Speed of Intracranial Clot Lysis With Intravenous Tissue Plasminogen Activator Therapy
Sonographic Classification and Short-Term Improvement
Andrei V. Alexandrov, MD; W. Scott Burgin, MD; Andrew M. Demchuk, MD, FRCP(C); Ashraf El-Mitwalli, MD; James C. Grotta, MD

Background—Arterial recanalization precedes clinical improvement or may lead to hemorrhage or reperfusion injury. Speed of clot lysis was not previously measured in human stroke.

Methods and Results—Transcranial Doppler (TCD) and the National Institutes of Health Stroke Scale (NIHSS) were used to monitor consecutive patients receiving intravenous tissue plasminogen activator (tPA), before tPA bolus and at 24 hours. Patients with complete or partial recanalization of the middle cerebral or basilar artery on TCD were studied. Recanalization was classified a priori as sudden (abrupt appearance of a normal or stenotic low-resistance signal), stepwise (flow improvement over 1 to 29 minutes), or slow (>30 minutes). Recanalization was documented in 43 tPA-treated patients (age 68±17 years; NIHSS score 16.8±6, median 15 points). tPA bolus was given at a mean of 135±61 minutes after symptom onset. Recanalization began at a median of 17 minutes and was completed at 35 minutes after tPA bolus, with mean duration of recanalization of 23±16 minutes. Recanalization was sudden in 5, stepwise in 23, and slow in 15 patients. Faster recanalization predicted better short-term improvement (P=0.03). At 24 hours, 80%, 30%, and 13% of patients in these respective recanalization groups had NIHSS scores of 0 to 3. Symptomatic hemorrhage occurred in only 1 patient, who had stepwise recanalization 5.5 hours after stroke onset. Slow or partial recanalization with dampened flow signal was found in 53% of patients with total NIHSS scores >10 points at 24 hours (P=0.01). Complete recanalization (n=25) occurred faster (median 10 minutes) than partial recanalization (n=18; median 30 minutes; P=0.0001).

Conclusions—Rapid arterial recanalization is associated with better short-term improvement, mostly likely because of faster and more complete clot breakup with low resistance of the distal circulatory bed. Slow (>30 minutes) flow improvement and dampened flow signal are less favorable prognostic signs. These findings may be evaluated to assist with selection of patients for additional pharmacological or interventional treatment. (Circulation. 2001;103:2897-2902.)

Key Words: ultrasonics • thrombolysis • stroke • recanalization • prognosis

Arterial recanalization indicates successful thrombolysis and often precedes early clinical improvement in ischemic stroke.1,2 The degree of arterial recanalization can be determined by angiographic classification, such as Thrombolysis In Myocardial Infarction (TIMI) flow grades,3 or sonographic Thrombolysis In Brain Ischemia (TIBI) residual flow grades, which were designed specifically for intracranial vessels.4 Compared with angiography, sonographic waveforms determined by transcranial Doppler (TCD) had 91% sensitivity and 93% specificity for complete (TIMI grade III) recanalization versus persisting occlusion.5 TIBI flow grades on TCD also correlate with baseline stroke severity and predict short-term improvement after thrombolysis with tissue plasminogen activator (tPA) in acute ischemic stroke.4 These results parallel observations in cardiology that the amount of TIMI residual flow is related to successful thrombolysis with tPA.3,4 Timing of recanalization determined in vitro represents an outcome measure of thrombolysis when clot is exposed to tPA with or without externally applied ultrasound.6,7 This is often determined as the time of complete clot dissolution with washout to distal vasculature and veins. In human stroke, the timing of maximum completeness of recanalization correlates with clinical recovery as predicted from animal models.8 However, recanalization is a process that often begins many minutes before restoration of cerebral blood flow, because tPA binding and activity on the clot surface are proportionate to the area exposed to blood flow. Once recanalization starts,
clot softens and partially dissolves, allowing some (often minimal) residual flow improvement. This flow brings more tPA to bind with fibrinogen sites. This continuous process facilitates clot lysis and improves residual flow until the clot breaks up under the pressure of arterial blood pulsations.

Therefore, the speed of clot lysis can be measured through the duration of flow improvement with real-time ultrasound monitoring with TIBI residual flow signals and other previously reported parameters such as intensity of flow signals, appearance of microembolic signals, and velocity/pulsatility changes (presented below). The speed of recanalization was not previously measured in human stroke; however, it may represent an important parameter of thrombolysis. For example, prolonged clot breakup delays the occurrence of complete recanalization and therefore may be associated with longer duration of cerebral ischemia. Sudden blood flow increase, on the other hand, may disrupt the blood-brain barrier and lead to edema or hemorrhage.

In this study, we aimed to determine the speed of recanalization using continuous monitoring of the residual flow signals with TCD during tPA infusion. Our goal was to determine the beginning, duration, and timing of maximum completeness of arterial recanalization using a priori developed sonographic classification and to correlate these findings with the amount of recanalization and short-term improvement after thrombolysis for acute ischemic stroke.

Methods

A standard TCD protocol and continuous TCD monitoring have been incorporated into our routine emergency assessment of stroke patients. Briefly, an experienced sonographer performed bedside TCD examination using a validated fast-track insonation protocol to identify the presence and site of arterial occlusion. Residual flow signals at the presumed clot location were identified with the TIBI grading system, and a 2-MHz pulsed-wave transducer was fixed in a steady position over the temporal bone window with a standard head frame (Marc series, Spencer Technologies). No delay in thrombolytic therapy was experienced as a result of TCD examination.

Between January 1999 and September 2000, we studied 73 consecutive patients with symptoms of acute ischemic stroke who received intravenous tPA and underwent TCD examination (3 had no occlusion, and 5 had no temporal windows). tPA was given in a standard 0.9-mg/kg dose (10% bolus, 90% continuous infusion over 1 hour) within the first 3 hours after symptom onset. In selected patients presenting between 3 and 6 hours of onset or with other risk for hemorrhagic complications, tPA was given in a dose of 0.6 mg/kg (15% bolus, 85% continuous infusion over 30 minutes). This experimental protocol was approved by the University of Texas Committee for Protection of Human Subjects.

National Institutes of Health Stroke Scale (NIHSS) scores were obtained before tPA bolus and at 24 hours by a neurologist not involved in TCD monitoring. Flow changes on TCD were documented by an experienced sonographer before NIHSS scoring and interpreted with the TIBI flow-grading system. Treating physicians were informed of TCD results in terms of the presence and location of intracranial occlusion. TCD monitoring was performed for at least 60 minutes during tPA infusion and extended up to 2 hours when feasible. The depth for gated monitoring was selected with a previously published algorithm that identifies the worst TIBI flow grade signal in the middle cerebral (MCA) or basilar artery (BA) stems. For example, in patients with presumed distal M1 MCA occlusion, this segment was monitored at a depth of 55 to 45 mm. We also described and validated our criteria for M2 MCA and BA occlusions. During monitoring, the transducer position was readjusted when necessary, eg, if the patient was restless. In our validation studies, we showed that the waveform analysis and not the velocity measurements was predictive of vessel patency. For the purposes of this article, patients who experienced complete or partial recanalization of the MCA or BA according to previously published criteria were included in the analysis.

The speed of intracranial clot lysis was assessed with sonographic classification of the beginning, duration, and timing to maximum completeness of arterial recanalization that was developed based on previous studies. The beginning and duration (continuation) of recanalization was determined when one of the following flow signal changes was detected on TCD (Figure 1): (1) waveform change by ≥1 TIBI residual flow grade (eg, absent to minimal, minimal to blunted, and minimal to normal); (2) appearance of embolic signals (transient high-intensity signals of variable duration); (3) flow-velocity improvement by ≥30% at a constant angle of insonation; (4) signal intensity and velocity improvement of variable duration at constant gain/sample volume/scale settings; and (5) appearance of flow signals with variable (>30%) pulsatility indexes and amplitude of systolic peaks.

Maximum completeness (or amount) of recanalization was determined when the highest TIBI flow-grade signal (normal>stenotic>dampened) appeared during TCD monitoring. The amount of recanalization was assessed with previously reported criteria. Normal and stenotic signals indicate complete recanalization (TIMI grade III, equivalent to low resistance to flow). Dampered signals indicate partial recanalization (TIMI grade II, equivalent to increased resistance to flow).

To measure speed of intracranial clot lysis, recanalization was classified a priori as follows (Figure 2): I, sudden (abrupt appearance of a normal or stenotic low-resistance signal); II, stepwise (gradual flow improvement over 1 to 29 minutes); and III, slow (flow improvement over ≥30 minutes).

Statistical analysis included χ², t test, and Kendall-r and Spearman correlation to determine significance based on a directional hypothesis (1-tailed test) that early recanalization produces better recovery.

Results

A total of 65 patients with arterial occlusion on pretreatment TCD were monitored during infusion. Mean age was 68 ± 17 years, and mean pretreatment NIHSS score was 16.8 ± 6 (median 15 points; first quartile 13 points, third quartile 22 points). tPA bolus was given at 135 ± 61 minutes after symptom onset (median 121 minutes; first quartile 106 minutes, third quartile 172 minutes). Occlusion sites were M2 MCA segment 21%, M1 MCA 49%, tandem MCA and internal carotid artery (ICA) occlusion 16%, terminal ICA 5%, and vertebrobasilar vessels 9%. A standard full dose of intravenous tPA was given in 55 patients, and an experimental low dose was given in 10 patients (Table 1).

Of 65 patients treated, 43 (66%) had recanalization documented by TCD. Of those who had recanalization, 37 (67%) received the 0.9-mg/kg tPA dose and 6 (60%) received the 0.6-mg/kg tPA dose.

Recanalization began 23 ± 19 minutes (median 17 minutes) and was completed 42 ± 23 minutes (median 35 minutes) after tPA bolus. Mean duration of recanalization was 23 ± 16 minutes (median 17 minutes; first quartile 10 minutes, third quartile 30 minutes). Patients who received the 0.9-mg/kg tPA dose had mean duration of 24 ± 17 minutes, and those treated with the 0.6-mg/kg dose had a mean recanalization time of 16 ± 9 minutes (P = NS). Median speed of MCA clot recanalization was 17 minutes for distal MCA occlusion tandem to an ICA lesion, 28 minutes for M2 segment, and 30...
minutes for M1 segment. The site of occlusion and completeness of recanalization are shown in Table 2.

Recanalization was sudden in 5, stepwise in 23, and slow in 15 patients. Faster recanalization (sudden and stepwise) predicted better short-term improvement (Spearman’s correlation $P=0.03$). At 24 hours, 80%, 30%, and 13% of patients with sudden, stepwise, and slow recanalization, respectively, had NIHSS scores of 0 to 3 (Table 3). Symptomatic hemorrhage occurred in only 1 patient, who had stepwise recanalization 5.5 hours after stroke onset. Completeness of recanalization also predicted better short-term improvement. Normal and stenotic TIBI flow signals were seen in 84% of patients with NIHSS scores of 0 to 3 at 24 hours compared with dampened flow signal found in 53% of patients with total NIHSS scores $>10$ points at 24 hours (Table 4; $P=0.01$).

The amount of recanalization (determined as complete or partial) was inversely proportional to its duration: 88% of complete recanalizations were sudden and stepwise, whereas 67% of partial recanalizations were slow (Table 5; $P=0.001$). Complete recanalization had median duration of 10 minutes (first quartile 4 minutes, third quartile 15 minutes, mean $\pm SD$ 12 $\pm$ 11 minutes, $n=25$) compared with partial recanalization with median duration of 30 minutes (first quartile 16 minutes, third quartile 40 minutes, mean 32 $\pm$ 18 minutes, $n=18$, $P=0.0001$).

**Discussion**

Our study shows that the speed of intracranial arterial recanalization on TCD correlates with short-term improvement after tPA therapy. Short duration of arterial recanaliza-
tion is associated with better short-term improvement, mostly likely because of faster and more complete clot breakup with low resistance of the distal circulatory bed. Slow (≥30 minutes) flow improvement and dampened flow signals that indicate partial recanalization are less favorable prognostic signs. Therefore, the speed of clot lysis as well as the amount and timing of arterial recanalization are important factors that can influence the success of thrombolytic therapy. Our

**TABLE 1. Occlusion Site and tPA Dose**

<table>
<thead>
<tr>
<th>Artery</th>
<th>n (%)</th>
<th>0.9 mg/kg</th>
<th>0.6 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2 MCA</td>
<td>14 (21)</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>M1 MCA</td>
<td>32 (49)</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>MCA/ICA</td>
<td>10 (15.4)</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>TICA</td>
<td>4 (6)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>VB</td>
<td>5 (7.6)</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

MCA/ICA indicates tandem distal MCA/proximal ICA occlusion; TICA, terminal ICA; and VB, vertebrobasilar occlusion.

**TABLE 2. Occlusion Site and Completeness of Recanalization**

<table>
<thead>
<tr>
<th>Artery</th>
<th>n</th>
<th>Complete</th>
<th>Partial</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2 MCA</td>
<td>14</td>
<td>36%</td>
<td>28%</td>
<td>36%</td>
</tr>
<tr>
<td>M1 MCA</td>
<td>32</td>
<td>38%</td>
<td>25%</td>
<td>37%</td>
</tr>
<tr>
<td>MCA/ICA</td>
<td>10</td>
<td>30%</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>TICA</td>
<td>4</td>
<td>25%</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>VB</td>
<td>5</td>
<td>60%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
sonographic classification of the occurrence and speed of arterial recanalization provides this information in real time. Our study has limitations because TCD does not offer imaging of intracranial vessels and relies on operator experience. Also, in the presence of multiple occlusions, TCD selection of the target vessel may be erroneous and less informative. Nevertheless, our prospectively validated scanning protocol and flowgrading system help to monitor stroke patients undergoing thrombolysis with good agreement with angiography.14

In their experiments with ischemic stroke in rats, Yang and Betz11 showed that blood-brain barrier disruption was greater with good reperfusion, which suggests that fast recovery of cerebral blood flow may produce additional damage to the brain. Our data indicate that rapid recanalization leads to better short-term improvement compared with slow and partial flow recovery. Our findings that dramatic recovery occurs more often with faster and complete clot lysis are in agreement with experimental data that a shorter depolarization time after reperfusion leads to a smaller extent of ischemic damage.15 Also, positron-emission tomography studies in humans suggest that early postsischemic tissue hyperperfusion may not be detrimental by itself.14

The utility of transcranial 2-MHz ultrasound should be considered in future studies of thrombolytic therapies, particularly if a new-generation tPA, a new dose, or experimental external devices to enhance the effect of tPA are subjected to clinical trials. Continuous TCD monitoring provides a noninvasive tool for real-time measurement of the beginning, speed, timing, and amount of arterial recanalization. This advantage is linked to a low-megahertz diagnostic ultrasound frequency that allows spatial resolution with a wavelength of 0.77 mm sufficient to focus ultrasound on a proximal branch of the circle of Willis. This spatial resolution allows reasonable precision in measurement of residual flow signals that cannot be achieved with a kilohertz-range of frequencies.

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### TABLE 3. Duration of Recanalization and Short-Term Improvement

<table>
<thead>
<tr>
<th>Duration</th>
<th>Complete</th>
<th>Partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden</td>
<td>5 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Stepwise</td>
<td>17 (74%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>Slow</td>
<td>3 (20%)</td>
<td>12 (80%)</td>
</tr>
</tbody>
</table>

Complete (TIMI grade III equivalent) recanalization had shorter duration compared with partial TIMI grade II recanalization, \(2 \times 3 \chi^2 = 0.001\).

Although a kilohertz range might better enhance tPA activity,7,15–17 it requires “blind” application of external devices. A combination of kilohertz tPA-enhancing frequencies and megahertz monitoring frequencies in the same device may prove to be the best way to apply and dose-control ultrasound-enhanced clot lysis with tPA. Our data also indicate that slow recanalization with a dampened flow signal is a less favorable prognostic sign for short-term improvement, which is similar to other studies that have documented persisting occlusion as a poor prognostic sign.2,18,19 Our findings of slow recanalization and dampened flow signals can be linked to persistent distal arterial occlusion when the clot recanalizes partially or moves to a distal arterial segment. The phenomenon of a dampened flow signal can be present with relatively successful proximal recanalization but compromised distal perfusion, resulting in a pulsatile high-resistance waveform. In addition to distal clot location, this waveform can be produced by stagnant flow in the distal microcirculatory bed, activated platelet aggregation, swelling, and other factors that affect ischemic brain tissue and endothelial function. Therefore, this flow pattern may prove particularly useful in selecting patients for further interventions or for additional pharmacological treatment to inhibit platelet function, reduce edema, or reduce a possible inflammatory response, with a goal to improve brain microcirculation in partially reperfused tissues.

In conclusion, unlike other arterial systems, intracranial arteries can be easily assessed and monitored with externally applied ultrasound during thrombolysis. This real-time information on flow dynamics may prove useful in developing future therapies and in patient selection for interventional procedures.

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### TABLE 4. TIBI Flow Grades and Short-Term Improvement

<table>
<thead>
<tr>
<th>NIHSS 24 h</th>
<th>Sudden</th>
<th>Stepwise</th>
<th>Slow</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 points (n=13)</td>
<td>10 (76%)</td>
<td>7 (54%)</td>
<td>7 (51%)</td>
</tr>
<tr>
<td>4–9 points (n=13)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>≥10 points (n=17)</td>
<td>2 (16%)</td>
<td>5 (38%)</td>
<td>9 (53%)</td>
</tr>
</tbody>
</table>

Dampened TIBI flow grade signals indicating partial recanalization were seen in 53% of patients with poor short-term improvement, Spearman correlation \(P=0.01\).

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### References


4. Demchuk AM, Burgin WS, Christou I, et al. Thrombolysis in Brain Ischemia (TIBI) transcranial Doppler flow grades predict clinical...
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