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Stroke 2004;35:2722-2725; originally published online Sep 16, 2004;

DOI: 10.1161/01.STR.0000143321.37482.b3

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ISSN: 1524-4628

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Ultrasound Identification and Lysis of Clots

Andrei V. Alexandrov, MD

Abstract—Poor recovery after systemic tissue plasminogen activator (tPA) therapy could result from the initial severity of ischemic insult and slow and incomplete thrombolysis. Persisting arterial occlusions can be identified at bedside using portable diagnostic ultrasound by detecting residual flow signals around the thrombus (thrombolysis in brain ischemia [TIBI] flow grades). A narrow pulsed ultrasound beam can be steadily aimed at the thrombus/residual flow interface, exposing more thrombus surface and structures to tPA, and tPA activity can be enhanced with 2 MHz transcranial Doppler (TCD). A randomized, multicenter, clinical trial called CLOTBUST (Combined Lysis of Thrombus in Brain ischemia using transcranial Ultrasound and Systemic tPA) trial showed a 49% rate of complete recanalization or dramatic clinical recovery from stroke within 2 hours after tPA bolus when tPA infusion was continuously monitored with TCD, compared with 30% among patients who received tPA without ultrasound monitoring ($P=0.03$, number needed to treat, 5). Early complete recanalization was sustained at 2 hours by 38% of monitored patients compared with 12.7% controls. The CLOTBUST Trial showed a trend toward sustaining complete recovery at 3 months (41.5% versus 28%, modified Rankin Scale scores 0 to 1), subject for a pivotal phase III trial. Ultrasound is an inexpensive, noninvasive, real-time monitoring tool to identify nonresponders to systemic tPA and select patients with persisting occlusions for intraarterial interventions. Early brain perfusion augmentation, complete recanalization, and dramatic clinical recovery are feasible goals for ultrasound-enhanced thrombolysis. (*Stroke*. 2004;35[suppl I]:2722-2725.)

Key Words: outcomes ■ stroke ■ thrombolysis ■ tissue plasminogen activator ■ ultrasonography, Doppler, transcranial

Intravenous tissue plasminogen activator (tPA) infusion is the fastest way to initiate thrombolytic therapy; however, poor recovery can be expected in up to 50% of patients, likely as a result of the initial severity of ischemic insult and slow and incomplete thrombolysis.^{1,2} When given intravenously, tPA delivery to the thrombus is dependent on the residual flow to and around the arterial obstruction, and better residual flow signals are associated with higher recanalization rates in stroke patients treated with tPA.³

A 2-MHz pulsed-wave diagnostic ultrasound beam can serve several purposes. First, it can be used to identify the presence of obstructive intracranial thrombus in a vessel. Second, it can provide real-time bedside monitoring of thrombolysis. And finally, it can augment residual flow and speed up thrombolysis, allowing patients to recover from stroke more rapidly and completely.

Diagnosis of an Acute Arterial Occlusion

An acute arterial occlusion is different from chronic because it is often partial and incomplete, being a dynamic process of thrombus propagation, reocclusion, and infrequent spontaneous recanalization with or without pre-existing atheroma. A better term to describe such obstruction is a "lesion amenable to intervention."⁴ Ultrasound can rapidly identify patients with these lesions regardless of baseline stroke severity. With good temporal windows, an experienced operator can accomplish this in 2 minutes, and in patients with suboptimal windows it takes

<15 minutes. Ultrasound testing can be performed at bedside simultaneously with neurological examination, vital signs monitoring, and drawing blood, causing no delay in tPA administration.^{2,3}

The key ultrasound findings for the diagnosis of a lesion amenable for intervention include: (1) 1 of 4 abnormal thrombolysis in brain ischemia (TIBI) waveforms⁵ in the vessel supplying a territory affected by ischemia; and (2) evidence of flow diversion or collateralization⁶⁻¹⁰ to compensate for this lesion.

In the absence of flow diversion or collateralization, other findings can point to thrombus presence and location such as stenotic velocities, embolic signals, and flow pulsatility changes in vessels proximal and distal to suspected obstruction.^{11,12} With these criteria, a non-image-guided Doppler ultrasound can identify thrombus location with accuracy >90% for the middle cerebral artery (MCA) and internal carotid artery (ICA). Once this thrombus/residual flow interface is found, a narrow 3- to 10-mm pulsed-wave ultrasound beam can be steadily aimed at thrombus location (Figure 1) to monitor the effect of a thrombolytic drug.

Monitoring Thrombolytic Therapy With Ultrasound

Delaying tPA therapy within 3 hours of symptom onset in favor of patient selection with imaging methods that are more time-consuming than a noncontrast CT is unjustified because

Received June 9, 2004; accepted August 5, 2004.

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Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000143321.37482.b3

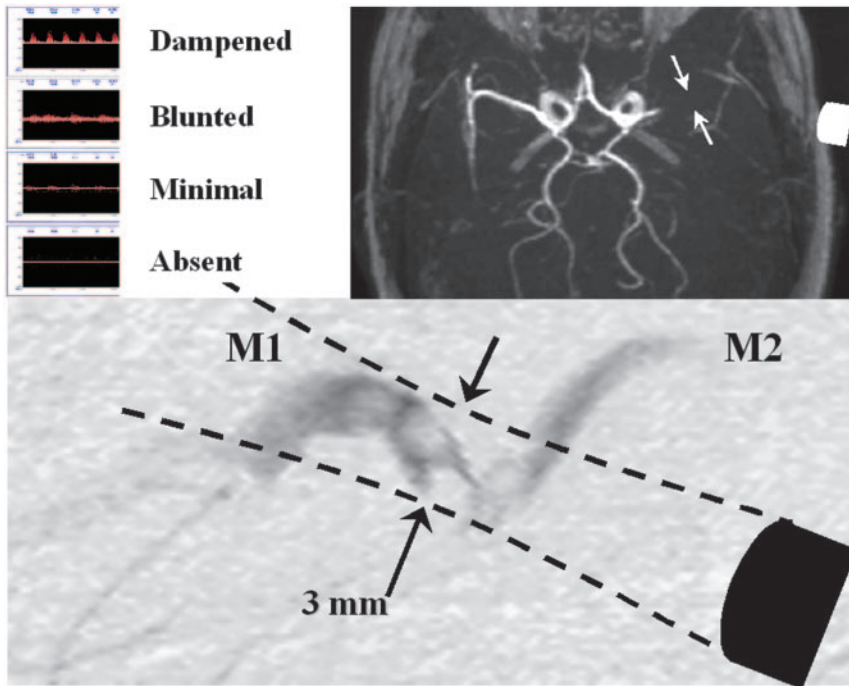


Figure 1. Abnormal thrombolysis in brain ischemia (TIBI) flow grades (upper left images), and acute middle cerebral artery occlusion location on magnetic resonance angiography (white arrows) with relative ultrasound transducer position on the skull (white insert, upper right image). Lower image illustrates residual flow around sausage-like middle cerebral artery thrombus during catheter angiography. Black arrows indicate transcranial Doppler focal zone where TIBI signals are obtained. Black dotted lines demonstrate projected path of a 2 MHz ultrasound beam generated by a single crystal transducer (black inserted object).

tPA efficacy decreases with time¹³ and the first noticeable improvement of flow to the brain occurs at a median time of 17 minutes after tPA bolus.² Median time to completion of recanalization is 35 minutes after bolus,² and those patients who complete recanalization before the end of 1 hour of tPA infusion are 3.5× more likely to achieve favorable outcome at 3 months.¹⁴

An average rate of spontaneous complete recanalization of the MCA occlusion appears to be about 6% per hour during the first 6 hours after symptom onset.¹⁵⁻¹⁷ Systemic tPA increases complete recanalization rate to 12.7% per hour in the control

group of the Combined Lysis of Thrombus in Brain ischemia using transcranial Ultrasound and Systemic tPA (CLOTBUST) Trial (Figure 2). The likelihood of early recanalization of the M2 MCA occlusion with systemic tPA is 44%; M1 MCA, 22%; and ICA or TICA, <10%.¹⁸ Patients with persisting MCA or terminal ICA occlusion have only 10% chance to recover completely at 3 months,¹⁹ and we use this information to justify an experimental intraarterial procedure to lyse or remove thrombus even after full-dose intravenous tPA.

Early arterial reocclusion affects up to 25% of tPA-treated patients, more commonly those with partial or incomplete

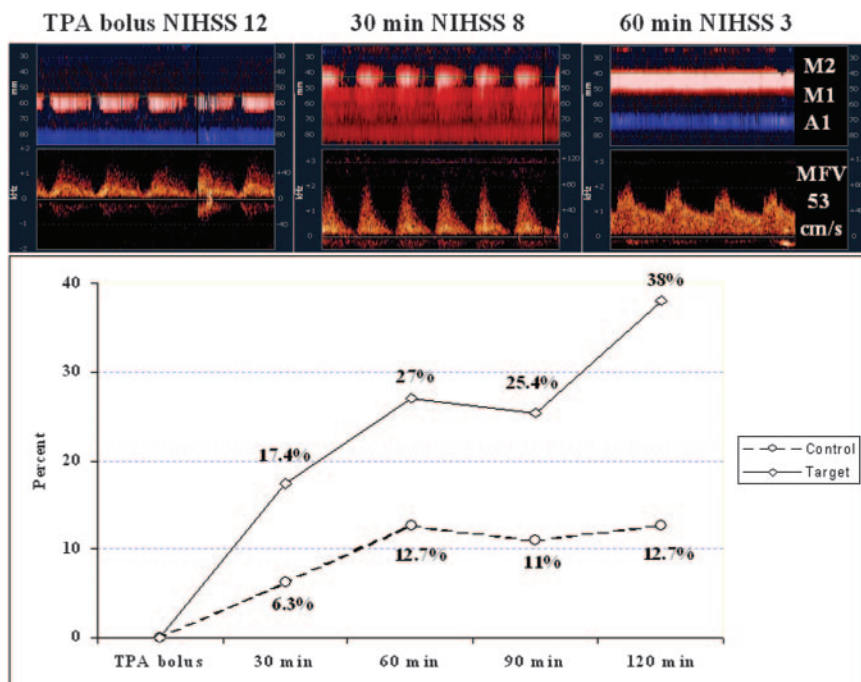


Figure 2. Complete early middle cerebral artery recanalization on power-motion transcranial Doppler and serial NIHSS scores (upper row). A graph below shows sustained complete recanalization rates in the target patient group and controls in the CLOTBUST Trial at time intervals after tPA bolus.

initial recanalization.^{19,20} Arterial reocclusion accounts for two thirds of patients who experience deterioration following improvement with tPA therapy.¹⁹ Intracranial arterial reocclusion occurs at an average time of 65 minutes after bolus.²⁰ After early reocclusion there is a 33% chance of favorable outcome at 3 months, compared to 50% in patients with stable early recanalization.¹⁹

Early complete recanalization is closely associated with dramatic clinical recovery,^{20,21} and the timing of brain reperfusion detected by transcranial Doppler (TCD) and subsequent clinical improvement with reversal of ischemic brain damage show an S-shaped correlation seen in a baboon model of ischemic stroke.^{22,23} However, one third of early complete recanalizations do not result in immediate clinical improvement. Despite this, one third of patients with silent recanalizations recover completely at 3 months.²⁴

Ultrasound Enhanced Thrombolysis—CLOTBUST Trial

In the past 30 years, numerous scientists showed in experimental models that ultrasound facilitates the activity of fibrinolytic agents within minutes of its exposure to thrombus and blood containing drugs.^{25–32} The mechanisms of ultrasound-enhanced thrombolysis include improved drug transport, reversible alteration of fibrin structure, and increased tPA binding to fibrin^{25–34} for frequencies ranging from kHz to those used in diagnostic ultrasound.^{33,34} Although kHz frequencies penetrate better with less heating, a combination of tPA with an experimental kHz delivery system resulted in excessive risk of intracerebral hemorrhage (ICH) in stroke patients.³⁵

We used diagnostic 2 MHz TCD to evaluate acute stroke patients and reported an unexpectedly high rate of complete recanalization and dramatic clinical recovery when tPA infusion was continuously monitored with TCD for diagnostic purposes.²¹ The analysis of phase I clinical data³⁶ allowed us to predetermine a sample size of a phase II clinical trial that was powered to demonstrate 20% difference in the primary activity end-point of complete recanalization and dramatic clinical recovery within 2 hours after TPA bolus.³⁷

The CLOTBUST Trial was a phase II, multicenter, randomized, clinical trial (Houston, Texas; Barcelona, Spain; Edmonton and Calgary, Canada). All patients with acute ischemic stroke were treated with 0.9 mg/kg intravenous tPA within 3 hours of symptom onset. All patients had MCA occlusions on pretreatment TCD and were randomized to continuous monitoring with TCD (target group) or placebo monitoring (control). Safety end-point was symptomatic ICH. Primary combined activity end-point was complete recanalization on TCD or dramatic clinical recovery to a total National Institutes of Health Stroke Scale (NIHSS) score ≤ 3 , or improvement by ≥ 10 NIHSS points within 2 hours after TPA bolus. Secondary end-points included outcomes at 3 months by the modified Rankin Scale (mRS) score.

All 126 projected patients received tPA and were randomized 1:1 to continuous monitoring (median NIHSS 16) or control (median NIHSS 17). Age, occlusion location (M1-MCA or M2-MCA) on TCD, and time to tPA bolus were similar. Symptomatic ICH occurred in 3 target patients

(4.8%, CI₉₅ 1.0 to 13.3) and 3 controls (4.8%, CI₉₅ 1.0 to 13.3). Complete recanalization or dramatic clinical recovery within 2 hours after tPA bolus (primary end-point) were observed in 31 (49%, target) versus 19 patients (30%, control), $P=0.03$, number needed to treat, 5. At 3 months, 22 (41.5%, target) and 14 patients (28%, control) achieved favorable outcomes (mRS 0 to 1).

In stroke patients treated with intravenous tPA, continuous TCD monitoring of intracranial occlusion safely augments tPA-induced arterial recanalization, producing a trend toward sustained improvement at 3 months, subject to a properly powered phase III trial. The phase II CLOTBUST Trial provides clinical evidence for existence of ultrasound-enhanced thrombolysis in humans that can amplify the existing therapy for ischemic stroke. Early brain perfusion augmentation, complete recanalization, and dramatic clinical recovery are feasible goals for ultrasound-enhanced thrombolysis.

Acknowledgments

CLOTBUST is an Investigator Sponsored Trial (A2207s; Genentech, Inc). Study sites and onsite principal investigators include Houston, Texas (James Grotta); Barcelona, Spain (Carlos Molina); and Edmonton (Maher Saqqur) and Calgary (Andrew Demchuk), Canada. A.V.A., Principal Investigator, is supported by the National Institutes of Health Career Development Award (1 K23 NS-02229–01).

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