Ischemic Stunning of the Brain
Early Recanalization Without Immediate Clinical Improvement
in Acute Ischemic Stroke
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Background and Purpose—Early arterial recanalization (ER) with intravenous tissue plasminogen activator (tPA) can lead to dramatic clinical recovery, whereas some patients do not experience immediate clinical improvement.

Methods—Consecutive patients received tPA 0.9 mg/kg IV within 3 hours after symptom onset. All had M1 or M2 middle cerebral artery occlusions on pretreatment transcranial Doppler. Patients were continuously monitored for 2 hours after bolus. ER was defined as the Thrombolysis in Brain Ischemia intracranial flow increase by ≥1 grade. Stroke severity (National Institutes of Health Stroke Scale [NIHSS]) and recovery (modified Rankin Scale) were assessed independently of transcranial Doppler.

Results—One hundred twenty patients (mean age, 68±15 years; 63 women; median NIHSS, 17; range, 5 to 29; 90% with ≥10 points) received tPA at a median of 120 minutes, 50% within the first 2 hours. ER was observed in 73 patients (32 complete, 41 partial). No immediate clinical changes (n=23) or worsening (by 1 to 6 points on NIHSS, n=4) was observed in 37% of ERs (nonresponders). Complete ER was found in 8 of these 27 patients. At 24 hours, 22 of 27 patients (82%) had persisting deficits of NIHSS ≥10 points, yet 37% of these nonresponders (10 of 27) still achieved good outcome (modified Rankin score, 0 to 2) at 3 months. Among nonresponders with good outcome, 100% had detectable residual flow signals, and 70% had compensatory flow diversion on prebolus transcranial Doppler compared with 65% and 29% of nonresponders with poor outcome (P<0.05). Compared with responders (n=46), nonresponders had similar prebolus median NIHSS of 16 to 17 points, bolus times of 120 to 132 minutes, median speed of thrombolysis (30 minutes), and ER times of 190 to 193 minutes after onset. Reocclusion occurred in 3 of 4 patients with clinical worsening, 30% of other nonresponders, and 22% of responders. Symptomatic hemorrhage rate was 4% in both groups. At 3 months, mortality was 33% in nonresponders compared with 9% in responders (P=0.001).

Conclusions—After successful arterial ER with tPA therapy, lack of early clinical changes or worsening is relatively common (37%) and appears to be independent of time to tPA bolus or reperfusion. However, with tPA alone, at least one third of these nonresponders still achieved good outcomes at 3 months, suggesting the possibility of a “stunned brain” syndrome with delayed recovery. Several different mechanisms may potentially account for this phenomenon.

Key Words: recovery of function ■ stroke ■ thrombolysis ■ tissue plasminogen activator ■ ultrasonography
3 months, thus supporting the concept of brain stunning. We also sought to determine whether other factors such as reocclusion or symptomatic hemorrhage may play a role in lack of early response to recanalization.

Subjects and Methods
We studied consecutive patients with M1 or M2 middle cerebral artery (MCA) occlusion on pretreatment TCD according to previously validated criteria who were treated with standard intravenous tPA. tPA was given in a dose of 0.9 mg/kg, maximum of 90 mg (10% bolus, 90% continuous infusion), within the first 3 hours after symptom onset according to the NINDS-rt-PA study criteria.1 Treating physicians determined patient eligibility for tPA therapy regardless of prebolus TCD findings and did not participate in outcome assessment.

Patients were included in the analysis if they had an M1 or M2 MCA occlusion on pretreatment TCD according to previously published criteria.1 Our TCD criteria for proximal MCA occlusions have 91% sensitivity and 98% specificity compared with angioigraphy.12 Before tPA bolus, an experienced sonographer identified residual flow signals through the temporal bone at the presumed thrombus location in the MCA using the Thrombolysis in Brain Ischemia (TIBI) flow grading system.13 Flow diversion signs to a neighboring artery indicating transcortical collateralization of flow were noted when present.14 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 in the M1 or proximal M2 MCA segment was selected, and TCD monitoring for 2 hours after tPA bolus was performed according a protocol approved by the University of Texas Committee for Protection of Human Subjects.

Arterial recanalization was determined at bedside as complete, partial, or none through the use of previously validated TCD criteria that predict angiographic flow recovery grades.15 Briefly, complete recanalization was diagnosed when a normal waveform or a low-resistance stenotic signal appeared at selected depths of insonation suggesting low resistance of the distal circulatory bed and its rapid flow opacification.11,13 The beginning of recanalization was diagnosed if the flow signals improved in amplitude and intensity.1 Partial recanalization was diagnosed when signals improved by at least 1 TIBI flow grade and if abnormal signals (high-resistance damped signals or flattened systolic phase with a “blunted” waveform) were still seen in the MCA. Patients with complete or partial recanalization within 2 hours after tPA bolus had ER. No change in the abnormal flow signals during TCD monitoring was regarded as no ER. Our TCD criteria to predict the Thrombolysis in Myocardial Infarction (TIMI) grade III recanalization on angiography had 91% sensitivity and 93% specificity.11 Speed of thrombolysis was measured in minutes from the start of flow improvement during TCD monitoring to the arrival time of the highest TIBI flow grade using previously described criteria.7 Recanalization was diagnosed when TCD showed flow worsening by ≥1 TIBI flow grade15 and there was no intracranial hemorrhage on repeated CT or MRI. Flow changes were determined from the real-time TCD display by an experienced sonographer who was present at bedside for the entire 2 hours after tPA bolus and was not involved in the assessment of clinical outcomes.

The Alberta Stroke Program Early Computerized Tomography Scores (ASPECTS)16 were determined from pretreatment CT scans by a stroke neurologist unaware of the purposes of the study. ASPECTS scores represent an overall assessment of 10 MCA regions with good interobserver reproducibility for quantifying early ischemic changes.16 CT was repeated urgently in all patients with signs of neurological worsening regardless of TCD findings. CT scan was repeated as soon as feasible if patients had persistent neurological deficits despite complete recanalization or reocclusion on TCD as a result of clinical suspicion of possible hemorrhagic transformation. CT scans were interpreted by a neuroradiologist who was unaware of the purposes of this study. Symptomatic hemorrhage was diagnosed by treating physicians when repeated brain imaging showed intracranial hemorrhage associated with clinical worsening by ≥2 NIHSS points.

Clinical stroke severity was assessed with NIHSS scores, with improvement defined following the pivotal trial of intravenous tPA therapy:1 NIHSS scores were obtained within the first 2 hours after tPA bolus and at 24 hours after symptom onset by treating stroke neurologists who were not blinded to TCD findings of recanalization, reocclusion, or persisting occlusion when relevant to clinical decision making but who were unaware of the purposes of the study. Nonresponders were identified as those patients with ER who had no change or decrease in NIHSS score by ≥4 points at 2 and 24 hours after stroke onset. Responders had improvement by ≥4 NIHSS points within the first 2 hours (immediate) and 24 hours (early) after stroke onset. Modified Rankin Scale (mRS) scores were obtained at 3 months by a neurologist who was unaware of acute TCD and NIHSS findings and the purposes of this study. A favorable outcome was defined as mRS scores of 0 to 1 and good outcome as mRS scores of 0 to 2 at 3 months.17 Statistical analysis included descriptive statistics, χ² tests for dichotomous variables, and Student’s t tests for continuous variables. Mann-Whitney nonparametric test was used for unequally distributed variables.

Results
We studied a total of 120 patients with MCA occlusions on prebolus TCD. Their mean age was 68±15 years; 63 were women. Before tPA bolus, their median NIHSS score was 17 (range, 5 to 29 points), and 90% of all patients had scores ≥10 points. Patients received a tPA bolus at a median of 120 minutes after symptom onset; 50% of them were treated within the first 2 hours.

ER was observed in 73 patients (61%); 32 patients (27%) had complete recanalization within 2 hours after tPA bolus, and 41 patients (34%) had partial recanalization (Figure 1). No clinical changes (n=23) or worsening by 1 to 6 points on the NIHSS (n=4) was observed in 27 of 73 patients with ER (37%). Among nonresponders, 8 had complete ER, and 19 had partial ER. At 24 hours, severe neurological deficits (NIHSS ≥10 points) were found in 22 of 27 nonresponders (82%). Despite a lack of improvement within the first 24 hours, 7 of 27 nonresponders (26%) achieved favorable outcome (mRS, 0 to 1); an additional 3 nonresponders (11%) achieved mRS 2 at 3 months (Figure 2).

Pretreatment Findings in Nonresponders
Prebolus NIHSS (median, 16 to 16; range, 6 to 29 points) and ASPECTS score (mean, 8 to 9; SD, 3) were similar in nonresponders who recovered at 3 months compared with those who did not (Student’s t test, P=NS). All patients who
recovered at 3 months (n=10) had detectable (TIBI, 1 to 3) residual flow signals on TCD before tPA bolus, whereas 6 of 17 nonresponders with poor outcome had prebolus TIBI flow grade 0 (Fischer’s exact test, \( P=0.042 \)). Among those who recovered at 3 months, 7 of 10 (70%) had signs of compensatory flow diversion on prebolus TCD compared with 5 of 17 nonresponders (29%) who failed to recover at 3 months (Fischer’s exact test, \( P=0.049 \)).

**Additional Data on Nonresponders and Responders to Early Recanalization**

Both nonresponders (n=27) and responders (n=46) had similar pretreatment median NIHSS scores of 16 to 17 points, bolus times at 120 to 132 minutes after symptom onset, median speed of thrombolysis of 30 minutes, and median ER times of 190 to 193 minutes after onset (Mann-Whitney test, \( P=NS \)). Complete ER occurred in 8 of 27 nonresponders (30%) and 24 of 46 responders (52%). Repeated CT within 120 minutes of tPA bolus showed progression of early ischemic changes or edema in all 8 nonresponders with complete ER. These changes included extension of sulcal effacement and loss of gray-white matter differentiation. No formation of frank hypointensity or hypodensity of brain tissues in the involved arterial territory was noted. CT was not repeated in responders.

Partial ER occurred in 19 of 27 nonresponders (70%) and in 22 of 46 responders (48%). Reocclusion occurred in 3 of 4 ER patients with clinical worsening (75%), in 7 of 23 other nonresponders (30%), and in 10 of 46 responders (22%) (\( \chi^2, 5.40, df=2, P=0.067 \)).

At 24 hours, severe neurological deficits (NIHSS score \( >10 \) points) were found in 22 of 27 nonresponders (82%) compared with 11 of 46 responders (24%) (\( \chi^2, P<0.001 \)). Favorable and good outcomes in patient subgroups are shown in Figure 3. Symptomatic intracerebral hemorrhage rate was 4% in both the nonresponder and responder groups (\( P=NS \)). Mortality was 4 of 46 responders with ER (9%), 9 of 27 nonresponders (33%), and 18 of 47 (38%) among those who did not have any ER (\( \chi^2, P=0.001 \)).

**Discussion**

In our study, lack of clinical improvement was observed in one third of patients with ER, and four-fifths of these non-responders had persisting severe neurological deficits at 24 hours. This lack of early clinical response to complete or partial recanalization appears to be independent of time from stroke symptom onset to tPA bolus or reperfusion. However, at least one third of these nonresponders achieved good outcomes by 3 months, suggesting the possibility of stunned brain with delayed recovery.

Among nonresponders, all patients who recovered at 3 months had detectable residual flow signals on admission, which correlates with a greater likelihood of response to thrombolysis compared with absent flow signals. Furthermore, most of these patients also had signs of compensatory flow diversion on TCD that point to transcortical collateralization of flow despite the presence of severe ischemia. However, baseline CT and NIHSS scores were similar among nonresponders, and other mechanisms and predictive variables need to be established to identify those patients with ischemic stunning of the brain.

Most nonresponders experienced partial recanalization, but because of the presence of high-resistance waveforms, this finding actually indicates persisting distal arterial occlusion or possibly a no-reflow phenomenon. However, a quarter of patients with complete low-recanalization on TCD, or TIMI grade III flow equivalent, also lacked early clinical response, suggesting that mechanisms other than persisting occlusion or no reflow may account for the failure to show clinical recovery despite ER.

The rate of symptomatic hemorrhage was similarly low in both responders and nonresponders. Arterial reocclusion was more common in nonresponders (41%) and was detected in 3 of 4 patients with clinical worsening. However, reocclusion alone may not explain all cases when early clinical improvement was lacking. We therefore hypothesize that reperfusion injury may...
play a role in some patients with complete recanalization, thereby precluding early clinical improvement. No clinical improvement after complete recanalization may also imply that reperfusion may have occurred too late to salvage brain tissue. In our study, the timing of recanalization and speed of thrombolysis were similar in both responders and nonresponders. Thus, other tests measuring tissue metabolism may be necessary to separate reperfusion injury from late and ineffective recanalization.

In our study, CT was repeated when clinically indicated in nonresponders and showed progression of early ischemic changes without formation of frank hypodensity. This finding suggests the persistence of potentially reversible ischemic injury to the brain because these early ischemic changes do not always predict a lack of response to thrombolysis and poor stroke outcome. However, because CT showed progression of ischemic changes in all nonresponders with complete proximal recanalization, CT may not be helpful in identifying those who will recover at 3 months despite lacking initial clinical improvement.

In summary, we hypothesize that several potential mechanisms may predispose brain tissue to ischemic stunning, including edema formation without hypotension, no-reflow phenomenon with or without persisting distal occlusion, proximal reocclusion, and possibly additional reperfusion injury that may be targeted by different combination therapies with thrombolysis in the future. Delayed recovery of brain function may still occur in these patients and may be mediated by a variety of mechanisms, including relatively late but still nutritive recanalization, resolving brain edema, delayed improvement in microcirculation in ischemic tissues, and neuronal reorganization.

Our study has limitations because MRI, diffusion/perfusion, or spectroscopy studies were not obtained acutely. MRI may also identify cerebral lesions developing late after thrombolysis. Furthermore, TCD can detect recanalization only in the M1 or proximal M2 MCA segments. Although our criteria for occlusion and recanalization were successfully implemented at other centers, TCD cannot be used to quantify cerebral blood flow in the ischemic area or collaterals. Because TCD indirectly shows parenchymal reperfusion, our results should be used for hypothesis generation, not to prove suggested mechanisms of how the brain does not respond to ER.

In conclusion, clinical responses to ER appear more heterogeneous that can be expected from animal models of cerebral ischemia. The relative contribution of several potential mechanisms should be a focus for a prospective study incorporating a variety of structural and functional neuroimaging methods to assess brain circulation and tissue responses to ER.

Acknowledgments

Dr Alexandrov is supported by NIH 1 K23 NS02229–01 Career Development Award. Dr Labiche is supported by NIH Fellowship Training Grant 1-T32-NS07412-01A1 awarded to the Stroke Program, University of Texas–Houston Medical School. We are grateful for the efficient technical support provided by Spencer Technologies, DWL, and Multigon Industries during the project.

References

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Stroke. 2004;35:449-452; originally published online January 15, 2004; doi: 10.1161/01.STR.0000113737.58014.B4

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