Are There Time-Dependent Differences in Diffusion and Perfusion Within the First 6 Hours After Stroke Onset?

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Background and Purpose—Stroke heterogeneity in computed tomography-based studies has been attributed as main cause for missing efficacy of intravenous tissue plasminogen activator (tPA) therapy within 3 to 6 hours. We investigated early time-dependent differences in acute stroke pathophysiology by multiparametric magnetic resonance imaging (MRI).

Methods—Stroke MRI of 112 acute ischemic stroke patients within <6 hours were dichotomized into a <3-hour group (n=52) and a 3- to 6-hour group (n=60). Infarct volume was determined on days 5 to 8. Lesion volumes were determined for apparent diffusion coefficient (ADC_man) and the subregion with ADC values <550×10⁻⁶ mm²/s (ADC <550), and for the time-to-peak (TTP) delay of 2 to 4 seconds, 4 to 6 seconds, 6 to 8 seconds, and >8 seconds. A subsample analysis was performed for occlusions of the middle carotid artery (MCA) trunk (n=36) and MCA branches (n=30), and for all patients treated by intravenous tPA (n=70).

Results—ADC and TTP lesion volumes were not different within <3 hours compared with volumes at 3 to 6 hours. In patients receiving intravenous tPA (n=70), there were no significant differences in ADC_man, TTP >2 seconds, and infarct volume (days 5 to 8) between the 2 groups. There was a greater proportion of ADC <550/ADC_man, which was most pronounced in patients with MCA trunk occlusions after 3 to 6 hours and a larger mismatch in the <3-hour group compared with that of the 3- to 6-hour group. In MCA branch occlusions, there was a less severe TTP delay after 3 to 6 hours. However, all differences missed the significance level (P>0.05) after correction for multiple testing.

Conclusions—We observed no significant time-dependent differences within 6 hours after stroke onset in degree and volume of diffusion and perfusion impairment. An exclusion from intravenous tPA solely based on a rigid 3-hour time window seems unjustified in MRI-confirmed ischemic stroke. (Stroke. 2004;35:000-000.)

Key Words: ischemia ▪ magnetic resonance imaging ▪ magnetic resonance imaging, diffusion-weighted ▪ stroke, acute ▪ thrombolysis

Intravenous therapy with tissue plasminogen activator (tPA) is effective if initiated within 3 hours after stroke onset.1 The extension within a 3- to 6-hour time window did not prove effective in the European Cooperative Acute Stroke Study II study2 or in several other trials.3–5 A number of factors may have contributed to this failure, but stroke heterogeneity has been cited as the main cause.6 Apparently, this heterogeneity does not nullify the efficacy of intravenous tPA treatment within the time period of <3 hours but does not allow effective treatment without patient selection within 3 to 6 hours.

The success of the Prolyse in Acute Cerebral Thromboembolism Trial II study7 within the 6-hour time window might be attributed at least in part to the design focused on the angiographically proven middle cerebral artery (MCA) occlusion. It was argued that an appropriate selection of stroke patients might extend the window also for intravenous thrombolysis toward 6 hours after stroke onset.8,9 Noncontrast computed tomography alone appears to have little predictive value on lesion growth.10–12 Multiparametric MRI, however, can delineate large volumes of tissue at risk for infarction13,14 even beyond the 3-hour time window.15

We investigated early time-dependent differences in perfusion and diffusion parameters in acute stroke by multimodal MRI with the hypothesis of a shrinking “tissue at risk.” Several perfusion and diffusion parameters were compared between patients examined in the <3-hour time window versus those examined after 3 to 6 hours. We sought to characterize the “tissue at risk” by analyzing the degree and the volume of ADC decrease16,17 and perfusion delay.18

Patients and Methods

Imaging

One-hundred twelve consecutive patients with an ischemic stroke caused by a vessel occlusion in the anterior circulation within 6 hours after stroke onset and a completed follow-up imaging on days 5 to 8...
were identified in a retrospective analysis of our prospective stroke database from February 2000 to August 2003. An additional MRI was performed in most of the cases (n=89) after 24 hours. There were no limitations caused by other MR findings, age, or severity of symptoms. Multiparametric MRI was performed immediately after clinical evaluation and before possible thrombolysis with tPA. The lesion volume was determined on computed tomography of days 5 to 8 if MRI was not feasible because of extensive monitoring devices from intensive care. A stroke neurologist assessed the National Institutes of Health Stroke Scale (NIHSS) score at each imaging time point. Informed consent was obtained from all patients. The ethical committee approved the study. Forty patients and 68 patients, respectively, were subjects of previous studies with different focus.

MRI studies were performed on a 1.5-T clinical whole-body scanner (Magnetom Symphony/Sonata, Siemens) using a standard head coil. The measurements included an axial diffusion-weighted imaging (DWI) sequence, a perfusion-weighted imaging (PWI) sequence, a magnetic resonance angiography (MRA), and in most of the cases a fluid-attenuated inversion recovery (FLAIR) sequence. The table time was <20 minutes in most of cases. Sequence parameters have been described recently.19

**Determination of Occlusion Type, Postprocessing, and Statistical Analysis**

The localization of vessel occlusion was determined from the initial MRA study. Occlusion type was categorized as follows20: (1) occlusion of the internal carotid artery (ICA) in the neck with accompanying MCA embolism (ICA/MCA); (2) occlusion of the intracranial bifurcation of the ICA (carotid “T” occlusion [CTO]); (3) MCA and anterior cerebral artery occlusion without CTO (ACA/MCA); (4) proximal MCA trunk occlusion (MCA trunk); (5) MCA trifurcation lateral to the medial lenticulostriate arteries (MCA trif); and (6) single or multiple MCA branch occlusion with free trifurcation (MCA branch).

Recanalization was analyzed from the follow-up MRI study after 24 hours on the basis of the PWI and MRA studies. Reperfusion within <20% volume of the initial TTP abnormality was classified as “failed reperfusion;” other incomplete and complete recanalization/reperfusion were classified as “successful reperfusion.”

Postprocessing of the DWI and PWI image data was performed offline using SCAN from the University of California Stroke Attack Team. The ADC was determined on a pixel-by-pixel basis using the Stejskal–Tanner equation and the b values of 0 and 1000 of the trace images. After manual delineation of ADC lesion volumes (ADC_man), the lesion volumes with severe ADC decreases (ADC < 550) were determined using a threshold function (550×10^6 mm²/s). Remaining volumes in ADC_man with ADC values of >550×10^6 mm²/s are indicated by ADC > 550 (Figure 1). Additionally, the ratio of ADC < 550/ADC_man was determined. For PWI, the changes in T2* were expressed as change in relaxation rate (ΔR2*), where R2* = 1/T2* and calculated as ΔR2*(t) = ln[I(t)/I0]/TE, where S0 is the signal intensity at the time point t after injection of the contrast agent, S0 is the signal intensity without contrast agent, and TE is the echo time. Principles of the indicator dilution theory for nondiffusible tracers were applied to the analyzed concentration time curves. Time-to-peak (TTP) delay maps were calculated as time delay from the peak of the arterial input function to the maximum of S0 changes within the affected hemisphere. The arterial input function was determined from pixels at the location of the MCA contralateral to the side of infarct, where the bolus shape was high and steep and the full width at half-maximum was small.21

The brain volume with a perfusion deficit was manually delineated in comparison to the contralateral hemisphere. Using a threshold function within this region, TTP delay volumes in steps of 2 to 4 seconds, 4 to 6 seconds, 6 to 8 seconds, and >8 seconds were classified, following previous reports.18 The entire lesion volume with a delay of >2 seconds was summarized as TTP >2 seconds. The mismatch volume was defined as TTP >2 seconds – ADC_man (VOL_mism). The b=0 images of the DWI scan of days 5 to 8 were used as T2-weighted images for manual delineation of final lesion volumes (infarct). If MRI was not feasible on days 5 to 8 because of extensive monitoring devices from intensive care, outcome lesion volume was determined by manual delineation on a computed tomography scan (n=6).

Statistical analysis was performed using SPSS 11.02. Data were dichotomized into a <3-hour group and a 3- to 6-hour group. A Mann–Whitney U test for independent samples was used to evaluate significant differences (P < 0.05) between groups of lesion volumes (ADC < 550, ADC_man, TTP >2 seconds, the TTP delay volumes, and VOL_mism) and also the ratio of ADC < 550/ADC_man. Infarct volume was determined in patients treated with intravenous tPA therapy. Significant differences were primarily reported without correction for multiple testing to avoid type 2 error (false acceptance of the null hypothesis). Bonferroni correction for multi-

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**Table 1.**

<table>
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<th>Variable</th>
<th>&lt;3 h</th>
<th>3–6 h</th>
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<td>Time of MRI, h</td>
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<td>0.5</td>
<td>3.7</td>
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<tr>
<td>NIHSS day 0</td>
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<td>5</td>
<td>13</td>
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<tr>
<td>NIHSS day 7</td>
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<tr>
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<td>39</td>
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<td>15</td>
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<tr>
<td>TTP &gt;2 sec, mL</td>
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<td>105</td>
<td>162</td>
</tr>
<tr>
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<td>91</td>
<td>123</td>
</tr>
<tr>
<td>Infarct, mL</td>
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<td>97</td>
<td>59</td>
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<tr>
<td>ADC &lt; 550/ADC_man</td>
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<td>0.21</td>
<td>0.39</td>
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<table>
<thead>
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<th>n</th>
<th>%</th>
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<th>%</th>
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<td>21</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>IV IPA</td>
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<td>73</td>
<td>32</td>
<td>53</td>
</tr>
<tr>
<td>IA IPA</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Double-blinded trial</td>
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<td>0</td>
<td>8</td>
<td>13</td>
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<tr>
<td>Craniotomy</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>0</td>
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</table>

There were no significant differences between groups after correction for multiple testing except for time of initial MRI. NIHSS indicates National Institutes of Health Stroke Scale; IV, intravenous; IA, intra-arterial.
ple tests has been performed in a second step. Pearson correlation coefficient and results of a linear regression analysis with time as an independent variable are reported for the parameters ADC_man, TTP >2 seconds, and VOL_mism.

Results
One-hundred twelve patients (41 women and 71 men, age 62±13 years [mean ± SD]) with MRI within 6 hours (3.0±1.0 [mean ± SD] hours) after stroke onset and on days 5 to 8 were analyzed. Initial NIHSS score was 13.6±4.7. Patients were treated conservatively (acetyl salicylic acid and low-molecular-weight heparin; n=24), with early hemicranectomy (n=2), by intravenous tPA (n=70), or with intra-arterial tPA (n=8). Eight patients were treated within a randomized, placebo-controlled, double-blinded acute stroke trial. Patients were categorized in 2 groups: (1) patients with MRI <3 hours (<3-hour group, n=52) and (2) patients with MRI 3 to 6 hours after stroke onset (3- to 6-hour group, n=60).

The following occlusion types were observed (<3-hour group/3- to 6-hour group): proximal ICA/MCA (n=5/13), CTO (n=5/10), combined ACA/MCA (n=2/2), MCA trif (8/1), MCA trunk (n=17/19), and MCA branch (n=15/15). There were more patients treated with intravenous tPA therapy in the <3-hour group than in the 3- to 6-hour group, and more patients were treated with intra-arterial tPA therapy in the 3- to 6-hour group (Table).

There were no significant differences between the <3-hour group and the 3- to 6-hour group in the following parameters (Table): entire ADC lesion volume (ADC_man), ADC <550, TTP >2 seconds lesion volume (Figure 1), mismatch volume, TTP delay volumes, and the NIHSS score evaluated on day 0 and on days 5 to 8. Correlation analysis revealed no significant correlation of the parameters ADC_man (R=0.009, P=0.925), TTP >2 seconds (R=0.052, P=0.596), and VOL_mism (R=0.059, P=0.545) with time (Figure 2). Only the ratio of severe ADC decreases (ADC <550/ADC_man) was larger in the 3- to 6-hour group than in the <3-hour group (0.39 versus 0.32; P=0.049). This difference missed the significance level of P=0.05 after correction for multiple testing, as did all further differences reported.

To correct for the considerable heterogeneity of occlusion types between the <3-hour group and the 3- to 6-hour group, an analysis of the largest subsamples [patients presenting with occlusion of the MCA trunk (n=36) and MCA branches (n=30)] was performed. Patients with occlusion of the MCA trunk showed a larger mismatch volume (200 versus 139 mL, P=0.047) in the <3-hour group compared with the 3- to 6-hour group. The TTP >2 seconds volume was not significantly different between both groups (P=0.051). Patients in the 3- to 6-hour group showed a considerably larger ratio of severe ADC decreases (ADC <550/ADC_man; 0.32 versus 0.49, P=0.017) within the entire ADC lesion. There were no significant differences in other lesion volumes (Figure 3). In patients with occlusion of MCA branches, there was a smaller volume with a TTP delay of >8 seconds and a
larger volume with a TTP delay of 2 to 4 seconds, and a significantly larger volume in the 3- to 6-hour group (Figure 3).

Because of the heterogeneity in therapy regimens of the entire groups imaged at 3 hours and at 3 to 6 hours, the comparison of infarct volumes of days 5 to 8 (Figure 4a) and the analysis of recanalization data (Figure 4b) were performed only in patients receiving intravenous tPA. In these patients, the ADC_man and TTP >2 seconds lesion volumes and final lesion volumes on days 5 to 8 were not significantly different in the <3-hour group (n=38) as compared with the 3- to 6-hour group (n=32) (Figure 4).

Discussion

The novel aspect of our study is the comparison of the degree and the volume of the diffusion and perfusion abnormality in a <3-hour group and a 3- to 6-hour group after onset of ischemic stroke; we tested the hypothesis that the “tissue at risk” is shrinking. In our study of 112 stroke patients, there were no significant differences between the entire <3-hour group and the entire 3- to 6-hour group after stroke onset in both lesion volumes of perfusion or diffusion abnormality and of mismatch volume (Table, Figure 1b through 1d).

The subsample of patients receiving intravenous tPA (n=70), there were no differences in initial DWI and PWI lesion volumes or in final infarct volume between patients treated <3 hours and after 3 to 6 hours. Thus, we observed no inferior effect of intravenous tPA beyond the 3-hour time window concerning the infarct volumes in our sample. The missing differences in lesion volumes between the time windows were in line with the study of Rother et al.15

Small differences in initial MRI parameters became apparent foremost after categorization into occlusion types. The subgroup of patients with occlusion of the MCA trunk (n=36) showed a smaller mismatch volume 3 to 6 hours after stroke onset. Without change of the total ADC lesion volume, there was a larger volume with severe ADC decreases (ADC <550) within 3 to 6 hours after stroke onset, reflecting the more severe metabolic impairment. Patients with occlusion of MCA branches (n=30) did not show differences in lesion volumes of perfusion or diffusion abnormality and mismatch volume but showed a less severe TTP delay (Figure 3). However, it has to be acknowledged explicitly that after correction for multiple tests, none of these significant differences was seen anymore.

These observations suggest that there are very small differences in diffusion and perfusion indicating a marginally decreasing volume of salvageable tissue. Neither these small differences nor the lower recanalization rate after 3 to 6 hours showed a measurable effect on final infarct volume after tPA (Figure 4). Thus, our data give no explanation for the diminishing benefit from intravenous tPA after 3 to 6 hours. The increasing likelihood of hemorrhage over time has been considered as an obvious reason for this effect.22 However, a
recent analysis of pooled computed tomography-based stroke trials found no association between the time from symptom onset to start of treatment and the occurrence of substantial hematoma.\(^\text{23}\)

In line with several authors, we considered ADC decreases $<550 \times 10^{-9}$ mm$^2$/s as severe.\(^\text{24–28}\) We observed no ADC lesion growth over time but a greater volume of severe ADC decreases (ADC $<550$) within the entire ADC lesion (0.39 versus 0.32). There was a lower proportion of severe ADC decreases (ADC $<550$/ADC$_{\text{man}}$) within $<3$ hours, especially in occlusions of the MCA trunk (0.32 versus 0.49).

Both the volume\(^\text{13,14}\) and the severity\(^\text{18–29}\) of the initial perfusion deficit are associated with the growth of the initial DWI lesion at follow-up imaging. After categorization into occlusion types, we observed a larger mismatch volume in MCA trunk occlusion at $<3$ hours. In patients with MCA branch occlusions, the TTP delay of $>8$ seconds was larger and the tissue volume with a TTP delay of 2 to 4 seconds was smaller at $<3$ hours than at 3 to 6 hours (Figure 3). Given that a TTP delay $>4$ seconds correlates with functional deficit and that the hyperperfused tissue and TTP delay $>6$ seconds correlate with infarct volume,\(^\text{18}\) our observations may indicate toward a higher risk of lesion growth at $<3$ hours or marginally more salvageable tissue.

One of the drawbacks of the study is that most of the patients were examined near the 3-hour cutoff within 2 to 4 hours after symptom onset (Figure 2a). Problems caused by a somewhat inaccurate determination of the time point from symptom onset cannot completely be ruled out. This possible stochastic error might obscure further time-dependent differences. However, these data reflect the clinical reality of acute stroke management, and the 3-hour cutoff derived from the available clinical information is important for therapy decisions in many centers. Inherent limitations of the perfusion MRI methodology should also be considered. Especially in patients with steno-occlusive disease, the usage of the AIF solely based on a rigid 3-hour time window seems not justified in MRI-confirmed ischemic stroke.

**Conclusion**

Based on our MRI data, the “tissue at risk” and thus the salvageable tissue are not significantly shrinking within 6 hours after stroke onset. An exclusion from intravenous tPA solely based on a rigid 3-hour time window seems not justified in MRI-confirmed ischemic stroke.

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