Monitoring Intravenous Recombinant Tissue Plasminogen Activator Thrombolysis for Acute Ischemic Stroke With Diffusion and Perfusion MRI

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Background and Purpose—Intravenous recombinant tissue plasminogen activator (rtPA) administration is an effective therapy for ischemic stroke when initiated within 3 hours and possibly up to 6 hours after symptom onset. To improve patient selection, a fast diagnostic tool that allows reliable diagnosis of hemorrhage and ischemia, vessel status, and tissue at risk at an early stage may be useful. We studied the feasibility of stroke MRI for the initial evaluation and follow-up monitoring of patients undergoing intravenous thrombolysis.

Methods—Stroke MRI (diffusion- and perfusion-weighted imaging [DWI and PWI, respectively], magnetic resonance angiography, and T2-weighted imaging) was performed before, during, or after thrombolysis and on days 2 and 5. We assessed clinical scores (National Institutes of Health Stroke Scale [NIHSS], Scandinavian Stroke Scale [SSS], Barthel Index, and Rankin scale) at days 1, 2, 5, 30, and 90. Furthermore, we performed volumetric analysis of infarct volumes on days 1, 2, and 5 as shown in PWI, DWI, and T2-weighted imaging.

Results—Twenty-four patients received rtPA within a mean time interval after symptom onset of 3.27 hours and stroke MRI of 3.43 hours. Vessel occlusion was present in 20 of 24 patients; 11 vessels recanalized (group 1), and 9 did not (group 2). The baseline PWI lesion volume was significantly larger ($P=0.008$) than outcome lesion size in group 1, whereas baseline DWI lesion volume was significantly smaller ($P=0.008$) than final infarct size in group 2. Intergroup outcome differed significantly for all scores at days 30 and 90 (all $P<0.01$). Intragroup differences were significant in group 1 for change in SSS and NIHSS between day 1 and day 30 ($P=0.003$) and for SSS only between day 1 and day 90 ($P=0.004$).

Conclusions—Stroke MRI provides comprehensive prognostically relevant information regarding the brain in hyperacute stroke. Stroke MRI may be used as a single imaging tool in acute stroke to identify and monitor candidates for thrombolysis. It is proposed that stroke MRI is safe, reliable, and cost effective; however, our data do not prove this assumption. Early recanalization achieved by thrombolysis can save tissue at risk if present and may result in significantly smaller infarcts and a significantly better outcome. (Stroke. 2000;31:1318-1328.)

Key Words: magnetic resonance imaging, diffusion-weighted ■ magnetic resonance imaging, perfusion-weighted ■ recanalization ■ thrombolysis

Four large trials have investigated the efficacy of recombinant tissue plasminogen activator (rtPA) for intravenous thrombolysis in patients with acute ischemic stroke.1–3a On the basis of the National Institute of Neurological Disorders and Stroke (NINDS) trial, rtPA is approved by the Food and Drug Administration in the United States for thrombolytic therapy within 3 hours of ischemic stroke onset and is considered to be a cost-effective treatment.4 In Europe, rtPA has not yet been approved but is used in centers experienced with this therapeutic approach in individual patients presenting within 3 hours (in selected cases within up to 6 hours) after the onset of stroke symptoms if there are no early CT signs of infarction of more than one third of the middle cerebral artery (MCA) territory or clinical signs of a large hemispheric infarction.1

However, the need remains for a stroke imaging tool that is fast, has a sufficiently high sensitivity for detecting both intracerebral hemorrhage (ICH) and ischemia within the first 6 hours, can identify the tissue at risk if present, and shows occlusion of major arteries at the base of the brain. The advent of new MRI techniques such as perfusion- and diffusion-weighted imaging (PWI and DWI, respectively) has...
revolutionized diagnostic imaging in stroke.5–12 It is presumed that the difference (mismatch) between abnormal areas on DWI and PWI (with PWI>DWI) represents the ischemic tissue at risk, which is potentially salvageable.6,8,11,13 Several investigators have found a significant correlation of DWI and PWI changes with follow-up T2-weighted imaging (T2WI) changes as well as with neurological outcome as assessed by the National Institutes of Health Stroke Scale (NIHSS) and the Barthel Index (BI).5–8,11,14 These authors conclude that different infarct patterns can be identified by means of DWI and PWI in hyperacute stroke, which may allow a more rational selection of therapeutic strategies based on the presence or absence of tissue at risk. However, all these studies suffer from a small number of patients investigated in the relevant time window for therapeutic intervention, absence of a sufficiently standardized stroke MRI protocol, and lack of patients treated with rtPA, with the exception of one study, which reports 6 rtPA patients in whom stroke MRI was performed 2.66 hours, on average, after thrombolytic therapy.15 The purpose of the present study was to assess the feasibility of stroke MRI in the initial evaluation and follow-up monitoring of patients with hyperacute ischemic stroke who received intravenous thrombolytic therapy.

Subjects and Methods

Patients

Our target group consisted of patients receiving thrombolysis for hyperacute ischemic stroke. Stroke onset was defined as the last time the patient was known to be without any neurological deficit. Exclusion criteria were an age of <18 years or >80 years, a significant preexisting neurological deficit (modified Rankin scale [MRS] >1), a history or CT findings of severe cerebral microangiopathy or multi-infarct dementia, unstable vital signs, or general MRI contraindications. Eleven patients from an earlier publication are included in this analysis16,17; 4 of these underwent stroke MRI examination after rtPA was administered, and 2 had lacunar infarcts. All patients had a CT scan before enrollment in the study, and all patients received open-labeled rtPA. We performed thrombolysis with 0.9 mg/kg body wt rtPA according to the European Cooperative Acute Stroke Study (ECASS) II study protocol.1 To avoid selection bias, the indication for thrombolysis was based exclusively on the clinical status and CT findings in all patients according to ECASS II criteria, and not on stroke MRI, which was the modality under investigation. Eleven patients received rtPA within the first 3 hours, and 13 patients received rtPA within 3 hours to 5.33 hours after symptom onset (3.27±1.39 hours). To avoid any delay in initiating treatment due to investigational stroke MRI, the neuroradiologist on call was paged from the neurological emergency room upon patient arrival. After an initial assessment of the neurological status, including the history, stabilization of vital parameters, and stroke emergency care, we performed CT. When possible, the preparation of the rtPA infusion and the initiation of stroke MRI took place simultaneously; an rtPA bolus (10% of the total dose) was given, and the continuous infusion was started during stroke MRI. Immediately after stroke MRI, the patient was admitted to the neurological critical care unit or to the stroke unit for further monitoring and therapy. For patient safety, a neurological stroke fellow experienced in neurological critical care was present throughout the MRI examination: oxygen saturation and ECG were monitored continuously, and blood pressure was measured intermittently. We obtained informed consent from all patients or their next of kin. The study protocol was approved by the local ethics committee.

Imaging and Clinical Assessment

All patients were examined with a state-of-the-art CT scanner (PQ 2000, Picker) and immediately thereafter with a 1.5-T whole-body MR imager (EDGE, Picker) equipped with enhanced gradient hardware for echo planar imaging (EPI). For the MRI examination, we used a circular polarized head coil. We performed stroke MRI on days 1 (initial scan), 2, and 5 (day 5 without rtPA). The stroke MRI protocol included an axial T2-weighted fast spin echo sequence, an axial fluid-attenuated inversion recovery EPI sequence, an axial isotropic DWI spin echo EPI sequence (b=0, 333, 666, and 1000 s/mm²), time-of-flight magnetic resonance angiography (MRA), and PWI with an axial T2-weighted gradient echo EPI sequence (40 data sets during and after injection of 25 mL Gd-DTPA [Magnevist, Schering AG] with a power injector [5 mL/s]). Mean transit time (MTT) is defined as the quotient of cerebral blood volume divided by cerebral blood flow (CBF). Perfusion maps were calculated from the concentration time curves as the normalized first moment of the concentration time curve, ie, the time that divides the area under the concentration curve (relative cerebral blood volume) into 2 equal parts (relative MTT or time to midpoint).16 Quantitative CBF measurement17 was not performed because of the requirement of extensive postprocessing and thus nonavailability for bedside use. Because quantitative CBF measurements and thus MTT were not available, we chose the unspecific term “perfusion map” instead of MTT map. The complete stroke MRI protocol takes 15 minutes, and an additional 5 to 10 minutes are necessary for patient positioning and transfer. Postprocessing of the MRIs was performed by using commercial image analysis software and a workstation (Picker VISTAR). All neuroimaging studies were cross-read by staff neuroradiologists. Infarct volumes were measured in a semiautomatic fashion: We outlined manually the lesion volume, multiplied it by the slice thickness, and added up the slice volumes. To define the initial infarct volume, we used the images acquired with the strong DWI sequence (b=1000 s/mm²). The location and size of the tissue at risk were determined on the basis of perfusion maps generated from PWI, whereas the final infarct volume was determined on day 5 according to T2WI. We defined a volume ratio of PWI/DWI ≥1.2 (ie, the PWI lesion being at least 20% larger than the DWI lesion) as a relevant perfusion-diffusion mismatch that indicated the presence of tissue at risk. Furthermore, we calculated the difference between PWI and DWI volumes as an absolute measure of tissue at risk. Initial and follow-up vessel status were assessed by MRA, with MRA on day 2 used to evaluate persisting arterial occlusion or recanalization. Group assignment was retrospective. Patients with vessel occlusion that was subsequently recanalized were arbitrarily assigned to group 1, and those with no subsequent recanalization were assigned to group 2. Those patients who had no anterior territory stroke (patient 24, posterior cerebral artery occlusion) or no vessel occlusion at all were assigned to group 3. We assessed clinical data at days 1, 2, 5, 30, and 90 by use of NIHSS,3 SSS,18 BI,19 and MRS.20 We defined a favorable outcome as NIHSS ≤2, SSS ≤54, BI ≥95, and MRS ≤1. All clinical scores were obtained by a senior neurology resident or a stroke fellow, who were video-trained and certified for application of the NIHSS.21

Statistical Analysis

For statistical analysis, we used a standard software package (StatView 4.5, Abacus Concepts). Demographic data, time intervals of examinations and onset of rtPA infusion, and descriptive statistics of scores are given as mean or median values with SD and range. Spearman’s rank correlation was used to determine the correlation between lesion volumes and neurological scores. Because our data are not normally distributed, we used nonparametric tests (Mann-Whitney U test and Wilcoxon signed rank test) to determine whether there were significant differences between initial and follow-up lesion volumes, scores, and interindividual differences in morphological and functional outcome between those patients with successful recanalization of the occluded vessel (group 1) versus those without recanalization (group 2). The group differences regarding the localization of vessel occlusion was assessed by a Fisher exact test.
Results
We examined 24 patients (12 men and 12 women, mean age 63.4 years, range 44 to 78 years) who had received thrombolysis for acute ischemic stroke with a standardized stroke MRI protocol within the first 1.5 hours to 9 hours (mean±SD 3.43±1.78 hours, 23 patients within 5.75 hours) after stroke onset. The time interval between CT and MRI ranged from 15 minutes to 5.5 hours (1.25±1.14 hours), with 14 examinations being performed within 1 hour after CT. All patients received rtPA according to ECASS II criteria1 within 6 hours after symptom onset (3.27±1.39 hours, range 0.75 to 5.33 hours). Sixteen of the 24 patients had stroke MRI before or at initiation of thrombolytic therapy. Of the other 8 patients, 7 had stroke MRI within 1.5 hours after rtPA bolus administration, and 4 had stroke MRI within 30 minutes. All but 1 of these 8 patients had a vessel occlusion according to the baseline MRA, showing that no or only incomplete recanalization after rtPA had yet occurred; the other patient had a lacunar infarction. The mean time interval between stroke MRI and rtPA for all 24 patients was 0.15±1.09 hours (−1.75 hours [MRI before rtPA] to 4 hours [MRI after rtPA]). Four of the 24 patients had no initial vessel occlusion in the anterior cerebral circulation according to MRA but showed lesions on initial DWI (group 3). Three of these patients had lacunar infarctions (DWI volumes <8 mL) without early CT signs and without (PWI/DWI <0.5, 2 patients) or only a minimal (PWI/DWI 1.6, 1 patient) PWI/DWI mismatch, and 1 patient had a distal posterior cerebral artery occlusion. NIHSS on day 1 was fairly similar11–13,15 in these patients. Outcome was good in 3 patients (NIHSS and MRS on day 90 was 0 points) and moderate in 1 patient (NIHSS/MRS was 4/2). Because these patients did not have a vessel occlusion in the anterior circulation and thus, according to our present understanding, are not the optimal rtPA candidates, they were excluded from further analysis.

Seven patients each presented with either a proximal or a distal MCA main stem occlusion, 4 had an MCA branch occlusion, and 2 had a distal internal carotid artery (ICA) occlusion according to the initial MRA. All but 1 of these 20 patients had an abnormal initial DWI scan and a perfusion-diffusion mismatch (ie, tissue at risk, PWI/DWI >1.2) of >20% (mean 8.07%, range 0.81% to 29.9%). In the 1 patient with an initial proximal MCA occlusion but without PWI/DWI mismatch (patient No. 11) the oedematous vessel recanalized during the MRI examination between MRA and PWI, as shown by Doppler ultrasound immediately after MRI. He had a good outcome, with only a minimum facial weakness left at day 90 (NIHSS 1, SSS 56, BI 100, and MRS 1). In 11 (55%) of 20 patients, vessels recanalized after rtPA according to follow-up MRA on day 2. We thus divided the 20 patients into 2 groups: group 1 (n=11) consisted of the patients with recanalization (Figure 1), and group 2 (n=9) consisted of those without recanalization (Figure 2). The mean time interval for delivery of rtPA was greater in group 2 than in group 1 (3.72±1.13 hours and 2.76±1.48 hours, respectively), although this difference did not reach statistical significance (P=0.13, Mann-Whitney U test). The initial clinical deficit was higher in group 2 (median NIHSS 15 versus 10 in group 1, median SSS 19 versus 28 in group 1), which was not due to a higher proportion of left hemispheric infarctions and thus worse disability scores in group 2 versus 1 (7 and 4 versus 6 and 3), and did not reach statistical significance (P=0.11 for NIHSS on day 1 and P=0.063 for SSS on day 1, Mann-Whitney U test). Also, there was no difference between groups 1 and 2 regarding the proportion of proximal (ICA and proximal MCA mainstem) and distal (distal MCA main stem and branches) occlusions (P=0.65, Fisher exact test). There was a considerable difference in the mean values of mismatch (PWI/DWI) between group 1 (26.27) and group 2 (8.13); however, the median values were fairly similar (3.65 versus 4.73), and neither the difference of PWI/DWI nor of PWI-DWI between groups 1 and 2 was statistically significant (P=0.97 and P=0.305, Mann-Whitney U test). Also, baseline DWI and PWI lesion volumes did not differ between groups 1 and 2 (P=0.102 and P=0.23 by Mann-Whitney U test).

Two patients (Nos. 15 and 17) experienced a symptomatic secondary hemorrhage after treatment with rtPA, which was identified on day-2 stroke MRI. One late death occurred in each group between days 30 and 90. 1 because of pulmonary embolism (patient 4) and the other due to cardiopulmonary failure (patient 15). See Table 1 for demographic data, time windows, and day-1, day-30, and day-90 scores. See Table 2 for baseline and outcome lesion sizes, mismatch ratio, and PWI-DWI volume difference.

Analysis of Intragroup and Intergroup Outcome
All neurological scores and outcome scales differed significantly between groups 1 and 2 on day 30 (NIHSS, SSS, BI, and MRS, P=0.004; Mann-Whitney U test). There was a slight decrease in statistical significance between groups 1 and 2 on day 90 (NIHSS, SSS, BI, and MRS, P=0.008; Mann-Whitney U test). Within group 2, SSS and NIHSS from day 1 and day 30 or 90 did not differ significantly. In group 1, however, there was a significant difference between the neurological scores on day 1 and day 30 (SSS and NIHSS, P=0.003). The difference between NIHSS on day 1 and day 90 barely missed statistical significance (P=0.0505) because of the 1 deceased patient with a formal NIHSS of 42 points (death is not coded in the NIHSS). The difference between day-1 and day-90 SSS was still highly significant (P=0.004).

Correlation and Difference of Initial and Follow-Up Infarct Volumes
The day-1 PWI lesion volumes of either group did not correlate with day-2 lesion volumes on DWI or with day-5 lesion volumes on T2WI (all r<0.6, all P=NS; Spearman). Day-1 DWI volumes and day-2 DWI volumes did not correlate at all in group 2, whereas lesion volumes on day 1 (DWI) and day 5 (T2WI) were significantly different (P=0.008, Wilcoxon), with day-5 T2WI always being larger. In group 1, DWI volumes on days 1 and 2 correlated significantly (r=0.697, P=0.037; Spearman). There also were significant correlations for DWI on day 2 (P=0.0038, r=0.964) and PWI on day 2 (P=0.045, r=0.708) with T2WI on day 5 in group 1 but not in group 2. Day-1 PWI and day-5 T2WI volumes differed significantly in group 1 (P=0.008, Wilcoxon); however, day-1 DWI and day-5 T2WI volumes
did not \( P=0.155 \), Wilcoxon). There was no relationship between lesion size and recanalization.

**Correlation and Difference of Absolute Infarct Volumes With Outcome**

In group 2, lesion volumes on days 1, 2, and 5 did not correlate with any outcome score, nor did the day-1 DWI lesions in group 1. However, DWI volume on day 2 and even more T2WI volume on day 5 correlated in group 1 with all outcome scales except the BI (day-2 DWI/NHSS, \( P<0.01 \) and \( r=0.88 \); day-5 T2WI/NHSS, \( P=0.006 \) and \( r=0.88 \); day-5 T2WI/SSS, \( P<0.01 \) and \( r=0.68 \); and day-2 DWI and day-5 T2WI/MRS, \( P<0.05 \) and \( r=0.71 \)). There was neither a correlation between PWI lesion on any day with any score in any group nor a correlation of mismatch ratio or absolute mismatch volume and any outcome score in any group. See Table 3 for summary of group data and statistical analysis.

**Discussion**

Despite the enthusiastic reports on the diagnostic potential of DWI and PWI in hyperacute ischemic stroke,\textsuperscript{7,8,11,22} substantial doubts remain regarding the feasibility, utility, and cost-effectiveness of this method.\textsuperscript{23} We performed stroke MRI within an average time interval of 1.25 hours after CT and 3.43 hours after symptom onset in 24 patients. Thrombolysis was started without any unnecessary delay within an average of 3.25 hours after symptom onset before stroke MRI in 8 of 24 patients and during or after stroke MRI in 16 of 24 patients.
patients. Four of the 8 patients who were imaged after initiation of thrombolysis were imaged within 30 minutes, and another 3 were imaged within 1.5 hours after the onset of therapy. Thus, the present study shows the feasibility of stroke MRI in hyperacute stroke patients. Although safety and reliability were not investigated with predefined parameters, the overall performance of stroke MRI was excellent. No obvious complications due to contrast agents or the MRI itself were seen, all images were of high quality and could be interpreted, and there were no ambiguous decisions regarding the presence or absence of abnormalities on DWI and PWI.

The need for an all-round diagnostic tool with which all the important pathophysiological aspects of hyperacute stroke can be investigated is evident. Such a method must answer 5 decisive questions: (1) Where and how large is the actual area of irreversible ischemic brain damage? (2) How old is the infarction? (3) Is there tissue at risk, and how much tissue is at risk? (4) Is there a vessel occlusion, and where is it? (5) Is there an intracerebral hemorrhage or another underlying nonischemic disease? Presently, the decision to initiate intravenous rtPA treatment is based on clinical findings and CT scanning. The reported diagnostic yield of CT within 3 hours after symptom onset is low (50% to 70%).17,24,25 DWI may delineate infarcted brain tissue in <1 hour after symptom onset, probably within minutes, although there is accumulating evidence that in the very early stage of stroke, there may be reversible DWI changes.27 PWI and DWI reveal the ischemic tissue potentially at risk.8 We would like to stress,
however, that PWI renders only relative information regarding CBF and that the volumetric difference of DWI and PWI does not directly represent the penumbra, which is a more complex pathophysiological concept of the presence of a nonfunctional but potentially salvageable area of brain tissue.28 A PWI/DWI mismatch may, however, reflect the ischemic penumbra to a certain extent and therefore make it possible to pragmatically estimate the size of tissue at risk of irreversible infarction. MRA can reliably assess the cerebral vessel status.29 The utility of MRI to demonstrate hyperacute primary ICH is still a matter of controversial discussion. It has been shown that susceptibility-weighted images, such as the T2-weighted source images of PWI, allow a definitive diagnosis of ICH within the first hours of stroke.30 Although hyperacute subarachnoid hemorrhage is difficult to detect on MRI,31 certain sequences seem to be promising;32 however, the clinical presentation of subarachnoid hemorrhage rarely mimics that of acute ischemic (or hemorrhagic) stroke. Stroke MRI as a single diagnostic tool provides critical data that have the potential to guide therapeutic decisions in hyperacute stroke patients.

Of course, a single-center study with 24 patients cannot provide meaningful statements as to cost-effectiveness. It seems reasonable, though, that by eliminating the need for CT and Doppler ultrasound in the initial evaluation of acute stroke patients, stroke MRI may indeed be more cost-effective. In all of our patients, the necessary information was available initially and at follow-up. The data are consistent

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<th>Day-30 NIHSS, SSS, BI, MRS</th>
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<td>3.75</td>
<td>0.25</td>
<td>13, 24</td>
<td>1, 56, 90, 1</td>
<td>0, 58, 100, 0</td>
</tr>
<tr>
<td>24 E.R.</td>
<td>74/Female</td>
<td>3.50</td>
<td>4.50</td>
<td>−1.00</td>
<td>12, 23</td>
<td>0, 58, 95, 1</td>
<td>0, 58, 100, 0</td>
</tr>
<tr>
<td>Mean: SD or median</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1: 1–11</td>
<td>62.9 ± 9.1</td>
<td>3.00 ± 1.61</td>
<td>2.76 ± 1.48</td>
<td>0.20 ± 0.66</td>
<td>10, 28</td>
<td>0, 58, 100, 0</td>
<td>0, 58, 100, 0</td>
</tr>
<tr>
<td>Group 2: 12–20</td>
<td>61.4 ± 10.4</td>
<td>4.08 ± 2.14</td>
<td>3.72 ± 1.13</td>
<td>0.36 ± 1.57</td>
<td>15, 19</td>
<td>13, 27, 35, 4</td>
<td>8, 32, 60, 3</td>
</tr>
<tr>
<td>Group 3: 21–24</td>
<td>68.0 ± 6.9</td>
<td>3.25 ± 1.19</td>
<td>3.69 ± 1.55</td>
<td>0.44 ± 0.66</td>
<td>12.5, 24</td>
<td>5, 57, 92, 5</td>
<td>0, 58, 100, 0</td>
</tr>
<tr>
<td>All patients</td>
<td>63.4 ± 9.3</td>
<td>3.43 ± 1.78</td>
<td>3.27 ± 1.39</td>
<td>0.15 ± 1.09</td>
<td>11.5, 24</td>
<td>2.5, 50.5, 90, 1.5</td>
<td>1.5, 53.5, 95, 1</td>
</tr>
</tbody>
</table>

TI indicates time interval; SD, symptom onset. Demographic data and neurological scores are summarized for each patient. Time windows from SO to stroke MRI and to rtPA therapy are given. The TI between rtPA and stroke MRI was negative when MRI was performed before bolus administration, zero when the bolus was given during the start of the MRI examination, and positive when MRI was performed after initiation of rtPA therapy. At the base of the table, mean ± SD or median values, as appropriate, are given for all patients and split for groups 1–3.

* Patients with symptomatic hemorrhage due to thrombolysis.

TABLE 1. Demographic Data, Time Windows, and Day-1, Day-30, and Day-90 Scores
with the pathophysiological understanding of vessel occlusion, the presence or absence of tissue at risk, and the morphological and clinical outcome, which ultimately depends on timely vessel recanalization or permanent occlusion. Stroke MRI cannot determine in which patients vessel occlusion will persist and in which patients vessel recanalization will occur (no imaging modality can answer this question at present), although recanalization rates tend to be lower with more proximal vessel occlusions (carotid T and proximal MCA), an observation also made in patients treated with intra-arterial thrombolysis.33 However, we speculate that stroke MRI can answer the critical questions of who may profit from recanalization, in whom recanalization should be achieved by all means, and in which patients there is no tissue at risk or no ischemic disease at all but only an excessive risk of hemorrhage due to thrombolytic therapy. The utility of stroke MRI, although not proven yet by analysis of predefined parameters in a prospective study, is likely to be the early identification of those patients in whom the outcome and final infarct size, ultimately the patient’s fate, have not yet been determined.

### TABLE 2. Location of Vessel Occlusion, Baseline Stroke Scales, Lesion Sizes at Baseline, and Outcome, Mismatch Ratio, and Difference

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Patient</th>
<th>Baseline NIHSS, SSS</th>
<th>MRA Day 1</th>
<th>DWI Day-1 Lesion Size, mL</th>
<th>PWI Day-1 Lesion Size, mL</th>
<th>Mismatch Day-1 PWI/DWI</th>
<th>ΔPWI-DWI, mL</th>
<th>T2WI Day-5 Lesion Size, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P.S.</td>
<td>10, 28</td>
<td>Proximal M1</td>
<td>6.87</td>
<td>171.04</td>
<td>24.90</td>
<td>164.17</td>
<td>28.88</td>
</tr>
<tr>
<td>2</td>
<td>W.D.</td>
<td>10, 43</td>
<td>M2</td>
<td>36.35</td>
<td>62.41</td>
<td>1.72</td>
<td>26.06</td>
<td>42.6</td>
</tr>
<tr>
<td>3</td>
<td>L.K.</td>
<td>6, 40</td>
<td>M2</td>
<td>15.099</td>
<td>50.47</td>
<td>3.34</td>
<td>35.37</td>
<td>16.02</td>
</tr>
<tr>
<td>4</td>
<td>J.L.</td>
<td>22, 4</td>
<td>Proximal M1</td>
<td>69.68</td>
<td>215.72</td>
<td>3.10</td>
<td>146.04</td>
<td>29.92</td>
</tr>
<tr>
<td>5</td>
<td>A.S.</td>
<td>11, 24</td>
<td>Distal M1</td>
<td>28.71</td>
<td>142.9</td>
<td>4.98</td>
<td>114.19</td>
<td>28.07</td>
</tr>
<tr>
<td>6</td>
<td>M.R.</td>
<td>5, 37</td>
<td>Distal M1</td>
<td>5.779</td>
<td>96.29</td>
<td>16.66</td>
<td>90.51</td>
<td>10.21</td>
</tr>
<tr>
<td>7</td>
<td>J.R.</td>
<td>7, 36</td>
<td>M2</td>
<td>17.54</td>
<td>64.04</td>
<td>3.65</td>
<td>46.5</td>
<td>5.94</td>
</tr>
<tr>
<td>8</td>
<td>G.R.</td>
<td>10, 35</td>
<td>M2</td>
<td>0.2</td>
<td>0.3</td>
<td>1.67</td>
<td>0.1</td>
<td>1.6</td>
</tr>
<tr>
<td>9</td>
<td>E.F.</td>
<td>8, 28</td>
<td>Distal M1</td>
<td>0.79</td>
<td>150.10</td>
<td>190.00</td>
<td>149.31</td>
<td>13.36</td>
</tr>
<tr>
<td>10</td>
<td>U.R.</td>
<td>19, 10</td>
<td>Proximal M1</td>
<td>3.92</td>
<td>153.34</td>
<td>39.12</td>
<td>149.42</td>
<td>53.39</td>
</tr>
<tr>
<td>11</td>
<td>H.R.</td>
<td>13, 24</td>
<td>Proximal M1</td>
<td>16.84</td>
<td>13.64</td>
<td>0.81</td>
<td>−3.2</td>
<td>29.58</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2</th>
<th>Patient</th>
<th>Baseline NIHSS, SSS</th>
<th>MRA Day 1</th>
<th>DWI Day-1 Lesion Size, mL</th>
<th>PWI Day-1 Lesion Size, mL</th>
<th>Mismatch Day-1 PWI/DWI</th>
<th>ΔPWI-DWI, mL</th>
<th>T2WI Day-5 Lesion Size, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>R.B.</td>
<td>15, 17</td>
<td>Proximal M1</td>
<td>20.68</td>
<td>246.73</td>
<td>11.93</td>
<td>226.05</td>
<td>184.76</td>
</tr>
<tr>
<td>13</td>
<td>H.F.</td>
<td>9, 35</td>
<td>Distal M1</td>
<td>88.4</td>
<td>244.06</td>
<td>2.76</td>
<td>155.66</td>
<td>190.62</td>
</tr>
<tr>
<td>14</td>
<td>K.H.</td>
<td>18, 10</td>
<td>Proximal M1</td>
<td>48.5</td>
<td>133.5</td>
<td>2.75</td>
<td>85.0</td>
<td>226.4</td>
</tr>
<tr>
<td>15</td>
<td>M.M.</td>
<td>18, 13</td>
<td>Distal M1</td>
<td>17.57</td>
<td>30.04</td>
<td>1.71</td>
<td>12.47</td>
<td>43.54</td>
</tr>
<tr>
<td>16</td>
<td>L.L.</td>
<td>15, 22</td>
<td>Distal M1</td>
<td>35.575</td>
<td>168.29</td>
<td>4.73</td>
<td>132.71</td>
<td>49.06</td>
</tr>
<tr>
<td>17</td>
<td>V.P.</td>
<td>22, 6</td>
<td>Distal ICA</td>
<td>11.15</td>
<td>333.47</td>
<td>29.91</td>
<td>322.32</td>
<td>200.05</td>
</tr>
<tr>
<td>18</td>
<td>L.F.</td>
<td>13, 19</td>
<td>Proximal M1</td>
<td>12.66</td>
<td>133.6</td>
<td>10.55</td>
<td>120.94</td>
<td>15.39</td>
</tr>
<tr>
<td>19</td>
<td>I.H.</td>
<td>11, 26</td>
<td>Distal ICA</td>
<td>25.24</td>
<td>132.2</td>
<td>5.24</td>
<td>106.96</td>
<td>144.23</td>
</tr>
<tr>
<td>20</td>
<td>H.L.</td>
<td>9, 27</td>
<td>Distal M1</td>
<td>16.86</td>
<td>60.43</td>
<td>3.58</td>
<td>43.57</td>
<td>29.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 3</th>
<th>Patient</th>
<th>Baseline NIHSS, SSS</th>
<th>MRA Day 1</th>
<th>DWI Day-1 Lesion Size, mL</th>
<th>PWI Day-1 Lesion Size, mL</th>
<th>Mismatch Day-1 PWI/DWI</th>
<th>ΔPWI-DWI, mL</th>
<th>T2WI Day-5 Lesion Size, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>C.F.</td>
<td>11, 26</td>
<td>No occlusion</td>
<td>2.47</td>
<td>0.12</td>
<td>0.05</td>
<td>−2.35</td>
<td>4.88</td>
</tr>
<tr>
<td>22</td>
<td>M.R.</td>
<td>15, 24</td>
<td>No occlusion</td>
<td>4.08</td>
<td>2.12</td>
<td>0.52</td>
<td>−1.96</td>
<td>15.35</td>
</tr>
<tr>
<td>23</td>
<td>E.R.</td>
<td>13, 24</td>
<td>No occlusion</td>
<td>8.17</td>
<td>13.7</td>
<td>1.68</td>
<td>5.33</td>
<td>16.54</td>
</tr>
<tr>
<td>24</td>
<td>E.R.</td>
<td>12, 23</td>
<td>P2</td>
<td>18.6</td>
<td>0.00</td>
<td>0.00</td>
<td>−18.6</td>
<td>54.3</td>
</tr>
</tbody>
</table>

Mean±SD and/or median

Group 1: 1–11

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.35</td>
<td>20.52</td>
<td>(median 10.5)</td>
</tr>
<tr>
<td>21.04</td>
<td>55.68</td>
<td>26.27</td>
</tr>
<tr>
<td>22.90</td>
<td>83.48</td>
<td>83.48</td>
</tr>
<tr>
<td>24.90</td>
<td>164.17</td>
<td>23.6</td>
</tr>
</tbody>
</table>

Group 2: 12–20

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.74</td>
<td>24.68</td>
<td>(median 22.9)</td>
</tr>
<tr>
<td>164.7</td>
<td>95.87</td>
<td>8.13</td>
</tr>
<tr>
<td>18.91</td>
<td>133.96</td>
<td>133.96</td>
</tr>
<tr>
<td>32.23</td>
<td>120.94</td>
<td>120.94</td>
</tr>
</tbody>
</table>

Group 3: 21–24

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.33</td>
<td>7.26</td>
<td>(median 6.55)</td>
</tr>
<tr>
<td>3.99</td>
<td>6.55</td>
<td>0.56</td>
</tr>
<tr>
<td>5.18</td>
<td>38.61</td>
<td>5.18</td>
</tr>
<tr>
<td>10.19</td>
<td>84.93</td>
<td>10.19</td>
</tr>
</tbody>
</table>

All patients 11.5, 24

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.33</td>
<td>21.68</td>
<td>(median 9.15)</td>
</tr>
<tr>
<td>109.1</td>
<td>91.95</td>
<td>15.18</td>
</tr>
<tr>
<td>15.18</td>
<td>38.61</td>
<td>87.77</td>
</tr>
<tr>
<td>38.61</td>
<td>84.93</td>
<td>59.76</td>
</tr>
</tbody>
</table>

M1 indicates MCA main stem; M2, MCA branch; P2, posterior cerebral artery branch; and NA, not applicable. Sites of vessel occlusion and lesion sizes at baseline and outcome of each patient are summarized. Perfusion-diffusion mismatch is given as the quotient and the difference of PWI and DWI. At the base of the table, mean±SD values and median values, as appropriate, are given for all patients and split for groups 1–3.

*Patients with symptomatic hemorrhage due to thrombolytic.
TABLE 3. Statistical Results: Mann-Whitney U Test, Wilcoxon Test, and Spearman Correlation

<table>
<thead>
<tr>
<th>Parameter Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with initial occlusion (N=20)</td>
<td>n=11</td>
</tr>
<tr>
<td>Median day-30 NIHSS, SSS, BI, MRS</td>
<td>0, 58, 100, 1</td>
</tr>
<tr>
<td>DWI 1 (mean±SD), mL</td>
<td>18.35±20.52</td>
</tr>
<tr>
<td>DWI 2 (mean±SD), mL</td>
<td>25.28±24.33</td>
</tr>
<tr>
<td>PWI 1 (mean±SD), mL</td>
<td>101.83±69.42</td>
</tr>
<tr>
<td>PWI 2 (mean±SD), mL</td>
<td>27.14±59.55</td>
</tr>
<tr>
<td>T2WI 5 (mean±SD), mL</td>
<td>23.60±15.84</td>
</tr>
</tbody>
</table>

Mann-Whitney U test
- NIHSS 30: P=0.002
- SSS 30: P=0.003
- BI 30: P=0.004
- MRS 30: P=0.002
- NIHSS 90: P=0.008
- SSS 90: P=0.005
- BI 90: P=0.004
- MRS 90: P=0.006

Wilcoxon
- NIHSS 1/NIHSS 30: P=0.003, P=0.594
- NIHSS 1/NIHSS 90: P=0.051, P=0.363
- SSS 1/SSS 30: P=0.003, P=0.173
- SSS 1/SSS 90: P=0.004, P=0.666
- DWI 1/DWI 2: P=0.203, P=0.028
- DWI 1/T2WI 5: P=0.155, P=0.008
- PWI 1/DWI 2: P=0.017, P=0.018
- PWI 1/T2WI 5: P=0.008, P=0.110

Spearman
- DWI 2/NIHSS, MRS: P<0.05 All P=NS
- T2WI 5/NIHSS, SSS: P<0.01 All P=NS
- DWI 1/DWI 2: P=0.037, r=0.697, P=0.115, r=0.643
- DWI 1/T2WI 5: P=0.168, r=0.436, P=0.220, r=0.433
- PWI 1/DWI 2: P=0.373, r=0.297, P=0.431, r=0.321
- PWI 1/T2WI 5: P=0.186, r=0.418, P=0.144, r=0.517
- DWI 2/T2WI 5: P=0.0038, r=0.964, P=0.115, r=0.643
- PWI 2/T2WI 5: P=0.045, r=0.708, P=0.565, r=−0.257

NS indicates not significant. The numbers after the scores/examinations indicate the day the respective score was performed. Values were considered to be significant at P=0.05 and highly significant at P=0.01. All significant P values are in boldface. A high correlation is assumed with r>0.7. To illustrate possible trends toward significance, we gave the exact P values even if there was no statistical significance. Mann-Whitney U test was performed for intragroup comparison, and Wilcoxon signed rank test was used for intragroup comparison. Spearman signed rank testing was performed for correlation analysis.

Presumably, the reason for any therapeutic effect of rtPA is recanalization of the occluded artery. The true recanalization rate of intravenous rtPA in ischemic stroke is not known presently but is estimated to be ≈50%. In addition, there may be a substantial number of early spontaneous recanalizations. Older nonrandomized studies with small numbers of patients report recanalization rates of 25% to 50% for intravenous thrombolysis33,34 but >90% when the agent is given intra-arterially.35 An intra-arterial thrombolysis study using prourokinase randomized 180 patients and showed a recanalization rate of 67%.25 However, the intravenous rtPA trials, including ECASS I and II, NINDS, and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS), did not assess whether clinical improvement depended on initial vessel occlusion with subsequent recanalization after thrombolytic therapy or on the rate of spontaneous vessel reopening. Our group of patients, in which a recanalization rate of 55% was seen after intravenous thrombolysis, is too small to give a reliable estimate of the true recanalization rate after intravenous thrombolysis. Although the level of significance decreased for all outcome scales from day 30 to day 90 because of 1 death after pulmonary embolism in group 1, intergroup and intragroup comparisons demonstrate a significant benefit of recanalization. Patients without recanalization had a significant increase in infarction size from day 1 to day 5 (P=0.008), and the difference between lesion volumes in groups 1 and 2 was highly significant on day 2 (P=0.015) and even more on day 5 (P=0.006). There also were significant correlations for DWI on day 2 (P=0.0038 and r=0.964) and PWI on day 2 (P=0.045 and r=0.708) with T2WI on day 5 in group 1 but not in group 2, indicating further infarct dynamics and progressive infarct growth even after 24 hours in patients with persisting vessel occlusion.

Interestingly, the presence of tissue at risk and thus a potential for infarct growth was bound to a vessel occlusion in all our patients. This finding is consistent with the observation of other authors involving a smaller group of patients.36 A larger patient cohort, however, is needed to render sufficient evidence for this observation. On rare occasions, a good collateral flow may result in a good clinical outcome, despite persisting vessel occlusion (Figure 3). Our findings strengthen the hypothesis that early lysis of an obliterating thrombus by rtPA with subsequent recanalization of a major cerebral artery is the basis for an improved clinical outcome in many patients. This event can be monitored effectively by stroke MRI. Furthermore, baseline stroke MRI renders relevant information that may allow the identification of ideal candidates for thrombolytic therapy and also the identification of those patients who are not. On the basis of stroke MRI criteria, we suggest that patients who are most suitable for thrombolytic therapy are likely to be those who present with a proximal vessel occlusion in the anterior cerebral circulation and tissue at risk of infarction as defined by DWI and PWI. Additionally, our data suggest that recanalization should be achieved by aggressive means in these patients, because a persisting vessel occlusion is associated with large infarcts and an unfavorable clinical outcome.

The recently published study by Marks et al15 reports 12 patients with early stroke MRI within 3 hours to 5 hours. Six of their 12 patients received rtPA at 1.95 hours, on average, after stroke onset (range 51 minutes to 2.75 hours). The mean time interval between rtPA infusion and stroke MRI was 2.66 hours (range 1.75 to 4.17 hours), with all MRI examinations being performed after thrombolytic therapy was initiated.
Five of the 6 rtPA patients had smaller PWI than DWI volumes, suggesting early recanalization. An important next step is an rtPA case-control study in which patients are matched for demographic factors, initial stroke severity, time windows, and stroke MRI criteria, such as vessel occlusion, DWI lesion size, and diffusion-perfusion mismatch. However, our cohort of 51 acute ischemic stroke patients imaged within 6 hours after symptom onset with stroke MRI presently lacks a sufficient number of non-rtPA patients for matching.

The present study also has some limitations: The fact that stroke MRI was performed in 8 patients after initiation of thrombolysis is an important point that has to be addressed. PWI findings can be significantly altered if performed 1 to 2 hours after thrombolytic therapy as a consequence of partial or complete recanalization. Although 4 of these 8 patients were imaged within 30 minutes and another 3 were imaged within 1.5 hours after rtPA bolus administration, we cannot exclude an effect of rtPA at that point. One patient did not have an occlusion but a lacunar infarction, most probably of microangiopathic origin. Seven of 8 patients had a vessel occlusion according to the baseline MRA (1 distal ICA, 3 proximal M1, 2 distal M1, and 1 M2 occlusions), so that at least complete recanalization had not occurred yet. All but 1
of these 7 patients had a PWI-DWI mismatch; the 1 patient experienced recanalization between the assessment of MRA and PWI. Marks et al15 deduced recanalization after thrombolytic therapy from clinical improvement and a lack of PWI-DWI mismatch in their patients. This speculation would be unnecessary if MRA were performed at baseline in their study. Another point of criticism in the present study is the rather late assessment of recanalization by day-2 MRA. Reperfusion within the first few hours after stroke may be much more important than late reperfusion. One may assume, however, that the patients in whom vessels did not recanalize within 8 to 10 hours after stroke onset were those with a persistent occlusion and a poor outcome as opposed to those who experienced early recanalization and thus saved a more or less large area of tissue at risk. Late reperfusion at a time point when there is no longer any tissue at risk is not of use for the patient and may even cause harm via reperfusion injury and symptomatic parenchymal hemorrhage. On the other hand, a recent subgroup analysis of ECASS II data showed that late reperfusion may be associated with a better outcome than no reperfusion,32 and even after 6 to 8 hours, a salvageable tissue at risk as shown by DWI and PWI may still be present (Schellinger et al, unpublished data, 2000). Also, there was a statistical trend toward a significant difference in baseline NIHSS and SSS scores, with those patients in the nonrecanalization group (group 2) having more severe strokes. Baseline DWI and PWI lesion volumes were slightly but not significantly larger. This may, in part, account for the better outcomes in group 1 at days 30 and 90 and thus lead to a bias in favor of recanalization. We believe that this trend is at least partially due to the slightly larger number of left hemispheric infarctions and more proximal occlusions in group 2. This reflects the experience that recanalization rates are lower in more proximal MCA or carotid T occlusions33 and that moderately severe left as opposed to right hemispheric infarctions show a median difference in stroke severity of 5 NIHSS points.38 Thus, the natural course of patients with proximal and left-sided vessel occlusions is worse than that of others. On the other hand, they may constitute a subgroup of patients that profit most from recanalization. Stroke MRI may be useful to identify those patients not suitable for thrombolysis because of extensive infarctions and those with large infarctions and a tissue at risk still present, which might be saved by more aggressive therapeutic means.50 –42

In addition to a higher diagnostic and prognostic potential, stroke MRI is feasible and appears to be safe and reliable in patients with hyperacute hemispheric ischemia. When stroke MRI is available, time-consuming diagnostic efforts with different modalities are not needed, because the vascular status is reliably assessed, and the presence or absence of ICH can be determined. The findings on stroke MRI are consistent with the general understanding of stroke pathophysiology and predict morphological as well as functional outcome. Early recanalization has the potential to save tissue at risk if present and thus may lead to smaller infarctions and a better neurological outcome. We believe that the utility of stroke MRI is implicit, because it can define the patient target group for thrombolytic therapy and monitor thrombolysis in acute ischemic stroke and is suitable for follow-up evaluation of stroke patients.

Acknowledgments

We want to express our gratitude to all members of the Heidelberg Neurocritical Care, Stroke, and Intermediate Care Unit’s medical and nursing staff as well as to all members of the Department of Neuroradiology medical and technical staff. Without the help of all our colleagues and team members, this study could not have been accomplished. Furthermore, we thank Dr Conradt, Institute of Biomedical Statistics, University of Heidelberg, Heidelberg, Germany, for his advice and the Department of Medical Illustrations for the professional photographic and art work.

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Monitoring Intravenous Recombinant Tissue Plasminogen Activator Thrombolysis for Acute Ischemic Stroke With Diffusion and Perfusion MRI
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Stroke. 2000;31:1318-1328
doi: 10.1161/01.STR.31.6.1318

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/31/6/1318

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