Extraparenchymal Bleeding Predicts an Unfavorable Outcome in Patients With Hemorrhagic Transformation

To the Editor:

We read with interest the recent article by Fiorelli et al.1 The authors confirmed the reliability of hemorrhagic transformation (HT) as a diagnosis which, as we have found, could be made by either a neuroradiologist or a trained neurologist.2 However, of greater clinical relevance was the fact that they found that only severe HT (parenchymal hematoma 2 [PH2] in ECASS I1) was associated with an unfavorable outcome. As shown in the Table, the same result emerged from the Multicentre Acute Stroke Trial–Italy (MAST-I) analysis.3

We have found that severe HT is very often associated with intraventricular or subarachnoid bleeding. This finding, together with but independent of cerebral edema, made the prognosis unfavorable in our study. The severe HT (PH2) definition of ECASS I points to a “significant space occupying effect” and includes the presence of a “clot remote from the infarct area.”

But the ECASS I investigators did not specifically assess the effect of the intraventricular or subarachnoid bleeding on the prognosis. This finding and not HT per se is the real adverse effect of thrombolytic treatment, and we wonder whether any results from ECASS and NIH studies have been published on this point. We need confirmation of our funding on the prognostic variance with ECASS I, the MAST-I investigators defined the framework of MAST-I should be made with caution. At any case, comparisons between our data and those collected in counterparts (OR 1.3, 0.65 to 2.61).

EH2 was observed in 91% (77% to 97%) of EH+ patients as opposed to 70% (54% to 83%) of their EH− counterparts (OR 1.3, 0.65 to 2.61). Our data are therefore not in favor of the hypothesis that the risk for disability and death is increased in association with EH. The numbers are too small, however, to rule out type 2 errors. In any case, comparisons between our data and those collected in the framework of MAST-I should be made with caution. At variance with ECASS I, the MAST-I investigators defined unfavorable outcome as an RS of ≥3 at 6 months after stroke. Our opinion is that rather than EH, the mass effect caused by PH and the resulting compression of functioning brain tissue is the primary determinant of poor outcome. However, topics of crucial importance like this certainly deserve further studies. Between-cohorts analyses can help, especially if made using individual data and after having verified the extent to which the information drawn from different sources is comparable.

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Response

We are grateful for the interest shown by Candelise et al in our article concerning the prognosis of hemorrhagic transformation of a cerebral infarct. In the ECASS I cohort, 34 of 71 patients (48%) with parenchymal hematoma (PH) at day 1 had an associated extraparenchymal hemorrhage (EH+). At 3 months all these 34 patients had a poor outcome, defined as a Rankin score (RS) of ≥1 (100%, 95% CI 90% to 100%), as opposed to 90% (79% to 97%) of patients with PH but no EH (EH−). The analysis of risk expressed in terms of odds ratio did not reveal a significant additional risk of poor outcome associated with EH (OR 1.09, 95% CI 0.54 or 2.19). Poor outcome defined as an RS of ≥2 was observed in 91% (77% to 97%) of EH+ patients as opposed to 70% (54% to 83%) of their EH− counterparts (OR 1.3, 0.65 to 2.61).

Our data are therefore not in favor of the hypothesis that the risk for disability and death is increased in association with EH. The numbers are too small, however, to rule out type 2 errors. In any case, comparisons between our data and those collected in the framework of MAST-I should be made with caution. At variance with ECASS I, the MAST-I investigators defined unfavorable outcome as an RS of ≥3 at 6 months after stroke. Our opinion is that rather than EH, the mass effect caused by PH and the resulting compression of functioning brain tissue is the primary determinant of poor outcome. However, topics of crucial importance like this certainly deserve further studies. Between-cohorts analyses can help, especially if made using individual data and after having verified the extent to which the information drawn from different sources is comparable.

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Clinical Relevance of Detecting Asymptomatic Embolic Signals in Acute Stroke

To the Editor:

Kaposzta and colleagues successfully performed bilateral transcranial Doppler (TCD) examination and other measure-
ments in 100 of 119 patients with acute anterior circulation infarction within 72 hours of stroke onset. Asymptomatic embolic signals (AES) were detected over the side of stroke in 16 patients; presence of AES was associated with significant carotid stenosis/occlusion, whereas absence of AES was associated with lacunar infarction in patients without significant carotid disease and potential cardiac embolic sources. I wish to make the following comments.

First, the authors reported that 19 of the 119 consecutive patients did not have an acoustic window for the bilateral TCD examination. Exclusion of other patients was not mentioned in the article. Did any patient/relative refuse to participate in the study? Was there any patient who could not tolerate the 1-hour TCD examination because of unstable conditions and/or restlessness?

Second, early use of aspirin has been shown to be beneficial in acute ischemic stroke, but antiplatelet agents and anticoagulants were withheld in the 30 patients who underwent the serial TCD examinations. Although there was no difference in the frequency of prior use of aspirin between patients with AES and those without AES, I am interested to know whether the dosage of aspirin is related to the presence of AES.

Third, it is important to note how the authors classified the stroke subtypes according to the presumed etiology. Ten of the 16 patients positive for AES were classified under the etiological category of significant carotid artery disease, and 2 of them had coexistent potential cardiac embolic sources but were not classified under the category of “coexistent causes.” In addition, patients were put under the category of “lacunar stroke” only when significant carotid artery disease and potential cardiac embolic sources were excluded. Thus, the classification of patients into the different etiological subtypes had been different from what was stated in the Methods section. More than 22 patients of the cohort had potential cardiac embolic sources, and more patients would be in the category of “coexistent causes.” It is interesting to note that patients with significant carotid artery disease can present with lacunar strokes and that carotid endarterectomy reduces the risk of recurrent stroke of both lacunar and nonlacunar types. On the other hand, it may be impossible to confirm the real cause of stroke in patients who have both significant carotid artery disease and potential cardiac embolic sources.

Fourth, I found the results subsection entitled “Localization of Embolic Source” rather confusing. In my opinion, the results of the entire 90-minute period of AES detection should be presented together because localization of the embolic source would be interpreted on an individual basis according to the available information. In addition to a cardiac or aortic arch source of emboli, simultaneous AES over both the middle cerebral artery and the common carotid artery can also arise from the common carotid artery proximal to the site of ultrasonic monitoring.

Fifth, the stroke severity was omitted in the article. The information is of great relevance since the presence of AES was found to be related to a higher risk of death. It is possible that the presence of AES was associated with carotid occlusion and that carotid occlusion resulted in severe strokes with a high case fatality rate.

Finally, the authors’ results indicate that presence of AES is associated with carotid occlusion rather than potential cardiac embolic sources, but the clinical relevance of early TCD detection of AES is unclear. Only 1 of 16 patients with AES (6.3%) had a recurrent stroke while 12 patients without AES (14.3%) had recurrent strokes (10 patients) or transient ischemic attacks (2 patients), suggesting that AES are really asymptomatic events with little clinical consequence. There is no documented role of urgent carotid endarterectomy, and the benefit of carotid endarterectomy is unknown in patients with established carotid occlusion. Although long-term anticoagulation is indicated in stroke patients with potential cardiac embolic sources such as atrial fibrillation, the controversy lies in when to start anticoagulation.

Thus, early extracranial carotid sonography for significant carotid artery disease and appropriate screening for potential cardiac embolic source are clinically relevant, and detection of AES by TCD may not alter the clinical management.

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Response

We thank Dr Cheung for his interest in our article. In reply to his specific questions, first, no patients were unable to tolerate the 1-hour TCD examination. We found that a commercially available transducer fixation device (Spencer Technologies) was great assistance in probe fixation. Second, all patients who were taking aspirin had been treated with doses ranging from 75 to 300 mg per day. The number of patients who were embolic signal–positive means that the study is not sufficiently powered to examine relationships between aspirin dose prior to admission and rates of embolization. In addition, we didn’t feel that this was an issue of major interest. Third, Cheung is very critical of our stroke subtyping, but we feel he has not read our manuscript with sufficient care and has failed to distinguish between carotid stenosis and occlusion. Stroke subtyping was performed as described in our paper, with a diagnosis of carotid artery stroke being made if there was ≥50% stenosis in the symptomatic internal carotid artery territory. If there were other potential stroke causes in addition to the carotid stenosis, a diagnosis of coexistent stroke was made. There were 10 patients who had carotid artery stroke, but an additional 2 patients had carotid stenosis with other coexistent causes of stroke. These were tabulated in our Table 1 as coexistent. In addition to describing the group of patients with carotid artery disease, who could have either stenosis or occlusion, we specifically looked at patients with carotid occlusion to determine whether embolization distal to the stump could occur. This group of patients included the 2 with other potential stroke causes.

Fourth, we attempted to localize the embolic source in 2 ways. (1) In all patients we recorded simultaneously from both middle
cerebral arteries. Bilateral embolic signals, or embolic signals on the asymptomatic side, are suggestive of a central or cardiac cause of embolism. (2) In patients in whom embolic signals were detected at the time of recording, we insonated the symptomatic MCA and the ipsilateral CCA simultaneously for an additional 30 minutes. We are unclear as to where his figure of 90 minutes comes from, but if Dr Cheung means that we should add the additional 30 minutes of middle cerebral artery recording to the 120 minutes already performed, we feel this would be inappropriate and make it more difficult to analyze the data. We can compare the detection of embolic signals among the group of 100 patients only if recordings of similar duration have been made throughout the group.

Finally, as stated in our article, “the number of strokes and deaths in our study was very small, making firm conclusions difficult to draw” on the relationship between stroke and death and asymptomatic embolic signals. Our data have suggested that this is an area worth looking at in more detail, but further larger studies would first need to be performed. Nevertheless, our results suggest this is an area worth investigating further. The analysis performed by Cheung on our data is misleading. While, indeed, only 1 of 16 patients with embolic signals did have a recurrent stroke, the 3 causes of death may have been related to further stroke. Postmortem examinations were not performed. Additionally, in his reanalysis he assumes that all emboli-negative patients who had recurrent stroke and/or death had recurrent stroke rather than death. This was not the case.

We would entirely agree that the use of asymptomatic embolic signal detection in this context is a research technique, and further studies are required to evaluate its clinical usefulness. These will be aided by technical advances in the technique, particularly analysis systems that will allow automated analysis of the large quantities of Doppler data produced.

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Reduced ICA Diameter and Reduced Stroke Risk

To the Editor:

I read with interest the report from Rothwell and Warlow1 describing a reduced risk of stroke with reduced internal carotid artery (ICA) diameter distal to severe symptomatic carotid stenosis. In postulating a reason, the authors state that postste- nostic narrowing must indicate low intraluminal pressure due to reduced flow across the stenosis, and then conclude that the low flow is less likely to dislodge emboli.

An alternative hypothesis is that the narrow ICA is a result of remodeling in response to a reduced blood velocity. Labropoulos et al2 have found evidence for compensatory arterial enlargement in areas of small hemodynamically insignificant plaque in carotid, coronary, and lower-limb arteries. These plaques, although small, would cause localized increase in blood velocity that may be triggering the enlargement process, bringing the blood velocity closer to its original value. If the same mechanism is causing the decrease in ICA diameter, this would imply that the reduced blood velocity occurs prior to the diameter change and that the low velocity has been present long enough for remodeling to occur.

The reduction in blood velocity can occur either because of reduced supply through a proximal tight, hemodynamically significant stenosis or because of reduced demand in the distal vascular bed. In my experience of lower-limb duplex scanning, the arterial diameter is not normally reduced distal to a tight stenosis even though the blood pressure is reduced, as shown by a low ankle brachial pressure index. Indeed, a reduction in diameter would increase the vascular resistance and could further reduce flow to an ischemic region. I feel it is more likely that the reduced ICA diameter occurs in response to a reduced demand in the distal vascular bed caused by previous embolic occlusions.

Rothwell and Warlow1 state that patients with poststenotic narrowing of the ICA have a low risk of stroke on follow-up but a high frequency of major stroke in the past and a high frequency of infarction in the ipsilateral cerebral hemisphere compared with patients without poststenotic narrowing. These past episodes would have reduced the blood flow in the affected hemisphere and would be consistent with the remodeling hypothesis.

The lower risk of subsequent stroke may arise in 2 ways. First, the reduced blood flow means that the blood velocity through a given stenosis is reduced, the shear stress is less, and therefore the risk of shedding emboli is reduced. Second, the fact that remodeling takes time means that patients with narrow ICAs are more likely to have stable plaque which has already passed through the higher-risk acute stages.

Supporting evidence for the remodeling hypothesis may be available from below-knee unilateral amputees. Superficial femoral diameters could be measured bilaterally and the ratio in amputees compared with normal values. If there is evidence for remodeling, the time course could be studied by serial measurements after amputation.

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G20210A PRTH Gene Mutation and Other Trombophilic Polymorphisms in Patients With Cerebral Vein Thrombosis

To the Editor:

The prevalence of some gene polymorphisms associated with inherited thrombophilia and its potential relevance in the ischemic stroke of young women was recently described in Stroke.1 At variance with patients with ischemic stroke, an increased risk of cerebral vein thrombosis (CVT) has been associated with the G20210A prothrombin (PRTH) gene mutation and oral contraceptive drugs. This finding was consistent with those in previous studies.2-3 In another study, a higher-than-normal prevalence of factor V Leiden mutation among CVT patients was reported.4 According to previously described methods,5 we have screened these 2 polymorphisms plus the homozygosity for the thrombolabile variant (677TT) of the methylenetetrahydrofolate reduc-tase (MTHFR) gene in 10 consecutive patients (4 men and 6 women; mean age 36.7 years; mean age at first event 35.1 years) referred to our center because of a history of CVT. In all cases, cerebral angiography and/or MRI showed a complete or partial lack of filling of at least 1 sinus. No patient showed venous malformations at the site of thrombosis. Differences in allele frequencies were tested by the Fisher exact test. Five of the 10 CVT patients (50%) were heterozygotes for the G20210A PRTH variant. This frequency was significantly higher (6.3%, P = 0.0004) than that in a group of healthy controls subjects matched for sex and age (n=259: 144 women and 115 men;

mean $\pm$ SD age 36.7 $\pm$ 12.8 years), from the same ethnic background. The frequency of factor V Leiden and of the MTHFR polymorphism in patients with CVT were 10% (1/10) and 33.3% (3/9), respectively, ie, twice as much as that found in controls (5.8% [15/259] and 17.4% [45/259], respectively). Two patients had the MTHFR genotype and the G20210A PRTH variant simultaneously; 1 carried the PRTH and the factor V Leiden variants. On the whole, 3 patients (33.3%) showed the coexistence of 2 thrombophilic genes; this was significantly different from the prevalence of the coexistence among healthy subjects (5/259, 1.9%; $P = 0.0019$). Three CVT patients had a family history of venous thromboembolism; all were heterogeneous for the G20210A PRTH variant. Four patients showed recurrent venous thromboembolism; among them, 3 carried the G20210A PRTH variant and 2 showed the association of the latter with factor V Leiden or with the MTHFR 677TT genotype. In our female patients, 2 of 6 experienced CVT while using oral contraceptives; none of the polymorphisms was present in both cases.

The coexistence of PRTH and factor V mutation has been strongly associated with juvenile and recurrent venous thromboembolism. The MTHFR variant increases the risk of deep-vein thrombosis in factor V Leiden carriers. Despite the limitations of the sample size, these data confirm the role of the G20210A PRTH variant as a predisposing factor for CVT. Our data also indicate that thrombophilic genes often coexist in patients with CVT. Whether (and the extent to which) thrombosis at this unusual site reflects a sustained hypercoagulable state needs to be further evaluated.

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No Side Effects After Low-Dose Amphetamine Administration in Stroke Rehabilitation

To the Editor:
We have previously reported the use of dextroamphetamine to enhance recovery from motor and language deficits subsequent to stroke. However, some clinicians have questioned the safety of the use of a stimulant drug in stroke patients. We have now followed a series of patients with no side effects of low-dose amphetamine administration as an adjunct to stroke rehabilitation. The protocol, which we have found to be safe, specifies that patients be entered between days 10 and 40 after stroke onset. Hemiplegic/aphasic patients are administered an oral dose of 10 mg of dextedrine or placebo 30 minutes before relevant therapies for 10 sessions. We monitor blood pressure of all patients before and within each treatment session and document any adverse reactions. We found no adverse reaction notations in any chart in a series of patients followed over a 1-year. Additionally, there were no differences in the blood pressure readings between drug-versus placebo-treated groups. Following are our subject definitions and blood pressure comparisons.

Forty-four stroke subjects with hemiplegia and/or aphasia and a radiologically verified lesion were studied. Criteria for entry into the study required that subjects have a single unilateral thromboembolic infarction and hemiplegia and/or aphasia, as defined by impairment level assessments. Exclusion criteria specified that none of the subjects have a terminal medical condition such as AIDS or cancer, other coincident neurological disease, history of psychiatric illness or extensive alcohol or drug abuse, unstable cardiac dysrhythmia or hypertension not controlled by medication (160/100 mm Hg), or untreated hyperhyroidism. Additionally, subjects could not be receiving $\alpha$-adrenergic antagonists or agonists, major or minor tranquilizers, or be aged $>80$ years. Written informed consent was obtained from each subject before the study, and the research protocol was approved by the institutional review for human subjects at each of the participating medical centers.

The study group consisted of 28 amphetamine and 16 placebo patients. The mean age of the treatment group was 61 years; the mean age of the placebo group was 61 years. There were 11 men and 17 women in the amphetamine group and 9 men and 7 women in the placebo group. In this blinded study, patients were entered between days 16 and 42 after onset and received an oral dose of 10 mg of amphetamine (dextedrine) or placebo on an alternating cycle of every third/fourth day for 10 sessions, paired with relevant therapies. Thirty minutes after drug/placebo administration, subjects began 1 hour to 1 hour 45 minutes of physical and/or language therapy, depending on their deficits. Documentation of side effects was made for all subjects across the study period. Blood pressure was monitored before and during the 10 treatment sessions in all subjects. Median systolic and diastolic blood pressure measurements were compared in the amphetamine- and placebo-treated subjects. The Wilcoxon rank sum test was performed on the difference of the medians between the 2 groups. Blood pressure readings of all subjects at baseline and across the 10 sessions were analyzed. Comparisons were made before drug administration (baseline) and 90 minutes into therapy sessions (within session) (see the Table for median blood pressure readings and within each treatment session and document any adverse effects).
scores for each group). There was not a significant difference from baseline to within-session measure on either systolic ($P=0.1912$) or diastolic ($P=0.4056$) differences for the 2 groups. In addition, at no time during the 12-month course of the study was there documentation of any negative event that could be attributed to amphetamine administration.

These data suggest that in patients with well-controlled hypertension, the effects of low-dose amphetamine administration are negligible. The data also support previous findings which suggest that toxic symptoms with doses $<15$ mg are rare. The subjects in this study may not represent all types of stroke subjects because of our careful exclusion criteria and patient screening. However, we did have patients with severe neurological impairments and other concomitant medical conditions who tolerated this low alternating dose without report of negative side effects.

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Transfemoral Digital Subtraction Angiography for Assessment of Vertebral Artery Occlusion in Rats

To the Editor:

The major disadvantage in rat models of global cerebral ischemia is the difficulty of occluding the vertebral artery through the alar foramina because the electrocoagulations are done “blind.” This mode of vertebral vessel occlusion is often unsatisfactory, and while postoperative selection on the basis of righting responses, EEG, and pupillary size is used in cerebral 4-vessel occlusion models, there is no substitute for demonstrating the completeness of the vascular occlusion. This “blind” vertebral occlusion technique might also explain the wide variation in cerebral blood flow measurements after brain 4-vessel occlusion. Furthermore, in the case of cerebral 2-vessel occlusion of the vertebral arteries, no validation parameter is available for confirmation that complete vertebral artery occlusion has been achieved. For all these reasons, we suggest the method of transfemoral digital subtraction angiography (DSA), which can be used for validation of successful vertebral artery electrocoagulation in rat models of global cerebral ischemia. DSA is the gold standard for the assessment of vascular occlusion. The DSA technique offers many advantages: it is a minimally invasive technique (5% mortality rate of 20 rats investigated), with high morphological resolution (Figures 1 and 2), which can be used repeatedly. When a DSA catheter (Tracker 10; Boston Scientific) was used with radiographic guidance, no traumatic disruptions of the arterial blood vessel system were obtained in any of the rats examined. The use of a maximum of 1.5 mL of contrast solution (Solutrast; Byk Gulden) had no marked influence on rat arterial blood gases, mean arterial blood pressure, or heart rate. After DSA, some animals adopted a hunchedbacked posture after femoral artery ligation and walked with extended paws for about 1 week. However, rapid collateralization of vessels in the area of occluded arteries into the rat groin area leads to partial recovery of the blood supply to the paws.

In the present study, assessment of adequate rat vertebral vessel electrocoagulation was demonstrated with transfemoral DSA. In 33% of the animals (6 of 20), only an incomplete vertebral vessel occlusion was achieved (Figure 1). In contrast, Figure 2 demonstrates a complete rat vertebral vessel occlusion.

Figure 1. Incomplete vertebral occlusion. Injection of contrast medium into the subclavian artery shows a high-grade stenosis of the vertebral artery at the C-1 level (arrow). Occlusion is incomplete, and there is filling of the distal vertebral and basilar artery.

Figure 2. Complete vertebral occlusion. Injection of contrast medium into the left subclavian artery shows filling of the left vertebral artery in the cervical portion (a, white arrow). A later phase of the angiogram shows stasis of the contrast media at the C-1 level (b, black arrow) and no filling of the distal vertebral artery or basilar artery. Complete occlusion of the vertebral artery has been achieved.
in an earlier phase of vessel filling (1a) and a later state of contrast medium injection (1b).

In summary, transfemoral DSA seems to be a reliable technique for the validation of the completeness of vertebral artery occlusion in rat models of global cerebral ischemia (2- or 4-vessel occlusion).

The present study was financially supported in part by the Medical Faculty of the University of Heidelberg (FSP Geriatrie). The authors wish to thank Roland Galmbacher and Stephanie Schöppenthau for technical assistance.

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G20210A PRTH Gene Mutation and Other Trombophilic Polymorphisms in Patients With Cerebral Vein Thrombosis
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