tPA: A Rural Network Experience

To the Editor:

We read with considerable interest the report of the Order of St Francis (OSF) Stroke Network in Peoria,1 discussing their early experience promoting the use of intravenous tissue plasminogen activator (IV tPA) in central Illinois. Since 1996 we have been somewhat differently organized in Minnesota for a similar phase IV assessment of this important therapy. Our initial report in 19982 presented 60 patients collected over 14 months, a quantity similar to the current OSF report. It was our judgment then, and our main criticism now of the OSF report, that such a limited number of patients precludes any meaningful statistical analysis of data and conclusions must be viewed with great reservation. Our most recent report3 of 151 patients accumulated over 34 months—now 252 patients over 43 months, as presented at the recent American Stroke Association 25th Annual Stroke Conference—still is limited by marginally adequate numbers. It has, however, provided us with sufficient data to apply multivariate analysis to questions about size, rural/urban location and academic affiliation of treating hospitals, specialty expertise of supervising physicians, pretreatment patient risk factors, accuracy of pretreatment CT interpretation, incidence and predictors of poor outcomes including symptomatic intracerebral hemorrhage (ICH) and ICH-related death. Our steering committee of volunteer stroke neurologists has reviewed CT images on every patient with a poor outcome; we obtained posttreatment CT scans on approximately 70% of patients and so know much about asymptomatic ICH. All CT images, regardless of clinical outcome, have been reviewed by a neuroradiologist blinded to all clinical details. This process has given us confidence that IV tPA in Minnesota has been reasonably safe over the last 3 years and not detectably different from the statistically robust National Institute of Neurological Disorders and Stroke study.4 Our initial and motivating concerns of 1996 have gradually been lightened, though we realize that our conclusions are yet tentative and can’t completely counter the skeptical concerns of many of our local colleagues. We will publish our data in full when we have accumulated 300 patients, later this year.

Our process has been different from the OSF effort. The OSF Network appears to be centrally directed, while our IV tPA treating hospitals have been independent after the initial orientation and nominal “training.” Our observation tools evolved over the first 2 years of our organization, and on behalf of those now organizing or implementing such clinical programs, we have some questions for the OSF authors: How were the widely distributed medical facilities recruited and organized, for this and other stroke projects? Were/are there CME education-presentations only, or more specific arrangements? Was a specific Stroke/tPA Champion named at each site? How is communication maintained between the various facilities? How are peripheral sites encouraged and given feedback about their performance in following the protocol? Who are the “certified staff” who perform National Institutes of Health Stroke Scale testing and collect data in the peripheral sites; how are they trained and their scoring validated? Who pays for the efforts at the peripheral sites?

This lengthy questionnaire still leaves many issues to be addressed. It seems likely to us that local factors of personnel availability, interest, and enthusiasm will determine the direction and depth of efforts at any facility, and so some unevenness will be inevitable in overall results of a given “center.” This inhomogeneity is itself worthy of documentation and analysis. As participants in the broad national effort to bring IV tPA therapy from the stroke center out into mainstream practice, we can only applaud the OSF group for their work and encourage the continuation and improvement of such practical demonstration projects.

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Response

We would like to acknowledge Davenport and colleagues for their comments on our work. Their efforts to bring acute stroke therapy to more patients in their area of Minnesota also deserve to be commended. We agree that one weakness of our study is the small number of patients that were followed up. However, the intent of our study was to examine whether intravenous rtPA can be safely given to patients at facilities other than a large regional medical center. The patient outcomes we observed in our study were similar to or perhaps slightly better than what was seen in the National Institute of Neurological Disorders and Stroke Trial, and no significant differences were seen between the “hub” facility and the other participating hospitals. Growing evidence from several studies examining the use of rtPA since approval in 1996 further supports the safety and efficacy of rtPA administration using the Food and Drug Administration guidelines, including the Minnesota experience by Hanson et al.1-5

The organization of the OSF Stroke Network is, in fact, very different from the Minnesota group. The primary goal of our network was to provide support to small community hospitals (68 to 251 beds) so that they have the infrastructure in place to deliver up-to-date stroke care at their facilities. There is an uneven distribution of neurologists throughout most parts of rural areas in the United States. This lack of neuroscience support and
expertise remains the biggest challenge to delivery of acute stroke therapies. It has become more evident that such support is critical to protocol compliance to ensure the success and good outcome of rtPA therapy. Protocol deviation is likely related to poor outcome. Supporting small rural hospitals from a hub or regional medical center may be one model offering assistance to these facilities to safely deliver acute stroke care. A manuscript is currently being prepared on the organization of the OSF Stroke Network; however, we will briefly answer several questions by Davenport et al.

The OSF Stroke Network is now a 21-hospital organization facilitating a systematic team approach to provide stroke care in Central Illinois. The initial recruitment of potential facilities began with meetings with individual hospital administration and presentations to the medical staff at each rural hospital. A letter of agreement was developed for sites outlining requirements for participation. There are neither financial obligation nor required transfer of patients to the hub. Network hospitals were individually asked to determine the level of stroke care they felt they could provide. In the agreement, participating hospital administration agreed to support the development of a stroke program at the local institution (ranging from community education to acute treatment). One key person at each site is identified as the local champion to lead their stroke care program. Each network facility was provided with a resource manual, which contained stroke management protocols, CareMaps for patient management, outcome monitoring, and marketing tools. The hub, therefore, played a facilitative role to the participating sites. In addition, a standardized data collection form was developed and used by participating centers to follow their acute stroke patients. OSF Saint Francis Medical Center agreed to train the local staff, facilitate a systematic team approach to provide stroke care in each site. The Stroke Network infrastructure has made an impact on the ability of rural hospitals to deliver up-to-date stroke care at each site. The Stroke Network infrastructure has made an impact on the ability of rural hospitals to deliver state of the art stroke care. How to perfect it and maintain the momentum remains to be assessed.

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Diffusion-Weighted Magnetic Resonance Imaging in Brain Death

To the Editor:

The case report on diffusion-weighted imaging (DWI) in brain death by Lövblad and Bassetti in the February issue of Stroke may be appealing but deserves elaboration. The DWI studies in the case report show widespread ischemia, and the MR angiography shows absence of flow in the intracranial portion of the carotid arteries. However, it is not stated in the report whether there was flow void in the extracranial carotid arteries. Its presence may have suggested a diagnosis of bilateral carotid artery occlusion (eg, due to dissection) resulting in bilateral hemispheric infarction as the cause for the patient’s coma. Additionally, the authors did not comment on whether there was flow in the basilar artery. This information may have been available to the authors but was not commented on in the text.

However, much more disturbing is that this communication wrongly suggests that an imaging modality can diagnose brain death even when the clinical examination shows some remnant of brain stem reflexes. We are not certain what the authors meant by “The neurological examination after the MRI showed an intubated comatose patient who had deteriorated neurologically.” It is possible that the patient had met the criteria for brain death, but the authors did not provide details on clinical testing.

Brain death is the irreversible loss of function of the brain and brain stem. The diagnosis of brain death in adults in the United States is not, as the authors stated, “usually supported by confirmatory tests.” The article quoted here did not propose that view. The guidelines proposed by the American Academy of Neurology stated that “. . . confirmatory test is not mandatory but desirable when specific components of the clinical testing cannot be reliably performed. . . .” Differences in recommendations for confirmatory tests after a clinical diagnosis of brain death exist in European countries and are even mandatory in Italy, Luxembourg, and Holland. In addition, the Swiss brain death code requires mandatory repeat testing by two physicians, and confirmatory tests are considered optional (“facultative”).

Before a clinical examination is performed, the proximate cause should be known, and obviously a compatible neuroimaging study does not obviate a search for confounders. It is incorrect to state that “on the basis of the imaging findings it was concluded that the patient had entered a state of brain death,” and we truly hope this was merely an oversight.

It is a seeming contradiction of our time, as much as we embrace high technology and innovative equipment, that we have to continue to use a clinical approach in the determination of brain death. No matter what, brain death remains a clinical diagnosis. Unless the authors can provide a comprehensive neurological examination with a detailed apnea test, the claim that this is the first example of a DWI image of brain death should be withdrawn.

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To the Editor:

Lövblad and Bassetti in the February 2000 issue of *Stroke* described the DWI findings of an elderly woman with ischemic heart disease who suddenly became comatose and developed generalized convulsions. The neurological examination revealed a deeply comatose subject with bilateral pyramidal signs and partially preserved brain stem reflexes. MRI imaging of the brain performed 1 day later revealed diffusely increased signal on the DWI sequence, a herniated temporal lobe, and areas of hemorrhage in the right basal ganglia. On the basis of such findings, the authors diagnosed brain death.

The diagnosis of brain death, also termed death by neurological criteria, relies on the presence of coma of irreversible origin, brain stem areflexia, and apnea. The diagnosis is entirely clinical, and confirmatory testing is required only in patients in whom specific components of clinical testing cannot be reliably evaluated.2 The diagnosis is particularly complex in patients with coma of undetermined origin. In such cases, prolonged observation is warranted, and testing to determine absent cerebral blood flow should be performed.2 Imaging studies are often used to confirm that a neurological catastrophe that could lead to death by neurological criteria has occurred. The Guidelines for Determination of Death published in the United States by the President’s Commission indicate that imaging studies are useful only to help determine the cause of coma and to limit the period of observation.2 When confirmatory tests such as cerebral angiography or transcranial Doppler examination are used, the anterior and posterior circulation should be examined.2

Abnormal signal on DWI sequences and associated decreases in apparent diffusion coefficient likely represent non-Brownian diffusion of water as a result of energy failure and cytotoxic edema.1–4 DWI abnormalities may be nonspecific and may occur with nonischemic insults. DWI may be normal in patients with evolving strokes.5,6 DWI abnormalities may occur at cerebral blood flow levels as high as 41 mL/100 g/min, while brain death implies absent blood flow to the brain.4 Standard axial and coronal MRI imaging may readily identify signs of transtentorial or diencephalic herniation.6 Nevertheless, such findings do not necessarily indicate irreversible brain injury or brain death, because they may occur in patients who do not meet clinical criteria for brain death.6

In our opinion, the imaging findings described in this unfortunate woman suggest a diffuse ischemic insult to the brain, with resultant compartment shifts. The absent flow-void signal in the carotid arteries can not be interpreted as a sign of brain death unless the extracranial carotid arteries are patent and absent flow is also documented in the posterior circulation. Diagnosing brain death in this patient was particularly difficult, as the cause of coma was not certain.

MRI imaging may have a role in the diagnosis of brain death, as observational studies performed in recent years have already suggested. Ishii and colleagues7 considered absence of the intracranial carotid arteries above the supraclinoid portions, diffuse cerebral swelling, as well as tonsillar and central herniation findings suggestive of brain death. Such findings were noted in a small case series study but have not been validated in larger studies and have not been compared with cerebral angiography. It is possible that 3D time-of-flight MR angiography may give a false diagnosis of brain death in patients with increased intracranial pressure, reduced cerebral perfusion pressure, and very slow blood flow. Given the enormous ethical implications that the diagnosis of death by neurological criteria carries, caution should be exerted before embracing these new techniques as confirmatory diagnostic tools. These DWI findings cannot be considered specifically diagnostic of brain death.

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Response

We thank Drs Phan, Wijdicks, Chalela, and Kasner for giving us the opportunity to be more precise on certain points that might be misunderstood in our recent article in *Stroke.*1 We agree that brain death is, as Drs Phan and Wijdicks state, a clinical diagnosis,2 and we did not intend to imply that DWI could replace or even challenge the well-accepted methods of establishing this diagnosis. The aim of our paper was to report new MRI findings with DWI that may in the future be used to support the clinical diagnosis of brain death. In our patient, it was MRI that first suggested brain death. This diagnosis was, however, clinically confirmed immediately after the radiological testing. The clinical examination, which we did not report in detail in our short communication, revealed loss of signs of brain and brain
Correlates of Clinical Brain Death

We were not able to visualize intracranial vessels on MR angiography (MRA); these brain death. The reported clinical examination and evolution allow us to test was not performed. Despite this limitation, we believe that the patient was not considered a potential organ donor, an apnea dissection, either clinically or on spin-echo MRI. There was also no flow in the basilar artery, either on spin-echo imaging or in the MRA. We do not consider the conventional time-of-flight (TOF) MRA method we performed (using a slab covering the intracranial carotid arteries) to be suitable for examination of the extracranial carotid arteries since they are located peripherally, even if flow could be detected at the edge of the slab in small vessels in the areas corresponding to the extracranial arteries. Also, TOF sequences are prone to signal degradation due to blood flow disturbances.

In addition to what was mentioned in our report, we performed a first-pass 3D gadolinium-enhanced MRA of the head and neck vessels, which covered the arteries of the brain and neck from the aortic arch to the circle of Willis; this sequence is much less prone to flow-related artifacts than conventional TOF sequences and is closer to conventional angiography than TOF sequences in its capacity to demonstrate vascular occlusions. Using this method, we could see patent extracranial carotid arteries on both sides but no intracranial vessels: neither the internal carotid arteries nor the basilar artery were present (Figure), even in the later time series. There was also no visible string sign compatible with dissection.

While it is a method which has proved to be of interest for the investigation of cerebral ischemia, we are also well aware that DWI is very sensitive to tissular damage, and may also be nonspecific and even provide false-negative or false-positive results for ischemia under certain circumstances. DWI, indeed, demonstrates changes in tissular motion which have to be completely elucidated; it can, however, explore interesting underlying pathophysiological changes in ischemic states; DWI and ADC changes have been observed to be reversible in experimental models of ischemia, but this is still debated. However, there seem to exist thresholds of ADC changes under which reversibility is less likely. Also, the extent anatomically and ADC-wise makes such recovery in our patient rather unlikely, in our opinion.

In summary, we believe that DWI could become a further ancillary diagnostic tool supporting but not required for the diagnosis of brain death, in addition to cerebral angiography, Doppler ultrasound, and conventional MRI. This was the intended message of our report.

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First-pass dynamic gadolinium-enhanced 3D MR angiography of the carotid arteries (TR 7.8 ms, TE 3.5 ms, field of view 225×300 mm, 140×160 matrix) acquired in the coronal plane, the slab covering parts of the upper neck and head regions. This arterial phase image shown in the frontal projection shows both external carotid arteries and branches to be filled with contrast. There is no filling of the intracranial carotid arteries or the basilar artery. Filling of these vessels also did not occur in the later phases.

stem function, and the patient died later the same day. Because the patient was not considered a potential organ donor, an apnea test was not performed. Despite this limitation, we believe that the reported clinical examination and evolution allow us to consider our DWI findings as new MRI correlates of clinical brain death.

As to the technical points raised, there was no flow in the intracranial arteries on spin-echo imaging and there were no visible intracranial vessels on MR angiography (MRA); these findings, in addition to herniation, are previously reported MRI correlates of clinical brain death. We were also not able to demonstrate a proximal cause: there was no evidence of carotid dissection, either clinically or on spin-echo MRI. There was also no flow in the basilar artery, either on spin-echo imaging or in the MRA. We do not consider the conventional time-of-flight (TOF) MRA method we performed (using a slab covering the intracranial arteries) to be suitable for examination of the extracranial carotid arteries since they are located peripherally, even if flow could be detected at the edge of the slab in small vessels in the areas corresponding to the extracranial arteries. Also, TOF sequences are prone to signal degradation due to blood flow disturbances.

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Ultrasound Assessment of Brain Perfusion

To the Editor:

We read with great interest the recent article by Seidel et al.1 on visualization of brain perfusion with harmonic imaging. The authors observed a homogeneous dose-dependent increase in the brightness of brain parenchyma in 12 healthy volunteers after intravenous bolus application of a perfluoropropane-containing echo contrast agent and concluded that it is possible to detect brain perfusion with ultrasound. We would like to add our experience with another ultrasound technique related to brain perfusion and in this way encourage further research on this new topic. In all echo-contrast–specific imaging techniques, interaction between ultrasound waves and microbubbles depends on acoustic pressures. Harmonic imaging exploits the fact that at lower transmit powers, echoes reflected from microbubbles...
Contrast-burst imaging in healthy individual. A, Basic gray-scale image in an axial diencephalic plane of section showing the ipsilateral region of the thalamus (T) and the lentiform nucleus (L), frontal pole on the left side. B, Basic contrast-burst image before echo-contrast agent application. C, 10 seconds after echo-contrast agent application, visualization of small branches of the intracranial vessels (small arrows). D, 20 seconds later, clear increase of optic intensities in the ipsilateral brain hemisphere; nonperfused areas such as the frontal horns of the lateral ventricles can be identified (large arrow).

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exhibit harmonics of the transmit signal. Harmonic frequencies can be separated from the unwanted fundamental frequency by filter settings. At higher acoustic pressures, compared with harmonic imaging examinations, microbubbles undergo destruction, fusion, and splitting. This phenomenon has been termed stimulated acoustic emission. Signals resulting from bubble destruction are interpreted as flow signal and can be displayed color coded even from stationary or low-flow microbubbles. For this reason, ultrasound techniques that enable detection of these signals are appropriate for the detection of parenchymal cerebral echo-contrast enhancement that is associated with brain perfusion. We performed contrast-burst imaging (CBI) examinations, an ultrasonic method exploiting stimulated acoustic emission, in healthy individuals to evaluate whether this technique is useful for transcranial ultrasound. CBI is derived from power mode but has improved spatial resolution and a high sensitivity for the detection of microbubbles by use of sequences of broadband pulses and a high pulse-repetition frequency. CBI examinations in 8 healthy individuals (mean age 38.9 years) were performed after bolus application of 4 g of galactose-based microbubbles. A Siemens Sonoline Elegria ultrasound system equipped with a 2.5-MHz phased-array 90° sector transducer was used. Instrument setting was comparable to that in the study of Seidel and coworkers.1 Series of 45 to 70 images were acquired at a frame rate of 0.5 Hz. Ultrasound investigations in a diencephalic scanning plane were performed unilaterally using the transtemporal approach. Insonation depth was 10 cm and frame rate 0.5 Hz. All investigations were digitally recorded and evaluated offline. Regional cerebral echo contrast in the thalamus and the lentiform nucleus was quantified by calculating peak intensities (PIs) (in arbitrary units ranging from 0 to 4095) and time-to-peak intensities (TPI) from time-intensity curves. Echo-contrast enhancement with characteristic time-intensity curves could be observed in all individuals in both regions of interest (see Figure) PIs ranged between 1364 and 2098 (mean ± SD, 1623.3 ± 345.5) units in the thalamus and between 1142 and 2881 (mean 2142.5 ± 642.1) in the lentiform nucleus. Mean TPIs were 34.8 ± 17.1 and 32.5 ± 13.2 seconds for the thalamus and the lentiform nucleus, respectively.

In accordance with previously published studies, Seidel et al convincingly described the potential usefulness of harmonic imaging examinations to assess cerebral parenchymal brain perfusion.2–4 In addition, our experience shows that ultrasound techniques using higher transmit powers enable identification of microbubble destruction in brain parenchyma and in this way may serve as a diagnostic tool to assess brain perfusion despite considerable attenuation of ultrasound signals through the intact skull. Few data on ultrasonic detection of brain perfusion have previously been published.1–4 Nevertheless, assessment of brain perfusion with ultrasound opens a new and exciting research field in transcranial neurosonology that was formerly restricted to pure identification of large vessels. We agree with Seidel et al that these new techniques cannot be compared with diffusion/perfusion-weighted MRI or PET. Evaluation of quantitative parameters is not possible because of the nonlinear relationship of microbubbles and acoustic intensities, the depth-dependent attenuation of the transmitted ultrasound pulses, and many other physical factors. However, preliminary data indicate that semiquantitative analysis of harmonic imaging examinations may identify hypoperfused brain areas in acute stroke.4 Considering the widespread availability of duplex scanners in neurological hospitals on the one hand and the potential therapeutic consequences that may result from an early knowledge about localization and extent of hypoperfused brain areas in acute stroke on the other hand, establishment of these techniques for a larger stroke population could become an important contribution to improve stroke management.

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Response

There is a pronounced difference in the imaging technology in the article published by our group using harmonic gray-scale imaging and the technique introduced by Wilkening et al using contrast-burst imaging, which is derived from power Doppler technology. With CBI, a high pulse-repetition frequency in combination with a wall filter suppresses the tissue signal and also most flow signals. High ultrasound energy that is associated with the destruction of microbubbles produces broadband noise in the Doppler spectrum. Consequently, a part of this noise signal will fall into pass band of the wall filter and will be displayed. Postert et al used that technology in 8 volunteers and showed signals in the brain using the transtemporal approach.

The major problem of ultrasound contrast imaging for the quantification of brain perfusion, especially the nonlinear relationship of microbubble concentration in the tissue and the ultrasound intensities, could not be solved with this technology. Potentially, the high frame rate of the CBI could be used to evaluate the relationship between time-to-peak values and tissue perfusion. This should be analyzed further.

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Hyperglycemia and Extracellular Glutamate in the Ischemic Brain

To the Editor:

In their recent Stroke contribution, Li and colleagues present data showing an enhancement of glutamate accumulation in the ischemic rat cerebral cortex following glucose administration. The results presented are comparable to those in a prior publication by this group on the relationship between extracellular glutamate levels in the ischemic rat forebrain and hyperglycemia. Hippocampal glutamate levels were unaffected. The result is of particular interest in that an elevation of glutamate levels in the extracellular milieu, in conjunction with the excitotoxic actions of this amino acid, could account for the generally accepted notion that preischemic hyperglycemia exacerbates brain damage due to transient global or forebrain ischemia. Unfortunately, readers of the article are apt to be misled by the authors’ discussion of existing literature on the effects of hyperglycemia on extracellular glutamate levels. They have neglected to mention both an earlier publication by their own group showing that topically applied glucose induced a decrease in glutamate levels in the ischemic human brain as well as another report describing a glucose-induced reduction in extracellular glutamate levels in the caudate nucleus of rats following cardiac arrest. The reduction in glutamate levels has been attributed to an ability of glucose to fuel glutamate uptake by astrocytes during ischemia. The results also contrast with our own findings of reductions in extracellular cerebral cortical glutamate levels in the ischemic brain following topical or systemic administration of glucose.

Of particular concern to us is the failure of the authors to acknowledge that Choi et al actually described a significant reduction in hippocampal dialysate glutamate concentrations following glucose administration, stating only that there was no increase in these experiments. This misrepresentation of data is then compounded by the Editorial Comment, which cites the findings of Choi et al as a hyperglycemia-enhanced increase in extracellular glutamate concentrations during ischemia, rather than the significant decrease that was actually observed. Although the question of whether hyperglycemia facilitates or reduces ischemia-evoked glutamate efflux will now inevitably become a contentious issue, we believe that both the paper and the Editorial Comment contain misleading representations of the existing literature which deserve examination.

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Response

In their letter to the editor, Drs Phillis and O’Regan comment on our findings that hyperglycemic rats subjected to 15 minutes of forebrain ischemia show a more pronounced increase in extracellular glutamate concentration in the neocortex (but not in the hippocampus) than normoglycemic ones, and they criticize our failure to recognize that other studies have shown that glucose administration in fact decreases glutamate release during ischemia. We regret that the results of these articles were not discussed. We should have recognized the study of Swanson et al which was published in 1994. We missed the 1999 article by Phillis et al simply because it came to our attention after our article had been submitted and was in press. We did not quote the results of Kanthan et al because the data were obtained from epileptic tissues. Finally, we quoted the article by Choi et al but noted only that they did not observe an increase in glutamate release, failing to mention that they actually observed a decrease.

The differences in results are relevant to 2 main scientific issues. One is related to the question of whether an enhanced glutamate release may explain why hyperglycemic animals show exaggerated tissue damage, particularly in the neocortex. Our results, but not those of Choi et al., Phillis et al, or Swanson et al, are compatible with this possibility. The second issue is related to the ability of glucose, when provided in excess, to sustain glutamate reuptake by astrocytes and other cells under ischemic conditions, explaining the decrease in glutamate release observed by other groups.

The discrepancies in results are probably related to differences in methodology, particularly in the mode of administration of
glucose and the model of ischemia. Our results are based on systemic administration of glucose and on a model which gives such dense ischemia that glycogen and glucose stores are depleted within a few minutes. Because the exogenous supply of glucose is dwindling, and the Na⁺, K⁺, Cl⁻, and Ca²⁺ gradients are dissipated, it is difficult to envisage a force for the continued reuptake of glutamate. The situation is different in the studies of Kanthen et al⁴ and Swanson et al,² who continuously administered glucose, together with normal concentrations of Na⁺ and K⁺, by the microdialysis catheters. This argument cannot be applied to the results of Phillis et al.³ However, these authors reported plasma glucose values of 30 mM in the preischemic period, which suggests sustained anaerobic glycolysis.

Another factor of potentially large importance is the duration of ischemia. It would have been of interest to know whether any of the other groups²-⁵ observed a worsening of tissue damage in hyperglycemic subjects. As remarked by Choi et al.,⁵ the ischemia induced in their experiments could have been of such moderate degree that an enhanced glucose supply improved the bioenergetic state, as observed by Folbergrová et al⁶ in experimental middle cerebral artery occlusion.

A third factor is the influence of hyperglycemia on intracellular and extracellular pH, which are probably decisive variables determining adverse effects of glucose on the damage incurred. These variables have been determined in our model,⁹ but are difficult to evaluate in the experiments described in several studies.²-⁵

Clearly, the results reported in our study and those observed in the other studies are not comparable, but it is interesting to note that glutamate release during ischemia varies with the experimental conditions and with the areas used for sampling. We are, therefore, left without clear answers to 2 important questions: (1) Is the exaggeration of damage in hyperglycemic animals related to the extracellular glutamate? and (2) Does hyperglycemic reduce glutamate release, or enhance glutamate uptake in the ischemic brain?

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Is Transcranial Magnetic Stimulation of the Motor Cortex a Prognostic Tool for Motor Recovery After Stroke?

To the Editor:

The recent and important study from Pennisi et al¹ has focused attention on the ability of a noninvasive and relatively simple technique, which can be carried out at the patient’s bedside and is potentially useful in gathering prognostic information on the future recovery of motor function, especially of the hand. Due to the growing amount of reports produced in this field,²-⁴ I believe that there should be some consensus on a few prerequisites for future studies in this area. This proposal is an attempt to limit the (only apparent) controversies of the related literature, which in my opinion are due mainly to selection and methodological bias.

It is a common experience that two groups of stroke patients, although similarly affected in hand function in the early days after the stroke, can recover in a quite different way. This might be ascribed to various reasons, including short-term phenomena that are known to disappear in a few days, such as the perilesional edema, and the functional block of still-living neurons and fibers (others, on the contrary, are going to die in the same period because of a cascade of mechanisms that lead to enlargement of the original volume of lesion); the prevalently cortical or subcortical site of lesion; the total volume of lesioned area; the interindividual variability in middle cerebral artery perfusion territory and/or topography of motor output to the hand muscles (including the number of multiple representations of the same muscles in separate clusters of motoneurons within the primary motor cortex); the presence and amount of ipsilateral corticospinal fibers;⁵ and the role of the unaffected (it should not be called “healthy”) hemisphere. By taking as an example the Pennisi et al study,¹ most of the relevant information, as defined above, is missing on both clinical and neurophysiological grounds. We know only that the examined patients had complete hand palsy at the onset; nothing is written about the arm, shoulder, face, and leg muscles. More importantly, the transcranial magnetic stimulation (TMS) examination was not repeated immediately before discharge from the hospital, a period during which most of the short-term phenomena would have been resolved.

The motor evoked potential (MEP) was defined “normal” on the healthy—or rather the “unaffected”—side at days 1 and 365, but is this information really relevant? It is indeed known that MEPs which are exceptionally and progressively larger than normal can be elicited during follow-up from the unaffected hemisphere of stroke patients, when the affected hemisphere remains inevitable.⁴ This hyperexcitability has been ascribed to the experience-dependent increase of synaptic efficiency in the
unaffected motor cortex, which on its own might exert a depressive modulation on the affected motor areas via corticocortical, transcallosal connections; therefore, the hyperexcitability of the unaffected hemisphere might represent a bad prognostic indicator for recovery.

By positioning the stimulating coil (a large, nonfocal type) at the vertex, one misses the definition of the hot spot site, that is, the scalp position from which TMS triggers MEPs of largest amplitudes and minimal latencies with the lowest amount of stimulus intensity. There are international standards now available (to which one of the coauthors of the study by Pennisi et al has contributed) that properly define all these items for clinically oriented studies.

It is also important to consider that most of the population in the study of Pennisi et al recovered very little at follow-up. Does this sample reflect the wide variety of recovery levels seen in the real life? In the literature as well as in the clinical experience of every neurologist there is a significant fringe of patients who recover within a few days or weeks from even a complete palsy of the hand. This type of patient, probably because of good recovery, does not come back as an outpatient. It would have been extremely interesting to have recruited a few cases with a better recovery as the final outcome, in order to test properly the prognostic validity of the method and to avoid the “floor effect” caused by the comparison of TMS with a unidirectional phenomenon (no recovery or poor recovery), which is not representative of the variety of final outcomes following a stroke.

Very little is written about the drugs used in the tested patients, despite the fact that some drugs are known to interfere with the excitability of motor cortex.

In conclusion, I feel that the TMS has accumulated sufficient scientific credence to be proposed as a relevant tool in predicting the functional outcome from stroke in the very early stages. However, to avoid an accumulation of literature with little or no clinical repercussion (as has been the case until now), there should be an effort to recruit a larger number of patients (multicenter studies?) in a series that is designed well in statistical terms, is truly representative of the general population affected by stroke, and is tested with the appropriate methodology.

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Response
The comment by Dr Rossini contains some very helpful suggestions for future studies of the prognostic value of TMS in stroke but also questions the methodology used in our study. Indeed, the electrophysiological study was not repeated after a few weeks, but this was not crucial here, because the primary aim was to determine whether early TMS (within days from stroke) was useful in predicting long-term motor outcome. Of course, if mechanisms involved in the clinical recovery are to be investigated in detail, TMS sessions and clinical assessments need to be repeated over time. Also, use of the focal stimulating coil is crucial in this respect, but this was not the aim of this work. Large circular coils are powerful, widely available, and convenient for most clinical applications of TMS, and they are certainly sufficient to determine whether early motor responses are present or not. If a method of investigation becomes complicated and time consuming, it is unlikely to be adopted by clinicians, except in a few highly specialized centers. Our study focused on hand strength and dexterity, because of its functional importance in humans and also because hand muscles are particularly easy to activate with TMS, even under difficult conditions. For the sake of conciseness, motor function of other areas was not detailed in the paper, but from global clinical scores (National Institutes of Health Stroke Scale) it is clear that the population was rather homogeneous at stroke onset and that global deficits were moderate to severe. Indeed, the population sample was limited, so that ultimate recovery of our patients may not reflect the outcome of the general population. However, one of the selection criteria was absence of MEP in the affected hand within 48 hours from stroke. We know from previous studies1–2 that patients with persistent responses early after stroke recover better, so that simply this selection criterion could have influenced the final outcome. As for drugs used, we generally avoid in stroke patients the administration of central nervous system depressants, which can alter the level of consciousness and hamper recovery and rehabilitation. Moreover, to rule out effects of drugs, associated diseases, or level of arousal on corticospinal excitability; only patients with normal responses on the “unaffected” side were included. Finally, we believe that the role of ipsilateral corticospinal fibers in the process of recovery remains purely speculative, because they represent <10% of motor cortex output, the majority of which ultimately crosses in the segmental cord,3 and that many other mechanisms must be considered.

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Pharmacological Preconditioning With Lipopolysaccharide in the Brain

To the Editor:

In a recently published article in Stroke, Ahmed et al have, conversely to their hypothesis, shown that a low dose of lipopolysaccharide (LPS) is capable of inducing delayed neuroprotection against cerebral ischemia. This result is particularly interesting with regard to increasing evidence that LPS exerts a preconditioning effect in both myocardium and brain, with a better knowledge of biochemical pathways that could be involved in such a process.

A pretreatment with a low dose of LPS has been known for many years to reduce ventricular arrhythmia and infarct size resulting from experimental myocardial ischemia. Such a beneficial effect appears 8 to 24 hours after LPS administration and implicates several mechanisms, such as cytokine release, neutrophil infiltration, as reported by Ahmed et al , could be an early step to the development of brain ischemic tolerance. As recently demonstrated, these data support the finding of endothelial nitric oxide synthase in cerebral blood vessels. Occlusion preconditioning induces cerebral blood flow, and expression of protective antioxidant enzymes such as catalase or superoxide dismutase. In the brain, the first evidence of LPS-induced preconditioning has been described by Tasaki et al. Nevertheless, one of the major difference with heart ischemic preconditioning is the time of occulsion–induced preconditioning, the neuroprotection induced by LPS is delayed from 2 to 4 days after LPS administration, with a maximum effect at 3 days. The LPS-induced preconditioning is partly dependent on TNF-α release, which could trigger the other mechanisms involved in such a neuroprotection process.

Whereas LPS-induced and occlusion-induced preconditioning in the brain share the same delay in generating neuroprotection, we have demonstrated that the mechanisms involved are different. Occlusion preconditioning induces in cerebral cortex the expression of 70-kDa heat-shock protein, a potent mediator of brain ischemic tolerance, when LPS induces an increase expression of endothelial nitric oxide synthase in cerebral blood vessels. As recently demonstrated, these data support the findings that LPS-induced preconditioning is associated with preservation of microvascular perfusion, possibly mediated by nitric oxide. The absence of deleterious effect of polymorphonuclear neutrophils infiltration, as reported by Ahmed et al, could be the reflection of a balance between favorable and unfavorable effects of LPS administration, in which low doses seem to mediate a cascade of events that lead to ischemic tolerance. In this perspective, as in myocardium, recent data suggest that administration of a low dose of LPS is able to induce the expression of superoxide dismutase in the brain concurrent with the development of brain ischemic tolerance. Recent evidence for ischemic tolerance in the human brain and the insufficiency of usual preventive therapy implicate the development of new pharmacological targets for stroke treatment. LPS-induced preconditioning could be considered in this field as a particularly interesting pharmacological model.

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Response

We thank Drs Deplanque and Bordet for their comments on our recent article. The main thrust of our study is the unusual observation that LPS could substantially increase polymorphonuclear neutrophils infiltration into the ischemic brain but at the same time reduce brain injury. This finding challenges the conventional view on a deleterious role of neutrophils in ischemic brain injury. In this regard, it is interesting to note that other inflammatory cells such as macrophage and lymphocytes were also salutary, but not detrimental, in rodent spinal cord injury models.

The view of Drs Deplanque and Bordet on the development of brain tolerance to ischemia highlights a newly emerged neuroprotective role of LPS priming. Oxygen free radicals are known to contribute to ischemic brain injury. Superoxide dismutase, a potent antioxidant, has been shown to reduce vasogenic brain edema and ischemic brain injury. Recently, endothelial nitric oxide synthase (eNOS) has also been shown to confer neuroprotection. Thus, induction of cytoprotective genes such as superoxide dismutase and eNOS, as suggested by Drs Deplanque and Bordet, is a plausible mechanism of LPS action. However, further studies are needed to fully delineate the molecular mechanisms of LPS-induced brain tolerance to ischemia.

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