

# Biomarkers of cerebral injury in cardiac surgery

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## ABSTRACT

The present study aims to reveal the changing patterns of cerebral biomarkers and the underlying predictive factors as a consequence of cardiac surgery. Literature retrieval of articles on S100 and S100B of recent 20 years were made in the MEDLINE database, Highwire Press and Google search. Quantitative data of S100 and S100B along with neuron-specific enolase were carefully screened, collected and statistically analyzed. The biomarkers appeared earlier and lasted longer in the cerebrospinal fluid than in the serum. All three biomarkers exhibited a similar kinetic trend in the bloodstream, reaching a peak value at the end of cardiopulmonary bypass (CPB). In adults, serum biomarkers may recover to normal earlier than in pediatrics undergoing a cardiac surgery. The patients undergoing off-pump surgery had the minimal elevations of cerebral biomarkers comparing to all other cardiac surgeries under CPB, low core temperature and/or hypothermic circulatory arrest. In patients with pre- or postoperative neurological disorders, the biomarkers in the serum elevated even before operation and persisted longer time than those without neurological disorders. The serum concentrations of the biomarkers showed direct correlation with CPB duration and core temperature. Cardiac operations may lead to cerebral damage and blood-brain barrier changes, as a consequence of CPB and low core temperature. The cerebral biomarkers including S100, S100B and neuron-specific enolase may precisely reflect the cerebral damages in cardiac surgery. Attention has to be paid to the attenuations of cerebral damage by modifying the surgical conditions of CPB and core temperature. (*Anadolu Kardiyol Derg* 2014; 14: 638-45)

**Key words:** cardiopulmonary bypass, cerebrospinal fluid, circulatory arrest, deep hypothermia induced, S-100 calcium-binding protein beta subunit, S100 proteins

## Introduction

S100 proteins and neuron-specific enolase (NSE) are the most commonly used biomarkers of cerebral injury for the assessment of neurological disorders. S100 proteins are small, acidic proteins with a molecular weight of 10-12 kDa. The S100 protein family comprises several members characterized by different tissue-expressing specificities (1). An S100 protein consists of two distinct EF-hands, 4  $\alpha$ -helical segments, a central hinge region and a C-terminal extension (1). S100B protein is highly expressed in astrocytes, Schwann cells and non-nervous cells such as melanocytes, chondrocytes, adipocytes, certain neuronal populations and skeletal myofibers, and becomes transiently expressed in several other cell types in pathological conditions (1). Within cells, S100B is found in the form of a homodimer and exerts regulatory effects on  $Ca^{2+}$  homeostasis, cell proliferation, differentiation and motility, protein phosphorylation, transcription

and the organization of the cytoskeleton (1). S100B is transiently released into the cerebrospinal fluid (CSF) and blood in case of brain damage as a result of brain-blood-barrier alterations (2). Enolases are found as dimers resulting from the association of three distinct subunits ( $\alpha$ ,  $\beta$  and  $\gamma$ ). The  $\alpha$ -subunit is expressed in most tissues and the  $\beta$ -subunit only in muscle. NSE is the  $\gamma\gamma$  isoform of the glycolytic enzyme enolase with a molecular weight of 78 kDa, expressed primarily in neurons, in central and peripheral neuroendocrine cells, and in certain rare tumors, such as small-cell lung cancer, neuroblastoma and melanoma (3). Moreover, NSE is found in platelets and erythrocytes, particularly after hemolysis, and therefore hemolysis may cause a falsely positive NSE increase (3). As NSE is not actively secreted into the bloodstream, it is passively released by cell destruction only; its elevation in the late phases of injury may be explained by delayed cell deaths (4). NSE is only in negligible amounts in the peripheral blood. CSF and serum NSE levels increased

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remarkably after ischemic stroke, intracerebral hemorrhage and parenchymal brain injury (5).

Blood-brain barrier dysfunction secondary to cerebral damages may precipitate the delivery of these cerebral specific proteins from the astroglial or Schwann cells into CSF and blood circulation (6, 7). During cardiac operations, neurological disorders often develop and are believed to be the results of thromboembolism and systemic inflammatory reactions (8). The cerebral biomarkers were firstly reported to assess neurological disorders that were associated with cardiac surgery in 1992. Since then, continuous reports described on these biomarkers in different cardiac operations, in particular, in comparison between on-pump and off-pump in recent years (9, 10). However, controversies remain on which factors associated with cardiac surgery may lead to increased biomarkers of cerebral injury, and therefore necessitates a meta-analysis on the relevant aspects.

## Methods

### Literature retrieval

A comprehensive literature search for relevant articles published between the year ranges 1992-2012 were conducted. The search terms included "S100", "S100B ( $\beta$ )", "cardiopulmonary bypass", "off-pump coronary artery bypass", "circulatory arrest, induced", "profound hypothermic circulatory arrest", "cardiac surgery", "congenital heart defects", "heart valves", "coronary artery bypass", "aortic surgery" and "cardiac surgical procedures". Quantitative data of S100 and S100B measured in the unit of  $\mu\text{g/L}$  were screened, while the results of NSE that were reported in these reports were also collected. Articles or groups of patients reported in articles with missing or obscure data, or the results of the biomarkers described in a narrative or an illustrative way were considered of no value for the quantitative analysis and were thus excluded from this study.

### Patient information

As a result, a total of 69 articles were obtained, including 4533 patients with the three above-mentioned biomarkers expressed in quantitative values. Of them, genders could be tracked in 2538 patients from 78 cohorts, with 1772 males and 766 females with a male-to-female ratio of 2.3:1. Their ages were  $54.6 \pm 23.3$  years (range, 9 days-82 years; median 63 years). Table 1 showed the cardiac surgical procedures performed on the patients. The parameters of cardiac operations were summarized in Table 2.

### Neurological disorders

Patients with preoperative neurological disease (a history of stroke, spinal cord injury, stenosis of cervical or intracranial arteries) and postoperative neurological complications (paralysis, delayed consciousness regaining, loss of consciousness, convulsions and stroke) were defined as neurological disorder group ( $n=416$ ); while those without pre- and postoperative neurological disorders were defined as control group ( $n=4117$ ). The prevalence of neurological disorders in this patient setting was 10.1%.

**Table 1. Cardiovascular surgical procedures**

Operation	Report, n (%)
Aorta replacement	6 (8.7)
Coronary artery bypass grafting	35 (50.7)
Coronary artery bypass grafting, aorta replacement	2 (2.9)
Coronary artery bypass grafting, off-pump coronary artery bypass	8 (11.6)
Coronary artery bypass grafting, valve replacement	3 (4.3)
Coronary artery bypass grafting, valve replacement, aorta replacement	5 (7.2)
Correction for congenital heart defects	7 (10.1)
Off-pump coronary artery bypass	2 (2.9)
Valve replacement percutaneous implantation	1 (1.4)
Total	69 (100)

**Table 2. Conditions of cardiac operations**

Condition	n	Mean	Range	Median
Duration of cardiopulmonary bypass, min	124	$111.1 \pm 40.8$	29-227	155.7
Crossclamp time, min	91	$65.6 \pm 28.4$	28-175	66
Circulatory arrest time, min	15	$35.5 \pm 9.5$	22-60	34
Operation time, min	16	$242.6 \pm 104.1$	34-423	233.5
Lowest core temperature, °C	112	$27.9 \pm 6.6$	18.8-37	30.5
Profound hypothermia, °C	28	$17.7 \pm 3.8$	18.8-23.9	20
Moderate hypothermia, °C	17	$27.3 \pm 1.0$	25-28	28
Mild hypothermia, °C	67	$32.3 \pm 1.9$	28.2-37	32

### Biomarkers and sampling

Of them, 2772 (61.2%) patients from 45 reports were for S100B, 1761 (38.8%) patients from 24 reports were for S100, and in addition 1189 (26.2%) patients from 16 reports were for NSE. The biomarkers were detected in serum in 64 (92.8%) reports, in CSF in 2 (2.9%) reports, and in both serum and CSF in 3 (4.3%) reports.

For S100, S100B and NSE measurements, blood and CSF were sampled before operation ( $T^0$ ), during the course of cardiopulmonary bypass (CPB) ( $T^1$ ), at the end of CPB ( $T^2$ ), and postoperative hours 1, 4, 6, 12, 14, 24, 48, 72 and 120 ( $T^3$ - $T^{11}$ ). However, NSE was only detected in serum rather than in CSF in these reports.

### Reference values

Seven detection techniques were applied in the investigations of these biomarkers. The immunoradiometric assay was the most commonly used method representing 47.4% (36/76 cohorts), and the immunolumimetric assays were the second most commonly used method representing 34.2% (26/76 cohorts) (Table 3). The reference values of the biomarkers in the serum and CSF were listed in Table 4 (11-14).

**Table 3. Detecting methods of the biomarkers**

Assay	S100, n (%)	S100B, n (%)	NSE, n (%)
Immunoluminometric	4 (20)	17 (42.5)	3 (18.8)
Immunometric	1 (5)		3 (18.8)
Immunofluorometric		2 (5)	3 (18.8)
Luminometric			1 (6.3)
Immunoradiometric	14 (70)	18 (45)	4 (25)
Electrochemoluminescence immunoassay		1 (2.5)	
Enzyme-linked immunosorbent assay	1 (5)	2 (5)	2 (12.5)
Total	20 (100)	40 (100)	16 (100)

NSE- neuron-specific enolase

**Table 4. Reference values of the biomarkers in the serum and cerebrospinal fluid (11-14)**

Sample	S100	S100B	Neuron-specific enolase
Serum, µg/L	0.5	0.2	10
Cerebrospinal fluid, µg/L	0.098	0.81	--

**Statistical analysis**

Data were expressed as mean±standard deviation. Comparisons between groups were conducted with unpaired t-test, and linear correlations were assessed between independent and dependent variables.  $p < 0.05$  was considered statistically significant.

**Results**

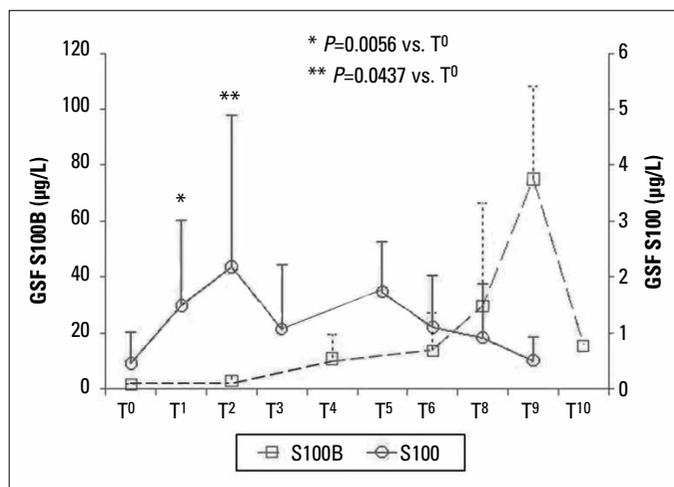
**S100**

S100 in the CSF began to increase during the operation, peak at T<sup>2</sup> and decreased significantly at T<sup>3</sup>. There showed a small second peak at T<sup>5</sup>, then decreased gradually and returned to the base value at T<sup>9</sup> (Fig. 1). S100 in the serum reduced a little comparing with T<sup>0</sup>. It reached to its peak value at T<sup>2</sup> and decreased significantly at T<sup>3</sup>. Then it reduced to a low level at T<sup>5</sup> even lower than T<sup>0</sup> (Fig. 2). A significant direct correlation was noted between CSF S100 and serum S100 ( $Y=0.0951X + 0.9708, r=0.6740, p=0.0334$ ).

Comparison of serum S100 between pediatric and adults showed a significant decrease in the adults at T<sup>8</sup> after the operation ( $0.26 \pm 0.18 \mu\text{g/L}$  vs.  $0.80 \pm 0.65 \mu\text{g/L}$ ,  $p=0.0093$ ) (Fig. 3).

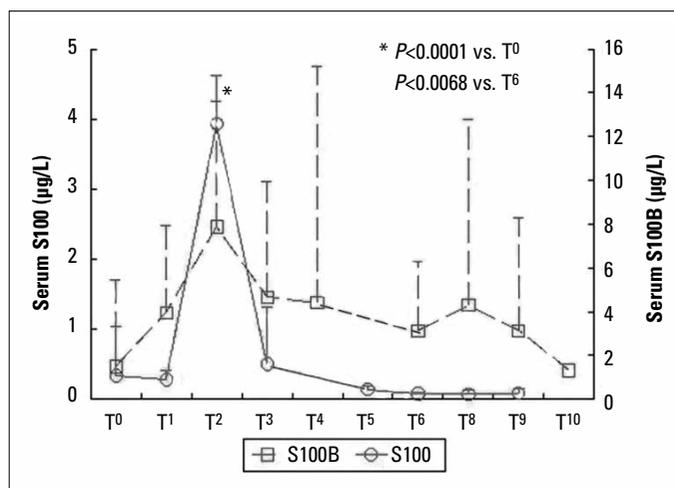
The serum S100 level of the control group patients at T<sup>0</sup> was  $0.62 \pm 0.86 \mu\text{g/L}$ , reached a peak value of  $2.47 \pm 2.34 \mu\text{g/L}$  at T<sup>2</sup>, and there was a significant decrease to  $0.57 \pm 0.66 \mu\text{g/L}$  at T<sup>8</sup> with significant differences between the two points. The neurological disorder group patients had a significantly increased serum S100 level at T<sup>0</sup> when comparing with that of the control group patients, however they did not display a significant increase at T<sup>2</sup> (Fig. 4).

CSF S100 showed a significant difference at T<sup>2</sup>, and a decrease at 14 h in the control, while in the neurological disorder



**Figure 1. Kinetics of cerebrospinal fluid S100B and a comparison with cerebrospinal fluid S100**

CSF - cerebrospinal fluid; T<sup>0</sup> - before operation; T<sup>1</sup> - during the course of cardiopulmonary bypass; T<sup>2</sup> - at the end of cardiopulmonary bypass; T<sup>3-6</sup> - postoperative hours 1, 4, 6 and 12; T<sup>8-10</sup> - postoperative hours 24, 48 and 72



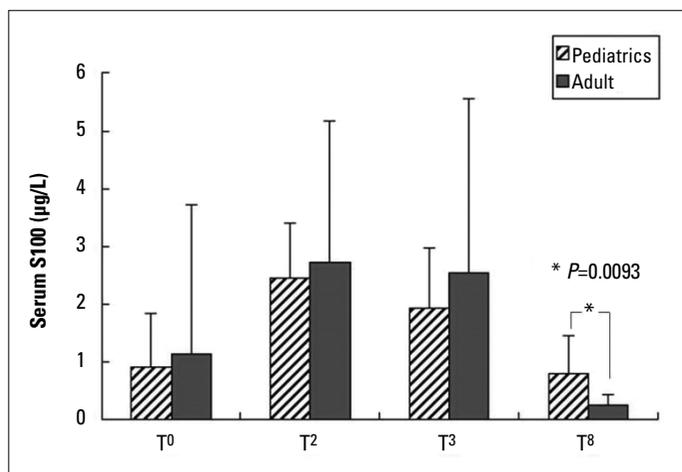
**Figure 2. Kinetics of serum S100B and a comparison with serum S100**

T<sup>0</sup> - before operation; T<sup>1</sup> - during the course of cardiopulmonary bypass; T<sup>2</sup> - at the end of cardiopulmonary bypass; T<sup>3-6</sup> - postoperative hours 1, 4, 6 and 12; T<sup>8-10</sup> - postoperative hours 24, 48 and 72

der group, it showed a similar trend but did not reach significant difference (Fig. 5). A close direct correlation was found between serum S100 values at T<sup>8</sup> and duration of CPB ( $r^2=0.5983, p=0.0016$ ), whereas serum S100 values at T<sup>2</sup> did not show any significant correlation with duration of CPB ( $r^2=0.0715, p=0.2003$ ). There was a feeble negative correlation between serum S100 values at T<sup>2</sup> and the minimal core temperature during CPB ( $r^2=0.2563, p=0.0560$ ), but the negative correlation between serum S100 values at T<sup>8</sup> and the core temperature was insignificant ( $r^2=0.0846, p=0.1565$ ).

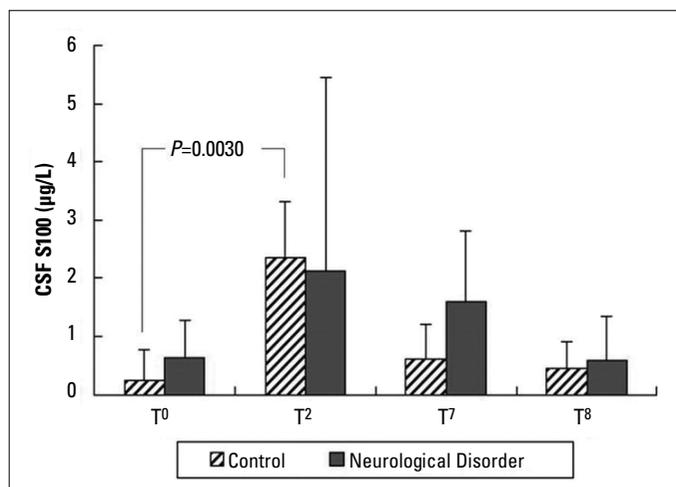
**S100B**

CSF S100B showed a different changing trend from serum S100. It increased gradually and had a delayed peak at T<sup>9</sup> after the operation (Fig. 1). But serum S100B showed a similar trend with serum S100 with a peak value at T<sup>2</sup> (Fig. 2). No significant



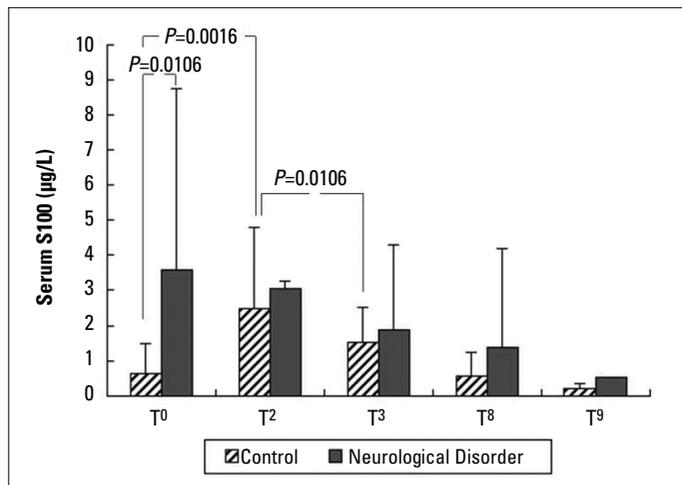
**Figure 3. Comparison of serum S100 between pediatric and adult patients**

T<sup>0</sup> - before operation; T<sup>2</sup> - at the end of cardiopulmonary bypass; T<sup>3</sup> - postoperative hour 1; T<sup>8</sup> - postoperative hour 24



**Figure 5. Comparison of cerebrospinal fluid S100 between patients with and without neurological disorders**

CSF - cerebrospinal fluid; T<sup>0</sup> - before operation; T<sup>2</sup> - at the end of cardiopulmonary bypass; T<sup>7</sup> - postoperative hour 14; T<sup>8</sup> - postoperative hour 24



**Figure 4. Comparison of serum S100 between patients with and without neurological disorders**

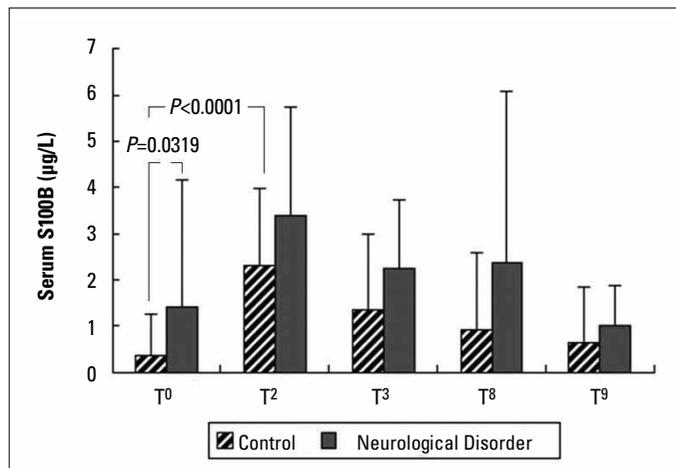
T<sup>0</sup> - before operation; T<sup>2</sup> - at the end of cardiopulmonary bypass; T<sup>3</sup> - postoperative hour 1; T<sup>8-9</sup> - postoperative hours 24 and 48

correlation was noted between CSF and serum S100B concentrations ( $Y=-0.0039X+1.2277$ ,  $r=-0.1418$ ,  $p=0.3809$ ). CSF S100B and CSF S100 did not correlate ( $Y=-20.282X+45.395$ ,  $r=-0.4674$ ,  $p=0.2136$ ), but serum S100B and serum S100 did ( $Y=0.1162X+0.9947$ ,  $r=0.8512$ ,  $p=0.0076$ ).

Serum S100B and CPB duration correlated both at T<sup>2</sup> ( $Y=0.0169X+0.9378$ ,  $r=0.4087$ ,  $p=0.0040$ ) and 24 h after the operation ( $Y=0.0136X-0.8996$ ,  $r=0.4714$ ,  $p=0.0032$ ), so did serum S100B and the lowest temperature during cardiac surgical procedures (T<sup>2</sup>:  $Y=-0.0889X+4.9112$ ,  $r=-0.4370$ ,  $p=0.0048$ ; T<sup>8</sup>:  $Y=-0.0288X+1.4700$ ,  $r=-0.3504$ ,  $p=0.0430$ ).

Serum S100B of the control group was  $0.36\pm 0.91$  µg/L at T<sup>0</sup> with a significant increase to  $2.30\pm 1.68$  µg/L at T<sup>2</sup> ( $p<0.0001$ ). In the neurological disorder group, serum S100B at T<sup>0</sup> was significantly higher in comparison to the control ( $p=0.0319$ ) (Fig. 6).

There were significant differences in S100 values between patients undergoing different surgical procedures and between



**Figure 6. Comparison of serum S100B between patients with and without neurological disorders**

T<sup>0</sup> - before operation; T<sup>2</sup> - at the end of cardiopulmonary bypass; T<sup>3</sup> - postoperative hour 1; T<sup>8-9</sup> - postoperative hours 24 and 48

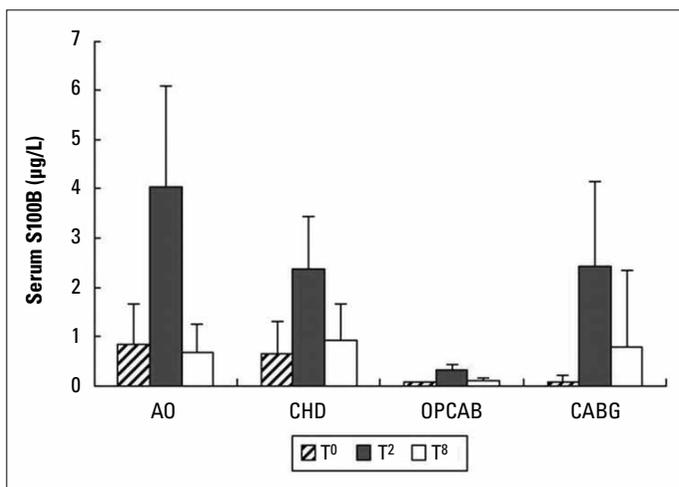
different time sampling of the same surgical patient group. Serum S100 levels were the highest in the patients receiving an aortic operation, higher in the patients undergoing a congenital heart defect correction or coronary artery bypass grafting and the lowest in the patients with an off-pump coronary artery bypass (Fig. 7).

**NSE**

Serum NSE did not increase during CPB, but peaked at T<sup>2</sup>, reached to a second peak at T<sup>6</sup>, followed by a gradual decrease and returned to base level at T<sup>11</sup> (Fig. 8). It did not correlate significantly with serum S100 or S100B (with S100:  $Y=0.5445X-5.3833$ ,  $r=0.5400$ ,  $p=0.1671$ ; with S100B:  $Y=0.0822+0.1485$ ,  $r=0.6038$ ,  $p=0.1129$ ).

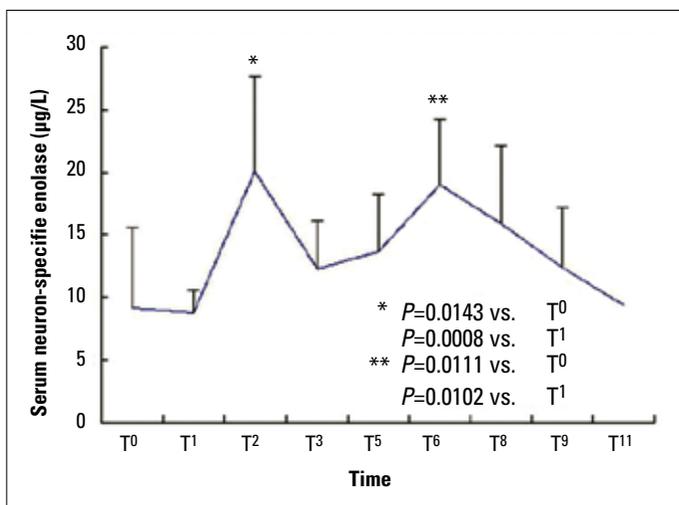
**Discussion**

Intellectual and cognitive dysfunctions were found in 16-38% of patients following cardiac operations with CPB. Minute fatty



**Figure 7. Comparison of serum S100B between patients undergoing different cardiac operations. Significant differences were noted between any two groups and between any two detections of each group**

AO - aortic surgery; CABG - coronary artery bypass grafting; CHD - correction for congenital heart defects; OPCAB - off-pump coronary artery bypass; T<sup>0</sup> - before operation; T<sup>2</sup> - at the end of cardiopulmonary bypass; T<sup>8</sup> - postoperative hour 24



**Figure 8. Kinetics of serum neuron-specific enolase**

T<sup>0</sup> - before operation; T<sup>1</sup> - during the course of cardiopulmonary bypass; T<sup>2</sup> - at the end of cardiopulmonary bypass; T<sup>3</sup> - postoperative hour 1; T<sup>5-6</sup> - postoperative hours 6 and 12; T<sup>8-9</sup> - postoperative hours 24 and 48; T<sup>11</sup> - postoperative hour 120

microemboli have been taken as the major source of brain injury. Millions of emboli in the cerebral arterioles were found in the brains of 22 autopsies that died after CPB, whereas in brains of control with hypertension or leukoaraiosis or Alzheimer's disease with no history of open-heart surgery, the emboli were absent (15). Adverse effects of CPB could result in cerebral injury as evidenced by the decrease in regional cerebral blood flow and improvement of cerebral perfusion 6 months after coronary artery bypass (16). During hypothermic CPB with  $\alpha$ -stat management of PaCO<sub>2</sub>, cerebral pressure autoregulation is well maintained. During hypothermic CPB with pH-stat management of PaCO<sub>2</sub>, cerebral pressure autoregulation is impaired, consistent with relative hypercarbia (17). In piglet experimental models, an exhaustion of cerebral energy reservoirs was dem-

onstrated during the course of profound hypothermic circulatory arrest at a core temperature of 18°C and rewarming (18). Release of S100 protein showed higher values in patients undergoing standard CPB than after minimal extracorporeal circulation (19). Prolonged mechanical ventilation and increased the number of bypassed coronary arteries also contributed to impaired verbal memory and deteriorated cerebral blood perfusion (16). Perioperative cerebral impairment can be reduced in cardiac operations without the use of CPB, for example, in off-pump coronary artery bypass (20). Thus, many studies have focused on the evaluation of biomarkers of cerebral injury between off-pump versus on-pump.

Accumulating evidence has shown a decline in brain Mg<sup>+</sup> in response to brain injury. Serum Mg<sup>+</sup> concentrations negatively correlated with S100B levels, particularly in patients receiving infusions of low-dose Mg<sup>+</sup>. The administration of MgSO<sub>4</sub> at 10 mg/min significantly reduced the serum S100B concentration. Nevertheless, CPB resulted in increased serum S100B concentration irrespective of Mg<sup>+</sup> supplementation or serum S100B concentrations (21). MgSO<sub>4</sub> treatment confers neuroprotection by restoration of blood brain permeability in hypoxia-ischemia (22). Volatile anesthetics, in particular isoflurane and sevoflurane, significantly reduced disturbances in Mg<sup>+</sup> concentrations in the brain circulation (23). Sevoflurane was likely associated with the worst cognitive outcome as assessed by neuropsychologic tests, as prolonged brain injury was seen with desflurane (24). Further studies on accuracy of S100B protein as a prognostic marker and of neuroprotective effect of magnesium sulfate remain to be demonstrated (25).

With cerebral injury, the neurological specific biomarkers are released into CSF and then the systemic circulation. The low molecular weight of S100 proteins, compared with NSE, allows a more rapid and easier release across the blood-brain barrier into the systemic circulation, thus potentially giving a higher sensitivity to detect brain injury (26). Martens et al. (27) described that S100 correlated significantly with bypass time, cross clamp time and lowest temperature during CPB, probably due to the use of non-pulsatile CPB. Rasmussen et al. (28) reported that S100 at 24 hours correlated well with the duration of CPB, but not with measures of cognitive dysfunction. From the present study, we may find two peaks of serum S100 protein. The release of S100 protein was actually biphasic after brain injury as described in the literature previously, with a first upregulation starting at 3-5 hours and a second 48 hours after the insult (29). Similarly, as explained by Kuzumi et al. (14), S100B protein could show an early and a late release patterns: the early pattern may develop during and up to 5 hours after CPB probably due to sub-clinical brain injury, while the late release pattern may occur during postoperative hours 15-48, implying further perioperative neurological impairments.

In patients receiving coronary artery bypass, S100B remained elevated for 40-44 hours after operation (30); while serum S100B was elevated during the operation of valve replacement, peaked at the end of the operation, and decreased gradually after the

operation (31, 32). S100B upregulation varied in different parts of the brain: upregulation is highest in the penumbra region, and not in the infarct region, indicating that S100B release after a cerebral ischemia could be as a consequence of hypoxic, but not dead cells, in the penumbra. Postoperative cognitive performance and S100B had weak correlation (33). S100B values exceeding 0.3 µg/L point to an unfavorable postoperative neurological outcome (34). Patients undergoing a cardiac surgery under hypothermic circulatory arrest had significant higher levels and prolonged rise of S100B at 24 hours (35, 36). Ashraf et al. (37) found persistently increased S100B levels were associated with longer intubation times. They found S100B did not correlate the duration of CPB, but peak S100B levels correlated cross clamp time in the centrifugal pump. Animal experiments showed supportive results to clinical observations. Hypothermic or normothermic circulatory arrest on animal models resulted in significant increase in CSF or serum S100B concentrations after reperfusion (38, 39). Nevertheless, serum S100B in blood of cardiomy suction may be beyond cerebral origin. S100B after CPB with cell saving device was the same as after off-pump operation (40). S100B was abundant both in the blood from the surgical field and in the shed mediastinal blood postoperatively, thus autotransfusion of such blood may disturb the S100B profile (41). As linear analysis revealed no significant relation between S100B levels and neuropsychological outcome, the significance of early S100B levels after cardiac surgery was doubted and it therefore warrants further investigation (42).

NSE has been considered of the value of neurological prediction. Serum NSE may increase during and after cardiac surgery (43). Serum NSE significantly elevated at 6-30 hours after skin closure in patients undergoing valve replacement surgery (44); while it peaked at 72 hours following coronary artery bypass (31). The elevation of serum NSE may persist until 6 months after cardiac surgery in relation to neuropsychological impairment of the patients (43). Hypothermic CPB was more likely to cause higher level of NSE rather than the normothermic (45). Off-pump cardiac surgery may significantly reduce serum NSE concentration. As NSE exists in the erythrocytes and platelets, hemolysis during CPB and the use of cardiomy suction may be associated with higher levels of NSE of non-neural sources (46).

In the past, the postoperative stroke rate was high following open heart operations; but it has been significantly reduced to 0.48% by a recent study on a large cohort of patients (47). Retrograde cerebral perfusion during cardiac operations may potentially protect the patients from embolic strokes (48). In the present study, a similar prevalence of neurological disorders following cardiac operations to what have been reported in the literature was presented (49). Moreover, the biomarkers appeared earlier and lasted longer in the CSF than in the serum. All three biomarkers reached peak values at the end of CPB, displaying a similar kinetic trend in the bloodstream. In adults, serum biomarkers may recover to normal earlier than in pediatrics undergoing a cardiac surgery. Patients undergoing off-pump

surgery had minimal elevations of biomarkers comparing to all other cardiac surgeries under CPB, low core temperature and/or hypothermic circulatory arrest. In patients with pre- or post-operative neurological disorders, the biomarkers in the serum elevated even before operation and lasted longer than those without neurological disorders. It was obvious to highlight the inherent relation between these serum biomarkers and the conditions of CPB, such as CPB duration and the minimal core temperatures.

## Conclusion

The present study illustrated that cerebral damages may be associated with cardiac surgery in the conditions of CPB and hypothermia. The cerebral biomarkers including S100, S100B and NSE could be reliable indicators reflecting the cerebral damages secondary to cardiac surgery. Modifications of the adjunct cardiac surgical techniques, such as minimizing the duration of CPB, application of normothermic heart operations, avoidance of deep hypothermic circulatory arrest and use of retrograde cerebral perfusion may prevent the patients from postoperative neurological impairments.

**Conflict of interest:** None declared.

**Peer-review:** Partially external peer-reviewed.

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