Transcranial Doppler Ultrasound Criteria for Recanalization After Thrombolysis for Middle Cerebral Artery Stroke

W. Scott Burgin, MD; Marc Malkoff, MD; Robert A. Felberg, MD; Andrew M. Demchuk, MD, FRCP; Ioannis Christou, MD; James C. Grotta, MD; Andrei V. Alexandrov, MD

Background and Purpose—Transcranial Doppler (TCD) can demonstrate arterial occlusion and subsequent recanalization in acute ischemic stroke patients treated with intravenous tissue plasminogen activator (tPA). Limited data exist to assess the accuracy of recanalization by TCD criteria.

Methods—In patients with acute middle cerebral artery (MCA) occlusion treated with intravenous tPA, we compared posttreatment TCD with angiography (digital subtraction or magnetic resonance). On TCD, complete occlusion was defined by absent or minimal signals, partial occlusion by blunted or dampened signals, and recanalization by normal or stenotic signals. Angiography was evaluated with the Thrombolysis In Myocardial Ischemia (TIMI) grading scale.

Results—Twenty-five patients were studied (age 61 ± 18 years, 16 men and 9 women). TCD was performed at 12 ± 16 hours and angiography at 41 ± 57 hours after stroke onset, with 52% of studies performed within 3 hours of each other. Recanalization on TCD had the following accuracy parameters compared with angiography: sensitivity 91%, specificity 93%, positive predictive value (PPV) 91%, and negative predictive value (NPV) 93%. To predict partial occlusion (TIMI grade II), TCD had sensitivity of 100%, specificity of 76%, PPV of 44%, and NPV of 100%. TCD predicted the presence of complete occlusion on angiography (TIMI grade 0 or I) with sensitivity of 50%, specificity of 100%, PPV of 100%, and NPV of 75%. TCD flow signals correlated with angiographic patency ($\chi^2 = 24.2, P < 0.001$).

Conclusions—Complete MCA recanalization on TCD accurately predicts angiographic findings. Although a return to normal flow dynamics on TCD was associated with complete angiographic resumption of flow, partial signal improvement on TCD corresponded with persistent occlusion on angiography. (Stroke. 2000;31:1128-1132.)

Key Words: angiography • recanalization • thrombolysis • ultrasonography

The advantages of transcranial Doppler (TCD) evaluation of cerebral vessels include the fact that it is a low-cost, noninvasive bedside assessment. However, in the context of acute stroke, digital subtraction angiography (DSA), magnetic resonance angiography (MRA), and computed tomography angiography (CTA) are more commonly used. These methods are more expensive and more time consuming and do not provide continuous blood flow monitoring.

As experience with cerebral thrombolysis increases, there is mounting evidence that improved outcomes are associated with recanalization and improved brain perfusion.1–4 With intra-arterial thrombolysis,2 recanalization can be monitored by the use of concurrent angiography, but recanalization is not routinely evaluated after intravenous thrombolysis.3,5 Information about recanalization may help to determine patient prognosis and direct further management.6 TCD offers an inexpensive and continuous means of monitoring vessel patency.

TCD criteria for identifying intracranial occlusion and recanalization have been described previously.5–9 Accuracy parameters for TCD assessment of middle cerebral artery (MCA) occlusion were established previously.7,8,10 However, the accuracy of TCD in identifying recanalization after thrombolysis remains unknown. The goal of the present study was to compare TCD findings after intravenous thrombolysis with subsequent angiography to determine accuracy parameters for identifying MCA recanalization.

Subjects and Methods

We evaluated patients who received intravenous tissue plasminogen activator (tPA) from November 1996 through July 1999 and who had baseline and follow-up TCD according to a prospective protocol designed to identify the presence of an MCA occlusion and subsequent recanalization. Data on subsequent angiography were collected as part of ongoing quality-assurance evaluation. For TCD, a single-channel 2-MHz machine was used (Multigon 500M, DWL Multi-Dop-T, Marc 500 headframe, Spencer Technologies, Inc). tPA was
given intravenously within the first 3 hours after stroke onset at a standard Food and Drug Administration–approved dose of 0.9 mg/kg, to a maximum of 90 mg, or at a dose of 0.6 mg/kg, to a maximum dose of 60 mg, started between 3 and 6 hours, as part of an experimental treatment protocol approved by the University of Texas Committee for the Protection of Human Subjects.

Complete occlusion was diagnosed by TCD when absent or minimal signals (Figure 1) were found at 1 or more MCA depths (>40 to 65 mm) and accompanied by flow diversion to the anterior (ACA) or posterior (PCA) cerebral arteries (mean flow velocity ACA > contralateral MCA or PCA > contralateral MCA). We defined a minimal flow signal as a short peak systolic spike with no end-diastolic flow. In this case, either terminal internal carotid artery or PCA flow signals had to be identified from the ipsilateral temporal window to exclude suboptimal ultrasound penetration through the bone. Absent or minimal flow signals were confirmed by insonation from the contralateral temporal window.

Partial occlusion: Delayed systolic flow acceleration and a MFV < 30 cm/s

Dampened flow signal: Pulsatile signal with normal acceleration, MFV decrease of >30% compared to normal side, and positive end-diastolic flow

Complete recanalization: Low resistance flow with a significant focal velocity increase; may also be seen in hyperemia

Normal flow signal: Low resistance flow with no significant difference in velocities compared to the normal side

We diagnosed partial occlusion if blunted or dampened signals (Figure 1) were found at >1 MCA depth (40 to 65 mm) with flow diversion signs to the ACA or PCA. A blunted flow signal was identified when delayed (>0.2 seconds) systolic flow acceleration was present with a pulsatility index (PI) < 1.2 (PI = (peak systolic velocity − end-diastolic velocity)/mean flow velocity). This PI range indicates low-resistance flow diversion in a branching vessel (ACA) or a residual positive end-diastolic flow at the site of occlusion (MCA). A dampened flow signal was identified when normal systolic flow acceleration was present in the pulsatile MCA waveform with mean flow velocity ≤ 70% of the contralateral MCA and positive end-diastolic flow with variable PI values.

Complete recanalization was diagnosed if low-resistance stenotic or normal signals (Figure 1) were found throughout the MCA stem (depths 40 to 65 mm) with no other signs of persisting distal occlusion (i.e., dampened distal signal or flow diversion). In cases with residual stenosis on TCD, low-resistance flow indicates patency and perfusion of the distal vasculature (see criteria below).
Angiographic studies after thrombolysis included DSA, MRA, or CTA. DSA was the standard for comparison regardless of the time it was performed. If only MRA or CTA was obtained, the test performed closest to treatment was used as the best available standard. MCA flow was graded on the angiograms according to the Thrombolysis In Myocardial Infarction (TIMI) criteria.\textsuperscript{12} The application of these criteria to cerebral vessels has been reported previously.\textsuperscript{2} Complete occlusion (TIMI grade 0 or I) was defined as no or minimal perfusion with no opacification of the distal vessels on DSA and no reconstitution of distal flow on MRA or CTA (Figure 1).

Partial occlusion (TIMI grade II) was defined as an obstruction that resulted in a delayed opacification of the distal vessels on DSA and appearance of distal slow-flow signals of decreased intensity on MRA or CTA. Complete recanalization (TIMI grade III) was defined as unimpeded perfusion of the distal vasculature (Figure 1), regardless of whether a residual stenosis or a focal flow gap was present (Figures 2 and 3).

Accuracy parameters included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Sensitivity represents the proportion of patients with a positive TCD who

This is an example of distal MCA flow improvement from partial occlusion (blunted signal, left spectrum) to complete recanalization (right spectrum) in the presence of a proximal ICA occlusion. Following TPA therapy, there is delayed systolic flow acceleration in the MCA because it is supplied via anterior cross-filling (angiogram, arrows). The presence of a low resistance flow throughout the MCA stem (40-65 mm) and an improvement in MFV of 15 to 30 cm/sec indicate MCA patency.
Correlation of TCD Findings With Angiography

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<td>TCD</td>
<td>(TIMI 0-I)</td>
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<td>Complete occlusion</td>
<td>5</td>
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<td>Partial occlusion</td>
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<td>Complete recanalization</td>
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also had positive results on the test considered the standard of accuracy, in this case angiographic TIMI grades. When the same comparison is used, specificity is the proportion with negative results. Predictive values indicate the probability of disease (PPV) or absence of disease (NPV) based on the results of the test. \( \chi^2 \) Analysis was used to correlate TCD waveform findings with vessel patency at angiography.

**Results**

Emergent TCD identified 25 patients with MCA occlusion who had the following characteristics: age 61±18 years (range 31 to 93 years); 16 men, 9 women; and 13 left MCA occlusions and 12 right MCA occlusions. Of these, 20 patients were treated with a standard tPA dose within the first 3 hours after stroke and 5 with a lower dose between 3 and 6 hours. All patients were evaluated by repeat TCD and subsequent angiography: 12 patients had DSA, 11 had MRA, and 2 had CTA. Repeat TCD was performed at 12±16 hours (range 2 to 48 hours) and angiography at 41±57 hours (range 3 to 264 hours) after stroke onset with an average delay of 29±52 hours (range 0 to 240 hours) between the studies. Fifty-two percent of angiographic studies were performed within 3 hours after TCD, 20% within 3 to 24 hours, and 28% after 24 hours.

At repeat TCD after tPA infusion, MCA occlusion was found in 5 (20%) of 25 patients, partial occlusion in 9 (36%) of 25, and complete recanalization in 11 (44%) of 25. In comparison, subsequent angiography revealed complete occlusion in 10 (40%) of 25, partial occlusion in 4 (16%) of 25, and complete recanalization in 11 (44%) of 25 patients.

Complete recanalization on TCD predicted TIMI grade III flow on angiography with the following accuracy parameters: sensitivity 91%, specificity 93%, PPV 91%, and NPV 93%. To predict partial occlusion (TIMI grade II), TCD had sensitivity of 100%, specificity of 76%, PPV of 44%, and NPV of 100%. TCD predicted complete occlusion on angiography (TIMI grade 0 or I) with sensitivity of 50%, specificity of 100%, PPV of 100%, and NPV of 75%. TCD criteria for partial and complete occlusion, the inverse of recanalization, predicted partial occlusion at angiography (TIMI grade 0 to II) with accuracy parameters as for TIMI grade III. The TCD waveforms correlated with vessel patency at angiography (\( \chi^2 = 24.2, P<0.001 \); Table). Typical patterns of complete occlusion, partial occlusion, and complete recanalization are provided (Figures 1 through 3).

**Discussion**

Our study has shown the sensitivity and specificity of TCD in predicting MCA recanalization after tPA treatment. We also showed that abnormal MCA waveforms correlate with angiographic presence of occlusion. TCD evidence for partial occlusion (blunted or dampened flow signals) should be interpreted as a predictor of a persisting MCA occlusion at angiography.

Previous studies have shown that TCD can determine the presence of MCA occlusion and that it can be used to monitor recanalization, but the number of angiographic studies performed was insufficient to determine accuracy parameters for recanalization. In the present study, complete MCA recanalization on TCD was present if a low-resistance flow was found with ≥70% velocity compared with the contralateral MCA. Although TCD may not reliably differentiate residual stenosis or hyperemia after reperfusion, our criteria allow accurate prediction of TIMI grade III, because low-resistance flow, regardless of velocity increase, predicts rapid opacification of distal vessels. Repeat TCD examination may be required to differentiate hyperemia (decreasing velocities) from residual stenosis (a persistent focal velocity increase).

Information obtained from TCD regarding MCA recanalization has clinical importance. Recovery after intravenous tPA is associated with recanalization and resumption of flow. Previous studies showed that recanalization corresponds to clinical improvement seen in some patients during or shortly after intravenous tPA infusion. The question remains as to what to do with patients who do not experience early recovery. Whether the continued neurological deficit is due to persistent occlusion has important clinical implications. The lack of clinical recovery or worsening of neurological deficit was associated with persistent occlusion or recollusion in 50% of patients who received intravenous tPA at our center. These patients would be potential candidates for intra-arterial therapy used in a bridging protocol.

The Intra-Arterial Prourokinase for Acute Ischemic Stroke Trial (PROACT II) showed a benefit in acute ischemic stroke patients who received intra-arterial thrombolysis. However, of the 474 patients who received diagnostic angiograms, only 180 were eligible for treatment on the basis of PROACT II criteria. Bedside diagnosis of MCA flow status can minimize the number of diagnostic angiograms required to find a treatable MCA occlusion.

Our data show that TCD can accurately predict complete recanalization (PPV 91%) and complete occlusion (PPV 100%). Findings of partial occlusion on TCD were relatively sensitive but not highly specific compared with angiography, with partial occlusion representing complete angiographic occlusion in 44% of cases but rarely representing complete recanalization. Therefore, tPA nonresponders with TCD findings of complete or partial occlusion are likely to have persisting occlusion on angiography and thus may be potential candidates for further intervention. Conversely, the remaining 27% of patients treated with intravenous tPA who have persistent neurological deficit despite recanalization might be spared the risk and expense of an angiogram that is unlikely to reveal a treatable thrombus.

Our study has limitations. Factors that affect TCD accuracy include the absence of temporal windows, the unavailability of ultrasound contrast materials in the United States, and time delays between TCD and angiography.
delay could have been evaluated if follow-up TCD had been performed immediately after subsequent angiography. However, this is not a part of a standard clinical protocol for TCD at our center. The delay may slightly overestimate the rate of recanalization, because some patients may have experienced delayed recanalization during the first 3 days. However, some patients may have also experienced reocclusion or had MCA clot propagation, thus affecting correlation for partial or complete occlusion. DSA was not performed in all patients, and a substantial portion of patients in our study had MRA. This imaging modality is inferior to DSA, particularly for visualization of slow flow or severe stenosis. Nevertheless, it is often used in clinical practice, and TCD performance is judged against MRA. Also, patients included in this study were selected on the basis of pre-tPA TCD evidence of MCA occlusion. Reports by others, as well as our previous observations, indicate good accuracy of TCD as a screening tool in this setting, and the accuracy parameters after tPA infusion continue to confirm the accuracy of TCD. Although the results of the present study cannot be applied to arteries other than the MCA, the predictive value of abnormal MCA waveforms suggests the need for further evaluation of waveforms throughout the circle of Willis.

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References

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