Baroreflex Sensitivity to Predict Malignant Middle Cerebral Artery Infarction

Marek Sykora, MD, PhD; Thorsten Steiner, MD; Andrea Rocco, MD, PhD; Peter Turcani, MD, PhD; Werner Hacke, MD, PhD; Jennifer Diedler, MD

Background and Purpose—Hemicraniectomy has been shown to be an effective treatment of life-threatening edema (LTE) in malignant middle cerebral artery infarction when performed early. Identifying patients who will develop LTE is therefore imperative. We hypothesize that autonomic shift toward sympathetic dominance may relate to LTE formation. We aimed to investigate the predictive potential of baroreflex sensitivity (BRS) as a marker of autonomic balance for calculating the course of large middle cerebral artery infarction.

Methods—Patients with middle cerebral artery infarction $\geq 2/3$ of the territory and BRS measurement at admission were analyzed. BRS was estimated using the cross-correlational method. Demographic, clinical, and radiological data including stroke severity, infarct size, and basal ganglia involvement were recorded. Malignant course with LTE was defined as clinical deterioration and midline shift $\geq 5$ mm in the first 48 hours.

Results—Eighteen (62.8%) patients developed LTE. Patients with LTE had lower BRS (2.3 versus 4.4 mm Hg/ms, $P=0.007$), larger infarcts (214 versus 144 mL, $P=0.03$), more frequent involvement of the basal ganglia (14 versus 4, $P=0.03$), and more often underwent thrombolysis combined with endovascular intervention (6 versus 0, $P=0.04$). In a multivariate model, BRS (OR, 0.36; CI, 0.14–0.93; $P=0.03$) and basal ganglia involvement (OR, 11.53; CI, 1.15–115.9; $P=0.04$) were independent predictors for LTE. This model correctly classified 86.2% of the malignant cases.

Conclusions—Decreased BRS, mirroring sympathetic activation, and basal ganglia involvement were associated with development of malignant course with LTE in large middle cerebral artery infarction. The predictive relevance of our findings needs to be confirmed in further studies. (Stroke. 2012;43:714-719.)

Key Words: autonomic ■ baroreflex ■ basal ganglia ■ malignant ■ middle cerebral artery ■ stroke

A malignant course with space-occupying, life-threatening brain edema (LTE) is the most feared complication of large middle cerebral artery (MCA) infarctions. Early retrospective studies as well as conservative arms from the recent randomized controlled studies on decompressive surgery report mortality rates up to 80%.1,2 Hemicraniectomy has clearly been shown to reduce mortality and disability when performed within 48 hours of symptom onset in patients up to 60 years of age and gained Level A recommendation from the European Stroke Organisation for the treatment of malignant MCA infarction.3 Nevertheless, in patients developing a malignant course, evidence exists that mortality rates and functional outcome may be even better if surgical treatment is started earlier, before clinical deterioration occurs.4 For these reasons, the early identification of patients at risk for developing LTE in large MCA infarction is of great importance for therapeutic decisions. Several clinical and radiological parameters have been suggested to predict the development of LTE, lacking, however, sufficient predictive power to guide potential surgical therapy before herniation occurs.5 Solely the size of ischemic lesion seems to be a reasonable sensitive and specific predictive parameter for the malignant course.6 However, not all patients with large MCA infarctions develop LTE. Thus, other factors than infarct volume might be involved in the formation of LTE after large MCA infarction. We hypothesize that stroke-induced autonomic shift to sympathetic hyperactivity may relate to brain edema formation. In an animal model, $\beta$-blockers given before the induction of experimental ischemia lead to a reduction in infarct volume by 40%.7 Beta-blockers were able to significantly reduce the brain edema in models of traumatic brain injury and improved the outcome in patients with traumatic brain injury.8–10 In our previous study, decreased baroreflex sensitivity (BRS) indicating sympathetic activation and impaired blood pressure regulation was strongly associated with the size of perihematomal

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edema in patients with intracerebral hemorrhage. Most recently, a post hoc analysis of the Cerebral Hematoma And NXY Treatment Trial study showed that antidiurenergic medication reduced perihematomal edema after intracerebral hemorrhage.

Therefore, we aimed to investigate the predictive value of BRS, a marker of autonomic balance, among other possible predictors, to calculate the course of large MCA infarction.

Methods

Population
From 2007 to 2010, patients with acute ischemic stroke admitted to our stroke unit or neurological intensive care unit were screened for inclusion into an open, prospective database partially reported elsewhere. Briefly, this database prospectively collected patients with acute stroke in whom a nonbiased measurement of BRS is applicable. At the time of the BRS measurement, included patients had to be free of antihypertensive therapy or cardiovascular active treatment for at least 24 hours. If applicable, the type of previous antihypertensive therapy has been noted. Patients with a history of stroke, atrial fibrillation, myocardial infarction, diabetes mellitus or admission level of HbA1c >6%, chronic renal failure, or other medical conditions known to affect autonomic functions are excluded from the BRS measurements, because these conditions may confound the results.

For the purposes of the recent study, we retrospectively extracted patients from the aforementioned database with BRS measurement within the first 24 hours after onset, fulfilling the following criteria for large MCA territory infarction.

Definition of Large MCA Infarction
Large MCA infarction was defined as (1) clinical signs of MCA territory infarction with a National Institutes of Health Stroke Scale score ≥18 on admission or after deterioration; (2) CT angiographic or MR angiographic evidence of internal carotid artery occlusion, MCA main trunk occlusion, or the combination of both; and (3) large MCA infarction on follow-up CT or MR of at least two thirds of the MCA territory.

Primary End Point Definition
The primary end point was the development of malignant course with LTE defined as (1) decrease of consciousness to ≥1 on Item 1a of the National Institutes of Health Stroke Scale and/or clinical deterioration of ≥4 points in the National Institutes of Health Stroke Scale score in the first 48 hours after stroke onset; (2) midline shift ≥5 mm at the level of septum pellucidum seen in the first or second follow-up CT or MR (24–48 hours); and (3) no other obvious cause for neurological deterioration.

Clinical Assessment, Stroke Classification, Stroke Volume, and Recanalization
At admission, patients were scored using the National Institutes of Health Stroke Scale. According to our local protocol, the neurological status was checked using the National Institutes of Health Stroke Scale regularly every 6 hours for the first 72 hours after admission. The stroke volume was calculated from the first follow-up CT or MRI scan using the a×b×c×0.5 method, as described previously. The involvement of basal ganglia was recorded. In detail, basal ganglia involvement was rated as present if at least two thirds of the cumulative area including the head of caudate nucleus + putamen + globus pallidus was affected. Strokes were classified according to the Trial of ORG 10172 in Acute Stroke Treatment criteria. History of hypertension and previous antihypertensive therapy was noted and included into the analysis. Demographic, clinical, and laboratory parameters including admission blood pressure, admission blood glucose, fasting blood glucose on the second day, C-reactive protein, leukocyte count, and body temperature on admission were recorded. The extent of recanalization was determined by transtemporal Doppler on Day 2 according to the Thrombolysis in Brain Ischemia flow grading system. Recanalization was defined as Thrombolysis in Brain Ischemia 4 or 5.

Clinical Management
The decision on surgical decompression was made consensually based on the infarct size, clinical deterioration, and signs of developing space-occupying edema. Patients who did not fulfill the criteria for LTE in the first 24 hours, but underwent an early decompressive hemicraniectomy (<24 hours) due to the very large infarct size, were excluded from the analysis. In this subgroup, the development of LTE could not be rated.

Assessment of Spontaneous BRS
Blood pressure for spontaneous BRS assessment was measured noninvasively using the Finometer device (FMS, Finapres Medical Systems BV, Amsterdam, The Netherlands). This device uses a volume clamp method to capture beat-to-beat (continuous) values of blood pressure and pulse rate in the finger artery. A cuff of appropriate size was attached to the middle finger of the nonhemiparetic hand of the patient in supine position and the hand was maintained at heart level. Using the Finometer device, continuous blood pressure and pulse rate for BRS assessment were recorded within 24 hours after stroke onset, usually on admission, for a period of 10 minutes. Baroreflex sensitivity was calculated using the sequential crosscorrelation method. This method calculates the crosscorrelations between a 10-second series of continuous systolic blood pressure and a 10-second series of interbeat intervals delayed by 0, 1, 2, 3, 4, and 5 seconds. The delay giving the highest correlation between the changes in systolic blood pressure and the changes in interbeat interval is selected if significant at a preset level (P=0.01). Then the regression slope is recorded as 1 BRS value. Subsequently, the process is repeated for series of systolic blood pressure and interbeat interval samples 1 second later. BRS gain values were expressed in ms/mm Hg.

Ethics
The local ethics committee approved the study. All patients or their next of kin gave written informed consent.

Statistics
Distribution of the data was visualized using histograms and tested using the 1-sample Kolmogorov-Smirnov test. For normally distributed data, the results are presented as mean, range, and SD and for nonnormally distributed data as median, range, and interquartile range. For comparison between the groups, Fisher test, Mann-Whitney U test, or Student unpaired t test was used, as appropriate. Correlation analysis using Spearman or Pearson correlation coefficient was used to explore the univariate associations between the variables. Partial correlations and multivariate regressions were used to adjust for possible confounders. When significant in the univariate analysis, variables entered a stepwise logistic regression model to study the relationship between predictive variables and dependent variables. Independent predictors from the multivariate analysis were used to create a score to predict LTE as follows: receiver operator curve analysis was used to estimate BRS cutoff points to predict LTE. Based on these cutoff points, the linear BRS variable was recoded into a categorical, trichotomous variable. The trichotomous BRS variable, infarct volume, basal ganglia involvement, and therapy were included into a stepwise multivariate regression model. The final B estimates of this model were then used to weight the score. Receiver operator curve, areas under the receiver operator curve (c-statistic), and 95% CI were calculated as a measure of predictive ability of the score. Values of P<0.05 were considered statistically significant in all tests. All statistics were performed using statistical software SPSS 19.0 for Windows.

Results
Twenty-nine patients with large MCA territory infarctions fulfilling the mentioned criteria were extracted from the
database and entered the analysis. Demographic, clinical, and radiological characteristics are presented in Table 1. Twenty-three of 29 patients (79.3%) were naive to previous antihypertensive treatment. Of the 6 patients with a positive history of antihypertensive therapy, 2 were taking their medication only irregularly. In 4 patients on antihypertensive therapy, the BRS assessment was timed to 24 hours after the last dose of medication was taken. The median time from onset of symptoms to BRS measurement in the whole cohort was 12 hours (range, 2–24 hours; interquartile range, 12.5). Fifteen (51.7%) patients received conservative treatment, 7 (24.1%) patients intravenous thrombolysis, 6 (20.7%) combined intravenous thrombolysis and endovascular treatment, and 1 (3.4%) patient was treated solely endovascularly. In total 8 (9.4%) patients had recanalized on Day 2 (Thrombolysis In Brain Ischemia 4 or 5). The mean midline shift at 24 to 48 hours was 5.37 mm (range, 0–11 mm; SD 2.97). Eighteen (62.8%) patients developed malignant course with life-threatening edema. Patients developing LTE had lower median BRS (median 2.3 mm Hg/ms versus 4.4 mm Hg/ms, P=0.007), had larger infarcts (median 214 mL versus 144 mL, P=0.03), more frequently had involvement of basal ganglia (14 versus 4, P=0.03), and more frequently were treated with intravenous thrombolysis combined with endovascular intervention (6 versus 0, P=0.04). Recanalization rate did not differ between LTE and no LTE patients (4 versus 4, P=0.43). All 18 patients with LTE underwent decompressive hemicraniectomy. Table 2 gives the demographic, clinical, and radiological characteristics including BRS and laboratory parameters for both groups.

BRS inversely correlated with midline shift measured at 24 to 48 hours after admission (r=−0.6, P=0.001). After adjustment for infarct volume, the inverse correlation between BRS and midline shift remained significant (r=−0.44, P=0.02). Neither infarct volume nor basal ganglia involvement correlated with BRS (r=−0.27, P=0.16 and r=−0.1, P=0.55).

In a multivariate logistic stepwise regression model to predict LTE including BRS, type of initial therapy, basal ganglia involvement, and infarct volume, only BRS (b=−0.13; OR, 0.36; CI, 0.14–0.93; P=0.03) and basal ganglia involvement (b=2.44; OR, 11.53; CI, 1.15–116; P=0.04) remained independent predictors for LTE (Table 3). This model including BRS and basal ganglia involvement correctly classified 86.2% of the LTE cases with a sensitivity of 88.9% and a specificity of 81.8%, false-positive rate 11%, and false-negative rate 18%. Excluding BRS from multivariate modeling resulted in a drop of the predictive ability of the model to 72.4% of correctly classified LTE cases, leaving basal ganglia involvement the only significant predictor.

Receiver operator curve analysis was used to identify BRS cutoffs and thereby define 3 different BRS categories: BRS range 0 to 2.5 ms/mm Hg, BRS range 2.51 to 4 ms/mm Hg, and BRS >4 ms/mm Hg. Including BRS ranges into the multivariate analysis together with basal ganglia involvement, infarct volume and type of therapy resulted in the same model fit as the model using BRS as a continuous variable (correctly classifying 86.2%). BRS ranges and basal ganglia involvement remained the only significant predictors for LTE (b=−2.7; OR, 0.07; CI, 0.01–0.57; P=0.01 and b=3.2; OR, 24.9; CI, 1.2–495.3; P=0.03; Table 3).

Based on this model, we constructed a score to predict LTE as follows: BRS in the range 0 to 2.5 ms/mm Hg was scored with 2 points, BRS in the range 2.51 to 4 ms/mm Hg was scored with 1 point, and BRS >4 ms/mm Hg was scored with 0 points. Basal ganglia involvement was scored with 1 additional point, resulting in a score ranging from 0 to 3 points. The receiver operator curve analysis of this score yielded a c-statistic of 0.89 (P<0.001; 95% CI, 0.79–1). With 0 points, the risk for LTE was 0%, with 1 point the risk was 20%, with 2 points 63.6%, and with 3 points the risk was 100%.

Discussion

Autonomic changes arise at stroke onset and may relate to stroke severity as well as to localized damage in the central autonomic network.13,18 Our findings suggest that impairment of the autonomic regulation may relate to malignant course with edema formation in large MCA infarction. Of importance, autonomic shift as measured by BRS seems to precede the development of life-threatening edema.

Because data on this topic are scarce, we can only speculate on the possible underlying mechanisms. First, decreased BRS indicates a shift of the autonomic balance toward sympathetic hyperactivity. A shift to sympathetic predominance has been previously shown to be associated with proinflammatory cytokine production, hyperglycemia, and increased blood–brain barrier permeability.19–21 In turn, these mechanisms have been proposed to be involved in brain edema formation.22–24 Arterial baroreflex function has been shown to be an important determinant of acute cerebral ischemia in rats with MCA occlusion. Baroreflex dysfunction was significantly associated with increased levels of proinflammatory factors interleukin–1 and interleukin-6 as well as with infarct growth.25 In line with the latter, an interesting study by Ai et al showed in humans that MCA infarcts

**Table 1. Demographic and Clinical Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (range, SD)</td>
<td>53.9 (15–73, 13.5)</td>
</tr>
<tr>
<td>Sex, males, no. (%)</td>
<td>11 (37.9)</td>
</tr>
<tr>
<td>Previous hypertension, no. (%)</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>Previous antihypertensive treatment, no. (%)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Stroke volume, mL, median (range, IQR)</td>
<td>190 (120–325, 86)</td>
</tr>
<tr>
<td>NIHSS at admission, median (range, IQR)</td>
<td>20 (13–25, 5)</td>
</tr>
<tr>
<td>Basal ganglia involvement, no. (%)</td>
<td>18 (62.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown, no. (%)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Cardioembolism, no. (%)</td>
<td>8 (27.6)</td>
</tr>
<tr>
<td>Other determined, no. (%)</td>
<td>5 (17.2)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale.
encompassing the insula, one of the principal autonomic and baroreflex regulatory areas, are more prone to growth. Second, impaired BRS in acute stroke is associated with blood pressure derangements including hypertensive crises and increased blood pressure variability. Because cerebrovascular autoregulation seems to be impaired in acute ischemic stroke, in particular in malignant MCA infarction, wide fluctuations in blood pressure may significantly alter cerebral perfusion and contribute to infarct growth and edema development. Indeed, patients with LTE in our series had significantly higher blood pressure variability in the first 24 hours as compared with non-LTE patients (data not shown).

Another important finding is the significance of basal ganglia involvement for the development of LTE. Based on vascular anatomy, we suppose that basal ganglia involvement may be a surrogate for more proximal MCA trunk occlusion...
with less collateral flow. Previous studies suggested attenuation of lentiform nucleus to be a sign for complete internal carotid and/or MCA trunk occlusion and to be predictive for fatal edema. Patients with M1-MCA occlusion and patent anterior temporal artery, which arises at the level of lenticulostriate arteries feeding basal ganglia, are less prone to develop brain edema and have better survival. Furthermore, basal ganglia infarction may possibly contribute to foramen Monro blockade resulting in rapidly increasing intracranial pressure and clinical deterioration.

The strength of our study is that we have included only patients with large MCA infarcts, with >2/3 of MCA territory affected. This allowed us to focus on other potential predictors than the infarct volume, which role has been ported nonradiologic predictors as age, history of hypertensive disease, and admission temperature on admission could be confirmed in our series, and insufficiently validated nonradiologic predictors than the infarct volume, which role has been ported nonradiologic predictors as age, history of hypertensive disease, and admission temperature on admission could be confirmed in our series, as a trichotomous variable.

### Table 3. Final Logistic Regression Models to Predict a Malignant Course With LTE*

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>CI</th>
<th>P</th>
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<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRS, per ms/mm Hg</td>
<td>0.36</td>
<td>0.14–0.93</td>
<td>0.03</td>
</tr>
<tr>
<td>Basal ganglia involvement, present/absent</td>
<td>11.53</td>
<td>1.15–116</td>
<td>0.04</td>
</tr>
<tr>
<td>Infarct volume per mL</td>
<td>...</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>Type of therapy, conservative, IV rtPA, IV rtPA + intervention, intervention only</td>
<td>...</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRS range (0–2.5 ms/mm Hg, 2.51–4 ms/mm Hg, and &gt;4 ms/mm Hg)</td>
<td>0.07</td>
<td>0.01–0.57</td>
<td>0.01</td>
</tr>
<tr>
<td>Basal ganglia involvement, present/absent</td>
<td>24.9</td>
<td>1.2–495.3</td>
<td>0.03</td>
</tr>
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<td>Infarct volume per mL</td>
<td>...</td>
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<td>Type of therapy, conservative, IV rtPA, IV rtPA + intervention, intervention only</td>
<td>...</td>
<td>...</td>
<td>NS</td>
</tr>
</tbody>
</table>

LTE indicates life-threatening edema; BRS, baroreflex sensitivity; IV rtPA, intravenous recombinant tissue plasminogen activator; NS, nonsignificant.

*Model 1 including BRS as a continuous variable and Model 2 including BRS as a trichotomous variable.

### Conclusions

Decreased BRS indicating sympathetic activation and basal ganglia involvement might play a role in the development of malignant course with life-threatening edema in large MCA infarction. The possible predictive relevance of our findings needs to be confirmed in further studies.

### Sources of Funding

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