Carotid Plaque Texture Analysis Can Predict the Incidence of Silent Brain Infarcts Among Patients Undergoing Carotid Endarterectomy

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Objective. To evaluate the correlation between microembolism (ME) and incidence of silent brain infarcts during carotid endarterectomy.

Materials and methods. Patients were assessed using transcranial Doppler, carotid ultrasound and pre- and postoperative magnetic resonance imaging (MRIs). The clinical status, need for shunt insertion and significant decrease in the blood flow in the middle cerebral artery were recorded. All data were analysed using multivariate regression models.

Results. Out of the 76 patients examined, 17 (22%) had new postoperative lesions seen on MRI. Three of them (4%) were symptomatic, 14 (18%) were asymptomatic. The multivariate regression models showed that ME is a potent predictor of 'silent' ischemic brain lesions, at \( p < 0.001 \) (OR [95% CI]—1.1 [1.05, 1.2]). Digital plaque texture analysis predicted ME \( (p = 0.028; \text{OR [95% CI]} = 0.32 [0.12, 0.89]) \). The risk of ME increases steadily with the decrease in the echogenicity of the plaque.

Conclusions. ME is a potent predictor of 'silent' ischemic brain lesions among patients with carotid stenosis. An analysis of plaque texture can predict the degree of ME during endarterectomy and is more precise than the standard GSM.

Keywords: Carotid plaque; Ultrasonography; GSM analysis; Microembolism.

Introduction

Microembolism (ME) is a common consequence of an unstable carotid plaque\(^1\text{–}^5\) and its role as a significant cause of neurological events is well established.\(^6\text{–}^9\)

A number of investigators have assessed the relation between the carotid plaque morphology, ME and ultimate detection of new ischemic changes in the brain.\(^10\text{–}^{16}\) Naghavi et al.\(^2,3\) and also Vermeer et al.\(^17\) demonstrated the importance of ME in patients with carotid disease, who were treated conservatively.

There is a need for a diagnostic tool which can determine the possible risk of ME. Standard GSM analysis of plaque morphology is widely used\(^18\text{–}^{21}\) but has some important drawbacks limiting its value. An interesting refinement of the gray-scale median (GSM) analysis of carotid plaque has been proposed by Lal et al., who compared a detailed pixel distribution analysis with the histology of carotid plaque.\(^22\)

This study has two aims. Firstly to evaluate the correlation between ME and the incidence of silent brain infarcts during carotid endarterectomy. Secondly to compare two methods used for ultrasound analysis of carotid plaque—the standard GSM analysis and the refined, detailed plaque texture analysis in predicting the risk of ME.

Patients and Methods

Some 76 patients scheduled for surgical treatment of carotid stenosis, were included in the study, which was carried out in the Department of Vascular Surgery and Angiology of Bielany Hospital, Warsaw, Poland. The study group consisted of 55 men and 21 women (average age 64 ± 5.7 years). The indications for endarterectomy of the internal carotid artery were consistent with accepted criteria for the procedure.\(^23\text{–}^{25}\)

All patients had two ultrasound analyses of the plaque (standard GSM and the detailed plaque texture...
All of them received an MRI examination before and after surgery in order to detect the incidence of new ischemic brain lesions. Intraoperatively, ME was monitored by means of transcranial Doppler (TCD). The removed atherosclerotic plaques were assessed visually and histologically. The two-ultrasound analysis methods were compared against the incidence of perioperative ME. All the operations were performed under regional anesthesia. This was a prospective, single centre study. All patients included in the study were symptomatic (history of amaurosis fugax, TIA or stroke) with carotid stenosis ≥ 70%, and underwent pre- and postoperative neurological assessment and MRI. The ethical committee required exclusion of asymptomatic patients in order to justify the use of routine preoperative MRI. TIA was defined as a new-onset focal abnormality lasting < 24 h. The exclusion criteria were: presence of significant cardioembolic conditions (atrial fibrillation, valvular pathology, heart failure), absent ‘acoustic window’ for TCD. Overall 51 patients out of a total 127 were excluded (10 — 7.8% due to absent TCD trace, 17 — 13.4% due to cardioembolic conditions, 21 were asymptomatic — 16.5%, 3 — 2.4% had no preoperative MRI performed). All patients signed a consent form prior to treatment and were informed about the purpose of NMR examinations. The study was approved by the local Ethics Committee.

**Carotid ultrasound**

The plaques were visualized using a linear 7.5-MHz probe in a longitudinal projection using the same Siemens Sonoline Elegra unit. The registered frames were then assessed to identify the best quality frame for evaluating gray-scale. All images were registered at a minimal depth (4 cm), without magnifying (zoom). This enabled a constant image resolution, maintaining the same frequency—24 frames per second (fps) for images in B mode and 16 fps for color Doppler presentation. The power range was 73 and 26 dB, respectively. Images were registered digitally and transferred to a computer in TIFF format.

**GSM analysis**

A standard GSM histogram of a plaque was obtained as published by Elatrozy et al. and has been commonly used by many researchers. The DPTA analysis, was obtained as published by Lal et al. using the Image Pro Plus (Media Cybernetics, Silver Spring, USA) program. This method enables the factorization of gray scale for an unrestricted number of gray scale ranges (partitions). Similarly to Lal’s report we chose partitions of gray scale corresponding to the echogenity of chosen tissues (blood, lipid, muscle, fibrous tissue and calcium—five partitions overall). The first three partitions were predominantly hypoechogenic, whereas the last two (four and five) were predominantly hyperechogenic. The mean GSM (and ranges) for blood, or other tissues with similar echogenity (e.g. recent intraplaque hematoma or hemorrhage) was 3.5 (0–9), for areas with echogenity similar to that of lipid was 16 (10–31), for areas with echogenity similar to muscle tissue was 41 (32–74), for areas with echogenity similar to fibrous tissue was 87 (75–111) and for those with echogenity similar to calcified tissues was 121 (112–255). Plaque pixels were further mapped in five different colors depending on their GSM range (Fig. 1).

The reference points (normalized for every tissue in every subject) were: partition 1 (blood)—lumen of the artery; partition 2 (lipid)—subcutaneous tissue; partition 3 (muscle)—the sternocleidomastoid muscle; partition 4 (fibrous)—the anterior rectus abdominis sheath; partition 5 (calcium)—the transverse process of a cervical vertebra. The sum of all five partitions was equal to 100% of the plaque area.

Partitions 1, 2 and 3 are naturally hypoechogenic, partitions 4 and 5 are naturally hyperechogenic. All the partitions were summarized and arbitrarily dichotomized taking cut-off point on the median of the mean GSM ranges for the partitions. We choose a median cut-off point to test the hypothesis that patients with a lower index have different chances of the outcome event than patients with a higher index—this has been derived from the fact that hypoechogenic plaques are of greater risk than the hyperechogenic ones. Fig. 1 shows a sample of a final result of a DPTA analysis of the ultrasound image of a carotid plaque. The small table at the bottom of the figure shows the percentile content of the plaque area for all five partitions corresponding to the echogenity of the relevant tissues (1–5).

**ME detection**

Intraoperatively, the blood flow in the middle cerebral artery (MCA) was monitored in all patients using a TCD unit (Pioneer/EME Nicolet, USA). The registration of blood flow values and ME phenomenon was performed at all stages of the surgical treatment. Patients with an absent ‘acoustic window’ were excluded from the analysis. ME was registered at three stages of the operation (I—dissection of the
arteries, II—clamping of the arteries and III—clamp release and restoration of the cerebral blood flow).

ME signals were defined as transient high-intensity signals which were usually unidirectional within the velocity spectrum, having a duration of less than 0.3 s, an intensity of more than 4 dB above the background velocity spectrum, and accompanied by a characteristic chirping sound.28

MRI examinations

MRI were performed routinely before (2 days prior to) and on the 2nd day following the operation. The presence of infarcts was rated identically in the preoperative and postoperative examinations. We defined infarcts as focal hyperintensities on T2-weighted images that were ≥ 3 mm.17 Proton density scans were used to distinguish infarcts from dilated perivascular spaces. Lesions in the white matter also had to have corresponding prominent hypointensities on T1-weighted images to distinguish them from other white matter lesions. We performed axial T1-, T2-, weighted scans. The MRI diagnosis was made by an experienced radiologist, blinded to other results.

Histology and visual plaque examination

The fresh plaques were visually examined during surgery for potential characteristics causing the ME signals (or their absence) (1) ulceration/disintegration, (2) thrombus/subendothelial hemorrhage, and (3) solidity (Stork et al.8). Each surgical specimen was obtained en bloc and then sectioned to optimize correlation with the B-mode images and histology. The plaques were examined by a histopathologist, who was blinded to the ultrasound and perioperative results. The removed plaques were placed in buffered formalin and sliced into paraffin specimens for routine stainings: hematoxylin–eosin (H–E) and phosphotungstic acid hematoxylin (PTAH). All the specimens were examined for the presence of ulceration, necrotic core, hemorrhage, fibrosis, hyalinization and calcification. Three groups of plaques were identified using a classification from Denzel et al.29—(1) combined plaques: including one or more features predictive of possible embolisation from the plaque: thrombus present, ulcerations, plaque disintegration, intraplaque hemorrhage, (2) fibrous plaque and (3) solid plaque.29 The definitions of plaque status were based on Sitzer et al.30

Statistics

The definition of ‘outcome events’ was based on: (1) the appearance of perioperative neurological complications (amaurosis fugax, TIA, reversible ischemic event and stroke), and (2) the appearance of a new ischemic lesion in the MRI exam. Shunt insertion and
a major (>60%) decrease of blood flow in MCA were also considered as possible risk factors for complications. The influence of selected factors on the appearance of an ‘outcome event’ was examined using step-wise multivariate logistic regression models. The ‘goodness of-fit’ of the models was verified by the Hosmer–Lemeshow test. Their predictive value was tested with the use of ROC curves. The value of 0.05 was accepted as statistically significant. Calculations were performed with the use of the Stata 7.0 program.

Results

Association between ME and the appearance of new ischemic lesions in the MRI

Of 76 patients examined four had perioperative cerebrovascular events (one major-stroke and three minor events—TIA). Three of these four patients had new ischemic lesions detected by the MRI postoperatively (4%). Apart from these, new ischemic lesions in the postoperative MRI were detected in 14 patients with no apparent neurological symptoms (‘silent’—18%). Overall 17 of the 76 operated patients (22%) had new ischemic lesions on the postoperative MRI.

The basic data regarding the ME at the three stages of operation (dissection of the arteries, clamping and clamp release) are presented in Table 1. The logistic regression model for all new ischemic lesions (symptomatic and ‘silent’) revealed, that ME was a potent predictor of new ischemic lesions, even if they were not detected clinically. The statistical significance of the phenomenon was extremely high ($p<0.001$) and was comparable only to a visual assessment of the removed plaques ($p<0.005$)—see Table 2. The model had very good fit, with a predictive value of 0.987 (Fig. 2). Shunt insertion and a significant decrease in the blood flow in MCA (related closely to the need for shunt insertion) did not influence the incidence of new ischemic lesions.

The GSM was a median of 16 (0–29) for the group with detected brain infarcts and a median of 38 (12–49) for the group with no new perioperative infarcts. There was also an excellent correlation between the GSM values (entered as quartiles) and the DPTA partition values (Pearson $\chi^2=55.97$, $p=0.0001$).

Association between the plaque morphology and the rate of ME

The multivariate logistic model showed that perioperative neurological complications were best predicted by the DPTA analysis ($p=0.029$, OR [95% CI]—0.05 [0.003, 0.73]). The additional independent predictive factors were: visual assessment ($p=0.007$, OR [95% CI]—0.01 [0.001, 0.31]) and histology examination ($p=0.006$, OR [95% CI]—27.5 [2.56, 294.5]). The standard GSM analysis did not have a predictive value ($p>0.1$). The low precision of estimates (wide confidence intervals) is the result of a low rate of

Table 2. The logistic model for new ischemic lesions in the brain

<table>
<thead>
<tr>
<th>N=76</th>
<th>OR [95% CI]</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulated sum of hits (overall ME)</td>
<td>1.1 [1.05, 1.2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visual examination (1, 2 vs 3)</td>
<td>0.05 [0.006, 0.39]</td>
<td>0.005</td>
</tr>
<tr>
<td>Shunt insertion</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Decrease of flow in the MCA</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Histopathology (1 vs 2, 3)</td>
<td>0.42</td>
<td></td>
</tr>
</tbody>
</table>

The grades 1 and 2 of visual examination stand for plaques with features of potential characteristics causing the ME signals, grade 3 of visual examination for plaques with features of plaques lacking potential characteristics causing ME. Histology grade 1 stand for combined plaques having one or more of the features predicting the possible embolisation. Histology grades 2 and 3 stand for plaques lacking features predicting the possible embolisation (Section 2).

Relationship between ultrasound findings and perioperative complications

The multivariate logistic model showed that perioperative neurological complications were best predicted by the DPTA analysis ($p=0.029$, OR [95% CI]—0.05 [0.003, 0.73]). The additional independent predictive factors were: visual assessment ($p=0.007$, OR [95% CI]—0.01 [0.001, 0.31]) and histology examination ($p=0.006$, OR [95% CI]—27.5 [2.56, 294.5]). The standard GSM analysis did not have a predictive value ($p>0.1$). The low precision of estimates (wide confidence intervals) is the result of a low rate of

![Fig. 2. ROC for new ischemic lesions (detected by NMR).](image-url)
complications. The model has good fit, its predictive value is 0.88 (Fig. 3).

The model defined patients with a percentile content of partitions 1, 2 and 3 (hypoechogenic) exceeding 72% of the plaque area as a high risk group having a significantly greater chance of perioperative complications. Based on this cut-off point—the DPTA index was defined as a summarized percentile content of partitions 1, 2 and 3 (hypoechogenic ones) exceeding 72% of the plaque area.

The patients having a content of partitions above 72% of the plaque area were defined as the predominantly hypoechogenic group—as opposed to the hyperechogenic group (where the percentile content of partitions 1, 2 and 3 was less than 72% of the plaque area) (Figs. 4–7).

In an additional univariate analysis of correlation between the GSM values (ranges divided into quartiles) and the incidence of perioperative complication, we found no direct association between the GSM values and the increasing rate of hits (divided in quartiles): Pearson $\chi^2=0.981, p=0.806$.

The relationship between ME and perioperative complications

A logistic model for microembolism (ME > 5) (Table 3) showed that patients qualified by the DPTA index as hyperechogenic with plaques visually assessed as solid had significantly lower incidence of ME (OR=$0.32$, 95% CI=[0.12, 0.89], $p=0.028$ for DPTA and OR=$0.05$, 95% CI=[0.006, 0.39], $p=0.005$ for visual assessment; area under ROC=0.77, Fig. 8). The standard GSM analysis did not correlate with the rate of ME ($p>0.1$).
The association between plaque morphology (DPTA analysis) and the rate of ME
The linear regression model for the DPTA index demonstrated that with an increase in the hypoecho-genic contents of the plaque (partitions 1, 2 and 3), a significant rise in the number of hits is seen \( p = 0.004 \) (8.37 [2.66, 13.88]). Patients defined by DPTA analysis as hypoechogenic ones had a significantly \( (p < 0.05) \) higher chances of ME, than the hyperechogenic ones (Fig. 9).

Discussion

Earlier investigations have demonstrated an association between perioperative ME and stroke. The high incidence of silent brain infarcts underlines the importance of the ME phenomenon during surgery, thus stressing the need for its registration. In our study, we found that that a significant number of patients (22%) were having new ischemic lesions—this is consistent with Roh et al.’s report. Fourteen out of 76 patients with no apparent symptoms had new ischemic lesions—this supports other data. Wolf et al. demonstrated a significant association between artery dissection and perioperative stroke.

The cut-off point of 10 emboli at the first stage of operation was defined as a risk factor. In our study—we found the cut-off point to be at 5 hits. Above that level a significant increase in the risk of perioperative complications is seen. That risk is increased by 5% with each 1 hit rise in the microemboli count.

A possible explanation for the lower cut point than that of other authors is that the patients in this study

Table 3. The logistic model assessing the relation between rate of hits (ME) and the chances of perioperative complications (for plaques stratified by the DPTA analysis) (see ROC curve—Fig. 8)

<table>
<thead>
<tr>
<th></th>
<th>OR [95% CI]</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPTA analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo vs hyperechogenic</td>
<td>0.32 [0.12, 0.89]</td>
<td>0.028</td>
</tr>
<tr>
<td>Visual assessment 1, 2 vs 3</td>
<td>0.05 [0.006, 0.39]</td>
<td>0.005</td>
</tr>
<tr>
<td>Histopathology assessment 1 vs 2, 3</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>GSM analysis (Adobe)</td>
<td>&gt;0.1</td>
<td></td>
</tr>
<tr>
<td>26–50 vs 0–25 (GSM)</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>51–80 vs 0–25</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Above 80 vs 0–25</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Test for the model goodness-of-fit</td>
<td>( p = 0.34 )</td>
<td></td>
</tr>
<tr>
<td>Area under ROC: 0.77</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Visual examination and histology grading presented along with the Table 2 and in Section 2.
were symptomatic prior to the operation. This may have had an impact on the higher incidence of unstable plaques among our patients. It is, however, difficult to estimate the bias of symptomatic patients on plaque morphology and the rate of ME. The minimum time interval between the stroke and the operation was 6 weeks. Such an interval may influence plaque morphology due to well known healing processes that may occur inside the lesion.1–3

Another finding of this study was that preoperative DPTA analysis of a carotid plaque increases prediction of perioperative neurological complications \((p=0.029, OR\ [95\% CI]\ =0.05 [0.003, 0.73])\). The standard GSM analysis was not predictive \((p>0.1)\). The results correlated well with a visual assessment \((p=0.007, OR\ [95\% CI]\ =0.01 [0.001, 0.31])\) and histology exam \((p=0.006, OR\ [95\% CI]\ =27.5 [2.56, 294.5])\).

The standard GSM is already widely used. Its methodology, particularly with regard to reproducibility and interobserver variability has been thoroughly investigated.26 It should, however, be underlined that the method possesses several, significant limitations and simplifications:

- the GSM median incorporates average histogram values from the entire atherosclerotic lesion.
- It does not identify focal changes in the examined plaque.

The refined, GSM-derived method of ultrasound analysis—the carotid plaque texture analysis seems to be an advance in refining non-invasive research on the highlighted problems regarding unstable carotid plaque. Through the subordination of certain ultrasound features typical for selected tissues, the method of plaque texture analysis enables a more precise recognition of focal changes.

The results of the study indicate, that the DPTA predicts the risk of perioperative complications and of ME much more precisely than the well known standard GSM analysis. That, together with the finding of a direct correlation between the plaque morphology and the rate of ME (as assessed by DPTA) has several potential clinical implications: (1) support for plaque morphology analysis as one of the criteria for carotid surgery, (2) studies on the non-invasive detection of intraplaque, focal lesions should probably be anticipated in the near future and (3) the ability to detect unstable plaque features may lead to a reconsideration of current indications for carotid surgery by dichotomizing patients into two groups: those in urgent need of surgery (unstable plaques, high risk of thromboembolism) and those requiring routine, elective carotid surgery (stable, high-grade stenosis plaques). Finally, the information on the rate of ME during the operation is important feedback to the surgeon dissecting the arteries and could play an important role in training and quality control for carotid endarterectomy, helping to reduce the ME.

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16. **Sabetai MM, Tegos TJ, Clifford C, Dhanjil S, Belcaro G, Kakkos S et al.** Carotid plaque echogenicity and types of silent


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