Letters to the Editor

Preators of Hematoma Growth?

To the Editor:

I read with much interest the article, “Multivariate Analysis of Predictors of Hematoma Enlargement in Spontaneous Intracerebral Hemorrhage,” by Fujii and colleagues. I fully agree with the authors on the importance of identifying factors responsible for the increase in volume of intracerebral hemorrhage, since the hematoma “growth” is common and because this is associated with neurological deterioration. While their multivariate analyses revealed 5 independent “predictors” for hematoma enlargement, Fujii and colleagues pointed out in their Discussion section that 3 of the 5 factors (ie, a short time interval from onset, the presence of disturbed consciousness, and irregularly shaped hematoma) were related to the natural time course rather than acting as risk factors. The authors further postulated that the stabilization of hematoma formation takes some time, that disturbed consciousness can be a consequence of hematoma enlargement rather than a cause, and that irregularly shaped hematomas may indicate bleeding from multiple arterioles. Regarding their findings and interpretations, I would like to make the following comments.

First, the great majority of intracerebral hematomas are caused by bleeding from arteries or arterioles under systemic arterial pressure, and so hematomas will “grow” for some time, until the hematoma enlargement is counteracted by increasing regional intracranial pressure; eventually, bleeding ceases because of hemostasis. In a similar study, Brott and colleagues performed baseline CT scans in patients with intracerebral hemorrhage within 3 hours of onset and repeated the scans at regular intervals after the first scans. Brott and colleagues reported 26% of substantial hematoma growth between the baseline and 1-hour CT scans and 12% of substantial hematoma growth between the 1- and 20-hour CT scans. In the article by Fujii and colleagues, the patients had their first CT scans within 24 hours of onset of symptoms and their second scans within 24 hours of admission. Considering the postulation by Fujii and colleagues that active bleeding of hematoma formation largely stabilizes within 6 hours of onset, the study by Brott and colleagues reflects the early stage of hematoma stabilization rather than growth. Similarly, the patients of Fujii and colleagues should be divided into 2 groups, according to the time of onset (ie, <6 or >6 hours) before the univariate and multivariate analyses are performed to reveal the respective factors for the initial hematoma stabilization and the subsequent hematoma growth.

Second, the symptomatology of intracerebral hematoma is affected by its location, volume, and rate of formation. In the study by Brott and colleagues, hematoma growth was defined by an increase in hematoma volume by >33% of the baseline volume (ie, 10% increase in diameter); the definition was simple and clear. In contrast, Fujii and colleagues defined hematoma growth by either (1) hematoma volume increased by >50% of the initial scans (ie, 14.5% increase in diameter) plus an absolute increase of >2 cm3 or (2) an absolute increase of hematoma volume by >20 cm3. It seems that the 2 definitions are rather unequal. For example, a hematoma enlarged from 0.9 cm3 to 3 cm3 (ie, an increase of 2.1 cm3 or 233%) may be well tolerated but an enlargement by >20 cm3 is likely to cause clinical deterioration. In fact, the mortality rate is affected by the hematoma volume; about 5% of patients with hematomas <30 cm3 will die, about 35% at volumes between 30 and 50 cm3, and about 85% at volumes of >50 cm3. I would therefore suggest that Fujii and colleagues should use either the relative change in hematoma volume or the absolute increase, but not both, in their analyses.

Finally, I wonder whether Fujii and colleagues can include some data on the conscious state and neurological deficits within the first 24 hours of admission. It is clinically important to see if the initial hematoma stabilization in the first 6 hours and subsequent hematoma enlargement are correlated with clinical deterioration.

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Response

We thank Dr Cheung for his comments on our recent report. First, we did not divide our patients into 2 groups according to the time of onset before performing the analyses because of the following reasons: (1) the majority of the 627 patients were admitted within 6 hours of onset (Table 1), (2) only 2 of the 88 patients with hematoma growth were admitted more than 6 hours after onset, and (3) we intended to emphasize the fact that the incidence of hematoma growth was extremely rare in the patients admitted >6 hours after onset. Although we performed multiple logistic regression analysis of the 519 patients admitted within 6 hours of admission, we showed that the incidence of hematoma growth significantly increased as the level of consciousness deteriorated.

TABLE 1. Relationship Between the Incidence of Hematoma Growth and Clinical Factors in 627 Patients With Spontaneous Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hematoma</th>
<th>Incidence of Hematoma Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Interval to admission, h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1.0</td>
<td>41</td>
<td>151</td>
</tr>
<tr>
<td>1.1–3.0</td>
<td>37</td>
<td>193</td>
</tr>
<tr>
<td>3.1–6.0</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>6.1–24</td>
<td>2</td>
<td>106</td>
</tr>
<tr>
<td>Consciousness on admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alertness</td>
<td>25</td>
<td>287</td>
</tr>
<tr>
<td>Confusion</td>
<td>19</td>
<td>104</td>
</tr>
<tr>
<td>Somnolence</td>
<td>16</td>
<td>69</td>
</tr>
<tr>
<td>Stupor/coma</td>
<td>28</td>
<td>79</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>539</td>
</tr>
</tbody>
</table>

*The incidence of hematoma growth significantly increased as the interval between onset and admission increased.
†The incidence of hematoma growth significantly increased as the level of consciousness deteriorated.

hours of onset (Table 2), we could not find major differences in the statistical results between the 2 patient groups admitted within 6 hours of onset and between 6 and 24 hours after onset.

Second, we initiated these studies to find possible ways of preventing patients with spontaneous intracerebral hemorrhage from clinical deterioration due to hematoma growth. Thus, we determined the definition of hematoma growth after looking at a number of cases to assess predictors of definite enlargement of hematoma likely to result in neurological deterioration. As Dr Cheung mentioned, an enlargement of >20 cm³ is likely to cause clinical deterioration. However, if we use only the relative change (>50%), we cannot regard a hematoma enlarged from 45 cm³ to 65 cm³ as hematoma growth. On the other hand, in pontine hemorrhage, a hematoma enlarged from 4 cm³ to 6 cm³, (ie, an increase by 2 cm³) is likely to cause neurological deterioration. Hence, we should use both parameters in assessing definite hematoma growth likely to result in clinical deterioration in intracerebral hematomas at unspecified sites, although we can use either the relative change in hematoma volume or the absolute increase in dealing with a particular site of hematoma (for example, putaminal hemorrhage). Finally, our databases for the previous studies do not contain parameters regarding the conscious state and neurological deficits within the first 24 hours after admission, although we have the data on the relationship between the level of consciousness disturbance at admission and hematoma growth (Table 1). Thus, we cannot provide any actual data on the conscious state and neurological deficits within the first 24 hours after admission. However, hematoma growth according to our definition seems to be clearly correlated with clinical deterioration because almost all of the 88 patients with hematoma growth had clinical deterioration after admission as a matter of course (owing to the concept of our definition).

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### Predicting Early Deterioration or Improvement in Ischemic Stroke by Transcranial Doppler

**To the Editor:**

I read with great interest the recent *Stroke* article by Toni and colleagues.¹ In this study, early deterioration and early improvement were defined by a decrease or an increase, respectively, of 1 or more points in the Canadian Neurological Scale score from hospital admission to 48 hours after stroke onset. Among the baseline clinical characteristics, the findings from CT scans on admission, and the 6-hour transcranial Doppler (TCD) findings, only normal 6-hour TCD and abnormal 6-hour TCD were identified by logistic regression as the respective predictors of early improvement and deterioration.¹ Regarding their findings and interpretations, I would like to make the following comments.

First, a change of one Canadian Neurological Scale score is a reliable indicator of occlusion of the distal portion of the middle cerebral artery (MCA). I think the TCD change...
Predictive Values, Sensitivity, and Specificity of Absence or Presence of Early Hypodensity at Baseline CT Scans With Respect to Improving or Deteriorating Early Clinical Course of the Patients¹

<table>
<thead>
<tr>
<th>Type of Early Clinical Course</th>
<th>CT Findings of Early Hypodensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Improvement</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>19/42 (45%)</td>
</tr>
<tr>
<td>Negative predictor value</td>
<td>43/51 (84%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>19/27 (70%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>43/66 (65%)</td>
</tr>
</tbody>
</table>

¹Data are derived from Table 2 of Toni et al¹ using identical definitions of all terms as presented in that article. See also their Table 3 for comparison; when combining asymmetry and no-flow from the 6-hour transcranial Doppler as the indicator for deterioration, the respective positive and negative predictive values, sensitivity, and specificity are 31%, 92%, 85%, and 48%.

could also be caused by extrinsic compression onto the MCA from the developing cytotoxic edema, since the infarct was large enough to involve the whole MCA territory of that deteriorating patient.

Finally, early hypodensity on the baseline CT scans (see Table 2 of Toni et al¹) appears to predict early improvement and deterioration with comparable predictive values, sensitivity, and specificity as the TCD changes (see my accompanying Table and Table 3 of Toni et al¹). Thus, early hypodensity on the baseline CT scans predicts deterioration, and normal appearance on the baseline CT scans predicts improvement. As emphasized by Harold Adams, Jr, in his review article on treating ischemic stroke as an emergency,¹ the first few hours after stroke onset is the golden time window for intervention, and so precious time should not be wasted in ancillary diagnostic tests aiming at determining the likely cause of stroke or the presence of an arterial occlusion. My interpretation of the data from Toni and colleagues¹ is that neither TCD performed a few hours after stroke onset nor serial TCD examinations would add to the information which is already available from recognizing early cerebral infarction in the baseline CT scan.

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**Response**

We thank Dr Cheung for his appreciation of our article and for the opportunity he gives us to clarify some points.

A change of 1 point in the Canadian Neurological Scale score is a valid indicator of clinical change.¹ Moreover, the definition of deterioration we adopted has already been used in a number of previous works,² which makes our results comparable to those of other groups.

Approximately 10% of TCD examinations were unsuccessful due to lack of temporal bone acoustic window, a percentage in line with that reported in the literature. It was not our aim to demonstrate that early TCD is better than CT in predicting the early clinical course, given the emphasis we placed on CT in our previous works.³,⁴ However, considering only patients in whom early TCD can be performed, the multivariate analysis selected TCD and not CT findings as independent predictors of the clinical course. On the other hand, TCD and CT provide complementary rather than redundant information. In an emergency setting, when CT results may be completely negative, knowing whether MCA stem or branches are occluded can definitely help clinicians make therapeutic decisions.

The serial TCD study was aimed at providing further insight into the “vascular” pathophysiology of different clinical courses. In particular, in our series progression of arterial occlusion could be ruled out as cause of clinical deterioration, while early spontaneous recanalization was detected in both deteriorating and improving patients. Finally, we believe that in the single case in which we observed a shift of the TCD signal from asymmetry to no-flow, many explanations can be hypothesized. However, the possibility that this might have been determined by an extrinsic compression on the MCA stem exerted by brain edema is not supported by evidence in the literature.

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**Is the Increasing Volume of Carotid Endarterectomy Justified?**

To the Editor:

I read with interest the recent article by Huber et al¹ regarding carotid endarterectomy (CEA) volume in Florida since the Asymptomatic Carotid Atherosclerosis Study (ACAS) advisory was released. In this article, the authors made one statement that is unwarranted. They state in the discussion that “the morbidity and mortality rates reported in the study are consistent with those from multicenter carotid endarterectomy trials.” However, data from Table 5 of their paper would appear to contradict this assertion.

In the first report of the North American Symptomatic Carotid Endarterectomy Trial (NASCET),² the mortality was 0.6%. In the ACAS,¹ the perioperative mortality was 0.1%. In the study of Huber et al, the mortality in a mixed population of symptomatic and asymptomatic patients between the ages of 75 and 84 was 1.2%. Above age 84, the mortality was 2.2%. The latter value is close to 4 times higher than the NASCET mortality figure and 22 times higher than the ACAS rate. This is hardly comparable to multicenter trials. High rates of perioperative mortality in elderly patients have also recently been reported by Wennberg and colleagues.³ In their analysis of over 100 000 Medicare beneficiaries undergoing CEA in 1992 and 1993, the 30-day mortality
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2445

response

We appreciate Dr Chaturvedi’s interest in our recent article, “Effect of the Asymptomatic Carotid Atherosclerosis Study on Carotid Endarterectomy in Florida,”1 and appreciate the opportunity to respond. Dr Chaturvedi objected to a sentence in the “Discussion” which stated that “the morbidity and mortality rates reported in the study are consistent with those from multicenter carotid endarterectomy trials.” He went on to point out that the mortality rate in those patients >84 years of age was 4-fold.

We share Dr Chaturvedi’s concerns about the increased risk procedures on the morbidity and mortality rates seen in patients >84 years in our study cannot be assessed from the database. Interestingly, we have recently reported that severity of illness, myocardial infarction, and central nervous system complication, but not octogenarian status per se, correlated with mortality after carotid surgery in Veterans Affairs Medical Centers.3 Thus, due to the limitations of the database, we do not feel that our results should be used to justify or incriminate carotid endarterectomy in any selected population.

Last, Dr Chaturvedi asked how the data from our study should be used and whether the additional medical expenditure after release of the ACAS results was worthwhile. He stated that carotid endarterectomy for asymptomatic patients in the “real world” is not as worthwhile as blood pressure control, and he suggested that third-party payers may want to reconsider reimbursement for carotid endarterectomy in asymptomatic elderly patients. We concluded our article with a challenge to further analyze the cost-effectiveness of carotid endarterectomy for asymptomatic stenosis and noted that the results of the ACAS,7,8 noted that Cronenwett et al8 reported that carotid endarterectomy for asymptomatic stenosis was not cost effective for patients >75 years of age, using a threshold of $50 000/quality-adjusted life-year saved. It is imperative that we continue to reanalyze health care expenditure to assess optimization of our resources. However, the decisions about resource utilization, such as reimbursement for carotid endarterectomy in elderly asymptomatic patients, should be based on data from sound clinical trials rather than opinion, regardless of how strongly held.

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References


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Serum S-100 Protein in Stroke and Cardiac Surgery

To the Editor:

We have read with interest the articles1-3 and correspondence4 of Butterworth and Missler, which discuss the correlation of S-100 protein levels with cerebral infarction and hemorrhagic strokes. The authors suggest that S-100 protein levels may be a reliable marker of continuing cerebral insult or unresolved injury, whereas the peak levels are a function of the pathological process and mechanism of release.

Our data suggest that the observation of S-100 protein in the serum does not reflect only astrocyte death. Reversible cell injury, active secretion, and blood-brain barrier dysfunction all contribute to the explanation of our finding of high serum levels and normal postoperative neurological recovery. The utility of the S-100 protein as a marker of cerebral infarction in cardiac surgery appears limited. There is evidence that S-100 has a pathological role in mediating cerebral injury in high concentrations.6,11 We are currently investigating this intriguing theory.

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Response

We found the comment of Wong and Bonser to our report1 and that of Buttnner et al2 concerning S-100 protein blood levels in acute ischemic stroke very interesting. Wong and Bonser report increased S-100 serum levels of patients after cardiac surgery with circulatory arrest. They found an increase of S-100 beginning 5 minutes after the end of cardiopulmonary bypass, which peaked at the end of the operation. Peak levels reached up to 3.38 μg/L S-100 serum concentration. The levels returned to normal within 24 hours.

This suggests a kinetic of S-100 serum levels that is different from that reported by Buttnner and coworkers.2 We found S-100
serum levels as high as those reported by Wong and Bonser only in patients with lethal ischemic stroke or trauma (Missler et al, unpublished data, 1997). Therefore, we suggest that the S-100 measured by Wong and Bonser in patients after circulatory arrest does not only originate from the brain, but may also be S-100a or S-100a0, which originates from muscle tissue after temporal ischemia. Interestingly, we found similar results in a small population of patients after coronary bypass surgery (Missler et al, unpublished, 1998). For better understanding of the author’s findings, they need to report the laboratory method they used. The method we used for the study published in Stroke was developed and validated by us. Therefore, we know that our assay predominantly measures S-100b and cross-reacts with S-100a in an amount of 7% and with S-100a0 in an amount of 0.05% to 0.1%. As reported by Usui et al., S-100a0 reaches serum concentrations up to 7 μg/L after cerebral arrest. Most of the studies published during the last 2 years made use of the BYK-Sangtec immunoradiometric assay. To the best of our knowledge, complete validation data of this assay have not been published yet. Therefore, we do not know whether this assay is absolutely specific for S-100b. The data of Wong and Bonser, however, suggest that in their study there is a cross-reactivity with S-100a or S-100a0, because none of their patients with peak S-100 serum levels of up to 3.38 μg/L suffered from a neurological deficit.

It has been shown that S-100 is a valid marker of isolated damage to the central nervous system. However, we agree with the authors’ conclusion that given a laboratory method that is not absolutely specific for S-100b, S-100 protein is of limited use as a marker of cerebral damage in patients after heart surgery. The same problem, however, exists in patients suffering from poly-trauma. To better access brain damage in these patients, serum markers are required that are absolutely specific for the central nervous system (for example glial fibrillary acidic protein).

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In the article there is no detailed description of the environmental conditions, especially those that affect the circadian rhythms of the patients. Based on personal experience as a patient and as a subject in clinical trials, hospitalized for 3 to 7 days, as well as a parent staying for many weeks with a hospitalized child, I know how disruptive such an environment can be to the normal sleep/awake cycle, and it definitely feels like “jet lag syndrome.” Currently, I am not familiar with a well-controlled study documenting circadian rhythms under such “real-life hospital” conditions.

The “control” group in this paper is not an appropriate control for these effects, because they were studied in their homes and not exposed to the disruptive hospital environment. As for the “6-month reversibility,” was this observed after the same period of hospitalization as the initial one, which was reported to range between 1 and 7 (median, 3) days? If this is not the case, then once again this may not be appropriate for comparison of circadian variations.

I am fully aware of the practical difficulties in establishing the proper control groups, but without such data it is possible to assume that the environmental conditions of the hospitals themselves could have made a significant contribution to the disappearance of the circadian fluctuations in heart rate variability; the contribution of the infarction per se cannot be determined.

A. Bar-Ilan, PhD
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Response
We are delighted with Dr Bar-Ilan’s interest in our study1 concerning the effects of stroke on the circadian fluctuation of heart rate variability. We agree that a hospital environment may influence the normal sleep/awake cycle.

In our study, all the ECG recordings for the patients, ie, in the acute phase, at 1 month (data not presented) and at 6 months, were performed in the hospital. At the follow-up visits, the patients spent a few days in the same hospital department and under the same environmental conditions as in the acute phase.

However, we could show that the sleep/awake cycle of heart rate variability had normalized by 6 months after the brain infarction in the stroke patients. Thus, these patients could maintain their normal circadian rhythm of heart rate variability in the hospital despite the various potentially disruptive factors. Therefore, our conclusion is that stroke itself is the major determinant of the observed disappearance of the circadian fluctuation of heart rate variability.

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Predictors of Hematoma Growth?
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