Real-time Validation of Transcranial Doppler Criteria in Assessing Recanalization During Intra-arterial Procedures for Acute Ischemic Stroke
An International, Multicenter Study

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Background and Purpose—We sought to evaluate the diagnostic accuracy of ultrasound criteria for recanalization during real-time transcranial Doppler monitoring of intra-arterial reperfusion procedures in acute ischemic stroke patients in an international, multicenter study.

Methods—Consecutive acute ischemic stroke patients with proximal intracranial occlusions underwent intra-arterial reperfusion procedures with simultaneous real-time transcranial Doppler monitoring at 3 tertiary-care stroke centers. Residual flow signals at the site of angiographically confirmed occlusions were monitored at a constant transtemporal insonation angle using a standard head-frame. Recanalization was assessed simultaneously by digital subtraction angiography and ultrasound using thrombolysis in myocardial infarction and thrombolysis in brain ischemia (TIBI) criteria, respectively. Independent readers blinded to digital subtraction angiography performed validation of TIBI flow grades. The interrater reliability for assessment of TIBI grades was investigated.

Results—We evaluated time-linked real-time digital subtraction angiography transcranial Doppler images from 96 diagnostic digital subtraction angiography runs during intra-arterial reperfusion procedures in 62 acute ischemic stroke patients (mean age, 59±17 years; 58% men; median baseline National Institutes of Health Stroke Scale score, 18 [interquartile range 12–21]; median time from symptom onset to intra-arterial procedure initiation, 240 minutes [interquartile range 163–308]). The interrater reliability for evaluation of TIBI grades and assessment of recanalization was good (Cohen κ: 0.838 and 0.874, respectively; P<0.001). Compared with angiography, transcranial Doppler had the following accuracy parameters for detection of complete recanalization (TIBI 4 and 5 versus thrombolysis in myocardial infarction 3, flow grades): sensitivity, 88% (95% confidence interval, 72%–96%); specificity, 89% (79%–95%); positive predictive value, 81% (65%–91%); negative predictive value, 93% (84%–98%); and overall accuracy 89% (80%–94%).

Conclusions—At laboratories with high-interrater reliability, TIBI criteria can accurately predict brain recanalization in real time as compared with thrombolysis in myocardial infarction angiographic scores. (Stroke. 2013;44:394-400.)

Key Words: angiography ■ recanalization ■ stroke ■ transcranial Doppler ■ ultrasonics

Early restoration of blood flow is strongly associated with improved functional outcomes and reduced mortality in acute ischemic stroke (AIS) patients treated with intravenous thrombolysis (IVT).1–3 Transcranial Doppler (TCD) is a bedside, noninvasive tool for the real-time monitoring of reperfusion therapies by quantifying residual flow grades at the site of occlusion.4–7 The investigators of the Interventional Management of Stroke study have developed a set of ultrasound criteria for the early identification of AIS patients, with persisting occlusions at the end of intravenous tissue plasminogen activator (IV tPA) infusion, who may benefit from rescue intra-arterial (IA) thrombolysis.4 However, limited data exist concerning the validation of ultrasonographic criteria for detection of recanalization against the gold standard of digital

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Subjects and Methods

Study Population
We evaluated consecutive AIS patients with proximal intracranial occlusions who underwent IA reperfusion procedures (IA thrombolysis, thrombectomy, thromboaspiration, balloon angioplasty, and stenting) at 3 tertiary-care stroke centers (Birmingham, Alabama; Barcelona, Spain; Athens, Greece) from April 2007 to March 2011. Stroke severity pretreatment was evaluated using the National Institutes of Health Stroke Scale score. All patients had an urgent noncontrast brain CT at the end of IV tPA infusion, were also considered as potential candidates to undergo IA rescue reperfusion procedures. Persisting occlusion was diagnosed at the end of IVT using the same set of TCD criteria across all centers. All patients with persisting occlusion at the end of IVT underwent diagnostic DSA before the initiation of IA reperfusion procedures. Cases with no occlusion at the time of initial diagnostic DSA (false-positive TCD diagnosis of proximal intracranial occlusion) were excluded from the present analyses.

Patients with angiographically confirmed intracranial occlusions received continuous TCD monitoring (Power-motion Mode Doppler TCD, Spencer Technologies; EZ-Dop, DWL) at the site of the worst detectable residual flow signals at a constant angle with trans-temporal insonation using previously published protocol (Figure 1). We used a standard head-frame (Marc series; Spencer Technologies) to maintain a constant angle of vessel insonation. In patients with vertebro-basilar occlusions, TCD monitoring at the top of the basilar flow was performed through the trans-temporal window using previously described localization criteria on power-motion mode Doppler (Figure 2). Patients with absent temporal windows or who were not monitored during IA reperfusion procedures with TCD were excluded from further analyses. Functional status at 3 months was assessed using the modified Rankin scale score. Favorable functional outcome was defined as a modified Rankin scale score of 0–2. The study protocol and ongoing TCD angiography validation study were approved by the ethics committee or the institutional review board of our institutions.

Ultrasound Assessment of Recanalization
Recanalization was assessed in real time by TCD using the previously published thrombolysis in brain ischemia (TIBI) criteria. To ensure blinding of TCD waveform interpretation, sonographers digitally stored real-time spectral waveforms and documented timing of the recordings (ie, 13:27:57 through 13:28:02, 1 sweep, or 13:33:18, start for continuous recordings) in the angiography suite when diagnostic dye injections were made by interventionalists. After cases were completed, interventionalists selected runs to grade thrombolysis in myocardial infarction (TIMI) scores. Time corresponding TCD waveforms were then collected from participating sites and sent to offline blinded review. The assessment of recanalization using TIBI grading flow system was performed by experienced neurosonologists who did not participate in monitoring of IA reperfusion procedures and evaluated stored TCD waveforms.

Complete recanalization was diagnosed, during and at the end of IA reperfusion procedures if flow improved to TIBI grades 4 to 5 (Figure 1). Partial recanalization was identified if flow improved by ≥1 grade from the baseline but not to grades 4 to 5 on the TIBI scale. TCD diagnostic protocol was identical in all participating centers.

Figure 1. Transcranial Doppler (TCD) recordings (A) showing the presence of blunted flow signals (thrombolysis in brain ischemia [TIBI] II) on the proximal (M1) part of right middle cerebral artery (MCA) in a patient with a right M1 MCA occlusion (thrombolysis in myocardial infarction [TIMI] 0) on angiogram (B). Real-time TCD monitoring (C) documented complete reperfusion (TIBI V) 35 minutes after the initiation of intra-arterial thrombolysis. Complete reperfusion (TIMI III) was also confirmed on postprocedural angiogram (D). Red arrow identifies a knob (used for tightening of TCD head-frame) that is placed laterally on the forehead to avoid interference with angiographic views of the affected vessels.
Angiographic Assessment of Recanalization

Recanalization was graded on the angiograms according to the TIMI criteria by neurointerventionalists independently of each other and blinded to the ultrasound findings. The application of these criteria to cerebral vessels has been reported previously. Complete occlusion (TIMI grade 0–1) was defined as no or minimal perfusion with no opacification of the distal vessels on DSA. Partial recanalization (TIMI grade 2) was defined as an obstruction that resulted in a delayed opacification of the distal vessels on DSA. Complete recanalization (TIMI grade 3) was defined as unimpeded perfusion of the distal vasculature regardless of whether a residual stenosis or a focal flow gap was present (Figure 1). The pre- and postprocedural protocols regarding IA reperfusion therapies were identical across 3 participating centers as previously described.

Statistical Analyses

The accuracy parameters (sensitivity, specificity, positive predictive value, negative predictive value (NPV), and overall accuracy) for TCD to detect recanalization against the gold standard of DSA were calculated after computation of true-positive, false-positive, true-negative, and false-negative values. The adjusted Wald method, which provides the best coverage for binomial confidence intervals (CI) when samples are <150, was used for computation of 95% CI for the rates of accuracy parameters.

We also planned to establish our interrater reliability of TIBI flow grading using TCD images of different TIBI flow grades recorded during IA reperfusion procedures. Two readers evaluated independently 60 stored TCD images of different TIBI grades, and the reliability between readers was determined using Cohen κ coefficient as previously described: κ = 0.81, very good/excellent agreement; 0.61 ≤ κ < 0.81, good agreement; 0.41 ≤ κ < 0.60, fair agreement; and κ < 0.41, slight/poor agreement. Finally, we evaluated the association of complete recanalization at the end of IA procedures (diagnosed either by TCD or DSA), with favorable functional outcome at 3 months (modified Rankin scale score of 0–2) on multivariable logistic regression models adjusting for potential confounders (demographic characteristics, vascular risk factors, pretreatment stroke severity, treatment with IV tPA before the initiation of IA reperfusion procedures). Associations are presented as odds ratio with corresponding 95% CIs. The statistical package for social science (version 11.5 for Windows; SPSS Inc, Chicago, IL) was used for statistical analyses.

Results

We evaluated time-linked real-time DSA-TCD images from 96 diagnostic DSA runs during IA reperfusion procedures in 62 consecutive AIS patients (mean age, 59±17 years; 58% men; median baseline National Institutes of Health Stroke Scale score, 18 [interquartile range, 12–21]; median time from symptom onset to IA initiation, 240 minutes [interquartile range, 163–308]) with proximal intracranial occlusions diagnosed by TCD and confirmed by DSA. Baseline characteristics of the study population are shown in Table 1. Terminal internal carotid artery and proximal (M1) middle cerebral artery (MCA) were the 2 most common locations of proximal intracranial occlusions (37% and 35%, respectively). A total of 22 patients (36%) received IVT before the initiation of IA reperfusion procedures for persisting arterial occlusions. Only 1 patient pretreated with IVT had no occlusion at the time of the initial diagnostic DSA and was not included in the present analyses. Thus, the diagnostic sensitivity of TCD for detecting persisting arterial occlusions at the end of IVT was 96% (22/23) with corresponding 95% CI, 77% to 100%.

The interrater reliability for evaluation of TIBI grades and assessment of complete recanalization in our pilot study were very good (Cohen κ: 0.838 and 0.874, respectively; P<0.001). Compared with angiography, TCD showed 29 true-positive, 4 false-negative, 7 false-positive, and 56 true-negative studies for detection of complete recanalization (TIBI 4 and 5 versus TIMI 3 flow grades). The accuracy parameters of TCD against DSA for diagnosis of complete recanalization were as follows: sensitivity, 88% (95% CI, 72%–96%); specificity, 89% (79%–95%); positive predictive value, 81% (65%–91%); NPV, 93% (84%–98%); and overall accuracy, 89% (80%–94%). Most false-positive TCD cases of complete recanalization (71%) were graded with TIMI grade 2 (partial recanalization) on angiography. Suboptimal angle of insonation caused by headframe displacement owing to head movements during the...
Table 2. Accuracy Parameters for Detecting Complete, Partial, and Any (Complete or Partial) Recanalization by Transcranial Doppler

<table>
<thead>
<tr>
<th>Recanalization</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Overall Accuracy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>88% (72%–96%)</td>
<td>89% (79%–95%)</td>
<td>81% (65%–91%)</td>
<td>93% (84%–98%)</td>
<td>89% (80%–94%)</td>
</tr>
<tr>
<td>Partial</td>
<td>69% (53%–82%)</td>
<td>91% (81%–97%)</td>
<td>84% (68%–94%)</td>
<td>81% (70%–89%)</td>
<td>82% (73%–89%)</td>
</tr>
<tr>
<td>Any</td>
<td>92% (83%–96%)</td>
<td>88% (68%–96%)</td>
<td>96% (87%–99%)</td>
<td>78% (58%–91%)</td>
<td>91% (83%–95%)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NPV, negative predictive value; and PPV, positive predictive value.
diagnostic ability of ultrasound to detect proximal intracranial occlusions in comparison to CTA in 90 AIS patients. In 4 cases where complete recanalization was diagnosed with follow-up ultrasound, a second CTA was performed and recanalization was confirmed in all cases. Levi et al. sought to evaluate the association of continuous 2-hour TCD monitoring after tPA bolus with complete recanalization at 24 hours after stroke onset diagnosed by MRA in 27 patients with MCA occlusions treated with systemic thrombolysis. They reported that major TIBI grade change (improvement by ≥3 grades) during the post-thrombolysis TCD monitoring period was independently associated with major reperfusion on MRA at 24 hours after stroke onset, along with higher odds of attenuation of infarct core growth improvement and excellent 90-day functional outcome. Nevertheless, they did not explore the accuracy parameters of TCD against MRA for diagnosis of complete recanalization, while the elapsed time interval between the end of TCD monitoring and MRA was >16 hours. The main strengths of the present report in comparison to previous studies include the larger sample size, the inclusion of patients with locations of intracranial occlusions other than MCA, the validation of TIBI flow grades in real time against the gold standard of DSA, and the assessment of interrater reliability for ultrasound diagnosis of recanalization using stored images and blinded readers.

Certain potential clinical implications of our observations should be acknowledged. First, previous independent studies have already highlighted the role of TCD as an ideal screening tool for combined IV/IA lysis protocols because it has the ability to identify and reject those patients who achieved early recanalization not yet accompanied with neurological recovery or to select patients with persistent occlusions that may be suitable candidates for further interventional reperfusion procedures. Consequently, our findings provide reassurance to clinicians that patients with persisting intracranial occlusions on TCD monitoring should be considered for IA procedures without requesting additional confirmatory neuroimaging studies. Moreover, ultrasound may be used for monitoring of IA reperfusion procedures to diminish the number of contrast injections that are thought to increase the risk of hemorrhagic complications.

Last and most important, TCD can yield accurate diagnostic information regarding recanalization status at bedside in patients with contraindications to MRA or CTA or in centers with limited 24-hour availability to these neuroimaging modalities. Our group has also previously highlighted the potential of TCD in providing hemodynamic information, diagnosing air embolism, and detecting early reclosure early and immediate after IA reperfusion procedures.

Our study has limitations, including the need for considerable sonographer expertise to complete and interpret testing promptly and efficiently during IA reperfusion procedures. For instance, the correct placement of head-frame to secure a constant angle of insonation and the ability to accurately identify and interpret residual flow changes may preclude the wide adoption of ultrasound for assessment of recanalization unless an operator-independent TCD system is developed. Furthermore, in patients with vertebrobasilar artery occlusions, TCD monitoring with a head-frame can only detect downstream flow changes, whereas sonographer has to switch to hand-held insonation to direct the ultrasound beam along the occluded artery through the suboccipital approach. In addition, ultrasound cannot be used for noninvasive diagnosis of recanalization in patients with absent temporal windows unless ultrasound contrast agents are approved in the United States for intracranial studies. Also, discomfort and agitation may be caused by the tight head-frame fixation in nonsedated patients who undergo continuous TCD monitoring. The former technical challenges and requirements indicate that our results might be difficult to reproduce in centers with lesser experience with TCD monitoring and consequently limit the wider application of this ultrasound modality during IA reperfusion procedures.

It should be also acknowledged that tissue reperfusion imaging MRI or extent of infarction imaging was not systematically assessed across participating centers. Besides, it may be argued that the thrombolysis in cerebral infarction grading system might be more appropriate for the angiographic assessment of reperfusion. In the present study, we evaluated recanalization using the TIMI grading score, given the familiarity and extensive experience of our group with the former score. Moreover, previous studies comparing the diagnostic accuracy of TCD against DSA for assessing recanalization have also used the TIMI grading score. Finally, DSA collateral vessel grading was not systematically measured at baseline because the aim of the present study was to evaluate the correlation of TCD versus DSA in assessing recanalization. Our multicenter group is currently investigating, in an ongoing study, the diagnostic yield of TCD against DSA in collateral vessel grading, and we also plan to investigate the association of collateral circulation graded on TCD and DSA with early functional outcomes.

On the other hand, it should be noted that specific contraindications also exist for the other established neuroimaging methods that are currently used for assessment of recanalization status (eg, pacemakers for MRA, renal insufficiency for CTA). Notably, in a study comparing neurosonology with correlative angiography (MRA or CTA) in 58 AIS patients,

### Table 3. Association of Complete Recanalization With Favorable Functional Outcome (mRS Score of 0–2) at 3 Months in Univariable and Multivariable Logistic Regression Analyses (Adjusting for Demographics, Vascular Risk Factors, Pretreatment Stroke Severity, and Intravenous Thrombolysis)

<table>
<thead>
<tr>
<th></th>
<th>Coefficient (SE)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Coefficient (SE)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Recanalization</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis by TCD</td>
<td>1.540 (0.588)</td>
<td>4.67 (1.48–14.76)</td>
<td>0.009</td>
<td>2.627 (1.213)</td>
<td>13.83 (1.28–148.98)</td>
<td>0.030</td>
</tr>
<tr>
<td>Diagnosis by DSA</td>
<td>1.779 (0.580)</td>
<td>5.92 (1.90–18.47)</td>
<td>0.002</td>
<td>2.564 (1.101)</td>
<td>12.97 (1.50–112.27)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; DSA, digital subtraction angiography; mRS, modified Rankin scale; OR, odds ratio; and TCD, transcranial Doppler.

Our study has limitations, including the need for considerable sonographer expertise to complete and interpret testing promptly and efficiently during IA reperfusion procedures. For instance, the correct placement of head-frame to secure a constant angle of insonation and the ability to accurately identify and interpret residual flow changes may preclude the wide adoption of ultrasound for assessment of recanalization unless an operator-independent TCD system is developed. Furthermore, in patients with vertebrobasilar artery occlusions, TCD monitoring with a head-frame can only detect downstream flow changes, whereas sonographer has to switch to hand-held insonation to direct the ultrasound beam along the occluded artery through the suboccipital approach. In addition, ultrasound cannot be used for noninvasive diagnosis of recanalization in patients with absent temporal windows unless ultrasound contrast agents are approved in the United States for intracranial studies. Also, discomfort and agitation may be caused by the tight head-frame fixation in nonsedated patients who undergo continuous TCD monitoring. The former technical challenges and requirements indicate that our results might be difficult to reproduce in centers with lesser experience with TCD monitoring and consequently limit the wider application of this ultrasound modality during IA reperfusion procedures.

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MRI was inconclusive or not possible because of extensive movement artifacts or contraindications in 19% of the study patients. In additional 14% critically ill patients, MRI could not be performed because of insufficient ability to monitor vital parameters in the scanner. In contrast, ultrasound examination was possible and conclusive in 93% of the studied cases.

Conclusions
Our findings confirm the validity of the TIBI scale versus TIMI recanalization assessment in acute stroke in real time. We provided data indicating that at laboratories with high-interrater reliability and sharing standard insonation protocols, TIBI criteria can accurately predict brain reperfusion. Consequently, TCD can be useful in monitoring recanalization status in AIS patients undergoing IVT and can assist in the selection of individuals who may undergo rescue IA reperfusion procedures. It may also offer additional hemodynamic information during these procedures and substantially limit the amount of contrast infusions or help correct potentially harmful perfusion changes. Finally, given the fact that recanalization is currently used as a biomarker of therapeutic activity in early phase trials of reperfusion therapies in AIS, ultrasound may be used as an alternative, cost-effective noninvasive modality for accurate detection of recanalization.

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Disclosures
None.

References


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