Intravenous thrombolysis with tissue plasminogen activator (tPA) is effective in carefully selected patients treated within 3 hours of symptom onset. Although tPA is the only proven therapy for acute stroke, only 3% to 4% of all stroke patients are currently treated. The limited use of tPA is due in part to safety concerns of neurologists, internal medicine, and emergency physicians and the narrow 3-hour therapeutic window. A number of diagnostic tests and procedures are needed within this time window that require optimal logistics: clinical evaluation of the acute ischemic stroke (AIS) patient, cerebral CT for exclusion of intracranial hemorrhage, blood tests to exclude hemorrhagic diathesis, and application of the thrombolytic drug itself.

Extension of the therapeutic window would be an important step toward a broader application; however, thrombolytic therapy within a 6-hour time window did not prove effective in the intention-to-treat group of the European Cooperative Acute Stroke Study (ECASS) II trial. It was argued that the selection of stroke patients likely to respond to thrombolysis might improve functional outcome within the 3-hour time window and extend the window toward 6 hours after stroke onset. Multiparametric MRI techniques fulfill a number of prerequisites for the definition of a potential tPA-responsive subgroup: MRI is fast, is suitable for the examination of AIS patients, and delivers information about tissue likely to benefit from thrombolysis. Diffusion-weighted MRI (DWI)
serves as the earliest indicator of ischemic tissue changes. Perfusion-weighted MRI (PWI) delineates hypoperfused tissue, and the combination of DWI and PWI shows a characteristic pattern of tissue at risk of infarction, a small area with diffusion slowing representing the ischemic core and a surrounding penumbra area with normal diffusion but tissue hypoperfusion. This mismatch area (PWI-DWI) represents tissue that is likely to benefit from timely reperfusion.

To date, only small series of acute stroke patients within a time window relevant for thrombolysis have been studied by multiparametric MRI, and little is known about the impact of thrombolysis on MRI parameters. We studied 139 AIS patients as part of a German Stroke Excellence Network Initiative (Kompetenznetzwerk Schlaganfall) within the first 6 hours of symptom onset and during follow-up with MRI to answer several questions. First, what is the prevalence and size of mismatch and lesion volumes in AIS patients? Second, how does tPA affect the recanalization rate in this open-label, nonrandomized study group? Third, do the time point of thrombolysis and recanalization rate affect functional outcome? Fourth, what is the effect of the vascular occlusion pattern on mismatch volume and functional outcome? Finally, is MRI feasible for multicenter studies?

Materials and Methods

Patients

Analyses are based on data obtained within the Kompetenznetzwerk Schlaganfall Study Group B5 from January 1999 to March 2001. Five university hospitals (Berlin, Düsseldorf, Hamburg, Heidelberg, and Mannheim) with organized stroke triage systems, specialized stroke care units, experience in the use of tPA for AIS, and expertise in stroke MRI participated. Consecutive patients with sudden onset of middle cerebral artery (MCA) stroke were included in this nonrandomized, open-label group comparison. All patients were studied with a multiparametric stroke MRI protocol within 6 hours of symptom onset and for follow-up. Patients were treated in stroke units or, if necessary, in intensive care units. The National Institutes of Health Stroke Scale (NIHSS) score was assessed immediately before the initial MRI. The modified Rankin Scale (mRS) was used to assess disability on day 90 after stroke either by telephone or in person. Both the initial NIHSS and the mRS were obtained by experienced local stroke neurologists. Informed consent was obtained. The study was approved by the local ethics committees.

Patients were divided into 2 therapeutic groups: the no thrombolysis group with conservative treatment and the thrombolysis group with thrombolytic therapy. The no thrombolysis patients were excluded from thrombolytic therapy on the basis of exclusion criteria or because of refused consent. Conservative treatment was defined as thromboocyte aggregation inhibitor and low-molecular-weight heparin given subcutaneously as a prophylactic for deep venous thrombosis. Full-dose heparin aiming to double the partial thromboplastin time was applied in individual patients with high-grade symptomatic artery stenosis, carotid dissections, or atrial fibrillation. Thrombolysis group patients received tPA (0.9 mg/kg alteplase, Boehringer Ingelheim) according to either the ECASS II criteria within the 6-hour time window (Hamburg and Heidelberg) or the National Institute of Neurological Disorders (NINDS) criteria within the 3-hour time window (Düsseldorf and Mannheim). In the Berlin center, only patients in the no thrombolysis group were recruited. Baseline characteristics, lesion volumes, mismatch ratio, occlusion types, recanalization, and functional outcomes were compared between groups. Data on a subgroup of patients from Heidelberg were recently published with respect to DWI and PWI lesion volumes and their correlation with clinical stroke severity.

All patients eligible for thrombolysis received a CT study either before or immediately after the MRI protocol to exclude intracerebral hemorrhage. MRI was performed before thrombolysis (n=63) or immediately after application of tPA (n=10; median, 65 minutes; range, 12 to 120 minutes). MRI follow-up was performed on days 1 and 7.

We anticipate that a not-further-specified number of patients in both groups was not included in the study for the following reasons: (1) MRI scanner was not available, (2) consent for MRI study was refused, (3) initial NIHSS was poor (NIHSS ≥25), or (4) tPA therapy was refused. Additional patients were not eligible because of lack of follow-up data for the following reasons: (1) MRI scanner was not available, (2) MRI follow-up or clinical scoring was refused, or (3) MRI study was incomplete because of technical reasons or the subject’s inability to cooperate.

MRI

MRI studies were performed on 1.5-T clinical whole-body scanners with echo-planar capabilities (Magnetom Symphony, Siemens (Hamburg, Düsseldorf, and Berlin), Magnetom Vision, Siemens (Mannheim), and Marconi EDGE (Heidelberg)). All centers performed acute stroke MRI protocols, including an axial DWI sequence, a PWI sequence, a time-of-flight MR angiography (MRA) of the intracranial arteries, and a T2-weighted sequence. The scanning time was <20 minutes. Typical sequence parameters were described elsewhere.

Postprocessing

Postprocessing of the DWI and PWI image data was performed offline in each participating center with locally established software. For PWI, the changes in T2* were expressed as a change in the relaxation rate (ΔR2*, where R2* = 1/T2*) and calculated as ΔR2*(t) = −ln[S(t)/S0]/TE, where S(t) is the signal intensity at 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. A gamma variate fit was used on a pixel-by-pixel basis to compute parameter images of time to peak of signal drop. Areas with hyperintensities in DWI and perfusion deficits in PWI were delineated, and lesion volumes were calculated. The mismatch ratio was determined from the initial DWI and PWI volumes (PWI/DWI). The final infarct volume was assessed from the T2-weighted MRI on day 7. Intracerebral hemorrhage was assessed on T2*-weighted baseline images for PWI.

Recanalization was assessed from the follow-up MRI study on day 1 on the basis of the PWI and MRA studies according to the modified Thrombolyis in Myocardial Infarction (TIMI) criteria for perfusion and vessel status (TIMI 0=no recanalization/reperfusion; TIMI 1=minimal recanalization/reperfusion (<20%); TIMI 2= incomplete recanalization/reperfusion; TIMI 3=complete recanalization/reperfusion). Vessel occlusion type was determined from the MRA study and described as follows: 0=no vessel occlusion, 1= internal cerebral artery occlusion at origin, 2=carotid-T occlusion, 3=proximal MCA trunk occlusion, 4=distal MCA trunk occlusion, and 5=M2 occlusion.

Statistical Analysis

If not stated otherwise, data are presented as median and range for continuous and as counts and percentages for categorical variables. Univariate comparisons were performed with the Mann-Whitney U test and Fisher’s exact test, depending on the scale of the variable. All probability values of the univariate comparisons should be corrected descriptively as resulting from explorative data analysis. Correlations were computed with Spearman’s rank correlation. Multiple logistic regression (backward variable selection) was performed to investigate the effect of several variables simultaneously on outcome. For all computations, SPSS 10.0 (SPSS Inc) was used.
Results

We enrolled 139 consecutive patients (50 women, 89 men; median age, 63 years; range, 0 to 89 years). Patients were divided into 2 groups: 63 patients were in the no thrombolysis group, which received conservative treatment, and 76 were in the thrombolysis group, which received tPA. The 2 groups did not differ in terms of age and sex, but the initial NIHSS was lower ($P=0.002$) and time to MR was longer ($P=0.002$) in the no thrombolysis group. Five patients had symptomatic intracerebral hemorrhage (2 with and 3 without thrombolysis). Ten patients died within the follow-up period (4 with and 6 without thrombolysis). Further details on baseline characteristics and outcome are given in Table 1.

Median time to thrombolysis was 180 minutes (range, 45 to 333 minutes). Forty-five patients were treated within the 3-hour time window and 31 within the 3- to 6-hour time window. MRI was performed 180 minutes (range, 75 to 360 minutes) after the start of symptoms.

Mismatch Ratio and Lesion Volumes

A relevant mismatch ( mismatch ratio $>1.2$) was present in 120 of 139 patients (86.3%). MRA demonstrated vessel occlusion in 90% of patients. The mismatch ratio did not differ ($P=0.39$), whereas mismatch volume was smaller in the no thrombolysis group ($P=0.032$). Mismatch ratio and mismatch volume did not differ in the subgroups of patients treated within the 3-hour and 3- to 6-hour time windows (mismatch ratio, $P=0.75$; mismatch volume, $P=0.69$). The final lesion volume (T2-weighted MRI on day 7) was smaller in the thrombolysis group, although it did not reach statistical significance (35 versus 73 mL; range, 1.6 to 377 and 0 to 685 mL; $P=0.44$). Details are given in Table 1. Initial DWI ($r=0.56$) and PWI ($r=0.76$) volumes correlated with the final lesion volumes on T2-weighted MRI (day 7). Moderate correlations were found for DWI ($r=0.44$) and PWI ($r=0.48$) lesion volumes with initial NIHSS score.

Patients Without Mismatch

Of the 19 patients without a mismatch (mismatch ratio $<1.2$), 8 (42%) had no vessel occlusion on MRA compared with 6 of 120 patients (5%) in the group with a mismatch (Table 2). Two characteristic patterns were identified. First, 8 patients without mismatch but patent vessels and normal PWI had small initial DWI lesion volumes (median, 3 mL; range, 1 to 43 mL) and final infarct volumes (median, 10 mL; range, 0 to 54 mL), less severe initial NIHSS scores (median, 10; range,

| TABLE 1. Baseline and Outcome Characteristics of Patients Not Treated or Treated With tPA (univariate analysis). Numbers are given in median and [range]. |
|---|---|---|---|
| No Thrombolysis | Thrombolysis | Total Study Population |
| (n=63) | (n=76) |
| Age, y | 63 (20–86) | 62 (22–89) | 0.938 | 63 (20–89) |
| Female sex, n (%) | 23 (36) | 27 (35) | 0.522 | 50 (36) |
| Time to MRI, min | 210 (75–360) | 150 (75–345) | 0.002 | 180 (75–360) |
| Time to thrombolysis, min | 180 (45–333) | 180 (45–333) |
| NIHSS score day 0 | 10 (1–25) | 13 (5–24) | 0.002 | 12 (1–25) |
| DWI volume, mL | 22 (0.2–254) | 22 (0.3–218) | 0.663 | 22 (0.2–254) |
| PWI volume, mL | 116 (0–349) | 152 (0–378) | 0.033 | 138 (0–394) |
| Mismatch volume, mL | 58 (0–34) | 113 (0–322) | 0.032 | 88 (0–388) |
| Mismatch ratio (PWI/DWI) | 2.6 (0–66) | 3.7 (0–190) | 0.385 | 3.4 (0–190) |
| T2-weighted volume, d 7, mL | 73 (0–685) | 35 (1.6–377) | 0.44 | 36 (0–685) |
| Symptomatic ICH, n (%) | 3 (4.8) | 2 (2.6) | 0.66 | 5 (3.6) |
| TIMI 2–3, n (%) | 11 (21.2) | 23 (32.4) | 0.22 | 34 (27.2) |
| TIMI 1–3, n (%) | 17 (32.7) | 47 (66.2) | $<0.001$ | 64 (51.2) |
| Dichotomized mRS at 90 d (0–1), n (%) | 8 (42) | 44 (37) | 0.023 | 50 (36) |
| Dichotomized mRS at 90 d (0–2), n (%) | 25 (39.7) | 46 (60.5) | 0.017 | 71 (51.1) |
| | | | | |
| *Univariate analysis. ICH indicates intracerebral hemorrhage. Values are median (range) when appropriate. |

| TABLE 2. Patients With and Without Relevant Mismatch |
|---|---|---|
| No Mismatch | Mismatch |
| (ratio $<1.2$) | (ratio $>1.2$) |
| (n=19) | (n=120) |
| Age, y | 59 (30–74) | 64 (20–89) |
| Time to MR, min | 180 (90–345) | 180 (75–360) |
| Time to thrombolysis, min | 180 (90–333) | 180 (45–305) |
| Thrombolytic therapy, n | 9 | 67 |
| NIHSS score on day 0 | 13 (1–20) | 12 (2–25) |
| DWI volume, mL | 18.6 (0.2–254) | 22 (0.5–166) |
| PWI volume, mL | 2.1 (0–252) | 142 (14–394) |
| Mismatch ratio (PWI/DWI) | 0.8 (0–1.2) | 4 (1.2–190) |
| Mismatch volume, mL | 0 (0–34) | 105 (4.3–388) |
| T2-weighted volume on day 7, mL | 30 (0–421) | 38 (1.3–685) |
| Dichotomized mRS at 90 d (0–2), n (%) | 13 (68) | 58 (48) |
| Dichotomized mRS at 90 d (0–1), n (%) | 8 (42) | 44 (37) |

Values are median (range) when appropriate. Statistical analysis was not performed because of the small numbers in the no mismatch group.
1 to 17), and good functional outcomes (mRS ≤2, 87.5%). Second, 8 patients with initial DWI lesion volumes >70 mL (median, 174 mL; range, 73 to 254 mL) had large final infarct volumes (median, 194 mL; range, 17 to 421 mL), high initial NIHSS scores (median, 17; range, 7 to 20), and poor clinical outcomes (mRS ≥3 in 5 of 8 patients, 62.5%).

Effect of tPA on Recanalization Rate

Data on vessel recanalization were available in 125 of 139 patients (90%). The recanalization rates according to TIMI criteria are given in Tables 3 and 4. Proximal and distal MCA occlusions (types 3 to 5) represented the majority of occlusions in the thrombolysis group (n=53 [69.7%] versus 38 [60.3%] in the no thrombolysis group). Dichotomized TIMI criteria for TIMI 0 to 1 (no recanalization or minimal recanalization) and TIMI 2 to 3 (recanalization with residual perfusion deficit and complete recanalization) did not show an effect of tPA in the thrombolysis group. Recanalization had an effect on the mRS: 67.6% patients with TIMI 2 to 3 had a good outcome (mRS at 90 days, ≤2) compared with 42.7% of patients with TIMI 0 to 1 (P=0.016; dichotomization mRS ≤1 versus 2 to 6, P=0.001). Dichotomization in TIMI 0 (33.9%) versus TIMI 1 to 3 (64.1%; P=0.001) showed a comparable effect.

Effect of Occlusion Type on Functional Outcome and Mismatch Volume

The distribution of occlusion types is given in Table 4. In general, patients with occlusion types 1 to 3 had worse functional outcomes (mRS ≤2, 39.5%) than those with occlusion types 4 to 5 (mRS ≤2, 68.2%; P=0.003; mRS ≤1 versus 2 to 6, P<0.001). Occlusion types 1 to 3 showed larger mismatch volumes (median, 108 mL; range, 0 to 388 mL) than types 4 to 5 (median 48 mL; range, 0 to 206 mL; P=0.02).

Effect of Multiple Variables on Functional Outcome

Multiple logistic regression analysis was performed to detect simultaneous influences on functional outcome (dichotomized mRS ≤2). Age, thrombolytic therapy within 3 hours, T2 lesion volume on day 7, and initial NIHSS had a significant effect on outcome (Table 6). Thrombolytic therapy within 3 to 6 hours showed a trend toward a better outcome that was not as strong as tPA therapy within 3 hours (odds ratios: for 3-hour group, 0.14; for 3- to 6-hour group, 0.35). Dichotomizing mRS ≤1 versus 2 to 6 resulted in a significant effect of thrombolysis in the 3- to 6-hour time window (P=0.02). No effect was seen for the mismatch ratio, mismatch volume, initial DWI and PWI volumes, recanalization rate, time of thrombolytic therapy, and occlusion type.

Discussion

DWI is highly sensitive for the detection of even small ischemic lesions and thus improves the diagnostic capabilities.

---

### TABLE 3. Distribution of Recanalization Rates

<table>
<thead>
<tr>
<th>TIMI</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Dichotomized TIMI 0-1</th>
<th>2-3*</th>
<th>Dichotomized TIMI 0</th>
<th>1-3†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lysis, n (%)</td>
<td>35 (67.3)</td>
<td>6 (11.5)</td>
<td>11 (21.2)</td>
<td>...</td>
<td>41 (78.8)</td>
<td>11 (21.2)</td>
<td>35 (67.3)</td>
<td>17 (32.7)</td>
</tr>
<tr>
<td>Lysis, n (%)</td>
<td>24 (33.8)</td>
<td>24 (33.8)</td>
<td>14 (19.7)</td>
<td>9 (12.7)</td>
<td>48 (67.6)</td>
<td>23 (32.4)</td>
<td>24 (33.8)</td>
<td>47 (66.2)</td>
</tr>
</tbody>
</table>

TIMI 0=no recanalization/reperfusion; TIMI 1=minimal recanalization/reperfusion; TIMI 2= incomplete recanalization/reperfusion; TIMI 3=complete recanalization/reperfusion.

*P=0.22; †P=0.001.

### TABLE 4. Distribution of Vascular Occlusion Types and Recanalization Rates

<table>
<thead>
<tr>
<th>Occlusion Types</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lysis, n (%)</td>
<td>9 (14.3)</td>
<td>14 (22.2)</td>
<td>2 (3.2)</td>
<td>17 (27)</td>
<td>7 (11.1)</td>
<td>14 (22.2)</td>
</tr>
<tr>
<td>TIMI 1–3, n</td>
<td>...</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Lysis, n (%)</td>
<td>5 (6.6)</td>
<td>12 (15.8)</td>
<td>6 (7.9)</td>
<td>30 (39.5)</td>
<td>15 (19.7)</td>
<td>8 (10.5)</td>
</tr>
<tr>
<td>TIMI 1–3, n</td>
<td>...</td>
<td>5</td>
<td>3</td>
<td>23</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

Vessel occlusion types were defined as follows: 0=no vessel occlusion; 1=internal cerebral artery occlusion at origin; 2=carotid-T occlusion; 3=proximal MCA occlusion; 4=distal MCA occlusion; 5=M2 occlusion.
of brain imaging in AIS patients. Several studies in smaller patient samples stimulated hopes that a multiparametric approach (T2-weighted imaging, DWI, PWI, and MRA) providing visualization of the vessel status, extent of the ischemic tissue damage, and extent of the perfusion deficit may help to identify criteria useful for the selection of patients likely to benefit from tPA therapy. Furthermore, it was argued that MRI might help to extend the currently narrow time window (0 to 3 hours after symptom onset) of safely treating AIS patients with tPA to beyond 3 hours.7

Many stroke neurologists consider multiparametric MRI a new evolving standard of care in AIS,6 and as a consequence, MRI is increasingly considered the sole imaging modality in acute stroke studies.

One of the main criticisms of recent MRI studies has been that study populations were relatively small and useful criteria in regard to patient selection and clinical neuroradiological outcomes were yet to be established. In particular, investigators were encouraged to combine multicenter data for the analysis performed in this study.23

We aimed to further study the effect of tPA therapy on MRI parameters and outcome using a multicenter approach.

### TABLE 5. Baseline and Outcome Characteristics of Patients Treated With tPA Within ≤3 Hours and 3 to 6 Hours

<table>
<thead>
<tr>
<th></th>
<th>Lysis≤3 h (n=45)</th>
<th>Lysis 3–6 h (n=31)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61 (22–87)</td>
<td>66 (32–89)</td>
<td>0.35</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>13 (29)</td>
<td>14 (45)</td>
<td>0.22</td>
</tr>
<tr>
<td>Time to MR, min</td>
<td>140 (75–300)</td>
<td>210 (120–345)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to thrombolysis, min</td>
<td>180 (45–180)</td>
<td>225 (185–333)</td>
<td>. . .</td>
</tr>
<tr>
<td>NIHSS score on day 0</td>
<td>13 (5–22)</td>
<td>13 (5–24)</td>
<td>0.24</td>
</tr>
<tr>
<td>DWI volume, mL</td>
<td>24 (0.3–187)</td>
<td>21 (2.5–218)</td>
<td>0.72</td>
</tr>
<tr>
<td>PWI volume, mL</td>
<td>153 (0.2–333)</td>
<td>143 (0–378)</td>
<td>0.91</td>
</tr>
<tr>
<td>Mismatch ratio (PWI/DWI)</td>
<td>3.6 (0.5–190)</td>
<td>4.1 (0–25)</td>
<td>0.75</td>
</tr>
<tr>
<td>Mismatch volume, mL</td>
<td>115 (0–322)</td>
<td>113 (0–277)</td>
<td>0.69</td>
</tr>
<tr>
<td>T2-weighted volume on day 7, mL</td>
<td>30 (1.6–318)</td>
<td>41 (2–377)</td>
<td>0.41</td>
</tr>
<tr>
<td>TIMI 2+3, n (%)</td>
<td>15/43 (34.9)</td>
<td>8/28 (28.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>TIMI 1–3, n (%)</td>
<td>33/43 (76.7)</td>
<td>14/28 (50)</td>
<td>0.024</td>
</tr>
<tr>
<td>Dichotomized mRS, 90 d (0–2), n (%)</td>
<td>29 (64.4)</td>
<td>17 (54.8)</td>
<td>0.48</td>
</tr>
<tr>
<td>Dichotomized mRS, 90 d (0–1), n (%)</td>
<td>19 (42.2)</td>
<td>16 (51.6)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Values are median (range) when appropriate.
*Univariate analysis.

### TABLE 6. Influence of Parameters on Functional Outcome Multiple Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variables in final model</th>
<th>mRS 0–2 vs 3–6</th>
<th>mRS 0–1 vs 2–6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>OR</td>
</tr>
<tr>
<td>Age</td>
<td>0.003</td>
<td>1.07</td>
</tr>
<tr>
<td>Sex*</td>
<td>0.315</td>
<td>0.56</td>
</tr>
<tr>
<td>Thrombolysis &lt;3 h†</td>
<td>0.002</td>
<td>0.10</td>
</tr>
<tr>
<td>Thrombolysis 3–6†</td>
<td>0.124</td>
<td>0.35</td>
</tr>
<tr>
<td>Final infarct volume</td>
<td>0.001</td>
<td>1.02</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.001</td>
<td>1.26</td>
</tr>
</tbody>
</table>

Additional variables not in final model

<table>
<thead>
<tr>
<th>Variables</th>
<th>mRS 0–2 vs 3–6</th>
<th>mRS 0–1 vs 2–6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mismatch ratio</td>
<td>0.908</td>
<td>1.00</td>
</tr>
<tr>
<td>Mismatch volume</td>
<td>0.864</td>
<td>0.97</td>
</tr>
<tr>
<td>DWI</td>
<td>0.876</td>
<td>0.97</td>
</tr>
<tr>
<td>PWI</td>
<td>0.854</td>
<td>1.04</td>
</tr>
<tr>
<td>Recanalization rate‡</td>
<td>0.133</td>
<td>0.41</td>
</tr>
<tr>
<td>Time to MR</td>
<td>0.989</td>
<td>1.00</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval. Adjustment for study center was performed.
*Reference: male.
†Reference: No thrombolysis.
‡Reperfusion versus no reperfusion.
We collected data from 139 AIS patients who were studied within the first 6 hours of acute stroke onset and during follow-up. Several predictors of a favorable outcome were identified in the multiple regression analysis. Patients who were most likely to achieve neurological independence (mRS, 0 to 2) were younger, had milder baseline stroke severity (NIHSS score), and were treated with tPA. This tPA benefit was achieved although the initial NIHSS score was higher in the thrombolysis group ($P=0.002$).

Of 76 patients, 31 received intravenous tPA within the 3- to 6-hour time window. The beneficial effect of tPA was independent from the 3-hour or 3- to 6-hour time window (univariate analysis, $P=0.48$); however, thrombolysis in the 3-hour time window appeared more effective than in the 3- to 6-hour time window (multiple logistic regression analysis). This result is interesting in light of previous efforts to expand the time window toward the 6-hour time limit in CT-based AIS therapy studies.2,20,22 Although the NINDS investigators concluded that the benefits of treatment declined significantly toward the end of the 3-hour treatment window,25 ECASS I showed positive results in the intention-to-treat population, thereby raising hopes for successful thrombolysis within the 6-hour time window. The collaborators in the Standard Treatment with Alteplase to Reverse Stroke (STARS) study found positive results comparable to those of the NINDS study, although the median time from stroke onset to tPA treatment was shifted toward the end of the 3-hour treatment window (2 hours 44 minutes).26 Furthermore, 2 recent meta-analyses, which included NINDS and ECASS I and II,27 respectively, all prospective randomized trials,28 showed a significant reduction in death and dependence in patients treated with thrombolytic therapy up to 6 hours after symptom onset, albeit with a nonsignificantly better effect within the 3-hour time window. Overall, treatment with tPA was associated with the best effect and lowest complication rate.

One might hypothesize that a reasonable explanation for worse outcomes within a delayed time window might be smaller volumes of tissue at risk of infarction, worse initial NIHSS, larger initial DWI volumes, or larger final infarct volumes. However, we did not find differences in these parameters in the subgroups in the 3-hour and 3- to 6-hour time windows. We therefore conclude that MRI has the potential to become a valuable tool for selecting patients likely to benefit from thrombolysis beyond the rigid 3-hour time window. Larger series are necessary to support these findings.

Recanalization Rates and Effect on Functional Outcome

Recanalization rates are not well studied in AIS patients treated with intravenous tPA. The large tPA trials,1,5,20,24,29,30 did not determine vessel status or recanalization rates. Studies with small series of patients showed significant reperfusion in tPA-treated AIS patients, perhaps related to thrombolytic treatment.1,3 Recurrent transient Doppler sonography studies revealed surprisingly high recanalization rates, up to 70%, with intravenous tPA within the first 6 hours3,33–35 that were comparable to recanalization rates with intra-arterial thrombolysis (66% for the recombinant prourokinase group compared with 18% for the control group, $P<0.001$).36 A recent SPECT study could not confirm a comparable metabolic recovery after thrombolysis,37 and it appears important to consider the method used for the determination of recanalization. We used criteria that have been successfully used in myocardial infarction studies and recent Doppler ultrasound-based studies. In our study, the dichotomization of the TIMI grades had considerable impact on the data: Recanalization occurred in 32.4% ($P=0.02$) of the tPA-treated group if the dichotomized TIMI 2 to 3 was assessed, whereas 66.2% ($P<0.001$) of the patients recanalized within the first 24 hours with dichotomized TIMI 1 to 3 criteria. Whether TIMI 1 (minimal reperfusion in PWI $\leq20\%$ of the initial PWI volume) is sufficient to give the impression of recanalization on TCD examinations is an important question to be answered by future studies.

It is obvious that nutritional reperfusion is likely to contribute to smaller final infarct volumes and favorable outcome.35,36,38 In our series, tPA therapy showed a trend toward smaller T2-weighted lesion volume on day 7 in the thrombolysis group (median: 29; range: 1.3 to 377 mL) than in the no-thrombolysis group (median: 73 mL; range: 0 to 685 mL; $P=0.079$). Because thrombolytic therapy favored recanalization, it is likely that the beneficial effect of thrombolysis on functional outcome is mediated by higher recanalization rates and smaller lesion volumes.

Patients Without Mismatch

We found a large number of patients with a relevant mismatch (93%) and vessel occlusion in MRA (90%). The mismatch volume representing tissue at risk of infarction was considerable (median, 88 mL; range, 0 to 388 mL). Patients without mismatch are likely to present with spontaneous recanalization, lacunar infarcts, or large, scarcely collateralized hemispheric infarcts resulting from proximal vessel occlusions. We found 2 subgroups in our population of 19 patients without a relevant mismatch (mismatch ratio $<1.2$) that support this view (Table 2). The first subgroup (n=8) had small initial DWI lesion and final infarct volumes, patent vessels, and normal PWI. These patients had either lacunar strokes or spontaneously recanalized peripheral branch occlusions and had good functional outcomes. The other subgroup presented with large DWI and PWI lesion volumes and MCA or carotid artery occlusions (occlusion types 1 to 3). Even at a very early imaging time point (210 minutes after stroke onset), patients had no relevant mismatch and accordingly developed large final infarct volumes and poor functional outcomes.

One might ask whether thrombolysis should be limited to patients with DWI/PWI mismatch. In our series, thrombolysis was performed in 9 of 19 patients without mismatch, and no firm conclusions can be derived from this small number. The rationale for thrombolytic therapy is the lysis of an obliterating thrombus with restoration of blood flow and salvage of hypoperfused tissue at risk of infarction as identified by stroke MRI. From the mismatch concept, one might assume that patients without mismatch are the least likely to benefit from tPA treatment. However, recent reports of partial reversibility of DWI lesions in AIS patients with early
reperfusion indicate that this is a complex issue.11,21 Given the currently available database, patients with vessel occlusion and DWI/PWI mismatch with tissue at risk for infarction clearly seem to be the target group that should have the greatest potential to benefit from thrombolysis. On the other hand, it appears important to evaluate the potential treatment benefit from thrombolysis in patients without such a mismatch. Without such data, there appears to be no justifiable reason to limit intravenous thrombolytic treatment to patients with a DWI/PWI mismatch.

Another question concerns patients with proximal vessel occlusions and scarce collateralization. From the data in this series, we see no reason not to perform systemic thrombolysis in case of a large mismatch. In these patients who are at risk of malignant MCA infarction,39 MRI can be particularly helpful to indicate early those patients in whom intensive supervision and ultimately early hemicraniectomy may be necessary.40

This study has several limitations. Patients were consecutively enrolled, and no screen log was assessed to document patients who were not eligible. No randomization to the 2 treatment arms was performed, nor was the study placebo controlled. The decision of whether to administer tPA was at the discretion of the evaluating physician at each center, and MRI was performed after the start of tPA treatment in 10 patients. This potentially introduced bias, and no tPA-treated patients were included in Berlin. Additionally, the difference in time to MRI between the IPA and no tPA groups was 1 hour and might have influenced the difference in mismatch volumes. In the absence of placebo-controlled, randomized trials, observational data can supplement our knowledge. This multicenter analysis provides the largest sample size of patients with hyperacute MRI and tPA treatment, and the results are of value for future acute MRI controlled trials. Judging from our results, a future prospective, randomized, controlled clinical trial would require 120 patients per arm to achieve statistical power, 80%.

In conclusion, we have shown in a multicenter, open-label, nonrandomized study that MRI is feasible in patients undergoing subsequently tPA therapy. TPA therapy has a beneficial effect on final infarct volumes and functional outcome in AIS patients with evolving MCA stroke, although the initial NIHSS score was significantly higher in the thrombolysis group. This was demonstrated not only in the rigid 3-hour time window but also in an extended 3- to 6-hour time window without the introduction of bleeding complications. Multiparametric MRI can delineate large volumes of tissue at risk of infarction beyond the 3-hour time window, and this information facilitates a benefit-to-risk weighting for intravenous tPA therapy. On the basis of those results, we see motivation for larger prospective trials using MRI in addition to careful clinical safety criteria for patient selection to study the possibility of a safe and successful therapy beyond a 3-hour time window.

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**References**


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