Prediction of Malignant Middle Cerebral Artery Infarction Using Computed Tomography-Based Intracranial Volume Reserve Measurements

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Background and Purpose—Early decompressive surgery in patients with malignant middle cerebral artery (MCA) infarction improves outcome. Elevation of intracranial pressure depends on both the space occupying brain edema and the intracranial volume reserve (cerebrospinal fluid [CSF]). However, CSF volume was not investigated as a predictor of malignant infarction so far. We hypothesize that assessment of CSF volume in addition to admission infarct size improves early prediction of malignant MCA infarction.

Methods—Stroke patients with carotid-T or MCA main stem occlusion and ischemic lesion (reduced cerebral blood volume [CBV]) on perfusion CT were considered for the analysis. The end point malignant MCA infarction was defined by clinical signs of herniation. Volumes of CSF and CBV lesion were determined on admission. Receiver-operator characteristics analysis was used to calculate predictive values for radiological and clinical measurements.

Results—Of 52 patients included, 26 (50%) developed malignant MCA infarction. Age, a decreased level of consciousness on admission, CBV lesion volume, CSF volume, and the ratio of CBV lesion volume to CSF volume were significantly different between malignant and nonmalignant groups. The best predictor of a malignant course was the ratio of CBV lesion volume to CSF volume with a cut-off value of 0.92 (96.2% sensitivity, 96.2% specificity, 96.2% positive predictive value, and 96.2% negative predictive value).

Conclusions—Based on admission native CT and perfusion CT measurements, the ratio of ischemic lesion volume to CSF volume predicts the development of malignant MCA infarction with higher accuracy than other known predictors, including ischemic lesion volume or clinical characteristics. (Stroke. 2011;42:3403-3409.)

Key Words: computed tomography ■ intracranial volume reserve ■ malignant middle cerebral artery infarction ■ stroke

Ischemic stroke initiates a pathophysiological cascade that leads to the formation of brain edema. This edema represents an additional volume within the fixed internal volume of the skull. The edematous increase of brain volume occurs at the expense of other compartments. Usually, the space occupied by cerebrospinal fluid is the first displaced structure that is squeezed out into the spinal canal. This compensatory mechanism allows for an increase of the brain volume without or with only little changes of the intracranial pressure. However, in larger edema this intracranial volume reserve is exhausted and even small extra increases of the brain volume cause a severe intracranial pressure elevation. In ≈10% of stroke patients, such a significant edema develops secondary to massive middle cerebral artery (MCA) infarction. The resulting increase in intracranial pressure and the tissue shifts with subsequent brain herniation are associated with mortality rates of nearly 80%, thus having framed the term malignant MCA infarction. In patients with malignant MCA infarction, decompressive surgery (hemispherectomy) was shown to reduce mortality and to increase the number of patients with favorable neurological outcome when performed within 48 hours of stroke onset, particularly when undertaken before signs of herniation appear. Therefore, several studies aimed to identify factors that allow early prediction of a malignant course in patients with extensive MCA infarction. The imaging predictors investigated so far mostly involved measurements of infarct size or cerebral midline shift, neurovascular status, and brain perfu-
We hypothesized that in addition to the infarct volume, the intracranial volume reserve represented by the cerebrospinal fluid (CSF) is a major determinant of a malignant course in patients with extensive MCA infarction. It is pathophysiologically reasonable to assume that the ratio of infarct volume to CSF volume will be significantly associated with a malignant course because these volumes influence the extent of brain shift and herniation in opposite ways. Therefore, the aim of the present study was to assess the accuracy of the ratio of infarct volume to CSF volume in predicting malignant MCA infarction and to compare this ratio with known predictive values for a malignant course. Because an early prediction and the use of a robust widely available imaging technique are desirable, we used a stroke imaging protocol based on native CT and whole brain perfusion CT images at admission for volume measurements.

Materials and Methods
Patients
We retrospectively analyzed data of all ischemic stroke patients admitted between December 2008 and September 2010 at the University Hospital of Münster, Germany, a tertiary care center. The inclusion criteria for this study were: (1) acute ischemic MCA stroke; (2) native CT, CTA, and perfusion CT performed on admission; (3) proximal vessel occlusion (carotid-T or MCA main stem); (4) readily visible perfusion deficit with presence of an infarct lesion (reduced cerebral blood volume [CBV]); and (5) follow-up imaging available. These inclusion criteria were chosen to ensure that only patients who were at risk for development of a malignant MCA infarction were considered for the analysis. At our institution, native CT and perfusion CT imaging is part of the routine protocol for patients with suspected stroke and admission <6 hours after symptom onset or with an unknown time of symptom onset. The end point malignant MCA infarction was defined as follows: (1) secondary decline of consciousness ≥1 point on the NIHSS because of cerebral edema; (2) anisocoria attributable to herniation; or (3) death attributable to herniation.15 All patients were admitted to the stroke unit or neurological intensive care unit and clinical signs for malignant MCA infarction were determined at least every 8 hours by an experienced neurologist. Two investigators (J.M. and H.W.) independently extracted data and assessed the occurrence of the end point malignant MCA infarctions blinded to the intracranial volume measurements. Disagreements were solved after discussion of the record details. Patients were excluded from the study when (1) a second ischemic stroke, a hemorrhagic transformation, or secondary intracerebral hemorrhage occurred; (2) the end point of malignant MCA infarction could not be determined because of continuous shift and herniation in opposite ways. Therefore, the aim of this study was to assess the accuracy of the ratio of infarct volume to CSF volume in predicting malignant MCA infarction and to compare this ratio with known predictive values for a malignant course. Because an early prediction and the use of a robust widely available imaging technique are desirable, we used a stroke imaging protocol based on native CT and whole brain perfusion CT images at admission for volume measurements.

Image Protocol
Acute stroke imaging protocol consisted of standard native CT, CTA, and dynamic whole-brain volume perfusion CT using a 128-slice CT scanner (Somatom Definition AS+; Siemens Medical Solutions; native CT: 120 kV, 340 mA, 5.0-mm slice reconstruction, 1.0-mm increment, 0.6-mm collimation, 0.8 pitch, and H30s soft kernel; CTA: 120 kV, 175 mA, 1.0-mm slice reconstruction, 1-mm increment, 0.6-mm collimation, 0.8 pitch, H20f soft kernel, 80 mL Ultravist 370 and 50 mL NaCl flush at 4 mL/s, scan start 6 seconds after bolus tracking at the level of the ascending aorta; perfusion CT: 4-dimensional adaptive spiral covering 96-mm scan length, 80 kV, 200 mA, 5.0-mm slice reconstruction, 5-mm increment, 0.6-mm collimation, 0.8 pitch, H20f soft kernel, 30 mL Ultravist 370, and 30 mL NaCl flush at 6 mL/s, 45-second scan time). Native CT was also used for follow-up imaging of final infarct size and brain swelling.

Image Postprocessing
CBV perfusion maps from perfusion CT images were generated on a workstation supplied by the vendor (Syngo mmwp VE36A; Siemens) with dedicated software for volume perfusion CT. Native CT images were skull-stripped and normalized to MNI-152 space by linear affine transformation with 12 degrees of freedom. Binary masks of intracranial CSF space of the healthy hemisphere (down to the level of the foramen magnum) in admission native CT were obtained by thresholding (22 HU) skull-stripped images with noise reduction (Analyze 10.0; AnalyzeDirect).

Volumetric Image Analyses
Further image analysis involved precise measurements of absolute volume of the ischemic lesion on CBV perfusion maps, volume of final demarcated infarct, volume of intracranial CSF, and intracranial volume (Figure 1). We further measured the maximum volume of brain tissue shifts across the midline on follow-up CT to determine the effect of the ratio of CBV lesion volume to CSF volume on this quantitative imaging marker of brain swelling. The ischemic lesion volume was determined by semiautomated slice-by-slice segmentation of the area of reduced CBV representing infarct core. For segmentation of infarct core, CBV maps were presented at a fixed window center defined by the CBV viability threshold for ischemic brain published elsewhere (2.0 mL×100 g−1),16 with manual adjustment of window width for optimal contrast. The volume of the final infarct and volume of brain shift across the midline were segmented slice-by-slice on the last follow-up native CT before craniectomy or the native CT showing the maximum extent of demarcated infarct and midline shift in cases without decompression. In addition to the absolute volumes, normalized volume measurements were calculated by dividing the ischemic lesion volume, CSF volume, volume of tissue shifts across the midline, and final infarct volume by intracranial volume to account for variability in cranial sizes.

Voxel-Based Probability Map
For each group (malignant and nonmalignant infarcts), standardized maps were generated to depict voxel-wise probability distribution of infarction, CSF volume reserve, and maximum brain shift over the midline. The probability maps were calculated from segmented binary masks of final infarct volume, CSF volume, and volume of tissue shifts across the midline coregistered to MNI-152 space using the corresponding skull-stripped anatomic image file as a template (FLIRT 5.5, FMRIB Software Library; Analyze 10.0, Analyzedirect). To establish symmetry of hemisphere pathology, all masks of ischemic lesion volume and volume of tissue shifts across the midline were transformed to the right and left hemisphere, respectively. Image analysis was performed blinded to the clinical course and to follow-up imaging.

Statistical Analysis
Patient groups (malignant versus nonmalignant MCA infarction) were compared using Student t test (normal distribution) and Wilcoxon rank-sum test (non-normal distribution) for quantitative
variables and $\chi^2$ test for categorical variables. Normal distribution was tested using Shapiro-Wilk test. Spearman correlation coefficients were used to analyze correlations between volume measures. The level of significance was defined as a 2-tailed $P<0.05$.

We determined the discriminatory power and the optimal cut-off values for differentiation among the patient groups using receiver-operating characteristic curves. Cut-off values were chosen to maximize the sum of sensitivity and specificity. Two-sided confidence intervals were calculated using the Wilson procedure with a correction for continuity.20 Areas under the curve were calculated and compared using $\chi^2$ tests. Data analysis was performed using SAS 9.2.

### Results

Within the study period, 1460 patients with the clinical diagnosis of acute ischemic stroke were examined with native CT and perfusion CT. From these, 64 fulfilled the inclusion criteria. Twelve patients were excluded for the following reasons: mechanical ventilation for other reasons than reduced level of consciousness ($n=1$); hemicraniectomy before signs of herniation or edema ($n=3$); reduced level of consciousness due to other reasons than intracranial volume expansions ($n=2$); and second ischemic stroke, hemorrhagic transformation, or secondary intracranial hemorrhage ($n=6$). Overall, 52 patients were left for analysis. Of those, 26 (50%) developed a malignant MCA infarction and 26 did not. Main characteristics of patients are summarized in Table 1. Patients with malignant MCA infarction were significantly younger than patients without malignant MCA infarction. The proportion of patients with a decreased level of consciousness on admission was more frequent in the malignant MCA infarction group. Sixteen patients (61.5%) with malignant MCA infarction were treated with hemicraniectomy. Table 2 shows intracranial volume measurements including times from symptom onset to imaging. Patients with malignant MCA infarction showed larger CBV lesion volumes on admission (median, 231.0 mL; interquartile range [IQR], 220.4 mL versus median 68.8 mL; IQR, 10.9 mL; $P<0.001$; Figure 2A) and larger stroke volumes on follow-up CT (mean, 305.0±132.6 mL versus 99.3±69.2 mL; $P<0.001$). CSF volumes were significantly lower in patients with malignant MCA infarction (mean, 143.1±50.2 mL versus 199.1±80.7 mL; $P=0.004$). The voxel-based probability map of CSF demonstrates a higher probability of volume reserves in the external CSF space and in the ventricles in patients without a malignant MCA infarction (Figure 2B). The ratio of CBV lesion volume and CSF volume was significantly larger in patients with a malignant course (median 1.812 and IQR 1.170 versus median 0.451 and IQR 0.455; $P<0.001$). Also, the volume of brain tissue shifts across the midline was significantly larger in patients with malignant MCA infarction compared to those without (median 1.812 and IQR 1.170 versus median 0.451 and IQR 0.455; $P<0.001$). The time of symptom onset was unknown in 3 patients of both groups.

We further assessed the effect of lesion volume and CSF volume on the volume of brain tissue shifts across the midline on follow-up CT, which is a quantitative structural correlate.
of localized brain edema. The CBV lesion volume was significantly correlated with the volume of brain tissue shifts across the midline (0.895; \(P<0.001\)) and the CSF volume showed a nonsignificant inverse relationship with the midline tissue shifts (\(0.132; P=0.349\); Figure 3A, B). The ratio of CBV lesion volume and CSF volume significantly correlated with the volume of brain tissue shifts across the midline, median (IQR) 0.027 (0.020) 0.001 (0.002) \(P<0.001\); Figure 3A). No patient with CBV volumes <75 mL (n=14) and all patients with CBV volumes >223 mL (n=15) had a malignant MCA infarction develop (Figure 3A). Twenty-three patients had CBV volumes between these values, with 2 of those having a malignant course and 2 having a nonmalignant course.

Using receiver-operating characteristic curves analysis, we calculated the cut-off values of clinical measures and CT-based volume measurements with the highest predictive values for the development of malignant MCA infarction (Table 3). NIHSS score at admission >11.5 shows a moderate sensitivity (88.0%) but rather low specificity (38.5%).

Absolute CBV lesion volumes \(>161.6 \text{ mL}\) and CBV volumes normalized to the intracranial volume \(>0.13\) predict the malignant course with moderate sensitivity (88.5% for absolute volume and 80.8% for normalized volume) and specificity (92.3% for absolute volume and 92.3% for normalized volume). The highest predictive values were found for the ratio of CBV lesion volume and CSF volume (96.2% sensitivity, 96.2% specificity, 96.2% positive predictive value, 96.2% negative predictive value). Because both the proportion of malignant infarcts as well as the proportion of predicted malignant infarcts (by CBV/CSF) was 50%, and because there was 1 false-negative prediction and 1 false-positive prediction, the values for sensitivity, specificity, positive predictive value, and negative predictive value are identical. No differences were observed whether the ratio of absolute or of normalized volumes was used. The area under the receiver-operating characteristic curves (area under the curve) for the ratio of CBV lesion volume to CSF volume was 0.995, which was significantly larger than the area under the curve of any other predicting factor (for details see online Supplemental Table; http://stroke.ahajournals.org).
Discussion

In this cohort study of patients with extensive MCA infarction, we investigated the hypothesis that the ratio of infarct volume and intracranial volume reserve allows a better prediction for the development of malignant MCA infarction compared to other clinical and imaging parameters. We identified several parameters that were significantly associated with a malignant course, including younger age, a decreased level of consciousness on admission, a larger CBV lesion volume, and a smaller CSF volume on admission. Receiver-operating characteristic curves analysis of all parameters identified the ratio of CBV lesion volume and CSF volume, with a cut-off value of $>0.92$ as the most powerful predictor for the development of a malignant MCA infarction. This is reasonable from a pathophysiological point of view because the intracranial volume reserve must be exhausted by the edema before the additional volume causes significant tissue shifts and brain herniation. The inverse relationship of CSF volume to brain tissue shift across the midline that was, however, statistically not significant and the positive correlation between CBV lesion volume and brain tissue shifts across the midline corroborate this pathophysiological consideration. Moreover, it reflects the clinical observation that age-related cerebral atrophy can protect older patients from development of a malignant infarction.\(^8,^9\)

Cerebral edema after ischemic stroke usually peaks between 3 and 5 days after stroke.\(^1\) However, in a given patient it is not predictable at which time the edema causes significant brain tissue shifts with subsequent herniation and clinical deterioration. Several studies were performed to identify parameters that allow a prediction of a malignant course after extensive MCA infarction to guide decisions regarding hemicraniectomy. Clinical parameters, such as coma on admission, high scores on the NIHSS, or early nausea and vomiting are easily accessible but the predictive values are low.\(^9,^10,^14\)

Early signs of infarction on CT including a hyperdense MCA sign or a hypodensity involving $>50\%$ of the MCA territory had acceptable sensitivities but low specificities in most studies.\(^9,^21,^22\) Using perfusion CT, the infarct permeability area was shown to be an independent predictor for the development of infarcts requiring hemicraniectomy.\(^8\) Compared to native CT, perfusion CT allows a better prediction for the development of malignant MCA infarction.\(^9\) With our recent study, however, we showed that using the ratio of CBV lesion volume and intracranial volume reserve increases the predictive accuracy compared to those of the CBV lesion volume alone. CBV measurements were used in our study to determine the ischemic lesion volume because they were shown to be the best parameter to describe the infarct core by early perfusion CT.\(^1\) In our study, on average we predicted a malignant course as early as 182 and 134 minutes after symptom onset in the malignant and the nonmalignant group, respectively. Measuring the ischemic lesion volume by MRI diffusion-weighted imaging was assumed to provide the best predictive values so far. In a study of 28 patients in whom MRI was performed within 14 hours after symptom onset, a lesion volume $>145\text{ mL}$ showed a sensitivity of 100% and a specificity of 94% for the development of a malignant course.\(^11\) Another study that included 37 patients, 11 of whom had development of a malignant course, showed MRI within

Figure 2. Voxel-based probability maps A, Probability distribution of final infarcts (right hemisphere) and tissue shifts across the midline (left hemisphere). B, In the nonmalignant group, the cerebrospinal fluid (CSF) map demonstrates a higher probability of volume reserves, particularly in the perisylvian and frontal subarachnoid space and in the ventricles.
6 hours to predict a malignant MCA infarction with a sensitivity of 87% and a specificity of 91%. The lesion volume cut-off value was 82 mL. However, this cut-off value could not be validated in another larger study that demonstrated a high specificity of 98% but a low sensitivity of 52% for lesion volumes of 82 mL. Generally, a major drawback of the use of MRI as a predictive parameter is the limited availability and feasibility in acute stroke imaging, particularly in severely ill stroke patients requiring mechanical ventilation. An advantage of using perfusion CT is that it can be obtained rapidly in acute stroke patients at the time of their emergency department presentation.

Our study has strengths and limitations. The end point malignant MCA infarction was assessed by 2 independent investigators who were blinded for the imaging volume measurements. For reasons of quality assurance, clinical signs of herniation and focal brain swelling are assessed and recorded at least every 8 hours at our institution, thus allowing an early detection of a malignant course. Patients who underwent hemicraniectomy before the development of clinical symptoms of malignancy were not considered for the analysis to ensure that malignant MCA infarction was defined by specified criteria and not by individual clinician’s judgments and decisions. Moreover, because of the strict inclu-

### Table 3. Prediction of Malignant Middle Cerebral Artery Infarction

<table>
<thead>
<tr>
<th>Predicting Factors</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>Positive Predictive Value, % (95% CI)</th>
<th>Negative Predictive Value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased level of consciousness on admission</td>
<td>52.0 (31.8–71.7)</td>
<td>84.6 (64.3–95.0)</td>
<td>76.5 (49.8–92.2)</td>
<td>64.7 (46.5–79.7)</td>
</tr>
<tr>
<td>NIHSS score on admission &gt;11.5</td>
<td>88.0 (67.7–96.9)</td>
<td>38.5 (20.9–59.3)</td>
<td>57.9 (40.9–73.3)</td>
<td>76.9 (46.0–93.8)</td>
</tr>
<tr>
<td>CBV lesion volume &gt;161.6 mL</td>
<td>88.5 (68.7–97.0)</td>
<td>92.3 (73.4–98.7)</td>
<td>92.0 (72.5–98.6)</td>
<td>88.9 (69.7–97.1)</td>
</tr>
<tr>
<td>Normalized CBV lesion volume &gt;0.13</td>
<td>80.8 (60.0–92.7)</td>
<td>92.3 (73.4–98.7)</td>
<td>91.3 (70.5–98.5)</td>
<td>82.8 (63.5–93.5)</td>
</tr>
<tr>
<td>CSF volume &lt;159.9 mL</td>
<td>73.1 (52.0–87.7)</td>
<td>73.1 (52.0–87.7)</td>
<td>73.1 (52.0–87.7)</td>
<td>73.1 (52.0–87.7)</td>
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<tr>
<td>Normalized CSF volume &lt;0.12</td>
<td>73.1 (52.0–87.7)</td>
<td>73.1 (52.0–87.7)</td>
<td>73.1 (52.0–87.7)</td>
<td>73.1 (52.0–87.7)</td>
</tr>
<tr>
<td>CBV lesion volume/CSF volume &gt;0.92</td>
<td>96.2 (78.4–99.8)</td>
<td>96.2 (78.4–99.8)</td>
<td>96.2 (78.4–99.8)</td>
<td>96.2 (78.4–99.8)</td>
</tr>
</tbody>
</table>

CBV indicates cerebral blood volume; CI, confidence interval; CSF, cerebrospinal fluid; NIHSS, National Institutes of Health Stroke Scale.
sion criteria, only patients who were at risk for development of a malignant course were considered for the analysis. Thus, the 2 groups were well-balanced. Our study is limited by its retrospective design and a validation of the findings in a prospective study is required. Moreover, the image analysis software used in this study is not universally available. However, commercial perfusion software often includes algorithms to perform automated classification of voxels into brain tissue, vessels, and CSF, which can be used to calculate the measures presented in this study.

Conclusions
The ratio of ischemic lesion volume to CSF volume predicts the development of malignant MCA infarction in patients with expansive MCA stroke with high sensitivity, specificity, negative predictive value, and positive predictive value. Based on native CT and perfusion CT, the prediction of a malignant course can be made as early as on admission. Moreover, this imaging technique is widely available and feasible in severe stroke patients, thus making it an ideal supporting tool in therapeutic decision-making concerning hemicraniectomy.

Disclosures
None.

References
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Supplemental table. AUC comparisons of predicting factors

<table>
<thead>
<tr>
<th>Predicting Factors</th>
<th>AUC</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased level of consciousness on admission</td>
<td>0.683</td>
<td>&lt; 0.001</td>
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<tr>
<td>NIHSS on admission</td>
<td>0.599</td>
<td>&lt; 0.001</td>
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<tr>
<td>CBV lesion volume</td>
<td>0.931</td>
<td>0.046</td>
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<tr>
<td>Normalized CBV lesion volume</td>
<td>0.908</td>
<td>0.018</td>
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<tr>
<td>CSF volume</td>
<td>0.723</td>
<td>&lt; 0.001</td>
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<tr>
<td>Normalized CSF volume</td>
<td>0.719</td>
<td>&lt; 0.001</td>
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<tr>
<td>CBV lesion volume/CSF volume</td>
<td>0.995</td>
<td>reference</td>
</tr>
</tbody>
</table>

*P-value of the comparison of the AUC of each of the predicting factors with the AUC of the ratio of CBV lesion volume to CSF volume (Chi-Square, 1 df), AUC, area under the curve.