Accuracy of a Novel Risk Index Combining Degree of Stenosis of the Carotid Artery and Plaque Surface Echogenicity

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Background and Purpose—The purpose of this study was to determine the accuracy of a risk index in symptomatic or asymptomatic carotid stenoses.

Methods—Consecutive patients presenting 50% to 99% carotid stenoses were included. A semiautomated gray scale-based color mapping (red, yellow, and green) of the whole plaque and of its surface was achieved. Surface was defined as the region located between the lumen (Level 0) and, respectively, 0.5, 1, 1.5, and 2 mm. Risk index was based on a combination of degree of stenosis and the proportion of the red color (reflecting low echogenicity) on the surface or on the whole plaque.

Results—There were 67 (36%) symptomatic and 117 (64%) asymptomatic carotid stenoses. Risk index values were higher among symptomatic stenoses (0.46 mean versus 0.29; \( P < 0.0001 \)); on receiver operating characteristic curves, risk index presented a stronger predictive power compared with degree of stenosis or surface echogenicity alone. Also, in a regression model including age, gender, degree of stenosis, surface echogenicity, gray median scale of the whole plaque, and risk index, risk index measured within the surface region located at 0.5 mm from the lumen was the only parameter significantly associated with the presence of symptoms (OR, 4.89; 95% CI, 2.7–8.7; \( P = 0.0000002 \)). The best criterion to differentiate between symptomatic and asymptomatic stenoses was a risk index value \( > 0.36 \) (sensitivity and specificity of 78% and 65%, respectively).

Conclusions—Risk index was significantly higher in the presence of symptoms and could therefore be a valuable tool to assess the clinical risk of a carotid plaque. (Stroke. 2012;43:00-00.)

Key Words: carotid stenosis ■ Doppler ultrasound ■ stroke

At present, the decision whether to intervene or not on carotid stenoses relies mainly on the severity of the degree of stenosis. Several studies demonstrated, however, that many highly stenotic lesions remain asymptomatic even after years, whereas others, with a more moderate degree of stenosis, tend to progress and are responsible of a stroke or transient ischemic attack much more rapidly.\(^1\)\(^2\) Degree of stenosis alone may therefore not be sufficient to evaluate the risk of stroke and additional markers are therefore needed to better identify subgroups of high-risk patients who would benefit most from surgery or angioplasty. Plaque morphology also plays an important role in the occurrence of cerebrovascular events and may be a predictor of the risk of ipsilateral stroke as well.\(^1\)\(^-\)\(^9\) Two types of advanced carotid artery disease are described: 1 form, stable and unlikely to produce symptomatic embolization and a second form, although not necessarily being more stenotic, unstable, and at high risk of cerebrovascular disease.\(^10\)\(^11\) To take into account the hemodynamic factor as well as the structure of the plaque, we developed on ultrasound a risk index (RI) based on a combination of degree of the stenosis and echogenicity of plaque surface. The aim of our study was to evaluate the accuracy of this RI in a cohort of consecutive patients presenting symptomatic or asymptomatic carotid stenoses and to compare this method with other well-established parameters including degree of stenoses alone and gray median scale of the whole plaque.

Patients and Methods
Consecutive patients presenting a 50% to 99% carotid stenosis were included in the study. During a 3-year period from 2006 to 2009, we identified 162 patients presenting a 50% to 99% carotid stenosis. There were 2 groups of patients: patients with a history of a recent...
Table 1. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>No. of Patients (N=162)</th>
<th>Symptoms Positive</th>
<th>Symptoms Negative</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>75.6</td>
<td>76.1</td>
<td>NS</td>
</tr>
<tr>
<td>Female gender (n=111)</td>
<td>16 (24%)</td>
<td>28 (24%)</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender (n=118)</td>
<td>47 (70%)</td>
<td>71 (61%)</td>
<td>NS</td>
</tr>
<tr>
<td>Tobacco (n=47)</td>
<td>20 (30%)</td>
<td>27 (23%)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>High blood pressure (n=137)</td>
<td>52 (78%)</td>
<td>85 (73%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia (n=113)</td>
<td>42 (63%)</td>
<td>71 (66%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (n=44)</td>
<td>15 (22%)</td>
<td>29 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>Antiplatelet treatment (n=111)</td>
<td>40 (60%)</td>
<td>71 (61%)</td>
<td>NS</td>
</tr>
<tr>
<td>Statins (n=96)</td>
<td>34 (51%)</td>
<td>62 (53%)</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary disease (n=54)</td>
<td>16 (24%)</td>
<td>38 (32%)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive family history* (n=66)</td>
<td>20/43 (47%)</td>
<td>46/91 (51%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

The following steps were performed: the plaque was outlined automatically at its surface on its longitudinal section. For this, an algorithm was used to delineate the boundary between the color flow and the surface of the plaque. At the adventitial border, the plaque was outlined manually. All carotid plaques were then normalized with the use of the reference values of 0 (blood) and 190 (adventitia). Color mapping of the whole plaque and of its surface used red, yellow, and green according to the gray scale value. For this we used the following 5 thresholds: gray scale values <60, 50, 40, 30, and 20 mapped in red; between 60 and 90, 50 and 80, 40 and 70 mapped in yellow; and >90, 80, 70, 60, and 50 mapped in green. For each plaque, the proportion of each color present on the whole plaque and on its surface was assessed automatically. The surface was defined as the region located between the lumen (Level 0) and, respectively, 0.5, 1, 1.5, and 2 mm.13-15 RI was derived from a previous work, which evaluated the ability of different parameters to predict cerebrovascular events in a cohort of patients with carotid stenoses. In a logistic regression model, only degree of stenosis and the predominance of the red color on the surface of the plaque were independent predictors of the presence of symptoms. RI was based on a combination of degree of stenosis and the proportion of the red color on the surface or on the whole plaque and was further calculated with the following formula:

\[
\text{RI} = -1 + \exp (-8.98404 + 0.0458 \times \text{degree of stenosis} + 0.06018 \times \text{proportion of red on the surf})
\]

Gray Scale Median Assessment of the Whole Plaque

Gray scale median (GSM) values of the whole plaque were obtained according to the method described by El-Barghouty and colleagues.16 After automatic delineation of plaque surface on its longitudinal section and manual outlining at the adventitial border, the GSM of the frequency distribution of gray scale values of the pixels within the whole plaque was used as the measurement of the echogenicity. All carotid plaques were also normalized with the use of the reference values of 0 (blood) and 190 (adventitia).

Magnetic Resonance Imaging

In symptomatic patients, brain MRI was performed within a timespan of 48 to 72 hours; in asymptomatic patients, brain MRI was performed within a delay of 30 days after the detection of the carotid stenosis. The following sequences were used for evaluation: diffusion-weighted, T2-weighted, and fluid-attenuated inversion recovery. A lesion was considered as related to the carotid stenosis if located in the ipsilateral cortical or subcortical area with an embolic aspect or in a watershed area. When present on diffusion-weighted sequences, the lesion was considered as acute. Lacunar lesions were not considered as related to the carotid stenosis when associated with signs of diffuse microangiopathy. Lesions were considered as silent whenever not associated to neurological symptoms but still in the territory of the stenosed carotid artery. All images were reviewed by an experienced neuroradiologist (K.L.) who was not aware of the clinical history.

Statistics

Statistical analysis was performed according to t test (2-tailed). Receiver operating characteristic curves comparisons and logistic regression analysis were performed by means of MedCalc program and SPSS. A probability value of <0.05 was chosen as the level of significance.

Results

One hundred eighty-four 50% to 99% carotid stenoses from 162 patients were evaluated, 67 (36%) symptomatic and 117 (64%) asymptomatic. Twenty-two patients presented bilateral stenoses. MRI lesions considered as related to the carotid stenosis were present in 64 cases (35%). The baseline
characteristics of the patients are further given in Table 1. The proportion of moderate stenosis was significantly higher in the asymptomatic group, whereas high-grade stenoses were more frequently found in the symptomatic group (P < 0.01).

The risk index was calculated in every patient, for every surface level, and for the 5 different thresholds. The mean value of the RI was significantly higher among symptomatic stenoses (0.46 ± 0.29, P < 0.0001; Figure 1). We calculated the mean RI values obtained from different surface levels and from the analysis of the whole plaque; the highest value was found within the 0- to 0.05-mm region (Figure 2). Furthermore, on receiver operating characteristic curves, RI showed higher values than degree of stenosis or surface echogenicity alone (Figure 3) and in a logistic regression model including age, gender, risk index, GSM of the whole plaque, RI measured within the surface region located at 0.5 mm from the lumen and based on the threshold of 60, 60, and 90, and >90 was the best predictor of the presence of symptoms (OR, 4.89; 95% CI, 2.7–8.7; P = 0.000002). On grounds of receiver operating characteristic curves, we found that the best criterion to differentiate between symptomatic and asymptomatic stenoses was RI of >0.36 (sensitivity and specificity of 78% and 65%, respectively; Table 2; Figure 3). The cutoff values for the other parameters are shown in Table 2. We found similar predictive values of the studied variables regarding the presence or absence of lesions on MRI (Table 2). An important proportion (42 of 117 [35%]) of patients with asymptomatic stenoses presented a RI >0.36. However, when looking at the presence of silent ischemic lesions on MRI, we found a statistically significant difference between the groups with a high >0.36 (4 of 42) and a low RI (<0.36; 0 of 75; P < 0.01).

An interrater agreement of 88% was obtained using either the cutoff value of 0.36 or a difference of ±0.15 for the RI calculation between the 2 investigators. The lowest difference observed between the 2 investigators was 0.0 and the highest of 0.4 (mean value of all the differences observed between the 2 investigators was 0.1). The κ value was 0.86.

**Discussion**

Although a number of characteristic features of plaque morphology, including echogenicity, structure, and surface, has been associated with an increased subsequent risk of cerebrovascular events, it is not known which 1 of these different parameters is actually the best predictor of such events. Most of the previous studies, focused on plaque morphology, mainly considered whole plaque features. Besides visual analysis of plaque echogenicity,17,18 the most frequently method used for this purpose in recent years has been the GSM analysis with longitudinal, multiple cross-sectional views as well as with pixel intensities distribution as an expression of plaque heterogeneity.19–24 The attempts to stratify carotid plaques according to clinical risk and using the GSM method have, however, not been uniformly successful, possibly because the GSM method represents a median value of different plaque components, attenuating thereby the effect of plaque regions at higher risk. Only few ultrasound-based studies focused on plaque surface characteristics. Their results showed, however, evidence of low interobserver agreement as well as low predictive values.25,26 Moreover, it is known that the reliability of the ultrasound detection of plaque surface reduces as the degree of stenoses increases.27

There has been 1 attempt in recent years to evaluate ultra-
sonographically the surface of the plaque by measuring the fibrous cap; the method, however, was limited by the resolution of ultrasound ranging from 200 to 600 μm and therefore not appropriate in some cases with very thin fibrous caps. Various ultrasound studies put emphasis on the relation between hemodynamic and morphological parameters of the carotid plaque. Most of these considered in their analysis the whole plaque rather than the plaque surface. Gronholdt et al followed the incidence of ipsilateral ischemic strokes in asymptomatic and symptomatic patients and observed that echolucent plaques causing ≥50% diameter stenosis were associated with an increased risk of future stroke in symptomatic but not in asymptomatic individuals. In another study, Aburahma and colleagues analyzed patients with >60% asymptomatic carotid stenoses according to ultrasonic plaque morphology and found that patients with heterogeneous plaques had a higher incidence rate of late stroke, transient ischemic attack, and progression to >70% or 70% stenosis than patients with homogeneous plaques. Only a few studies considered plaque surface and degree of stenosis. Rothwell and coworkers with the use of conventional angiography included 3007 subjects from the European Carotid Surgery Trial (ECST) and found that plaque surface irregularity was associated with an increased risk of ipsilat-

Table 2. Criterion, Sensitivity, and Specificity of the Different Variables Studied According to the Presence of Symptoms or Lesions on MRI

<table>
<thead>
<tr>
<th>Presence of Symptoms</th>
<th>Degree of stenosis</th>
<th>GSM whole plaque</th>
<th>Proportion of red color within 0–0.5 mm</th>
<th>RI 0–0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion</td>
<td>&gt;70%</td>
<td>≤43</td>
<td>&gt;85%</td>
<td>&gt;0.36</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>65</td>
<td>85</td>
<td>64</td>
<td>78</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>50</td>
<td>48</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>Area Under the Curve</td>
<td>0.62</td>
<td>0.69</td>
<td>0.74</td>
<td>0.757</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.544–0.695</td>
<td>0.62–0.76</td>
<td>0.67–0.78</td>
<td>0.69–0.81</td>
</tr>
</tbody>
</table>

GSM indicates gray scale median; RI, risk index.

Figure 4. Example of a symptomatic plaque with RI of 0.68 (A–B) and of an asymptomatic plaque with RI of 0.02 (C–D). RI indicates risk index.
eral ischemic stroke on medial treatment at all degrees of stenosis. Another recent study by Griffin et al sought to determine in ultrasonic images of internal carotid artery plaques the diagnostic value of a juxtaluiminal an echogenic area in the absence of a visible echogenic cap. In a multiple logistic regression model, increasing stenosis (mild, moderate, severe), GSM <15 and an echogenic cap ≥8 mm were associated with hemispheric symptoms. These different parameters were however only considered separately in all of the mentioned studies and a combined approach has so far not been reported. Only 1 study established a score that included degree of stenosis, plaque surface irregularity, echolucency, and texture; the Total Plaque Risk Score resulted in being a strong predictor of subsequent ischemic events in 1348 subjects followed for 12 years. There are, however, limited data regarding the reproducibility of the score taking into account the fact that inter- and intrarater agreement has been often reported as low when echogenicity and plaque surface were analyzed visually.

We have found in our study that RI values, based on the combination of degree of stenosis and plaque surface echogenicity, were significantly higher among symptomatic stenoses (Figure 1). Also, on the receiver operating characteristic curve, RI showed higher values as compared with degree of stenosis or surface echogenicity alone (Figure 3). Using the cutoff value of 0.36, this method differentiated symptomatic and asymptomatic stenoses with a sensitivity and specificity of 78% and 64%, respectively (Table 2). We calculated further the mean RI values obtained from different surface levels and from the analysis of the whole plaque and found the highest value within the 0- to 0.5-mm region (Figure 2). Moreover, in the present study, RI as well as surface echogenicity of the plaque yielded better predictive values than those obtained with the GSM method, reinforcing the hypothesis that echogenicity of plaque surface may be even a stronger predictor than the 1 of the whole plaque (Figures 3 and 4). When further correlating RI with the presence of lesions on MRI in the symptomatic group, we also found similar predictive values as for the presence of symptoms (Table 2). Interestingly, in the asymptomatic cohort, more than one third of the patients presented a RI >0.36. However, the presence of silent ischemic lesions on MRI was increased in this group as compared with those with a low RI (P<0.01), suggesting that RI may potentially identify high-risk plaques within an asymptomatic cohort (data not shown).

Conclusions

Among different parameters studied, including age, gender, degree of stenosis, surface echogenicity, gray median scale of the whole plaque, and RI, only RI measured within the surface region located at 0.5 mm from the lumen was significantly associated with the presence of symptoms. The best criterion to differentiate between symptomatic and asymptomatic stenoses was >0.36. RI may be therefore a valuable tool to assess the clinical risk of a carotid stenosis and should be further investigated in a prospective study.

Acknowledgments

We thank Miss Florence Saumier and Miss Donatienne Wynar for her excellent technical assistance.

Sources of Funding

This study was granted by the Swiss National Scientific Fonds (32003B-116215).

Disclosures

None.

References


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Stroke. published online March 8, 2012:

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2012/03/07/STROKEAHA.111.634766