Letters to the Editor

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Standardization of Carotid Ultrasound

To the Editor:

The article by Ranke et al in the February issue of Stroke represents an excellent advancement in Doppler grading of carotid artery stenosis. Since many surgeons now depend on Doppler ultrasound for decisions for carotid endarterectomy because of the costs and dangers of angiography and the cost and resolution problems of magnetic resonance imaging, it is of paramount importance that the accuracy of vascular laboratories be improved. Use of the continuity principle with Doppler ultrasound offers the greatest hope of correlating Doppler hemodynamics with angiographic morphology if velocities representative of the mean velocity can be consistently measured. The initial trial of this principle was disappointing due to the problems with the unknown angle of continuous-wave Doppler and the limited resolution of then-current angiography. Also, without biplane angiography the shape of the stenotic lumen, which greatly affects the relationship of velocity ratios, was not known. Our analysis of the results of Ranke and coworkers indicates a systematic asymmetry of the lumen exists, resulting in the intrastenotic/distal velocity ratio increasing the estimated severity by 18% over that expected if the stenosis in the lumen cross-section progressed in a symmetrical way.

To deal with the angle problem, we have found that handheld 2 megahertz pulse wave Doppler probes, interrogating the internal carotid artery stenosis and distal segment with a focal distance of 4 cm, agree well with velocity ratios from color Doppler imaging. Handheld pulse-wave Doppler ensures a consistent low angle and reaches the internal carotid artery well beyond turbulence. Our results, preoperative to carotid endarterectomy, indicate that many laboratories are overestimating the severity of carotid stenosis, leading to some unjustified surgery.

The authors’ answers to the following questions will be helpful in exploring the velocity ratios. What was the maximum resolution of their angiograms? How did they deal with the shrinking size of the distal internal carotid artery in cases of preocclusive stenosis? What is their 95% confidence interval for the range of data in their Figure 1? Can they provide their formula for calculating the percent stenosis over the range of velocity ratios? Can they confirm the formula?

Percent diameter stenosis = \( a \times \left[ b - \sqrt{c / \text{velocity ratio}} \right] \)

where \( a = 0.9986, b = 1.139, \) and \( c = 1.176 (R^2 = 0.93, \) standard error of the estimate = 9.2%).

Thus, we can confirm Dr Spencer’s formula as a reasonable calculation of diameter stenosis from the mean velocity ratio. Our digital subtraction angiography unit was based on a 1024×1024 matrix with a maximum resolution of 3.5 line pairs/mm. None of our patients had a preocclusive stenosis with a collapsed distal lumen, but 3 patients had stenosis diameter of >90% compared with the luminal diameter cranially, according to the NASCET definition. In preocclusive carotid stenosis, both angiographic percentage calculation based on the distal

Figure 1. Correlation of diameter reduction with area reduction obtained from biplane angiographic views (n=79 carotid artery stenoses), based on the formula

Diameter reduction = \( \left( 1 - \sqrt{1 - \text{area reduction} \times x} \right) \times 100\% \)

where \( x \) represents the stenosis asymmetry index, calculated from the maximal stenosis diameter \( D_{\max} \) and the minimal diameter \( D_{\min} \) as \( x = D_{\max} / D_{\min} \). An asymmetry index \( x = 1 \) indicates an axisymmetric stenosis.

Response

We appreciate Dr Spencer’s thoughtful comments with regard to our study, particularly since the milestone article of Spencer and Reid1 stimulated our work on Doppler grading of carotid stenosis based on the principle of continuity of flow. As Dr Spencer correctly points out, our data indicate a systematic asymmetry of the stenotic lumen. As a corollary of the eccentric shape of the stenotic lumen, maximal percent diameter stenosis values according to the NASCET definition are higher than the corresponding cross-sectional area values: Dr Spencer calculated an 18% increase over the stenosis values based on the axisymmetric model from our data. The relationship between diameter stenosis and area stenosis in our study is plotted for various degrees of luminal asymmetry in Figure 1. The more eccentric the lumen shape, the more linear the correlation of diameter stenosis and area reduction. Our original formula for nonlinear regression analysis was

Percent diameter stenosis = \( a \times \left[ b - \sqrt{c / \text{velocity ratio}} \right] \)


carotid diameter and the intrastenotic velocity/distal velocity ratio will underestimate the degree of stenosis when the distal carotid diameter is reduced. With the NASCET method, such lesions are classified angiographically as 95%. Classification as reduced or not reduced is sometimes difficult and can lead to observer variability with use of the NASCET stenosis definition. In 1979, Spencer and Reid first described reduced Doppler frequencies downstream to a tight stenosis. Carotid Doppler offers the opportunity for hemodynamic analysis. Evaluation of downstream velocity together with the velocity ratio could increase diagnostic accuracy in precocious stenoses with reduced flow. In our study, a mean velocity ratio >10 in combination with a mean velocity <0.26 m/s in the high cervical carotid artery increases sensitivity for detection of >90% stenosis to 100% with a specificity of 90%. The 95% confidence interval for the correlation of angiographic stenosis with predicted stenosis values using the mean velocity ratio (Figure 1 in our article) is plotted in Figure 2.

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Standardization of Carotid Ultrasound

To the Editor:

In a recent publication1 the authors reported a significant contribution to the standardization and normalization of duplex scanning for carotid stenosis. My purpose is to add a simple fluid mechanics analysis that supports their ratio of time-averaged blood flow velocity measured in the internal carotid intrastenotic segment to the time-averaged velocity in the downstream normal arterial segment.

Applied to the internal carotid artery, the law of conservation of mass requires that the time-averaged blood flow through the stenotic segment equal that in the downstream normal segment. Using the NASCET method, the percent diameter stenosis is 100(1−D1/D2), where D1 and D2 are the internal diameters of the stenotic and normal segments, respectively. The time average blood flow is IID2 V/4, where V is the spatial average velocity. Conservation of mass gives V1/D12=V/D22, or V1/V2=[1/(1−% stenosis/100)]2 and % diameter stenosis=100[1−(V2/V1)1/2]. Because the velocities in this simple formulation are both time and spatial (cross-section) averages and duplex scanning focuses on midstream velocities, these equations can be used in 2 situations. The above equations are good approximations for internal carotid arteries with mild or no stenosis because the time-averaged flow through both the stenotic segment and the distal segment have similar parabolic velocity profiles.2 Comparative V1/V2 data from Figure 1 and the above equation for 0%, 25%, and 50% stenosis are 0.7 versus 1.0, 1.5 versus 1.8, and 3.0 versus 4.0, respectively. When % diameter stenosis exceeds 50%, the flow through the stenotic segment becomes turbulent, the velocity profile is blunted, and the mean velocity is close to the midstream velocity. For laminar flow in the downstream normal segment, the velocity profile is parabolic and the spatial mean velocity is one half the peak (midstream) velocity.2 For this clinically important range, V1/V2=[2I/(1−% stenosis/100)]2 and % stenosis=100[1−(V2/V1)2]. Comparative data from Figure 1 and Table 2 and these equations for 60%, 70%, and 80% stenosis give V1/V2 values of 4.0 versus 3.1, 5.0 versus 5.6, and 10 versus 12.5, respectively. These simplistic theoretical results correspond with the author’s measured values and support the use of their velocity ratio.

However, there may be some drawbacks. We have found it difficult to obtain velocities in the normal downstream internal carotid artery in patients with high carotid bifurcations when the stenosis is long and when the artery is tortuous. The velocity in the normal downstream segment must be measured 4 to 5 cm distal to the stenosis to allow for reestablishment of a near-parabolic velocity profile. Because of flow into the external carotid artery, this method is not applicable to distal common carotid stenosis; however, in this case the ratio of the velocity in the stenotic common carotid segment to that in the more proximal normal common carotid artery is hemodynamically valid and should give acceptable results.

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Response

Dr Archie’s fluid mechanics analysis is based on the assumption that carotid artery stenoses are concentric. In this sense his model is simplistic: predicted velocity ratios are higher than measured ratios because of the asymmetric stenotic lumen. A 70% diameter reduction with concentric lumen yields higher velocity ratios than a 70% eccentric stenosis with higher cross-sectional area. Our data indicate that carotid stenoses are more or less eccentric. Because the individual shape of the stenotic lumen cannot be predicted from Doppler measurements, we must rely on the estimation from nonlinear regression analysis, as shown in Figure 1 in our article.1 What Doppler really tells us is cross-sectional area reduction, not diameter stenosis.

Dr Archie points out that reference measurement in the high cervical internal carotid artery is sometimes difficult. Less than 5% of our patients were ineligible for distal velocity ratio measurement: with sensitive color Doppler systems and suitable curved array or sector probes (ie, the ATL C7-4 and P5-3 probes) we could show the internal carotid 4 to 5 cm downstream in the majority of our patients. Patients with distal carotid stenosis or common carotid stenosis were not included in our study, but application of a “reversed velocity ratio” gave good results in our clinical practice, as correctly supposed by Dr Archie.

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Transcranial Doppler Monitoring of Carotid Artery Oclusion During Endarterectomy

To the Editor:

I read with great interest the article, “Predicting the Effect of Carotid Artery Oclusion During Carotid Endarterectomy: Comparing Transcranial Doppler Measurements and Cerebral Angiography,” by Doblar and colleagues.1 In this study, 45 patients were separated into 3 groups according to the presence of collaterals on 4-vessel cerebral angiography, and mean flow velocity (FVm) over the middle cerebral artery and EEG were continuously monitored during carotid endarterectomy. The collaterals are the anterior communicating artery (ACoA) and the posterior communicating artery (PCoA) on the side of surgery. I would like to raise the following comments.

First, evidence-based guidelines for carotid endarterectomy are available.2 The surgery is highly effective in preventing stroke among patients with symptomatic high-grade carotid artery stenosis but much less beneficial in patients with asymptomatic high-grade stenosis.3 4 In the study by Doblar and colleagues,1 41 of 45 patients did not have ischemic symptoms before carotid endarterectomy, the mildest stenosis was only 35%, and 5 perioperative strokes were encountered (see their Table 1). I am interested to know the indications of carotid endarterectomy in the patients with only 35% stenosis as well as the degree of stenosis and symptomatic status of the 5 patients who developed perioperative strokes.

Second, absence of collaterals on cerebral angiography may represent an adequate arterial system (ie, no need for collateral) or inadequate collaterals despite a high-grade stenosis. This is why cerebral angiography is an excellent anatomic but a poor functional tool. In the study of Doblar and colleagues,1 all group 3 patients had a nonfunctioning ACoA or anatomic hypoplasia or stenosis of the A1 segment of the anterior cerebral artery on cerebral angiography. The findings suggest inability to derive a good blood flow from the ACoA even if more collaterals are needed physiologically. This, together with a significantly greater severity of contralateral internal carotid artery stenosis, probably account for the findings on transcranial Doppler studies.

Third, the definitions of the “minimum FVm during occlusion,” the “prerelease FVm during occlusion,” and the “maximum FVm after release” do not have any physiological basis, because FVm varies continuously. The findings of a “significant” difference between the “average FVm during occlusion” and the “minimum FVm during occlusion,” between the “prerelease FVm during occlusion” and the “minimum FVm during occlusion,” and between the “average FVm 2 minutes after release” and the “maximum FVm after release” in group 1 and/or group 2 probably reflected greater variability of FVm in these groups when compared with that in group 3 (see Table 2 of Doblar et al1); there is no evidence of “progressive recruitment of collaterals during the occlusion period.”

Fourth, the mean arterial blood pressure was highest in group 3 during occlusion when FVm was lowest (see their Table 3). In contrast to the authors’ interpretations in the discussion, the findings probably indicated the physiological response to low FVm resulting from carotid clamping and poor collaterals.

Finally, EEG can provide physiological evidence of cerebral ischemia, and EEG was continuously monitored in the study.1 Nevertheless, EEG results were not provided in the article. I wonder whether the EEG results correlated well with the transcranial Doppler information and whether the EEG data predicted the occurrence of perioperative ischemia.

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Response

We thank Dr Cheung for his interest in our study.1 We published the article to illustrate value of knowing the functional status of the cerebral collateral pathway(s) in predicting the
response of mean middle cerebral artery blood flow velocity (FVm) to acute internal carotid artery (ICA) occlusion and release during carotid endarterectomy (CEA). Our study population was too small to draw conclusions regarding risks and benefits of operating on patients with combinations of symptomatic versus asymptomatic, high-grade, or low-grade ICA stenosis. Such a study, the ACAS multicenter CEA trial, has been published and has increased the impetus for surgeons to operate on asymptomatic patients with ICA stenoses of $\leq 60\%$. Two of our patients had low-grade ICA stenosis. The group 1 patient with occluded bilateral vertebral arteries and an occluded left subclavian artery had transient arm weakness in the postoperative period. The group 2 patient was symptomatic with transient ischemic attacks before surgery and had no postoperative deficit.

One patient of 45 suffered a stroke (Table 1); there were not 5 strokes in the study, as stated in Dr Cheung’s letter. The rate of 1/45 (2.2%) is consistent with American Heart Association guidelines for CEA. The patient who suffered a postoperative stroke was symptomatic with transient ischemic attacks before surgery, had 99% stenosis of the ICA, lacked a functional ACoA, and was dependent on the ipsilateral PCAo for collateral blood flow. Back-bleeding from the arteriotomy site was noted to be abnormal during the surgical procedure, and an emboli shower lasting 2.5 seconds occurred during surgical dissection before carotid artery occlusion. Forty-one discrete emboli were seen. Baseline FVm was 36 cm/s, with a blood pressure of 133/76 mm Hg. FVm ranged from 19 to 33 cm/s during the 10-minute occlusion, and blood pressure was maintained above baseline at 158/88 mm Hg. Seven emboli were detected after reperfusion. No hyperemia was observed. The EEG was abnormal due to a shift to lower frequencies. Four patients experienced reversible ischemic neurological deficits and not strokes (Table 1). In the first, the patient with a transiently weak arm, 3 emboli were detected after release of the cross-clamp and complete restoration of middle cerebral artery flow without hyperemia. The second, who presented with amaurosis fugax before CEA and suffered a stroke after diagnostic angiography in preparation for CEA, experienced mild transient mental status changes after CEA. There were significant EEG changes during the 7-minute period of occlusion, accompanied by a 74% reduction in FVm. Blood flow velocity was unstable during the occlusion. This is a rare occurrence in our experience and was suggestive of severely compromised collateral circulation. Ipsilateral FVm was 30% above preocclusion baseline following release of the cross-clamp for <1 minute. Two emboli were detected after cross-clamp release. The third patient was confused and experienced a seizure postoperatively without EEG changes or emboli. The fourth patient experienced asymmetry in the EEG with slowing and amplitude changes during cross-clamping. Mild hyperemia persisted for 20 minutes after release of the clamp.

Dr Cheung suggests that the FVm measurements summarized in our Table 3 “have no biological basis, because FVm varies continuously.” We agree that FVm does change during the various stages of CEA surgery and during the occlusion period. This is the reason we reported the data in this fashion. We believe that it is important to specify precisely when the measurements were taken when reporting such data. Whether or not Dr Cheung agrees with our interpretation of the change in FVm during the occlusion period, ie, “recruitment of collaterals,” it is clear from our data that there is a statistically significant increase in FVm as the occlusion period progresses (Table 2). Beat-to-beat FVm data, not presented in the manuscript, demonstrate in some cases 2 components of the response after the initial decrease with cross-clamping: a small but immediate increase in FVm followed by a progressive increase in FVm. We have observed that the compensatory response of the collateral circulation has at least 2 time constants: the short time constant response may be a function of vascular compliance and the longer time constant is related to the redistribution of flow in the collateral circulation.

Dr Cheung further stated that the blood pressure was higher during occlusion when FVm was the lowest, indicating “the physiological response to low FVm resulting from carotid clamping and poor collaterals.” We are in partial agreement on this point also, because it does not occur in all patients. We have observed that carotid cross-clamping in both anesthetized and awake patients results in a spontaneous increase in systolic blood pressure in the range of 20 mm Hg in approximately 25% of patients (authors’ unpublished clinical data, 1995–1999). Anesthesiologists routinely take measures to increase blood pressure in anticipation of carotid cross-clamping. We either administer intravenous phenylephrine or decrease the depth of anesthesia to increase blood pressure to the desired level during carotid occlusion. This detail of the anesthetic management of these patients was inadvertently not discussed in our “Subjects and Methods” section because “it is universally accepted that the blood pressure during carotid occlusion should be maintained at or up to 20% higher than the patient’s highest resting blood pressure when awake.”

Regarding the EEG data, there were ischemic changes in the EEG in 6 patients. Two of those patients experienced postoperative neurological deficits. One was the patient with postoperative stroke, and the second was the patient who experienced a stroke after angiography. Four other patients developed asymmetry and mild loss of amplitude and/or slowing in the EEG during the occlusion period that returned to baseline upon reperfusion. There was no correlation between the FVm value during occlusion and EEG changes. Persistent changes, not transient correctable changes, in EEG are associated with stroke. In our institution, EEG is primarily used as an indicator for the insertion of an intra-arterial shunt in the anesthetized patients.

In summary, the nature of the functional collateral pathway(s) influence the response to carotid occlusion (see our Table 2). Our data suggest that clinical studies of the cerebrovascular response to carotid cross-clamping should include consideration of the primary pathways of collateral circulation. Otherwise, pooling of data from patients with significantly different functional collateral pathways could lead to misinterpretation of the cerebrovascular response to occlusion.

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Early Ischemic Recurrence and Microembolic Signals Detected by Transcranial Doppler

To the Editor:

I read with great interest the article, “Microembolic Signals and Risk of Early Recurrence in Patients With Stroke or Transient Ischemic Attack,” by Valton and colleagues. In this study, an early, random, 20-minute sampling of microembolic signals (MES) by use of transcranial Doppler (TCD) over the middle cerebral artery on the side of recent stroke or transient ischemic attack (TIA) in a selected cohort of 73 patients was found to be an independent risk factor for early ischemic recurrence (EIR). In the article, EIR was arbitrarily defined as (1) recurrent TIA or stroke in patients presenting with TIA or (2) clinical deterioration not due to hemorrhagic transformation and cerebral edema in those presenting with stroke. Their findings and conclusions raised 2 interesting points. First, their data indicated that the prediction of EIR by detecting MES on TCD has a sensitivity of 62.5% (5/8), a specificity of 84.6% (55/65), a positive predictive value of 33.3% (5/15), and a negative predictive value of 94.8% (55/58). Thus, absence of MES on TCD is reassuring in an individual patient, but presence of MES does not have a high predictive value for EIR. Second, the protective effect of antiplatelet therapy on the risk of EIR in the Cox model suggests that early use of antiplatelet therapy may lessen the risk of EIR and perhaps reduce the need of performing TCD to detect MES. In this regard, I fully agree with Valton and colleagues that stroke patients are often restless and uncooperative in the acute stage, making prolonged TCD monitoring technically difficult.

Before we consider routine screening of MES using TCD in stroke patients who are similar to the cohort of the present study, several methodological issues are worth remembering. First, the timing (2 ± 2 days, mean ± SD) and duration (20 minutes) of TCD monitoring raised a serious concern of sampling error. Of the 7 patients who had MES on the initial monitoring, only 4 were found to have MES on repeat TCD monitoring. The practical issue is, therefore, how soon after cerebral ischemia we should arrange TCD monitoring. In addition, the 20-minute period of sampling is short, because presence or absence of MES was used in the study to separate the cohort into 2 groups and the number of MES reflects the intensity of arterial thromboembolism. I would like to know the mean, median, and range of the number of MES in the 15 patients, the reason that bilateral TCD was arranged for repeat monitoring, and the time interval between the TCD detection of MES and the occurrence of EIR. Specifically, I wonder whether a large number of MES is predictive of an imminent risk of EIR.

Second, EIR consisted of 2 strokes and 6 TIAs. Apparently, the TIAs occurred in 6 patients presenting with TIA, and the strokes affected 2 patients presenting with stroke. Initial deterioration following stroke is not uncommon and can result from many causes other than EIR. Diagnosing EIR in stroke patients simply by excluding hemorrhagic transformation and cerebral edema on CT scan is insufficient. I wonder whether the findings and conclusions would be the same when only the 23 patients presenting with TIA are considered and whether detecting MES on TCD is relevant only for recurrent TIA. Furthermore, I am interested in knowing how many of the 50 patients presenting with stroke had initial deterioration due to hemorrhagic transformation and cerebral edema on CT scan.

Third, the importance of carotid plaque ulceration is equal to or greater than that of the degree of stenosis in the association with MES. I wonder whether carotid plaque ulceration is better than MES in predicting EIR in the cohort.

Fourth, the interobserver agreement for diagnosing MES in the study was excellent, but the recordings of only 32 patients were analyzed by a second independent observer. My concern is how the selection was made and why the recordings of all patients were not independently analyzed.

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Response

We thank Dr Cheung for his interest in our study. We admit that earlier and longer-duration monitorings might have detected more patients with MES. The mean, median, and range values of MES were 2.4, 1, and 1 to 7, respectively. Several factors limited the number of bilateral and repeat transcranial Doppler sittings: poor patient cooperation, lack of a bone window, and short duration of stay in our department. The mean ± SD delay between detection of MES and EIR was 4 ± 5 days. Four of the 5 patients with MES who had EIR had only 1 MES. Therefore, our data do not permit exploration of the relationship between the number of MES and the delay from monitoring to recurrence.

We are confident in our diagnosis of EIR. Six patients who were included after TIA (3 patients) or reversible ischemic neurological deficit (3 patients) were asymptomatic when EIR occurred. A patient had a stroke in the anterior cerebral artery territory after a stroke in the middle cerebral artery territory. Another patient had sudden and transient worsening of his hemiparesis. A control CT scan excluded hemorrhagic transformation and cerebral edema in all cases, and general causes of deterioration were also carefully excluded. Subgroup analysis of patients who presented with TIA is not feasible because only 3 such patients had EIR. Of the 50 patients who presented with stroke, 5 deteriorated because of cerebral edema. There were no symptomatic hemorrhagic transformations.

We have previously reported that microembolism is associated with angiographic evidence of carotid plaque ulceration. Therefore, it is rational to speculate that plaque ulceration could also be associated with increased risk of early recurrence.
Surgery for Cerebral Amyloid Angiopathy–Related Hemorrhage

To the Editor:

The report by Izumihara et al adds to an existing body of evidence that neurosurgery does not have a significant adverse influence on outcome from cerebral amyloid angiopathy–related hemorrhage (CAAH). Although surgery for CAAH appears to be relatively safe, its effectiveness as an intracerebral hemorrhage in general remains controversial.

The authors identified 3 clinical factors (patients aged over 75 years, a parietal hematoma, and intraventricular hemorrhage) that had an adverse effect on postoperative outcome. However, Glasgow Coma Scale score, which has been shown to be one of the most powerful determinants of outcome in intracerebral hemorrhage, was unfortunately not included in this analysis. This is an important clinical factor, which in our experience with a smaller group of CAAH patients results in a poorer outcome.

Because the report by Izumihara et al examines one of the largest cohorts of patients with pathologically diagnosed CAAH, it would have been clinically useful to confirm this finding for the homogeneous population in their multiple logistic regression analysis of risk factors. Nearly one third of the patients (n=12) had their operation >3 days after hemorrhage onset, suggesting that the good outcome may well have reflected good preoperative Glasgow Coma Scale scores.

Finally, possession of the apolipoprotein E (APOE) e4 allele has recently been recognized as an adverse prognostic factor in intracerebral hemorrhage. It will be interesting to examine whether this genetic determinant of outcome applies to all types of intracerebral hemorrhage (eg, hypertensive deep intracerebral hemorrhage, CAAH, and thombolytic-related intracerebral hemorrhage). In addition, we can as yet only speculate whether surgical intervention will have less benefit or more benefit for an e4 carrier compared with a noncarrier.

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Response

We appreciate the comments of Drs McCarron and Nicoll regarding our recent article. They point out that the preoperative neurological condition in patients with intracerebral hemorrhage has been one of the most powerful determinants of the postoperative outcome in several previous studies and that the apoE e4 allele has recently been reported to be an adverse prognostic factor. In our retrospective study, the preoperative neurological condition was assessed not with the Glasgow Coma Scale, but instead with the Japan Coma Scale in some patients, and depended on other clinical data (demographics, medical history, and radiographic characteristics, especially hematoma size).

Accordingly, we excluded it from the multiple logistic regression model. We also have a great interest in the apoE e4 allele as a risk factor for cerebral amyloid angiopathy with hemorrhage and an adverse prognostic factor in patients with cerebral amyloid angiopathy–related hemorrhage. On the other hand, the apoE e2 allele has recently been reported to be a risk factor for cerebral amyloid angiopathy with hemorrhage. Further genetic studies might elucidate the relationship between cerebral amyloid angiopathy and hemorrhage and a different prognostic factor in patients with cerebral amyloid angiopathy–related hemorrhage.

We indicated that neurosurgery could be performed relatively safely and did not deteriorate the outcome in patients with cerebral amyloid angiopathy–related hemorrhage. Moreover, we elucidated 3 risk factors for an adverse postoperative outcome (parietal hematomas, age ≥75 years, and intraventricular hemorrhages). Certainly, our study does not demonstrate that neurosurgery is effective in improving the outcome. In our series, however, 4 patients with a large hematoma had a good outcome. At present, the diagnosis of cerebral amyloid angiopathy involves histological examination of surgical or autopsy specimens. Accordingly, nonsurgical treatments have been investigated mainly in autopsy cases. Therefore, we consider it difficult to compare surgical and nonsurgical treatments for patients with cerebral amyloid angiopathy–related hemorrhage.

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Should We Screen for Familial Intracranial Aneurysm?

To the Editor:

I read with interest the analysis of Crawley et al1 regarding screening for familial aneurysms. This mathematical modeling concluded that screening is not an effective way of reducing morbidity and mortality from ruptured intracranial aneurysms in individuals with a history of more than one affected first-degree relative with a ruptured intracranial aneurysm. I take exception to this paper on one very important account, namely, the authors’ assumption of surgical morbidity for the clipping of intracranial aneurysms. They used a figure of 8.0% for the risk of morbidity that resulted in death or dependence in everyday living from surgery on unruptured aneurysms. They state that this figure was taken from a meta-analysis published in 1998 by Raaymakers et al.2

The study of Raaymakers et al shows that for patients with non-giant anterior circulation aneurysms, the mortality rate was only 0.8% and morbidity was only 1.9%. It was the patients with giant posterior circulation aneurysms who had a mortality rate of 9.6% and a morbidity of 37.9% that skewed the overall figures to the 8% number used by Crawley et al in this study. Statistically, between 92% and 95% of aneurysms identified by routine screening methods will be non-giant anterior circulation aneurysms. The vast majority of the other 5% to 8% of aneurysms will be non-giant posterior circulation aneurysms. The projected morbidity and mortality rates for patients who were considered in this mathematical screening model will have expected surgical morbidity and mortality of very close to the 1.9% and 0.8% range.

In my own published series,3 looking at the outcome of patients with unruptured aneurysms, we found that morbidity and mortality was totally dependent on size. In all non-giant aneurysms, morbidity was seen in 5.9% of the cases, with mortality in 1.3% of the cases. However, if we looked at all totally incidental aneurysms that were asymptomatic at the time of presentation, the total morbidity and mortality rate for non-giant aneurysms fell to 3%. Similarly, looking at all aneurysms <1 cm in diameter, surgical morbidity was <2%.4

I suggest that the modeling used by Crawley et al is based on an invalid assumption, because the vast majority (probably in the order of 98%) of aneurysms that might be identified by MR and digital subtraction angiography screening for familial aneurysms are likely to be non-giant aneurysms. Almost all of these are likely to be non-giant anterior circulation aneurysms. Because none of these aneurysms are likely to be symptomatic, the great preponderance of aneurysms that are identified also tend to be small aneurysms, probably <1 cm in diameter.

I therefore suggest that if the correct morbidity and mortality figures for surgical treatment of intracranial aneurysms were used, screening for familial intracranial aneurysms in a high-risk population would be found to be highly effective in reducing both morbidity and mortality and cost savings.

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Response

We thank Dr Solomon for his interest in our model designed to assess the value of screening for unruptured cerebral aneurysms.1 We accept that the figures used in the calculations used to model the outcome of health related interventions are somewhat arbitrary, and surgeons who believe they can do better than average will understandably take exception to the findings. However, to provide figures that allow physicians and healthcare providers to decide on the appropriateness of introducing a general policy of screening for aneurysm, it is necessary to use figures based on an overall average assessment of risks. To be applicable to health care in general, the average figures should be taken from as large a representative sample of different centers as possible. Hence, we used data taken from the Raaymaker et al2 systematic analysis of 61 separate studies, which is likely to provide a good sample of both representative patients and representative centers. Our conclusions can therefore be applied across the wide range of centers and types of patients included in their analysis.

Dr Solomon takes exception to the fact that we used an overall average figure of 8%, taken from the study of Raaymaker et al, for the risk of morbidity resulting in death or dependency from surgery on unruptured aneurysms, on the grounds that the figure includes the risks of surgery for patients with giant aneurysms as well as those with smaller aneurysms. It is certainly true that the risk of surgery is greater with larger aneurysms than smaller ones, but when carrying out a screening procedure on an asymptomatic patient, the physician does not know the size of any aneurysm that may be detected. Hence, we were correct to use the average risk calculated from a series that included all comers and all sizes of aneurysms. The figures Dr Solomon quoted from Raaymaker et al,2 namely, a combined mortality and morbidity of 2.7% for surgery on non-giant anterior circulation aneurysms, were estimated according to a multivariate analysis that included only 29 of the 61 studies included in that review. As the authors state,2 this provides only a rough estimate, and the figures we used based on the overall analysis of all 61 studies are much more robust. The figures we used are supported by the recent report from the International Study of Unruptured Intracranial Aneurysm Investigators,4 in which the overall rate of surgery related morbidity and mortality was 17.5% at 30 days and 15.7% at 1 year in their group of patients having no previous history of subarachnoid hemorrhage.

Our conclusions may not apply to individual patients (eg, if their risks of rupture are much higher than average) or individual surgeons (eg, if their results are very much better than average). Similarly, our conclusions may also not apply if an aneurysm has already been detected during CT scanning, when the figures for the risk of surgery and of spontaneous rupture will need to be adjusted according to the size of the known aneurysm. However, even with very safe surgery, screening for asymptomatic aneurysm is not cost effective. This is because the main determinant of the utility of screening for aneurysm is not the risk of surgery, but the risk of spontaneous rupture. Thus, our model demonstrates that if Dr Solomon adopts a policy of screening with MR angiography and operating on all asymptomatic unruptured aneurysms, and he maintains his published1 combined mortality and morbidity rate of 3%, he will save only 1.7 strokes over 10 years for every thousand patients screened, at a cost of over £1.8 million ($3 million) per stroke saved.

We therefore reaffirm our conclusion that a general policy of screening for aneurysms should not be advocated, even in units with a low surgical morbidity. This does not mean that exceptions can not be made for individual cases.
Using Pathophysiology in Acute Stroke Trials

To the Editor:

Muir and Grosset1 recently gave their views on why neuroprotective therapies have not worked. They raised issues of trial methodology and some pathophysiological considerations. We would like to add further comments from the pathophysiological viewpoint. We believe that assessment of the state of cerebral perfusion—initial hypoperfusion as well as extent of early reperfusion—will permit optimal evaluation of the efficacy of these agents and the mechanisms by which they have their therapeutic effects.

Hypoperfusion is the final common pathway for all etiologic mechanisms of cerebral ischemia. Neuroprotective agents were developed as adjunctive or alternative approaches to the primary strategy of restoring blood flow. The efficacies of the various neuroprotective agents were demonstrated in experimental stroke models, where perfusion status was strictly controlled. In the case of permanent middle cerebral artery occlusion models, limitation of brain damage was found through salvage of the tissue with mild to moderate ischemia around the core of severe ischemia. Other agents were studied in temporary occlusion models of uniform duration.

Unlike experimental stroke models, human stroke is a very heterogeneous process, with marked variation in the mechanism, extent, severity, and duration of ischemia. Depending on the cause of the ischemia, fluctuations in perfusion may also occur. In addition, when early reperfusion does occur, it has been found to be a major determinant of clinical outcome at 3 months,2 and so far the only efficacious therapies have been those that restore perfusion.3–5 In MR studies, the major determinant of the enlargement of ischemic lesion volume is the presence of a larger surrounding region of hypoperfusion.6

Therefore, in the design and evaluation of clinical trials of neuroprotective agents, those pathophysiological factors that cannot be controlled for in the design (for example, the extent and severity of hypoperfusion and early reperfusion) could be controlled in the statistical analyses. In prior trials it is possible that beneficial effects were masked by uncontrolled differences in perfusion and reperfusion status between treatment and control groups, or that the agents themselves altered tissue perfusion.

The rational approach to drug development and evaluation is to make use of what knowledge we have about ischemic stroke pathophysiology in humans. The results of the PROACT II study, which tested intra-arterial recombinant prourokinase in acute stroke patients with angiographically demonstrated occlusion at the M1 or M2 segments of the middle cerebral artery, showed that the reperfusion treatment window in human stroke can be extended to 6 hours when patients are selected on the basis of their pathophysiology.2 A current trend is to advocate using MR patterns of diffusion and perfusion abnormalities to guide therapy and clinical trials of neuroprotective agents, but target patterns have yet to be standardized. Several clinical trials using MRI are in progress, and they may answer questions regarding the utility of pathophysiologically based measures in clinical trial selection and evaluation.6

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References


Response

We thank Drs Baird and Warach for their comments proposing an alternative approach to the problems that we attempted to highlight. We agree on the starting premise that pathophysiology must be taken into account in clinical trial design and that knowledge of cerebral perfusion is essential. Our suggested solution was to seek a homogeneous study population by restricting trial entry based on perfusion (or similar) imaging: their alternative is to enter all patients and to use post hoc stratification in statistical analyses. This solution has the attraction that it would ensure larger numbers of patients for trials and provide information on drug safety and tolerability in the eventual (broad) target population with clinically diagnosed stroke. Although this may be practical, reliance on post hoc analyses risks compromising the validity of trial results. Unless the baseline perfusion characteristics are factored in at the time of randomization, it is impossible to ensure balanced treatment allocation, and there is increased likelihood of false-positive or false-negative results. Clinical trials would have to be powered on the basis of this post hoc analysis and may therefore need to be much larger. We would suggest that prerandomization perfusion imaging and a clearly defined basis for stratification are essential for either proposal: provided that these prerequisites are addressed, the decision on whether to structure a trial as restrictive or all-inclusive may depend on the stage of drug development and the attitudes of the steering committee.

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Influence of Arterial Blood Pressure on Cerebrovascular Reactivity

To the Editor:

In the May 1998 issue of Stroke, Dumville et al7 showed that the classic CO2 test to assess cerebrovascular reactivity (CVR)
may produce misleading results unless simultaneous changes in arterial blood pressure (ABP) are taken into account. A similar finding has recently been reported by Hetzel et al.2

The possibility of interactions among CO2, ABP, and cerebral blood flow (CBF) has been raised previously.3–5 The fact that 2 recent studies1,2 focusing on CVR arrived at similar conclusions despite significant differences in the populations studied reinforces the message that ABP has to be included as a significant covariate in any attempts to quantify the effects of CO2 on CBF velocity (CBFV), as usually measured with Doppler ultrasound in the middle cerebral artery. Dumville et al1 examined 56 patients with carotid artery disease (CAD) with a mean age of 67±8 years; the group studied by Hetzel et al2 comprised 81 healthy volunteers with ages ranging from 19 to 74 years. CVR in the latter group was slightly higher than in the former (3.6±1.6%/mm Hg versus 3.4±1.5%/mm Hg), but multiple regression analysis has shown that when the effect of ABP is taken into account, the CVR of the CAD patients dropped to 2.76±1.2%/mm Hg.1 Although Hetzel et al2 have obtained a significant correlation between ABP and end-tidal CO2, with a slope of 0.55 mm Hg/mm Hg CO2, they have not reported on corrected values of CVR when the influence of ABP is removed.

By studying healthy volunteers, Hetzel et al2 did not have the opportunity to observe the effects of ABP on the misclassification of subjects in relation to preestablished thresholds of CVR. In their patient population, Dumville et al1 reported that inclusion of ABP led to 14 patients showing a compromised CVR instead of only 8 when the conventional measure of CVR was adopted. Moreover, we have shown that in 4 patients the observed increase in CBFV during the CO2 test was primarily caused by ABP, a phenomenon that is also mentioned by Hetzel et al2 as illustrated in their Figure 3.

Different methodological approaches are probably behind the variability in CVR values observed in the literature.6 Attempts to quantify and to compensate for the contribution of ABP are likely to produce an even greater disparity of results unless greater care is taken by thoroughly testing differing methodological alternatives,6 performing sensitivity analysis of parameters,4 and assessing reproducibility of results.2 Inclusion of ABP as a covariate also requires careful consideration of dynamic changes.7,8 In the study of Hetzel et al2 it is not clear whether a plateau in CBFV was established at each of the 4 phases of their study or whether the time delay between step changes in CO2 and the rise in CBFV was corrected for, as described by Dumville et al.1 Changes in ABP, either spontaneous or induced by the CO2 test, will produce different effects on CBFV, depending on the status of cerebral pressure-autoregulation.8,9 Because it is not possible to exert absolute control over the time course of these variables during clinical tests, dynamic modeling of the interaction between CO2, ABP, and CBFV is likely to play a major role in bringing further refinements to clinical applications of CVR testing.

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Response

Studies by Dumville and colleagues1 and our group2 both report on the influence of CO2 on ABP during Doppler CO2 testing in humans. This variable CO2 effect on CBFV and ABP can lead to a misinterpretation of the results of cerebrovascular reactivity testing. Dumville and colleagues1 reported 4 cases in a group of 56 patients undergoing carotid endarterectomy with false overall pictures of CO2 reactivity, and we2 reported 1 case with the same phenomenon in our study. Both studies emphasize the covariance of CO2 effects on ABP and CBFV. Therefore, Doppler CO2 testing monitors not only the CO2-induced vasodilation of cerebral arterioles with increase in CBFV but also the efficacy of cerebral autoregulation in maintaining stable cerebral blood flow with respect to increases in ABP. In patients and controls nonlinear fluctuations, especially rapid changes in ABP, correspond to similar changes in CBFV. This phenomenon, illustrated in Figures 2 and 3 in our article2 is characteristic of a high-pass filter response.3 Variations in ABP of >0.1 Hz produce similar variations in CBFV.4,5 In our opinion, such variations of ABP, and not the linear increase in ABP, influence predominantly the CBFV. Multiple linear regression analysis without respect to the frequency of ABP variations will neglect this physiological fact of such a threshold-related influence. In patients with high-grade obstructions of brain-supplying arteries, cerebral autoregulation will be compromised because of missing effective collateral supply. Therefore, CO2- and ABP-induced vasomotor response must be differentiated from passive ABP-induced changes in CBFV.

In our study neither the dynamics of ABP variations nor stable hypercapnic state were considered. Steady-state conditions could not occur with our rebreathing method. For that reason, we refrained from correcting CO2 reactivity results for changes in ABP.

The time delay between dynamic changes in PetCO2 and the rise and fall in CBFV is a characteristic that provides additional information about the vasomotor response.5 This was not considered in our study, which could explain the most pronounced increase in ABP at the end of our CO2 test. We perform an ongoing study with respect to time delays between PetCO2, ABP, and CBFV. First results in patients with severe carotid stenosis showed a highly significant correlation between CO2 reactivity and time delay of the fall in CBFV at the end of hypercapnia. The realignment of this time delay as performed by Dumville et al1 may miss some insights into the pathophysiological dynamics of cerebrovascular responses in time. Their multiple linear regression analysis is the correct approach to consider linear interactions between the simultaneously measured parameters. Contrary to the usual analysis of CO2 reactivity, this might prevent underestimating the degree of hemodynamic compromise, especially in patients with
already-diminished vasomotor response. Beat-to-beat analysis is necessary to quantify and report corrected values of CO$_2$ reactivity, and the analysis must also allow for a nonlinear relationship between parameters. Dynamic modeling of the interaction between the parameters will be the next step in the analysis of CO$_2$ reactivity with respect to the dynamics of cerebral autoregulation by considering amplitudes and time delays.

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Standardization of Carotid Ultrasound
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