Ultrasound-Enhanced Thrombolysis
From Bedside to Bench

Georgios Tsivgoulis, MD; Andrei Alexandrov, MD

See related article, pages 1470–1475.

Intravenous tissue plasminogen activator (tPA) infusion is the fastest and easiest way to initiate reperfusion therapy in acute stroke. However, poor recovery can still 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

Clinical improvement and functional independence after stroke usually occur after arterial recanalization.3–6 A recent meta-analysis showed that recanalization is associated with a 4- to 5-fold increase in the odds of a good final functional outcome and a 4- to 5-fold reduction in the odds of death.7 These results lend strong support to the hypothesis that recanalization is the mechanism of how systemic tPA increases the likelihood of recovery from stroke and the use of recanalization as a surrogate end point in phase II trials of reperfusion agents in acute ischemic stroke.

Over the past 30 years, in vitro and animal studies have provided evidence that thrombolysis with tPA can be enhanced with ultrasound. Although the mechanisms are still not fully understood, it is known that ultrasound accelerates enzymatic fibrinolysis primarily through nonthermal mechanisms by increasing transport of drug molecules into the clot.8,9 Mechanical effects of ultrasound radiation forces have the ability to influence drug transport. In addition, ultrasound can promote the motion of fluid through and around the thrombus, an effect called streaming.10

In the clinical setting, enhancement of thrombolysis by ultrasound has recently been documented in patients with acute ischemic stroke in the CLOTBUST (Combined Lysis of Thrombus in Brain ischemia using transcranial Ultrasound and Systemic TPA) trial, a phase II randomized multicenter international trial. Real-time monitoring of the residual flow signals in the middle cerebral artery with diagnostic 2-MHz pulsed wave transcranial Doppler augments tPA-induced arterial recanalization (sustained complete recanalization rates: 38% versus 13%).11 This enhancement of tPA activity did not result in an increase in symptomatic intracerebral hemorrhage rates that were 4.8% in each group. Additional application of microspheres during sonothrombolysis seems to increase its effect on recanalization,12,13 subject of an international microspheres dose-escalation trial called TUCSON (NCT00504842).

In this issue of Stroke, Eggers et al14 report the results of a small single-center randomized study on diagnostic duplex ultrasound-enhanced thrombolysis in patients with acute M1 middle cerebral artery occlusions. Subjects were randomized into a target group (n=19) receiving 1 hour of continuous monitoring using a 1.8-MHz pulsed-wave ultrasound and into a control group (no ultrasound monitoring, n=18). Compared to the control group (nonultrasound), patients in the target group (ultrasound) had higher complete or partial recanalization rates at the end of the 1-hour insonation period (58% versus 22%). Also, patients in the ultrasound group showed greater improvement in National Institutes of Health Stroke Scale values at days 1 and 4 after stroke onset and a trend toward better functional outcomes at 3 months as determined by the Barthel Index and the modified Rankin Scale. However, 3 subjects from the ultrasound group (16%) developed a symptomatic intracranial hemorrhage (sICH) as did one (6%) in the nonultrasound group (P=0.60). The study was stopped by the investigators because inclusion frequency was very low and because the strong tendency toward an increased sICH rate in the target group was confirmed by the analysis based on CT morphology.

The authors should be congratulated on the robust study methodology including blinded off-line analysis of stored ultrasound data and on the comprehensive ultrasound protocol that they implemented in order to capture recanalization and reocclusion in real-time in a homogeneous group of patients with proximal middle cerebral artery occlusions and absent residual flow. Of note, though, is that no sample size estimation was performed; thus, the study discontinuation based on a sample size calculation, when to stop the trial dependently on occurrence of sICH. The fact that continuous ultrasound-monitoring was not performed at a stable angle of insonation is another study limitation.

Nevertheless, the sICH rate of 16% found in the active group is alarming and should be evaluated in context with the recently published results of TRanscranial low-frequency Ultrasound-Mediated thrombolysis in Brain Ischemia (TRUMBI) trial.15 This single-center randomized trial was terminated after 26 patients were enrolled with a 36% rate of sICH when tPA was administered with a 300-kHz nonimaging therapeutic ultrasound. The investigators also found atypical hemorrhages either in the subarachnoid or in the ventricular space or at remote parenchymal locations distant to the infarct core. Although 1.8-MHz diagnostic duplex and

The opinions in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Comprehensive Stroke Center, Department of Neurology, University of Alabama at Birmingham, Birmingham, Ala.

Correspondence to Andrei Alexandrov, RWUH M226 619 19th St S, Birmingham, AL, 35249-3280. E-mail avalexandrov@att.net


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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.107.505594
300-kHz pulsed ultrasound are very different in their acoustic properties, both technologies share the same features such as multibeam configuration that exposes large volumes of ischemic brain tissues compared to transcranial Doppler, and lack of proper dose-escalation studies that determine the minimum and possibly safe amount of ultrasound energy necessary to enhance thrombolysis.

The underlying mechanism causing these high rates of hemorrhage is not clear, but the summation of reflected waves can produce “hot spots” of ultrasound energy accumulation. Multibeam configuration of brain and vessel exposure to ultrasound should be carefully designed and tested in ultrasound dose-escalation studies to avoid formation of standing waves. The occurrence of subarachnoid hemorrhage, particularly led to speculation standing waves induced by high repetition frequency of ultrasound, can stretch small vessels and promote blood leakage. Other biological effects that might have contributed to the observed concerning rate of sICH may be related to vasodilatation from ultrasound and opening of the blood-brain barrier. The recent findings of Reinhard et al., showing that abnormal permeability of the human blood-brain barrier can be induced by wide-field low-frequency insonation, are in line with the former hypothesis and also indicate that the observed excessive bleeding rate with low-frequency sonothrombolysis might be attributable to primary blood-brain–barrier disruption by ultrasound.

In conclusion, the present study is an important continuation of work with transcranial duplex for sonothrombolysis by one of the pioneer groups in this area. The higher recanalization rates achieved in patients treated with ultrasound-enhanced thrombolysis confirm the results of previous small size safety trials indicating that the thrombolytic efficacy of tPA can be enhanced by diagnostic-frequency ultrasound. Because duplex-imaging technologies are widely available, sonothrombolysis with duplex should be carefully evaluated in the context of further prospective clinical trials. However, further bench research is also needed to evaluate the safety, intensity dosages, and optimal frequency for mechanical augmentation of reperfusion therapy with ultrasound to bring these innovative technologies to bedside.

Disclosures
A.A. served as consultant to ImaRx Therapeutics and is on the speaker bureau for Genentech, Inc.

References

Key Words: ischemia • thrombolysis • ultrasound
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Stroke. 2008;39:1404-1405; originally published online March 13, 2008;
doi: 10.1161/STROKEAHA.107.505594
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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World Wide Web at:
http://stroke.ahajournals.org/content/39/5/1404