Timing of Recanalization After Microbubble-Enhanced Intravenous Thrombolysis in Basilar Artery Occlusion

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**Background and Purpose**—Information about early recanalization of basilar artery occlusion after systemic tissue plasminogen activator remains unknown. We aimed to determine the timing of recanalization in basilar artery occlusion treated with systemic thrombolysis, microbubbles, and continuous transcranial Doppler monitoring.

**Methods**—We studied 20 patients with <12 hours basilar artery occlusion treated with intravenous tissue plasminogen activator, 2 hours continuous ultrasound, and 3 boluses of microbubbles. Transcranial Doppler assessed recanalization at different time points. Outcome was assessed using the National Institutes of Health Stroke Scale and modified Rankin scale. Patients were considered to be independent if modified Rankin scale score was <3 at 90 days.

**Results**—Median admission National Institutes of Health Stroke Scale was 18.5 (interquartile range 16 to 26.5) and median time to treatment was 180 minutes (range, 80 to 720 minutes). Rate of complete recanalization raised progressively: at 1 hour 10%, at 2 hours 20%, at 6 hours 35%, and at 24 hours 50%. In 10 patients (50%), no recanalization was observed at 24 hours. Median discharge National Institutes of Health Stroke Scale was 14 (interquartile range 1 to 30). Degree of National Institutes of Health Stroke Scale improvement was related to time of recanalization: median discharge National Institutes of Health Stroke Scale—1 for recanalization between 0 and 6 hours, 11 for recanalization between 6 and 24 hours, and 30 if no recanalization occurred ($P=0.002$). At 3 months, mortality was 35%. Only one patient (10%) who recanalized within 24 hours died as compared with 60% of nonrecanalizers ($P=0.029$). Rate of independent patients progressively decreased as time to recanalization increased ($P=0.006$).

**Conclusions**—In acute basilar artery occlusion, endovenous tissue plasminogen activator, microbubbles, and continuous ultrasound leads to early recanalization in a significant number of patients and this is associated with favorable outcome. Immediate intravenous tissue plasminogen activator treatment should be the first therapeutic option in these patients.

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**Key Words:** acute stroke ■ basilar ■ microbubbles ■ neursonology ■ TCD ■ thrombolysis
after symptom onset. Twenty-five patients with suspected BAO were urgently evaluated and underwent extracranial and TCD ultrasound examination. Those who presented baseline TCD-documented BAO were included in the study. We excluded patients with an inadequate transforaminal window (n=2), treated with intraarterial procedures (n=1), or with isolated vertebral occlusion and patent contralateral vertebral and basilar arteries (n=3). Informed consent was obtained from all patients or their next of kin. The study protocol was approved by the local ethics committee.

Clinical and Transcranial Doppler Protocol
On arrival to the emergency department, patients underwent standard clinical, neurological, and cardiologic examination; electrocardiogram, blood chemistry, and CT or MRI. An experienced sonographer performed TCD examination to assess intracranial arteries using a standard scanning protocol (TCD 100 mol/L; Spencer Technologies or Multidop DWL). Sonographers were not blinded to clinical and brain imaging data.

Basilar artery segments were defined according to insonation depth as proximal (<85 mm) and distal (>85 mm). Presumed thrombus location and residual flow signals were determined by the presence of abnormal flow signals using the Thrombolysis In Brain Ischemia11 flow grading system. Complete occlusion was considered when Thrombolysis In Brain Ischemia grades were 0 to 1. Location of occlusion was determined as proximal or distal. Patients were treated with the combination of tPA plus 2-hour continuous 2-MHz TCD monitoring plus 3 boluses of 400 mg/dL of the galactose-based microbubbles (Leovist) given at 2, 20, and 40 minutes after tPA administration. An experienced sonographer manually held the ultrasound probe and continuously insonated the occlusion location through the transforaminal window during 2 hours after tPA bolus. In all cases, patients were in the same supine position and the head was bent to the front placing the chin over the sternum and slightly to the side. A folded pillow is very helpful to maintain this position. The probe can then be advanced behind the pillow to the transforaminal window and the sonographer must manually hold it. Continuous TCD monitoring followed by repeat fast-track assessments determined timing and degree of recanalization at 1, 2, 6, and 24 hours after tPA bolus according to previously published criteria.12,13 Briefly, recanalization on TCD was diagnosed as “partial” when dampened signals appeared in a previously demonstrated absent or minimal flow (ie, when a proximal occlusion becomes a distal occlusion). “Complete” recanalization on TCD was diagnosed if the end diastolic flow velocity improved to normal or elevated values (normal or stenotic signals). No change in the abnormal waveforms indicated “no recanalization.” We scored recanalization as complete, partial, or none at specified time points after tPA bolus.

Neurological status was assessed on the patient’s arrival, at 24 hours, and at discharge using the National Institutes of Health Stroke Scale14 (NIHSS) by a certified neurologist. A 24-hour CT scan determined the presence of hemorrhagic transformation. We considered hemorrhagic transformation as symptomatic if a neurological worsening (NIHSS increase >4 points) was accompanied by the presence of blood on follow-up CT scan. Stroke subtype was determined according to modified Trial of Org 10 172 in Acute Stroke Treatment (TOAST)15 classification. Modified Rankin scale16 was used to assess clinical outcome at 90 days; patients were considered to be independent if modified Rankin Scale score was <3.

Statistical Analysis
Descriptive and frequency statistical analysis were obtained and comparisons were made using the SPSS 12.0 statistical package. Statistical significance for intergroup differences for categorical variables was assessed χ2 test. For continuous variables, the Mann–Whitney U test was used. P<0.05 was considered statistically significant.

Results
A total of 20 consecutive patients with a TCD-documented BAO treated with intravenous tPA (0.9 mg/kg), continuous ultrasound, and microbubbles were included (40% women; mean age, 67±15 years; range, 38 to 95 years). Distribution of arterial occlusion site was proximal 14 (70%) and distal 6 (30%). Eleven patients underwent a multiparametric MRI before tPA treatment as the neuroimaging technique. In all 11 cases, BAO was found on MR angiography sequences confirming TCD findings. Time to treatment did not differ according to occlusion location (proximal 170 minutes, distal 222 minutes; P=0.11). Median admission NIHSS was 18.5 (interquartile range (IR) 16 to 26.5) and median time to treatment was 180 minutes (range, 80 to 720 minutes). Only 2 patients were treated beyond 6 hours. Distribution according to TOAST etiologic classification was atherothrombotic 40%, cardioembolic 35%, and undetermined 25%.

The rate of complete recanalization raised progressively was at 1 hour after treatment, 10%; at 2 hours, 20%; at 6 hours, 35%; and at 24 hours, 50%. A flow improvement (recanalization partial or complete) was observed within 6 hours after treatment in 40% (n=8) and between 6 and 24 hours in 10% (n=2). In 10 patients (50%), no recanalization was observed at 24 hours. A detailed distribution of recanalization rates is shown in Figure 1.

Median NIHSS at discharge was 14 (IR 1 to 30). The degree of NIHSS improvement was related to time of recanalization; median discharge NIHSS was: 1 (IR 0 to 7.5) for recanalization between 0 and 6 hours and 11 (IR 5 to 17) for recanalization between 6 and 24 hours and 30 (IR 15 to 30) if no recanalization occurred (P=0.002; Figure 2). At 3 months, the mortality rate was 35%. Only one of the patients (10%) who recanalized within 24 hours died as compared with 60% of those who did not recanalize (P=0.029). At 3 months, 45% were independent. The rate of independent patients progressively decreased as time to recanalization increased: 88%, 50%, and 11% for recanalizations between 0 and 6 hours, 6 and 24 hours, and no recanalization at 24 hours, respectively (P=0.006; Figure 2). Occlusion location (P=0.4) and etiologic (TOAST) subtype (P=0.57) did not influence recanalization. None of the patients experienced a symptomatic hemorrhagic transformation.

Discussion
Our study demonstrated for the first time that combined treatment with endovenous tPA, microbubbles, and continuous ultrasound in acute BAO leads to early recanalization in...
a significant number of patients; and this is associated with a favorable outcome.

Up-to-date data about early recanalization with systemic thrombolysis in acute BAO remained unknown and the reported rates of recanalization with endovascular therapies were thought to be slightly higher. Therefore, in the last years, several studies had questioned intravenous tPA as an effective therapy for acute BAO treatment suggesting primary intraarterial procedures as the first therapeutic option. However, primary intraarterial therapies may delay treatment onset due to lack of immediate availability of endovascular facilities or other technical and anatomical problems that preclude catheter access to thrombus location. In contrast, the mean door-to-needle time for intravenous tPA is commonly set under 60 minutes in most stroke centers. Our study shows that microbubble plus ultrasound-enhanced intravenous thrombolysis safely leads to relatively high rates of early reperfusion as soon as 60 minutes after tPA bolus, and this is associated with favorable short- and long-term outcome. The rate of recanalization with intravenous tPA progressively decreases in the following hours and up to 50% of the patients do not recanalize within 24 hours leading to disability and death. Our 24-hour recanalization rate is comparable to the 52% recanalization rate at 24 hours found in a previous study. Our study describes the temporal profile during the first hours; our therapeutic model combining ultrasound and microbubbles may potentially lead to faster recanalization than conventional systemic thrombolysis alone. Therefore, results may not be fully generalized.

Interestingly, our results suggest that delayed recanalization between 6 and 24 hours may still be clinically beneficial. These data may indicate that ischemic tolerance in the posterior circulation may be higher than in carotid territories, where reperfusion beyond 12 hours seems to be ineffective. Further research should confirm the efficacy of an extended therapeutic window. Finally, occlusion location or etiologic subtypes do not seem to influence response to systemic thrombolysis in terms of recanalization; therefore, this information should probably not be considered when deciding the therapeutic strategy. Nevertheless, conclusions about subgroup analysis in small sampled studies should always be handled with care.

The combination of microbubbles and ultrasound has previously shown to increase the fibrinolytic power of tPA in experimental models. In patients with stroke with middle cerebral artery occlusion, administration of microbubbles during continuous 2-MHz ultrasound monitoring accelerated and increased the completeness of tPA-induced recanalization. In patients with BAO, the observed 35% rate of complete recanalization at 2 hours is slightly lower that the 54% rate observed in patients with middle cerebral artery occlusion, suggesting a lower efficacy of systemic thrombolytic drugs in the posterior circulation. Our study also shows that continuous insonation of presumed clot location and recanalization monitoring is safe and feasible in BAO. However, in contrast to middle cerebral artery occlusions in which a headset allows probe fixation, in BAO, a sonographer needs to continuously manually hold the probe making this technique even more explorer-dependent. Our study design offers recanalization information only according to TCD findings; the fact that no other confirmatory techniques were used may be a limitation, especially because TCD recanalization criteria are not validated in BAO. However, previous studies had reported a high concordance between TCD and other imaging techniques in acute BAO. In our study, baseline TCD assessment of basilar artery flow showed a high concordance with MR angiographic findings. The fact that BAO is a rare condition avoids the possibility of performing large single-center studies, the relatively limited number of patients in our study should be considered as a limitation.

**Conclusion**

Patients with acute BAO should receive immediate intravenous tPA treatment as the first and fastest therapeutic option keeping intraarterial procedures as a rescue tool for those in whom reperfusion is not achieved.

**Disclosures**

None.
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