**Increased Serum Levels of the S-100 Protein Are Associated With Hypoxic Brain Damage After Cardiac Arrest**

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**Background and Purpose**

Patients resuscitated from cardiac arrest have a high early mortality rate. Prognostic evaluation based on clinical observations is uncertain and would benefit from the use of biochemical markers of hypoxic brain damage. The astroglial protein S-100 is an established biochemical marker of central nervous system injury. The purpose of the present study was to validate the use of serum determinations of S-100 with regard to outcome after cardiac arrest.

**Methods**

Levels of serum S-100 were measured with a radioimmunoassay in 41 patients the first 3 days after out-of-hospital cardiac arrest. The main outcome variable was fatal outcome within 14 days.

**Results**

S-100 levels were increased after cardiac arrest compared with controls with the highest levels observed the first day. S-100 levels day 1 and 2 correlated to the degree of coma as well as to the time of anoxia. Seventeen patients died within 14 days after the cardiac arrest. The deceased patients had increased S-100 levels on days 1 through 3 compared with survivors. All patients (100%) with an S-100 level of \( \geq 0.2 \) on day 2 after the cardiac arrest died within 14 days, and 89% of the patients with levels below this limit value survived (positive and negative predictive values). The corresponding predictive values on day 1 were 71% and 85%, respectively.

**Conclusions**

The present study shows that hypoxic brain damage after cardiac arrest can be estimated by measurement of serum S-100 concentrations. The method can be used in early prognostic evaluation of short-term outcome after cardiac arrest. (Stroke. 1998;29:473-477.)

**Key Words:** cerebral ischemia, global heart arrest prognosis proteins

An increasing proportion of patients who suffer out-of-hospital cardiac arrest can initially be successfully resuscitated and hospitalized alive. However, the ultimate prognosis for such patients remains unfavourable in many cases, and mortality during the first weeks has been reported to be approximately 50%.1 The possibility of predicting outcome in the early phase after onset has been repeatedly evaluated by using factors present at resuscitation as well as registering various aspects of neurological impairment during the first days of hospitalization.2 However, despite improvements in early prognostic evaluation, there is still a high degree of uncertainty, and there is a need for valid biochemical markers of brain damage in the early phase after global ischemia.

The astroglial protein S-100 is an established marker of central nervous system injury. Elevated levels of S-100 have been observed after focal ischemia in cerebrospinal fluid3 and recently also in serum,4 but there are no previous reports concerning serum S-100 levels after global ischemia induced by cardiac arrest. However, increased serum levels of S-100 have been observed to correlate with the duration of circulatory arrest after cardiopulmonary bypass and have been associated with neurological complications.5,6 This may be explained by hypoxia during the perfusion period but could alternatively be attributed to the diffuse air embolism during this procedure.

In the present study we assayed serum S-100 levels in patients resuscitated after out-of-hospital cardiac arrest. The aim was to validate the use of serum determinations of S-100 in general hypoxic brain damage and its predictive value with regard to short-term outcome.

**Subjects and Methods**

During an 18-month period, 48 patients who had survived at least 24 hours after resuscitation from out-of-hospital cardiac arrest were treated at the intensive care unit at Sahlgrens Hospital in Göteborg, Sweden. Of these patients, 41 were included in the present study: 34 entered the study the first day after the arrest and 7 the second day. The remaining 7 patients could not be included within 48 hours for technical reasons.

Serum samples for S-100 protein determination were taken during the first 3 days after the arrest. The S-100 concentrations were measured with use of a commercial radioimmunoassay (AB Sangtec Medical), according to the instructions of the manufacturer. The sensitivity of the assay is 0.2 μg/L. Serum samples were also analyzed with regard to creatine kinase heart-type isoenzyme (CK-MB). The estimated time from cardiac arrest to restoration of...
TABLE 1. The Reaction Level Scale (RLS 85)

| 1 | Alert. No delay in response. Oriented. |
| 2 | Drowsy or confused. Responsive to light stimulation. |
| 3 | Very drowsy or confused. Responsive to strong stimulation. |
| 4 | Unconscious. Localizes but does not ward off pain. |
| 5 | Unconscious. Withdrawing movements on pain stimulation. |
| 6 | Unconscious. Stereotype flexion on pain stimulation. |
| 7 | Unconscious. Stereotype extension on pain stimulation. |
| 8 | Unconscious. No response to pain stimulation. |

For details and definitions, see Starmark et al. 7

spontaneous circulation (anoxia time) was calculated from data taken from ambulance reports and clinical case records. The level of coma grade at income was assessed with the Reaction Level Scale (RLS) 85,7 which defines eight steps, from RLS 1 (fully awake) to RLS 8 (deeply comatose without pain reaction) (see Table 1). The RLS 85 correlates well with the Glasgow Coma Scale. A standard clinical and neurological examination, including a second determination of coma level, was carried out by a neurologist (H.R.) at days 1 through 4 (mean, 3.4).

Upon arrival at the intensive care unit, most patients were sedated or anesthetized, and adequate oxygenation was secured by mechanical ventilation. Patients no longer in need of ventilation support were transferred to a coronary unit. Hypotension was treated with inotropic drugs. Parenteral infusions were given for alimentary and fluid support. If patients could take oral medication and the arrest was judged to result from ischemic heart disease, a -blocker and aspirin were given if there were no contraindications. In the case of recurrent ventricular fibrillation or ventricular tachycardia, intravenous lido- caine was the first-line treatment. In cases of acute myocardial infarction, thrombolysis or acute percutaneous transluminal coronary angioplasty was considered.

Reference S-100 levels were determined in a population of healthy blood donors \(n=50\) aged 18 to 60 years. Serum samples for S-100 determination were also collected from neurologically healthy patients \(n=16\) aged 52 to 95 years who suffered from acute myocardial infarctions. The samples were collected within 48 hours after onset of chest pain.

The study was approved by the medical ethics committee of the University of Gothenburg. Informed consent was given by all patients or, in the case of unconscious patients, by relatives.

Results

The mean patient age of the study population was 68.2 years (range, 21 to 89 years); of the 41 patients, 10 were women and 31 men. Thirty-three patients had known cardiovascular disease (hypertension, angina pectoris, cardiac failure, previous cardiac infarction, and atrial fibrillation), 2 had a history of a previous minor cerebral infarction (>1 year before the cardiac arrest), 1 had epilepsy, and 2 were drug abusers. Three patients had no previously known disease before the heart arrest. In 33 cases the cardiac rhythms observed by the ambulance team were ventricular fibrillation, in 2 asystole, and in 4 electromechanical dissociation; in the remaining 2 the type was not registered. Twenty-six patients developed laboratory and electrocardiographic signs of a myocardial infarction during the first 48 hours after admission. In 2 cases intoxication (heroin and alimemazine, respectively) was considered the cause of the cardiac arrest; in 1 the cardiac arrest was associated with status epilepticus; in 6 isolated cardiac arrhythmia was assumed to be the cause; in 2 coronary angiography revealed stenosis of myocardial vessels; and in 4 cases the etiology of the heart arrest remained unclear. The study group was divided into five groups, according to the Glasgow Outcome Scale score at day 14. Ten patients were judged to have a good recovery, 4 moderate disability, and 9 severe disability; 1 remained in a permanent vegetative state. Seventeen patients died.

The mean S-100 concentrations of the cardiac arrest patients on days 1 through 3 were increased compared with those in the healthy blood donors, who in all cases had levels below 0.2 \(\mu g/L\), the detection level of the assays (Fig 1). The samples were collected at a mean±SE time of 11.2±1.1 hours on day 1, 36.8±1.3 on day 2, and 61.5±1.6 on day 3 after the collapse.

The anoxia time (mean±SE, 21.2±2.0 minutes) correlated with the levels of S-100 at days 1 and 2 \((r=0.50, P=0.01, r=0.60, P=0.001\), respectively; Spearman rank correlation test). The RLS ranking (coma grade) on admission (mean±SE, 6.4±0.4) correlated with the S-100 concentrations at day 2 \((r=0.49, P=0.01)\) but not at day 1 \((r=0.35, NS)\). Twenty-six patients were anesthetized or sedated after admission to the intensive care unit; 5 remained anesthetized/sedated when the neurological examination was due. The RLS rankings of the remaining 21 patients at this examination (mean±SE, 4.6±0.5) correlated with the S-100 concentrations at days 1 and 2 \((r=0.60, P=0.001, r=0.70, P=0.001\), respectively). The S-100 levels of the 5 anesthetized/sedated patients in all cases were ≤0.2 \(\mu g/L\).

In 1 case the neurological examination revealed a focal sign, implying a minor stroke, but the CT scan was normal. CT scans were performed in 2 additional patients during the initial phase in comatose patients. In 12 cases discrete, low-attenuat- ing areas were seen, and minor cerebral infarctions were suspected. The S-100 levels of these 3 patients were <0.2 \(\mu g/L\) at days 1 through 3.
The mean ± SE CK-MB level of the patients who developed acute myocardial infarctions during the first 48 hours after admission was 127 ± 31.2 µg/L. In the myocardial infarction control group (ie, patients without signs or symptoms of neurological disease and with no history of cardiac arrest), the mean maximal serum CK-MB level was 107 ± 25.5 µg/L, and the S-100 concentrations in all cases were <0.2 µg/L.

Mean values of S-100 at days 1 through 3 were higher in patients who died within 14 days compared with survivors (Fig 1). Details concerning the 17 deceased patients are given in Table 2. The mean ± SE time of anoxia was 14.6 ± 2.0 minutes among the surviving patients and 28.5 ± 2.6 minutes among the deceased patients (P <.001; Mann-Whitney U test). The RLS rankings at arrival in these groups were 5.1 ± 0.7 and 7.9 ± 0.1 respectively (P <.001) and at the neurological examination were 2.5 ± 0.5 and 6.9 ± 0.4, respectively (P <.001). The mean age of the two groups were 68.5 ± 2.8 and 67.9 ± 4.7 years, respectively.

Only one surviving patient remained comatose at day 14. The S-100 concentrations of this patient were ≤0.2 µg/L on days 1 through 3. This patient continued to be in a vegetative state and died at day 61.

Using the sensitivity of the S-100 radioimmunoassay method of 0.2 µg/L as a cutoff value, the frequencies of higher and lower levels S-100 on days 1 and 2 were compared with regard to mortality within 14 days (Table 3). The positive predictive value of the S-100 test at day 1 for fatal outcome within 14 days was 71%, and the negative predictive value was 85% (P <.01; the Fisher exact test). At day 2 the corresponding figures were 100% and 89%, respectively (P <.001).

### Table 2. Description of Patients Decreased Within 14 Days After Cardiac Arrest

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial Rhythm</th>
<th>Anoxia Time, min</th>
<th>RLS Grade</th>
<th>Etiology of Arrest</th>
<th>Time of Death, Day</th>
<th>Terminal Death Cause</th>
<th>S-100 level, µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/46</td>
<td>A</td>
<td>45</td>
<td>8</td>
<td>Epilepsy</td>
<td>2</td>
<td>ABD*</td>
<td>2.69</td>
</tr>
<tr>
<td>M/85</td>
<td>VF</td>
<td>23</td>
<td>5</td>
<td>MI</td>
<td>2</td>
<td>ABD</td>
<td>0.66</td>
</tr>
<tr>
<td>M/47</td>
<td>EMD</td>
<td>15</td>
<td>8</td>
<td>Intoxication</td>
<td>2</td>
<td>ABD</td>
<td>2.344</td>
</tr>
<tr>
<td>M/81</td>
<td>EMD</td>
<td>30</td>
<td>8</td>
<td>MI</td>
<td>3</td>
<td>ABD</td>
<td>2.302</td>
</tr>
<tr>
<td>M/75</td>
<td>EMD</td>
<td>30</td>
<td>8</td>
<td>MI</td>
<td>3</td>
<td>ABD</td>
<td>1.38</td>
</tr>
<tr>
<td>M/33</td>
<td>VF</td>
<td>22</td>
<td>6</td>
<td>MI</td>
<td>4</td>
<td>ABD</td>
<td>0.2</td>
</tr>
<tr>
<td>M/80</td>
<td>VF</td>
<td>29</td>
<td>8</td>
<td>MI</td>
<td>5</td>
<td>ABD</td>
<td>0.603</td>
</tr>
<tr>
<td>M/79</td>
<td>VF</td>
<td>17</td>
<td>6</td>
<td>MI</td>
<td>6</td>
<td>ABD</td>
<td>0.668</td>
</tr>
<tr>
<td>M/74</td>
<td>EMD</td>
<td>40</td>
<td>6</td>
<td>MI</td>
<td>7</td>
<td>ABD</td>
<td>1.318</td>
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<tr>
<td>M/67</td>
<td>VF</td>
<td>36</td>
<td>8</td>
<td>MI</td>
<td>7</td>
<td>ABD</td>
<td>3.000</td>
</tr>
<tr>
<td>M/63</td>
<td>VF</td>
<td>55</td>
<td>7</td>
<td>MI</td>
<td>7</td>
<td>ABD</td>
<td>1.038</td>
</tr>
<tr>
<td>M/75</td>
<td>A</td>
<td>32</td>
<td>8</td>
<td>MI</td>
<td>7</td>
<td>ABD</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>F/80</td>
<td>VF</td>
<td>15</td>
<td>6</td>
<td>MI</td>
<td>10</td>
<td>MI</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>F/21</td>
<td>VF</td>
<td>25</td>
<td>7</td>
<td>WPW</td>
<td>10</td>
<td>ABD</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>M/89</td>
<td>VF</td>
<td>22</td>
<td>8</td>
<td>MI</td>
<td>11</td>
<td>ABD</td>
<td>0.366</td>
</tr>
<tr>
<td>M/81</td>
<td>VF</td>
<td>23</td>
<td>3</td>
<td>MI</td>
<td>13</td>
<td>CF</td>
<td>&lt;0.2</td>
</tr>
</tbody>
</table>

A indicates asystole; VF, ventricular fibrillation; EMD, electromechanical dissociation; RLS, Reaction Level Scale; WPW, Wolff-Parkinson-White syndrome; MI, myocardial infarction; ABD, anoxic brain damage; and CF, cardiac failure. Ellipses indicated that the patient was not included at this time.

- *Cause of death confirmed by autopsy.
- †Patient deceased.

### Discussion

Our observations that all patients who had serum S-100 levels above the discriminatory level of 0.2 µg/L at day 2 died within 14 days, whereas almost 90% of the patients with a level below this limit survived, are important. Few previous methods evaluated thus far have been shown to predict early mortality after hospital admission with equally high accuracy. S-100 is derived from astroglial cells, and brain injury has previously been associated with increased serum levels of this protein.4–6

Accordingly, the increased levels of S-100 observed in the present study were strongly correlated with known predictors of neurological impairment after cardiac arrest, ie, the time of...
Serum S-100 and Cardiac Arrest

systemic anoxia\(^1\) and coma level determined \(>24\) hours after the arrest.\(^1\)

The main outcome variable in the present study was death within 14 days. This period of time was chosen because it previously has been shown that the cumulative mortality in patients resuscitated after cardiac arrest reaches a plateau after 14 days.\(^10\) Fourteen of the 17 deceased patients died as a consequence of anoxic brain damage. In 2 of the 3 remaining patients, the terminal cause of death was myocardial infarction. However, these 2 patients were comatose (RLS 6) at the time of the neurological examination, indicating hypoxic brain damage, and levels of S-100 were also slightly above the limit value on day 2. The coexistence of brain damage and myocardial damage is understandable because cardiac arrests are often caused by myocardial infarction. Furthermore, cerebrovascular lesions are associated with an increased risk of cardiovascular complications.\(^11\) In contrast, all patients with myocardial infarction without circulatory arrest in the myocardial infarction control group had normal S-100 levels (<0.2 \(\mu g/L\)), and thus increased concentrations of S-100 cannot be directly attributed to myocardial ischemia per se. Death was not associated with anoxic brain damage in only 1 of the 3 cases mentioned above. This patient, who died of cardiac failure at day 13, was conscious at the neurological examination (RLS 3) and had an S-100 level of <0.2 \(\mu g/L\). Two of the patients who died of anoxic brain damage and the only surviving comatose patient at day 14 had levels of <0.2 \(\mu g/L\). This may be because the cutoff level is too high, but the rationale for the choice of this level is the sensitivity of the S-100 radioimmunoassay, which is 0.2 \(\mu g/L\). It is also possible that the anoxic brain damage was less severe in these 3 patients, because they all survived for \(\geq 10\) days. However, it can be concluded that the high predictive value of S-100 determinations at day 2 with regard to fatal outcome within 14 days is also valid if anoxic brain damage is chosen as the major outcome variable.

During day 1, 4 surviving patients had increased S-100 levels (\(\geq 0.2\) \(\mu g/L\)) that normalized on day 2 (to <0.2 \(\mu g/L\)). Three of these patients had an unfavorable outcome (severe disability) according to the Glasgow Outcome Scale score, whereas one had a good recovery. However, with respect to outcome, there was no statistically significant difference between surviving patients with S-100 levels above the limit value on day 1 and those with low levels. It has previously been shown that S-100 levels are transiently increased immediately after cardiopulmonary bypass in patients without cerebral symptoms, whereas persistently high levels on day 2 are correlated with neurological complications.\(^5,6\) It has been speculated that this initial S-100 increase after cardiopulmonary bypass resulted from a temporal brain edema and/or blood-brain barrier dysfunction.

The exact mechanism of the release of S-100 to serum after cardiac arrest is unclear. Global interruption of the cerebral circulation causes general brain edema and selective neuronal death in vulnerable areas of the brain, and extended anoxia time leads to infarctions in cortical and subcortical regions.\(^9,12,13\) The initial rise of S-100 may reflect a possibly reversible early brain edema in combination with a disturbance of astroglial cell membrane integrity and blood-brain barrier function. Still high or increasing levels on day 2 indicate persistent changes and perhaps also ischemic damage of the astroglial cells.

The etiology of the heart arrest was cardiac in all deceased patients except 2. In 1 the heart arrest was associated with a convulsive status epilepticus, and the autopsy showed anoxic changes, including brain edema. The very high S-100 level observed in this case is understandable in view of the extended length of anoxia, although it cannot be excluded that the epilepsy per se contributed to the fatal brain damage. The other patient with different etiology suffered from heroin intoxication. Because the time of anoxia was relatively shorter in this patient, it is possible that the intoxication itself aggravated the course of the disease.

No previous clinical study has systematically investigated S-100 serum levels after cardiac arrest. However, serum levels of a soluble neuronal protein, neuron-specific enolase (NSE), have been shown to be increased after systemic anoxia in humans.\(^14\)–\(^18\) Roine and coworkers\(^14\) showed the practical value of serum NSE analyses in the clinical setting. They measured serum NSE 24 hours after cardiac arrest and, using a cutoff level of 17 \(\mu g/L\), the positive predictive value was 89% and the negative predictive value 79% with regard to persistent unconsciousness or death within 1 week. Although their study design differs from ours, serum S-100 determinations seem to be advantageous, because the positive and negative predictive values for samples taken on day 2 with regard to mortality within 14 days are 100% and 89%, respectively.

Biochemical markers of hypoxic brain damage are needed in the early phase after global ischemia. Although clinical parameters such as the time of circulatory arrest and the degree of coma in the initial days after the collapse predict outcome,\(^1,9\) these parameters are not always available. The time of circulatory arrest may be unknown, and the degree of coma cannot be properly estimated in sedated or anesthetized patients. Furthermore, serum determinations of S-100 are simple to perform and eliminate the problem with interobserver variation during evaluation of clinical signs.

The present study shows that the increase of serum S-100 levels after cardiac arrest reflects the degree of hypoxic brain damage and predicts the short-term outcome. Determination of serum S-100 concentrations after cardiac arrest will supplement the clinical assessment of patients and prove useful in the evaluation of therapeutic intervention.

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