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.1 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 common2,3 and because this is associated with neurological deterioration.2 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.1 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.4 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.3 In a similar study, Brott and colleagues2 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.2 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.5 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 phase 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 symptomaticotolgy of intracerebral hematoma is affected by its location, volume, and rate of formation.4 In the study by Brott and colleagues,2 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 volume5: 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.

Raymond T.F. Cheung, MBBS, PhD, MRCP
Division of Neurology
Department of Medicine
Queen Mary Hospital
Hong Kong

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

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 decreased 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 studies1–3 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 cm$^3$ is likely to cause clinical deterioration. However, if we use only the relative change (>50%), we cannot regard a hematoma enlarged from 45 cm$^3$ to 65 cm$^3$ as hematoma growth. On the other hand, in pontine hemorrhage, a hematoma enlarged from 4 cm$^3$ to 6 cm$^3$, (ie, an increase by 2 cm$^3$) 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 studies1–3 do not contain parameters regarding the clinical characteristics, the findings from CT scans on admission, between 6 and 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).

Yukihiko Fujii, MD, PhD
Department of Integrated Neuroscience

Ryuichi Tanaka, MD, PhD
Department of Neurosurgery
Brain Research Institute
Niigata University
Niigata, Japan


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 liable to interobserver and intraobserver variability, even though the Canadian Neurological Scale has been rigorously tested for reliability, validity, and efficiency.2 I wonder whether Toni and colleagues have tried other definitions of improvement and deterioration, such as a change of 2 or more points in the Canadian Neurological Scale scores.

Second, Toni and colleagues3 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>Type of Early Clinical Course</th>
<th>Positive predictive value</th>
<th>Negative predictor value</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>19/42 (45%)</td>
<td>43/51 (84%)</td>
<td>19/27 (70%)</td>
<td>43/66 (65%)</td>
</tr>
<tr>
<td>Deterioration</td>
<td>16/51 (31%)</td>
<td>38/42 (90%)</td>
<td>16/20 (80%)</td>
<td>38/73 (52%)</td>
</tr>
</tbody>
</table>

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.

Danilo Toni, MD  
Marco Fiorelli, MD  
Corrado Argentino, MD  
Department of Neurological Sciences  
University “La Sapienza”  
Rome, Italy

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 in a stroke or the presence of an arterial occlusion. My interpretation of the data from Toni and colleagues 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.

Raymond T.F. Cheung, MBBS, PhD, MRCP  
Division of Neurology  
Department of Medicine  
Queen Mary Hospital  
Hong Kong


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), the mortality was 0.6%. In the ACAS, 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. In their analysis of over 100 000 Medicare beneficiaries undergoing CEA in 1992 and 1993, the 30-day mortality
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.

Seemant Chaturvedi, MD
Department of Neurology
Wayne State University
Detroit, Michigan


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 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 article1) 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 1.0%; NASCET,2 0.6%; VA/Symp,3 3.3%; VA/Asymp,4 1.9%; ACAS,5 0.2%) and combined perioperative stroke/mortality (ECST,1 3.3%; NASCET,2 5.8%; VA/Symp,3 6.5%; VA/Asymp,4 4.7%; ACAS,5 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.6 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 al7 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.

Thomas S. Huber, MD, PhD
John K. Cuddeback, MD, PhD
Douglas A. Dame, MBA
Timothy C. Flynn, MD
James M. Seeger, MD
1 Department of Surgery, University of Florida College of Medicine, Gainesville, Florida
2 Department of Surgery, Gainesville Veterans Administration Medical Center, Gainesville, Florida
3 Duke University School of Medicine, Durham, North Carolina

Letters to the Editor 2445

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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.

Carl Wong, MA, MB, FRCS, FRCSEd
Robert S. Bonser, MRCP, FRCSEd
Department of Cardiothoracic Surgery
University Hospital Birmingham
Queen Elizabeth Medical Centre
Birmingham, United Kingdom

Letters to the Editor

S-100 Protein in Stroke and Cardiac Surgery

To the Editor:

We have read with interest the articles of Butterworth and Missler, which discuss the correlation of S-100 protein release with cerebral infarction and hemorrhagic strokes. The authors suggest that S-100 protein levels may be a reliable index of the mass of injured brain and the patient’s prognosis and may facilitate differentiation of hemorrhagic and nonhemorrhagic strokes. However, we would like to report that this use of S-100 protein to estimate the extent of cerebral damage cannot be extrapolated to other clinical scenarios in which cerebral injury may occur.

Open-heart surgery is associated with a small but significant incidence of stroke. Surgery requiring hypothermic circulatory arrest for reconstruction of the aortic arch is associated with an incidence of stroke of 5% to 12%. If coronary artery bypass grafting (CABG) is 3% to 6%, several biochemical markers of cerebral injury have been investigated as potential substitutes for neurological deficit on examination and were routinely discharged from hospital between 7 and 10 days postoperatively. In the HCA group, S-100 protein levels were elevated within 5 minutes of commencing cardiopulmonary bypass and reached a mean of 0.6 μg/L (95% confidence interval [CI], 0.46 to 0.74 μg/L). S-100 protein levels peak at the end of operation in both the CABG and HCA groups reached a mean of 1.16 μg/L (95% CI, 0.253 to 2.07 μg/L) and 2.68 μg/L (95% CI, 1.99 to 3.38 μg/L), respectively.

These levels far exceed the peak levels of 0.41 μg/L and 1.8 μg/L reported by Missler and Buttnert respectively at 2–3 days following de novo stroke. At 24 hours, S-100 protein levels had returned to normal in the CABG group but were still elevated in the HCA group (1.0 μg/L; 95% CI, 0.62 to 1.38 μg/L). Because the half-life of S-100 is approximately 2 hours, levels should have fallen to near normal in the HCA group. This finding suggests continued S-100 secretion postoperatively, which correlates with reports that HCA causes a greater degree of cerebral injury than CABG.


Response

We found the comment of Wong and Bonser to our report concerning that of Bütter et al regarding 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.

This suggests a kinetic of S-100 serum levels that is different from that reported by Bütter and coworkers. We found S-100
Letters to the Editor

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.

A. Bar-Ilan, PhD

Phanos Ltd

Rehovot, Israel


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.

Juha T. Korpelainen, MD, PhD
Kyösti A. Sotaniemi, MD, PhD
Vilho V. Myllylä, MD, PhD
Department of Neurology
University of Oulu
Oulu, Finland

Predicting Early Deterioration or Improvement in Ischemic Stroke by Transcranial Doppler
Raymond T.F. Cheung

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