Predictors 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 S-onset 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 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.

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>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 1–3 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 hemorrhages 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 1–3 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 likely to result in neurological deterioration, such as a change of 2 or more points in the Canadian Neurological Scale score. Toni and colleagues correctly pointed out the technical limitation of TCD: a poor acoustic window in some patients. While TCD may be useful in the acute management of ischemic stroke, I would like to know the percentage of stroke patients who were found to have a poor acoustic window during the same period of the present study.

Third, Toni and colleagues interpreted a TCD change from asymmetry to no-flow between 24 and 48 hours after stroke onset as a possible indication 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 Patients*

<table>
<thead>
<tr>
<th>CT Findings of Early Hypodensity</th>
<th>Improvement</th>
<th>Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive predictive value</td>
<td>19/42 (45%)</td>
<td>16/51 (31%)</td>
</tr>
<tr>
<td>Negative predictor value</td>
<td>43/51 (84%)</td>
<td>38/42 (90%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>19/27 (70%)</td>
<td>16/20 (80%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>43/66 (65%)</td>
<td>38/73 (52%)</td>
</tr>
</tbody>
</table>

*Data are derived from Table 2 of Toni et al 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 al 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,3 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.4 In their analysis of over 100 000 Medicare beneficiaries undergoing CEA in 1992 and 1993, the 30-day mortality
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rate was 2.46 for patients between the ages of 80 and 84 and 3.60 in patients over age 85.

Huber et al also do not comment on an important issue, namely, the extrapolation of the ACAS results to patients beyond the original study cohort. In the ACAS, the upper age limit was 79. Surgeons in Florida apparently believe that the modest clinical benefit seen in the ACAS can be extended to patients above age 80. The data described above would indicate, however, that there is little justification for operating on elderly, asymptomatic individuals with prevailing community-based perioperative mortality rates.

How should health policy makers respond to the report of Huber and colleagues? Is the additional $56 million spent in Florida money well spent in terms of stroke prevention? In a country in which hypertension is adequately controlled in fewer than 1 in 4 patients, I would suggest that the public health benefits of effectively treating hypertension far exceed the value of CEA on asymptomatic patients using “real world” performance data. In addition, third-party payers may want to reconsider routine reimbursement of CEA on asymptomatic elderly patients, since it is likely that many of these patients are deriving no benefit from the procedure.

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Response

We appreciate Dr Chaturvedi’s interest in our recent article, “Effect of the Asymptomatic Carotid Atherosclerosis Study on Carotid Endarterectomy in Florida,” 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 greater than that in NASCET and 22-fold greater than in ACAS. Dr Chaturvedi’s comments are correct, and the statement merits clarification. Our statement referred to the overall perioperative mortality and central nervous system complication rates (see Table 4 in the article) over the 5 years of the study rather than those for the various demographic groups. The overall perioperative mortality and central nervous system complication rates ranged from 0.8% to 1.3% and 0.8% to 1.1%, respectively. These values are well within the range of the rates for perioperative mortality (ECST, 1.0%; NASCET, 0.6%; VA/Sympt, 3.3%; VA/Asympt, 1.9%; ACAS, 0.2%) and combined perioperative stroke/mortality (ECST, 3.3%; NASCET, 5.8%; VA/Sympt, 6.5%; VA/Asympt, 4.7%; ACAS, 2.3%) reported in the multicenter trials. Although the statement in the Discussion section could have been clarified by referring the reader to the appropriate table, we feel that the objectionable statement was taken somewhat out of context. The remaining sentences in the paragraph that followed the statement outline the limitations of the database and the potential inaccuracy of the morbidity and mortality data. Furthermore, it should be emphasized that patients aged >84 years accounted for only 3.8% of all those in the study and that NASCET and ACAS represent only two of the reported multicenter trials.

Dr Chaturvedi further criticized the manuscript by stating that we failed to comment on the extrapolation of the ACAS data to patients beyond the study cohort, and he stated that our data do not support carotid endarterectomy in elderly, asymptomatic patients. We share Dr Chaturvedi’s concerns about the increased procedural volume in patients outside the ACAS cohort and the higher reported morbidity and mortality rates in patients >84 years of age, the group with the largest percent procedural increase. However, we would urge caution regarding the interpretation of our data. Although there was a dramatic increase in the volume of carotid endarterectomies in Florida after release of the ACAS results, it cannot be definitively determined that this was due to an increase in asymptomatic patients, since the indications for the procedure were not available from the database. Furthermore, although the dataset likely underreports the morbidity and mortality rates, these rates do reflect all carotid endarterectomies performed throughout the state, regardless of indication, including those performed for stroke in evolution or in combination with coronary artery bypass. The impact of these higher 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. 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 Cronenwett et al 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 assure 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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The curve of S-100 protein release during CABG and HCA is sharp and lasts for 1 to 2 days at most. This contrasts with the more progressive release from de novo stroke over 1 to 2 weeks. Thus, the total area under the curve (AUC) S-100 release after thromboembolic and hemorrhagic strokes is many times greater than that during CABG or HCA, despite the higher peak levels. Therefore, the presence of elevated levels of serum S-100 protein would seem to be a 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. We are currently investigating this intriguing theory.

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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.3,4 S-100a0 reaches serum concentrations up to 7 μg/L after cardiac 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 polytrauma. 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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Circadian Rhythm of Heart Rate Variability Is Reversibly Abolished in Ischemic Stroke

To the Editor:

I read with great interest the article by Korpelainen et al.1 and was very impressed with the finding that the circadian fluctuation in heart rate variability was abolished in the stroke patients. However, I have some difficulty with their attributing this effect to the infarction. I completely agree with the statement that, “The most powerful environmental rhythmic regulator is presumably daylight.” It has been reported previously that (1) Light can suppress endogenous circadian amplitude;2 (2) photoperiod-responsive changes in human circadian rhythms may be suppressed by regular exposure to artificial light;3 and (3) exposure to light of a critical strength at a critical phase can even drive the human circadian pacemaker to its region of singularity, akin to temporarily “stopping” the human circadian clock.4

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.

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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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Is the Increasing Volume of Carotid Endarterectomy Justified?
Seemant Chaturvedi

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