Background and Purpose—We sought to study the role of MRI-derived cerebral blood flow (CBF) measurements for the prediction of lesion development in acute stroke patients.

Methods—Thirty-two patients were treated with tissue plasminogen activator. Diffusion-weighted (DWI) and perfusion-weighted MRI, T2-weighted imaging, and MR angiography were performed before treatment (2.8±0.9 hours after symptom onset) and on follow-up (days 1 and 7). CBF thresholds (12 and 22 mL/100 g per minute) were applied to bolus tracking MRI maps to determine predictive cutoff levels.

Results—In 21 patients (group A), the terminal lesion volume (T2-weighted imaging) was larger than the initial DWI lesion volume (89±93 versus 21±38 mL). In 11 patients (group B), the terminal lesion volume was smaller than the initial DWI lesion volume (7±27 versus 15±29 mL). The initial DWI lesion volume did not differ between both groups. The presence of a tissue volume ≥50 mL with a CBF value ≤12 mL/100 g per minute was predictive for lesion enlargement to day 7 in T2-weighted imaging (positive predictive value, 0.80).

Conclusions—The presence of a tissue volume ≥50 mL with a CBF value ≤12 mL/100 g per minute predicts further lesion growth in hyperacute stroke patients. MRI-derived CBF values, with all their present limitations, are valuable in early estimation of prognosis of stroke patients. (Stroke. 2002;33:2421-2425.)

Key Words: cerebral blood flow ■ magnetic resonance imaging ■ perfusion ■ stroke

The mismatch between diffusion- and perfusion-weighted MRI (DWI and PWI, respectively) defines “tissue at risk of infarction” in acute stroke patients. This tissue at risk is considered the target for thrombolytic therapy. Commercial software packages generate time to peak (TTP) maps that deliver robust images of tissue with delayed bolus arrival times. However, a TTP delay does not necessarily indicate critically diminished cerebral blood flow (CBF) but may be due to collateral flow. TTP maps therefore overestimate the ischemic tissue volume, especially in case of occlusive carotid artery disease.

Previous studies tested alternative PWI parameters such as cerebral blood volume, CBF, and mean transit time (MTT), aiming to find more reliable indicators of cerebral ischemia.

We calculated CBF parameter maps and applied a conversion factor derived from the positron emission tomography (PET) literature to generate quantitative CBF maps. Established CBF thresholds of cerebral ischemia (CBF ≤12 and ≤22 mL/100 g per minute) (CBF12 and CBF22, respectively) known from the literature were tested for their predictive value of lesion growth in hyperacute stroke patients.

Subjects and Methods

Patients
We enrolled 32 consecutive patients (6 women and 26 men, aged 60±14 years [median±SD]) with sudden onset of ischemic stroke during the last 6 hours (2.8±0.9 hours). Multiparametric MRI was performed immediately after clinical evaluation and CT scan and before intravenous thrombolysis with tissue plasminogen activator (tPA). Multiparametric MRI follow-up was performed on days 1 and 5 to 7. The National Institutes of Health Stroke Scale (NIHSS) score was assessed by a stroke neurologist at each imaging time point. Informed consent was obtained in all patients. The study was approved by the local ethics committee.

Imaging Methods
MRI studies were performed on a 1.5-T clinical whole body scanner (Magnetom Symphony, Siemens) with the use of a standard head coil. The measurements included an axial DWI sequence, a PWI sequence, MR angiography, and a T2-weighted sequence. The table time was <20 minutes in the majority of cases. MRI sequence parameters were detailed recently.

Postprocessing
Postprocessing of the DWI and PWI image data was performed offline with the use of custom-written software (MRVision) and MGH-Image on a Linux PC workstation.
Patient Data and Lesion Volumes in the Total Study Population, Groups A (With Lesion Enlargement) and B (Without Lesion Enlargement, and <50 mL CBF<sub>12</sub> and ≥50 mL CBF<sub>12</sub> Groups

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 5–7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n=32)</td>
<td>Day 0</td>
</tr>
<tr>
<td>Age, y</td>
<td>60 (35–90)</td>
<td>T2, mL</td>
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<tr>
<td></td>
<td>2.80 (1.60–4.75)</td>
<td>23 (0–377)</td>
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<tr>
<td>MRI After Stroke, h</td>
<td>20 (2–138)</td>
<td>1 (0–22)</td>
</tr>
<tr>
<td>ADC&lt;sub&gt;90&lt;/sub&gt;, mL</td>
<td>66 (6–214)</td>
<td>3 (0–19)</td>
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<tr>
<td>CBF&lt;sub&gt;12&lt;/sub&gt;, mL</td>
<td>102 (13–293)</td>
<td>14 (2–24)</td>
</tr>
<tr>
<td>TTP, mL</td>
<td>173 (9–322)</td>
<td>12 (2–4)</td>
</tr>
<tr>
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<td>50 mL CBF&lt;sub&gt;12&lt;/sub&gt; group (n=13)</td>
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<tr>
<td>CBF&lt;sub&gt;12&lt;/sub&gt;</td>
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<tr>
<td>ADC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>15 (9–312)</td>
<td>15 (8–24)</td>
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<tr>
<td>NIHSS Score</td>
<td>9 (2–19)</td>
<td>9 (2–19)</td>
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<tr>
<td>T2, mL</td>
<td>14 (2–24)</td>
<td>14 (2–24)</td>
</tr>
<tr>
<td>T2/ADC</td>
<td>83 (16–377)</td>
<td>83 (16–377)</td>
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<tr>
<td>NIHSS Score</td>
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<tr>
<td>≥50 mL CBF&lt;sub&gt;12&lt;/sub&gt; group (n=19)</td>
<td>56 (35–90)</td>
<td>T2/ADC</td>
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<td></td>
<td>2.95 (1.60–4.75)</td>
<td>14 (2–24)</td>
</tr>
<tr>
<td>Age, y</td>
<td>61 (41–74)</td>
<td>14 (2–24)</td>
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<tr>
<td>MRI After Stroke, h</td>
<td>27 (6–44)</td>
<td>14 (2–24)</td>
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<tr>
<td>ADC&lt;sub&gt;90&lt;/sub&gt;, mL</td>
<td>53 (13–108)</td>
<td>14 (2–24)</td>
</tr>
<tr>
<td>CBF&lt;sub&gt;12&lt;/sub&gt;, mL</td>
<td>134 (9–312)</td>
<td>14 (2–24)</td>
</tr>
<tr>
<td>TTP, mL</td>
<td>2.3 (0.4–14.1)</td>
<td>2.3 (0.4–14.1)</td>
</tr>
<tr>
<td>Mismatch Ratio</td>
<td>CBF&lt;sub&gt;12&lt;/sub&gt;/ADC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>50 mL CBF&lt;sub&gt;12&lt;/sub&gt; group (n=13)</td>
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<td>NIHSS Score</td>
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<td>83 (16–377)</td>
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<td>T2/ADC</td>
<td>2 (1–5)</td>
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<tr>
<td>NIHSS Score</td>
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<td>T2/ADC</td>
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<td>2.63 (2.00–4.25)</td>
<td>14 (2–24)</td>
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<tr>
<td>Age, y</td>
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<td>NIHSS Score</td>
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<tr>
<td>T2/ADC</td>
<td>2 (1–5)</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>NIHSS Score</td>
<td>3 (0–19)</td>
<td>3 (0–19)</td>
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</table>

* Mann-Whitney U test.

Results

All 32 patients were treated by systemic thrombolysis. tPA was given according to common treatment guidelines and if CT criteria with early infarct signs greater than one third of middle cerebral artery territory and absence of bleeding were met. Baseline parameters of the study population are summarized in the Table. No recanalization was observed in 12 patients. There was no significant difference in the mismatch ratio between group A and B in TTP/ADC and CBF<sub>12</sub>/ADC (P=0.327 and P=0.785, Mann-Whitney U test).

In the receiver operating characteristic analysis, a cutoff volume of 50 mL with a CBF value ≥12 mL/100 g per minute (50 mL CBF<sub>12</sub>) resulted in lesion enlargement with a balanced sensitivity and specificity of 0.71 and 0.66, respectively. The resulting positive predictive value of the 50 mL CBF<sub>12</sub> threshold for lesion enlargement was 0.80. Only 3 of the MRI examination and thus the start of thrombolytic therapy did not reach significance in our group (3 hours in group A versus 2.5 hours in group B; P=0.06). Final infarct volumes were larger than initial CBF<sub>12</sub> in 22 and smaller in 10 patients. There was no significant difference in the mismatch ratio between group A and B in TTP/ADC and CBF<sub>12</sub>/ADC (P=0.327 and P=0.785, Mann-Whitney U test).

Figure 1 shows ADC and CBF maps of a patient with cardioembolic stroke 2 hours after symptom onset.

In 21 patients (group A), the final lesion volume (T2-weighted imaging) was larger than the initial lesion volume (ADC<sub>90</sub>) (21 versus 89 mL). In 11 patients (group B), the initial ADC<sub>90</sub> lesion volume (7 mL) was larger (15 mL) than the final lesion volume. The initial ADC<sub>90</sub> volume did not differ significantly between both groups (P=0.25) (Figure 2), whereas the initial CBF<sub>12</sub> and TTP volumes (P=0.02 and P=0.00) and the final lesion volume (T2-weighted imaging on day 7) were larger in group A (P=0.01) (Table). Patients in group A were more severely affected (initial NIHSS score 15 versus 9; P=0.02). NIHSS scores on day 7 were correlated with the final lesion volume (r=0.79, P<0.05). Both groups differed concerning the distribution of the occlusion types (Figure 3). The difference between the groups at the time of MRI examination and thus the start of thrombolytic therapy did not reach significance in our group (3 hours in group A versus 2.5 hours in group B; P=0.06). Final infarct volumes were larger than initial CBF<sub>12</sub> in 22 and smaller in 10 patients. There was no significant difference in the mismatch ratio between group A and B in TTP/ADC and CBF<sub>12</sub>/ADC (P=0.327 and P=0.785, Mann-Whitney U test).

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**Figure 1.** ADC map (a) and CBF maps (c and d) of a 47-year-old patient with cardioembolic stroke 2 hours after symptom onset. Within the CBF map in panel c the later infarct area is fairly visible, whereas in panel d the CBF<sub>12</sub> area is tagged by threshold function.
19 patients with a volume ≥50 mL CBF12 did not present with lesion enlargement. These patients showed a slight decrease in lesion volume from initial ADC80 (89/78/25 mL) to T2-weighted imaging on day 7 (83/70/22 mL). Patients with ≥50 mL CBF12 tissue volume had larger initial ADC80 lesion volumes (P<0.01) and final infarct volumes (P<0.01). A lesion volume of <50 mL CBF12 showed a negative predictive value of 0.81.

Discussion
The prediction of lesion enlargement is of major interest for stroke management. Knowledge of potential lesion growth could alert clinicians and stroke unit staff and help in the early recognition of development of malignant middle cerebral artery infarction. Current imaging modalities do not reliably predict lesion growth early in the course of treatment. Although it was reported that the early presence of hypotenuation on CT scans is indicative of extended volumes of critically hypoperfused cortical tissue, the presence of early ischemic signs on CT does not correlate with an increased risk of adverse outcome after pTPA treatment.20

Recent studies reported a good correlation between DWI lesion volumes and NIHSS scores.21,22 These correlations did not hold true at very early time points after stroke onset when the DWI lesion volume was still maturing.23 A critical DWI lesion volume >145 cm³ was described as a useful parameter for the prediction of stroke patients at risk of malignant brain infarct.24 However, patients were studied as late as 14 hours after stroke onset. In our data, within 6 hours after stroke onset the ≥50 mL CBF12 criterion for lesion growth was highly predictive for lesion growth at an early time point. There was no case of substantial lesion decrease in this group. Since DWI and ADC maps mirror the metabolic status of the brain tissue, their development depends on the severity of the cerebral ischemia25 and is therefore variable. Supporting this association between CBF and ADC, we observed significantly larger ADC80 lesion volumes in the ≥50 mL CBF12 group (P<0.01).

On the other hand, there was no significant difference in initial ADC80 lesion volumes (P=0.25) between group A (lesion growth) and group B (no lesion growth). ADC normalization may occur in case of timely reperfusion,15,26 and it is therefore not likely that DWI and ADC maps alone serve as useful predictors for infarct growth early after stroke onset.

Previous PET studies showed that tissue below a critical CBF of 12 mL/100 g per minute was infarcted on late CT scans,27,28 whereas regions with CBF between 12 and 22 mL/100 g per minute represented tissue with uncertain chances of recovery or infarction.12,13 We used these well-established values in our study. We studied the value of CBF thresholds for the prediction of lesion enlargement and found that a critical tissue volume of 50 mL with a CBF reduction to <12 mL/100 g per minute predicts lesion enlargement. Interestingly, patients with ≥50 mL CBF12 volume did not present with higher initial NIHSS scores (Table), which emphasizes the limited value of clinical scores at early time points when successful thrombolysis may lead to recanalization and clinical recovery.

The study population is highly selected, and future studies must show whether the 50 mL CBF12 threshold is a reliable predictor in patients who do not receive thrombolytic treatment. Since this threshold was determined in a population with a high rate of recanalization, it may be that even smaller CBF12 volumes indicate lesion growth. On the other hand, the CBF12 ≥50 mL criterion for lesion enlargement was valuable in our selected patient group without severe signs of ischemia on CT. In our experience, the presence of a mismatch is a precondition for lesion growth. However, since all of these patients were treated with pTPA, there is a considerable chance for patients with mismatch to recover without presenting lesion growth.

In our series, patients with lesion growth presented with more proximal occlusions of the internal carotid artery and middle cerebral artery (Figure 3). We found a high variability of CBF volume in patients with identical occlusion types, and lesion development was obviously determined by the quality of the collateral blood flow and by eventual recanalization. This observation is in accord with a previous study that reported that CBF lesion volumes depend on the site of the vessel occlusion and that collateral blood flow determines the fate of tissue at risk of infarction.29,30 Compared with previ-
ous studies of CBF in stroke patients, our data were acquired early (2.8±0.9 hours). This may be one of the reasons why at least part of the tissue volume below the critical threshold of 12 mL/100 g per minute recovered after thrombolytic therapy. A similar observation was made by Heiss et al, who used the same CBF threshold for PET measurements.

The method used in the present study is considered a promising approach for MR-based absolute CBF measurements. By introducing a common conversion factor, MRI-based CBF values can be converted into absolute flow rates, and it was shown that CBF values obtained by MRI can be calibrated with other metrics such as PET in volunteers and in animals. In a recent study of Smith et al, the absolute CBF values for gray and white matter almost exactly matched the values known from the PET literature. On the other hand, CBF measurements in low-flow states, e.g., in hypoperfused oligemic tissue, do not reliably mirror physiological conditions. A single conversion factor for the whole hemisphere therefore seems insufficient. Future approaches might overcome these limitations and improve the accuracy of MRI-based CBF measurements.

Many clinical investigations use MTT or TTP maps because of the good contrast of hypoperfused tissue. However, the interpretation of summary parameters such as TTP or bolus arrival time is critical, and an accurate intradividual or interindividual comparison is impossible. TTP or MTT maps do not discriminate between still-nutritive collateral flow, oligemia in the area of tissue at risk of infarction, and severe ischemia. Additionally, numerical values from TTP maps are highly variable because of their dependence on cardiac output and proximal artery stenoses and therefore do not serve as predictors of lesion volumes or development.

Previous studies using quantitative measurements of CBF and cerebral blood volume in acute stroke patients showed divergent results. In a retrospective MRI approach, CBF values for core and penumbra were defined as 6 and 18.5 mL/100 g per minute. Others found a cutoff value of 0.59 of the contralateral CBF, which approximately corresponds to absolute values of 13 mL/100 g per minute, for the development of irreversibly damaged tissue in acute stroke within 6 hours after symptom onset. Grandin et al found a threshold of 34 mL/100 g per minute for infarction. A major issue in these studies was that mean values within large regions of interest were determined and that these region of interest measurements obscured the detection of relevant thresholds. The proposed prospective evaluation at a voxel level in a larger sample was done in the present study. In our data, the presence of a tissue volume ≥50 mL with a CBF value ≤12 mL/100 g per minute (50 mL CBF<sub>12</sub>) was predictive for further lesion enlargement in hyperacute stroke patients. However, this criterion was valuable in our selected patient group without severe signs of ischemia in CT. The group of patients with lesion enlargement showed more proximal vessel occlusions with significantly worse clinical scores on admission and on day 7. Thus, MRI-derived CBF values, with all their present limitations, are ready for application and valuable for estimation of the prognosis of stroke patients in context with other imaging modalities such as DWI, MR angiography, and T2-weighted imaging.

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Cerebral Blood Flow Predicts Lesion Growth in Acute Stroke Patients
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