Types of Recurrent Stroke in Survivors of Intracerebral Hemorrhage

To the Editor:

I read with great interest the recent article1 by Arakawa and colleagues. In this important study, Arakawa and colleagues followed up 74 patients with hypertensive brain hemorrhage for a mean of 2.8 years and reported higher diastolic blood pressure (DBP) but not higher systolic blood pressure (SBP) as the risk factor for recurrent brain hemorrhage. I would make the following comments.

First, recurrent stroke affected 9 of the 74 patients; the type of recurrent stroke was intracerebral hemorrhage (ICH) in 8 (89%) and ischemic stroke (IS) in 1 (11%).1 Although most of the recurrent strokes are of the same type as the first episode in patients surviving from IS, this may not apply to survivors of ICH. In a study by Yamamoto and Bogousslavsky,2 the recurrent strokes were of the same type as the initial strokes in 77% of patients with cardioembolic IS, 65% with nonlacunar noncardioembolic IS, 58% with ICH, and 48% with lacunar IS. I wonder whether Arakawa and colleagues have any explanation for the high consistency rate of 89% of recurrent ICH observed in their cohort. From our database of information prospectively gathered between October 1996 and January 1999 (Cheung, unpublished data, 1999), 138 of 607 stroke patients had a previous history of stroke. Of 120 patients with a previous history of IS, the type of recurrent stroke was IS in 108 (90%) and ICH in 12 (10%). Of 16 patients with a previous history of ICH, the recurrent stroke was ICH in 5 (31%) and IS in 11 (69%). Two patients had a history of subarachnoid hemorrhage; one had a recurrent ICH and the other a recurrent IS.

Second, arterial blood pressure was monitored monthly in the cohort of 74 patients, and the mean values of SBP and DBP were used in the analysis.1 I would like to know the range of the SBP and DBP in the 2 subgroups of patients as defined by the recurrent ICH. In addition, I wonder whether the SBP and DBP values were greater in the period immediately before the recurrent ICH, suggesting a close temporal relationship between blood pressure control and recurrent ICH.

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Response

We would like to thank Dr Cheung for his critical comments on our study.3

As has been pointed out by Dr Cheung, the recurrent stroke was predominantly hemorrhagic in our series of patients with brain hemorrhage, and the rate (89%) was rather higher than those reported in previous studies.2–4 However, the reported rates distribute in a wide range (Cheung, unpublished data, 51%; Passero et al.,5 65%; Yamamoto and Bogousslavsky,6 58%; Kumamoto et al.,7 81%). The variation probably results from a relatively small number of samples and events in each study (number of samples, 74 to 143; events, 9 to 27). Under such circumstances, even the occurrence of 1 ischemic event would affect the result considerably. Second, judging from the reports by Kumamoto et al.8 and our own,1 the Japanese may show a higher rate of hemorrhagic recurrence. Another plausible explanation for the variation is that some ischemic strokes (in particular, lacunar infarction) can be asymptomatic and may have been overlooked in some studies, including ours; we did not try to detect asymptomatic strokes systematically. Finally, the levels of blood pressure during the follow-up period is likely to influence the type of recurrence. Excessive antihypertensive medication promotes the occurrence of ischemic stroke in some patients, especially those with major cerebral arterial diseases. We make it a clinical rule to avoid the rapid and excessive control of poststroke blood pressure. In addition, major cerebral arterial diseases are less common in Japan than Western countries, although they are increasing in number. These conditions may have resulted in the higher recurrence rate of hemorrhagic stroke in our series of patients.

The range of blood pressure in our study was 125 to 149/75 to 96 mm Hg and 113 to 158/64 to 97 mm Hg for the recurrence and nonrecurrence groups, respectively. The average blood pressure measured immediately before rebleeding was 135/89 mm Hg in the recurrence group. The value was comparable to that during the follow-up period (P>0.05).

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SPECT-Derived Relative Perfusion Defect and CT-Derived Hypodense Region in Acute Intracerebral Hemorrhage

To the Editor:

In their recent, interesting article,1 Mayer and colleagues report that the flow deficit volume (FDV) was greater at the earlier hours after acute intracerebral hemorrhage (ICH) than at the later hours and that the CT-derived hypodense region was larger in the later scans than in the earlier scans. In this study, FDV was obtained by subtracting the CT-derived ICH volume from the volume of SPECT-derived relative perfusion defect.
There is a minor typing error in the text: “moderate-to-severe” global blood flow reduction on SPECT study was stated as an exclusion criteria in the “Study Population” subsection, whereas “mild-to-severe” global blood flow reduction on SPECT study was quoted in the “Validation of SPECT Analysis” subsection. Significant midline shift (>5 mm) on CT scan was an exclusion criteria, and the midline shift of the CT scan in Figure 1 in the article1 appears to be >5 mm. I would raise the following comments.

First, SPECT study can assess perfusion and predict prognosis for recovery.2,3 Nevertheless, SPECT study provides only a relative index of perfusion, and there is no true “zero-flow” region. In contrast to the tracer $^{99m}$Tc-hexamethylpropyleneamine oxime, which reveals relative blood flow, the tracer $^{99m}$Tc-ethylcysteinate-dimer (ECD) reflects not only relative perfusion but also the metabolic status of the brain tissue. Thus, $^{99m}$Tc-ECD is more specific for both functioning brain tissue and infarcted brain lesions.3

Second, the FDV was derived from both the CT and SPECT studies, and the time interval between the 2 kinds of imaging studies was not constant.1 The delay from onset of ICH should be based on the SPECT studies rather than the CT studies, because the SPECT-derived relative perfusion changed with time and the CT-derived ICH volume was constant over time. In fact, the time interval after ICH onset for the acute-phase SPECT scans (2 to 36 hours) overlapped with that for the subacute-phase SPECT scans (30 to 136 hours).

Third, univariate analysis and multiple regression analysis were done for the ratios of edema/ICH volume and of FDV/ICH volume, and then ICH volume was found to a significant factor behind the use of these ratios instead of edema and FDV, and I wonder whether ICH volume was a significant factor because it was used as the denominator.

Fourth, SPECT-derived relative perfusion defects were greater or equal to the corresponding CT-derived ICH volumes in 40 paired measurements, resulting in negative FDV values in 6 measurements. I wonder whether these negative values were used in the statistical analysis. I think negative FDV values should be replaced by zero, since negative FDV values do not have any physiological meaning.

Finally, CT-derived hypodense region in the acute-phase scans is, in theory, a combination of acute interstitial edema and ischemia due to elevated local tissue pressure. In contrast, CT-derived hypodense region in the subacute-phase scans is mainly contributed by vasogenic and inflammatory edema.4 I wonder whether there is any correlation between the CT-derived hypodense region and the FDV in the acute phase.

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Response
We thank Dr Cheung for his thoughtful comments regarding our article. When we designed our study, we accepted the inaccuracies inherent in analyzing SPECT and CT data obtained at different times and understood that no method of analysis would be completely satisfactory. Without image coregistration, we recognized that any attempt to quantify cerebral blood flow (CBF) within a small perihematoma region of interest (ROI) would be impossible, because there would be no way to know whether the ROI was precisely on the border of the clot. Instead, we developed a novel volumetric approach for measuring perfusion around each hematoma by subtracting CT-derived ICH volumes from theoretical SPECT-derived volumes of brain tissue with zero flow (based on the percent reduction in tracer counts compared with a mirror ROI on the contralateral side) to yield a “flow deficit volume.” This technique was originally developed and validated by Mountz2 as a method for quantifying perfusion in ischemic stroke. Obviously, these FDVs are a theoretical construct, because it is almost certain that CBF decreases gradually around a hemorrhage. Despite the inherent drawbacks of this method, including the potential for inaccuracy due to anatomic brain distortion or contralateral CBF reduction, the huge advantage was that we were able to obtain FDVs with good reliability regardless of how the ROI was drawn, as long as it was drawn widely. Imprecision may have also resulted from comparison of volumetric measurements obtained by different modalities (CT and SPECT), but we established the validity of this approach by demonstrating that both methods were able to estimate the volume of a brain phantom with reasonable accuracy (<2% error).

Obviously, the CT and SPECT studies could not be performed at exactly the same time, and this also may have led to inaccuracy. We attempted to obtain the acute-phase studies between 0 and 24 hours after ICH and the subacute-phase studies between 48 and 72 hours. The average interval between the CT and SPECT examination was 6.7 hours during the acute phase and 2.7 hours during the subacute phase. Although significant changes in ICH volume, edema volume, or perihematoma perfusion may have occurred during these intervals, we feel that this is unlikely. Because SPECT was not available on weekends, we allowed for protocol violations, including an initial SPECT as late as 36 hours after ICH and follow-up scans as early as 24 hours after the initial scan. One patient underwent SPECT 31.5 and 103.5 hours after ICH, and hence this “acute” SPECT was performed later than the earliest “subacute” study, which was obtained at 30 hours. We allowed this discrepancy because our intent was to measure trends in perfusion and because the degree of overlap was relatively small.

We analyzed FDV/ICH volume and edema/ICH volume to assess for factors that might influence the relative extent of perfusion and edema around a clot. These ratios were used to correct for ICH volume, which correlated strongly with both of these measurements. Given the variable timing of the SPECT scans, this analysis also provided us with an opportunity to confirm our main findings by looking at the effect of time after ICH on these ratios. In fact, time after ICH was the only variable found to influence the relative extent of perfusion around a hematoma, with longer intervals correlating with smaller FDV/ICH ratios, as expected. In retrospect, we agree with Dr Cheung that the observed negative correlation between ICH volume and edema/ICH volume is probably explained by inclusion of this variable in the denominator. We did not analyze FDV/edema volume because we felt the meaning of this ratio would be hard to interpret.

We used $^{99m}$Tc-hexamethylpropyleneamine oxime because we sought to assess perfusion. Use of $^{99m}$Tc-ECD would have confounded our analysis, because its uptake is related to perfu-
a lacunar infarction. An extensive work-up should be performed to precisely define the etiologic mechanism.

Finally, the clinical picture of AH is basically explained by a lesion involving both the corticospinal and the cerebello-thalamo-cortico-ponto-cerebellar tracts between the cortex and the pons. We totally agree that although it is a heterogeneous entity, AH can generally be attributed to small-vessel disease and is therefore a marker of more generalized cerebral vascular disease, even if it appears to predict a positive outcome. Nevertheless, faced with a given individual presenting with AH, it remains difficult to use this concept for specific management, and the specificity of lacunar syndromes should be closely reappraised.14

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Response
We appreciate the comments in the letter written by Drs Moulin and Bogousslavsky. While our series of 45 patients is clearly not a small series for a specific stroke syndrome, we regret and apologize for having omitted their series of AH patients.1 Our methodology a priori involved only the English literature, utilized a Medline search with the terms lacunar stroke and AH, and subsequently checking the references in all of the papers located on the Medline search. Current computer searches appear to be a bit more comprehensive, and we have since located a few other papers we had missed on the initial series of searches. Review of these articles does not seem to substantially alter any of our conclusions as written in the paper.2

We thank them also for their thoughtful comments regarding thalamic localization in AH and similar syndromes, as well as those regarding evaluation of a patient with AH. While we can

Ataxic Hemiparesis: An Old Debate for Lacune Aficionados

To the Editor:
We read the article by Gorman et al1 on ataxic hemiparesis (AH) with great interest. The authors studied a small series of 45 patients with AH and stressed that they had reviewed all previously published cases and series in English. Unfortunately, they overlooked our series of 100 stroke patients with AH published 4 years ago.2 Our study, which also cited findings from the English literature, gives substantial consideration to research described in the French literature.3–7 We agree with the clinical conclusions of Gorman et al that the clinical features of AH for the various locations are virtually identical. Although sensory disturbances are frequently associated with AH in the thalamic or capsular location, it is important to distinguish between the different clinical pictures in thalamic involvement: typical Déjerine-Roussy syndrome, “painful AH,” and “ataxic-hypesthesias syndrome.”8–11 Cerebellar ataxia is explained by an interruption of thisafferent pathway at the level of the ventral lateral nucleus. Moreover, we would like to stress the fact that the most typical picture of cranial paresis and homolateral ataxia can be observed only in infarcts involving the anterior cerebral artery territory. In this case, ataxia is explained by the involvement of the cortico-ponto-cerebellar pathway (Türck’s tract).12 A potential source of embolism—arterial or cardiac—is not uncommonly found (present in one quarter of our patients), and in addition, infarct may also be caused by a hemodynamic mechanism in the end-zone vascular territory.13 All these findings suggest that no definite correlation can be established between

sion as well as metabolism (eg, uptake is reduced in perfused but hypometabolic tissue). If the cortical hyperperfusion that we observed in some cases was not related to an increase in metabolic activity, which seems likely, ECD might not have detected it.

In 6 of 46 paired measurements, the SPECT-derived zero-flow volume was slightly smaller than the CT-derived ICH volume, yielding a negative FDV value. Viewed another way, however, with just one exception all FDV values exceeded or equaled the corresponding CT-derived ICH volume within a small margin of error (±2 mL), which we feel confirms the validity of our approach. We used these negative FDV values rather than zero in our analysis, because conceptually they indicate hyperperfusion. In fact, in the only instance of a large negative FDV (~8 mL) there was visible hyperperfusion in the ROI around the hematoma.

The pathophysiology of perihematoma brain injury in ICH is complex. We agree with Dr Cheung that on acute CT scans, hypodensity probably represents interstitial edema from leakage of plasma, and that during the subacute phase there is an additional component of inflammatory vasogenic edema. There was only a weak, nonsignificant correlation between FDV/ICH volume and edema/ICH volume during the acute phase (r=0.36, P=0.09), suggesting that the initial extent of perfusion deficit is not a particularly important determinant of edema in the acute stage of ICH.

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use statistics from a group study to help guide us when we have to make clinical decisions without data specific to an individual, statistics neither diminish the urgency nor replace the necessity to obtain etiologic information for each individual presenting with a stroke syndrome.

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Microembolic Signals and Early Recurrent Cerebral Ischemia in Carotid Artery Disease

To the Editor:

Valton et al1 in the October 1998 issue of Stroke report on finding early recurrence of cerebral ischemia in patients showing presence of microembolic signals (MES) as detected by Doppler sonography. Of considerable interest to us is their finding the association significant in cases of stroke or transient ischemic attack of presumed arterial origin. Our research supports similar conclusions, though our study was more restricted. Where Valton et al examined a more heterogeneous group of patients, we have been investigating the relationship between MES and early recurrence of cerebral ischemia in a particular group of patients, those with varying degrees of carotid stenosis and carotid occlusion.

We examined 87 patients with unilateral or bilateral carotid stenosis (a total of 107 stenoses) and 13 patients with carotid occlusion. The degree of narrowing (30% to 99%) was determined by duplex Doppler sonography and digital subtraction angiography. We classified 69 of the stenoses as moderate (30% to 69% reduction in diameter) and 38 as high grade (70% to 99%). In the group with moderate-grade stenosis 56 were asymptomatic and 13 symptomatic, whereas in the high-grade group 15 were symptomatic and 23 asymptomatic. Five of the 13 ICA occlusions were symptomatic; the remaining 8 patients with occluded ICA had no symptoms. Presence of MES was assessed using a Multi-Dop X4 TCD-8 DWL with a 2-MHz transducer (14 mm diameter), at an insonation depth ranging between 45 and 55 mm, with a sample volume of 8 mm. Signal intensity was measured relative to total screen background. A 64-point fast Fourier transform with a length of 2 ms was used. Two independent observers analyzed the recording offline. Intensity threshold (9 dB) was determined on analysis of 100 high-intensity Doppler speckles of the normal Doppler signal.

But what we would like to draw particular attention to is our results on patients with symptomatic carotid stenosis (moderate and high grade). All patients with symptomatic carotid stenosis and occlusion were admitted to the hospital with acute carotid territory ischemia. They were monitored for MES within 10 days of the onset of cerebrovascular symptoms. In an attempt to determine whether early recurrence of cerebral ischemia is related to the detected presence of MES, we collected background information on previous ischemic attacks or monocular blindness (30 days prior to hospital admission), later following up the patient’s course. Recurrent cerebrovascular events in the 15 to 30 days following admission were recorded. Six of 9 MES-positive patients with symptomatic carotid stenosis and occlusion had TIA either before or after the main ischemic event that precipitated admission, whereas only 4 of 24 MES-negative symptomatic patients had such events (P<0.05).

Detection of MES by TCD is contributing to better understanding the physiology of recurrent ischemic events in patients with carotid stenosis, focusing attention, as it does, on the part recurrent embolization plays. What Valton et al reported on, which our study corroborates, is the association between recurrent ischemic events and registration of MES by transcranial Doppler monitoring in particular groups of patients with cerebrovascular disease (in our case, carotid artery disease), both studies serving to underscore the instability of embolic plaque.

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