

Stroke

American Stroke
AssociationSM

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American
Heart Association



High Rate of Complete Recanalization and Dramatic Clinical Recovery During tPA Infusion When Continuously Monitored With 2-MHz Transcranial Doppler Monitoring

Andrei V. Alexandrov, Andrew M. Demchuk, Robert A. Felberg, Ioannis Christou, Philip A. Barber, W. Scott Burgin, Marc Malkoff, Anne W. Wojner and James C. Grotta

Stroke 2000;31;610-614

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214
Copyright © 2000 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online
ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/cgi/content/full/31/3/610>

Subscriptions: Information about subscribing to Stroke is online at
<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

High Rate of Complete Recanalization and Dramatic Clinical Recovery During tPA Infusion When Continuously Monitored With 2-MHz Transcranial Doppler Monitoring

Andrei V. Alexandrov, MD; Andrew M. Demchuk, MD, FRCPC; Robert A. Felberg, MD; Ioannis Christou, MD; Philip A. Barber, MRCP(UK); W. Scott Burgin, MD; Marc Malkoff, MD; Anne W. Wojner, MSN, CCRN; James C. Grotta, MD

Background and Purpose—Clot dissolution with tissue plasminogen activator (tPA) can lead to early clinical recovery after stroke. Transcranial Doppler (TCD) with low MHz frequency can determine arterial occlusion and monitor recanalization and may potentiate thrombolysis.

Methods—Stroke patients receiving intravenous tPA were monitored during infusion with portable TCD (Multigon 500M; DWL MultiDop-T) and headframe (Marc series; Spencer Technologies). Residual flow signals were obtained from the clot location identified by TCD. National Institutes of Health Stroke Scale (NIHSS) scores were obtained before and after tPA infusion.

Results—Forty patients were studied (mean age 70 ± 16 years, baseline NIHSS score 18.6 ± 6.2 , tPA bolus at 132 ± 54 minutes from symptom onset). TCD monitoring started at 125 ± 52 minutes and continued for the duration of tPA infusion. The middle cerebral artery was occluded in 30 patients, the internal carotid artery was occluded in 11 patients, the basilar artery was occluded in 3 patients, and occlusions were multiple in 7 patients; 4 patients had no windows; and 1 patient had a normal TCD. Recanalization on TCD was found at 45 ± 20 minutes after tPA bolus: recanalization was complete in 12 (30%) and partial in 16 (40%) patients. Dramatic recovery during tPA infusion (total NIHSS score < 3) occurred in 8 (20%) of all patients (baseline NIHSS range 6 to 22; all 8 had complete recanalization). Lack of improvement or worsening was associated with no recanalization, late recanalization, or reocclusion on TCD ($C = 0.811$, $P \leq 0.01$). Improvement by ≥ 10 NIHSS points or complete recovery was found in 30% of all patients at the end of tPA infusion and in 40% at 24 hours. Improvement by ≥ 4 NIHSS points was found in 62.5% of patients at 24 hours.

Conclusions—Dramatic recovery during tPA therapy occurred in 20% of all patients when infusion was continuously monitored with TCD. Recovery was associated with recanalization on TCD, whereas no early improvement indicated persistent occlusion or reocclusion. At 24 hours, 40% of all patients improved by ≥ 10 NIHSS points or recovered completely. Ultrasonic energy transmission by TCD monitoring may expose more clot surface to tPA and facilitate thrombolysis and deserves a controlled trial as a way to potentiate the effect of tPA therapy. (*Stroke*. 2000;31:610-614.)

Key Words: outcome ■ stroke, acute ■ thrombolysis ■ ultrasonography, Doppler, transcranial

The intravenous administration of tissue plasminogen activator (tPA) can dissolve thrombi and improve the long-term outcome of patients with acute ischemic stroke.^{1,2} In the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study, 47% of patients treated with tPA improved by ≥ 4 points on the National Institutes of Health Stroke Scale (NIHSS) at 24 hours.² In the placebo group, 39% of patients showed a similar improvement ($P = 0.06$, NS).² A post-hoc analysis showed that by 24 hours, 27% of tPA-treated patients improved by ≥ 10 points or resolved their neurological deficit completely compared with 12% in the placebo group ($P = 0.002$).³

The mechanism of early improvement is attributable to early brain tissue reperfusion and arterial recanalization.^{2,4-7} Transcranial Doppler (TCD) can be used to determine arterial occlusion and to continuously monitor recanalization during thrombolysis.^{6,7} We previously established the accuracy parameters of TCD diagnosis of intracranial arterial occlusion and recanalization compared with the use of angiographic studies.⁸⁻¹⁰ TCD had a sensitivity of 91% and a specificity of 93% to determine complete recanalization of the middle cerebral artery (MCA) in tPA-treated patients.⁹ TCD had a specificity of $\geq 90\%$ for other arterial segments, indicating that a normal TCD examination is highly predictive of arterial

Received November 3, 1999; final revision received December 17, 1999; accepted December 17, 1999.

From the Center for Noninvasive Brain Perfusion Studies (A.V.A., R.A.F., I.C., W.S.B., M.M., A.W.W., J.C.G.), Stroke Treatment Team, University of Texas–Houston Medical School; and Department of Clinical Neurosciences (A.M.D., P.A.B.), University of Calgary, Alberta, Canada.

Correspondence to Dr A. Alexandrov, MSB 7.044 6431 Fannin St, University of Texas, Houston, TX 77030. E-mail avalexandrov@worldnet.att.net
© 2000 American Heart Association, Inc.

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

patency at angiography.⁸ Furthermore, continuous clot exposure to ultrasound frequencies in the kilohertz to low megahertz range enhances tPA activity in vitro, and clot degradation with 1-MHz ultrasound irradiation was 1.8 times greater than that with tPA alone.^{11–15}

In the present study, we prospectively applied TCD to identify the occlusion site before the tPA bolus and to continuously monitor the residual flow signals during tPA infusion. The goal was to establish the rate of complete arterial recanalization during tPA infusion and its possible correlation with an early dramatic clinical improvement.⁷

Subjects and Methods

Consecutive patients who were treated with intravenous tPA and received continuous TCD monitoring between July 1998 and September 1999 were included in the study. tPA was administered in a standard 0.9 mg/kg dose (10% bolus, 90% continuous infusion over 1 hour) to patients presenting within the first 3 hours after symptom onset. In selected patients presenting between 3 to 6 hours of onset or with other risk for hemorrhagic complications, tPA was administered in a dose of 0.6 mg/kg (15% bolus, 85% continuous infusion over 30 minutes). This experimental protocol was approved by the University of Texas Committee for Protection of Human Subjects.

A standard TCD examination was performed in the emergency department before tPA bolus with a single-channel portable unit (Multigon 500M or DWL MultiDop-T). No delay in tPA administration was experienced as a result of the ultrasound examination. TCD was used to identify the site of intracranial occlusion according to previously published diagnostic criteria.⁸ Once the occlusion was diagnosed with handheld examination, the presumed clot location and residual flow around it were determined through the presence of abnormal flow signals (minimal, blunted, or dampened waveforms).⁸

To select the depth for single gate monitoring, the following algorithm was used.

Distal M1–M2 MCA Occlusion

The residual flow signals had to be found at 40 to 45 mm and the monitoring depth was set accordingly (Figure, A).

Proximal M1 MCA Occlusion

Monitoring was performed at 55 to 60 mm.

Asonic MCA Occlusion 1

If no signal could be obtained from the entire stem of an occluded artery, the flow void depth closest to the normal signal was selected. For example, monitoring depth was set at 60 to 65 mm if no MCA signals were found in the presence of a normal anterior cerebral artery.

Asonic MCA Occlusion 2

If no flow signals were detected from the distal part and the abnormal signals were obtained at the proximal part of the MCA, the monitoring depth was set at the depth that displayed the abnormal signal closest to the signal void depths.

Internal Carotid Artery Occlusion

If the internal carotid artery (ICA) was occluded without tandem proximal MCA occlusion, the distal MCA flow signal was monitored at 40 to 45 mm.

T-Type ICA Occlusion

If the terminal ICA was occluded with no or minimal signals from M1 and A1 segments, the MCA origin was monitored at 65 mm.

Basilar Artery Occlusion

A similar algorithm was applied to select depths of 80 mm (proximal basilar artery) or 100 mm (distal basilar artery).

Normal Pretreatment TCD

If a lacunar stroke was clinically suspected, a mid MCA depth of 56 mm was used for monitoring. If a small cortical stroke was suspected, a distal MCA depth of 35 to 40 mm was used for monitoring.

The sample volume (gate) was set at 11.8 mm (Multigon) or 15 mm (DWL). The power was set at a 100% level (Multigon) or 128 mW (DWL) for the duration of monitoring. For patients with MCA occlusion, the transducer was tightly fixed in position with a headframe (Marc series; Spencer Technologies) to maximize sound energy transmission and to maintain a constant angle of insonation (Figure, B). For patients with basilar artery occlusion, handheld monitoring was performed through the transforaminal window.

TCD monitoring was performed during the entire tPA infusion under direct visual control of the investigators. If any flow signal changes occurred, these data were interpreted on-line and the timing of change was documented. The flow signals at the proximal and distal arterial segments were documented at the end of tPA infusion, and TCD monitoring was discontinued at this point.

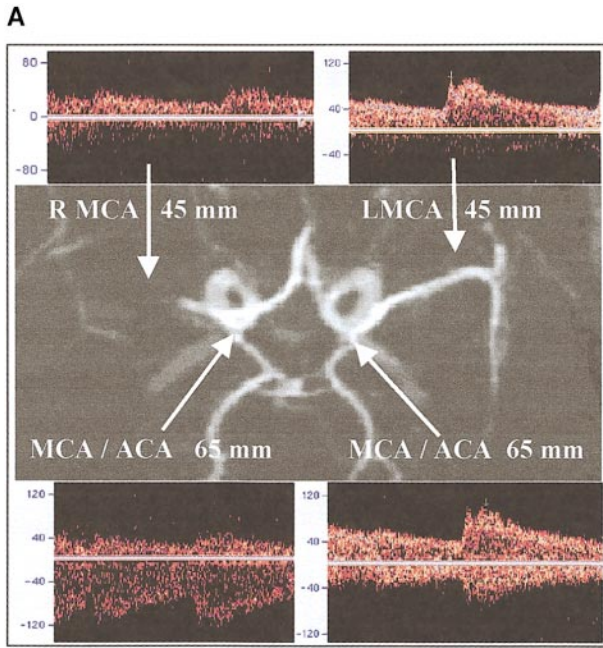
Recanalization was graded as complete, partial, or none according to previously validated criteria.⁹ Complete recanalization was diagnosed when a normal waveform or a low-resistance stenotic signal appeared at the selected depth of insonation. If a proximal arterial segment was monitored, the continuation of normal or low-resistance stenotic flow toward the distal arterial segment was confirmed. If the abnormal signals were still seen at the distal portion, partial recanalization was diagnosed. No change in the abnormal flow signals indicated that no recanalization has occurred. Reocclusion was diagnosed when the abnormal flow signals worsened in comparison with the baseline study or after a transient flow signal improvement during tPA infusion.

The NIHSS scores were obtained before and after tPA infusion by a neurologist who was not involved in TCD. Outcome measurements included the NIHSS scores at the end of tPA infusion and at 24 hours and modified Rankin scale scores at follow-up.² We used 4 measures of clinical recovery based on methods used in previous studies.^{2,3,7} “Dramatic recovery” was defined as a decrease in the total NIHSS score to <3 at the end of tPA infusion.⁷ “Early neurological improvement” was defined as a reduction in ≥ 10 points in the total NIHSS score or complete recovery.³ “Improvement” was defined as a reduction in the total NIHSS score by ≥ 4 points.² “Worsening” was defined as an increase in the total NIHSS score by ≥ 4 points.² At follow-up, a neurologist obtained modified Rankin scores during an outpatient visit or during a structured telephone interview. Statistical analysis included the χ^2 test and coefficient of contingency (C) to establish an association between recanalization and clinical recovery.

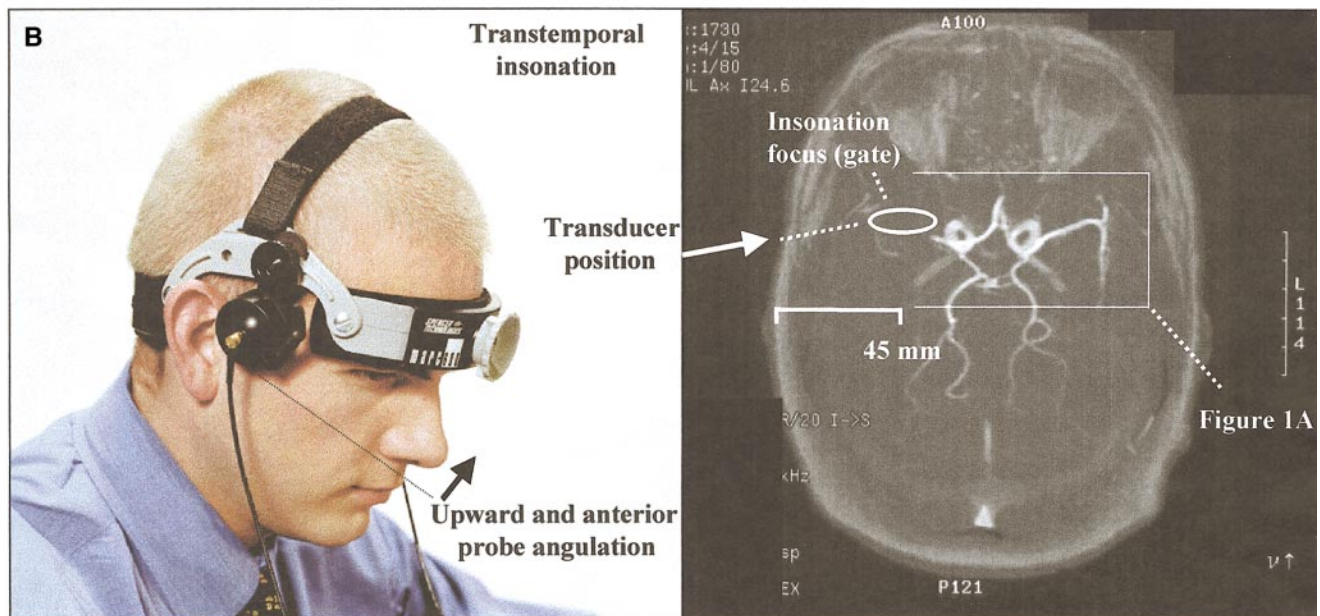
Results

Forty patients were studied (mean age 70 ± 16 years, range 32 to 93 years). Baseline stroke severity was 18.6 ± 6.2 NIHSS points (median 19 points, range 6 to 33 points). tPA bolus was administered at 132 ± 54 minutes from symptom onset, including 6 patients who were treated with a 0.6-mg/kg dose administered 120 to 360 minutes from time the patient was last known to be normal. At the prebolus TCD examination, the MCA was occluded in 30 patients (75%), the ICA was occluded in 11 patients (28%), and the basilar artery was occluded in 3 patients (8%). Multiple occlusions involving ICA and MCA were found in 7 (18%). Four patients had no windows of insonation (10%). Only 1 patient (2.5%) had a normal TCD examination before the tPA bolus.

TCD monitoring was started 125 ± 52 minutes after symptom onset and continued for the duration of tPA infusion in all patients. Evidence for complete or partial recanalization on TCD was found in 28 of 40 patients (70%) at 45 ± 20 minutes after the tPA bolus. Complete recanalization occurred in 12



A, MCA residual flow signals and depths of insonation. TCD shows delayed right MCA systolic flow acceleration (above baseline). Right anterior cerebral artery has normal flow acceleration (below baseline) and flow velocity greater than both MCAs, indicating flow diversion. These findings confirm MCA obstruction distal to the internal carotid artery bifurcation. Magnetic resonance angiography shows flow void in the distal right M1 MCA. A blunted flow signal in the distal right M1 MCA at a 45-mm depth was used to monitor tPA infusion in this case (see B). B, TCD monitoring of MCA residual flow signals. (B is reprinted with permission from Spencer Technologies, Inc)



patients (30%), and partial recanalization was found in 16 patients (40%) (Table 1).

Dramatic recovery during tPA infusion (total NIHSS score <3 by the end of tPA infusion) was observed in 8 patients (20%), all of whom had complete recanalization on TCD. Clinical recovery was associated with recanalization ($\chi^2=26.3$, $C=0.811$, $P<0.01$; Table 1). The baseline NIHSS score of patients who experienced dramatic recovery was 13.3 ± 5.6 points (median 13 points, range 6 to 22 points, age range 32 to 93 years). Complete recanalization was common in patients with cardioembolic occlusion (8 of 17, or 47%); however, this association was not significant (Table 2). If partial or complete recanalization was achieved by the end of tPA infusion, 43% of these patients (12 of 28) improved by ≥ 10 NIHSS points or recovered completely at 24 hours.

Overall, early improvement by ≥ 10 points or complete recovery was seen in 12 of 40 patients (30%) at the end of tPA infusion and in 16 patients (40%) by 24 hours. An improvement by ≥ 4 points was observed in 18 of 40 patients (45%) at the end of tPA infusion and in 25 patients (62.5%) by 24 hours.

No improvement was noted in 16 patients (40%) during tPA infusion and in 7 patients (17.5%) by 24 hours. Worsening of the neurological deficit occurred in 6 patients (15%) during tPA infusion and in 8 patients (20%) by 24 hours.

Digital subtraction angiography was performed in 10 patients, magnetic resonance angiography was performed in 9 patients, and CT-angiography was performed in 2 patients (total 53%). Angiography was performed at a median time of 34 hours after stroke onset, with 50% of angiograms obtained

TABLE 1. Clinical Recovery During tPA Infusion Combined With Continuous 2-MHz TCD Monitoring

Recanalization at End of tPA Infusion by TCD	Clinical Recovery at End of tPA Infusion		
	Dramatic: Total NIHSS Score <3	Partial: NIHSS Decrease by ≥4 points	None: No Change or Worsening
Complete	8	1	3
Partial	0	7	9
None*	0	2	10

Dramatic clinical recovery was associated with complete proximal arterial recanalization during tPA infusion ($C=0.811$, $P\leq 0.01$). Lack of improvement or worsening was due to persistent arterial occlusion on TCD. Worsening was defined as an increase in the NIHSS score by ≥ 4 points.

*No evidence of recanalization on TCD, including patients with no temporal windows.

within the first 24 hours. In all of these patients, angiography results confirmed TCD findings at the end of tPA infusion: 8 patients had normal vessels, 3 had intracranial stenoses, and 11 had persisting occlusion.

On TCD, 12 patients had persisting occlusion (30%), and 3 patients had late recanalization that occurred by 5 to 8 hours after stroke onset (7.5%). All these patients either worsened or had no clinical improvement within the first 24 hours. Symptomatic intracerebral hemorrhage occurred in 3 of 40 patients (7.5%). TCD detected complete recanalization in all 3 of these patients between 348 and 720 minutes preceding neurological deterioration.

Eight patients died within the first 3 months after therapy (overall mortality rate 20%), and 22 patients were available for long-term follow-up (1.5 ± 1.2 months). Of these, 11 patients achieved modified Rankin scores of ≤ 3 (50%), including 6 patients with modified Rankin scores of ≤ 1 who sustained early dramatic improvement. Two other patients who completely recanalized and improved dramatically during tPA infusion did not sustain the improvement in the long term because of a subsequent reocclusion. In the first patient, MCA recanalized 20 minutes after the tPA bolus, but reocclusion occurred at 40 minutes, and repeat CT scan at 65 minutes showed new cortical edema formation. Several hours later, this patient had late recanalization, developed a massive intracerebral hemorrhage, and died. The second patient had a $\geq 50\%$ residual basilar artery stenosis and despite receiving warfarin sodium had a recurrent fatal basilar artery thrombo-

TABLE 2. Arterial Recanalization and Stroke Pathogenic Mechanism

Mechanism	n	Recanalization		
		Complete	Partial	None
Cardioembolism	17	8	6	3
Large vessel atherosclerosis	12	3	5	4
Other (dissection, small vessel)	3	1	1	1
Undetermined	8	0	4	4

Complete recanalization was observed in 47% (8 of 17) of cardioembolic occlusions and 25% (3 of 12) of atherothrombotic large vessel occlusions ($\chi^2=6.4$, 6 *df*, $P=0.37$, NS). Stroke pathogenic mechanism was determined with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.¹⁷

sis 2 weeks after tPA treatment. Of 16 patients who recovered completely or improved by ≥ 10 NIHSS points by 24 hours, 3 (19%) did not sustain early improvement (2 died and 1 had late worsening of the neurological deficit with an outcome Rankin score of 4 points).

Discussion

Our study showed that dramatic improvement during tPA therapy occurred in 20% of all patients and that resolution of the neurological deficit was associated with complete recanalization on TCD. Early improvement by ≥ 10 points or complete recovery at 24 hours was seen in 40% of all patients; this finding was also associated with either complete or partial recanalization. No clinical improvement or worsening during tPA therapy and at 24 hours indicated persistent arterial occlusion, reocclusion, or late recanalization.

The response rate to tPA therapy at 24 hours was higher in our study than was expected on the basis of the results of the NINDS rt-PA Stroke Study. The NINDS trial showed that 27% of tPA-treated patients improved by ≥ 10 points or recovered completely at 24 hours, whereas 40% of our patients had the same amount of recovery. Also, 47% of tPA-treated patients in the NINDS rt-PA Stroke Study improved by ≥ 4 points at 24 hours, whereas in our study, 62.5% of patients had such an improvement. Different sample sizes, patient selection, and treatment regimens in the present small study compared with the NINDS trial preclude any conclusive comparison. For instance, the pretreatment median NIHSS score was 14 in the NINDS trial versus 19 in our study, and therefore the expected outcome in our study might have been worse than that in the NINDS trial. In addition, angiographic and sonographic studies showed that arterial occlusion and poor collateral flow are adverse prognostic factors in patients with ischemic stroke.^{6,10,16} Because 39 of 40 patients in our study had occlusions on TCD before treatment, the early improvement rate observed at 24 hours in the present study of 40% versus the rate of 27% in the NINDS trial is somewhat surprising.

The recanalization rate (30% complete, 40% partial) in the present study is higher than that previously reported by del Zoppo et al,¹ who also used intravenous tPA. With digital subtraction angiography, a 26% complete and partial recanalization rate for MCA stem occlusion was seen after 60 minutes of tPA infusion.¹ Again, caution must be exercised in a comparison of the present study with this report. Among other differences, del Zoppo et al¹ used a continuous infusion of alteplase that was initiated ≈ 5.5 hours after stroke onset without a bolus. Although we did not have a control group in the present study, complete recanalization was achieved in 30% of patients within 1 hour compared with previously reported 26% rate of spontaneous MCA recanalization seen over 4 hours.¹⁰

The present study had rates of recanalization and recovery after tPA therapy that were greater than those previously reported. One difference, of course, between the present study and previous trials is that we used continuous TCD monitoring throughout the tPA infusion. This raises the intriguing possibility that TCD somehow augments tPA-induced clot lysis. The synergistic effect of ultrasound and tPA has been

documented in vitro and in vivo experiments for frequencies up to 1.03 MHz.^{10–14} We hypothesize that continuous ultrasonic energy transmission focused on clot location by TCD monitoring may expose more clot surface to tPA. Ultrasound becomes scattered at the clot/residual flow interface, and the pressure gradients that were created may force more tPA molecules to lodge into the clot, thus facilitating thrombolysis. Although these comments remain speculative, our study supports further evaluation of the potential for TCD to promote thrombolysis through a prospective randomized trial.

Our data also indicate that patients who do not effectively lyse the clot during tPA infusion may be at a higher risk of remaining disabled or experiencing further stroke progression. These patients may be an ideal target group for a trial of more aggressive therapy such as combined intravenous and intra-arterial thrombolysis. In addition, a subgroup of patients with large vessel occlusion may benefit from early anticoagulation,¹⁷ and the use of ultrasound monitoring in this setting may be also be tested.

In conclusion, dramatic recovery during tPA therapy occurred in 20% of all patients when the infusion was continuously monitored with TCD. Recovery is associated with recanalization, while no early improvement indicated persistent occlusion or reocclusion. At 24 hours, 40% of all treated patients improved by ≥ 10 NIHSS points or recovered completely. Ultrasonic energy transmission by TCD monitoring may expose more clot surface to tPA and facilitate thrombolysis, and a controlled trial should be undertaken to determine whether TCD enhances reperfusion.

Acknowledgments

Drs Burgin and Felberg are supported by NIH Fellowship Training Grant 1-T32-NS07412-O1A1 for the Stroke Program, University of Texas–Houston Medical School. Dr Christou is supported by a Hellenic Ministry of Defense Visiting Clinician Grant, Athens, Greece. The authors gratefully acknowledge technical support provided by Multigon Industries, DWL/Neuroscan, and Spencer Technologies during the project.

References

1. del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan AJ, Ferbert A, Alberts MJ, Zivin JA, Wechsler L, Busse O, Greenlee R, Brass L, Mohr JP, Feldmann E, Hacke W, Kase CS, Biller J, Gress D, Otis SM. Recom-

- binant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol*. 1992;32:78–86.
2. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
3. Haley EC, Lewandowski C, Tilley BC. Myths regarding NINDS rt-PA Stroke Trial: setting the record straight. *Ann Emerg Med*. 1997;30:676–682.
4. Grotta JC, Alexandrov AV. tPA-associated reperfusion in acute ischemic stroke demonstrated by SPECT. *Stroke*. 1998;29:429–432.
5. Heiss W-D, Grond M, Thiel A, von Stockhausen H-M, Rudolf J, Ghaemi M, Lottgen J, Stenzel C, Pawlik G. Tissue at risk of infarction rescued by early reperfusion: a positron emission tomography study in systemic recombinant tissue plasminogen activator thrombolysis of acute stroke. *J Cereb Blood Flow Metab*. 1998;18:1298–1307.
6. Ringelstein EB, Biniek R, Weiller C, Ammeling B, Nolte PN, Thron A. Type and extent of hemispheric brain infarctions and clinical outcome in early and delayed middle cerebral artery recanalization. *Neurology*. 1992;42:289–298.
7. Demchuk AM, Felberg RA, Alexandrov AV. Clinical recovery from acute ischemic stroke after early reperfusion of the brain with intravenous thrombolysis. *N Engl J Med*. 1999;340:894–895.
8. Demchuk AM, Christou I, Wein TH, Felberg RA, Malkoff M, Grotta JC, Alexandrov AV. The accuracy and criteria for localizing arterial occlusion with transcranial Doppler. *J Neuroimaging*. 1999;9:57. Abstract.
9. Burgin SW, Felberg RA, Demchuk AM, Christou I, Grotta JC, Alexandrov AV. Ultrasound criteria for middle cerebral artery recanalization: an angiographic correlation. *Stroke* 2000;31:329. Abstract.
10. Alexandrov AV, Bladin CF, Norris JW. Intracranial blood flow velocities in acute ischemic stroke. *Stroke*. 1994;25:1378–1383.
11. Lauer CG, Burge R, Tang DB, Bass BG, Gomez ER, Alving BM. Effect of ultrasound on tissue-type plasminogen activator-induced thrombolysis. *Circulation*. 1992;86:1257–1264.
12. Kimura M, Iijima S, Kobayashi K, Furuhashi H. Evaluation of the thrombolytic effect of tissue-type plasminogen activator with ultrasound irradiation: in vitro experiment involving assay of the fibrin degradation products from the clot. *Biol Pharm Bull*. 1994;17:126–130.
13. Akiyama M, Ishibashi T, Yamada T, Furuhashi H. Low-frequency ultrasound penetrates the cranium and enhances thrombolysis in vitro. *Neurosurgery*. 1998;43:828–832.
14. Suchkova V, Siddiqi FN, Carstensen EL, Dalecki D, Child S, Francis CW. Enhancement of fibrinolysis with 40-kHz ultrasound. *Circulation*. 1998;98:1030–1035.
15. Behrens S, Daffertshoffer M, Spiegel D, Hennerici M. Low-frequency, low-intensity ultrasound accelerates thrombolysis through the skull. *Ultrasound Med Biol*. 1999;25:269–273.
16. Fieschi C, Argentino C, Lenzi GL, Sacchetti ML, Toni D, Bozzao L. Clinical and instrumental evaluation of patients with ischemic stroke within six hours. *J Neurol Sci*. 1989;91:311–322.
17. Adams HP, Bendixen BH, Leira E, Chang KC, Davis PH, Woolson RF, Clarke WR, Hansen MD. Antithrombotic treatment of ischemic stroke among patients with occlusion or severe stenosis of the internal carotid artery: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*. 1999;53:122–125.