The Unusually Shaped Bifrontal Hematoma

To the Editor:

We present a rare case of bifrontal hematoma resulting in death caused by a spontaneously ruptured aneurysm of the anterior communicating artery (ACoA). The hematoma was in the shape of a thick crescent, and the aneurysm was revealed on computerized tomography (CT) and CT angiography. A 60-year-old man suffering from hypertension and diabetes mellitus was admitted to the emergency service after having lost consciousness following vomiting and urinary incontinence. Examination revealed a tachypneic and irregular respiration. His score on the Glasgow Coma Scale was 5 (E,M,V). Both of his pupils were middilated, and direct and indirect light reflexes were decreased; deep tendon reflexes were decreased in all extremities, and he had a bilateral positive Babinski sign. He was admitted directly to the intensive care unit (ICU) from the emergency department. In the ICU, cardiopulmonary arrest developed. He was intubated, and a ventilator maintained his respiration. His radiological evaluation including CT revealed a thick, crescent-shaped bifrontal hematoma measuring 90 cm³ (Figure). He was grade 5 according to the World Federation of Neurological Surgeons grading scale. Conventional angiographic examination could not be performed because there was no indication of surgical approach and the patient’s clinical condition was not appropriate for transporting him to the angiography unit. On the second day of admission, the patient underwent a control CT and CT angiography. It demonstrated a 0.5-cm-diameter berry-shaped hematoma symmetrically in bifrontal localization on computerized tomography and CT angiography images. Upper slices also showed cerebrospinal fluid and hematoma levels in posterior horns of the lateral ventricles. Since the patient’s neurological status had been poor, a digital subtraction angiography was not performed. His operation was postponed until his status was stabilized. His neurologic and metabolic status quickly worsened, and his blood pressure decreased. He died on the third day of admission to the hospital.

Twenty-four percent of nontraumatic frontal lobe hematomas are caused by ruptured aneurysms of the anterior cerebral or ACoA. The frontal lobe hematoma is generally unilateral and it may be round, ovoid, triangular, linear, or rectangular. On the other hand, bilaterally frontal hematomas are less common than unilateral hematomas, and they present in a bilobed or butterfly shape. According to the literature, the known cause of bifrontal hematoma is ruptured aneurysm of the ACoA. Unilateral or bilateral frontal hematoma extending inward from the pericallosal cistern, caval-septal region, or interhemispheric fissure is most characteristic of ACoA aneurysm rupture. This kind of extension is also seen in the glial tumors and is called a butterfly tumor. Yock and Larson have classified CT findings of ruptured ACoA aneurysms including asymmetric subarachnoid hemorrhage, subarachnoid hemorrhage involvement of the anterior interhemispheric fissure, and septal hematoma. They also observed non–giant aneurysms and occasionally negative scans. We detected the hematoma symmetrically in bifrontal localization opening to the ventricle.

Weisberg and Stazio reported 2 patients with bifrontal hemorrhage. One was butterfly shaped and the other was bilobed. The bifrontal hematoma in our case, however, was in the shape of a thick crescent. General symptoms of frontal lobe hematomas include headache, vomiting, neck stiffness, seizures, and transient focal neurologic deficits. Neurologic signs are altered consciousness, motor deficits, gaze preference, nuchal rigidity, and sometimes aphasia. Our patient presented with loss of consciousness after vomiting. According to Pasqualin et al, the presence of a large hematoma, ventricular hemorrhage, and shift of ventricles is associated with poor prognosis. But Benoit et al concluded that the survival of the patient with intracerebral hematomas caused by aneurysmal rupture was more closely linked to the size and the localization of the hematoma than the localization of aneurysm or degree of midline shift. Tokuda et al reported that there had been a close correlation between the site of hematoma and that of the ruptured aneurysm. They found that poor outcome in patients with intracerebral hematoma seemed to be related to severity of clinical grade on admission. In our patient, we believe that the poor prognosis depended on the severity of the grade, which was caused by the bifrontal hematoma approximately 90 cm³ in volume.

In conclusion, bilateral frontal hematomas due to ruptured ACoA aneurysms may also appear in an unusual shape (eg, a thick crescent) in addition to the bifrontal butterfly shape.

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Re: Feasibility and Safety of Moderate Hypothermia After Massive Hemispheric Infarction

To the Editor:

We read with great interest the article by Schwab et al regarding hypothermia in acute ischemic stroke. The authors should be commended on their important work that possibly paves the way toward a randomized study exploring the efficacy of this mode of therapy in acute stroke. However, there are several points that merit further discussion before such a study could commence. Hypothermia is considered to be one of the most powerful methods of inducing cerebral protection in models of cerebral ischemia, hypoxia, and trauma. Postulated mechanisms of action of hypothermia include lowering excitatory amino acid secretion and downregulation of glutamate receptors, diminished production of reactive oxygen species, reduced consumption of tissue antioxidants, and reduced inflammatory response. Other postulated mechanisms include a nonspecific lowering of cerebral metabolic rate and changes in cerebral blood flow. However, as is the case with other potential neuroprotectants, mild hypothermia has long-term protective effects only when started either during or shortly after the neuronal injury. In their study, Schwab et al began to cool their patients relatively late after ischemic onset (mean 9 ± 2.2 hours [range 4 to 75 hours]), which might have reduced the efficacy of this method of neuroprotection. We are told, however, that some of the patients were cooled relatively earlier than others, and it would therefore be important to learn whether these patients had better outcome parameters than those who were cooled at later time points following the injury. Moreover, since hypothermia is suggested to work by neuronal protection and not merely by reducing intracranial pressure, it would be interesting to learn whether the early institution of hypothermia resulted in smaller infarcts (as depicted by neuroimaging) as compared with the late onset of hypothermia and to historical controls.

It is not a secret that despite its protective capabilities, hypothermia may also lead to a number of important side effects as detailed by Schwab et al. At least a few of these side effects may be related to the depth of hypothermia. Thus, several authors have shown that mild hypothermia produced by lowering the core temperature to 33°C or 34°C suffices to produce neuroprotection. Nevertheless, Schwab et al have lowered the core temperature further and that might also have contributed to the relatively large number of complications observed in the current study. It is therefore possible that in future studies, use of milder degrees of hypothermia could reduce the complication rate and improve the efficacy.

Another point that needs more specific attention is that of the effect of rewarming on the final outcome. Previous experimental data have shown that too rapid rewarming may result in excess mortality and disability in animal models and human data. However, the patients in the current trial were passively rewarmed at a relatively rapid pace (11 to 24 hours), and this may have limited the clinical efficacy and led to a rebound rise in intracranial pressure as suggested by the authors. Therefore, we would suggest that in future larger trials exploring hypothermia as a possible neuroprotectant in stroke, the rewarming phase would be longer and rewarming should be much more gradual over a few days.

Thus, experimental data from animal studies have proven hypothermia to be a very promising method for establishing neuronal protection. It seems that in order for similar results to be obtained in humans, one needs to adhere more closely to the timing of hypothermia initiation and rewarming and the depth of hypothermia that would produce the best results in humans with the minimal number of side effects.

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Response

We appreciate the interest of Drs Leker and Ovadia in our study. As they point out, many of the proposed mechanisms of hypothermia are beneficial only in a very narrow time window after the neuronal injury. In experimental stroke, this time...
window varies between 60 to 180 minutes after occlusion of the middle cerebral artery. Clearly, an ultra early treatment would be desirable. Still, this is currently not feasible. We would like to point out that, no matter how thrilling the prospect of hypothermia for neuroprotection may be, we applied this treatment only to reduce brain edema formation. The question of the effectiveness of hypothermia for neuronal protection cannot be answered on solid grounds. As we stated in our article, earliest induction of hypothermia was 10 hours after symptom onset, clearly a time window way beneath all experimental suggestions. Therefore it does not seem justified to analyze the difference between relative early or delayed induction of hypothermia. An ideal experiment to evaluate this in the clinical practice would be to look at the effect of very early cooling (<34°C attained within 6 hours of onset), using MR perfusion and DWI as each patient’s baseline predictor of the expected final infarct volume.

As stated in our article, target temperature in our patients was 33°C. A further decrease was not always avoidable. We recently reported our experience with an endovascular cooling catheter, an approach that may allow a better temperature control, thus avoiding significant deviations from target temperature. With the emerging catheter technology, it may allow more rapid cooling as well as more precise temperature control.

The two other points mentioned by Leker and Ovadia are well taken but difficult to answer. We have no data concerning the optimal temperature of hypothermia. So far, all studies have used target temperatures of 33°C to 34°C. It therefore seems prudent to choose similar target temperatures, in order to be able to compare effects and side effects. It is purely speculative whether milder degrees of hypothermia would produce fewer and less severe side effects. The same holds true for the speed of rewarming. A recent study from our department illustrates the importance of slow and controlled rewarming. The technical feasibility, though, remains doubtful, unless we have potent cooling devices to achieve exact temperature control. We feel that additional hypothermia trials examining different depths of cooling are sure to follow in the coming years.

Overall, as is true for many facets of stroke care, it would be desirable to stick as close to the experimental evidence as possible, but as we had to learn in many negative neuroprotectant trials, men and mice are different.

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Re: Crossed Nonaphasia in a Dextral With Left Hemispheric Lesions: A Functional Magnetic Resonance Imaging Study of Mirrored Brain Organization

To the Editor:

We read with great interest the article by Hund-Georgiadis et al., in which they presented a case report of a patient with crossed nonaphasia after left-hemispheric stroke. Functional MRI revealed “mirrored” brain organization not only for language but also for divided/selective attention, as assessed by the Stroop task. Both functions were lateralized to the right hemisphere.

The authors did not assess traditional right-hemispheric cognitive functions by means of functional MRI, such as visuospatial attention. They mention in their case description, however, that “the patient complained of problems in the visuospatial domain.” Neuropsychological testing revealed impaired processing of nonverbal material, whereas processing of verbal material was normal. Therefore, we suspect that visuospatial attention, which normally lateralizes to the right side of the brain, was lateralized to the left hemisphere in this case, providing further support for the authors’ claim that their patient showed “completely reversed,” ie, “mirrored,” cognitive functions. The case by Hund-Georgiadis et al agrees with our findings from a cohort of healthy subjects who were assessed for hemispheric dominance of language and visuospatial attention by means of functional transcranial Doppler ultrasonography and functional magnetic resonance tomography. We found that most subjects with atypical language lateralization indeed presented with a completely reversed brain organization, ie, visuospatial attention and language being lateralized into opposite hemispheres.

Additionally, our study demonstrated that not only can completely reversed functional anatomy exist without obvious penalty to brain functions, but partially reversed functional anatomy can as well.

Four of our 10 healthy subjects with right-hemispheric language dominance did not present with a “mirrored” brain organization. Rather, both language and visuospatial attention were lateralized to the same hemisphere. Furthermore, cognitive functions can vary significantly in the extent to which they lateralize. Clinicians need to be aware of the possibility of combined linguistic and visuospatial impairments of variable degrees after left- or right-hemispheric damage.

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Response

We thank Drs Flöel and Knecht for their interest in our study. We agree that the hemispheric dissociation of functions such as language and attention cannot be considered as a fixed pattern in each individual, although it is found in the majority of healthy subjects. This observation has important potential clinical implications, particularly in the evaluation of neuropsychological
An Unjustified Return to the Past

To the Editor:

We read with interest the article by Qureshi et al.1 regarding the role of conventional arteriography (CA) in evaluating patients with internal carotid artery (ICA) stenosis assessed by Doppler ultrasound (DUS) in general practice. Because we recently looked at this issue,2 and because we have performed all carotid endarterectomy (CEA) studies on the basis of DUS findings alone, we would like to comment on certain concerns raised by this article.

To determine whether it is appropriate to select patients on the basis of DUS studies performed at 20 different neurovascular laboratories, Qureshi et al.1 used CA to evaluate 130 patients referred to their endovascular service with symptomatic (≥50%) or asymptomatic (≥60%) ICA stenoses. The positive predictive value of DUS in identifying symptomatic and asymptomatic candidates for ICA intervention was 80% and 59%, respectively, with a false-positive value of 20% and 41%, respectively. In addition, the authors1 reported that an analysis on a subset of 41 patients who underwent DUS at their laboratory, accredited by the Intersocietal Commission for the Accreditation of Vascular Laboratories, revealed a false-positive value of 20% (8/41). In the light of these findings, Qureshi et al suggested that a large proportion of the patients referred to their service on the basis of DUS in general practice did not in fact have significant stenosis likely to benefit from ICA intervention, and that inappropriate ICA intervention could result in 1 in every 5 patients, even when studies were performed at the best ultrasound laboratories. While we might agree with their first point, we have some doubts as to the reliability of the DUS performed at most of the laboratories considered in this study.

At many institutions of many countries, DUS currently provides adequate physiological and imaging information for clinical decision-making and operative treatment in most patients with ICA stenosis, without the use of CA. The accuracy of DUS in classifying the severity of disease is higher than 90% in accredited laboratories, with experienced technicians and a physician’s careful review. After a technically adequate DUS (the likelihood of error has been even further reduced by the introduction of echo-contrast agents that have significantly helped in distinguishing between an occlusion and a pseudo-occlusion3), preoperative CA has rarely induced any changes to patient management, and in as few as 1 to 2% of CEA cases in several recent series.4–6 The DUS criteria adopted vary according to the angiographic standard used7–11 and should be tailored to specific institutional and individual situations. If DUS is used as a screening tool, a high sensitivity is required to avoid missing patients who might benefit from CEA. On the other hand, if DUS is used as the only preoperative test for ICA disease, a high specificity is also required in order to avoid performing any unnecessary CEA. However, DUS relies on the technical skills and experience of the operator.8,12 Each laboratory should validate its own criteria for grading ICA stenosis against CA before DUS can be considered a reliable diagnostic tool for patient selection. Criteria for grading ICA stenosis must be both machine- and laboratory-specific, bearing in mind that both velocity criteria and frequency shift criteria differ considerably in different duplex machines. Moreover, applying the same diagnostic criteria to different equipment is a potential source of inaccuracy, and using more than one make of scanner at the same laboratory involves applying different duplex criteria to each machine. In an era of continuous renewal of technologies and turnover of human resources, DUS machines and technologists also change, possibly affecting the outcome of DUS. Regular internal validation is consequently mandatory within each laboratory to achieve and maintain the highest level of DUS accuracy. The “alarming” findings reported by Qureshi et al on the inaccuracy of DUS in general practice should not cast a shadow on the effectiveness of the DUS method as a stand-alone screening and diagnostic tool; they are merely the expression of the laboratories’ failure to implement regular internal validation, even if they are accredited.

Moreover, Qureshi et al stated that it is their policy to perform CA for all patients with suspected ICA lesion, and not just for patients whose DUS is considered inadequate. Since the authors observed no complications in 94 patients who underwent CA alone, they concluded that “given the present low procedure-related morbidity and high degree of accuracy in centers with documented low morbidity, CA may be considered in each patient before a decision is made regarding ICA intervention”.1 Although this represents the preferred procedural tendency at many institutions where ICA stenting is routinely performed, this suggestion constitutes a return to the past and is frankly misleading. In fact, if we consider all 130 patients who underwent CA, including those treated by means of ICA stenting in the same session, the overall complication rate was 8.4% (11/130), with a neurological complication rate of 3.8% (5/130). This confirms the fact that CA carries a definite neurovascular risk in the evaluation of patients before CEA, even when it is performed by experienced hands.13 In the Asymptomatic Carotid Atherosclerosis Study4 in particular, the CA-related stroke rate was 1.2%, but this apparently low incidence is clinically relevant considering that all patients were asymptomatic and that CA alone accounted for nearly one half of all perioperative strokes.
Qureshi et al. stated that “all complications were directly related to use of larger catheters and delivery devices used for stenting.” but this is just a hypothesis. Many symptomatic and asymptomatic patients (on the basis of DUS findings in general practice) come to our university vascular service from various parts of the country. We find it more ethical, faster, safer, more cost-effective, and less invasive to repeat DUS at our laboratory rather than exposing patients (especially if they are asymptomatic) to an unnecessary additional CA-related risk, reserving the CA procedure for a few selected circumstances. We believe that, for ICA surgery to be justified, the risks have to be minimized as much as possible, so the current diagnostic trend must surely be noninvasive, as the Harvard group also recently pointed out.15

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Response

We appreciate the insightful comments by Ballotta and colleagues. As they correctly pointed out, variations in the quality of results among Doppler ultrasonographic laboratories preclude effective generalization of any results derived from a single site. The relative inaccuracy of carotid Doppler ultrasound in detecting carotid stenosis observed in our study may not be seen at other centers, as mentioned by Ballotta and colleagues.1,2 However, the converse may be true as well in that the high degree of accuracy reported by some centers may not be reproducible in general practice surroundings, where referrals are made on the basis of studies performed at many laboratories. Johnston and Goldstein3 compared the results of carotid Doppler ultrasound and contrast angiography in 569 consecutive patients evaluated for carotid endarterectomy. The rate of misclassification of carotid stenosis among patients undergoing carotid endarterectomies that were performed on the basis of Doppler ultrasound results alone was found to be 28%. Similar misclassification rates were found for patients evaluated at academic medical centers and community hospitals in the study performed by Johnston and Goldstein. The investigators recommended that surgical decisions be made with caution if they are based on the results of Doppler ultrasound alone. As Ballotta and colleagues correctly pointed out, each setting must have rigorous internal validations performed continuously to ensure the accuracy of Doppler ultrasound assessment of carotid stenosis. We agree that cerebral angiography does carry an inherent risk of complications that ranges from 0.5% to 4%.4–5 These include ischemic stroke, allergic reaction to contrast material, and local vascular complications related to femoral artery catheterization. Major complications are reported in 0.1% to 0.5% of the cases.4–6 However, carotid endarterectomy carries a higher risk of major complications (5% to 7% in large cross-sectional surveys), which varies according to patient population, surgeons, and centers.7,8 Therefore, our recommendation is that each center rigorously evaluate the accuracy of its noninvasive diagnostic practices to ensure that only patients who can potentially benefit from carotid endarterectomy are treated. This avoids exposure of patients to potential treatment-related complications in the absence of any anticipated benefit.

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Age-Adjusted Stroke Incidence Increase: Could Angiotensin AT1 Receptor Antagonists Enhance Stroke Prevention?

To the Editor:

A series of articles recently published in Stroke strongly suggest that age-adjusted stroke incidence is increasing. After a marked decline since the 1960s, the stroke mortality rate has plateaued since 1990 in both Japan1 and the United States.2 The in-hospital case-fatality rate for stroke, however, is declining in the United States,3 mainly because of better acute stroke treatment, although detection of milder cases of stroke through neuroimaging improvement may contribute to this trend.4 On the contrary, the age-adjusted stroke hospitalization rate increased by 18.6% between 1988 and 1997 in the United States.3 Even though the institution of more lenient criteria for hospitalization may partially explain this, this phenomenon strongly suggests an actual increase of age-adjusted stroke incidence,4 which could account for the leveling off of the stroke mortality rate despite the decrease of stroke case-fatality. Since the increased rate of hospitalization after stroke was limited to elderly patients >65 years, we quite agree with Tu5 that the stroke incidence increase may be due to more successful prevention of coronary heart disease (CHD) by increasing a population at higher risk for stroke, since CHD per se increases this risk.5 However, we are more reluctant to admit the role of aging per se, since the stroke hospitalization rate and therefore the suggested stroke incidence increase are age-adjusted. Furthermore, it should be noted that the prevalence increase of associated CHD was stable during the study period, in contrast to the prevalence of associated hypertension (33.6%; P=0.05), heart failure (31%; P=0.09), and diabetes (17.4%; P=0.17).

This significant increase in hypertension comorbidity is intriguing because the National Health and Nutrition Examination Survey (NHANES) III phases I and II showed only a slight decrease of well-controlled hypertension prevalence (from 29% to 27%) in the United States during the study period.4 Therefore, we would like to know the diagnosis criteria of hypertension used in their study and, in particular, whether the diagnosis was based on actual blood pressure data or only on the notion of a treated hypertension.

As indicated by Tu,4 suboptimal prevention of strokes may explain this incidence increase, and since hypertension control is plateauing in the United States and still improving in Japan,1 this raises the issue of stroke prevention efficiency by blood pressure (BP)-lowering drugs. The recent publication of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial7 has indeed clearly demonstrated that the BP-independent stroke protective effect of antihypertensive drugs is quite different according to their pharmacological class: in patients with a history of stroke and either normotension or hypertension, perindopril alone nonsignificantly decreased the risk of stroke recurrence by 5% in this trial,7 whereas for the same BP decrease, indapamide significantly decreased this risk by 29% in the Poststroke Antihypertensive Treatment Study (PATS).8 This almost 6-fold greater stroke risk reduction with a diuretic than with an ACE inhibitor is reminiscent of the almost 3-fold better stroke prevention observed in the MRC trial,9 with high doses of bendrofluazide as compared with propranolol, which led Brown and Brown to hypothesize that angiotensin II might be stroke protective.10 Finally, 2 recent metaanalyses11,12 have concluded that calcium antagonists (long-acting dihydropyridines and the short-acting diltiazem) were more stroke protective than conventional treatment by beta-blockers and/or thiazides. This brief review of the stroke-protective effect of the 4 major classes of antihypertensive drugs suggests that diuretics and calcium antagonists, which stimulate the renin angiotensin and sympathetic (RAS) systems,13,14 have a greater BP-independent stroke protective effect than beta-blockers and angiotensin-converting enzyme inhibitors (ACEI), both of which decrease angiotensin II formation,13 at least in hypertensive patients or in normotensive patients with a history of stroke but with a low prevalence of CHD (<16%). Indeed, in the unique Heart Outcomes Prevention Evaluation (HOPE) trial, performed in patients with a high prevalence of CHD (80%),15 ramipril has been shown to have a BP-independent protective effect not only for cardiac events but also for strokes.

How is it possible to explain the opposite link between stroke prevention and the activation of the RAS systems according to the low or high prevalence of CHD? A possible explanation may rely on the duality of the angiotensin receptors: the AT1 receptors responsible for the vasoconstrictive and proatherothrombotic effects of angiotensin II and the non–AT1 receptors (like AT2 and AT4 receptors), for which stimulation has been shown to decrease the severity of neurological outcomes in acute brain ischemia in rodents, through either more rapid collateral circulation recruitment16 or increased neuronal resistance to anoxia.17 The stimulation of these brain protective mechanisms by the RAS system—stimulating diuretics or calcium antagonists may explain their greater BP-independent stroke protective effect compared with that of beta-blockers and ACEI in populations with low initial prevalence of CHD. On the contrary, in populations with a high CHD prevalence (80%), as in the HOPE trial, the deleterious effect of blunting these non–AT1-mediated beneficial mechanisms is canceled out by the beneficial effect of blunting the AT1-mediated proatherothrombotic effect. This is all the more likely to occur when high doses of a tissue-specific ACEI such as ramipril are used, since they will efficiently prevent destabilization of highly prevalent atherosclerotic plaques. This resulted in a 3-times-greater prevention of cardiac events than of strokes (227 versus 70).15 Since myocardial infarctions and heart failures are per se major risk factors of strokes,5 it is very likely that a great proportion of stroke prevention in the HOPE trial was attributed to this highly effective cardiac event prevention.

Since ACEI and AT1 receptor antagonists (AT1RA) have comparable anti-atherothrombotic effects in experimental animals,18 whereas AT1RA stimulate angiotensin II formation by blunting the AT1-mediated negative feedback of renin secretion and, therefore, non–AT1-mediated anti-ischemic mechanisms, AT1RA may have a cutting edge over ACEI by better preventing stroke. To prove this superiority, we propose to compare these 2 drugs in patients at higher risk for stroke than for CHD, i.e., in elderly hypertensive patients or in patients with a history of stroke but low prevalence of CHD.

If AT1RA are proven superior to ACEI in stroke prevention, their association with low-dose diuretics might become the most eligible treatment for global primary and secondary cardiovascu lar prevention, which might help to forestall the predicted worldwide increase in stroke.19


The Unusually Shaped Bifrontal Hematoma
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