebral cortex in the anterior and middle cerebral artery territory.
2. Large and small cortical: infarcts with cortical distribution occupying more or less than 50%, respectively, of the entire anterior and middle cerebral artery territories.
3. Watershed infarction: hypodense areas involving cortical and subcortical areas in the periphery of the middle cerebral artery.
4. Diffuse white matter low-density changes: areas of low density, not well circumscribed, often in the periventricular area.
5. Basal ganglia ischaemic lesions: infarcts (hypodensities with diameter greater than 1 cm) or lacunae (hypodensities with diameter less than 1 cm).

Categories 1 and 2, regarded as embolic, were classified as pattern A brain infarcts and the remaining (3–5) categories were classified as pattern B brain infarcts. A normal CT brain scan or a scan showing unrelated pathology was considered as normal. CT scans were performed on patient presentation and analysed by a neuroradiologist (JMS).

**Statistical analysis**

This was performed with the SPSS for Windows statistical package (release 11.5, Chicago, Ill, USA). Chi-square and odds ratio methods were used to assess the association between symptoms and the categorical variables type of plaque and presence of echolucent juxtaluminal plaque components. The histogram textural features were compared with the Mann-Whitney U test. Kolmogorov-Smirnov test was used to assess normal distribution. Binary logistic regression was used to identify which textural features were independently associated with the presence of embolic infarcts. Hosmer and Lemeshow test was used to test model goodness-of-fit. The diagnostic value of the various texture features and regression model scores were assessed with the ROC curves method and expressed as area under the curve.17

**Results**

The CT brain scans were classified as normal (n = 56), having embolic infarction (discrete subcortical, n = 19 or cortical, n = 10, infarcts) in the middle or anterior cerebral artery territory (pattern A) or nonembolic pathology, pattern B, (watershed infarcts, n = 1, diffuse white matter lesions, n = 3, lacunae and basal ganglia infarctions, n = 12 and other pathology, n = 8).

The association between symptoms and CT brain scan infarct pattern is shown in Table 1. Embolic infarcts were significantly more common in the presence of symptoms, especially hemispheric ones. Because embolic infarcts were rare in asymptomatic hemispheres or in those with amaurosis fugax (embolic infarcts were observed in only 4 patients), all subsequent analysis was restricted to the 54 patients/sides that presented with hemispheric symptoms (25 embolic infarcts).

The degree of carotid stenosis was similar in stenoses associated with embolic infarction and non-embolic infarction/normal brain CT groups, 90% (interquartile range 84%–94%) and 90% (interquartile range 78.5%–94%), respectively, p = 0.83.

**Subjective plaque analysis**

An area of echolucent plaque adjacent to the lumen was equally frequent in both embolic (92%) and non-embolic infarction/normal brain CT groups (93%), p = 1.0. Discrete echogenic plaque components were less common in plaques with embolic infarction 44% (11/25) than in non-embolic infarction/normal brain CT groups 66% (19/29), but the difference was not significant (p = 0.11). Type 1 plaques were significantly more frequently associated with embolic infarcts in comparison with type 2 plaques (78% vs 37%, p = 0.032), as shown in Table 2.

**Objective plaque analysis**

Factor analysis of textural features selected the following independent characteristics (Appendix II): mean grey level (logarithmic form), PPCS10 (pixels with grey level ≤ 10) and GSM (group 1) (Appendix I), SGLDM correlation (group 2), SGLDM Information

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CT-brain scan pattern</th>
<th>Embolic infarcts</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Normal or non-embolic pathology</td>
<td>30</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Sympt</td>
<td>47</td>
<td>26 (36%)</td>
<td>73</td>
</tr>
<tr>
<td>Amaurosis Fugax TIAs</td>
<td>18</td>
<td>1 (5%)</td>
<td>19</td>
</tr>
<tr>
<td>Stroke</td>
<td>12</td>
<td>16 (57%)</td>
<td>28</td>
</tr>
</tbody>
</table>

**Table 1. Infarct distribution in the presence or absence of symptoms (embolic infarcts were more frequent in symptomatic patients, chi-square 8.05, p = 0.005)**

<table>
<thead>
<tr>
<th>Plaque type</th>
<th>CT-brain scan pattern</th>
<th>Embolic infarcts</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>7 (78%)</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>15 (57%)</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>3 (75%)</td>
<td>4</td>
</tr>
</tbody>
</table>

Type 1 plaques were significantly more frequently associated with embolic infarcts in comparison with plaques type 2 (p = 0.032, Fisher’s exact test). Type 3 plaques were rare and although more frequently associated with embolic infarcts, in comparison with plaques type 2, the difference did not reach statistical significance (p = 0.28, Fisher’s exact test). No type 4 plaques were encountered.
Measure-1 (InM-1) (group 3) and runlength RUNL. Run Percentage RP (group 4). Group 1 features are indicators of echolucency, while group 2, 3 and 4 are indicators of texture characteristics. Compared to mean and PPCS10, GSM showed better association with embolic infarction. Variable deciles were cross-tabulated with the presence of embolic infarction, recoded appropriately and treated as categorical for the purposes of logistic regression.

GSM: GSM deciles 1–6 (GSM 0–14.5) were associated with embolic infarction. Prevalence of embolic infarction in plaques with GSM below 14.5 (deciles 1–6) compared to above 14.5 (deciles 7–10) was 76% (19/25) and 45% (13/29), respectively (p = 0.02, odds ratio 3.9, 95% C.I. 1.2–12.6).

Median (interquartile range) GSM was lower for embolic infarction (6.4, 1.2–15.8) in comparison with non-embolic infarction/normal brain CT groups (15.2, 4.8–21.0), p = 0.12.

SGLDM correlation: Prevalence of embolic brain infarction in plaques with SGLDM correlation deciles 3–7 compared to deciles 1–2 and 8–10 combined was 61% (17/28) and 31% (8/26), respectively (p = 0.03, odds ratio 3.5, 95% C.I. 1.1–10.7).

SGLDM InM1: Prevalence of embolic brain infarction in plaques with SGLDM InM1 deciles 3–6 compared to deciles 1–2 and 7–10 combined was 68% (17/22) and 31% (10/32), respectively (p = 0.007, odds ratio 4.7, 95% C.I. 1.5–15.2).

RUNL RP: Prevalence of embolic brain infarction in plaques with runlength RP deciles 1–5 and 9–10 compared with deciles 6–8 was 55% (21/38) and 25% (4/16), respectively (p = 0.042, odds ratio 3.7, 95% C.I. 1.0–13.6).

Logistic regression model

This was constructed and checked using the forward and backward Wald methods. Only GSM, SGLDM correlation and SGLDM InM1 were retained by the final model, as shown in Table 3. RUNL RP, degree of stenosis, type of symptoms (TIAs or stroke), the presence of juxtaluminal echolucent components or discrete echogenic components were not included. Based on the Wald statistic and odds ratio, measures of plaque texture were more important than echolucency (GSM). Hosmer and Lemeshow test was not significant (p = 0.98), which indicated that the model fits adequately. Based on the model, sensitivity (embolic infarcts being correctly classified), specificity (absence or non-embolic infarcts being correctly classified) and accuracy (all cases being correctly classified) were 72%, 76% and 74%, respectively (Table 4, p < 0.001, Chi-square).

The diagnostic validity of the logistic regression model was also evaluated by testing its predicted probability with the ROC curves method. An area under the curve of 0.81 (95% C.I. 0.69–0.92) was found (Fig. 1); this was highly significant (p < 0.001) and significantly better (p = 0.02), than GSM (area under the curve 0.62). The distribution of model-derived predicted probability, in plaques associated or not with embolic infarcts is shown in Fig. 2. It is evident that plaques with a higher probability score were more frequently associated with embolic infarcts.

A scatterplot of GSM and SGLDM InM1, of plaques associated or not with embolic infarcts is shown in Fig. 3. Prevalence of embolic infarction ranged from 16.7% (in echogenic and heterogeneous plaques) to 66.7% (in echolucent and homogeneous plaques).

Discussion

The present study showed that computerised texture analysis of ultrasonic images of symptomatic carotid plaques can identify those that are associated with brain infarction improving the results achieved by GSM alone, confirming previous findings associating embolic brain infarcts with echolucent and homogeneous plaques.1,2,5,18 Our study is distinct from previous investigations since we employed computerised objective methods, which included established and novel texture analysis algorithms.2,18 In contrast to all previous texture applications this was done in a standardised fashion taking into account image resolution.4

Data analysis was restricted to symptomatic patients with stroke or TIAs only, after confirming that

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>S.E.</th>
<th>Wald statistic</th>
<th>p</th>
<th>OR</th>
<th>95% C.I. for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>SGLDM correlation</td>
<td>1.35</td>
<td>0.67</td>
<td>4.08</td>
<td>0.043</td>
<td>3.85</td>
<td>1.04</td>
</tr>
<tr>
<td>SGLDM InM1</td>
<td>1.90</td>
<td>0.71</td>
<td>7.12</td>
<td>0.008</td>
<td>6.71</td>
<td>1.66</td>
</tr>
<tr>
<td>GSM</td>
<td>1.59</td>
<td>0.70</td>
<td>5.17</td>
<td>0.023</td>
<td>4.90</td>
<td>1.25</td>
</tr>
<tr>
<td>Constant</td>
<td>−2.28</td>
<td>0.78</td>
<td>8.36</td>
<td>0.004</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. This table demonstrates the results of logistic regression, which identified three independent parameters associated with embolic infarction in patients presenting with hemispheric symptoms.
embolic brain infarction is rare in asymptomatic hemispheres or in patients with amaurosis fugax. Exclusion of asymptomatic plaques might be more appropriate in the search for the unstable features of the symptomatic carotid plaque since absence of purely asymptomatic patients may have prevented bias in data analysis, given the different biological behaviour of symptomatic and asymptomatic plaques.

We found no relationship between the presence of embolic infarction and degree of stenosis, in both univariate and multivariate analysis, which enhances the importance of plaque instability as the main determinant of embolic infarction. It is therefore evident that in the presence of a haemodynamically significant (ECST 50–99%) stenosis, unstable plaque morphology and not stenosis severity is associated with the presence of embolic infarction. The inclusion of less than 50% stenoses might have altered these results.

The present study showed that symptomatic plaques having very low GSM (less than 14.5) are associated with an increased prevalence of brain infarction. This is compatible with the association we found between type 1 plaque and cerebral infarction and validates further the value of GSM. However, computerised, objective, methods are far more reproducible than visual plaque analysis. Visual plaque analysis is affected by several parameters, including brightness adjustment, and probably not helpful as recently shown by our group. Similarly, objective study of plaque homogeneity was proven helpful in distinguishing embolic infarction, avoiding the use of semi-quantitative methodology. Texture analysis of the carotid plaque has been shown to predict silent brain infarcts following carotid endarterectomy more precisely than GSM.

The presence of a juxtaluminal echolucent component was not associated with an increased prevalence of embolic infarction, probably because this plaque characteristic was too common in both groups. The same results were found regarding discrete echogenic components.

Our findings could be tested in prospective natural history studies of symptomatic or asymptomatic patients with internal carotid artery stenosis. Although

<table>
<thead>
<tr>
<th>CT brain scan pattern</th>
<th>Predicted Group Membership</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Classification</td>
<td>Normal or non-embolic ischaemic changes</td>
<td>Embolic infarct</td>
</tr>
<tr>
<td>Normal or non-embolic ischaemic changes</td>
<td>22 (76%)</td>
<td>7</td>
</tr>
<tr>
<td>Embolic infarct</td>
<td>7</td>
<td>18 (72%)</td>
</tr>
</tbody>
</table>

Table 4. This table shows the predicted group membership based on the logistic regression model.
Carotid endarterectomy is indicated for most patients with appropriate symptoms and carotid stenosis ≥70% NASCET (≥ 83% ECST), being a cost-effective procedure, there is some controversy when the stenosis is between 50%–69% NASCET (approximately 70%–82% ECST), mainly because the number of patients needed to treat is much higher.19 Symptomatic patients with echolucent plaques having low GSM are known to be at increased risk of future stroke, including procedural risk during carotid angioplasty and stenting.

Plaques are 3-D structures that can be difficult to display entirely using a 2-D ultrasound image. It is possible that important parts of plaque contents may have been missed or could be simply out of plane during ultrasound capture and further studies on analysing plaque texture from 3-D sources (ultrasound or MRI) are warranted.27,28

In conclusion, embolic brain infarcts are associated with particular texture features of the ultrasonic image of the carotid plaque (echolucency and homogeneity). These findings support the use of ultrasound in the detection of the unstable carotid plaque. This methodology could be applied to prospective natural history studies of symptomatic patients not operated on or randomised trials of patients undergoing carotid angioplasty and stenting in order to identify high-risk subgroups for cerebral infarction.

Appendix I. Texture analysis methods

(i) Histogram measures

Total number of pixels, percentage of pixels below grey level 30 (PP < 30), percentage of pixels below grey level 50 (PP < 50), percentage of pixels of each of the 10 contours of the 0–255 grey level spectrum (PPC1–PPC10), the first 2 contours (grey level 0–51) analysed further into 5 sub-contours (PPCS1–PPCS5).

(ii) First order grey level parameters12,13

In this category the parameters are derived directly from the gray level histogram. They describe the gray level distribution without considering spatial independence; as a result they can only describe echolucency of texture and the overall variation characteristics within the region of interest (ROI). The parameters used from this category are: Mean grey level, variance, median (GSM), mode, kurtosis, skewness, energy and entropy.

(iii) The Spatial Grey Level Dependence Matrices (SGLDM)11

The SGLDM algorithm is based on the assumption that texture properties of an image are contained in the overall or “average” spatial relationship between the gray levels in the image. SGLDM is based on the estimation of the second order conditional probability density f(i,j,d,θ). Each value f(i,j,d,θ) represents the probability that two different resolution cells which are in the direction specified by an angle θ and have distance d, will have grey level values i and j respectively. The parameters used from this category are: Angular Second Moment (ASM), Contrast, Correlation, Variance (Sum of squares), Inverse Difference Moment (IDM) — Homogeneity, Sum Average, Sum Variance, Sum Entropy, Entropy, Difference Variance, Difference Entropy, Information Measure of Correlation-1 (InM1) and Information Measure of Correlation-2 (InM2).

ASM is a measure of homogeneity of the image. Homogeneous images have very few dominant grey-tone transitions, which result into higher readings. Contrast is a measure of the contrast or the amount of local variations present in an image. Images with large neighbouring grey level differences are associated with high contrast. Correlation is a measure of grey-tone linear-dependencies in the image and heterogeneity. Heterogeneous images have higher correlation values.11

![Fig. 3. Scatterplot of GSM vs SGLDM InM1, of plaques associated or not with embolic infarcts; the former tend to be more echolucent and homogeneous as becomes apparent using cut-off points derived from ROC curves (14.7 for GSM and −0.41 for SGLDM InM1 based on the best sensitivity and specificity). Prevalence of type A pattern ranged from 16.7% (right upper corner) to 66.7% (left lower corner).](image-url)
(iv) Grey level difference statistics (GLDS)\textsuperscript{14}

The GLDS algorithm is based on the assumption that useful texture information can be extracted using first order statistics of an image. The algorithm is based on the estimation of the probability density $p_d$ of image pixel pairs at a given distance $\delta = (\Delta x, \Delta y)$, having a certain absolute gray level difference value. Coarse texture images, result in low gray level difference values, whereas, fine texture images result in-pixel gray level differences with great variances. The parameters used from this category are: Entropy, Contrast, Mean, Angular Second Moment — Homogeneity, Energy.

(v) Grey level run length statistics (RUNL)\textsuperscript{15}

This technique is based on grey level run length of the image. If we examine the points that lie along some given direction (run lengths), we will occasionally find runs of consecutive points that all have the same grey level. In a coarse texture relatively long runs occur more often, whereas, fine texture contains primarily short runs. In a directional texture, the run lengths that occur along a given line should depend on the direction of the line. The parameters used from this category are:

- Short Run Emphasis (SRE), Gray Level Distribution (GLD), Run length distribution (RLD), Long Run Emphasis (LRE), Run Percentage (RP).

(vi) The Fourier power spectrum (FPS).\textsuperscript{14} Radial and angular features

The estimation of the power spectrum of an image using Fourier transform provides useful information about texture. Coarse texture will produce results concentrated near the transformation origin, while in images with smooth texture values it will be more spread out.

Appendix II. Results of factor (principal components) analysis

Principal components analysis of textural features results extracted eight factors.

- Factor 1 (overall echogenicity) accounted for about 64% of the total variability; mean (logarithmic form) correlated strongly with factor 1 (loading factor 0.98). PPCS10 and GSM (loading factors 0.89 and 0.85, respectively) were also considered.

- SGLDM correlation correlated with factor 2. Loading factor was 0.52.
- InM1 correlated with factor 3 (loading factor 0.78).
- Factor 4 correlated with runlength RP (loading factor 0.78).
- Loading factors for features correlated with factors 5–8 were less than 0.6; it was therefore decided not to include them in the analysis.

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Unstable Carotid Plaques and Brain Infarction

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