IS THERE A RELATIONSHIP BETWEEN SERUM S-100 β PROTEIN AND NEUROPSYCHOLOGIC DYSFUNCTION AFTER CARDIOPULMONARY BYPASS?

Stephen Westaby, FRCS^a
Kjell Saatvedt, MD, PhD^a
Samantha White, MA^a
Takahiro Katsumata, MD, PhD^a
Willem van Oeveren, PhD^b
Narendra K. Bhatnagar, FRCS^a
Stuart Brown, MBBS^a
Peter W. Halligan, PhD^c

Objectives: Over the past decade, the glial protein S-100 β has been used to detect cerebral injury in a number of clinical settings including cardiac surgery. Previous investigations suggest that S-100 β is capable of identifying patients with cerebral dysfunction after cardiopulmonary bypass. Whether detection of elevated levels S-100 β reflects long-term cognitive impairment remains to be shown. The present study evaluated whether perioperative release of S-100 β after coronary artery operations with cardiopulmonary bypass could predict early or late neuropsychologic impairment. **Methods:** A total of 100 patients undergoing elective coronary bypass without a previous history of neurologic events were prospectively studied. To exclude noncerebral sources of S-100 β , we did not use cardiotomy suction or retransfusion of shed mediastinal blood. Serial perioperative measurements of S-100 β were performed with the use of a new sensitive immunoluminometric assay up to 8 hours after the operation. Patients underwent cognitive testing on a battery of 11 tests before the operation, before discharge from the hospital, and 3 months later. **Results:** No significant correlation was found between S-100 β release and neuropsychologic measures either 5 days or 3 months after the operation. **Conclusion:** Despite using a sensitive immunoluminometric assay of S-100 β , we found no evidence to support the suggestion that early release of S-100 β may reflect long-term neurologic injury capable of producing cognitive impairment. (J Thorac Cardiovasc Surg 2000;119:132-7)

Surgery with cardiopulmonary bypass (CPB) is assumed to cause subtle cerebral injury that may be detectable on neuropsychologic measures in 30% to 70% of patients.¹⁻² Elevation of serum S-100 β levels has been shown to be a sensitive, although nonspecific, indicator of central nervous system damage (eg, stroke, head injury).³⁻⁵ S-100 β protein leaks from structurally damaged nerve cells into cerebrospinal fluid and secondarily across the blood-brain barrier.⁶

In recent years S-100 β has been used, in a research context, to identify cerebral injury after cardiac surgery in preference to the more labor-intensive neuropsychologic evaluations.^{7,8} Several studies suggest that transient elevations in levels of serum S-100 β protein reflect subclinical cerebral damage in the absence of frank neurologic signs.^{9,10} To date, however, no study has demonstrated that S-100 β levels reflect neuropsychologic performance. The aim of the present study was to determine whether S-100 β could predict early or late neuropsychologic and functional impairment after coronary bypass surgery with CPB. We attempted to avoid noncerebral sources of S-100 β by discarding cardiotomy suction blood.¹¹

Patients and methods

Study patients. With ethics committee approval we prospectively studied 100 patients undergoing elective first-time coronary bypass without a previous history of neurologic events or psychiatric illness. Those with acute coronary syndromes were excluded to eliminate the added anxiety of a recent illness. We also excluded patients with renal or hepatic

From Oxford Heart Centre, John Radcliffe Hospital,^a Oxford, United Kingdom, Department of Biomedical Engineering, University of Groningen, The Netherlands,^b and University Department of Experimental Psychology, Oxford, United Kingdom.^c

Financial support was received from Cobe Cardiovascular, Inc, Arvada, Colo. Haemoprobe, Groningen, The Netherlands, performed the S-100 β analysis.

Received for publication April 2, 1999; revisions requested June 11, 1999; revisions received July 21, 1999; accepted for publication Aug 18, 1999.

Address for reprints: S. Westaby, BSc, FRCS, MS, Oxford Heart Centre, John Radcliffe Hospital, Oxford OX3 9DU, England.

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0022-5223/2000 \$12.00 + 0 12/1/102818

Table I. *The neuropsychologic tests performed and a brief description of the cognitive domains evaluated*

<i>Neuropsychologic test</i>	<i>Cognitive domains</i>
Short Orientation-Memory- Concentration Test	General cognitive orientation
Rey Auditory Verbal Learning Test (1. immediate; 2. delayed)	Verbal memory
Grooved Pegboard Test	Psychomotor speed and manual dexterity
Bells Cancellation Task	Visual search and selective attention
Test A from the Adult Memory Information Processing Battery	Speed of information processing
Trail Making Test A	Attention shifting and psychomotor speed
Trail Making Test B	Attention shifting, response inhibition, and psychomotor speed
Digit Span Forward	Attention and auditory memory
Digit Span Backward	Attention and visual imagery
Stroop Neuropsychological Screening Test	Divided attention and response inhibition

dysfunction and diabetes. All patients required between 2 and 5 bypass grafts. Patients were part of a randomized clinical trial of a new coating agent of the CPB circuit (50 patients in each group), the results of which showed no statistically significant difference in S-100 β and neuropsychologic measures. Each patient consented to a detailed 11-part neuropsychologic examination, which was administered by a psychologist (Table I).

Anesthesia. On the day of the operation, patients were premedicated with morphine (10-15 mg) and scopolamine (0.3-0.4 mg). Anesthesia was induced with fentanyl (1 mg), pancuronium (8 mg), and etomidate (4-10 mg). Before CPB, anesthesia was maintained with a combination of oxygen, nitrous oxide, and halothane and during CPB with propofol (6 mg $\cdot$ kg⁻¹ $\cdot$ h⁻¹).

Conduct of the operation. All operations were performed with Cobe flat sheet membrane oxygenators and bypass circuits (COBE Cardiovascular Inc, Denver, Colo) and a pump flow of 2.4 L $\cdot$ m⁻² $\cdot$ min⁻¹ at between 32°C and 36°C. Vent suction was not used. The mean arterial pressure was maintained between 50 and 80 mm Hg and alpha-stat arterial carbon dioxide management was used. Myocardial protection was achieved with antegrade crystalloid cardioplegia. Shed mediastinal blood was minimized by careful surgery and was discarded to avoid noncerebral sources of S-100 β . Anticoagulation during CPB was monitored with the activated clotting time (Hemochron 800; International Technidyne Corp, Edison, NJ). Additional heparin was administered if the activated clotting time was shorter than 400 seconds. Heparin was neutralized by means of protamine chloride infusion (3 mg/kg) after the completion of CPB.

S-100 β analysis. Serum was analyzed for S-100 β protein concentration 24 hours before the operation (T1), 5 minutes before beginning CPB but after heparin injection (T2), immediately after termination of CPB but before protamine injection (T3), and 8 hours after the operation (T4). The serum or heparinized plasma samples were stored at -80°C until analyzed. S-100 β protein concentration was determined with the use of a new, more sensitive monoclonal immunoluminometric method (sensitivity 0.02 μ L) (Sangtec LIA 100, Sangtec Medical AB, Bromma, Sweden). This assay method uses 3 monoclonal antibodies, SMST 12, SMSK 25, and SMSK 28,

to detect the beta chains in the betabeta and the alphabeta dimers of S-100. Since S-100 β is a calcium-binding protein, plasma treated with ethylenediaminetetraacetic acid cannot be used, but heparin does not affect the results, as we showed in a separate unpublished validation study. The test is based on sandwich formation of immobilized ant-S-100 β antibody, S-100 β from the test sample and luminescence-labeled S-100 β antibody. The assay was performed according to the manufacturer's instructions and label was measured by means of flash luminescence (Lumat LB 9507, EG & G, Berthold, Germany).

Neuropsychologic and functional assessment. Each patient underwent a comprehensive neuropsychologic examination administered by a research psychologist (S. White). The National Adult Reading Test (NART) was used to estimate pre-morbid intelligence. Tests were carried out preoperatively (1 day before the operation), before hospital discharge (5 days after the operation), and again at 3 months after the operation. All tests have been described in detail elsewhere.¹²⁻¹⁶ Table I lists the neuropsychologic tests and provides a brief description of the cognitive domains evaluated.

In addition to neuropsychologic performance, functional and emotional measures were also measured before the operation and at 3 months' follow-up. These tests were as follows:

1. Short Form-36 (multidimensional measure of subjective health status)¹⁴
2. Health Complaints Scale (measures on somatic and cognitive complaints)¹⁵
3. BADs Dysexecutive Questionnaire (measures a range of problems commonly associated with dysexecutive impairment)¹⁶
4. Hospital Anxiety and Depression Scale¹⁴

Statistical analysis. Clinical data were expressed as mean and standard deviation. Blood test values were described as mean and standard error of the mean. Neuropsychologic performance was assessed by calculating the change scores (preoperative minus predischarge and preoperative minus follow-up) for each patient on every test. Likewise, change scores (preoperative minus follow-up) were also calculated for each of the 4 functional measures. Change scores were then correlated with the S-100 β measures taken at each of the 4 different time points. Computerized statistical analysis was under-

Table II. Patient characteristics including operative data

Variable	Result
No. of patients	100
Age (y)	64 ± 8
CPB (min)	48 ± 14
Crossclamp time (min)	29 ± 19
Extubation (min)	250 ± 365
Postop blood loss (mL)	1155 ± 470
Blood transfused (mL)	435 ± 408

Data are expressed as mean ± standard deviation. CPB, Duration of cardiopulmonary bypass; Extubation, time to extubation.

taken with the use of the SPSS for Windows (version 7) statistical program (SPSS, Inc, Chicago, Ill). Comparisons between groups were done with the Mann-Whitney test for unpaired data. Correlations between each of the mean S-100β time points and age, CPB time, crossclamp time, blood loss, blood transfusions, ventilatory times, and neuropsychologic performance were calculated by means of the Pearson correlation coefficient and, unless specified, adopted the .01 level as significant given the large number of comparisons. Because the distribution of S-100β values was generally skewed, these data are presented as median, 25th, and 75th percentiles.

Results

Patient characteristics and operative data are presented in Table II. One patient required re-entry for excessive postoperative bleeding and 1 had a stroke. After initial recovery, 1 patient had bowel necrosis develop and eventually died of multiple system failure (1% mortality).

The serum S-100β protein concentration at each time point is shown in Table III. In 90% of the patients the preoperative (T1) S-100β concentration was below the detection limit of the test (0.02 μ/L). The maximum value (0.140 μ/L [0.060/0.273 μ/L]) was detected at T4. There were 9 patients at this time point without detectable S-100β levels, and in 7 patients the S-100β protein could not be detected at any of the 4 time points. The 1 patient who had a stroke had S-100β levels as follows: T1, less than 0.02 μ/L; T2, 0.06 μ/L; T3, 0.25 μ/L; and T4, 0.09 μ/L. These levels were not significantly different from those of the other patients. Patients with undetectable levels of S-100β at T2 had significant lower levels of S-100β at T3 (0.06 μ/L [0/0.110 μ/L] vs 0.240 μ/L [0.120/0.330 μ/L]; $P < .0001$) and at T4 (0.090 μ/L [0.030/0.152 μ/L] vs 0.220 μ/L [0.115/0.355 μ/L]; $P < .0001$).

We found no correlation between maximum S-100β levels and crossclamp time ($r = 0.024$), perfusion time

Table III. S-100 levels at the different time points (μg/L)

Time point	Median	25th percentile	75th percentile
T1	<0.02	0	0
T2	<0.02	0	0.087
T3	0.120	0.043	0.297
T4	0.140	0.060	0.273

T1, S-100β concentration 24 hours before the operation; T2, 5 minutes before beginning CPB but after heparin injection; T3, immediately after termination of CPB but before protamine injection; T4, 8 hours after the operation.

($r = 0.025$), ventilatory times ($r = 0.065$), blood transfusions ($r = 0.09$), or total amount of fluid transfused ($r = 0.041$). However, the prebypass levels of S-100β (T2) correlated significantly with the postbypass level (T3) ($P < .0001$, $r = 0.57$) and postoperative level (T4) ($P = .0001$, $r = 0.4$). The postoperative S-100β (T4) values also correlated with age ($P = .017$, $r = 0.26$). Interestingly, those patients intubated for more than 5 hours had a significantly higher maximum serum value of S-100β than the others (0.240 μ/L [0.090/0.480 μ/L] vs 0.125 μ/L [0.060/0.240 μ/L]; $P = .04$).

Neuropsychologic performance. A total of 95 patients completed the preoperative assessment. The remaining 5 were eliminated from follow-up. The mean estimated IQ for the group was 108. Before hospital discharge (5 days after the operation), 79 patients could be assessed. Two patients were excluded because of stroke and multiple organ failure. The remaining 14 patients declined for reasons of ill health. However, 3 months after the operation, 89 patients had completed all tests. Pearson correlation coefficients for all serial time points for S-100β versus neuropsychologic and functional change scores are presented in Tables IV and V.

No significant correlations were found between the S-100β level at any time point and neuropsychologic change scores for any test. This was true even when the level of significance was dropped to the .05 level. Similarly, no significant correlations were found between S-100β measures at any time point and functional change scores. The correlation coefficients for the functional measures are reported in Table VI.

Discussion

It has been claimed that S-100β protein assay may be a useful method of detecting cerebral injury after cardiac surgery.^{8-10,17-19} However, to date no study has formally shown a relationship between serum S-100β levels and late neuropsychologic performance, the gold standard for subtle cerebral injury. The results of the present study did not show any relationship between S-100β (at any of the serial time points) and early (5 days

Table IV. Preoperative versus hospital discharge neuropsychologic change scores correlated against S-100 levels at the different time points

Neuropsychologic test	T1	T2	T3	T4
Short Orientation–Memory–Concentration Test	0.034	0.120	0.067	0.051
Rey Auditory Verbal Learning Test: Immediate Recall	0.014	–0.156	–0.064	0.054
Rey Auditory Verbal Learning Test: Delayed Recall	–0.147	–0.130	–0.190	–0.093
Grooved Pegboard Test	0.050	–0.016	0.074	0.053
Bells Cancellation Task	0.085	0.072	0.156	0.159
Test A from Adult Memory Information Processing Battery	0.100	–0.021	0.114	0.038
Trail Making Test A	–0.172	–0.061	–0.133	–0.117
Trail Making Test B	0.005	–0.207	–0.166	–0.151
Digit Span Forward	0.172	0.125	–0.024	–0.122
Digit Span Backward	–0.002	–0.110	–0.175	–0.202
Stroop Neuropsychological Screening Test	0.135	0.114	0.159	0.150

Figures indicate correlation coefficients. T1, S-100 β concentration 24 hours before the operation; T2, 5 minutes before beginning CPB but after heparin injection; T3, immediately after termination of CPB but before protamine injection; T4, 8 hours after the operation.

Table V. Preoperative versus 3 months' follow-up neuropsychologic change scores correlated against S-100 levels at the different time points

Neuropsychologic test	T1	T2	T3	T4
Short Orientation–Memory–Concentration Test	0.006	–0.011	–0.160	–0.130
Rey Auditory Verbal Learning Test: Immediate Recall	–0.043	–0.038	–0.059	–0.015
Rey Auditory Verbal Learning Test: Delayed Recall	0.043	–0.056	–0.192	–0.080
Grooved Pegboard Test	–0.077	–0.100	–0.003	–0.039
Bells Cancellation Task	0.002	–0.019	–0.132	–0.053
Test A from Adult Memory Information Processing Battery	0.037	–0.005	0.068	0.061
Trail Making Test A	–0.123	–0.083	–0.033	0.066
Trail Making Test B	0.027	–0.031	0.050	0.106
Digit Span Forward	0.188	0.154	–0.052	–0.130
Digit Span Backward	0.069	0.007	–0.047	–0.136
Stroop Neuropsychological Screening Test	0.064	–0.012	0.148	0.074

Figures indicate correlation coefficients. T1, S-100 β concentration 24 hours before the operation; T2, 5 minutes before beginning CPB but after heparin injection; T3, immediately after termination of CPB but before protamine injection; T4, 8 hours after the operation.

after the operation) or late (3 months after the operation) neuropsychologic outcome. This was also true for the functional measures at 3 months' follow-up.

The serum levels of S-100 β after uncomplicated cardiac operations follow a different pattern from those after acute ischemic cerebral events, wherein peak values occur after 3 days.^{20,21} Studies on S-100 β release during and after CPB have shown peak S-100 β levels soon after perfusion, presumably resulting from transient increase in permeability of the blood-brain barrier as part of the inflammatory response.^{8-10,18,19} Joensson and associates⁹ showed that S-100 β levels immediately after CPB did not correlate with cerebral outcome although grossly elevated levels of S-100 β 48 hours after the operation were associated with clinically obvious stroke.⁹ The early release of S-100 β after cardiac surgery may thus be a transient serum elevation without any relation to permanent neuronal damage.

However, the early S-100 β studies were interpreted without the awareness that S-100 β from noncerebral sources might confuse the issue by elevating overall levels.¹¹ In the present study, extracerebral S-100 β was reduced by discarding cardiectomy blood and not retransfusing shed mediastinal blood, which has been shown to contain high levels of S-100 β .¹¹ Consequently, our S-100 β levels were lower and also peaked later than in earlier reports.^{8-10,18-19} Lower levels might also be caused by other factors. We used a new, highly sensitive immunoluminometric assay test capable of detecting much lower levels of S-100 β , whereas in earlier studies levels of S-100 β below 0.2 μ L were not detectable. Consequently, more patients in our study had detectable levels of S-100 β . As most of these were at or below the previous less-sensitive level, it is likely that they contributed to the lowering of the mean levels, since previous studies in which less-sensitive

Table VI. Preoperative versus 3 months' follow-up functional change scores correlated against S-100 levels at the different time points

Functional test	T1	T2	T3	T4
Short Form-36	-0.161	0.014	0.105	0.051
Health Complaints Scale:				
Somatic Measures	-0.086	-0.121	-0.161	-0.123
Cognitive Measures	-0.011	0.095	0.028	0.071
Hospital Anxiety and Depression Scale:				
Anxiety	-0.036	0.011	-0.112	-0.041
Depression	-0.097	-0.097	-0.145	-0.112
BADS Dysexecutive Questionnaire:				
Self	-0.080	0.102	0.097	0.016
Other	0.058	-0.125	-0.064	-0.047

Figures indicate correlation coefficients. T1, S-100 β concentration 24 hours before the operation; T2, 5 minutes before beginning CPB but after heparin injection; T3, immediately after termination of CPB but before protamine injection; T4, 8 hours after the operation.

assays were used did not always include patients with undetectable S-100 β levels.

Grocott and colleagues¹⁰ described a weak but significant relationship between cerebral microemboli and S-100 β levels. In an experimental study, blood aspirated from the surgical field during CPB and reinfused into dogs generated a greater density of small capillary and arterial dilatations in the brain than CPB without cardiomy suction.²³ The presence of so-called small capillary and arterial dilatations was first demonstrated by Moody and colleagues²⁴ in autopsy specimens from patients who had undergone cardiac operations with CPB. There is evidence to suggest that lipid microembolism is the cause of these diffuse cerebral changes.²⁵ We have also shown that an arterial line filter can significantly reduce levels of S-100 β , although this early investigation was performed with cardiomy suction and the less-sensitive S-100 β assay.²⁶

A recent study by Backstroem and associates,²² using a kinetic model employing elimination rates of S-100 β during the first 5 hours after operation, found a positive correlation with early adverse cognitive outcome. The authors proposed early S-100 β elimination rate (as an expression of postbypass release) in preference to absolute levels to correct for contamination from extracerebral sources.⁹ However, the formula to calculate elimination rate requires a progressive decrease in postoperative levels, whereas our study without cardiomy suction shows an increase over this time frame. Consequently, for our study the calculation would have been meaningless for most patients.

Appearance of S-100 β in serum after CPB may indicate cellular damage, increased permeability of the blood-brain barrier, or both. Transient permeability of the blood-brain barrier to S-100 β protein could be caused by the inflammatory response generated by

CPB itself. Since the development of inflammation is time related, we might expect a positive correlation between perfusion time and S-100 β release. In fact, correlation between perfusion time and S-100 β levels has been an inconstant finding.^{8-10,18,19,27,28} Our present study found no relationship between S-100 β and perfusion time, although in general the duration of CPB was short. However, we did find a significant correlation between the prebypass value and the postbypass levels, and patients without detectable prebypass levels had significantly lower levels of S-100 β afterward, irrespective of perfusion time. These findings suggest that factors other than perfusion time may influence the release of S-100 β . Surgical injury and the anesthesia may well contribute to this release, and differences have been shown in valve, aortic aneurysm, and hypothermic circulatory arrest patients where S-100 β levels are greater and remain significantly higher for between 5 and 48 hours.¹⁸ In open cardiac operations (as opposed to coronary operations), the relationship between S-100 β and neuropsychologic outcome might be different irrespective of the contribution of cardiomy suction.

The finding of significantly higher S-100 β levels in patients requiring ventilation for more than 5 hours is interesting and consistent with a recent report claiming a relationship between postoperative S-100 β levels and prolonged intubation.²⁸ Cerebral edema has been demonstrated within an hour of CPB by magnetic resonance scanning in patients undergoing routine coronary bypass.²⁹ The swelling is variable and may similarly reflect transient change in permeability of the blood-brain barrier without injury to the brain itself. The transient increase in S100 β levels may then represent a reversible increase in the permeability of cellular and vascular membranes as opposed to structural neu-

ronal damage. All patients having coronary operations in this study were subjected to fast track and early extubation protocols (irrespective of age), so that shorter extubation time reflected early awaking and conscious awareness.³⁰

In summary, we were unable to demonstrate any correlation between serum S-100 β protein levels and early or late neuropsychologic impairment after elective coronary operations with CPB. It is possible that the transient passage of S-100 β from cerebrospinal fluid to serum bears little relationship to the type of neuronal injury necessary to produce impairment of neuropsychologic and functional measures.

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