Baseline Magnetic Resonance Imaging Parameters and Stroke Outcome in Patients Treated by Intravenous Tissue Plasminogen Activator

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Background and Purpose—We designed a prospective sequential pretreatment and posttreatment MRI study to assess the relation between neuroimaging parameters and clinical outcome in patients treated with intravenous recombinant tissue-type plasminogen activator (rtPA).

Methods—Patients with symptoms of acute hemispheric ischemic stroke were recruited. The National Institutes of Health Stroke Scale (NIHSS) score was assessed at baseline and at days 1, 7, and 60, and the modified Rankin scale (mRS) at day 60, by which outcome was classified in terms of independence (mRS score 0, 1, or 2) or severe disability or death (mRS score 3 through 6), was assigned. Multimodal stroke MRI was performed at presentation and repeated at day 1. MRI procedures included magnetic resonance angiography, T2* gradient-echo sequence, echoplanar imaging, and isotropic diffusion- (DWI) and perfusion-weighted (PWI) imaging. Patients were treated with intravenous rtPA after MRI completion.

Results—Twenty-nine patients (16 men and 13 women; mean ± SD age, 65 ± 14 years) underwent MRI; the mean time from symptom onset to treatment was 255 ± 62 minutes. Twenty-six patients had a vessel occlusion, and 15 patients experienced a partial (Thrombolysis in Myocardial Infarction [TIMI]-2) or total (TIMI-3) recanalization at day 1, whereas 11 patients had a persistent occlusion. Mean NIHSS scores at day 60 were 5.7 ± 5.4 if recanalization had occurred and 14 ± 2 in cases of persistent occlusion. According to the mRS, 13 patients were independent (mRS 0 through 2), whereas severe disability or death (mRS 3 through 6) was observed in 15 patients. A better outcome was observed when recanalization was achieved (r = −0.68, P = 0.0002). PWI volume and time to peak (TTP) within the DWI lesion assessed before therapy were correlated with day-60 NIHSS score (PWI volume: r = 0.51, P = 0.006, TTP: r = 0.35, P = 0.07). The day-0 DWI abnormality volume was well correlated with day-60 NIHSS score (r = 0.58, P = 0.001). Multiple regression linear analysis showed that 2 factors mainly influenced clinical outcome: (1) recanalization, with a high correlation with NIHSS score at day 60 (P = 0.0001) and (2) day-0 DWI lesion volume, which is closely associated with day-60 NIHSS score (P = 0.03).

Conclusions—Baseline DWI volume and recanalization are the main factors influencing clinical outcome after rtPA for ischemic stroke. (Stroke. 2003;34:458-463.)

Key Words: magnetic resonance imaging, diffusion-weighted ● magnetic resonance imaging, perfusion-weighted ● stroke outcome ● tissue plasminogen activator

Thrombolysis is of proven benefit for the treatment of acute ischemic stroke.1,2 Objective neuroimaging methods could be helpful to monitor individual patient response to therapy.3–8 Few prospective studies assessed the relation between initial MRI parameters and stroke outcome after thrombolysis.5–7 In this context, we designed a prospective pretreatment and posttreatment MRI study.

Patients and Methods

Inclusion and Exclusion Criteria

Patients with symptoms of acute hemispheric ischemic stroke were prospectively recruited. Inclusion criteria included the following: (1) symptom duration <7 hours, (2) absence of hemorrhage on head CT scan and gradient echo MRI, (3) acute cerebral ischemia involving the carotid territory, (4) National Institutes of Health Stroke Scale (NIHSS) score >4 present at the time of entry in the study, and (5) no contraindications to MRI or thrombolysis.

Exclusion criteria were as follows: (1) previous stroke or (2) preexisting neurological or psychiatric illness. Neurological impairment was assessed by using the NIHSS. NIHSS score was assessed at baseline and at days 1, 7, and 60, and the modified Rankin scale (mRS) at day 60, by which outcome was classified in terms of independence (mRS score 0, 1, or 2) or severe disability or death (mRS score 3 through 6), was assigned. All patients had a stroke risk factor assessment, baseline electrocardiogram, and routine blood analysis; those surviving >1 week had transesophageal echocardiogram.
ography and neck Doppler ultrasonography. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification was used for classifying stroke mechanisms.

CT and MRI Methods

CT Scan
CT scan was performed with a fourth-generation CT (Elscent CT Twin) before therapy. The mean time from symptom onset to CT was 2.6 ± 1 hours; follow-up CT scans were repeated at days 1 and 7.

Stroke MRI
Stroke MRI was performed at presentation and repeated on day 1. All MRIs were obtained with a 1.5-T whole-body MR imager (Siemens) equipped with enhanced gradient hardware for echoplanar imaging. The following sequences were performed: (1) time-of-flight MR angiography (repetition time [TR] 35 ms; echo time [TE] 6.4 ms; flip angle 20°; matrix 160 × 512; field of view 230 mm; excitation 1; acquisition time 6 minutes, 14 seconds. Three axial slabs (thickness 31.9 mm; partition 24; distance factor = 0.38) were placed over the entire circle of Willis. MIP reconstructions were used for postprocessing. (2) T2* gradient-echo sequence: TR 800 ms, TE 26 ms; flip angle 20°; thickness 5 mm; 20 axial slices; distance factor = 0.20; asymmetric matrix 256; number of acquisitions 2; acquisition time 6 minutes; field of view 250 mm. (3) Echoplanar imaging ischaemic diffusion: TR 4,700 ms; TE 118 ms; 19 axial slices; thickness 5 mm and no interslice gap; matrix 96 × 128; field of view 230 mm; excitation 1; acquisition time 23 seconds. Two levels of diffusion sensitization (b values = 0 and 1,000 s/mm²) were used in each of the 3 principal gradient directions (x, y, and z) were used to calculate the apparent diffusion coefficient (ADC). (4) Perfusion MRI, performed with gradient-echo echoplanar imaging, with the bolus-passage-of-contrast method (0.1 mmol/kg dose of gadodiamide dimeglumine) by power injector at 5 ml/second through a 0.9-mm access diameter into an antecubital vein, with TR 1.5 seconds; TE 29 ms; 7 slices; 5-mm slice thickness; field of view 230 mm; matrix 128 × 128 pixels. The slice position was obtained from the diffusion-weighted imaging (DWI) scan and was placed in the center of the diffusion lesion area. Perfusion maps were calculated from the concentration-time curve. TTP refers here to the time between the first T2*-weighted measurement and the bolus peak. Posttreatment images were coregistered to the pretreatment study. The study design was approved by the ethics committee of our institution (CCPRRB Lyon B).

Postprocessing Analysis
The measurement of DWI and perfusion-weighted imaging (PWI) abnormalities and ADC were performed on a dedicated MR workstation. The whole lesion volume was determined by multiplying the area of diffusion hyperintensity by the interslice gap. The DWI and PWI studies were run in corresponding slice positions. A PDI-DWI ratio ≥ 2 was defined as a significant mismatch.

Reproducibility Measurement
For the DWI and PWI volumes, 2 experienced observers (M.H., Y.B.) blinded to the severity of clinical deficit measured the lesions on 2 occasions, and the mean value was used; the interobserver and intraobserver variation in measurements was assessed by comparing the differences in measurements for 25 cases. The intraobserver and interobserver reliability in measured DWI and PWI lesion volumes was >0.9, with a mean deviation of <5% for intraobserver reproducibility.

Statistical Analysis
Time intervals and descriptive statistics of the NIHSS score and MRI characteristics are given as mean values, with the SD or median absolute deviation and range. For parameters that clearly deviated from a normal distribution, characteristics are given as medians with the 95% confidence interval (CI) of the median or range. We applied the Mann-Whitney U test for differences in medians or the Wilcoxon signed-rank test for the course of MRI differences between day 0 and day 1. Spearman rank correlation coefficients were calculated to determine the correlation between MRI parameters and NIHSS scores. Univariate and multiple linear-regression analyses were used to identify the MRI parameters most closely associated with day-60 NIHSS score. All univariate factors, such as baseline NIHSS score, baseline MRI parameters (DWI volume, PWI volume, TTP, and ADC value) and day-1 MR angiography (recanalization/occlusion) were included in the final multivariate model. A probability value < 0.05 was considered statistically significant. Statistical analysis was performed with a statistical software package (SPSS for Windows, 11).

Results
Clinical and MR Angiography Data
Of all stroke patients in the time interval studied (570 between March 2001 and March 2002), stroke MRI was performed in 70 consecutive patients for suspected acute ischemic stroke. Twenty-nine patients fulfilled the inclusion criteria. Sixteen men and 13 women underwent MRI before therapy. Their mean ± SD age was 65 ± 14 years, with an age range of 40 to 93 years. Risk factors included hypertension (n = 16), hyperlipidemia (n = 9), tobacco use (n = 7), diabetes mellitus (n = 5), previous ischemic stroke (n = 5), and atrial fibrillation (n = 12). After MRI completion and within the 7-hour time window, 29 patients received intravenous rtPA (0.8 mg/kg body weight) according to a protocol published elsewhere.11 MR angiography revealed an arterial occlusion in 26 patients: distal internal carotid artery occlusion (n = 7), proximal M1 occlusion (n = 15), proximal M2 occlusion (n = 3), or distal M2 occlusion (n = 1). The three patients without a demonstrated baseline occlusion had an infarct within the anterior choroidal artery territory. Fifteen patients experienced a total (Thrombolysis in Myocardial Infarction [TIMI]-3, n = 8) or partial (TIMI-2, n = 7) recanalization, whereas 11 patients had persistent occlusion. The mean time from symptom onset to treatment was 4.25 ± 1 hours. Patients with persistent occlusion had a higher mean baseline NIHSS score (18.5 ± 5) compared with those who were recanализed (13 ± 5.3, P = 0.026). Mean NIHSS scores at day 60 was 5.8 ± 6.4 if recanalization had occurred and 14 ± 2 in cases of persistent occlusion. According to the mRS, 13 patients were independent (mRS 0 through 2), whereas severe disability or death (mRS 3 through 6) was observed in 15 patients. A better outcome was observed when recanalization was achieved (r = −0.68, P = 0.0002).

Death occurred in 2 patients during the first week, and no recurrent stroke was observed during follow-up. The TOAST subtype was large-vessel disease in 12 patients, cardioembolic in 12 patients, small-vessel disease in 2 patients, and cryptogenic in 3 patients.

MRI Data at Day 0
The mean time from symptom onset to stroke MRI was 3.55 ±1.4 hours. Twenty-nine patients underwent day-0 MRI. The mean baseline whole DWI volume was 56 ± 63 cm³ (range, 4 to 213). The severity of NIHSS score was well correlated with DWI lesion volume. Despite a lower baseline NIHSS score in right hemisphere lesions (n = 13; NIHSS score, 11 ± 3 vs 16 ± 2 in the left hemisphere, n = 16; P = 0.0001), we found a significant (P = 0.02) difference in lesion size according to the right (92 ± 48 cm³) versus the left
Whole DWI lesion volume, cm$^3$ 0.62 0.0001  
DWI lesion volume matched to PWI slices, cm$^3$ 0.61 0.0001  
PWI abnormality volume, cm$^3$ 0.49 0.007  
PWI/DWI ratio at day 0 −0.33 0.081  
Mean ADC with DWI area, $10^{-6}$ mm$^2$/s −0.09 0.646  
Mean TTP within DWI area, s 0.37 0.048

(55±35 cm$^3$ hemisphere. The mean ADC value within the lesion was decreased in all patients 783±139 (range, 568 to 1092×$10^{-6}$ mm$^2$/s) compared with the reference ADC value (mean, 1211±120; range, 997 to 1441×$10^{-6}$ mm$^2$/s). The mean PWI volume was 129±54 cm$^3$ (range, 4 to 239). Seven patients did not have a PWI-DWI mismatch at day 0. The mean PWI-DWI mismatch volume was 86±52 (range, 0 to 165). Baseline MRI parameters according to day-0 NIHSS score are listed in Table 1.

**MRI Data at Day 1**

The follow-up MRI scan was performed at a median of 11.5 hours with a range between 8.6 and 16.3 hours in 29 patients. The mean DWI volume was 100±99 cm$^3$ (range, 4 to 379). The mean ADC value within the lesion was 753±198 (range, 471 to 1144×$10^{-6}$ mm$^2$/s) compared with the reference ADC value (mean, 1249±118, range, 927 to 1384×$10^{-6}$ mm$^2$/s). The mean PWI volume was 85±82 cm$^3$ (range, 0 to 295). The mean PWI-DWI mismatch volume was 33±42 cm$^3$ (range, 0 to 146).

The changes in DWI and PWI volumes and PWI-DWI ratios were statistically significant between day 0 and day 1 according to recanalization (Table 2). Figure 1 illustrates the course of MRI abnormalities between day 0 and day 1 in a left middle cerebral artery stroke associated with a significant baseline mismatch. (Figure 2 shows the course of MRI abnormalities in a left middle cerebral artery stroke without a significant baseline mismatch.

**Correlations**

**PWI Parameters**

Acute PWI volume and TTP within the DWI lesion were well correlated with day-0, -1, and -60 NIHSS scores. A better outcome was associated with a shorter TTP. Baseline TTP value within the DWI lesion were significantly delayed in patients with persistent occlusion (43±5 seconds) compared with those who were recanalized (33±2 seconds; $P=0.005$).

**DWI Volume and ADC Value**

The day-0 DWI abnormality volume was correlated with outcome NIHSS scores. Mean baseline ADC value within the lesion was not correlated with outcome NIHSS score.

**Mismatch Volume**

The day-0 mismatch volume was not correlated with baseline NIHSS score and outcome NIHSS score.

**PWI-DWI Ratio**

The day-0 PWI-DWI ratio was also not correlated with baseline and outcome NIHSS scores.

**Recanalization**

Recanalization was strongly correlated with clinical improvement, as demonstrated by all clinical outcome measures. We did not find any significant relation between the effect of recanalization on clinical outcome according to the day-0 PWI-DWI ratio.

**Treatment Delay**

Treatment delay was not correlated with day-60 NIHSS scores. Correlations between baseline MRI parameters and day-60 outcome NIHSS scores are depicted in Tables 3.

**Multiple Linear Regression Analysis Results**

Multiple regression linear analysis showed that 2 factors may influence clinical outcome (Table 4): (1) recanalization was highly correlated with NIHSS score at day 60 ($P=0.0001$) and (2) day-0 DWI lesion volume was closely associated with day-60 NIHSS score ($P=0.03$), $R^2=0.57$. ($R^2$ is the percentage of variance explained by the model.)

**TABLE 2. Changes in MRI Parameters Between Day 0 and Day 1 Based on Recanalization**

<table>
<thead>
<tr>
<th>Differences (Day 1) − (Day 0)</th>
<th>No (n=11)</th>
<th>95% CI</th>
<th>Yes (n=15)</th>
<th>95% CI</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volumes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI lesion volume, cm$^3$</td>
<td>48</td>
<td>11; 169</td>
<td>13</td>
<td>2; 31</td>
<td>0.014</td>
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<tr>
<td>PWI lesion volume, cm$^3$</td>
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<td>−15; 26</td>
<td>−51</td>
<td>−129; −35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PWI/DWI ratio</td>
<td>−1.28</td>
<td>−9.62; −0.085</td>
<td>−5.14</td>
<td>−12.65; −1.92</td>
<td>0.05</td>
</tr>
<tr>
<td>TTP values</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTP within DWI lesion(s)</td>
<td>−4.2</td>
<td>−9.5; 3.6</td>
<td>−6.4</td>
<td>−14.2; 19.3</td>
<td>0.34</td>
</tr>
<tr>
<td>TTP within PWI lesion(s)</td>
<td>−4.5</td>
<td>−7.8; 2.1</td>
<td>−5.2†</td>
<td>−31.5; −0.5</td>
<td>0.39</td>
</tr>
<tr>
<td>ADC values</td>
<td>−133</td>
<td>−215; 131</td>
<td>53.5</td>
<td>−142; 193</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test.
Discussion

The assessment of tissue viability requires 4 major factors: time, hemodynamics, tissue, and intervention. In recent years, combined DWI-PWI has become an important strategy in the investigation of acute stroke. Natural history studies have demonstrated that the pattern of a PWI lesion larger than the DWI lesion predicts subsequent expansion of the diffusion lesion. Prospective pre-post treatment MRI studies are scarce; therefore, additional data may be of interest. Patients with acute PWI-DWI mismatch who have had a documented arterial occlusion may have a favorable clinical response to thrombolytic therapy if successful recanalization.

Figure 1. PWI-DWI and MR angiography abnormalities between day 0 and day 1 in a 43-year-old woman who experienced a left middle cerebral artery (MCA) stroke; at baseline, clinical impairment was limited to a slight dysarthria, a right-hand weakness, and a right facial central palsy. Day-0 MRI was performed 150 minutes after stroke. Day 0: global hypoperfusion within the whole MCA territory (A) related to M1 occlusion (B), and a mild DWI abnormality was observed within the anterior insular cortex (C); (D) T2* MRI ruled out any acute hemorrhagic transformation. Intravenous tPA was given after MRI completion 190 minutes after stroke onset. Day-1 NIHSS score was 16. Day-1 perfusion map showed a large hypoperfused area within the MCA territory (E) associated with an increase of the DWI lesion (G) related to a persistent MCA occlusion at day 1. Day-60 NIHSS score was: 14.

Figure 2. PWI-DWI and MR angiographic abnormalities between day 0 and day 1 in a 62-year-old man who experienced a left MCA stroke; a severe right hemiplegia and global aphasia were observed 3 hours after the onset of stroke. Day-0 MRI was performed 200 minutes after stroke onset. Day-0 TTP map showed hypoperfusion within the MCA territory (A) and a large DWI abnormality (B), with an area of decreased ADC (C) without significant mismatch. MR angiography showed a proximal M2 occlusion (D). Intravenous tPA was given after MRI completion 230 minutes after stroke onset. Day-1 NIHSS score was 10; the right motor deficit cleared while severe aphasia persisted. Day-1 perfusion map (E) showed increased perfusion within the MCA territory and a moderate growth of a DWI lesion (F). MCA occlusion cleared on day-1 MR angiography (G).
occur.

There is typically minimal growth of the early DWI lesion and a clinical improvement. Conversely, patients who have had early DWI lesions that are similar or larger in size than the early PWI deficit may have little additional tissue at risk and therefore, a poor response to thrombolytic therapy. However, the exact pathophysiological basis of the mismatch is not clearly documented. Whether DWI lesion evolution always represents recruitment of the penumbra or other processes is still to be determined. However, the simple model of the DWI-PWI mismatch as a predictor of tissue outcome is still prevailing.”

The relations between acute MRI parameters and outcome NIHSS score have become a source of controversy. In contrast to a previous pre-post treatment study, a significant correlation between acute DWI lesion volume, PWI lesion volume, and baseline clinical severity was noted. These baseline MRI parameters were also well correlated with outcome NIHSS scores. Although the correlation of DWI-PWI with outcome scores depends on the time point of imaging, our time window for control MRI showed a favorable regression of mismatch in patients who were recanalized.

TTP is usually well correlated with stroke severity. A higher clinical severity on admission and a significant delay in baseline TTP were observed in patients who had persistent occlusion at day 1. These patients may have had poor collateral circulation, accounting for a low-flow state. The significant delay in baseline TTP within the DWI lesion in patients who had a persistent occlusion may be consistent with this low-flow state. This condition may favor more organized thrombi and subsequently lower sensitivity to treatment. The assessment of perfusion based exclusively on TTP might hamper our interpretation.

Although TTP and mean transit time are only indirect measures of tissue perfusion, the lesion borders are often more distinct than on regional cerebral blood flow and regional cerebral blood volume maps. Maps of TTP delay were shown to be correlated with stroke volume and outcome scores in clinical studies; therefore, they are commonly used for the assessment of a perfusion defect. Moreover, TTP maps are easy to generate, and the time required for postprocessing is minimal. There are also notable limitations to the TTP maps: TTP is only an indirect measure of tissue perfusion, and TTP delays may occur in patients with high-grade stenosis without acute stroke. However, in our study, none of the patients had a significant internal carotid artery stenosis.

In a recent study, PWI-DWI mismatch patients treated with rtPA had greater vessel recanalization. In our study, the degree of mismatch had no effect on the rate of early recanalization. Use of this mismatch ratio is not sufficient to adequately identify the absolute volume of tissue at risk. This may retrospectively be defined by the difference between baseline PWI volume and final infarct size as assessed by T2-weighted imaging. The time interval between CT scan and MRI may raise ethical concerns and should be decreased. Although stroke MRI is actually considered the best neuroimaging tool, the use of TPA has been validated on a CT scan basis; therefore, the combination of CT and MRI may still be justified.

MRI can delineate large volumes of tissue at risk of infarction beyond the 3-hour time window, and this information may facilitate a benefit-risk weighting for intravenous tPA therapy. Most of our patients were treated within this time window, with a better outcome if recanalization was achieved. However, like others, we cannot draw any clear conclusion regarding the effectiveness of tPA, because a randomized control group was not defined within a similar time window. According to our sample size, our results have to be interpreted carefully; therefore, a multicenter trial with large numbers of patients to assess the predictive value of these parameters is needed. Assessment of recanalization within a mean time of 11.5 hours may also represent a limitation, because acute recanalization is usually expected within 6 hours after tPA and is more frequently correlated with a better outcome within this time window.

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