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Correlation of Cerebrovascular Symptoms and Microembolic Signals With the Stratified Gray-Scale Median Analysis and Color Mapping of the Carotid Plaque

Roman Sztajzel, MD; Isabelle Momjian-Mayor, MD; Mario Comelli; Shahan Momjian, MD

Background and Purpose—To determine whether a stratified gray-scale median (GSM) analysis of the carotid plaque combined with color mapping correlated better with the presence of neurological symptoms and microembolic signals (MES) than a whole plaque measurement.

Methods—A total of 131 patients presenting 167 carotid stenoses between 30% and 99% were analyzed by ultrasound. Emboli detection was performed by transcranial Doppler. For each plaque, the GSM values at depth 0 mm (surface) and at one third (30) and one half (50) of the plaque thickness were compared with the values obtained for the whole plaque. The plaque pixels were mapped into 3 colors: red, yellow and green, depending on their GSM value.

Results—Mean GSM values were lower among symptomatic plaques, but a statistically significant difference between values of the whole plaque and those of the surface was obtained only for MES+ stenoses (P<0.01). In a proportional odds logistic regression model based on 4 subgroups with an increasing clinical risk (MES+/symptoms--; MES−/symptoms++; MES+/symptoms--; +; MES+/symptoms+), low mean GSM values and the predominant red color at the surface were independent factors associated with the presence of symptoms or MES (P<0.0005). Furthermore, compared with a whole plaque measurement, analysis of the surface values predicted systematically with a greater sensitivity and specificity (receiver operating characteristic curves) each one of these 4 subgroups.

Conclusions—Low mean GSM values and predominance of the red color at the surface correlated with most of the symptomatic or MES+ stenoses. This combined approach should be further investigated in a longitudinal study.

Key Words: carotid artery plaque ■ carotid stenosis ■ embolism ■ ultrasonography, Doppler, transcranial ■ stroke

Carotid plaque morphology constitutes, besides degree of stenosis, an important factor in determining the subsequent risk of embolic stroke. In 1998, a computerized approach, considered a more objective and quantitative method than visual analysis alone, was developed using gray-scale median (GSM) measurement. Various studies using this approach demonstrated that plaques with a low GSM value are more frequently encountered among symptomatic than asymptomatic patients and may carry an increased risk of cerebrovascular events. However, the conventional GSM analysis considers the median value of the whole atherosclerotic area and may not necessarily reflect the presence of regional components of the plaque. We reported previously that a regional stratified GSM analysis, combined with color mapping, showed a good correlation with different histopathological components of the carotid plaque and allowed the identification of determinants of plaque instability with good accuracy. The aim of the present study was to perform a stratified GSM measurement combined with color mapping of the carotid plaque and to evaluate whether this approach correlated with the presence of neurological symptoms and with the presence of microembolic signals (MES), which are thought to reflect plaque instability.

Patients and Methods
A total of 131 patients 49 to 93 years of age (mean 73 years) presenting 167 carotid stenoses between 30% and 99% were identified from our registry over a period of 3 years (2001 to 2004). All patients were referred from the department of neurology, internal medicine, or cardiovascular surgery. A stenosis was classified as symptomatic if stroke or transient ischemic attack occurred ipsilateral to the lesion within the last 3 to 6 months before investigation. Patients presenting an evidence of cardioembolic pathology were excluded from the study because this condition may also produce MES. Patients presenting an intracranial stenosis (distal carotid artery or middle cerebral artery [MCA]), which can generate MES, were excluded from the study as well. Ultrasound investigations, including longitudinal and transverse sections by color duplex imaging and by power mode, were performed with an Acuson XP 128/10 or Sequoia apparatus (7.5-MHz probe) for the establishment...
of degrees of stenosis. Degree of stenosis was further quantified according to well-established criteria. All patients also underwent transcranial Doppler as routine screening.

**MES Detection**

MES detection was performed in all patients. Transcranial monitoring (DWL Multi Dop X4 TCD-8) of the right and left MCAs was performed using a 2-MHz probe. Each MCA was recorded simultaneously at 2 insonation depths (range 45 to 55 mm). Patients without a good temporal bone window were excluded from the study. All patients were monitored during 60 minutes for MES within ~72 to 96 hours after the assessment of the carotid stenosis or the occurrence of the cerebrovascular event. The plaque was considered positive when ≥1 MES was detected on the ipsilateral MCA. MES were identified in accordance with the criteria established by the consensus on emboli detection. The analysis was not blinded to the subject’s identity because it was known that the patient had a carotid stenosis; however, identification of MES was performed independently of the analysis of the GSM of the plaque. The intensity threshold was fixed at >7 dB, and the sample volume was 4 to 5 mm.

**GSM Analysis**

The video signal from the ultrasound device was converted to a digital image format by a personal computer, and the images were analyzed with a 2- to 3-fold increase of the initial size. The GSM measurements were performed by 2 independent investigators (R.S. and I.M.) according to the method described previously. A program written in-house (by S.M.) in MATLAB was used to perform the analysis. All carotid plaques were first normalized by automatic linear scaling with the use of the values 0 and 195. After normalization, the plaque was outlined on its longitudinal section, delineated by the color Doppler flow imaging at its surface and by the adventitia at its bottom. The luminal margin was then outlined again to provide the precise location of plaque surface to the program and create a binary map of this surface. The distance of each plaque pixel from the surface was quantified in millimeters according to the resolution of the ultrasound scanner (144 pixels/inch for the Acuson Sequoia apparatus and 120 pixels/inch for the Acuson XP128). A profile of the regional GSM as a function of distance from the plaque surface could then be generated, thereby realizing a stratified determination of the GSM. For each plaque, the following strata were chosen for analysis: level 0, 30, and 50 (GSM 0, 30, and 50) corresponding respectively to the GSM values obtained at depth 0 mm (surface) and at one third (30) and one half (50) of the plaque thickness from its surface and compared with the values obtained for the whole plaque (Figure 1).

**Color Mapping of the Normalized Gray-Scale Plaques**

The plaque pixels were mapped into 3 different colors: red, yellow, and green, depending on their gray-scale value (Figure 1). We reported previously that color mapping of the plaque demonstrated a highly significant correlation between the predominant red color at the surface, corresponding to gray-scale values of <50, and the presence of determinants of unstable plaques. In the present study, the same threshold was used: the lowest gray-scale values <50 were mapped in red, and intermediate values between 50 and 80 mapped in yellow, and highest values >80 mapped in green. The predominant color of the whole plaque was visually assessed as well as the predominant color present on the plaque surface. These findings were correlated to the numeric values obtained by means of the stratified GSM analysis. The plaque was considered homogeneous when only 1 predominant color was present and heterogeneous when ≥2 different colors were present. All the plaques were evaluated by 2 independent investigators (R.S. and I.M.).

**Statistical Analysis**

Statistical analysis was performed with the Mann–Whitney test and correlations using a proportional odds logistic regression model. P values were adjusted for the number of comparisons. Sensitivity and specificity values were calculated according to receiver operating characteristic (ROC) curves.

**Results**

We analyzed 131 patients presenting 167 carotid stenoses. No difference was observed between the patients investigated by the Acuson XP128 or the Acuson Sequoia machine. Eight lesions were excluded from the study because of an important acoustic shadow rendering the measurement impossible, and 11 patients were excluded because of the absence of a temporal bone window. The baseline characteristics of the patients and of the stenoses are summarized in Table 1. There was a significant correlation between severity of stenoses (70% to 99%) and presence of symptoms (P=0.01). Eleven carotid occlusions contralateral to the stenosis were present and were excluded from the analysis. As shown in Figure 2, the mean GSM value was significantly lower among symptomatic patients at all levels (P<0.01, adjusted for the number of comparisons). No statistically significant difference was observed between the GSM values at the different
levels, although the values observed at levels 0 and 30 had a tendency to be lower than those of the whole plaque (mean values of 29 and 30, respectively, for the levels 0 and 30 versus 36 for the whole plaque; Figure 2).

Thirty-four carotid stenoses (33 patients) were MES+ (1 patient had bilateral stenosis of >70% and presented MES in both MCAs). The median number of MES was 2 and the range between 1 and 13. MES+ stenoses were more frequently symptomatic (21 of 34; 62%), whereas MES− stenoses more often asymptomatic (86 of 125; 68%; \( P < 0.02 \), adjusted for the number of comparisons). High (70% to 99%) degree stenoses were also more frequently associated with MES+ plaques (22 of 34; 65%) than moderate (30% to 69%) stenosis (12 of 34; 35%); however, the difference did not reach statistical significance (\( P = 0.09 \)). The mean GSM values were lower among MES+ than among MES− patients. However, the difference was only statistically significant when considering the GSM at the level 0 (\( P < 0.01 \) adjusted for the number of comparisons; Figure 3). No significant association was found between the presence of MES and the GMSs of the levels 30 (\( P = 0.35 \)), 50 (\( P = 0.056 \)), or the GSM of the whole plaque (\( P = 0.06 \)). In a proportional odds logistic regression model calculated on the grounds of 4 subgroups with an increasing clinical risk (MES−/symptoms− \( n = 86 \); MES−/symptoms+ \( n = 39 \); MES+/symptoms− \( n = 13 \); MES+/symptoms+ \( n = 21 \)) and including the covariates of degree of stenosis and antiplatelet treatment, low mean GSM values at the surface levels and predominance of the red color on the surface of the plaque were independent factors associated with the presence of symptoms or of MES. No significant correlation with degree of stenosis nor with the presence or absence of antiplatelet treatment (data not shown) was observed. Furthermore, compared with a whole plaque measurement by color mapping, analysis of the surface systematically predicted each 1 of these 4 groups with a greater sensitivity and specificity, calculated on the grounds of ROC curves (Figure 4).

The majority of the stenoses presented a heterogeneous pattern (119 of 159; 75% heterogeneous versus 40 of 159; 25% homogeneous); the same difference persisted whatever the degree of stenosis: for 30% to 49% stenoses, 5 of 15 (33%) homogeneous and 10 of 15 heterogeneous (66%); for 50% to 69% stenoses 13 of 61 (21%) homogeneous and 48 of 61 (79%) heterogeneous; and for 70% to 99% stenosis, 22 of 83 (26%) homogeneous and 61 of 83 (74%) heterogeneous. Heterogeneous plaques were more frequently symptomatic than the homogeneous ones (38 of 60; 64% versus 22 of 60; 36%; \( P = 0.022 \)). No significant differences were observed between the prevalence of homogeneous or heterogeneous plaques among MES+ or MES− plaques. There was a good interobserver agreement (R.S. and I.M.) with \( \kappa \) values between 0.73 and 0.76 for the different GSM measurements.

**Discussion**

Carotid plaque surface irregularity or ulceration are believed to play an important role in the risk of ischemic stroke. By exposing thrombogenic layers of the plaque such as the necrotic core, surface alterations may lead to subsequent thrombus formation, which may be responsible of emboliza-
Recent studies found a higher risk for subsequent stroke if angiographic evidence of an ulcerated plaque was demonstrated. However, only few ultrasound studies, addressing this particular question, have been performed so far, mainly because of a low interobserver agreement and a poor sensitivity and specificity reported with reference to the histological data. Furthermore, it has been shown that the reliability of the ultrasound detection of ulceration reduces as the degree of stenoses increases. There have also been only very few attempts to evaluate the plaque surface by means of a GSM computer-aided analysis. Tegos et al used a bending energy calculation to distinguish plaques with irregular or smooth surfaces but failed to separate these 2 groups of patients with this method. Our study showed that symptomatic or MES plaques presented significantly lower mean GSM values than asymptomatic or MES ones. These results

Figure 3. Comparison between stratified GSM values (levels 0, 30, and 50 and mean values of the whole plaque) of 34 MES+ and 125 MES− with 30% to 99% carotid stenoses (symptomatic or asymptomatic). The bars represent SD.

Figure 4. Sensitivity and specificity (ROC curves) of the predominant color of the whole plaque (green) or of the surface (blue) to predict 4 groups of patients: A, MES−/symptoms− (n=86); B, MES−/symptoms+ (n=39); C, MES+/symptoms− (n=13); D, MES+/symptoms+ (n=21).
TABLE 2. Proportional Odds Logistic Regression Model Calculated on 4 Subgroups Established According to the Increasing Clinical Risk

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR*</th>
<th>95% CI</th>
<th>*P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSM 0</td>
<td>0.96</td>
<td>0.95 to 0.98</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>GSM 30</td>
<td>0.97</td>
<td>0.95 to 0.98</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>GSM 50</td>
<td>0.98</td>
<td>0.96 to 0.99</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>GSM whole plaque</td>
<td>0.98</td>
<td>0.96 to 0.99</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Predominant color of the whole plaque</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red vs yellow</td>
<td>5.3</td>
<td>2.6 to 11.02</td>
<td>&lt;0.00048</td>
</tr>
<tr>
<td>Yellow vs green</td>
<td>2.6</td>
<td>0.77 to 9.02</td>
<td>0.124</td>
</tr>
<tr>
<td>Predominant color of the surface</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red vs yellow</td>
<td>12.8</td>
<td>3.6 to 40.4</td>
<td>&lt;0.00046</td>
</tr>
<tr>
<td>Yellow vs green</td>
<td>1.5</td>
<td>0.35 to 7.6</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*The odds ratio (OR) represents the likelihood of belonging to a superior risk category (increasing clinical risk: MES−/symptoms < MES+/ symptoms < MES−/−symptoms < MES+/+symptoms, ). For instance, the OR of 0.96 (GSM 0) means a likelihood of 4%, and an OR of 0.98 (GSM 50) means a likelihood of 2%.

are in agreement with previous studies performed with computer-aided analysis, which demonstrated that plaques associated with hemispheric symptoms are more hypoechoic than those associated with no symptoms. Furthermore, the analysis by stratum showed that the values at the surface (levels 0 and 30) tended to be lower for symptomatic or MES lesions. However, a statistically significant difference between mean GSM values of the whole plaque and of its surface was only obtained in the presence of MES, strongly suggesting a link between the presence of surface abnormalities and the emboli (Figure 2). In a proportional odds logistic regression model with 4 subgroups with increasing clinical risk, low mean GSM values and predominance of the red color at the surface were independent factors associated with the presence of symptoms or MES (Table 2). Accordingly, the odds ratio associated with these factors pointed systematically to a category of increased clinical risk (Table 2). Color mapping of the plaque further demonstrated that analysis of the surface predicted with a greater sensitivity and specificity than a whole plaque measurement the presence or absence of symptoms or of MES.

MES may represent plaque instability, as demonstrated in a study performed by Sitzer et al, who found in asymptomatic and recently symptomatic patients undergoing carotid endarterectomy a strong association between plaque ulceration, intraluminal thrombosis, and downstream cerebral MES. Moreover, the presence of MES has been associated in several studies with an increased risk of further cerebrovascular events in symptomatic as well as in asymptomatic patients. However, it should be noted that MES are frequently found among recently symptomatic patients but much more rarely among asymptomatic ones. Therefore, our findings suggest that low GSMs at the surface level, assessed either by the stratified analysis or by color mapping, were associated with the presence of MES and thereby may contribute to discriminate between low-risk (MES−) and high-risk (MES+) asymptomatic stenoses. However, whether the surface GSM values per se may identify high-risk asymptomatic stenoses independently of the presence of MES should be investigated in a longitudinal trial.

In contrast to previous studies performed with computer-aided analysis which reported a higher prevalence of the homogeneous pattern among symptomatic plaques, we found, on the basis of color mapping, an increased frequency of the heterogeneous pattern among symptomatic stenoses (P = 0.022). These opposite results may be attributable to the different methodologies used. El-Barghouty et al used a heterogeneity index in their analysis, defined as the difference between the GSM of the most echogenic and that of the most anechoic areas within the plaque. Wijeyaratne et al, using a computer-derived B-mode ultrasound gray-scale measurement, compared a single longitudinal view versus multiple cross-sectional views and found only 30% of the heterogeneous plaques to be symptomatic. Our approach consisted of an evaluation based on color mapping of the plaque with heterogeneity defined as the presence of ≥2 different colors. Thus, whether homogeneity or heterogeneity of the plaque constitutes a risk factor for stroke still remains a matter of debate and further trials comparing these different methods are needed to resolve this issue.

Conclusion

Low mean GSM values and predominance of the red color at the surface correlated with most of the symptomatic or MES+ stenoses and predicted them with greater sensitivity and specificity than a whole plaque measurement. The approach combining GSM stratified analysis and color mapping should therefore be investigated further in a longitudinal study.

References


