Letters to the Editor

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Clototripsy?

To the Editor:

The dramatic clinical recovery during tissue plasminogen activator (tPA) infusion with continuous transcranial Doppler (TCD) monitoring seen in 8 of 40 patients reported by Alexandrov et al\(^1\) is both exciting and unprecedented. The fact that their patients had more severe strokes than those in the NINDS study, with average NIHSS scores of 33% higher, is particularly impressive. Cardiologists are used to seeing marked clinical improvement in at least half their myocardial infarction patients when thrombolysis is performed within 3 hours of onset. The lack of an immediate clinical response to thrombolysis was noted in the first round of letters discussing the NINDS study\(^2\) and is consistent with my own clinical experience (in 10 or so cases) and that of other clinical neurologists.

The authors advance the hypothesis that the sound energy of TCD exposes more of the clot surface to tPA, presumably permitting more effective clot lysis. They argue for a controlled trial of thrombolysis with and without prolonged TCD. However, no study at any time with concomitant controls has replicated the NINDS results. Although ECASS-II\(^3\) demonstrated a 40.3% favorable outcome in the alteplase group, the placebo group did nearly as well (36.6%), even when the smaller subset of patients treated within 3 hours is considered. A recent community report (without controls) is less sanguine—reporting a 9% symptomatic intracerebral hemorrhage rate and a 30% any hemorrhage rate in 138 patients\(^4\) (note the authors). Combine the 2 studies, and any therapeutic advantage of tPA for ischemic stroke vanishes (because the symptomatic intracerebral hemorrhage rate in the NINDS study was 6%).

Nonetheless, the results reported by Alexandrov et al are exciting and should be followed up. However, a proper study of prolonged TCD in the management of acute ischemic stroke should include a control group not receiving thrombolytics at all, since the therapeutic efficacy of tPA in ischemic stroke is still under serious question. The initial group studied should be the large number of patients arriving in the emergency room between 3 and 6 hours after onset, those in whom thrombolytic therapy has not proven to be of any benefit. Ultimately, TCD should be studied by itself in the first 3 hours; but the academic and medical-legal establishments in the United States have made such a study impossible to carry out in this country. However, tPA is not yet approved for stroke treatment in Europe, and perhaps a study such as ECASS-III could properly investigate the dramatic clinical response to tPA and prolonged TCD by comparing the combination of tPA and TCD and tPA and TCD separately to placebo. Concurrent placebo controls are crucial, because the rate of good outcome in the placebo group has varied so widely in different studies. Historical controls just won’t do.

This would not be the first time in diseases affecting the brain that an effective therapy was found while investigating something else. Cade found lithium because he wanted to make urate salts more soluble. Valproic acid was discovered because it was used as the oily vehicle to dissolve a lipophobic drug being tested as an anticonvulsant.

Blood contains huge amounts of clotting factors and fibrinolytic factors. It is well known that most intracranial arterial occlusions resolve in time without any thrombolytic therapy, although too late to do the stroke patient any good. It is possible that prolonged TCD, by itself, allows the natural fibrinolytic factors already present in blood and endothelium to penetrate and dissolve the clot in time to benefit the patient.

Against this idea are the experimental results that ultrasound given to artificial clots in glass capillaries does not dissolve them unless tPA is present.\(^5\) However, glass capillaries do not contain endothelium and the cellular elements of blood. It is also well recognized that mechanical stress alters endothelial gene expression and platelet function. However, this is just theoretical quibbling. A significant clinical effect has likely been shown by Alexandrov, and it should be properly investigated further. A therapeutic effect of prolonged TCD by itself, if demonstrated, will likely have far wider application to human disease than just stroke.

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Response

We appreciate the thoughtful comments by Dr Robinson regarding potential enhancement of thrombolysis with transcranial Doppler ultrasound. However, we disagree with his interpretation of data on tPA efficacy.

First, clinical assessment of dramatic recovery during and shortly after tPA infusion was not a goal of the NINDS rt-PA study protocol that targeted the early improvement end point at 24 hours. In a post hoc analysis, 27% of tPA-treated patients recovered completely or had an improvement of ≥10 NIHSS points at 24 hours compared with 12% of placebo-treated patients (P=0.002).\(^1\) These data indicate that early dramatic recovery could have occurred during the NINDS rt-PA Stroke Study in some patients treated with tPA but without externally applied ultrasound.

Second, a 9% hemorrhage rate reported by Demchuk et al\(^2\) includes patients treated at 2 centers, Houston and Calgary, and this hemorrhage rate is more representative of the first steps in implementation of tPA therapy. Our own experience that replicates the NINDS rt-PA Stroke Study was published separately (7% symptomatic hemorrhage rate),\(^3\) and our ongoing assessment of tPA therapy in Houston (>300 patients treated from 1996 through 2000) indicates even lower rates of hemorrhage (unpublished data). A recent multicenter phase IV assessment of tPA by the STARS collaborators\(^4\) showed a 3.3% symptomatic hemorrhage rate despite protocol violations in 32.6% of patients. Outcome after tPA therapy relates to appropriateness,\(^5\) and...
hemo}{r}{high-risk}nic complications rate may be higher in community hospitals. However, the results of the NINDS rt-PA Stroke Study have been successfully replicated in several postapproval studies. The benefit from tPA therapy was seen even after the impact of hemorrhagic complications had been accounted for in the NINDS rt-PA Stroke Study: patients with advanced age and severe stroke had higher rate of intracerebral hemorrhage, but more of these patients recovered when treated with tPA compared with placebo.

Third, existing data indicate that withholding thrombolytic therapy and administering placebo in a patient otherwise eligible for intravenous TPA during the first 3 hours after stroke onset is unethical, at least in this country. However, we agree that a potential independent effect of external ultrasound on clot recanalization needs to be proved against placebo.

Perhaps this could be accomplished in patients presenting outside the conventional window for thrombolytic therapy. Laboratory research indicates that such an independent effect is most likely present with kilohertz range of frequency, and a 2-MHz transcranial Doppler may not be able to achieve this because of tremendous attenuation of sound energy through temporal bone. However, possible interactions of 2-MHz TCD with natural fibrinolytic factors, fibrin structure, and vessel wall factors may deserve further study.

Finally, dismissing the NINDS rt-PA Stroke Study data in view of the overall negative ECASS results and historic reports of hemorrhagic complications is incorrect. Our cohort study does not provide as strong evidence of clinical effect as does a well-conducted randomized trial such as the NINDS rt-PA Stroke Study. Although our data are intriguing and point to a possible synergistic effect of TCD and TPA, this question should be subjected to scientific scrutiny in a proper trial to demonstrate ultrasound-enhanced thrombolysis with TPA for stroke.

We are pleased that Dr Robinson shares our excitement in seeing dramatic clinical recovery during TPA infusion, and his letter raises several important points that need to be addressed in a prospective trial. Indeed, if a noninvasive diagnostic modality has a therapeutic effect on thrombolysis, this may open a new frontier in clinical applications of ultrasound.

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Contrast-Enhanced Transcranial Color-Coded Sonography in Acute Cerebral Infarction

To the Editor:

Postert and colleagues reported their successful use of an echo-contrast agent in transcranial color-coded sonography (TCCS) to overcome the problem of inadequate acoustic bone windows (IABW) in patients with acute ischemic stroke affecting the middle cerebral artery territory. Their results were both convincing and impressive, and CT angiography (CTA) was used as a gold standard for comparison in a subgroup of patients. Adding a galactose-based echo-enhancing agent permitted an adequate sonographic examination of the middle cerebral artery in 74 of 90 stroke patients (82%) with proven IABW. Two features of contrast-enhanced TCCS (CE-TCCS) are noteworthy: completion of the examination of the major arteries around the circle of Willis within 10 minutes; and feasibility of repeated examinations. I wish to raise the following issues for clarification and discussions by the authors.

First, some exclusion criteria were indicated in the article, but the number of patients excluded was not mentioned. Although I understand the rationale behind these exclusion criteria, I am interested in knowing how many patients were excluded because of galactosemia. More importantly, what adverse reactions may occur if galactose-based microbubbles is inadvertently injected into a patient with galactosemia? In addition, excluding patients with a history of cerebrovascular diseases or old ischemic lesions on CT scans may limit the applicability of CE-TCCS in patients with acute cerebral infarction.

Second, follow-up CT scan was performed within 7 days. In the subsection “CT and CTA,” CT findings were used to classify the extent of infarction involving the middle cerebral artery territory. I assume that the findings of the follow-up CT scan but not the initial CT scan were used in the classification. I am interested in knowing the shortest time interval between the 2 CT studies, because the full extent of cerebral infarction might not be appreciated if the second CT scan was performed soon after the first study. In addition, a description of the initial CT findings and the evolution of the CT findings may illustrate the predictive value of visualization of the middle cerebral artery.

Finally, the treatment time window for thrombolysis is short. One major limitation of conventional transcranial Doppler is the relatively long examination time, and the presence of IABW is rather common. Would the authors recommend CE-TCCS as the first-line transcranial sonographic study rather than wasting previous time with transcranial Doppler or unenhanced TCCS? On the other hand, CTA can reliably and quickly visualize the major arteries around the circle of Willis. I wonder whether adding CTA to an initial CT scan is a better tool to triage patients for acute thrombolysis, and serial contrast-enhanced TCCS may be used to monitor the middle cerebral artery when occlusion is seen on CTA.
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Response

We thank Dr Cheung for his interest in our article on CE-TCCS in acute stroke. In our study, 7 patients with insufficient temporal bone window had to be excluded because of previous infarction in the middle cerebral artery territory. The rationale behind this exclusion criterion was the fact that middle cerebral artery flow velocities in acute stroke patients may be considerably influenced by hemodynamic alterations due to old ischemic lesions. It is well known and could be confirmed in our study that a major part of acute stroke patients with middle cerebral artery mainstem or branch occlusions exhibit partial or complete recanalization of these vessels within the first days (1,2). However, larger studies on the long-term follow-up of transcranial Doppler examinations in stroke patients have not been performed. In our experience, individuals with large middle cerebral artery infarctions in the past frequently show reduced flow velocities and vessel pulsilities as compared to the unaffected side.

In our department we have performed CE-TCCS examinations since 1996 and have never observed a serious adverse event in any patient. In addition, no such case has been published in the literature. In screening studies, the incidence of galactosemia was between 4 and 10 per 100 000 newborns.3,4 In clinical practice, the probability of a galactose-based microbubble injection in a stroke patient who suffers from galactosemia seems to be very low. However, because such an injection may cause transient deterioration of neurological, hepatic, or other symptoms, careful evaluation of medical history is important.

We agree that early performance of follow-up CT examinations may lead to underestimation of the final infarction size. For this reason, we selected relatively long time intervals between the acute and follow-up examinations. In our study, the shortest time interval was 5 days.

In contrast to transcranial Doppler, TCCS allows rapid and reliable identification of intracranial arteries using the 2-dimensional B-mode image of brain parenchyma. This advantage is particularly important in patients suitable for thrombolysis or in agitated subjects. For this reason, we would recommend unenhanced TCCS examinations as the first-line imaging mode, when corresponding probes and experienced examiners are available. However, if intracranial arteries cannot be identified sufficiently, echo-contrast agent application should follow promptly in those centers experienced in CE-TCCS. Using CE-TCCS, diagnostically useful results can be obtained in >90% of all stroke patients, clearly exceeding the number of successful transcranial Doppler examinations in the same patients (5).

Measurement of Cerebral Blood Flow Volume in Healthy Adults Using Color Duplex Sonography

We are in accord with Dr Cheung that CT angiography may represent a reliable and quick alternative for the assessment of the vascular state of acute stroke patients. However, availability of spiral CT scanners is still limited, application of contrast agents is not possible in individuals with renal failure, and, more than in CE-TCCS, reliability of this method highly depends on the cooperation of the patient. In all those cases, CE-TCCS is an excellent method to identify patients with occlusions of the major intracranial arteries. In the follow-up phase, CE-TCCS allows timesaving and bedside monitoring of the intracranial vessels, particularly in critical ill patients.

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cycle days 6, 10, 12, 13, and 14), and during the luteal phase (cycle days 15, 16, 17, 20, and 24). All examinations were performed between 6 and 8 AM to minimize the effect of circadian rhythms on cerebral blood flow and metabolism. At the same time, cardiac output was investigated with Doppler sonography, and blood was sampled to determine the concentrations of 17β-estradiol and progesterone and the hematocrit level. To compare changes of velocities in the internal and external carotid arteries, the values of all Doppler parameters were standardized by relating them to the base value of average velocities from 2 initial examinations (days 3 and 6) and were given as percentages.

We found that increased concentration of 17β-estradiol corresponded to an increase in the mean and end-diastolic blood flow velocities within the internal carotid artery, with a higher rate of these increments between days 10 and 15 of the cycle and an established elevation in the luteal phase (Figure). The mean velocity increment amounted to $111 \pm 9\%$ of the base value, whereas the increment of the systolic velocity was much less pronounced, at only $102 \pm 12\%$ of the base value. As far as the external carotid artery is concerned, the end-diastolic and mean velocities were actually found to decrease with increased concentrations of 17β-estradiol (Figure). Cardiac output increased only slightly in the luteal phase of the cycle. The cross-sectional area of the examined vessels remained unchanged during the entire cycle, as did the hematocrit level.

Our results illustrate the existence of significant changes in the level of flow volume within the carotid arteries throughout the menstrual cycle. The increased velocities, prevailing over the most of the cycle, undoubtedly contribute to variability in the cerebral blood flow, as observed by Scheel et al., and may also be responsible for the relatively higher average cerebral blood flow observed in women. It is accepted that systolic velocity is mainly influenced by cardiac output, and the end-diastolic velocity is thought to increase with decreased peripheral vascular resistance. Thus, our results support the argument that the increased flow volume through the internal carotid artery, associated with high concentrations of plasma estrogen, is caused mainly by a decrease in vascular resistance in the brain, presumably due to the direct effect of estrogen on cerebral vessels. The contribution of increased cardiac output to the greater facilitation of cerebral blood flow was only minimal in our subjects. Furthermore, the flow increase was not correlated with the hematocrit level. Therefore, a relatively stable cardiac output with stable vascular capacity and decreased peripheral resistance in the territory supplied by the internal carotid artery should produce a decrease in flow volume through the external carotid artery—an effect that was actually found in our subjects. Because the reduced flow volume through the external carotid artery in women occurs throughout most of the menstrual cycle, it may appear, in an indiscriminate study, that the flow volume through the external carotid artery is lower in women than in men, an effect that Scheel et al were not able to explain.

In this letter we do not provide absolute values of intravascular blood flow volume in our subjects. Nevertheless, our data may be related to the results of Scheel et al., since we have measured the cross-sectional area of the examined vessels with manual tracing and have found them stable during the whole menstrual cycle. It may be of interest to add that we have found a significant difference in the cross-sectional area of the examined vessels between the systole and diastole. On the basis of 184 measurements, we have estimated this difference to be an average of $27.1 \pm 9.4\%$ (28.6 ± 4.6 mm$^2$ in systole and 22.5 ± 4.1 mm$^2$ in diastole, $t=27, P<0.001$) for the common carotid artery, and $14.6 \pm 13.5\%$ (12.7 ± 2.7 mm$^2$ in systole and 11.2 ± 2.6 mm$^2$ in diastole, $t=8, P<0.001$) for the internal carotid artery.
Scheel et al do not specify in which phase of the cardiac cycle they measured the diameter of the vessels, although the differences in the vessel caliber during systole and diastole appear to be quite substantial. Consistency in measurements with respect to the cardiac cycles may improve the reproducibility and decrease the variability of flow volume measurements. Which phase of the cardiac cycle should be selected for appropriate calculation of the vessel diameter and how the flow should be calculated as a product of this cross-sectional area and the flow velocities measured is, of course, a major question that needs to be addressed separately.

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Contrast-Enhanced Transcranial Color-Coded Sonography in Acute Cerebral Infarction
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