Speed of tPA-Induced Clot Lysis Predicts DWI Lesion Evolution in Acute Stroke

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Background and Purpose—We sought to evaluate the impact of the speed of recanalization on the evolution of diffusion-weighted imaging (DWI) lesions and outcome in stroke patients treated with tissue-type plasminogen activator (tPA).

Methods—We evaluated 113 consecutive stroke patients with a middle cerebral artery occlusion who were treated with intravenous tPA. All patients underwent multiparametric magnetic resonance imaging studies, including DWI and perfusion-weighted imaging before and 36 to 48 hours after administration of a tPA bolus. Patients were continuously monitored with transcranial Doppler during the first 2 hours after tPA administration. The pattern of recanalization on transcranial Doppler was defined as sudden (<1 minute), stepwise (1 to 29 minutes), or slow (>30 minutes).

Results—During transcranial Doppler monitoring, 13 (12.3%) patients recanalized suddenly, 32 (30.2%) recanalized in a stepwise manner, and 18 (17%) recanlized slowly. Baseline clinical and imaging parameters were similar among recanalization subgroups. At 36 to 48 hours, DWI lesion growth was significantly (P=0.001) smaller after sudden (3.23±0.5 cm³) compared with stepwise (24.9±37 cm³), slow (46.3±38 cm³), and no (51.7±34 cm³) recanalization. The slow pattern was associated with greater DWI growth (P=0.003), lesser degree of clinical improvement (P=0.021), worse 3-month outcome (P=0.032), and higher mortality (P=0.003).

Conclusions—The speed of tPA-induced clot lysis predicts DWI lesion evolution and clinical outcome. Unlike sudden and stepwise patterns, slow recanalization is associated with greater DWI lesion growth and poorer short- and long-term outcomes. (Stroke. 2007;38:955-960.)

Key Words: reperfusion ■ stroke ■ transcranial Doppler ■ treatment ■ ultrasound

The natural history of diffusion-weighted imaging (DWI) abnormalities after acute occlusion of a major cerebral artery is to grow progressively over time into the area of perfusion deficit.1,2 The extent of DWI lesion enlargement has been correlated with final infarct size and long-term clinical outcome.3–6 Therefore, DWI lesion growth has been proposed as a surrogate outcome measure in neuroprotective and thrombolytic trials.7,8 This idea is supported by the demonstration that DWI abnormality growth may be attenuated or even reversed, partially or completely, after early therapeutically driven recanalization.9,10

Systemic thrombolysis has demonstrated to be effective in improving long-term outcome in stroke patients when given within 3 hours of stroke onset.11 The beneficial effect of thrombolytic therapy in stroke is based on the ability of tissue-type plasminogen activator (tPA) to induce early recanalization. Recanalization is a dynamic process that usually begins shortly after tPA administration and that can be continuously monitored by transcranial Doppler ultrasonography (TCD). TCD monitoring provides a noninvasive tool for real-time measurement of the beginning, speed, timing, and degree of arterial recanalization. In unselected stroke patients, the speed of clot lysis during tPA infusion has been demonstrated to predict early clinical course and long-term outcome.12,13

The combination of TCD and multimodal magnetic resonance imaging (MRI) may provide valuable information of the effect of the pattern of clot dissolution during tPA infusion on ischemic tissue evolution and outcome. Therefore, we sought to investigate the impact of the speed of clot lysis during continuous TCD monitoring on the evolution of DWI lesions and clinical outcome in patients with a middle cerebral artery (MCA) occlusion treated with intravenous tPA.

Subjects and Methods

Subjects
Our target group consisted of patients with acute ischemic stroke admitted within the first 6 hours after symptom onset. Stroke onset was defined as the last time when patient was known to be without any neurological deficit. A total of 936 consecutive patients with nonlacunar stroke involving the vascular territory of the MCA were...
evaluated between February 2001 and October 2005. Eight-hundred sixty-seven (92.6%) of them underwent urgent carotid ultrasound and TCD examinations. Of these, 263 (28%) patients who had a documented MCA occlusion on TCD and who fulfilled the criteria for intravenous tPA treatment (0.9 mg/kg) were treated within 6 hours of stroke onset. One-hundred thirty-eight (14.7%) of these patients underwent a multiparametric MRI protocol including DWI, perfusion-weighted imaging (PWI), and magnetic resonance angiography (MRA) before tPA administration, which revealed a PWI-DWI mismatch >20%. Twenty-five patients were excluded because of claustrophobia or uncooperation (n=9) or lack of an adequate temporal bone window for TCD examination (n=16). Finally, 113 patients who were continuously monitored with TCD for 2 hours after tPA bolus administration were included in this study. Fifty-two patients who had participated in a previous study on the temporal profile of recanalization on TCD after tPA treatment were also included.14 Informed consent was obtained from all patients or their next of kin. The local ethics committee approved the study protocol.

TCD Assessment
A standard TCD examination was performed in the emergency department on admission before tPA administration with 1-channel, 2-MHz equipment (TCD 100 ML, Spencer Technologies, and DWL Multidop ×4). TCD assessment was performed by 2 certified sonographers with extensive experience in monitoring recanalization in acute stroke who were blinded to the clinical, radiological, and outcome data. A standard set of diagnostic criteria was applied to diagnose arterial occlusion. Proximal MCA occlusion was defined as the absence of flow or the presence of a minimal flow signal throughout the MCA at an insonation depth between 45 and 65 mm, accompanied by flow diversion in the ipsilateral anterior and posterior communicating arteries, according to the Thrombolysis in Brain Ischemia grading system.15 After the site of MCA occlusion was identified, continuous monitoring of the residual flow signals was performed with a Marc 500 headframe (Spencer Technologies) or DWL metal headframe to maintain tight transducer fixation and a constant angle of insonation. Continuous TCD monitoring of recanalization was conducted during 2 hours after tPA administration. The speed of clot lysis during continuous TCD monitoring was categorized into sudden (abrupt flow improvement lasting seconds), step-wise (gradual flow improvement during 1 to 29 minutes), or slow (flow improvement over 30 minutes)12 according to the time to flow improvement over 30 minutes)12 according to the time to flow. Changes on TCD in each patient were determined by 1 rater using direct visual control of the monitoring display. Recanalization on TCD was diagnosed as partial when blunted or dampened signals appeared in a previously demonstrated absent or minimal flow. Complete recanalization on TCD was diagnosed when the end-diastolic flow velocity improved to normal or elevated values (normal or stenotic signals).15 No change in the abnormal waveforms indicated that no recanalization had occurred. Reocclusion was defined as a worsening in waveforms on TCD performed at the time of neurological deterioration after documented recanalization.

MRI Protocol
MRI was performed with a 1.5-T whole-body imager system with a 24-mT/m gradient strength, 300-ms rise time, and an echoplanar-capable receiver equipped with a gradient override. The images obtained included the following: (1) axial DW echoplanar spin-echo sequence (4000 repetition time [TR]/100 echo time [TE]/2 acquisitions); (2) axial PW echoplanar-gradient-echo sequence (2000 TR/60 TE/40 acquisitions); and (3) MRA (30 TR/5.4 TE/15° flip angle). DW images were obtained with a single-shot spin-echo echoplanar pulse sequence with diffusion gradient b values of 0, 500, and 1000 s/mm² along all 3 orthogonal axes over 15 axial sections, 5-mm-thick sections, interslice gap of 1.5 mm, 240-mm field of view, and 96×128 matrix. The acquisition time for the DW images was 56 seconds. To minimize the effects of diffusion anisotropy, the DW data were automatically processed to yield standard isotropic DW images. PW images were acquired by using the dynamic first pass of a 0.1-mmol/kg bolus of gadolinium-based contrast material (Magnevist, Schering AG). The bolus of 15 mL of contrast material was injected in the antecubital vein by using an MR-compatible power injector (Spectris, Medrad Inc) and an injection speed of 5 mL/s for 3 seconds, starting 5 seconds after initiating the sequence, followed by a flush with 15 mL saline. The PW sequence generated a time-to-peak (TTP) map for each section position that was immediately available for interpretation at the console with all of the other images. Perfusion images were obtained with the use of 5-mm-thick sections, interslice gap of 1.5 mm, 240-mm field of view, and 128×128 matrices.

For MRA, we used a 3-dimensional time-of-flight sequence, with 1.5-mm-thick sections, 200-mm field of view, and 200×512 matrices, with a total acquisition time of 156 seconds. Tissue abnormality was considered in areas of high signal intensity on both DW images (reflecting decreased water motion) and TTP maps (reflecting delayed bolus arrival).

Volume measurements of the extent of tissue abnormality on DW images and on TTP maps were performed by a manual tracing technique by 1 neuroradiologist (A.R.) who was blinded to TCD, clinical, and outcome data. The perimeter of the area of abnormal high signal intensity was traced on each DW image and TTP map. Both slide distance and thickness were considered in the measurement of lesion volumes. All measured areas were multiplied by the slice distance to obtain the total lesion volumes for both DW images and TTP maps. A follow-up MRI was performed in all patients at 36 to 48 hours. This examination included DW images, MRA, and an additional transverse T2-weighted fast spin-echo (3000 TR/85 TE/2 excitations) or fast fluid-attenuated inversion recovery (9000 TR/110/2200 inversion time/2 excitations) sequence. DWI lesion growth or reversal of the initial DWI lesion was defined as an increase or decrease of >20% of the initial DWI lesion volume on follow-up MRI.

Clinical Assessment
We assessed clinical status at baseline and at 24 hours after symptom onset by means of the National Institutes of Health Stroke Scale (NIHSS), which was conducted by a neurologist or senior neurology resident not involved in obtaining sonographic information who was video trained and certified for application of the NIHSS.16 Early neurological deterioration or improvement was defined as an increase or decrease of 4 or more points on the NIHSS score after 24 hours from baseline assessment.15 An intracranial hemorrhage was considered symptomatic when the patient exhibited clinical deterioration causing an increase of 4 points on the NIHSS and if the hemorrhage was likely to be the cause of the neurological deterioration. The modified Rankin scale17 was used to assess clinical outcome at 90 days. We defined a good outcome as a modified Rankin score ≤2.

Statistical Analysis
The analysis was performed with SPSS 9.0 software (SPSS Inc). Statistical significance for intergroup differences was assessed by the 2-tailed Fisher’s exact test and Pearson’s 2 test for categorical variables and by Student’s t test, Mann-Whitney U test, and Kruskal-Wallis test for continuous variables. A level of P<0.05 was accepted as statistically significant.

Results
We studied a total of 113 patients (52 men, 61 women) with acute stroke caused by MCA occlusion treated with intravenous tPA. Demographic data, risk factor profile, and baseline clinical findings are shown in Table 1. Mean age was 71.5±12.4 years (range, 31 to 85 years). Median NIHSS score of the series on admission was 17 points (interquartile range, 15 to 19 points). Time elapsed between symptom onset and drug administration was 167.4±57.2 minutes (range, 71 to 272 minutes). The door-to-needle time was 62.2±26.1
minutes (range, 51 to 102 minutes). The time from symptom onset to MRI was 154.3 ± 27.3 minutes. The time elapsed from stroke onset to beginning of recanalization was 183 minutes. The time from stroke onset to the beginning of recanalization was 186 minutes. The time from symptom onset to the beginning of recanalization was 186 minutes. The time from symptom onset to the beginning of recanalization was 186 minutes. The time from symptom onset to the beginning of recanalization was 186 minutes. The time from symptom onset to the beginning of recanalization was 186 minutes.

On admission and according to TCD criteria, 73 (64.6%) showed a proximal occlusion (terminal internal carotid artery and M1 occlusions), and 40 (35.4%), a distal MCA occlusion. On baseline MRA, 28 (24.8%) showed a terminal internal carotid artery occlusion (T occlusion), 54 (47.8%) patients presented with an M1 occlusion, and 31 (27.5%) had an M2-M3 MCA occlusion. Recanalization was achieved during the first 2 hours of tPA bolus in 63 (55.7%) patients, with 34 (30.1%) partial and 29 (25.6%) complete recanalizations. The mean time from stroke onset to the beginning of recanalization was 183 ± 48 minutes. The time from stroke onset to partial and complete recanalization was 230.5 ± 119.2 and 284.6 ± 107.4 minutes, respectively. During 2-hour continuous TCD monitoring, 13 (12.3%) patients recanalized suddenly, 32 (30.2%) recanalized in a stepwise manner, and 18 (17%) showed a slow pattern of recanalization. Table 1 shows baseline characteristics across different sonographic patterns of recanalization. Overall, there were no differences regarding age, stroke severity, location of arterial occlusion, time to MRI, time to treatment, and beginning of recanalization among patients who experienced different patterns of speed of clot lysis after tPA administration. Early recanalization during TCD monitoring was detected in 11 (9.8%) patients. Recanalization occurred in 2 (15.2%), 6 (18.3%), and 3 (16.6%) patients who recanalized in a sudden, stepwise, and slow pattern, respectively.

Median baseline DWI and PWI lesion volumes were 42 cm³ (interquartile range, 3 to 108 cm³) and 188 cm³ (interquartile range 60 to 252 cm³), respectively. The mean change in DWI lesions on follow-up MRI was 38.46 ± 50.4 cm³. The DWI lesion enlarged in 91 (79.9%) patients but remained unchanged in 14 (13%), and in 8 (7.1%) patients, reversal of the initial DWI lesion was observed. Moreover, a good correlation (r = 0.52, P < 0.001) was found between the time from onset to maximum completeness of recanalization and DWI lesion growth during the first 36 to 48 hours. Figure 1a illustrates changes in DWI lesion volume from baseline to 36 to 48 hours according to the speed of tPA-induced clot lysis. The sudden pattern of recanalization was significantly associated with a smaller, final DWI lesion volume (P = 0.001, Kruskal-Wallis test) and a lower degree of DWI lesion growth during the first 24 hours after admission. The pattern of recanalization on TCD was significantly associated (P < 0.001) with the degree of clinical improvement at 24 hours (Figure 1b). Dramatic clinical recovery (>10 points in the NIHSS score) at 24 hours was seen in 10 of 13 (77%) patients who recanalized suddenly, in 16 of 32 (50%) of those who recanalized in a stepwise manner, and in 2 of 18 (11%) of those who did so slowly. Figure 2 shows the variation in NIHSS score at 24 hours and DWI lesion volume at 36 to 48 hours according to the speed of tPA-induced clot lysis.
hours according to the sonographic pattern of recanalization after thrombolysis. Twenty-four-hour baseline variation in the NIHSS score was inversely correlated ($r = -0.42$, $P = 0.001$) with the degree of DWI lesion enlargement at 36 to 48 hours. Moreover, the faster the speediness of clot dissolution on TCD, represented by sudden and stepwise recanalization, the greater was the degree of neurological improvement and the lesser the DWI lesion enlargement on follow-up MRI. Among patients who recanalized within 2 hours, a slow pattern was associated with greater DWI lesion growth ($P = 0.003$), a lesser degree of clinical improvement ($P = 0.021$), worse 3-month outcome ($P = 0.032$), and higher mortality ($P = 0.003$). Ninety-two percent, 59%, and 12% of patients who showed sudden, stepwise, and slow recanalization, respectively, became independent at 3 months (Table 2). Early clinical course, long-term outcome, and mortality rate in patients who recanalized in a slow pattern were comparable to those who remained occluded during the first 2 hours after tPA bolus.

**Discussion**

In stroke patients treated with systemic thrombolysis, the present study demonstrates that the speed of clot dissolution on TCD monitoring predicts DWI lesion evolution, early clinical course, and long-term outcome. A sudden pattern of arterial recanalization on TCD was associated with a lesser degree of DWI expansion, high rate of reversal of the DWI lesion, dramatic clinical recovery at 24 hours, and excellent 3-month outcome. Moreover, a slow pattern of recanalization was associated with a worse clinical course, poorer long-term outcome, and high mortality rate, in magnitude comparable to those who remained occluded during the first 2 hours after tPA bolus.

The beneficial effect of intravenous tPA therapy in stroke patients is attributable to the achievement of arterial recanalization, with early restoration of cerebral blood flow in the penumbral ischemic tissue. Serial MRI studies have shown that thrombolysis-induced recanalization may alter the natural evolution of the DWI lesion by attenuating DWI lesion growth or even reversing the initial DWI lesion.$^9,10$ Moreover, DWI lesion growth has been correlated with clinical recovery and final infarct volume, supporting the use of multimodal MRI as an imaging biomarker of efficacy in reperfusion therapies.$^5,8$ However, previous MRI studies did not monitor
recanalization in real time shortly after treatment; instead, they used MRA to assess artery reopening at later time points, mostly at 24 hours of stroke onset, which does not allow evaluation of the influence of the speed and temporal profile of recanalization on ischemic lesion evolution.

Differential patterns of recanalization speed are determined according to the duration of flow improvement on TCD, probably reflecting structural differences in clot composition. In fibrin-rich thrombi, tPA penetrates and distributes homogeneously, leading to an entire and rapid clot dissolution (sudden recanalization). In contrast, in well-organized and platelet-rich clots, permeation and distribution of tPA are limited, which may result in nonuniform clot softening and degradation from the outside layers of the clot. As a result, the clot gradually shrinks and moves distally, lodging in smaller arteries (stepwise or slow recanalization), which would prolong ischemia. Our study shows that the speed of artery reopening in patients with MCA occlusion is correlated with DWI lesion change after tPA treatment, independent of initial stroke severity, site of intracranial occlusion, and extent of baseline DWI and PWI volumes. We found a graded response in the extent of DWI change in relation to the speed of clot dissolution. Sudden recanalization was associated with a lower degree of DWI lesion expansion, probably indicating a faster and more complete restoration of cerebral blood flow. In contrast, stepwise and slow recanalization resulted in a greater increase of DWI lesion volume, reflecting delayed and incomplete recanalization. This finding is consistent with previous studies indicating that reperfusion occurring at early time points potentially leads to inhibition of DWI lesion growth in tPA-treated patients. In our study, however, recanalization was evaluated for 2 hours after tPA initiation, and the group of patients who remained occluded at 2 hours might in fact include patients with late but possibly still beneficial recanalization.

There is growing evidence concerning DWI lesion reversibility in stroke patients after intra-arterial or intravenous thrombolytic therapy. In our series, the DWI lesion reversal rate was 7%. This phenomenon mainly affects the white matter and basal ganglia. In a recent report, DWI normalization was found to occur in patients with early reperfusion and a less-severe initial apparent diffusion coefficient (ADC) decrease. In our series, sudden recanalization was clearly associated with DWI lesion reversal. Reversal of the initial DWI lesion was seen in 50% of patients who recanalized suddenly, in only 6% of those who recanalized in a stepwise manner, and in none of the patients who recanalized slowly or who did not recanalize. These observations suggest that DWI lesion reversibility is linked to the speed of early reperfusion of ischemic tissue.

Our study demonstrates that not only the timing but also the speed of tPA-induced clot lysis represents a major determinant of ischemic tissue evolution and outcome in acute stroke. We hypothesize that real-time assessment of recanalization better reflects treatment effect than the conventional time-point approach. For instance, the duration of cerebral ischemia may vary markedly, despite the same degree of recanalization at a predetermined time point. Variability of ischemia time may be even more pronounced as the longer the time point of recanalization is chosen. Sudden recanalization has been demonstrated to be a predictor of excellent neurological outcome after intravenous tPA treatment. In our series, among patients who recanalized suddenly, 86.7% experienced a dramatic clinical recovery at 24 hours, whereas stepwise and slow recanalization resulted in a less-favorable outcome. Moreover, we observed an inverse correlation between the extent of DWI growth and the degree of clinical improvement at 24 hours. The combination of continuous TCD monitoring and DWI provides complementary information on the impact of the dynamics of clot dissolution on ischemic tissue evolution and outcome. Therefore, speed of clot lysis on TCD and DWI lesion growth may represent ideal surrogate outcome measures in thrombolytic trials. However, a large multicenter validation of TCD patterns is required before it can be used as a surrogate marker of efficacy of tPA in stroke reperfusion trials.

This study has certain limitations. Although the location of arterial occlusion before treatment was comparable among different patterns of recanalization, our study was not sufficiently powered to exclude the effect of the site of intracranial artery occlusion on the speed of clot lysis and DWI lesion evolution. Moreover, we used TCD for continuously monitoring recanalization for 2 hours after treatment. However, continuous application of 2-MHz ultrasound may potentially amplify the effect of tPA on clot lysis, leading to relatively high rates of recanalization in our series.

### Table 2. Outcome Measures Among TCD Patterns of Recanalization on TCD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sudden, n=13</th>
<th>Stepwise, n=32</th>
<th>Slow, n=18</th>
<th>None, n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-hour recanalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>5 (40%)</td>
<td>20 (62%)</td>
<td>8 (45%)</td>
<td>...</td>
</tr>
<tr>
<td>Complete</td>
<td>8 (60%)</td>
<td>12 (38%)</td>
<td>10 (55%)</td>
<td>...</td>
</tr>
<tr>
<td>Reocclusion</td>
<td>2 (15%)</td>
<td>6 (18%)</td>
<td>3 (16%)</td>
<td>...</td>
</tr>
<tr>
<td>Symptomatic intracerebral hemorrhage</td>
<td>0</td>
<td>1 (3.1%)</td>
<td>1 (5.5%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Dramatic improvement</td>
<td>10 (77%)</td>
<td>16 (50%)</td>
<td>2 (11%)*</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>DWI lesion growth, cm³</td>
<td>3.23±10</td>
<td>24.9±37</td>
<td>46±38*</td>
<td>51±34</td>
</tr>
<tr>
<td>Final DWI volume, cm³</td>
<td>26.4±15</td>
<td>44.5±47</td>
<td>66.4±43*</td>
<td>79±62</td>
</tr>
<tr>
<td>Modified Rankin score &lt;2 at 3 months</td>
<td>12 (92%)</td>
<td>19 (59%)</td>
<td>2 (12%)*</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>16%</td>
<td>38%</td>
<td>42%</td>
</tr>
</tbody>
</table>

*P<0.05, Kruskal-Wallis test.
In conclusion, the speed of arterial recanalization during TCD monitoring predicts DWI lesion evolution, early clinical course, and long-term outcome in stroke patients treated with intravenous tPA. A sudden pattern of recanalization was associated with lesser DWI lesion growth, higher rate of reversal DWI, and dramatic clinical recovery. Patterns of recanalization on TCD may be helpful as a surrogate marker of efficacy in thrombolytic trials.

Disclosures
None.

References
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