Timing of Recanalization After Tissue Plasminogen Activator Therapy Determined by Transcranial Doppler Correlates With Clinical Recovery From Ischemic Stroke

Ioannis Christou, MD; Andrei V. Alexandrov, MD; W. Scott Burgin, MD; Anne W. Wojner, MSN, CCRN; Robert A. Felberg, MD; Marc Malkoff, MD; James C. Grotta, MD

Background—The duration of cerebral blood flow impairment correlates with irreversibility of brain damage in animal models of cerebral ischemia. Our aim was to correlate clinical recovery from stroke with the timing of arterial recanalization after therapy with intravenous tissue plasminogen activator (tPA).

Methods—Patients with symptoms of cerebral ischemia were treated with 0.9 mg/kg tPA IV within 3 hours after stroke onset (standard protocol) or with 0.6 mg/kg at 3 to 6 hours (an experimental institutional review board–approved protocol). National Institutes of Health Stroke Scale (NIHSS) scores were obtained before treatment, at the end of tPA infusion, and at 24 hours; Rankin Scores were obtained at long-term follow-up. Transcranial Doppler (TCD) was used to locate arterial occlusion before tPA and to monitor recanalization (Marc head frame, Spencer Technologies; Multigon 500M, DWL MultiDop-T). Recanalization on TCD was determined according to previously developed criteria.

Results—Forty patients were studied (age 70±16 years, baseline NIHSS score 18.6±6.2). A tPA bolus was administered at 132±54 minutes from symptom onset. Recanalization on TCD was found at the mean time of 251±171 minutes after stroke onset: complete recanalization occurred in 12 (30%) patients and partial recanalization occurred in 16 (40%) patients (maximum observation time 360 minutes). Recanalization occurred within 60 minutes of tPA bolus in 75% of patients who recanalized. The timing of recanalization inversely correlated with early improvement in the NIHSS scores within the next hour (polynomial curve, third order \( r^2 = 0.429, P < 0.01 \)) as well as at 24 hours. Complete recanalization was common in patients who had follow-up Rankin Scores if 0 to 1 (\( P = 0.006 \)). No patients had early complete recovery if an occlusion persisted for >300 minutes.

Conclusions—The timing of arterial recanalization after tPA therapy as determined with TCD correlates with clinical recovery from stroke and demonstrates a 300-minute window to achieve early complete recovery. These data parallel findings in animal models of cerebral ischemia and confirm the relevance of these models in the prediction of response to reperfusion therapy. (Stroke. 2000;31:1812-1816.)

Key Words: outcome ■ stroke, acute ■ thrombolysis ■ ultrasonography, Doppler, transcranial

The duration of cerebral blood flow (CBF) impairment correlates with irreversibility of brain damage in animal models of cerebral ischemia.1–7 Jones et al1 demonstrated that the release of middle cerebral artery (MCA) occlusion at up to 3 hours led to clinical improvement in an awake-primate model, and these findings were later replicated in other animal models.2–7 Jones et al1 also suggested an S-shaped relationship between the duration of ischemia and the reversibility of paralysis with subsequent brain infarction.

Clinical observations in humans suggest that spontaneous clot migration with brain reperfusion may lead to a spectacular shrinking deficit in patients with cardioembolic stroke.8,9 Other clinical studies have shown a direct correlation among infarct volume, timing of arterial recanalization, and stroke outcome.9–11 The National Institute of Neurological Disorders and Stroke trial of recombinant tissue plasminogen activator (tPA) showed that intravenous thrombolysis administered within the first 3 hours of cerebral ischemia facilitates clinical recovery compared with placebo-treated patients.12 However, no continuous vascular monitoring of patients with occlusions was performed in these studies, and the relationship between the timing of arterial recanalization and recovery from stroke in humans remains unclear.

We prospectively applied transcranial Doppler (TCD) for the diagnostic evaluation and monitoring of patients who receive intravenous tPA therapy. The aim of the present study was to correlate clinical recovery from stroke with the timing of arterial recanalization as determined with TCD monitoring.
Subjects and Methods
Consecutive patients who were treated with intravenous tPA and received continuous TCD monitoring between July 1998 and September 1999 were included in the study. tPA was administered in a dose of 0.9 mg/kg (10% bolus, 90% continuous infusion during 1 hour) to patients who presented within the first 3 hours after stroke onset according to a standard protocol. In selected patients who presented after 3 to 6 hours of onset or with other risk for hemorrhagic complications, tPA was administered in a dose of 0.6 mg/kg (15% bolus, 85% continuous infusion during 30 minutes). This experimental protocol was approved by the University of Texas Committee for Protection of Human Subjects.

The National Institutes of Health Stroke Scale (NIHSS) scores were obtained before treatment, at the end of tPA infusion, and at 24 hours by a neurologist who did not participate in the TCD. Rankin Scores were obtained by a neurologist independently of TCD findings at long-term follow-up (outpatient visit or structured telephone interview).

In the emergency department, an experienced sonographer performed all TCD studies using 1-channel 2-MHz portable equipment (Multigon 500M, DWL MultiDop-T, Neuroscan). A standard set of diagnostic criteria were applied to diagnose arterial occlusion.

We prospectively validated these criteria against angiography in patients with cerebral ischemia, and sensitivity for MCA, terminal and proximal internal carotid artery (ICA), and basilar artery occlusions were 93%, 81%, 94%, and 60%, respectively, with specificity of ≥96% for all segments.

After the site of intracranial occlusion was identified, continuous monitoring of the residual flow signals was performed with a Marc 500 head frame (Spencer Technologies) to maintain tight transducer fixation and a constant angle of insonation. We also developed and validated our TCD criteria for arterial recanalization for this study. When TCD was compared with digital subtraction angiography, our ultrasound criteria for complete MCA recanalization had 91% sensitivity and 93% specificity.

Briefly, recanalization on TCD was diagnosed as partial if the residual flow signals improved from absent or minimal to blunted or dampened signals (Figure 1). Complete recanalization on TCD was diagnosed if the end-diastolic flow velocity improved to normal or elevated values (normal or stenotic signals). Changes on TCD were determined by the investigators using direct visual control of the monitoring display. If no temporal windows were found, these patients were excluded from analysis.

The timing of arterial recanalization on TCD after the onset of symptoms was determined as the time of the earliest arrival of a normal or stenotic signal (complete recanalization) or a blunted or dampened signal (partial recanalization).

To correlate arterial recanalization and early recovery from stroke, we used the following measures of clinical recovery based on methods used in previous studies. "Dramatic or complete recovery" was defined as a decrease in the total NIHSS score to <3 at the end of tPA infusion or at 24 hours. "Improvement" was defined as the reduction in the total NIHSS score by ≥4 points. "Worsening" was defined as an increase in the total NIHSS score of ≥4 points.

Regression analysis was used to test the hypothesis that the timing of arterial recanalization correlates with early recovery from stroke as predicted from the primate model. Two-tailed P value was significant at ≤0.05.

Results
We studied 40 patients (17 men and 23 women) who were treated with tPA and continuously monitored with TCD. The mean age was 70±16 years, and their baseline mean NIHSS score was 18.6±6.2 points (median 19 points). The tPA bolus was administered at 132±54 minutes from stroke onset (range 65 to 348 minutes); included were 6 who were patients treated with a dose of 0.6 mg/kg within 3 to 6 hours. At the prebolus TCD examination, the MCA was occluded in 30 patients (75%), the ICA was occluded in 11 patients (28%), and the basilar artery was occluded in 3 patients (8%). Multiple occlusions that involved the ICA and MCA were found in 7 (18%) patients. Four patients had no windows of insonation (10%). Only 1 patient (2.5%) had a normal TCD examination before the tPA bolus.

Recanalization during continuous monitoring with TCD was found at the mean time of 251±171 minutes after stroke onset (maximum observation time 360 minutes): there was complete recanalization in 12 (30%) and partial recanalization in 16 (40%) patients. On TCD, 7 patients (or 25%) recanalized within the first 30 minutes, 14 (50%) recanalized within 31 to 60 minutes, 3 (11%) recanalized within 61 to 120 minutes, and 4 (14%) recanalized after the first 2 hours after tPA bolus administration (Figure 2).

The timing of arterial recanalization after stroke onset detected with TCD correlated with early improvement in the NIHSS scores within the next hour after recanalization (Figure 3). The best curve fit was a polynomial curve of the third order with $r^2=0.429$ and $P<0.01$. A similar correlation was seen at 24 hours. The best curve fit was a polynomial curve of the third order with $r^2=0.272$ and $P<0.01$.

Early complete recovery was seen in patients who received a tPA bolus within 210 minutes from stroke onset and achieved recanalization within 300 minutes after symptom onset. No change in the severity of neurological deficit was noted in 13 patients (32%), and worsening by >4 NIHSS points occurred in 6 (15%) patients in this study.

Twenty-two patients were available for follow-up (1.5±1.2 months). Eight patients died within the first 3 months after therapy (overall mortality rate of 20%). Six patients had modified Rankin Scores 0 to 1 (5 had complete recanalization and 1 had partial recanalization). Eight patients had Rankin Scores of 3 to 5 (none had complete recanalization, 6 had partial, and 2 had no recanalization; $\chi^2=10.5, 2 df, P=0.006$).

Recanalization occurred after the first 180 minutes after stroke onset in 9 patients (range 180 to 300 minutes), and 3 of these (or 33%) patients had excellent clinical recovery, reaching Rankin Score 0 to 1 by 1 to 3 months. Two patients who completely recanalized and improved dramatically during tPA infusion did not sustain the improvement on a long-term basis because of a subsequent reocclusion detected with follow-up TCD. No patients reached Rankin Score 0 to 1 at follow-up if an occlusion persisted on TCD for >300 minutes.

Discussion
The present study shows that the timing of arterial recanalization that occurs either spontaneously or as a result of tPA therapy as determined with TCD correlates with clinical recovery from stroke and demonstrates a 300-minute window to achieve early complete recovery. These data parallel findings in animal models of cerebral ischemia and confirm the relevance of these models in the prediction of response to reperfusion therapy.

In experiments in a primate model, Jones et al found that if CBF falls to <10 mL·100 g⁻¹·min⁻¹, brain function may recover after up to 2 hours of transient MCA occlusion. The
Figure 1. Top, No recanalization. A 60-year-old woman with right MCA stroke (pretreatment NIHSS score 14) had an M2 MCA occlusion on TCD with minimal antegrade flow signal (above baseline). tPA was initiated at 162 minutes after stroke onset. No significant change was noted on TCD, and the patient’s NIHSS score was 12 at the end of tPA infusion and at 24 hours. Rankin Score was 4 at 3-month follow-up.

Middle, Partial recanalization. A 71-year-old woman with left MCA stroke (pretreatment NIHSS score 21) had an M1 MCA occlusion on TCD with minimal antegrade flow signal (above baseline). tPA was initiated at 170 minutes after stroke onset. TCD showed partial flow recovery (dampened signal), and the patient’s NIHSS score was 14 at the end of tPA infusion and at 24 hours. Rankin Score was 3 at 2-month follow-up.

Bottom, Complete recanalization. A 75-year-old man with basilar artery (BA) stroke, locked-in syndrome, and pretreatment NIHSS score of 33 had a proximal BA occlusion on TCD with no detectable flow signal. tPA was initiated at 165 minutes after stroke onset. TCD showed restoration of a normal pulsatile flow signal throughout the BA stem at 20 minutes after tPA bolus. His neurological status started to improve within minutes of detected reperfusion, and his NIHSS score was 6 at the end of tPA infusion and at 24 hours. His follow-up Rankin score was 5 at 1-month follow-up (the patient required chronic mechanical ventilation due to obstructive pulmonary disease).
The correlation between CBF impairment and infarction over time was described as an infarction threshold. This line is a polynomial curve of the third order. In our study of humans treated with tPA, a similar type of correlation was seen between the timing of arterial recanalization determined with TCD and early clinical recovery from stroke.

Our study showed a 300-minute window to achieve arterial recanalization and complete early recovery after treatment with tPA. The fact that some patients with arterial occlusion and fixed neurological deficit recovered after late recanalization beyond the 3-hour time window approved for intravenous tPA deserves further scrutiny. It is important to remember that peak recanalization after the initiation of tPA therapy in the coronary circulation occurs ~90 minutes after drug administration. In the present study, recanalization after tPA occurred 75% of the time within 60 minutes of the start of the tPA infusion, and no patient completely recovered if the treatment began after 210 minutes from stroke onset. Therefore, to achieve recanalization by 300 minutes, intravenous tPA therapy must be started by the end of the traditional 3-hour time window in most patients.

Our data also indicate that the traditional window for intravenous tPA might be extended in some patients up to 4.5 hours to achieve early recovery, although our data cannot be extrapolated to functional recovery at 3 months due to limited follow-up time and our relatively small patient cohort. Nevertheless, the time window available for selected patients to recover completely after recanalization may be somewhat longer than predicted from animal models. Several factors, including heterogeneity of stroke pathogenic mechanisms, estimation of the time of onset, location of arterial occlusion, clot propagation, and collateralization of flow, may play a role in modifying this time window from patient to patient.

Although flow velocities determined by routine TCD cannot be used to measure CBF, our study showed that a complete or partial recovery of end-diastolic flow correlates with clinical improvement. In our previous studies in patients with acute ischemic stroke, we compared TCD findings with brain perfusion scans obtained with single-photon emission computed tomography with hexapropyleneamine-oxime as a tracer. A normal TCD examination correlated with normal or increased tracer uptake, whereas persistent occlusion on TCD was seen with minimal or absent tracer uptake. Normal and elevated end-diastolic velocities on TCD imply low resistance to flow in the cerebral vasculature and predict good distal vessel opacification on angiography and the resumption of flow in brain parenchyma. These findings are similar to Thrombolysis in Myocardial Infarction flow grade III, which is associated with successful coronary thrombolysis. With good correlation between TCD and other neuroimaging methods, recanalization on TCD qualitatively predicts CBF improvement in stroke patients, thus explaining the findings in the present study.

Among patients who had no change in the severity of neurological deficit or who worsened by ≥4 NIHSS points (47%), none had complete recanalization within 300 minutes, implying that persistent occlusion on TCD may be an indicator of severe ischemia. These patients may represent a target group for combined intravenous/intra-arterial thrombolysis in future trials.

The cause of worsening or lack of improvement in patients with recanalization may be explained by a number of mechanisms, although our study was not designed to answer this question. Two patients who worsened after recanalization within the first 180 minutes may have experienced reperfusion-induced injury. Three patients who reperfused after 300 minutes had hemorrhagic transformation.

The correlation between TCD findings and clinical recovery becomes less significant at 24 hours ($r^2=0.429$ decreases to $r^2=0.272$), implying that a more linear correlation may exist with late recovery. We found a correlation between clinical outcome as measured with Rankin Score and recanalization. However, the sigmoidal association between recanalization time and recovery was not seen with more delayed clinical assessment. For instance, reocclusion occurred in 2 patients in this study. Our prospective studies have shown that deterioration after improvement may be attributable to persistent arterial occlusion and reocclusion, which can occur in up to 15% of consecutive patients.

In conclusion, our study shows a correlation between arterial recanalization on TCD within 300 minutes of stroke.
onset and early complete clinical recovery in tPA-treated patients. These data parallel findings in animal models and confirm the relevance of these models in the prediction of response to reperfusion therapy.

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