Neurobehavioral Outcome Prediction After Cardiac Surgery
Role of Neurobiochemical Markers of Damage to Neuronal and Glial Brain Tissue

Manfred Herrmann, MD, PhD; Anne D. Ebert, PhD; Imke Galazky, MD; Michael T. Wunderlich, MD; Wolfram S. Kunz, PhD; Christof Huth, MD

Background and Purpose—The goal of the present study was to investigate the predictive value of neurobiochemical markers of brain damage (protein S-100B and neuron-specific enolase [NSE]) with respect to the short- and long-term neuropsychological outcomes after cardiac surgery with cardiopulmonary bypass (CPB).

Methods—We investigated 74 patients who underwent elective CABG or valve replacement surgery and who showed no severe neurological deficits after surgery. Patients were investigated with a standardized neurological examination and a comprehensive neuropsychological and neuropsychiatric assessment 1 to 2 days before surgery, 3 and 8 days after surgery, and 6 months later. Serial venous blood samples were taken preoperatively and 1, 6, 20, and 30 hours after skin closure. Protein S-100B and NSE were analyzed with immunoluminometric assays.

Results—Patients with severe postoperative neuropsychological disorders showed a significantly higher and longer release of neurobiochemical markers of brain damage. Patients who presented with a delirium according to DSM-III-R criteria 3 days after surgery had significantly higher postoperative S-100B serum concentrations. Multivariate analysis (based on postoperative NSE and S-100B concentrations and age of patients, type of operation, length of cross-clamp and perfusion time, and intraoperative and postoperative oxygenation) identified NSE and S-100B concentrations 6 to 30 hours after skin closure as the only variables that contributed significantly to a predictive model of the neuropsychological outcome. NSE, but not S-100B, release was significantly higher in patients undergoing valve replacement surgery.

Conclusions—Postoperative serum concentrations and kinetics of S-100B and NSE have a high predictive value with respect to the early neuropsychological and neuropsychiatric outcome after cardiac surgery. The analysis of NSE and S-100B release might allow insight into the underlying pathophysiology of brain dysfunction, thus providing a valuable tool to monitor and evaluate measures to improve cardiac surgery with CPB. (Stroke. 2000;31:645-650.)

Key Words: cardiac surgery ■ follow-up studies ■ nerve tissue protein S-100 ■ neuron-specific enolase ■ neuropsychology

Cardiac surgery with cardiopulmonary bypass (CPB) is one of the most frequently performed operations. Neurobehavioral disorders, including neuropsychiatric and neuropsychological deficits, are a very frequently reported sequela of CABG or valve replacement (VR) surgery. Both type of disorders lengthen the stay on the intensive care unit (ICU) or ward, and additional in-hospital room costs due to neuropsychological or neuropsychiatric disorders were calculated to be $6150 per patient.1 Due to improvements in CPB technique and cardiosurgical, anesthetic, and drug management, the relative number of patients with overt neurological complications such as stroke or seizures dropped to 2% to 5.4%.1,1 Improvements in CABG surgical procedures (cooling, pH management, arterial line filters, acid-producing substrate load) also lead to a substantial decrease in postoperative neuropsychiatric and neuropsychological complications and make these postoperative alterations more difficult to detect. Neuropsychological disorders, however, are still reported to occur in a considerable number of patients,5,6 and it has been repeatedly claimed that neuropsychological disorders have a major impact on the postoperative quality of life. Therefore, research in the past decade has focused on etiopathogenetic aspects and the identification of early predictors of neuropsychological and neuropsychiatric disorders after cardiac surgery.

Most recently, specific brain-originated proteins such as protein S-100B (S-100B) or neuron-specific enolase (NSE) gained particular attention as neurobiochemical correlates of...
adverse neurological outcome in patients after stroke, and traumatic brain injury, and brain damage caused by circulatory arrest or cardiac surgery with CPB. A more recent study by Kilmminster et al demonstrated that postoperative S-100B release was also associated with subtle neuropsychological deficits at 2 months after surgery. The majority of studies on neurobiochemical markers after cardiac surgery were restricted to the early postoperative period and investigated only neurobiochemical markers specific to either neuronal (NSE) or glial (S-100B) brain tissue.

The goal of the present study was to analyze the differential value of both NSE and S-100B for the prediction of short- and long-term neuropsychological and neuropsychiatric outcomes after cardiac surgery with CPB.

Subjects and Methods

Patients
From a consecutive series of 113 patients who participated in a Department of Thoracic and Cardiovascular Surgery study that investigated postoperative neuropsychological deficits, blood samples could be obtained from 74 patients according to the procedure described later. We excluded patients from the original study cohort for whom blood samples were hemolytic and patients who did not provide informed and written consent for additional blood samples to be taken or who did not correspond to the selection criteria of (1) elective cardiac surgery (CABG, VR, or a combination); (2) no simultaneous surgery, such as carotid endarterectomy; and (3) no severe postoperative disturbance of consciousness, signs of focal neurological deficits, or other type of adverse neurological outcome.

All patients underwent a comprehensive neuropsychological and neuropsychiatric assessment at the last or next to the last day before surgery and 3 and 8 days after surgery. At the follow-up examination 6 months later, 60 patients (82%) could be reevaluated with the same standardized protocol. The reasons for exclusion were death (n=2), refusal of the investigation (n=7), and nonappearance at the follow-up examinations for unknown reasons (n=5). The study was approved by the local ethics committee, and all patients gave informed and written consent to participate.

Methods

Cardiac Surgery
Standard CPB technique with membrane oxygenator, nonpulsatile flow, and mean arterial pressure control was used. Patients were hypothermic at 29°C, and PCO2 was kept constant at 40 mm Hg. Patients were extubated 8 to 12 hours postoperatively and transferred from the ICU between the first and third postoperative days. Fifty-five patients underwent CABG (median number of bypass grafts 4.0, range 2 to 7). Nineteen patients underwent VR surgery; this group consisted of 11 patients with aortal VR, 7 patients with mitral VR, and 1 patient with a combined VR. In 5 patients, VR was carried out with CABG. Table 1 shows the demographic and clinical data for both patient groups. The table also demonstrates that the VR and CABG groups did not differ significantly with respect to demographic variables or the intraoperative and postoperative cardiac status.

Neurobiochemical Analysis
Serial venous blood samples were collected before surgery and 1 hour after skin closure. Blood was allowed to clot, and after centrifugation (1000g, 10 minutes), serum was stored within 30 minutes at −80°C for later analysis. Serum S-100B and NSE were analyzed with the use of immunoluminometric assays (Sangtec) and a fully automated LIA-mat system. Sangtec 100 measures the β-subunit of S-100 as defined by 3 monoclonal antibodies. The range of S-100B serum concentrations in 95% of healthy subjects is <0.12 μg/L. NSE was measured with the use of monoclonal antibodies that bind to the γ-subunit of the enzyme. The sensitivity is reported to be <1.0 μg/L, and the reference range of serum concentrations of healthy subjects is <12.5 μg/L.

Neuropsychological and Neuropsychiatric Assessments
Patients were investigated with the use of a standardized neuropsychological examination and a comprehensive neuropsychological and neuropsychiatric assessment 1 to 2 days before surgery, 3 days after surgery (mean 2.8±0.48 days), 8 days after surgery (7.7±1.1 days), and 6 months later (24±4.6 weeks). The following procedures were used.

Neuropsychology
The neuropsychological portion of the study design followed the consensus statements on the assessment of central nervous system disorders after cardiac surgery and was based on test procedures that require a minimum of motor activity. The examination included the following cognitive domains: (1) orientation/global cognitive screening (Mini-Mental State Examination); (2) working and short-term memory (digit spans forward/backward [Wechsler Memory Scale–Revised], mental arithmetic); (3) long-term memory (word list learning and paired-associate word learning [Nürnberger Alters-Inventar], selective reminding [according to Buschke]); (4) visuospatial functions (mental rotation [LPS 50+], block design [Wechsler Adult Intelligence Scales], clock orientation); (5) attentional performance (alertness [simple reaction time], Go/Nogo [response selection/inhibition]) from the computerized Test Battery of Atten-

<table>
<thead>
<tr>
<th>TABLE 1. Demographic and Clinical Variables</th>
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<tbody>
<tr>
<td>CABG (n=55)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Intraoperative and postoperative cardiac status</td>
</tr>
<tr>
<td>Ejection fraction</td>
</tr>
<tr>
<td>Perfusion time, min</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
</tr>
<tr>
<td>Mean cardiac-index postoperative, L/m²</td>
</tr>
<tr>
<td>Min. intraoperative Hb, mmol/L</td>
</tr>
<tr>
<td>Min. postoperative PO2, mm Hg</td>
</tr>
<tr>
<td>Days on ICU (day of surgery included)</td>
</tr>
<tr>
<td>No. of defibrillations after CPB</td>
</tr>
</tbody>
</table>

*P values according to Mann-Whitney U or χ² tests.
tional Performance); and (6) language and executive functions (naming, oral word-controlled association tasks).

All patients were assessed by the same neuropsychologist (A.D.E.). At the postacute follow-up examinations, we used parallel and psychometrically evaluated test forms as described in earlier studies. The individual difference between preoperative and postoperative test performance was calculated in each patient, and only patients who scored below their preoperative level in 3 cognitive domains were considered to show neuropsychological disorders.

Neuropsychiatry

Neuropsychiatric assessments included the diagnosis of delirium on the basis of DSM-III-R criteria. Furthermore, we applied the Delirium Rating Scale to analyze the severity of delirious symptoms and the Brief Psychiatric Rating Scale to assess psychopathological changes.

Statistical data evaluation was performed with nonparametric tests for independent and related samples (Mann-Whitney U, Wilcoxon’s, and Friedman’s tests) and Spearman’s rank correlation coefficients. The threshold for significance was set at P<0.05, and all probability values reported in the following section are 2-tailed. Multivariate investigation of the predictive value of neurobiochemical markers was based on stepwise discriminant analyses. Receiver operating characteristic (ROC) curve analysis was used to identify the positive likelihood ratio (+LR) of postoperative serum concentrations with respect to the neuropsychological outcome.

Table 2 shows that all NSE concentrations, as well as the area under curve (AUC) values, were significantly higher in patients undergoing VR surgery (all P<0.01, Mann-Whitney U test), whereas S-100B values did not differ significantly between groups. S-100B AUC values were significantly correlated with the age of patients (r=0.313, P=0.012, Spearman’s rho), but no other significant correlations between S-100B AUC and cardio-surgical variables (intraoperative and postoperative oxygenation, hemoglobin or blood pressure values) were found.

NSE AUC correlated significantly with the total length of surgery (r=0.351, P=0.005), perfusion time (r=0.417), and the total length of operation (r=0.351, P=0.005). The threshold for significance was set at P<0.05, and all probability values reported in the following section are 2-tailed. Multivariate investigation of the predictive value of neurobiochemical markers was based on stepwise discriminant analyses. Receiver operating characteristic (ROC) curve analysis was used to identify the positive likelihood ratio (+LR) of postoperative serum concentrations with respect to the neuropsychological outcome.

Results

Neurobiochemical Markers of Brain Damage

Figure 1 illustrates that both S-100B and NSE serum concentrations significantly increased from the preoperative to the 1-hour postoperative time of blood sampling (NSE z=-7.35, P<0.0001; S-100B z=-7.40, P<0.0001; Wilcoxon signed rank test) followed by a continuous decrease during the next 29 hours (NSE x=127.8, df=3, P<0.0001; S-100B x=153.6, df=3, P<0.0001; Friedman’s test). Mean S-100B concentrations remained elevated during the entire postoperative sampling time, whereas mean NSE values were found within the normal range 20 hours after surgery. Table 2 shows that all NSE concentrations, as well as the area under curve (AUC) values, were significantly higher in patients undergoing VR surgery (all P<0.01, Mann-Whitney U test), whereas S-100B values did not differ significantly between groups. S-100B AUC values were significantly correlated with the age of patients (r=0.313, P=0.012, Spearman’s rho), but no other significant correlations between S-100B AUC and cardio-surgical variables (intraoperative and postoperative oxygenation, hemoglobin or blood pressure values) were found.

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Table 2. Preoperative and Postoperative S-100B and NSE Serum Concentrations

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=74)</th>
<th>CABG (n=55)</th>
<th>VR (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>CV, %</td>
</tr>
<tr>
<td>S-100B Preoperative</td>
<td>108.5</td>
<td>170.1</td>
<td>156.7</td>
</tr>
<tr>
<td>1 h</td>
<td>1859.3</td>
<td>1527.4</td>
<td>82.2</td>
</tr>
<tr>
<td>6 h</td>
<td>427.4</td>
<td>420.9</td>
<td>98.5</td>
</tr>
<tr>
<td>20 h</td>
<td>210.1</td>
<td>262.0</td>
<td>124.7</td>
</tr>
<tr>
<td>30 h</td>
<td>255.2</td>
<td>316.3</td>
<td>123.9</td>
</tr>
<tr>
<td>AUC, x10^6</td>
<td>10.3</td>
<td>8.4</td>
<td>82.0</td>
</tr>
<tr>
<td>NSE Preoperative</td>
<td>4.9</td>
<td>2.6</td>
<td>53.1</td>
</tr>
<tr>
<td>1 h</td>
<td>15.9</td>
<td>5.9</td>
<td>37.1</td>
</tr>
<tr>
<td>6 h</td>
<td>14.6</td>
<td>6.4</td>
<td>43.8</td>
</tr>
<tr>
<td>20 h</td>
<td>11.0</td>
<td>6.4</td>
<td>58.2</td>
</tr>
<tr>
<td>30 h</td>
<td>8.9</td>
<td>5.5</td>
<td>61.8</td>
</tr>
<tr>
<td>AUC, x10^6</td>
<td>2.36</td>
<td>1.1</td>
<td>46.6</td>
</tr>
</tbody>
</table>

*A values according to Mann-Whitney U tests.
Neuropsychological and Neuropsychiatric Outcomes

According to the criteria defined earlier, 39 patients (52.7%) presented with neuropsychological disorders 3 days after surgery. Eight days after surgery, this value dropped to 16 patients (21.6%), and 6 months later, only 2 patients (2.7%) reached the criteria for severe neuropsychological disorders. Eleven patients from the first and 6 patients from the second postoperative examination could not be classified due to missing values in ≥1 test procedure. The most affected cognitive domains were memory performance, executive functions, and attentional performance. The number of patients with neuropsychological disorders did not differ significantly between the CABG and VR group at any time of the investigation.

Seven patients (5 VR and 2 CABG; χ²=8.1, df=1, P=0.012, Fisher’s exact test) presented with delirium according to DSM-III-R criteria at the first postoperative assessment. At the second postacute examination, only 2 patients (1 VR, 1 CABG) showed a delirious state, and 6 months later, no patients exhibited psychopathological alterations. Patients who underwent VR surgery had significantly higher Delirium Rating Scale scores at both the first (z =−2.3, P=0.022, Mann Whitney U test) and second (z =−2.4, P=0.016) postacute examinations. Brief Psychiatric Rating Scale scores did not differ significantly between groups.

Patients with and without neuropsychological or neuropsychiatric disorders did not differ with respect to intraoperative or postoperative drug treatment.

Neurobiochemical Markers and Neurobehavioral Outcome

Patients with an adverse neuropsychological outcome had a significantly higher and longer postoperative release of both neurobiochemical markers. Figure 2 shows that NSE_AUC values were significantly elevated in patients with neuropsychological disorders at both the first and second investigations after surgery. Protein S-100B release was significantly elevated in patients who exhibited neurobiochemical deficits 3 days after surgery (S-100B_AUC z =−2.67, P=0.008). S-100B_AUC values 8 days after surgery were also higher in neurologically impaired patients; the difference, however, did not reach statistical significance (S-100B_AUC z =−1.2, P=0.263). The most significant difference in neurobiochemical release was measured 6 hours after surgery (NSE_AUC z =−2.6, P=0.009), whereas S-100B differed most significantly at the 20-hour blood sampling point (S-100B_AUC z =−2.2, P=0.028).

Patients who exhibited a delirious state 3 days after surgery had a significantly higher and longer S-100B release (S-100B_AUC z =−2.3, P=0.022) compared with all other patients. This significance increased when delirious patients were compared with patients without neuropsychiatric and neuropsychological alteration (S-100B_AUC z =−2.5, P=0.010). The most significant difference was reached 20 hours after skin closure (S-100B z =−2.8, P=0.003). NSE_AUC did not differ significantly between patients with and without neuropsychiatric alterations, although NSE concentrations at 6 ($z =−2.1, P=0.034$) and 20 ($z =−1.9, P=0.047$) hours after surgery were found to be significantly different between groups.

A multivariate approach using a stepwise discriminant analysis (neuropsychological outcome 3 days after surgery as dichotomized grouping variable and postoperative S-100B AUC and NSE release, as well as age, sex, time of perfusion, and type of operation, as independent predictor variables) resulted in a 68% correct classification (sensitivity 71.8, specificity 62.5). NSE concentration at 6 hours after surgery (Wilks’ $\lambda =0.881, P=0.008$) and S-100B values at 30 hours after surgery (Wilks’ $\lambda =0.778, P=0.001$) were the only variables that showed a significant contribution to this predictive model. When the same approach for the neuropsychological outcome prediction was used at 8 days after surgery, the NSE value at 6 hours after surgery was the only variable that contributed significantly (Wilks’ $\lambda =0.873, P=0.004$) to a prediction model with a 78% correct classification (sensitivity 50.0, specificity 79.0).

ROC curve analysis resulted in patients with serum NSE values of ≥11.8 μg/L at 6 hours after skin closure showing a +LR of 2.1 to exhibit neuropsychological disorders 3 days after surgery. Patients with S-100B concentration of ≥137 ng/L at the 20-hour sampling point were calculated to have a +LR of 2.3.

The group of patients participating at the 6-month follow-up examination did not differ significantly from the dropout group with respect to clinical, surgical, or neurobiochemical variables. However, due to a small sample size, no predictive values could be calculated with respect to the long-term neuropsychological outcome, although both patients with severe neuropsychological disorders 6 months after surgery presented with highly elevated NSE and S-100B release after surgery and spontaneously complained of diffic-
cultivates concerning memory and concentration in activities of daily living.

**Discussion**

The present study provides 2 major results. First, the release patterns of brain-originated proteins are associated with postoperative neurobehavioral disorders. Second, the postoperative release of NSE and S-100B might reflect different pathophysiology of brain dysfunction after cardiac surgery with CPB.

We found a significant decline in neuropsychological function in the postacute stage after surgery. This decline was mainly caused by memory and attentional disorders and executive dysfunction, thus corroborating the results of previous studies and reviews on neuropsychological disorders after cardiac surgery with CPB. Postacute neuropsychological disorders were found to be significantly associated with the postoperative release of both neurobiochemical markers of brain damage. Patients who presented with neuropsychological disorders after surgery had significantly higher and longer NSE and S-100B releases within the first 30 hours after the end of the operation. This finding remained substantial even when tested in a multivariate model and together with other variables known to be significantly associated with the neurobehavioral outcome of cardiac surgery. Compared with age of patients, type of operation, cross-clamp or perfusion time, and intraoperative and postoperative oxygenation, postoperative NSE and S-100B serum concentrations were the only variables that contributed significantly to a correct classification of the postoperative neuropsychological outcome. The results from discriminant and ROC analyses demonstrate that the most significant time window in which S-100B and NSE may have a predictive value is between 6 and 30 hours after surgery.

Our data confirm the results of a previous study by Kilminster et al, who found an association between S-100B release and neuropsychological dysfunction 2 months after cardiac surgery. Wimmer-Greinecker et al reported no association between neuropsychological function and S-100B and NSE serum concentrations in patients undergoing CABG. In the latter study, however, no significant neuropsychological change after surgery could be observed. This finding might be attributed to the methods applied in the study. The authors investigated only a very restricted range of cognitive functions, which were also tested with instruments known to be very sensitive to transfer or learning effects.

The number of patients with long-term neuropsychological deficits was very low in the present investigation. This finding obviously is caused by the fact that contrary to the majority of previous studies, we used very restrictive criteria to define an adverse neuropsychological outcome. The use of more moderate criteria (i.e., a performance >1.5 SD below the preoperative level in only 2 cognitive domains) would result in a prevalence rate of 25.9% of patients with neuropsychological deficits at 6 months after surgery. In this patient group with long-term neuropsychological disorders, postoperative serum concentrations of both S-100B and NSE were numerically higher; the difference, however, did not reach statistical significance (S-100B_AUC, z = -1.2, P = 0.216; NSE_AUC, z = -0.3, P = 0.973). Furthermore, the data from the present study indicate that the release patterns of neurobiochemical markers of brain damage are associated not only with the neuropsychological outcome but also with the neuropsychiatric outcome after cardiac surgery. Patients who presented with delirium according to DSM-III-R criteria 3 days after surgery had significantly higher postoperative S-100B serum concentrations. Interestingly, the difference between delirious and nondelirious patients was significant only for S-100B concentration, not for NSE concentrations, a fact that leads to the second point of our discussion.

In contrast to the majority of studies conducted so far, we included an analysis of both neurobiochemical markers of damage to glial and neuronal brain tissue. S-100B is part of a large family of Ca^2+ -binding proteins predominantly found in astrocytes and Schwann cells. Its biological function is largely unknown, but the release into peripheral blood seems to be associated with functional disturbance of membrane integrity and increased permeability of the blood-brain barrier. Recent studies suggest that S-100B might play both a detrimental and a beneficial role depending on the concentration and the time elapsed since brain injury. NSE is the dimeric isoenzyme of the glycolytic enzyme enolase that is predominantly found in the cytoplasm of neurons. The cytoplasmatic enzyme is not secreted into the extracellular liquid by intact neurons but, rather, set free by cell destruction. In the present study, we found highly elevated postoperative levels of both NSE and S-100B. We found significantly higher NSE, but not S-100B, release in patients undergoing VR surgery. This finding replicates the results of an earlier study by our group in which postoperative NSE release was found to be significantly higher in a group of VR patients who were matched exactly by sex, age, and preoperative cognitive status with another group of patients who were undergoing isolated CABG. These data indicate that VR surgery is associated with a higher degree of neuronal damage, leading to a higher release of NSE. Cerebral neuronal damage might be caused by transient or outlasting hypoxia as a consequence of microembolism or macroembolism. Embolic events, however, are more often detected in patients who undergo open heart surgery, and neuropsychological deficits were shown to be associated with the number of intraoperative microembolic signals only in patients undergoing VR surgery. These findings provide evidence that S-100B and NSE release after cardiac surgery with CPB not only reflects different type of brain dysfunction but also might mirror a different underlying pathophysiology. In a previous study that focused on patients with traumatic brain injury, we demonstrated that the kinetics and release patterns of NSE and S-100B may reflect complex neuronal/glial interactions. Differing release patterns of both proteins were associated with a different pathophysiology of head trauma as demonstrated with serial cranial CT and did not simply correlate with the severity of brain injury. Therefore, the analysis of neurobiochemical markers also might help to provide an understanding of the mechanism and pathophysiology of adverse neurological and neuropsychological outcomes in patients undergoing cardiac surgery. Furthermore, the investigation of damage to neuronal and glial brain tissue...
after cardiac surgery could support the monitoring and evaluation of new technical or surgical procedures or neuroprotective drug treatment introduced to improve the safety of cardiac surgery.

Taken together, the results of the present study demonstrate that the kinetics and release patterns of neurobiochemical markers of damage to neuronal (NSE) and glial (S-100B) brain tissue are significantly associated with the early neuropsychological and neuropsychiatric outcome of cardiac surgery with CPB. The analysis of NSE and S-100B release after cardiac surgery might allow insight into the underlying pathophysiology of brain dysfunction, thus providing a valuable tool to monitor and evaluate measures to improve cardiac surgery with CPB.

Acknowledgments
This study was supported in part by the Federal Ministry of Education and Research (grant 07-NBL-04/01-ZZ-9505), the State of Saxony-Anhalt, and the Research Commission of the Faculty of Medicine at Magdeburg University. Kits for the analysis of S-100B and NSE were provided by Byk-Sangtec Diagnostica (Dietzenbach, Germany). The authors thank the cardioanesthetists Drs Tober and Hann for allowing access to their data bank and for support during blood taking and the staff from the operating theater, ICU, and ward for extensive cooperation. We also greatly appreciate the comments of an anonymous reviewer of a previous version of the manuscript.

References
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Stroke. 2000;31:645-650
doi: 10.1161/01.STR.31.3.645

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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