ADVANCES

Ability of neuron-specific enolase to predict survival to hospital discharge after successful cardiopulmonary resuscitation

Johann Auer, MD; Robert Berent, MD; Thomas Weber, MD; Michael Porodko, MD; Gudrun Lamm, MD; Elisabeth Lassnig, MD; Edwin Maurer, MD; Herbert Mayr, MD; Christian Punzengruber, MD; Bernd Eber, MD

SEE ALSO PAGE 19.

ABSTRACT

Background: Accurate prediction of survival to hospital discharge in patients who achieve return of spontaneous circulation after cardiopulmonary resuscitation (CPR) has significant ethical and socioeconomic implications. We investigated the prognostic performance of serum neuron-specific enolase (NSE), a biochemical marker of ischemic brain injury, after successful CPR.

Methods: In-hospital or out-of-hospital patients with nontraumatic normothermic cardiac arrest who achieved return of spontaneous circulation (ROSC) following at least 5 minutes of CPR were eligible. Neuron-specific enolase levels were assessed immediately, 6 hours, 12 hours and 2 days after ROSC. Subjects were followed to death or hospital discharge.

Results: Seventeen patients (7 men, 10 women) were enrolled during a 1-year period. Median (range) NSE levels in survivors and non-survivors respectively were as follows: immediately after ROSC: 14.0 μg/L (9.1–51.4 μg/L) versus 25.9 μg/L (10.2–57.5 μg/L); 6 hours after ROSC: 15.2 μg/L (9.7–30.8 μg/L) versus 25.6 μg/L (12.7–38.2 μg/L); 12 hours after ROSC: 14.0 μg/L (8.6–32.4 μg/L) versus 28.5 μg/L (11.0–50.7 μg/L); and 48 hours after ROSC: 13.1 μg/L (7.8–29.5 μg/L) versus 52.0 μg/L (29.1–254.0 μg/L). Non-survivors had significantly higher NSE levels 48 hours after ROSC than surivors ($p = 0.04$) and showed a trend toward higher values during the entire time course following ROSC. An NSE concentration of >30 μg/L 48 hours after ROSC predicted death with a high specificity (100%: 95% confidence interval [CI] 85%–100%), and a level of 29 μg/L or less at 48 hours predicted survival with a high specificity (100%: 95% CI 83%–100%).

Conclusions: Serum NSE levels may have clinical utility for the prediction of survival to hospital discharge in patients after ROSC following CPR over 5 minutes in duration. This study is small, and our results are limited by wide confidence intervals. Further research on ability of NSE to facilitate prediction and clinical decision-making after cardiac arrest is warranted.

Key words: cardiopulmonary resuscitation; cardiac arrest; prognosis; predictive value of tests; outcome; neuron-specific enolase

Department of Cardiology and Institute of Laboratory Medicine I, General Hospital Wels, Austria

Received: June 7, 2005; final submission: Oct. 19, 2005; accepted: Nov. 14, 2005

This article has been peer reviewed.

Can J Emerg Med 2006;8(1):13-8

RÉSUMÉ

Contexte : La prédiction exacte de la survie après le congé de l'hôpital chez les patients dont la circulation spontanée a été rétablie après la réanimation cardiorespiratoire (RCR) a des implications éthiques et socio-économiques importantes. Nous avons étudié la performance pronostique de l'énolase neurone-spécifique (NSE) sérique, un marqueur biochimique de la lésion cérébrale ischémique, après une RCR réussie.

Méthodes : Les patients à l'hôpital et à l'extérieur de l'hôpital victimes d'un arrêt cardiaque normothermique non traumatique qui connurent un retour de la circulation spontanée (RCS) après 5 minutes de RCR furent admissibles. Les niveaux d'énolase neurone-spécifique furent évalués immédiatement, 6 heures, 12 heures, et 2 jours après le RCS. Les sujets furent suivis jusqu'à leur décès ou jusqu'à leur congé de l'hôpital.

Résultats : Dix-sept patients (7 hommes, 10 femmes) furent inscrits au cours d'une période d'un an. Les niveaux médians de NSE chez les survivants et les non-survivants respectivement étaient les suivants : immédiatement après le RCS : 14,0 μg/L (9,1–51,4 μg/L) par rapport à 25,9 μg/L (10,2–57,5 μg/L); 6 heures après le RCS : 15,2 μg/L (9,7–30,8 μg/L) par rapport à 25,6 μg/L (12,7–38,2 μg/L); 12 heures après le RCS : 14,0 μg/L (8,6–32,4 μg/L) par rapport à 28,5 μg/L (11,0–50,7 μg/L); et 48 heures après le RCS : 13,1 μg/L (7,8–29,5 μg/L) par rapport à 52,0 μg/L (29,1–254,0 μg/L). Les non-survivants présentaient des niveaux de NSE beaucoup plus élevés 48 heures après le RCS que les survivants (p = 0,04) et démontraient une tendance vers des valeurs plus élevées pendant toute la période suivant le RCS. Une concentration de NSE de > 30 μg/L 48 heures après le RCS prédisait le décès avec une spécificité élevée (100 % : intervalle de confiance [IC] de 95 % 85 %–100 %) et un niveau de 29 μg/L ou moins après 48 heures prédisait la survie avec une spécificité élevée (100 % : IC de 95 % 93 %–100 %).

Conclusions : Les niveaux sériques de NSE peuvent avoir une utilité clinique dans le cadre de la prédiction clinique de la survie jusqu'au congé de l'hôpital chez des patients ayant connu un RCS à la suite de la RCR d'une durée de plus de 5 minutes. La présente étude est de petite envergure et nos résultats sont limités par les intervalles de confiance larges. Des recherches plus approfondies sur la capacité du NSE à faciliter la prédiction et la prise de décision après un arrêt cardiaque sont justifiées.

Introduction

Overall survival from out-of-hospital cardiac arrest is approximately 3% to 5%.[1,2] To appropriately guide post-resuscitation management in cardiac arrest victims who achieve return of spontaneous circulation (ROSC), the apparent severity of hypoxic brain damage is usually considered. As a result, a predictive test with the potential of being applicable to comatose patients in the emergency department or critical care unit early after cardiopulmonary resuscitation (CPR) has great appeal.

Several clinical scales, electrophysiological techniques, and imaging methods have been found to facilitate recovery prediction in patients after cardiac arrest.[3–9] However, the final outcome of patients resuscitated from cardiac arrest typically remains unclear for a significant period of time. Recently, studies have suggested a possible prognostic role of nervous system–specific proteins and biochemical markers of cerebral tissue damage. Cerebrospinal fluid analysis has demonstrated the presence of a number of potentially prognostic enzymes.[10,11] Neuron-specific enolase (NSE) is an isoenzyme of the glycolytic enzyme enolase (2-phospho-D-glycerate hydrolase), and has been shown to be highly specific for neuronal tissue that is released into the cerebrospinal fluid and the cerebral and systemic circulation after neuronal damage.[12–15] Neuron-specific enolase is a dimeric enzyme composed of 2 γ-subunits, and is nearly exclusively located in cells of neuroectodermal origin.[16] In healthy individuals, NSE is only negligibly present in the peripheral blood. Various investigators have found an increase in serum NSE levels after neuronal damage associated with intracerebral hemorrhage, ischemic stroke and brain injury, indicating that NSE is both a sensitive and quantitative marker of parenchymal brain injury.[17–22] Reduced cerebral perfusion during CPR, and resulting cerebral ischemia, can cause leakage of cytosolic brain enzymes into the cerebrospinal fluid and blood. Previous studies have demonstrated elevated NSE levels in cerebrospinal fluid and serum in patients after cardiac arrest with CPR.[23–25] However, limited data are available on the predictive value of NSE levels on survival after CPR.[25–27]

This observational study was designed to investigate the prognostic ability of serum NSE concentration, as a biochemical marker of ischemic brain injury, to predict survival to hospital discharge in cardiac arrest victims with CPR of at least 5 minutes duration. The study was de-

https://doi.org/10.1017/S1481803500013324 Published online by Cambridge University Press

signed to be hypothesis generating rather than conclusive.

Methods

Patient population

All patients with ROSC after CPR of at least 5 minutes duration following non-traumatic normothermic in-hospital or out-of-hospital cardiac arrest, and admitted to the intensive care unit of the General Hospital in Wels, Austria, between April 2001 and March 2002 were eligible. Patients with a history of cancer before CPR and patients who were transferred to our institution from other intensive care units were excluded. Patient were also excluded if investigations or autopsy revealed a non-cardiac etiology for the cardiac arrest.

Venous blood samples for NSE analysis were obtained from an antecubital vein immediately after RSOC (baseline), and 6 hours, 12 hours, and 2 days later. Blood samples were collected directly into sampling tubes, allowed to coagulate, and centrifuged at 3000 rotations per minute for 10 minutes. All analyses were performed immediately after blood sampling. The study protocol was approved by the local Ethics Committee (Human Subjects Institutional Review Board).

Outcome variables

Clinical outcomes

All patients were followed to the point of death or survival to hospital discharge. Neurologic outcome was assessed using the Glasgow Coma Scale (GCS) score.[28] Functional neurologic recovery was assessed twice daily for the first 2 days after cardiac arrest. A GCS score of ≤7 was classified as poor neurologic outcome, and a score of ≥8 was classified as good neurologic outcome.

Laboratory analysis

The assay used to measure NSE is based on electrochemoluminescence immunoassay technology, and was performed on the Elecsys System (Roche Diagnostics, Germany). The normal range of NSE levels from this assay is 3–14 µg/L.

Statistical analysis

A 2-tailed sample size calculation was performed using following assumptions: p value 0.05; power 80%; 300% absolute difference of NSE levels at 48 hours between survivors and non-survivors; and an anticipated NSE level of 12 µg/L in the survivor group.[17] This generated a sample requirement of 8 patients per group.

Data are presented as medians (with range in parentheses) unless otherwise specified, and 95% confidence intervals (CIs) are included when appropriate. Continuous data (such NSE concentrations at baseline and peak) were compared using unpaired t tests or the Wilcoxon matched-pairs signed rank test as appropriate. Group comparisons between surviving and non-surviving patients were performed using the Mann–Whitney U test. A linear regression model was fit to examine the relationship between NSE concentration and time to ROSC. The accuracy of NSE levels to differentiate between survivors and non-survivors was evaluated with the use of receiver operating characteristic (ROC) analyses according to standard procedures. A p value <0.05 was considered to indicate statistical significance, and no adjustment was made for multiple statistical comparisons.

Results

Study population

Seventeen patients (7 men, 10 women) with a median age of 62 (range 34–86) years were enrolled in the study. Two patients with a history of cancer before CPR were excluded, as were 12 patients who were first admitted to other intensive care units and subsequently transferred to our institution. The underlying cause of cardiac arrest was deemed to be acute myocardial infarction in 12 patients; cardiomyopathy in 2 patients; valvular heart disease associated with left ventricular dysfunction in 2 patients; and no structural heart disease in 1 patient who had ventricular fibrillation. Three patients were deemed to have a non-cardiac cause for their arrest (stroke, pulmonary embolism and sepsis) and were therefore excluded from the analysis. The first documented cardiac rhythm was ventricular fibrillation in 11 patients and bradyasystole in 9 patients.

Clinical outcomes

Eight subjects (1 male) survived to hospital discharge) and 9 subjects (6 males) died in hospital. Survivors and non-survivors median ages were 59.3 (35–86) and 65.2 (34–79) years respectively (p = 0.46). Time from collapse until ROSC (defined as ECG activity associated with a palpable pulse and a measurable systolic blood pressure)[29] was 20.4 (6.5–48.5) minutes, 9.1 (6.5–34) minutes, and 26.4 (8.0–48.5) minutes in the total study population, survivors, and non-survivors respectively. Good neurologic outcome at 48 hours was achieved in 41.2% (n = 7) of subjects. The GCS score was 3 (3–15) and 10 (3–15) immediately after and 48 hours after the admission to the intensive care unit respectively.

https://doi.org/10.1017/S1481803500013324 Published online by Cambridge University Press

Neuron-specific enolase levels

Blood samples at all time points were not available for some patients: the NSE values at 6 hours and at 12 hours after ROSC were unavailable in 1 patient; and levels at 48 hours were unavailable in 3 patients (all of whom died). Table 1 shows the median and range in serum NSE levels for the various pre-defined intervals in the 2 study groups. Neuron-specific enolase values were non-significantly higher levels in non-survivors compared with survivors at each measured time point after ROSC (Fig. 1), and at 48 hours after ROSC non-survivors had significantly higher NSE levels than survivors (p = 0.04; Fig. 2). The secular trend of NSE levels over the 48-hour sampling period differed between non-survivors and survivors (Fig. 1). In survivors, NSE levels increased over 48 hours after ROSC, and in non-survivors NSE levels tended to decrease.

A 48-hour NSE level of >30 μg/L was highly specific (100%: 95% CI 85%–100%) for the prediction of death (sensitivity 79%: 95% CI 68%–88%). In contrast, a 48-hour NSE level of 29 μg/L or less was highly specific (100%: 95% CI 83%–100%) for the prediction of survival (sensitivity 78%: 95% CI 67%–89%). The overall accuracy of NSE to differentiate survivors and non-survivors following cardiac arrest was evaluated through ROC analysis. The area under the curve (AUC) was highest at 48 hours after ROSC (AUC = 0.87 ± 0.06; Fig. 3). There were no significant associations found between time until ROSC and individual peak serum levels of NSE on linear regression modelling.

Discussion

The decision to continue or withdraw active care following ROSC is frequently faced in both emergency departments and critical care units. This challenging issue has significant ethical and socioeconomic implications.[30,31] Results of CT and MRI can provide significant information in ischemic situations,[32] but both modalities have a limited capacity to identify generalized edema or differentiate between permanent and reversible injury. As a result, practical markers of ischemic brain damage associated with unfavourable outcome and early death would have significant clinical utility in the management of patients after CPR.

Our study, although small, suggests that elevated serum NSE levels in the first 2 days following CPR of at least 5 minutes duration may facilitate prediction of early death. Elevated serum NSE levels in patients after CPR indicate hypoxic brain damage and may correlate with outcome. Non-survivors of the index hospital stay had a non-significant increase in NSE levels immediately after ROSC and at 6 and 12 hours and had significantly higher NSE levels at 48 hours. The maximum NSE level measured within 48 hours after ROSC was also significantly higher in non-survivors. Neuron-specific enolase levels at 48 hours after ROSC predicted death with high accuracy. In addition, the secular trend of NSE levels over the first 2 days after ROSC may have prognostic relevance; while NSE levels rose over time in non-survivors, they tended to decrease in survivors. NSE concentrations that increase to 30 μg/L or more by 48 hours may portend an un-

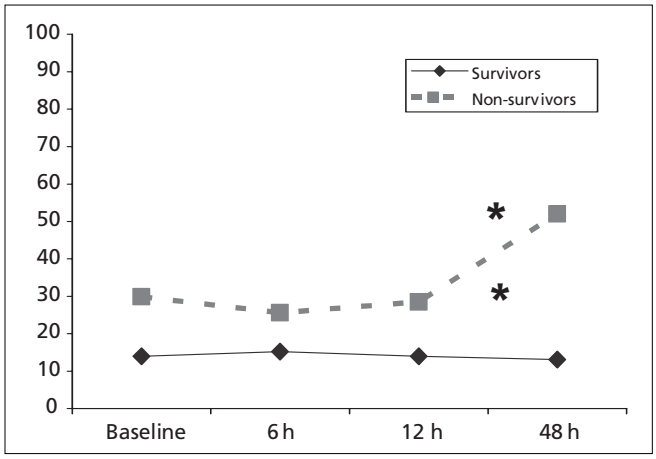

Fig. 1. Neuron-specific enolase levels in μg/L at baseline and 6, 12, and 48 hours after CPR in survivors and non-survivors. Values are expressed as median. * p = 0.04.

Table 1. Serum neuron-specific enolase (NSE) levels* for the two study groups

	NSE levels,† μg/L			
Study group	Baseline	6 h‡	12 h‡	48 h§
Survivors	14.0 (9.1–52.4)	15.2 (9.7–30.8)	14.0 (8.6–32.4)	13.1 (7.8–29.5)
Non-survivors	25.9 (10.2–57.5)	25.6 (12.7–38.2)	28.5 (11.0–50.7)	52.0 (29.1–254.0)
p value	0.12	0.69	0.48	0.04

*Values are expressed as median and range.
†Normal, 3–14 μg/L
‡NSE values at 6 and 12 h were unavailable for 1 patient.
§NSE values at 48 h were unavailable for 3 patients (all of whom died).

https://doi.org/10.1017/S1481803500013324 Published online by Cambridge University Press

favourable outcome. Only one patient with an NSE concentration at 48 hours after ROSC of less than 30 µg/L died during the index hospital stay.

To be clinically useful, a test for prediction of outcome after cardiac arrest must have a high specificity for an unfavourable outcome. Based on the assumption that the default approach is ongoing clinical care and further observation, high specificity is more important than high sensitivity as an unfavourable test result could lead to withdrawl of care earlier in some patients (thus the implications of a "false positive" test for a bad outcome are enormous). We found that an NSE level >30 µg/L at 48 hours after ROSC appears to predict death with a very high specificity. Neoplastic cells in neuroendocrine tumours, small cell carcinoma of the lung, and neuroblastoma usually produce NSE, hence the established role of NSE as a diagnostic marker since patients with these tumours usually have elevated NSE levels.[33–35] Since the frequency of such conditions in cardiac arrest survivors is low, it is unlikely this would interfere with the general prognostic ability of NSE. Our findings are consistent wtih the results of previous studies that found elavated serum NSE levels in cardiac arrest patients were indicative of unfavourable neurologic and survival outcome.[17,23,25,32]

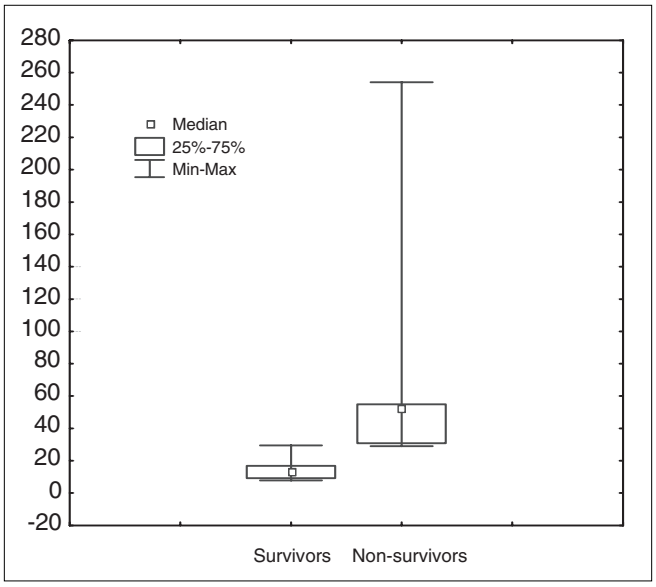

Fig. 2. Box-whisker plot showing neuron-specific enolase levels at 48 hours after CPR in survivors and non-survivors. Small box indicates median; dotted large box indicates the 25% to 75% interquartile range; whiskers indicate 95% confidence interval. *P* value for a difference between survivors and non-survivors is 0.04.

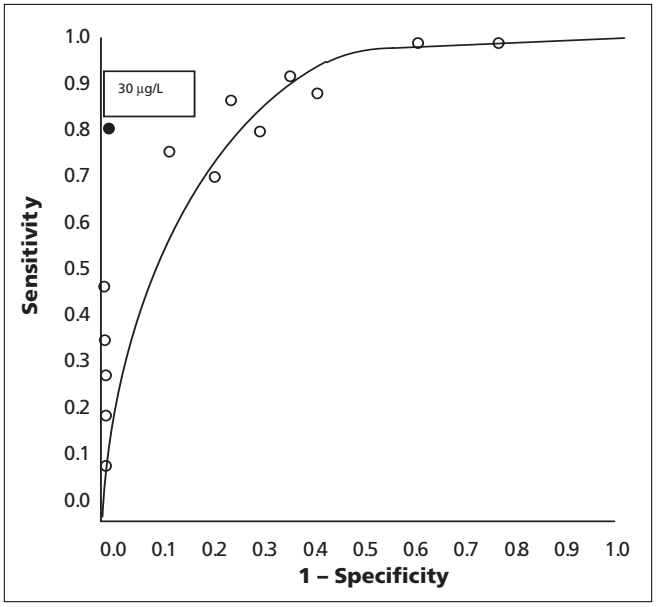

Fig. 3. Receiver operating characteristic curve for the overall performance of neuron-specific enolase to predict survival at 48 hours after return of spontaneous circulation.

Study implications and limitations

The major limitation of our study is the small sample size and resulting low power and wide confidence intervals. As a result of this and unadjusted multiple statistical comparisons, our data must be viewed as hypothesis generating rather than conclusive. The accuracy of NSE for outcome from cardiac arrest requires further evaluation. In addition, our study was observational and NSE levels were not used to make clinical decisions. This precludes our ability to comment on the incremental value of NSE, beyond other clinical, laboratory, or imaging modalities, in aiding decision making. It is our hope that this study will provide further encouragement for the development of large prospective clinical trials.

Conclusions

This study suggests that NSE levels in the first 48 hours after cardiac arrest with at least 5 minutes of CPR may facilitate the prediction of survival to hospital discharge. In particular, a NSE level >30 µg/L at 48 hours after ROSC may predict non-survival with a very high specificity. Because of our small sample size, this study has limited power and wide confidence intervals. Given this, and the methodology we employed, our results should be viewed as hypothesis generating. Further research is warranted to evaluate the potential role of NSE in outcome prediction and facilitation of decision making after cardiac arrest.

Competing interests: None declared.

References

1. Dorian P, Cass D, Schwartz B, et al. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 2002;346:884-90.
2. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. N Engl J Med 1999;341:871-8.
3. Longstreth WT Jr, Diehr P, Inui TS. Prediction of awakening after out-of-hospital cardiac arrest. N Engl J Med 1983;308:1378-82.
4. Levy DE, Caronna JJ, Singer BH, et al. Predicting outcome from hypoxic-ischemic coma. JAMA 1985;253:1420-6.
5. Scollo-Lavizzari G, Bassetti C. Prognostic value of EEG in postanoxic coma after cardiac arrest. Eur Neurol 1987;26:161-70.
6. Brunko E, Zegers de Beyl D. Prognostic value of early cortical somatosensory evoked potentials after resuscitation from cardiac arrest. Electroencephalogr Clin Neurophysiol 1987;66:15-24.
7. Madl C, Grimm G, Kramer L, et al. Early prediction of individual outcome after cardiopulmonary resuscitation. Lancet 1993; 341:855-8.
8. Morimoto Y, Kemmotsu O, Kitami K, et al. Acute brain swelling after out-of-hospital cardiac arrest: pathogenesis and outcome. Crit Care Med 1993;21:104-10.
9. Rupright J, Woods EA, Singh A. Hypoxic brain injury: evaluation by single photon emission computed tomography. Arch Phys Med Rehabil 1996;77:1205-8.
10. Vaagenes P, Mullie A, Fodstad DT, et al. The use of cytosolic enzyme increase in cerebrospinal fluid of patients resuscitated after cardiac arrest. Brain Resuscitation Clinical Trial I Study Group. Am J Emerg Med 1994;12:621-4.
11. Karkela J, Pasanen M, Kaukinen S, et al. Evaluation of hypoxic brain injury with spinal fluid enzymes, lactate, and pyruvate. Crit Care Med 1992;20:378-86.
12. Hans P, Bonhomme V, Collette J, et al. Neuron-specific enolase as a marker of in vitro neuronal damage. Part I: Assessment of neuron-specific enolase as a quantitative and specific marker of neuronal damage. J Neurosurg Anesthesiol 1993;5:111-6.
13. Marangos PJ, Schmechel DE. Neuron specific enolase, a clinically useful marker for neurons and neuroendocrine cells. Annu Rev Neurosci 1987;10:269-95.
14. Steinberg R, Gueniau C, Scarna H, et al. Experimental brain ischemia: neuron-specific enolase level in cerebrospinal fluid as an index of neuronal damage. J Neurochem 1984;43:19-24.
15. Schmechel D, Marangos PJ, Zis AP, et al. Brain enolases as specific markers of neuronal and glial cells. Science 1978;199:313-5.
16. Schmechel D, Marangos PJ, Brightman M. Neurone-specific enolase is a molecular marker for peripheral and central neuroendocrine cells. Nature 1978;276:834-6.
17. Schoerkhuber W, Kittler H, Sterz F, et al. Time course of serum neuron-specific enolase. A predictor of neurological outcome in patients resuscitated from cardiac arrest. Stroke 1999;30:1598-603.
18. Persson L, Hardemark HG, Gustafsson J, et al. S-100 protein and neuron-specific enolase in cerebrospinal fluid and serum: markers of cell damage in human central nervous system. Stroke 1987;18:911-8.
19. Schaarschmidt H, Prange HW, Reiber H. Neuron-specific enolase concentrations in blood as a prognostic parameter in cerebrovascular diseases. Stroke 1994;25:558-65.
20. Mabe H, Suzuki S, Mase M, et al. Serum neuron-specific enolase levels after subarachnoid hemorrhage. Surg Neurol 1991; 36:170-4.
21. Barone FC, Clark RK, Price WJ, et al. Neuron-specific enolase increases in cerebral and systemic circulation following focal ischemia. Brain Res 1993;623:77-82.
22. Cunningham RT, Watt M, Winder J, et al. Serum neurone-specific enolase as an indicator of stroke volume. Eur J Clin Invest 1996;26:298-303.
23. Martens P, Raabe A, Johnsson P. Serum S-100 and neuron-specific enolase for prediction of regaining consciousness after global cerebral ischemia. Stroke 1998;29:2363-6.
24. Dauberschmidt R, Zinsmeyer J, Mrochen H, et al. Changes of neuron-specific enolase concentration in plasma after cardiac arrest and resuscitation. Mol Chem Neuropathol 1991;14:237-45.
25. Fogel W, Krieger D, Veith M, et al. Serum neuron-specific enolase as early predictor of outcome after cardiac arrest. Crit Care Med 1997;25:1133-8.
26. Bassetti C, Bomio F, Mathis J, et al. Early prognosis in coma after cardiac arrest: a prospective clinical, electrophysiological, and biochemical study of 60 patients. J Neurol Neurosurg Psychiatry 1996;61:610-5.
27. Herrmann M, Ebert AD, Galazky I, et al. Neurobehavioral outcome prediction after cardiac surgery: role of neurobiochemical markers of damage to neuronal and glial brain tissue. Stroke 2000;31:645-50.
28. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480-4.
29. Koller-Strametz J, Fritzer M, Gwechenberger M, et al. Elevation of prostate-specific markers after cardiopulmonary resuscitation. Circulation 2000;102:290-3.
30. Jacobs P, Noseworthy TW. National estimates of intensive care utilization and costs: Canada and the United States. Crit Care Med 1990;18:1282-6.
31. Martens P, Haymerle A, Sterz F, et al. Limitation of life support after resuscitation from cardiac arrest: practice in Belgium and Austria. Resuscitation 1997;35:123-8.
32. Stelzl T, von Bose MJ, Hogl B, et al. A comparison of the prognostic value of neuron-specific enolase serum levels and somatosensory evoked potentials in 13 reanimated patients. Eur J Emerg Med 1995;2:24-7.
33. Burghuber OC, Worofka B, Schernthaner G, et al. Serum neuron-specific enolase is a useful tumor marker for small cell lung cancer. Cancer 1990;65:1386-90.
34. Zeltzer PM, Marangos PJ, Evans AE, et al. Serum neuron-specific enolase in children with neuroblastoma: relationship to stage and disease course. Cancer 1986;57:1230-4.
35. D'Alessandro M, Mariani P, Lomanto D, et al. Serum neuron-specific enolase in diagnosis and follow-up of gastrointestinal neuroendocrine tumors. Tumour Biol 1992;13:352-7.

Correspondence to: Dr. Johann Auer, Department of Cardiology and Intensive Care, General Hospital, Wels Grieskirchnerstraße 42 A-4600 Wels Austria; tel ++43-7242-415-2215, fax ++43-7242-415-3992, johann.auer@klinikum-wels.at