Time Course of Serum Neuron-Specific Enolase
A Predictor of Neurological Outcome in Patients Resuscitated From Cardiac Arrest

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Background and Purpose—The prediction of neurological outcome in comatose cardiac arrest survivors has enormous ethical and socioeconomic implications. The purpose of the present study was to investigate the prognostic relevance of the time course of serum neuron-specific enolase (NSE) as a biochemical marker of hypoxic brain damage.

Methods—Serial analysis of serum NSE levels was performed in 56 patients resuscitated from witnessed, nontraumatic, normothermic, in- or out-of-hospital cardiac arrest. The neurological outcome was evaluated with the use of the cerebral performance category (CPC) within 6 months after restoration of spontaneous circulation (ROSC). The Mann-Whitney U test was used to compare patients with good (CPC 1 to 2) and bad (CPC 3 to 4) neurological outcome. The diagnostic performance at different time points after ROSC was described in terms of areas under receiver operating characteristic curves according to standard methods.

Results—Patients with a bad neurological outcome (CPC 3 to 4) had significantly higher NSE levels than those with a good neurological outcome at 12 (P < 0.004), 24 (P = 0.04), 48 (P < 0.001), and 72 hours (P < 0.001) after ROSC. The maximum NSE level measured within 72 hours after ROSC was also significantly higher in patients with a bad neurological outcome (P < 0.001). The NSE value at 72 hours after ROSC was the best predictor of neurological outcome (area under the curve = 0.92 ± 0.04). In addition, we also found a significant difference in the time course of NSE concentrations during the first 3 days after ROSC.

Conclusions—Serum NSE levels are valuable adjunctive parameters for assessing neurological outcome after cardiac arrest. (Stroke. 1999;30:1598-1603.)

Key Words: cardiopulmonary resuscitation n heart arrest n neuron-specific enolase n outcome

The success of cardiopulmonary resuscitation is determined by the final neurological outcome of the individual patient. The severity of brain dysfunction caused by cardiac arrest ranges from mild or moderate cerebral disability to a vegetative state or brain death. The possibility of irreversible severe hypoxic brain damage must be taken into account with regard to postresuscitation treatment. The decision to continue, limit, or terminate intensive care therapy is a major problem with enormous ethical and socioeconomic implications in daily clinical practice.1 A false prediction of a bad outcome may cause the patient to be denied life-supporting treatment. On the other hand, a falsely optimistic prediction, although less serious from an ethical point of view, may lead to unnecessary prolongation of costly therapy.2 Therefore, an early estimation of the severity of brain injury in comatose cardiac arrest survivors is required.

For prediction of neurological outcome, a number of clinical scales, electrophysiological techniques, and imaging methods have been developed and are presently used in clinical practice.3-17 Nevertheless, the final neurological outcome of patients resuscitated from cardiac arrest often remains unclear for a long time. Recent studies also indicate the use of nervous system–specific proteins and biochemical markers of cerebral tissue damage. Enzyme analysis of cerebrospinal fluid (CSF) has shown a number of biochemical prognostic variables in the CSF.18-20

Neuron-specific enolase (NSE), an isoenzyme of the glycolytic enzyme enolase (2-phospho-D-glycerate hydrolase), was shown to be highly specific to neurons that are released into the CSF and the cerebral and systemic circulation when neuronal damage has occurred.21-26 NSE is a dimeric enzyme composed of 2 \( \gamma \)-subunits (\( \gamma_2 \)) and is nearly exclusively located in neurons and other cells of neuroectodermal origin such as those in neuroendocrine glands and neuroendocrine cells (APUD cells).27 Physiologically, NSE is present only in negligible amounts in the peripheral blood. Tumor cells in

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APUDoma, neuroblastoma, and small cell carcinoma of the lung are capable of producing NSE and are usually accompanied by elevated serum titers. For this reason, NSE has been established as a diagnostic and prognostic serum marker in the clinical management of these neoplasms.28–32 Recent studies showing an increase in CSF and serum NSE levels after ischemic stroke, intracerebral hemorrhage, and brain injury support the contention that NSE may also be a sensitive and quantitative marker of parenchymal brain injury.33–40 Cardiac arrest produces a period of temporary global cerebral ischemia that causes leakage of cytosolic brain enzymes into the CSF and into the blood. As a consequence of ischemia-induced cytoplasmic loss of NSE in neurons of the central nervous system, significantly elevated NSE levels in CSF and blood could be demonstrated in several previous studies.41–45

The purpose of the present study was to examine the time course of serum NSE concentrations in patients after successful cardiopulmonary resuscitation and to investigate the prognostic relevance of serum NSE levels in predicting the neurological outcome of cardiac arrest.

Subjects and Methods

Adult patients aged 18 to 75 years, admitted to the Department of Emergency Medicine at the University Hospital of Vienna after witnessed, nontraumatic, normothermic, in- or out-of-hospital cardiac arrest, were prospectively analyzed. The overall study period extended from July 1996 to March 1998. The procedures followed were in accordance with the ethical standards of the responsible committee for human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983.

Data of patients were collected according to the “Utstein Style.”46 Cardiac arrest was defined as the absence of both spontaneous respiration and palpable pulses, caused by underlying cardiac disease or hypoxia due to respiratory failure. Return of spontaneous circulation (ROSC) was defined as any return of a palpable arterial pulse. Basic and advanced cardiac life support was provided by the Vienna Ambulance Service or in hospital by emergency medical technicians and physicians, in accordance with a standard protocol.47 The resuscitation report of the ambulance physician or the hospital emergency physician was the source of information regarding whether the arrest had been witnessed, who had initiated the resuscitation, the response time from notification to arrival of the Vienna Ambulance Service or in hospital, and whether the arrest had been witnessed. If the arrest had been witnessed, the time of collapse was defined as the moment of the first symptom detected, and the patient at the start of arrest, the arrest was evaluated as having been witnessed. If the resuscitation was started before the arrival of the Vienna Ambulance Service, the case was classified as a bystander-initiated resuscitation. The interval from the time of collapse (presumed time of cardiac arrest) to basic and/or advanced life support was defined as “no-flow duration,” and the interval from the beginning of life support until ROSC or termination of resuscitative efforts was termed “low-flow duration.” The cumulative epinephrine dose was defined as the overall dose of subsequent epinephrine administered during advanced cardiac life support. Data were obtained from interviews with the ambulance physicians, paramedics, bystanders, and families and from online documented patient records. All patients were admitted to an intensive care unit, where standard medical management, including Foley catheters, arterial catheters, central venous catheters, Swan-Ganz catheters, artificial ventilation, and sedoanalgesia, were available and/or performed.

No patients were awake at the time of admission. Patients were excluded if no ROSC could be achieved or if spontaneous circulation returned within the first minute after collapse. Thus, all cases involved global brain ischemia with cessation of blood flow to the brain. Furthermore, we excluded patients with known neurological disorders, known neoplasms, and intracranial hemorrhage or ischemic stroke within the last 6 months because elevated NSE serum levels have been previously described for all these diseases.28–31,33–37,39,40,48,49

Patients in a terminal condition with known unfavorable overall and/or cerebral performance (overall performance category 3, 4 and/or cerebral performance category [CPC] 3, 4) before cardiac arrest were not eligible for the study. Death due to cardiorespiratory instability and due to cardiac arrest within 6 hours after the primary event was also defined as an exclusion criterion because serial analysis of serum levels of NSE was not available.

Blood samples were collected from the arterial catheter in the course of routine intensive care, within the first 6 hours and at 12, 24, 48, and 72 hours after ROSC. No additional invasive procedures were performed during the study. Primary caregivers were blinded so that therapeutic decisions could not be biased by the results of the study. Blood samples were allowed to clot for 20 to 30 minutes at room temperature and then centrifuged and frozen to below –18°C according to the manufacturer’s instructions. NSE serum levels were measured with the use of a standardized monoclonal radioimmunoassay (Prolifigen NSE IRMA, AB Sangtec Medical). This test is a monoclonal 2-site single incubation immunoradiometric assay. The monoclonal antibodies bind to the γ-subunit of the enzyme. Samples that showed visible hemolysis were not analyzed because of the relatively high content of NSE in red blood cells and platelets.50,51 The upper normal NSE concentration, defined as the 95th percentile value, was 12.5 μg/L of γ-enolase.

Recovery of cerebral function was evaluated prospectively on arrival and at regular intervals in the 6 months after ROSC with a 5-point outcome scale (a modified version of the Glasgow Outcome Scale) and expressed as CPC. The performance categories are defined as follows: CPC 1, conscious and alert with normal function or only slight disability; CPC 2, conscious and alert with moderate disability; CPC 3, conscious with severe disability; CPC 4, comatose or in a persistently vegetative state; and CPC 5, certified brain death or dead by traditional criteria. Cerebral and overall function were evaluated within the first 6 hours and at 12, 24, 48, and 72 hours, 1 week, and 1 and 6 months after ROSC. The best CPC achieved within 6 months after ROSC was used for calculation. CPC 1 and 2 were defined as good neurological outcome and CPC 3 and 4 as bad neurological outcome. If the CPC could not be evaluated because the patient died in sedoanalgesia, the patient was retrospectively excluded from the analysis.

Statistical Analysis

Data are given as mean and SD and for nonparametric distributions as median and interquartile range unless otherwise specified. Continuous data were compared with the unpaired t test or the Mann-Whitney U test, as appropriate. The χ² test or Fisher’s exact test was used to compare proportions. After logarithmic transformation of NSE levels, a repeated-measures ANOVA was used to evaluate the effect of time. For this analysis, only patients (n=26) with a complete set of NSE measurements (at 6, 12, 24, 48, and 72 hours after cardiac arrest) were included. The accuracy of NSE levels to differentiate between patients with good and bad CPC was evaluated with the use of receiver operating characteristic (ROC) analysis according to standard procedures. ROC analysis was performed with the software program LABROC, which was kindly provided by Dr Metz (University of Chicago [Ill]). Logistic regression was used for multivariate analysis, including the following independent variables: the maximum NSE level measured within 72 hours after cardiac arrest, the no-flow time and low-flow time, the cumulative dose of epinephrine, basic life support (yes/no), the location of cardiac arrest, age, and sex. All probability values are 2 tailed, and a P value <0.05 was considered to indicate statistical significance.

Results

General Characteristics

A total of 56 patients (mean age, 59±13 years; 33 men and 23 women) were enrolled in the study according to our inclusion
TABLE 1. Comparison of Patients With a Good and Bad Neurological Outcome After Cardiac Arrest in Terms of Patient Characteristics and Factors Pertaining to Cardiopulmonary Resuscitation

<table>
<thead>
<tr>
<th></th>
<th>Patients With Good CPC (n=28)</th>
<th>Patients With Bad CPC (n=28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>57±11</td>
<td>61±14</td>
<td>0.17</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>15 (53.6%)</td>
<td>18 (64.3%)</td>
<td>0.42</td>
</tr>
<tr>
<td>No-flow time, median (range), min</td>
<td>0.5 (0–14)</td>
<td>4.5 (0–20)</td>
<td>0.03</td>
</tr>
<tr>
<td>Low-flow time, median (range), min</td>
<td>10.5 (0–60)</td>
<td>15.5 (2–41)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cumulative dose of epinephrine, median (range), mg</td>
<td>2 (0–12)</td>
<td>4 (0–18)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time to admission, median (range), min</td>
<td>22.5 (0–121)</td>
<td>32 (0–58)</td>
<td>0.14</td>
</tr>
<tr>
<td>Basic life support, n (%)</td>
<td>18 (64.3%)</td>
<td>10 (35.7%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiac arrest out of hospital, n (%)</td>
<td>23 (82.1%)</td>
<td>27 (96.4%)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

criteria. Good neurological outcome was achieved in 50% (n=28) of patients, which consisted of 24 patients (85.7%) with CPC 1 and 4 patients (14.3%) with CPC 2. Those with a bad neurological outcome (n=28) consisted of 6 patients (21.4%) with CPC 3 and 22 (78.6%) with CPC 4. Twenty-six patients (46.4%) died after a median of 9 days (range, 2 to 181 days), including 21 (80.8%) with CPC 4, 4 (15.4%) with CPC 3, and 1 (3.8%) with CPC 2. Patients with a bad neurological outcome had a significantly longer no-flow duration (median, 4.5 minutes; range, 0 to 20 minutes) than those with a good neurological outcome (median, 0.5 minutes; range, 0 to 14 minutes; P=0.03) and received higher cumulative doses of epinephrine (median, 4 mg; range, 0 to 18 mg versus median, 2 mg; range, 0 to 12 mg; P=0.01). Bystander basic life support was provided significantly more frequently in patients with a good neurological outcome than in those with a bad neurological outcome (64.3% versus 35.7%; P=0.03). The general characteristics of the patients according to the outcome categories are given in Table 1.

NSE Levels

NSE levels were measured within the first 6 hours and at 12, 24, 48, and 72 hours after ROSC. Blood samples at all time points were not available for some patients. The NSE values within the first 6 hours and at 12 hours after ROSC could not be used for analysis in 8 patients because of hemolytic blood samples. At 24 hours after ROSC, 6 samples showed visible hemolysis; at 48 hours after ROSC, NSE values were missing in 7 patients (1 patient died, 1 patient was discharged to another hospital, 5 hemolytic samples). At 72 hours after ROSC, NSE values were not available in 19 patients (3 because of death, 2 because of discharge to another hospital, 9 because the arterial catheter had been removed, 5 hemolytic samples).

Within the first 6 hours after ROSC, NSE levels of patients with a good neurological outcome were not significantly different from those of patients with a bad neurological outcome (14.4±6.6 versus 12.4±3.2 μg/L; P=0.35). Patients with a bad neurological outcome had significantly higher NSE levels than those with a good neurological outcome at 12 hours (27.0±34.6 versus 12.8±4.4 μg/L; P=0.004), 24 hours (26.0±37.0 versus 14.9±8.1 μg/L; P=0.04), 48 hours (37.6±58.2 versus 11.9±5.7 μg/L; P<0.001), and 72 hours (32.0±57.4 versus 9.6±2.9 μg/L; P<0.001) after ROSC. The maximum NSE level measured within 72 hours after ROSC was also significantly higher in patients with a bad neurological outcome (45.2±57.3 versus 16.5±7.2 μg/L; P<0.001). Patients who died within 6 months after cardiac arrest had significantly higher maximum NSE levels (45.9±59.7 μg/L) than survivors (17.9±7.7 μg/L; P=0.006).

The accuracy of NSE levels to differentiate between patients with a good and bad neurological outcome was evaluated with the use of ROC analysis. The area under the curve (AUC) was highest at 72 hours (AUC=0.92±0.04; Figure 1) after ROSC. The AUC was 0.83±0.06 at 48 hours, 0.70±0.07 at 24 hours, and 0.80±0.07 at 12 hours. The AUC for the maximum NSE level measured within 72 hours after ROSC was 0.81±0.06. The cut points that lie closest to the left upper corner of the ROC curve and the cut points at which patients with a bad neurological outcome were identified with 100% specificity are shown in Table 2.

The time course of the NSE levels significantly differed between patients with a bad neurological outcome and those with a good neurological outcome (Figure 2). In the former group, NSE levels tended to increase, while in the latter, NSE levels tended to decrease (P<0.001).

In a multivariate logistic regression analysis, the maximum NSE level measured within 72 hours after cardiac arrest was
a significant and independent predictor of bad neurological outcome (odds ratio = 1.09; 95% CI, 1.01 to 1.19; \( P = 0.04 \)).

**Discussion**

The results of our study demonstrate that elevated serum NSE levels in the first 3 days (72 hours) after cardiac arrest are an indicator of hypoxic brain damage. NSE concentrations in the systemic circulation of cardiac arrest survivors correlate significantly with the neurological outcome of these patients. Patients with a bad neurological outcome had significantly higher NSE levels than those with a good neurological outcome at 12, 24, and 72 hours after ROSC. The maximum NSE level measured within 72 hours after ROSC was also significantly higher in patients with a bad neurological outcome. The NSE value at 72 hours after ROSC was the best predictor for neurological outcome. The AUC was highest at this time point (Figure 1). At the 100% specificity level, the sensitivity was 70% at 72 hours after ROSC. Moreover, the time course of NSE concentrations during the first 3 days after ROSC also seems to be relevant for the prognosis. We found a significant difference between the 2 outcome groups in the time course of NSE levels. While NSE levels tended to increase in patients with a bad neurological outcome, they tended to decrease in those with a good neurological outcome (Figure 2). If NSE concentrations increase by \( >15 \) \( \mu \text{g/L} \) between 12 and 72 hours, prognosis also seems to be bad.

A few patients with low concentrations of serum NSE suffered a bad outcome. This unfavorable outcome in the case of low NSE values might depend on several factors: (1) A remarkable rise in plasma NSE cannot be expected in cases of brain stem infarctions with impressive clinical dysfunction because these are often elicited by small tissue lesions with a minor loss of neurons. (2) Patients who die because of cardiocirculatory instability at an early stage (<6 hours after ROSC) might have regained functional neurological recovery if they had survived for a longer time. However, to avoid a false pessimistic prognostication, tests used in critical care are generally required to have a high specificity for bad outcome, with a high specificity being more important than a high sensitivity. For interpretation of serum NSE values, it is important that samples that show visible hemolysis are not analyzed because of the relatively high content of NSE in red blood cells and platelets.50,51

Early prognosis of neurological outcome in patients resuscitated from cardiac arrest is a major problem in daily clinical practice. The decision to continue, limit, or terminate intensive care therapy has enormous ethical and socioeconomic implications. Although there are various methods to determine neurological prognosis after cardiopulmonary resuscitation, the final outcome of patients often remains unclear for a long time. The assessment of neurological function by clinical scales or neurological examination is complicated by

### Table 2. NSE Values at 12, 24, 48, and 72 Hours After ROSC and Maximum NSE Level Within 72 Hours

<table>
<thead>
<tr>
<th>Cut Point Closest to Left Upper Corner of ROC Curve</th>
<th>NSE Level</th>
<th>Cut Point</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 h (n=42)</td>
<td>14.5</td>
<td>69.6</td>
<td>72.0</td>
<td></td>
</tr>
<tr>
<td>24 h (n=45)</td>
<td>17.9</td>
<td>56.0</td>
<td>80.0</td>
<td></td>
</tr>
<tr>
<td>48 h (n=41)</td>
<td>15.9</td>
<td>72.0</td>
<td>79.2</td>
<td></td>
</tr>
<tr>
<td>72 h (n=30)</td>
<td>14.6</td>
<td>75.0</td>
<td>94.1</td>
<td></td>
</tr>
<tr>
<td>Maximum NSE level within 72 h</td>
<td>16.3</td>
<td>75.0</td>
<td>82.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cut Point With 100% Specificity</th>
<th>NSE Level</th>
<th>Cut Point</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>38.5</td>
<td>17.4</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40.0</td>
<td>8.0</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.1</td>
<td>48.0</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.4</td>
<td>70.0</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.3</td>
<td>28.6</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NSE values are expressed in micrograms per liter.

**Figure 2.** Difference in the time course of NSE levels within 72 hours after ROSC between patients with a good neurological outcome (n=12) and those with a poor neurological outcome (n=14).
the use of central nervous system-depressant drugs. It is also impossible to distinguish between permanent and reversible neurological deficit at early clinical assessment. Modern imaging techniques such as CT scanning, MRI, and single-photon emission CT can provide significant information concerning the status of the brain in ischemic situations.12–17 However, these modalities cannot differentiate between permanently damaged brain tissue and reversible damage or edema in the acute phase. In addition, MRI and CT are known to have a limited capacity to detect generalized brain edema except in the most severe cases with markedly obliterated CSF spaces and abnormal signal intensity in the brain parenchyma. Furthermore, transportation of the artificially ventilated patient may impair the quality of imaging methods and may also make it difficult to provide adequate intensive care during imaging, especially in case of circulatory instability. The use of recorded evoked potentials for the prediction of neurological outcome seems to be a very reliable method for the assessment of irreversible hypoxic brain damage. Nevertheless, cases in which this method failed have also been reported.32,33 Therefore, practical and reliable indicators of global ischemic brain damage are urgently needed in the clinical management of patients resuscitated from cardiac arrest.

Our findings demonstrate that NSE serum levels reliably distinguish between patients with a good and bad neurological outcome at an early stage. NSE is an ideal indicator of neuronal damage, since the marker is specific for neuronal cells and is present only in low concentrations outside the nervous system, so that the measurements are not disturbed. The coincidental occurrence of other conditions with elevated serum NSE levels, such as small cell lung carcinoma or neuroblastoma, is rare enough not to interfere with prognostic assessment after cardiac arrest. Our cutoff values for NSE even at 72 hours are relatively low at 16.4 μg/L (normal value, 12.5 μg/L). The number of patients at 72 hours might not be enough to rely on this cutoff value only. Additionally, other groups have found higher levels of NSE to differentiate between patients with good and bad outcome. Therefore, these values must be examined prospectively in follow-up studies. However, this report confirms the results of previous clinical studies by Stelzl et al.43 Martens et al.44 and Fogel et al.45 Analyses of serum NSE levels in cardiac arrest patients are valuable adjunctive parameters for assessing outcome after ischemic brain damage. Serological detection of NSE may be a valuable diagnostic and prognostic tool in the clinical management of patients resuscitated from cardiac arrest. This report is intended to encourage further studies on larger series of patients.

The following useful conclusions can be drawn from our analysis: (1) The NSE value at 72 hours after ROSC is the best predictor for neurological outcome. (2) The time course of NSE concentrations during the first 3 days after ROSC also seems to be relevant for prognosis; it significantly differed between patients with a bad neurological outcome and those with a good neurological outcome.

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