Clinical Deterioration After Intravenous Recombinant Tissue Plasminogen Activator Treatment
A Multicenter Transcranial Doppler Study

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Background and Purpose—Patients may experience clinical deterioration (CD) after treatment with intravenous recombinant tissue plasminogen activator (rt-PA). We evaluated the ability of flow findings on transcranial Doppler to predict CD and outcomes on modified Rankin Scale.

Methods—Patients with acute stroke received intravenous rt-PA within 3 hours of symptom onset at four academic centers. CD was defined as an increase in the National Institutes of Health Stroke Scale (NIHSS) score by 4 points or more within 24 hours. Poor long-term outcome was defined by modified Rankin Scale ≥2 at 3 months. Transcranial Doppler findings were interpreted using the Thrombolysis in Brain Ischemia flow grading system as persistent arterial occlusion, reocclusion, or complete recanalization. Multiple regression analysis was used to identify transcranial Doppler flow as a predictor for CD after controlling for age, sex, baseline NIHSS, hypertension, and glucose.

Results—A total of 374 patients received intravenous rt-PA at 142±60 minutes (median pretreatment NIHSS score 16 points). At the end of intravenous rt-PA infusion, transcranial Doppler showed persistent arterial occlusion in 219 patients (59%), arterial reocclusion in 54 patients (14%), and complete recanalization in 101 patients (27%). CD occurred in 44 patients: 36 had persistent arterial occlusion or reocclusion (82%), 13 symptomatic intracerebral hemorrhage (29%), and both persistent occlusion/reocclusion and symptomatic intracerebral hemorrhage in 10 patients (23%). After adjustment, patient risk for CD with persistent occlusion was OR 1.7 (95% CI: 0.7 to 4) and with arterial reocclusion 4.9 (95% CI: 1.7 to 13) (P=0.002). Patient risk for poor long-term outcomes with persistent occlusion, partial recanalization, or reocclusion was OR 5.2 (95% CI: 2.7 to 9, P=0.001).

Conclusions—Inability to achieve or sustain vessel patency at the end of rt-PA infusion correlates with the likelihood of clinical deterioration and poor long-term outcome. Early arterial reocclusion on transcranial Doppler is highly predictive of CD and poor outcome. (Stroke. 2007;38:000-000.)

Key Words: acute stroke ■ diagnostic methods ■ outcome ■ transcranial Doppler ■ therapy ■ thrombolysis

Intravenous recombinant tissue plasminogen activator (rt-PA) remains the only treatment approved for acute stroke treatment in the 3-hour window based in the National Institute of Neurological Disorders and Stroke–rt-PA Stroke Study1 with the number needed to treat of eight to reverse one stroke completely at 3 months. However, half of rt-PA-treated patients remain severely disabled or die within this period of time. The modest recanalization rate of 25% to 30% observed with proximal large vessel occlusion may explain the limited effect of systemic thrombolysis alone and the poor outcome apparently associated with persisting occlusion.2,3 In addition, lower dose of intravenous rt-PA in patients presenting beyond 3 hours carries a risk of intracerebral hemorrhage. However, recanalization with dramatic recovery can still occur.4

Patients who received intravenous rt-PA may experience clinical deterioration after treatment (CD) with intravenous rt-PA. In the National Institute of Neurological Disorders and Stroke trial, CD within the first 24 hours occurred in 98 patients (16%); 43 were given rt-PA and 55 were given placebo.5 Baseline variables associated with CD included a less frequent use of prestroke aspirin and a higher incidence...
of early computed tomography changes of edema or mass effect or a dense middle cerebral artery sign. In addition, patients with CD were less likely to have a 3-month favorable outcome. However, there was no consistent vascular imaging protocol implemented in the trial to assess the arterial status of these patients and its bearing on CD.

This clinical deterioration’s phenomenon with intravenous rt-PA treatment has been described as being secondary to multiple causes, including hemorrhagic transformation,5,7 developing brain edema, persistent arterial occlusion after intravenous rt-PA treatment,6,9 or secondary factors such as cardiopulmonary decompensation. Urgent sonographic evaluation of patients who experience clinical deterioration within 24 hours after intravenous rt-PA treatment has not been well characterized.

Transcranial Doppler ultrasound (TCD) has the ability to provide noninvasive continuous monitoring of the arterial status while giving rt-PA treatment.10 TCD can quickly determine whether occlusion is present11 or whether recanalization has been achieved.8,12–14 In addition, continuous TCD monitoring may safely augment t-PA-induced arterial recanalization with a trend toward an increased rate of recovery from stroke.15

We evaluated the ability of the different flow findings on TCD to predict the onset of CD within 24 hours and to correlate with the long-term outcome on the modified Rankin Scale in patients with acute stroke who received intravenous rt-PA treatment in the 3-hour time window.

**Subjects and Methods**

This is a retrospective study of consecutive patients who presented with acute stroke during the first 3 hours after symptom onset at four stroke centers in North America and Europe. Patients received standard intravenous rt-PA therapy (0.9-mg/kg dose, maximum 90 mg, 10% bolus, 90% continuous infusion) that was initiated within the first 3 hours after symptom onset according to the National Institute of Neurological Disorders and Stroke protocol.1 Age, mild stroke (National Institutes of Health Stroke Scale [NIHSS] score ≤3), and computed tomography ASPECT score ≤7 were not considered as exclusion criteria for intravenous rt-PA treatment. Patients enrolled in clinical trials of ultrasound enhanced intravenous rt-PA thrombolysis were included into this analysis15 as those treated after 3 hours at similar or lower rt-PA doses, ie, 0.6 mg/kg (maximum 60 mg), using ethics committee-approved protocols.

Patients were included in this study if they had proximal arterial occlusion on their TCD (middle cerebral artery M1, M2, terminal internal carotid artery, tandem internal carotid artery/proximal middle cerebral artery, posterior cerebral artery, vertebral artery, basilar artery occlusions) according to criteria previously validated by our group.16,17 Our TCD criteria for proximal middle cerebral artery occlusion have been shown to have 91% sensitivity and 98% specificity when compared with angiography. Patients with no occlusion on their TCD (lacunars strokes) were excluded from our study. The cervical carotid artery status was assessed by carotid ultrasound that was done on the same admission.

Before intravenous rt-PA bolus, an experienced sonographer certified by American Society of Neuroimaging or TCD Flow Grading Examination (Health Outcomes Institute, 2000) identified residual flow signals at the presumed thrombus location using the Thrombolysis in Brain Ischemia (TIBI) flow-grading system.11 A 2-MHz transducer was positioned at a constant angle of insonation with a standard head frame (Marc series; Spencer Technologies). The depth that displayed the worst residual TIBI flow signal was selected. Patients were either continuously monitored with TCD starting before bolus for 2 hours or underwent intermittent TCD testing every 10 to 30 minutes using the previously published Institutional Review Board-approved protocol.15

![Figure 1. TCD flow finding during and at the end of intravenous rt-PA infusion.](http://stroke.ahajournals.org/cgi/content/first proofs only/2/1/2/DC1)
The follow-up TCD findings were defined as: persistent arterial occlusion, partial recanalization, complete recanalization, and recanalization (Figure 1). Arterial recanalization on TCD was determined using previously validated criteria. Recanalization on TCD was graded as complete, partial, or none according to the Thrombolysis in Myocardial Infarction criteria. In brief, complete recanalization was diagnosed when a normal waveform or a low-resistance systolic signal appeared at the selected depth of insonation (TIBI: 4 or 5), suggesting low resistance of the distal circulatory bed. These flow findings correlate with unobstructed passage of contrast agent on angiography. Partial recanalization was diagnosed if the abnormal signals (high resistance dampened signals or flattening of the systolic upstroke with “blunted” waveform) were still seen at the distal portion (TIBI: 2 or 3). No change in the abnormal flow signals indicated that no recanalization has occurred with minimal flow signal or absent flow corresponding to complete arterial occlusion on angiography (TIBI: 0 or 1). As mentioned, these TCD criteria for thrombolysis-associated recanalization in the proximal middle cerebral artery have been shown to have 91% sensitivity and 93% specificity when compared with angiography.

Reocclusion was first suspected by a sonographer when a decrease in the flow signal by 1 TIBI grade was seen on TCD display after complete or partial recanalization and vital signs remained stable. A worsening of flow signals by one TIBI grade indicates an increase in resistance to flow and therefore progression in the degree of arterial obstruction. Systemic reasons for worsening TCD flow (hypotension, bradycardia, low cardiac output, fever, and so on) were excluded by closely monitoring the patient’s vital signs, cardiac status, and chest x-ray.

The serial or continuous TCD waveforms were interpreted from the real-time display at the bedside by the same sonographer and the treating physician was informed of the result. Standard monitoring of vital signs (ie, blood pressure, pulse oximetry, and heart rhythm) was performed during rt-PA therapy as part of the thrombolysis emergency protocol. The indications for repeat computed tomography scanning included stroke symptom progression (CD), and a scheduled 24-hours posttreatment computed tomography scan as per protocol.

Neurologic status (NIHSS stroke score) was repeatedly assessed at baseline and during the first 2 hours after rt-PA bolus by the treating neurologist who, although not directly involved in TCD performance, was informed about worsening of flow signals on TCD if these occurred. All neurologists who performed serial neurologic examinations in the emergency room were certified in the NIHSS scoring. The NIHSS scores at 24 hours and modified Rankin Scale at 3 months were obtained by a neurologist who was not aware of TCD findings and the purposes of this study.

Clinical outcome measurements included the NIHSS scores at 2 hours after rt-PA bolus and at 24 hours. Clinical deterioration after intravenous rt-PA treatment was defined by increase in NIHSS score of 4 points or more, within 24 hours from intravenous rt-PA treatment. Symptomatic intracerebral hemorrhage was defined by ≥4 NIHSS points worsening within 1 week of stroke onset that, in the opinion of a treating physician, was linked to presence of blood on repeat head computed tomography or magnetic resonance imaging scan and was likely the cause of neurologic worsening. Poor long-term outcome was defined as modified Rankin Scale scores of 2 to 6 at 3 months follow up.

The extent of the computed tomography scan lesion was determined by the Alberta Stroke Program Early CT Score (ASPECTS). ASPECTS is a weighted volumetric scale used to score the degree of ischemic change present on an acute stroke patient’s computed tomography scan within the first 24 hours from symptom onset. The score applies to the middle cerebral artery territory only and ranges from 0 to 10 with 10 implying no evidence of ischemic change and 0 implying a complete middle cerebral artery territory infarct.

Statistical Methods

Descriptive statistics were expressed as means ± SD and median with range for continuous variables and as numbers (percentages) for categorical variables. Univariate analysis was performed by using two-sample Student t tests, Pearson χ² test, and Fisher exact test whenever appropriate. Multiple logistic regression was used to identify TCD flow as a predictor for CD after adjusting for confounding factors (age, sex, baseline NIHSS, systolic blood pressure, baseline glucose, and onset to intravenous rt-PA treatment time). Age, baseline NIHSS, systolic blood pressure, baseline glucose, and onset to treatment were entered as continuous variables in the multiple logistic regression analysis, whereas sex and TCD flow were entered as categorical variables. Results were considered significant if two-sided probability value was <0.05. The statistical package SPSS 13.0 (September 2004 release) was used for data analysis.

Results

A total of 374 patients with proximal arterial occlusion on their TCD received intravenous rt-PA at 142±60 minutes (women: 172 [46%], mean age 69±13, median age 71 years, range 31 to 96 years). Their median pretreatment NIHSS score was 16 points (range 3 to 34). An rt-PA bolus was given at 142±60 minutes (median 138, range 42 to 748 minutes). Median head computed tomography ASPECT score was 9 (range 0 to 10). Twenty-two patients (5.8%) received intravenous rt-PA treatment in the 3- to 6-hour window in one center (UTH) based on an experimental protocol approved by their local ethics committee.

Intravenous rt-PA was initiated within the first 150 minutes from symptom onset in 226 patients (61% of all patients). CD occurred in 44 patients (12%). Symptomatic intracerebral hemorrhage occurred in 30 patients (8%). Stroke pathogenic mechanisms were large-vessel atherosclerotic occlusive disease in 93 patients (25%), cardioembolic in 174 patients (46%), other etiology (ie, dissection) in 12 patients (3%), and undetermined in 95 patients (26%).

All patients had clinical and TCD examinations in the emergency room at a mean time of 140±75 minutes from symptoms onset (range 30 to 720 minutes).

Baseline TCD showed a proximal M1 middle cerebral artery occlusion in 185 patients (49.5%), M2 middle cerebral artery occlusion in 102 patients (27.4%), tandem middle cerebral artery/internal carotid artery occlusion in 61 patients (16%), terminal internal carotid artery in 16 patients (4.5%), anterior cerebral artery occlusion in one patient (0.25%), posterior cerebral artery occlusion in one patient (0.25%), vertebral artery occlusion in 3 patients (0.8%), and basilar artery occlusion in 5 patients (1.3%). At the end of intravenous rt-PA infusion, TCD showed persistent arterial occlusion in 137 patients and partial recanalization in 82 patients (total persisting arterial occlusion in 219 patients [59%]). Complete recanalization was seen in 101 patients (27%). Arterial reocclusion occurred in 54 patients (14%); of those, 24 patients had partial recanalization (44%) and 30 patients had complete recanalization (56%).

Clinical deterioration after intravenous rt-PA treatment occurred in 44 (12%) of all patients. Based on occlusion sites, CD was seen in patients with the terminal internal carotid artery occlusions (n=4 [9%]), proximal M1 middle cerebral artery occlusions (n=23 [52.3%]), tandem internal carotid artery/middle cerebral artery occlusion (n=7 [15.9%]), distal M2 middle cerebral artery occlusions (n=9 [20.5%]), and vertebral artery (n=1 [2.3%]) (P=0.294) (Table 1). Based on stroke mechanisms, CD occurred in 20 patients with cardioembolic (45.5%), large-vessel atherosclerosis 11 (25%), pa-
patients with other etiology (3 [6.8%]), and unknown etiology (10 [22.7%]) (P=0.49).

Based on TCD flow findings at the end of intravenous rt-PA treatment, the proportion of CD was significantly higher in patients with arterial reocclusion (14 of 44 [32%]) than patients with persistent arterial occlusion or partial recanalization (22 of 44 [50%]) and complete recanalization (8 of 44 [8%]) (χ²=12.49, P=0.002) (Table 1 and Figure 2).

Symptomatic intracerebral hemorrhage was found in 13 patients (29.5%), and both persistent occlusion/reocclusion and symptomatic intracerebral hemorrhage were found in 10 patients (23%) with CD. Presence of CD was significantly higher in patients with symptomatic intracerebral hemorrhage 13 patients (29.5%) versus 17 patients (5.2%) (P=0.001, Table 1).

After adjustment for age, sex, high blood pressure, baseline glucose, time to treatment, and stroke severity (baseline NIHSS score), patient risk for CD with persistent occlusion or partial recanalization was OR 1.7 (95% CI: 0.7 to 4, P=0.28), and with arterial reocclusion was 4.9 (95% CI: 1.7 to 13) (P=0.002) (Table 2). In addition, patient risk for poor long-term outcomes (modified Rankin Scale ≥2 at 3 months) with persistent occlusion, partial recanalization, or reocclusion was OR 5.2 (95% CI: 2.7 to 9, P=0.001).

### Discussion

Our study showed that the inability to achieve or sustain vessel patency at the end of rt-PA infusion correlates with the likelihood of CD within 24 hours from standard systemic thrombolytic treatment and poor long-term outcomes. Early arterial reocclusion after complete or partial recanalization on TCD is highly predictive of CD and poor outcomes regardless of primary occlusion site or stroke mechanism. These TCD

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**TABLE 1. Univariate Statistics Between Patient With and Without CD**

| Factors                              | Patient With CD, n=44 | Patient Without CD, n=330 | P  
|--------------------------------------|-----------------------|---------------------------|------
| Age, in years                        | 66.1±14.7             | 68.8±13.3                 | 0.2  
| Gender                               |                       |                           |      
| Male                                 | 26 (59%)              | 176 (23%)                 |      
| Female                               | 18 (41%)              | 154 (47%)                 | 0.472  
| Baseline NIHSS                       | 15.6±5.9              | 16.5±5.5                  | 0.308  
| Time to rt-PA treatment, minutes     | 149±48                | 142±62.5                  | 0.449  
| Systolic blood pressure, mm Hg       | 160.5±24.8            | 157±22                    | 0.365  
| Glucose, mg/dL                       | 146.8±61.2            | 149.1±74                  | 0.852  
| Symptomatic intracerebral hemorrhage | 13 (29.5%)            | 17 (5.2%)                 | <0.001  
| Toast classification                 |                       |                           | 0.49  
| Cardioembolic                        | 20 (45.5%)            | 154 (47%)                 |      
| Large-vessel atherosclerosis         | 11 (25%)              | 82 (24.8%)                |      
| Other (eg, dissection)               | 3 (6.8%)              | 9 (2.7%)                  |      
| Unknown                              | 10 (22.7%)            | 85 (25.8%)                |      
| Type of occlusion                    |                       |                           | 0.294  
| Middle cerebral artery M1            | 23 (52.3%)            | 162 (49.4%)               |      
| Middle cerebral artery M2            | 9 (20.5%)             | 93 (28.4%)                |      
| T internal carotid artery            | 4 (9%)                | 12 (3.7%)                 |      
| Tandem internal carotid artery/middle cerebral artery | 7 (15.9%) | 54 (16.4%) |      
| Basilar artery                       | 0 (0%)                | 5 (1.5%)                  |      
| Vertebral artery                     | 1 (2.3%)              | 2 (0.6%)                  |      
| TCD flow finding                     |                       |                           | 0.002  
| Persistent occlusion                 | 22 (50%)              | 197 (59.7%)               |      
| Reocclusion                          | 14 (31.8%)            | 40 (12.1%)                |      
| Recanalization                       | 8 (18.2%)             | 93 (28.2%)                |      

**Figure 2.** Proportion of patients with CD between TCD flow types.
Clinical Deterioration After IV rt-PA Treatment

TABLE 2. Multiple Logistic Regression for Patients With and Without CD

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted OR</th>
<th>95% CI for Adjusted OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCD flow</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete recanalization</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent or partial occlusion</td>
<td>1.65</td>
<td>0.66 to 4.15</td>
<td>0.28</td>
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<tr>
<td>Arterial occlusion</td>
<td>4.85</td>
<td>1.75 to 13.46</td>
<td>0.002</td>
</tr>
<tr>
<td>Age in years</td>
<td>0.98</td>
<td>0.96 to 1.01</td>
<td>0.25</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.84</td>
<td>0.42 to 1.67</td>
<td>0.62</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
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<td>0.98–1.02</td>
<td>0.47</td>
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<tr>
<td>Baseline glucose</td>
<td>0.99</td>
<td>0.99 to 1.03</td>
<td>0.37</td>
</tr>
<tr>
<td>Onset to treatment</td>
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<td>0.99 to 1.01</td>
<td>0.52</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>0.97</td>
<td>0.91 to 1.03</td>
<td>0.32</td>
</tr>
</tbody>
</table>

flow findings could be important for the treating physicians because further experimental interventional treatment like intraarterial rt-PA therapy (IMS protocol) or a mechanical device (Mercy catheter) could be planned in these circumstances in less than a 6-hour window.

Our study showed a trend toward CD occurring more commonly in patients with terminal internal carotid artery or proximal middle cerebral artery occlusion than in patients with distal middle cerebral artery occlusion. However, this difference did not reach statistical significance. An explanation of such an observation could be a commonly lacking collateral flow as well as the anticipated large size of stroke in the setting of a proximal occlusion.

Clinical deterioration was relatively common in this series, consistent with previous observations. Although early deterioration within 6 hours of stroke onset was found in 37.5% of patients enrolled in the European Cooperative Acute Stroke Study (http://stroke.ahajournals.org/login.teri.bca/cgi/content/full/32/3/661-R15#R15), only 16% had deterioration in the National Institute of Neurological Disorders and Stroke–rt-PA Stroke Study, similar to our findings.

Previous studies done by our group revealed that the timing of arterial recanalization after rt-PA therapy as determined by TCD correlates with clinical recovery from stroke and demonstrates a 300-minute window to achieve early complete recovery. In addition, the initial flow finding on TCD at the occlusion site defined by TIBI grade correlates with initial stroke severity, clinical recovery, and mortality in intravenous tPA-treated stroke patients. In our study, we explored the TCD flow finding at the end of intravenous rt-PA in comparison with a baseline TCD to predict further clinical deterioration after intravenous rt-PA treatment, which was not looked at in the first two studies.

In a few patients, CD occurred despite complete recanalization (eight patients) that was achieved with intravenous rt-PA treatment. The possible explanations for CD in this setting are either a progressive enlargement of the irreversibly damaged ischemic core to incorporate the surrounding penumbral regions, that the reperfusion may aggravate damage in the regions of moderate ischemia or hemorrhages after the reperfusion. A repeat head computed tomography scan after CD may distinguish symptomatic intracerebral hemorrhage or the formation of hypodensity (irreversible ischemia) or progression of brain edema as the likely causes. Although there is no treatment modality available for these events at this time, emerging cytoprotective drugs and procedures such as hypothermia may help reduce some of these risks.

The present study demonstrates that early reocclusion is associated with CD after adjusting by other confounders, which is in line with previous observations. Although CD was relatively frequent and associated with unstable vessel patency, our results should not be used to justify routine use of antiplatelets or anticoagulation simultaneously or shortly after intravenous rt-PA because the safety of these combinations to prevent reocclusion is largely unknown. However, further study of this question is certainly worthwhile, especially if done with TCD correlation to determine the exact incidence and timing of recanalization and reocclusion. Experience with thrombolysis for acute coronary occlusion has demonstrated that arterial recanalization can be augmented and reocclusion can be prevented by the use of antiplatelet therapy, especially the GPIIb IIIa antagonists.

The limitations of this study include, first, the fact that TCD is still an operator-dependent technique and requires specialized training for application in the acute stroke setting. This was addressed by ensuring that all sonographers were highly trained and certified in the application of TCD in the setting of acute stroke. Second, the study is a retrospective analysis of a prospective collaborative data set. Therefore, it is prone to the effect of confounders. We tried to eliminate this possible influence by adjusting for common known confounders. Finally, we used arbitrary (but logical) NIHSS cutoffs to define deterioration (increase in NIHSS ≥4 points).

As a consequence, it is possible that patients with slight clinical deterioration could have been missed.

In conclusion, CD is strongly associated with the inability to achieve or sustain arterial vessel patency regardless of the stroke mechanism or site of occlusion. Urgent vascular evaluation may help identify patients with vascular lesions persisting after the completion of intravenous rt-PA treatment who may be candidates for new therapies to prevent subsequent deterioration.

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Disclosures
A.V.A. is on a speakers bureau and has received honoraria from Genentech. A.M.D. is on a speakers bureau for BMS, Sonofi, AstraZeneca, and Hoffman Laroche. He is also a consultant for Terumo, BMS, and Sonofi. All other authors have nothing to disclose.

References


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