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# S100 and S100ß: biomarkers of cerebral damage in cardiac surgery with or without the use of cardiopulmonary bypass

## *S100 e S100ß: biomarcadores de dano cerebral em cirurgia cardíaca com ou sem o uso de circulação extracorpórea*

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*Abstract*

***Objective:*** **The present study is to describe the clinical impact of S100 and S100ß for the evaluation of cerebral damage in cardiac surgery with or without the use of cardiopulmonary bypass (CPB).**

***Methods:*** **Quantitative results of S100 and S100ß reported in the literature of the year range 1990-2014 were collected, screened and analyzed.**

***Results:*** **Cerebrospinal fluid and serum S100 levels showed a same trend reaching a peak at the end of CPB. The cerebrospinal fluid/serum S100 ratio decreased during CPB, reached a nadir at 6 h after CPB and then increased and kept high untill 24 h after CPB. Serum S100 at the end of CPB was much higher in infant than in adults, and in on-pump than in off-pump coronary artery bypass patients. ΔS100 increased with age and CPB time but lack of statistical significances. Patients receiving an aorta replacement had a much higher ΔS100 than those receiving a congenital heart defect repair. Serum S100ß reached a peak at the end of CPB, whereas cerebrospinal fluid S100 continued to increase and reached a peak at 6 h after CPB. The cerebrospinal fluid/serum S100ß ratio decreased during CPB, increased at the end of CPB, peaked 1 h after CPB, and then decreased abruptly. The increase of serum S100ß at the end of CPB was associated with type of operation, younger age, lower core temperature and cerebral damages. ΔS100ß displayed a decreasing trend with age, type of operation, shortening of CPB duration, increasing core temperature, lessening severity of cerebral damage and the application of intervenes. Linear correlation analysis revealed that serum S100ß concentration at the end of CPB correlated closely with CPB duration.**

***Conclusion:*** **S100 and S100ß in cerebrospinal fluid can be more accurate than in the serum for the evaluations of cerebral damage in cardiac surgery. However, cerebrospinal fluid biopsies are limited. But serum S100ß and ΔS100ß seem to be more sensitive than serum S100 and ΔS100. The cerebral damage in cardiac surgery might be associated with younger age, lower core temperature and longer CPB duration during the operation. Effective intervenes with modified CPB circuit filters or oxygenators and supplemented anesthetic agents or priming components may alleviate the cerebral damage.**

***Descriptors:*** **Cardiopulmonary Bypass. Cerebrospinal Fluid. Circulatory Arrest, Deep Hypothermia Induced. S100 Proteins.**

*Resumo*

***Objetivo:*** **O presente estudo descreve o impacto clínico de S100 e S100ß para a avaliação do dano cerebral em cirurgia cardíaca com ou sem o uso de circulação extracorpórea (CEC).**

***Métodos:*** **Os resultados quantitativos de S100 e S100ß relatados na literatura entre os anos 1990 e 2014 foram recolhidos, rastreados e analisados.**

***Resultados:*** **Os níveis do fluido cerebroespinal e níveis séricos S100 mostram uma mesma tendência, atingindo um pico no final da CEC. A relação de fluido cerebroespinal e soro S100 diminuiu durante a CEC, chegando a um nadir 6 h após a CEC, aumentando e mantendo alta até 24 h após a CEC. O soro S100 no final da CEC foi muito maior no infantil do que em adultos, e em pacientes de revascularização miocárdica com**

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| Abbreviations, acronyms & symbols | |
|---|---|
| CABG | Coronary artery bypass grafting |
| CPB | Cardiopulmonary bypass |
| CSF | Cerebrospinal fluid |
| OPCAB | Off-pump coronary artery bypass |
| POD | Postoperative day |

**CEC do que em pacientes sem CEC. ΔS100 aumentou com a idade e tempo de CEC, mas sem significância estatística. Os pacientes que receberam substituição da aorta tinham um ΔS100 muito maior do que aqueles que fizeram reparo dos defeitos cardíacos congênitos. Soro S100ß atingiu um pico no final da CEC, enquanto líquido cefalorraquidiano S100 continuou a aumentar e atingir um pico 6 h após a CEC. A proporção entre soro S100ß e líquido cefalorraquidiano diminuiu durante a CEC, aumentando no final da CEC, com pico 1 h após a CEC, em seguida, diminuiu abruptamente. O aumento de soro S100ß no final da CEC foi associado com o tipo de operação, menor idade, menor temperatura do coração e danos cerebrais. ΔS100ß exibiu tendência decrescente com a idade, tipo de operação, encurtamento da duração da CEC, o aumento da temperatura do coração, diminuindo a gravidade do dano cerebral e da aplicação de intervenções. Análise de correlação linear revelou que a concentração sérica de S100ß no final da CEC está intimamente relacionada com a duração do procedimento.**

***Conclusão:*** **Níveis de S100 e S100ß no líquido cefalorraquidiano podem ser mais precisos do que no soro para as avaliações de dano cerebral em cirurgia cardíaca. No entanto, as biópsias liquóricas são limitadas. Mas S100ß e ΔS100ß do soro parecem ser mais sensíveis do que o soro S100 e ΔS100. O dano cerebral em cirurgia cardíaca pode estar associado com a idade mais jovem, menor temperatura do núcleo e maior duração da CEC durante a operação. Intervenções eficazes com filtros modificados no circuito de CEC ou oxigenadores complementadas com agentes anestésicos ou componentes iniciadores podem aliviar o dano cerebral.**

***Descritores:*** **Ponte Cardiopulmonar. Líquido Cefalorraquidiano. Parada Circulatória Induzida por Hipotermia Profunda. Proteínas S100.**

## INTRODUCTION

S100 protein family members with a molecular mass of 10-12 kDa are acidic proteins characterized by their calcium-dependent biological effects[1]. It is expressed in different tissues, but shows brain tissue specific, and therefore implicated in cerebral damage. They may form into homodimers, heterodimers and even oligomers based on a calcium-dependent conformational change[1]. Most S100 proteins have a low binding affinity for calcium, which increase dramatically to control a cellular activity in the presence of a target[2]. This protein family represents the largest subgroup within the superfamily of EF-hand $Ca^{2+}$ binding proteins. $Ca^{2+}$ binding to the first EF-hand (helix I, loop and helix II) is weaker than binding to the second EF-hand (helices III and IV)[3]. S100ß, a 10.7 kDa protein, is a member of S100 protein family. It is highly expressed in astrocytes and is one of the most abundant soluble proteins in human brain, constituting 0.5% of them. S100ß functions as both an intracellular $Ca^{2+}$ receptor and an extracellular neuropeptide by way of the receptor for advanced glycation end-products, a main transducer of extracellular functions of this protein[1]. S100ß is displayed as a homodimer with a high binding affinity under all biological circumstances while the monomers are absent[1].

Blood-brain barrier dysfunction secondary to cerebral damages may expedite the release of these cerebral specific proteins from the astroglial or Schwann cells into cerebrospinal fluid (CSF) and blood circulation[4,5]. During cardiac operations, neurological disorders may occur and are believed to be the results of thromboembolism (embolism is not always caused by a thrombus, but can be air embolism, calcium embolism or detachment of atheromatous plaques from the aorta at the time of cannulation or decannulation) and systemic inflammatory reactions[6]. S100 and S100ß have been reliable serum markers of cerebral damage due to breakdown of the blood-brain barrier caused by head trauma, anoxia, ischemia, neoplasm and cardiac surgery[7]. Both hypo- and hypertension may also cause cerebral damage by impairment of cerebral autoregulation[8]. S100 and S100ß proteins leak from structurally damaged neurocytes into CSF and then across the blood-brain barrier. S100ß protein increases 50~100-fold after cardiac operation with cardiopulmonary bypass (CPB), supporting links between CPB, microembolization and cerebral damage[9] and indicating postoperative adverse neurologic outcomes[10]. However, debates remain with regard to the accuracy of the results during and early after the operation as well as the correlations between the expression of the proteins and the surgical conditions. In order to highlight these aspects, a comprehensive review is made based on quantitative data reported in the literature.

## METHODS

### Literature Retrieval

A literature search for English articles published from 1990 to 2012 concerning S100 and S100ß in relation to cardiovascular surgery in PubMed, Highwire Press and Google search engine yielded totally 69 publications[8-73]. The search terms included "S100", "S100ß(B)", "cardiopulmonary bypass" "off-pump coronary artery bypass", "circulatory arrest, induced", "profound hypothermic circulatory arrest", "cardiac surgery", "congenital heart defects", "heart valves", "coronary artery bypass grafting", "aortic surgery" and "cardiac surgical procedures". Quantitative data of S100 and S100ß measured in the unit of μg/L were screened, collected and analyzed. Articles or patient cohorts reported in articles with no quantitative data were excluded from this study.

### Sampling

Sampling times were before operation (baseline) ($T_0$), during CPB ($T_1$), at the end of CPB ($T_2$), 1, 4, 6, 12, 24, 48, and 72 h after operation ($T_{3-9}$).

### Indicators

The indicators of evaluating the cerebral damage included dynamics of CSF and serum S100(ß), ΔS100(ß), i.e., the difference between peak and baseline S100(ß)[14] and CSF/serum S100(ß) ratios.

### Subgroups

1) Age: There were 4 age subgroups: neonate, infant, child and adult;

2) Operation: The operations were classified as aorta, valve, congenital heart defect, coronary artery bypass grafting (CABG) and off-pump coronary artery bypass (OPCAB);

3) CPB duration: There were 2 subgroups based on whether the CPB duration was >100 minutes;

4) Core temperature: There were 3 subgroups according to core temperatures during CPB: deep hypothermia, mild and moderate hypothermia and normothermia;

5) Cerebral damage: The patients with cerebral damage were divided into either functional (confusion, agitation, disorientation, or epileptic seizures) or organic (stroke, stupor, or coma) subgroups. Those without cerebral damage were defined as control; and,

6) Intervene: Patients with utilizations of modified CPB circuit and oxygenators[25,26,60,72], cell saving reservoir[33], anesthetic agents and priming components (propofol[53], isoflurane[64], hydroxyethyl[46] and starch[42]) during the operation aiming at lessening the cerebral damage were defined as the Intervene Subgroup. Those without intervenes were defined as control.

### 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

### Patient information

The 69 articles reported the quantitative results of S100(ß) of 4439 patients: 20 (29.0%) on serum S100[8-30], 45 (65.2%) on serum S100ß[31-73], 2 (2.9%) on serum and CSF S100[74,75], 1 (1.4%) on serum and CSF S100ß[76] and 1 (1.4%) on CSF S100ß[77]. The 2 articles reporting CSF S100 comprised 22 patients with 15 males and 6 females with a median age of 63 years. All received a thoracic aorta operation with postoperative spinal cord injury in 2 (9.1%) patients; and the 2 articles reporting CSF S100ß included 49 patients with 28 males and 23 females (gender of 8 patients was unidentified) with a median age of 64 years. All received a thoracic aorta operation with postoperative spinal cord injury in 10 (20.4%) patients. The demographics of the patients with serum S100(ß) detections were listed in Table 1.

### Assays

Immunoradiometry, immunoluminometry and immunofluorometry were the 3 main assays used for the detection of the biomarkers (Table 1).

### Biomarkers

CSF and serum S100 levels showed a same trend during the early observational stage before $T_5$, increased at $T_1$, reaching a peak at $T_2$ and then gradually decreased. After $T_5$, CSF S100-serum S100 separation phenomenon was seen. The CSF/serum S100 ratio decreased from $T_1$, reached a nadir at $T_5$ and then increased and kept high till $T_7$ (Figure 1).

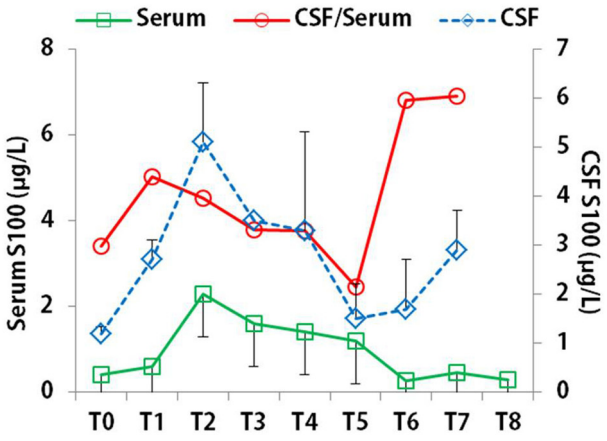


*Fig. 1 - Dynamics of CSF S100, serum S100 and CSF/serum S100 ratio. CSF=Cerebrospinal fluid*

Table 1. Demographics of patients with serum S100 and serum S100ß detections.

| Variable | S100 | S100ß |
|---|---|---|
| Report number | 20 | 45 |
| Patient number | 1741 | 2682 |
| Gender (male/female) | 1217/352 | 829/451 |
| Age | 51.8±26.1 (range, 3 days-77 years; median, 68 years) | 47.7±27.8 (range, 8.6 days-81 years; median, 62 years) |
| Operative conditions | | |
| CPB (min) | 98.1±36.5 (range, 48-217; median, 90.3) | 116.5±55.0 (range, 49-308; median, 103.2) |
| Crossclamp time (min) | 63.8± 31.5 (range, 29-175; median, 56) | 64.9±29.9 (range, 28-164; median, 60) |
| Hypothemic circulatory arrest time (min) | 43.1±24.2 (range, 26-60.2; median, 43.1) | 31.6±9.1 (range, 20-45; median, 32) |
| Core temperature (℃) | 30.1±4.4 (range, 18-34.5; median, 31.5) | 29.46±6.5 (range, 10.5-37; median, 32) |
| Age group, *n* (%) | | |
| Neonate | 25 (1.4) | 173 (6.5) |
| Infant | 17 (1.0) | 69 (2.6) |
| Child | 21 (1.2) | 18 (0.7) |
| Adult | 1678 (96.4) | 2422 (90.3) |
| Core temperature, *n* (%) | | |
| Deep hypothermia | 44 (2.6) | 278 (10.4) |
| Mild-moderate hypothermia | 1576 (93.9) | 2250 (83.9) |
| Normothermia | 58 (3.5) | 154 (5.7) |
| Operation, *n* (%) | | |
| Aorta replacement | 31 (1.8) | 192 (7.1)* |
| Valve replacement | 14 (0.8) | 156 (5.8) |
| Congenital heart defect repair | 64 (3.7) | 270 (10.0) |
| CABG | 1335 (76.7) | 1941 (72.2) |
| OPCAB | 229 (13.2) | 129 (4.8) |
| Not given | 68 (3.9) | |
| Cerebral damage, *n* (%) | 23 (1.3) | 121 (4.5) |
| Organic cerebral damage | 23 (100) | 65 (53.7) |
| *Stroke* | *3 (13.0)* | *58 (89.2)* |
| *Transient ischemic attack* | *1 (4.3)* | *0 (0)* |
| *Spinal cord injury* | *3 (13.0)* | *2 (3.1)* |
| *Subclinical cerebral damage* | *16 (69.6)* | *5 (7.7)* |
| Functional cerebral damage | 0 (0) | 56 (46.3) |
| Intervene (with modified filter, oxygenator or anesthetic agents) | 259 (14.9) | 330 (12.3) |
| Assay, *n* (%) | | |
| Immunoradiometry | 985 (56.6) | 891 (33.2) |
| Enzyme linked immunosorbent assay | 163 (9.4) | 235 (8.8) |
| Immunoluminometry | 161 (9.2) | 668 (24.9) |
| Immunofluorometry | | 500 (18.6) |
| Luminometry | | 128 (4.8) |
| Immunoassay | | 72 (2.7) |
| Electrochemoluminescence immunoassay | | 21 (0.8) |
| Not given | 432 (24.8) | 167 (6.2) |

**at least 5 patients had concurrent procedures. CABG=coronary artery bypass grafting; CPB=Cardiopulmonary bypass; OPCAB=off-pump coronary artery bypass*

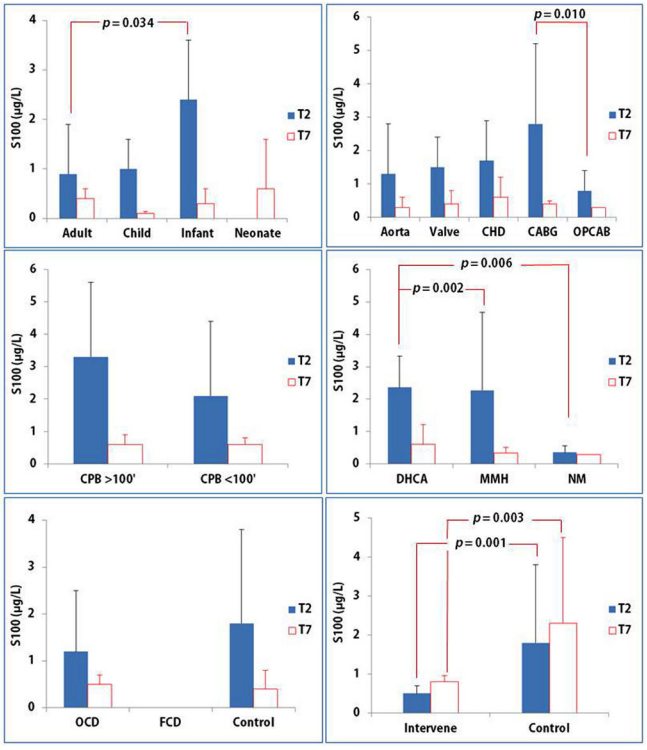


*Fig. 2 - An inter-subgroup comparison of serum S100 at $T_2$ and $T_7$. CABG=Coronary artery bypass; CHD=Congenital heart defect; DHCA=Deep hypothermia circulatory arrest; FCD=Functional cerebral damage; MMH=Mild-moderate hypothermia; NM=Normothermia; OCD=Organic cerebral damage; OPCAB=Off-pump coronary artery bypass; $T_2$=At the end of cardiopulmonary bypass; $T_7$=24 hours after cardiopulmonary bypass*

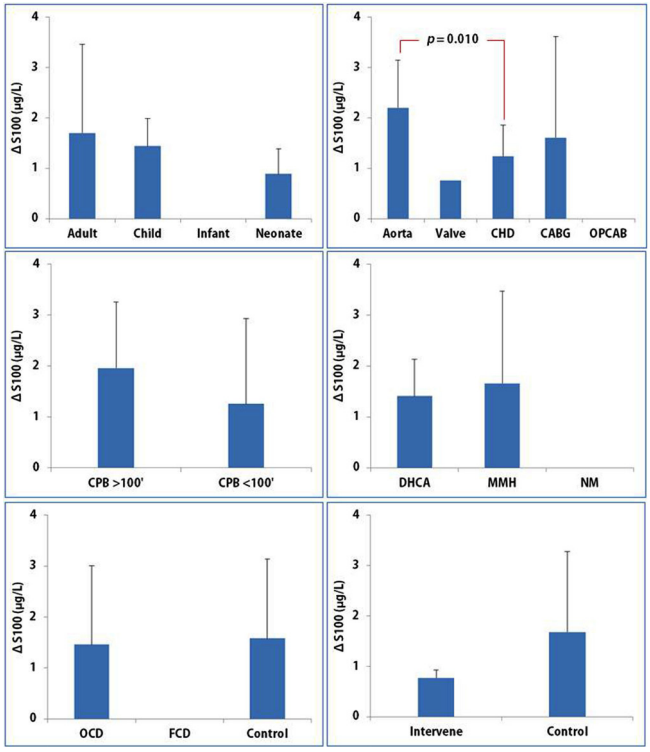


*Fig. 3 - An inter-subgroup comparison of serum ΔS100 at $T_2$ and $T_7$. CABG=Coronary artery bypass; CHD=Congenital heart defect; DHCA= Deep hypothermia circulatory arrest; FCD=Functional cerebral damage; MMH=Mild-moderate hypothermia; NM=Normothermia; OCD=Organic cerebral damage; OPCAB=Off-pump coronary artery bypass*

Serum S100 at $T_3$ was much higher in infant than in adults (2.4±1.2 µg/L *vs*. 0.9±1.0 µg/L, *P*=0.034) and in CABG patients than in OPCAB patients (2.8±2.4 µg/L *vs*. 0.8±0.6 µg/L, *P*=0.010). Patients with a CPB time >100 min had a higher serum S100 level at $T_2$ than those with a CPB time <100 min, but lack of a statistical significance, however, significant reductions were noted at $T_7$ in comparison to $T_2$ in both subgroups (CPB >100 min: 3.3±2.3 µg/L *vs*. 0.6±0.6 µg/L, *P*=0.005; CPB duration <100 min: 2.1±2.3 µg/L *vs*. 0.3±0.2 µg/L, *P*=0.016). Deep hypothermia circulatory arrest was associated with much higher serum S100 at $T_2$ than mild-moderate hypothermia and normothermia patients, and mild-moderate hypothermia with higher serum S100 than normothermia. No difference in the serum S100 levels was noted between patients with cerebral damage in particular stroke and those without. Intervenes with CPB filter, oxygenator, or anesthetic agents led to significant decreased serum S100 at $T_2$ and $T_7$ (Figure 2).

ΔS100 could be calculated in 25 series of patients in whom at least a baseline and a peak value were reported. The peaks were at $T_1$ in 5 (20%), $T_2$ in 16 (64%) and $T_3$ in 4 (16%) patient cohorts, respectively ($\chi^2$=7.5, *P*=0.023). ΔS100 increased with age and CPB time but lack of statistical significances. Patients receiving an aorta replacement had a much higher ΔS100 than those receiving a congenital heart defect repair, in line with the increasing trend with age. No difference was found in ΔS100 between deep hypothermia and mild-moderate hypothermia patients or between the organic cerebral damage and control patients. Intervenes led to a decrease of ΔS100 in comparison to non-intervene patients but no significance was found (Figure 3).

CSF and serum S100ß levels started to increase at $T_1$, but separation was noted since $T_2$. Serum S100ß reached a peak at $T_2$, whereas CSF S100ß continued to increase and reach a peak at $T_5$. Both recovered to normal at $T_7$. The CSF/serum S100ß ratio decreased at $T_1$, increased at $T_2$, peaked at $T_3$ and then decreased abruptly (Figure 4).

Serum S100ß at $T_2$ showed a successive decrease in the operation subgroups in a sequence of aorta, valve, congenital, CABG and OPCAB operations. Patients with organic and functional cerebral damages showed higher S100ß levels at $T_2$ than those without. Infant showed a little bit higher serum S100ß than adults, patients with CPB duration >100 min

showed higher serum S100ß than those with CPB duration <100 min, deep hypothermia and mild-moderate hypothermia were associated with higher serum S100ß than normothermia, and intervene led to reduced serum S100ß other than non-intervene, but no significances were found (Figure 5).

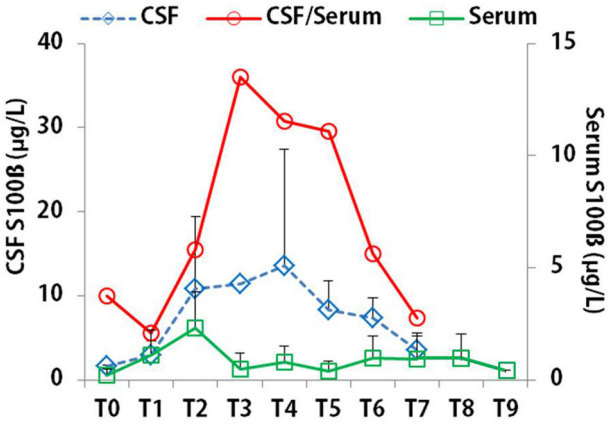


*Fig. 4 - Dynamics of CSF S100ß, serum S100ß and CSF/serum S100ß ratio. CSF=Cerebrospinal fluid*

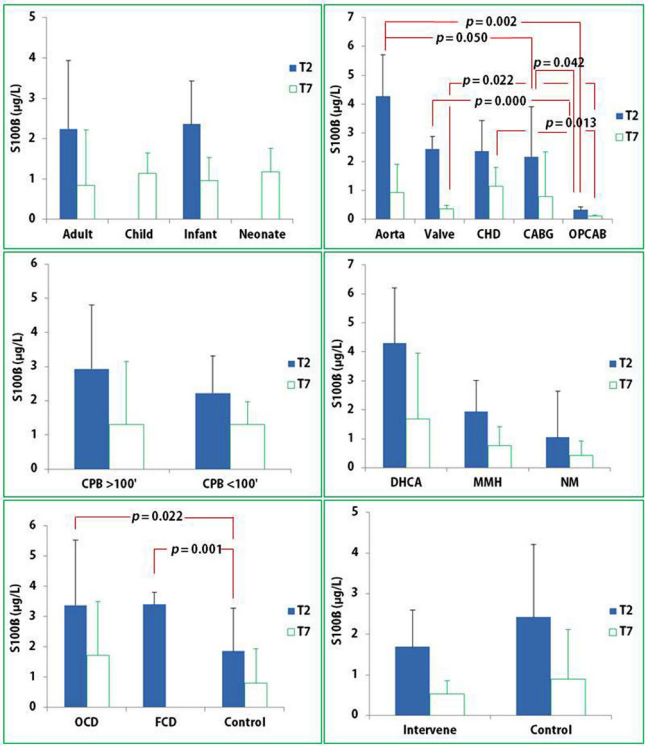


*Fig. 5 - An inter-subgroup comparison of serum S100ß at $T_2$ and $T_7$. CABG=Coronary artery bypass; CHD=Congenital heart defect; DHCA=Deep hypothermia circulatory arrest; FCD=Functional cerebral damage; MMH=Mild-moderate hypothermia; NM=Normothermia; OCD=Organic cerebral damage; OPCAB=Off-pump coronary artery bypass; $T_2$=At the end of cardiopulmonary bypass; $T_7$=24 hours after cardiopulmonary bypass*

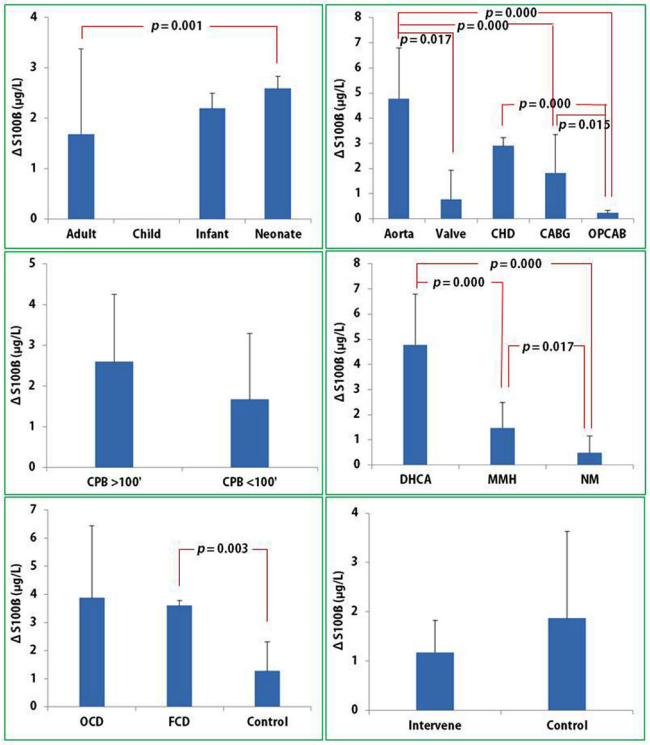


*Fig. 6 - An inter-subgroup comparison of serum ΔS100ß at $T_2$ and $T_7$. CABG=Coronary artery bypass; CHD=Congenital heart defect; DHCA=Deep hypothermia circulatory arrest; FCD=Functional cerebral damage; MMH=Mild-moderate hypothermia; NM=Normothermia; OCD=Organic cerebral damage; OPCAB=Off-pump coronary artery bypass*

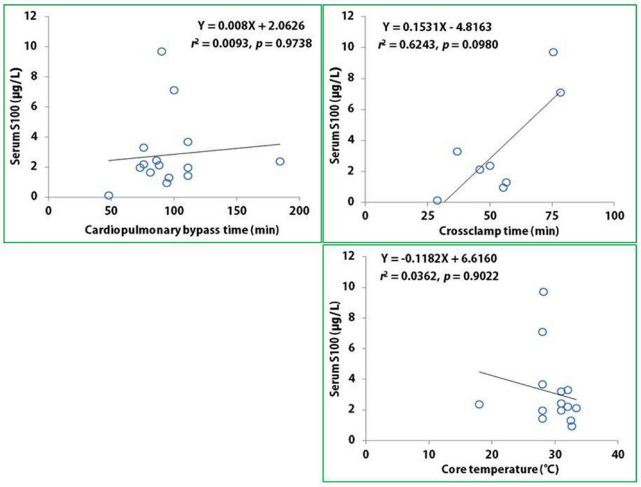


*Fig. 7 - Linear correlation analysis between serum S100 concentration at $T_2$ and cardiopulmonary bypass, crossclamp time and core temperature.*

ΔS100ß could be calculated in 51 series of patients. The peak values were present at $T_1$ in 5 (9.8%), $T_2$ in 36 (70.6%) and $T_3$ in 10 (19.6%) patient cohorts, respectively ($\chi^2$=48.9, $P$=0.000):

ΔS100ß displayed a decreasing trend with age, surgical operations (from aorta, valve, congenital, CABG to OPCAB), shortening of CPB duration, increasing core temperature, lessening severity of cerebral damage and the application of intervenes. Significant differences were present in age, surgical operation, core temperature and cerebral damage subgroups (Figure 6).

Linear correlation analysis did not reveal any significant correlation between serum S100 concentration at $T_2$ and CPB, crossclamp time and core temperature (Figure 7). However, serum S100ß concentration at $T_2$ correlated closely with CPB duration (Figure 8).

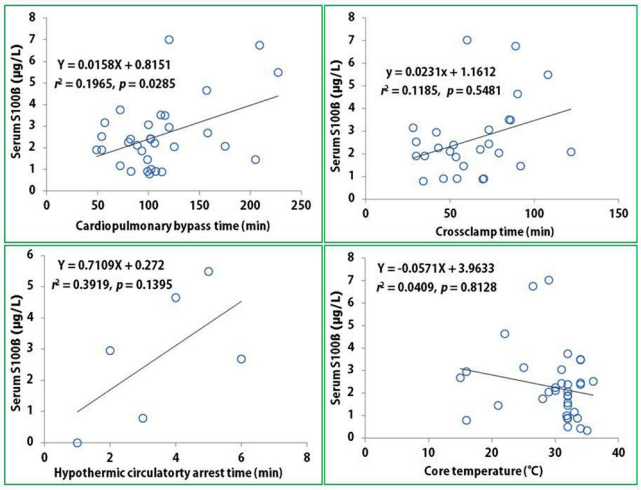


*Fig. 8 - Linear correlation analysis showed serum S100ß concentration at $T_2$ correlated closely with cardiopulmonary bypass duration.*

## DISCUSSION

Detectable concentrations of S100 were found 20 min after CPB[13]. On the operative day, CSF S100 levels increased with time for patients with spinal cord injury; whereas there was a non-specific increase of serum S100. In patients with spinal cord injury, CSF S100 was increased at 6 h after crossclamp removal[74].

Serum S100 reached the peak values at the end of CPB and decreased on postoperative day (POD) 1[11]. At the end of the operation, S100 decreased rapidly and progressively but remained significantly higher on POD 2[12]. S100 peaked 20 min after the start of CPB, being significantly higher than the baseline value[12] . Serum S100ß increased during CPB, peaked at the late phase of CPB[78], recovered to normal at 36 h after the operation[8] untill POD 6[32]. S100ß significantly increased 24 h after total circulatory arrest[79].

In studies showing a correlation between neurological deficit and elevated S100ß protein level after ischemic cerebral infarction, the blood level of S100ß protein consistently peaked on day 2 to 3 after the clinical event[80-82].

The release of S100ß from adipose tissue with surgery would be more extensive with more complex and longer operations. These patients are at a higher risk of cerebral damage and this confounding effect may explain the correlations between early rise in S100ß and neurological injury. In stroke, an elevation of S100ß correlates with the amount of the damaged brain tissue. Poor neurological outcome is related to S100ß levels. The peak levels of S100ß occur on day 3 following the stroke[83]. S100ß as an indicator of cerebral injury, however, is uncertain how autotransfusion of S100ß from extracerebral sources is like. There is good evidence to show that autologous blood recorery through cardiotomy suckers results in significantly higher serum levels of S100ß[84].

Some authors have determined that shed mediastinal blood collected during surgery by cardiotomy suction contained high levels of S100ß as well as chest tube blood used for autotransfusion after surgery. Therefore, early elevated serum S100ß levels immediately after cardiac operations may have been contaminated by extracerebral sources of S100ß[33]. Comparing the patients with retrograde cerebral perfusion with non-retrograde cerebral perfusion groups, the mean serum S100ß levels are 0.09 and 0.09 mg/L, preoperatively, 3.8 and 4.2 mg/L 30 minutes after CPB, and 0.82 and 0.53 mg/L on POD 1[52]. S100ß levels early after CPB are increased because of release from adipose tissue or thymus into cardiotomy suction. This masks neurally released S100ß. High levels of S100ß have been found in pleural drainage following thoracotomy, and in surgical wounds, mediastinal fat and skeletal muscle[85]. Neonates and infants had reduced S100ß at 24 h after surgery than before surgery. However, this finding may reflect dilution of the protein in serum from postoperative blood, colloid and crystalloid infusions in small babies[36]. The increases of S100ß in the early phase after cardiac surgery are not due to release of S100ß from brain alone but also from tissue outside the brain[86]. Therefore, S100ß protein is a nonspecific marker of tissue injury as glial fibrillary acidic protein might serve as a specific marker of cerebral damage after cardiac surgery[86]. Cerebral damage following cardiac surgery cannot be differentiated from cardiac or other tissue damage by measurement of S100ß levels until the initial elevation of S100ß due to non-brain tissue damage has declined, which does not occur for at least 24 h after surgery[86].

It has been reported that S100 correlated significantly with age, body surface area, nasopharyngeal temperature and $PaCO_2$ in infants and children[14]. However, it could be the result of dilution of the protein in serum from infusions of fluid and blood products[36]. Both older age and prolonged CPB duration correlated with levels of S100 protein at $T_0$, but the correlation was weak for both variables[19]. Serum S100 values at the end of CPB and POD 1 significantly correlated with CPB time[11]. The duration of absent cerebral perfusion time (duration of circulatory arrest minus retrograde cerebral perfusion) correlated well with S100 on POD 1[11].

In adults, S100 on POD 1 correlated with duration of circulatory arrest[11], and peak S100ß correlated with CPB time[32]. S100ß on POD 1 correlated with duration of absent cerebral perfusion time[11]. S100ß concentration at 5 h and 24 h correlated significantly with the duration of total circulatory arrest[35] and S100ß at 5 h negatively correlated with core temperature[35]. S100ß also correlated with the total embolus count at the arterial line[78], CPB time[57] and intubation duration[30]. In roller pump group, peak S100ß correlated with crossclamp time[34]. Ashraf et al.[34] reported S100ß did not correlate with duration of CPB time. Johnsson[87] reported no relationship between serum S100ß at 24 h after surgery and CPB duration, crossclamp time, or use of hypothermic circulatory arrest, and it did not correlate with 30-day surgical mortality.

Pulsatile flow lowers cerebral destruction than laminar flow[50]. S100 was nonsignificantly higher in cold than in warm CPB patients[63].The S100ß rise was significantly less in patients administered sevoflurane in comparison to total intravenous anesthesia[64]. CPB with covalent bonded heparin attached to the CPB circuit in combination with a reduced systemic heparin dose seemed to reduce the operative stroke[88].

The S100 level was elevated at the end of operation but returned toward normal at 5 h. A secondary increase in S100 protein level coincided with the clinical presentation of stroke on the day after the operation[27]. The peak values of S100ß were higher in died patients than in the survived[10]. Taggart et al.[27] reported 21 of 43 patients had an elevated serum S100ß value 4 h after the operation and none of the patients had neurological symptoms, and S100ß reached a peak value on PODs 2-3 in stroke patients[10]. Patient with cerebral infarction showed slightly increased S100ß during operation but decreased to normal concentration on POD 1. In patients with temporary left-side hemiplegia lasting 24 h after the operation, S100ß protein increased and reached its peak after aortic crossclamp removal, but decreased to a normal concentration on POD 1 while still hemiplegic. In patients with a conscious disturbance lasting 24 h, S100ß level was indistinguishable from the patients without neurological complications. There was a weak but significant correlation between peak concentrations of S100ß protein and aortic crossclamp time in the CPB group[47]. The patient with the highest S100 values at the end of CPB and on POD 1 presented postoperative stroke[11]. Permanent cerebral damage was associated with much higher serum S100 than transient[89]. However, the appropriate time to measure S100ß after CABG for prognostic value has not been established but is probably 5 h after surgery[24].

In the hypothermic circulatory arrest group, CPB time correlated with peak S100. Peak S100ß levels occurred in both the CABG and hypothermia circulatory arrest groups at the end of CPB. After 24 h, the S100ß levels returned to normal in the CABG patients but were still elevated in all cases in the hypothermia circulatory arrest group. CPB patients may face major treatment-related cognitive performance decline. Persistently high levels of neuron-specific enolase might be a useful biomarker to identify patients with cognitive performance deficits at discharge; while no significant correlation between S100ß levels and impaired cognitive function have been found[90]. High-dose propofol triggered short-term neuroprotection and long-term neurodegeneration in neuronal cultures from rat embryos[91]. A high dose of propofol (with plasma concentrations of 3.2 mg/mL) may offer advantages over a low dose of propofol (with plasma concentrations of 1.8 mg/mL) for brain protection during CPB[53]. Previous studies have shown that OPCAB is better than conventional CABG by decreasing the release of S100ß protein. Consequently, the pattern of S100ß release at different stages of OPCAB procedures has become a valuable indicator of the early detection of neuronal clinical and subclinical injury[36,92].

The present study revealed that CSF and serum S100 and S100ß began to increase during CPB, peaked at the end of CPB for each indicator. However, CSF 100 showed a second peak at $T_7$, and CSF S100ß continued to be high until $T_4$ and then gradually reduced. The results may indicate that S100 and S100ß concentrations in the CSF are more sensitive than in the serum for indicating cerebral damage during cardiac surgery. CSF/serum S100 and S100ß ratios may reflect the cerebral damage more accurately with a CSF-serum separation showing a sustained S100(ß) release from the damaged brain tissues. The separation trends displayed from $T_5$ for S100, and between $T_2$ and $T_7$ for S100ß, respectively. This may hint that physiological and hemodynamic properties of the two proteins can be different and therefore showing distinct metabolic features after cardiac surgery. Intra-subgroup comparisons of serum S100(ß) at $T_3$ and $T_7$ showed younger age, OPCAB, normothermia and positive intervene and even shorter CPB duration may reduce significantly the release of S100 and S100ß. Serum ΔS100 and ΔS100ß may also illustrate the severity of the cerebral damage during the operation. ΔS100, the difference between peak S100 and baseline S100, was reported to be 0.88 (0.48-3.23) in overall, 0.29 (0.18-0.44) in neonates and 1.1 (0.48-3.23) in infants[14]. In line with the results of serum S100(ß) at $T_3$ and $T_7$, the study showed discrepancy of ΔS100 between aorta and congenital heart defect operations as well as extensive discrepancies of ΔS100ß within age, operation, core temperature and cerebral damage subgroups. Despite the possible influence by the blood recovery transfusion, the indicators may still reflect the cerebral damage during cardiac surgery. In general, the release of S100 and S100ß may correlate with age, operative method, CPB duration, core temperature and the application of intervenes during the operation. CSF S100(ß) may be more reliable than serum S100(ß), however, too aggressive drainage of CSF carries the risk of cerebral hernia and subdural hemorrhage[93].

## CONCLUSION

S100 and S100ß in CSF can be more accurate than in the serum for the evaluations of cerebral damage in cardiac surgery.

However, CSF biopsies are limited. But serum S100ß and ΔS100ß seems to be more sensitive than serum S100 and ΔS100. The cerebral damage in cardiac surgery might be associated with younger age, lower core temperature and longer CPB duration during the operation. Effective intervenes with modified CPB circuit filters or oxygenators and supplemented anesthetic agents or priming components may alleviate the cerebral damage.

| **Authors' roles & responsibilities** | |
|---|---|
| SMY | Main Author |

REFERENCES

1. Carvalho SB. Structural and conformational effects of metal binding to the S100B cytokine. Tese orientada por Doutor Cláudio M. Gomes (ITQB-UNL) e Doutora Ana A. Coutinho (FC-UL) Mestrado em Bioquímica. 2011. Available from: http://repositorio.ul.pt/bitstream/10451/8475/1/ulfc103891_tm_Sofia_Carvalho.pdf

2. Liriano MA. Structure, dynamics and function of S100B and S100A5 complexes. ProQuest® Dissertations & Theses. Available from: http://gradworks.umi.com/35/26/3526916.html

3. Rezvanpour A, Shaw GS. Unique S100 target protein interactions. Gen Physiol Biophys. 2009;28 Spec No Focus:F39-46.

4. Raabe A, Seifert V. Fatal secondary increase in serum S-100B protein after severe head injury. Report of three cases. J Neurosurg. 1999;91(5):875-7.

5. Cata JP, Abdelmalak B, Farag E. Neurological biomarkers in the perioperative period. Br J Anaesth. 2011;107(6):844-58.

6. Murkin JM. Etiology and incidence of brain dysfunction after cardiac surgery. J Cardiothorac Vasc Anesth. 1999;13(4 Suppl 1):12-7.

7. Einav S, Shoshan Y, Ovadia H, Matot I, Hersch M, Itshayek E. Early postoperative serum S100 beta levels predict ongoing brain damage after meningioma surgery: a prospective observational study. Crit Care. 2006;10(5):R141.

8. Schmidt M, Scheunert T, Steinbach G, Schirmer U, Marx T, Freitag N, et al. Hypertension as a risk factor for cerebral injury during cardiopulmonary bypass. Protein S100B and transcranial Doppler findings. Anaesthesia. 2001;56(8):733-8.

9. Bonacchi M, Prifti E, Maiani M, Bartolozzi F, Di Eusanio M, Leacche M. Does off-pump coronary revascularization reduce the release of the cerebral markers, S-100beta and NSE? Heart Lung Circ. 2006;15(5):314-9.

10. Georgiadis D, Berger A, Kowatschev E, Lautenschläger C, Börner A, Lindner A, et al. Predictive value of S-100beta and neuron-specific enolase serum levels for adverse neurologic outcome after cardiac surgery. J Thorac Cardiovasc Surg. 2000;119(1):138-47.

11. Astudillo R, Van der Linden J, Radegran K, Hansson LO, Aberg B. Elevated serum levels of S-100 after deep hypothermic arrest correlate with duration of circulatory arrest. Eur J Cardiothorac Surg. 1996;10(12):1107-12.

12. Basile AM, Fusi C, Conti AA, Paniccia R, Trefoloni G, Pracucci G, et al. S-100 protein and neuron-specific enolase as markers of subclinical cerebral damage after cardiac surgery: preliminary observation of a 6-month follow-up study. Eur Neurol 2001;45(3):151-9.

13. Blomquist S, Johnsson P, Lührs C, Malmkvist G, Solem JO, Alling C, et al. The appearance of S-100 protein in serum during and immediately after cardiopulmonary bypass surgery: a possible marker for cerebral injury. J Cardiothorac Vasc Anesth. 1997;11(6):699-703.

14. Camci E, Tuğrul M, Korkut K, Tireli E. Blood S-100 protein concentration in children undergoing cardiac surgery. J Cardiothorac Vasc Anesth. 2001;15(1):29-34.

15. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M. Attempting to maintain normoglycemia during cardiopulmonary bypass with insulin may initiate postoperative hypoglycemia. Anesth Analg. 1999;89(5):1091-5.

16. Dar MI, Gillott T, Ciulli F, Cooper GJ. Single aortic cross-clamp technique reduces S-100 release after coronary artery surgery. Ann Thorac Surg. 2001;71(3):794-6.

17. Gao F, Harris DN, Sapsed-Byrne S. Time course of neurone-specific enolase and S-100 protein release during and after coronary artery bypass grafting. Br J Anaesth. 1999;82(2):266-7.

18. Jensen E, Sandström K, Andréasson S, Nilsson K, Berggren H, Larsson LE. Increased levels of S-100 protein after cardiac surgery with cardiopulmonary bypass and general surgery in children. Paediatr Anaesth. 2000;10(3):297-302.

19. Johnsson P, Lundqvist C, Lindgren A, Ferencz I, Alling C, Ståhl E. Cerebral complications after cardiac surgery assessed by S-100 and NSE levels in blood. J Cardiothorac Vasc Anesth. 1995;9(6):694-9.

20. Jönsson H, Johnsson P, Alling C, Westaby S, Blomquist S. Significance of serum S100 release after coronary artery bypass grafting. Ann Thorac Surg. 1998;65(6):1639-44.

21. Lloyd CT, Ascione R, Underwood MJ, Gardner F, Black A, Angelini GD. Serum S-100 protein release and neuropsychologic outcome during coronary revascularization on the beating heart: a prospective randomized study. J Thorac Cardiovasc Surg. 2000;119(1):148-54.

22. Matheis G, Abdel-Rahman U, Braun S, Wimmer-Greinecker G, Esmaili A, Seitz U, et al. Uncontrolled reoxygenation by initiating

cardiopulmonary bypass is associated with higher protein S100 in cyanotic versus acyanotic patients. Thorac Cardiovasc Surg. 2000;48(5):263-8.

23. Mazzei V, Nasso G, Salamone G, Castorino F, Tommasini A, Anselmi A. Prospective randomized comparison of coronary bypass grafting with minimal extracorporeal circulation system (MECC) versus off-pump coronary surgery. Circulation. 2007;116(16):1761-7.

24. Rasmussen LS, Christiansen M, Hansen PB, Moller JT. Do blood levels of neuron-specific enolase and S-100 protein reflect cognitive dysfunction after coronary artery bypass? Acta Anaesthesiol Scand. 1999;43(5):495-500.

25. Svenmarker S, Sandström E, Karlsson T, Häggmark S, Jansson E, Appelblad M, et al. Neurological and general outcome in low-risk coronary artery bypass patients using heparin coated circuits. Eur J Cardiothorac Surg. 2001;19(1):47-53.

26. Svenmarker S, Sandström E, Karlsson T, Jansson E, Häggmark S, Lindholm R, et al. Clinical effects of the heparin coated surface in cardiopulmonary bypass. Eur J Cardiothorac Surg. 1997;11(5):957-64.

27. Taggart DP, Mazel JW, Bhattacharya K, Meston N, Standing SJ, Kay JD, et al. Comparison of serum S-100beta levels during CABG and intracardiac operations. Ann Thorac Surg. 1997;63(2):492-6.

28. Wandschneider W, Thalmann M, Trampitsch E, Ziervogel G, Kobinia G. Off-pump coronary bypass operations significantly reduce S100 release: an indicator for less cerebral damage? Ann Thorac Surg. 2000;70(5):1577-9.

29. Westaby S, Johnsson P, Parry AJ, Blomqvist S, Solem JO, Alling C, et al. Serum S100 protein: a potential marker for cerebral events during cardiopulmonary bypass. Ann Thorac Surg. 1996;61(1):88-92.

30. Westaby S, Saatvedt K, White S, Katsumata T, van Oeveren W, Bhatnagar NK, et al. Is there a relationship between serum S-100beta protein and neuropsychologic dysfunction after cardiopulmonary bypass? J Thorac Cardiovasc Surg. 2000;119(1):132-7.

31. Abdul-Khaliq H, Schubert S, Fischer T, Böttcher W, Harke C, Alexi-Meskishvili V, et al. The effect of continuous treatment with sodium nitroprusside on the serum kinetics of the brain marker protein S-100beta in neonates undergoing corrective cardiac surgery by means of hypothermic cardiopulmonary bypass. Clin Chem Lab Med. 2000;38(11):1173-5.

32. Anderson RE, Hansson LO, Vaage J. Release of S100B during coronary artery bypass grafting is reduced by off-pump surgery. Ann Thorac Surg. 1999;67(6):1721-5.

33. Anderson RE, Hansson LO, Liska J, Settergren G, Vaage J. The effect of cardiotomy suction on the brain injury marker S100beta after cardiopulmonary bypass. Ann Thorac Surg. 2000;69(3):847-50.

34. Ashraf S, Bhattacharya K, Zacharias S, Kaul P, Kay PH, Watterson KG. Serum S100beta release after coronary artery bypass grafting: roller versus centrifugal pump. Ann Thorac Surg. 1998;66(6):1958-62.

35. Bhattacharya K, Westaby S, Pillai R, Standing SJ, Johnsson P, Taggart DP. Serum S100B and hypothermic circulatory arrest in adults. Ann Thorac Surg. 1999;68(4):1225-9.

36. Bokesch PM, Appachi E, Cavaglia M, Mossad E, Mee RB. A glial-derived protein, S100B, in neonates and infants with congenital heart disease: evidence for preexisting neurologic injury. Anesth Analg. 2002;95(4):889-92.

37. Carrier M, Denault A, Lavoie J, Perrault LP. Randomized controlled trial of pericardial blood processing with a cell-saving device on neurologic markers in elderly patients undergoing coronary artery bypass graft surgery. Ann Thorac Surg. 2006;82(1):51-5.

38. de Baar M, Diephuis JC, Moons KG, Holtkamp J, Hijman R, Kalkman CJ. The effect of zero-balanced ultrafiltration during cardiopulmonary bypass on S100b release and cognitive function. Perfusion. 2003;18(1):9-14.

39. Diegeler A, Hirsch R, Schneider F, Schilling LO, Falk V, Rauch T, et al. Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. Ann Thorac Surg. 2000;69(4):1162-6.

40. Dworschak M, Franz M, Czerny M, Gorlitzer M, Blaschek M, Grubhofer G, et al. Release of neuron-specific enolase and S100 after implantation of cardioverters/defibrillators. Crit Care Med. 2003;31(8):2085-9.

41. Flom-Halvorsen HI, Ovrum E, Brosstad F, Tangen G, Ringdal M, Oystese R. Effects of two differently heparin-coated extracorporeal circuits on markers for brain and myocardial dysfunction. Perfusion. 2002;17(5):339-45.

42. Gazzolo D, Masetti P, Kornacka M, Abella R, Bruschettini P, Michetti F. Phentolamine administration increases blood S100B protein levels in pediatric open-heart surgery patients. Acta Paediatr. 2003;92(12):1427-32.

43. Grocott HP, Croughwell ND, Amory DW, White WD, Kirchner JL, Newman MF. Cerebral emboli and serum S100 beta during cardiac operations. Ann Thorac Surg. 1998;65(6):1645-9.

44. Groom RC, Quinn RD, Lennon P, Welch J, Kramer RS, Ross CS, et al; Northern New England Cardiovascular Disease Study Group. Microemboli from cardiopulmonary bypass are associated with a serum marker of brain injury. J Extra Corpor Technol. 2010;42(1):40-4.

45. Ilcol YO, Basagan-Mogol E, Cengiz M, Ulus IH. Elevation of serum cerebral injury markers correlates with serum choline decline after coronary artery bypass grafting surgery. Clin Chem Lab Med. 2006;44(4):471-8.

46. Iriz E, Kolbakir F, Akar H, Adam B, Keceligil HT. Comparison of hydroxyethyl starch and ringer lactate as a prime solution regarding S-100 beta protein levels and informative cognitive tests in cerebral injury. Ann Thorac Surg. 2005;79(2):666-71.

47. Ishida K, Gohara T, Kawata R, Ohtake K, Morimoto Y, Sakabe T. Are serum S100 beta proteins and neuron-specific enolase predictors of cerebral damage in cardiovascular surgery? J Cardiothorac Vasc Anesth. 2003;17(1):4-9.

48. Jönsson H, Johnsson P, Birch-Iensen M, Alling C, Westaby S, Blomquist S. S100B as a predictor of size and outcome of stroke after cardiac surgery. Ann Thorac Surg. 2001;71(5):1433-7.

49. Krnjak L, Trunk P, Gersak B, Osredkar J. Correlation of serum S100B concentration with hospital stay in patients undergoing CABG. Acta Clin Croat. 2008;47(4):221-6.

50. Kusch B, Vogt S, Sirat AS, Helwig-Rohlig A, Kasseckert S, Moosdorf R. Serum S-100 beta protein release in coronary artery bypass grafting: laminar versus pulsatile flow. Thorac Cardiovasc Surg. 2001;49(3):179-83.

51. Lardner D, Davidson A, McKenzie I, Cochrane A. Delayed rises in serum S100B levels and adverse neurological outcome in infants and children undergoing cardiopulmonary bypass. Paediatr Anaesth. 2004;14(6):495-500.

52. LeMaire SA, Bhama JK, Schmittling ZC, Oberwalder PJ, Köksoy C, Raskin SA, et al. S100 beta correlates with neurologic complications after aortic operation using circulatory arrest. Ann Thorac Surg. 2001;71(6):1913-8.

53. Ma G, Chen J, Meng X, Deng L, Gao Y, Meng J. High-dose propofol reduces S-100ß protein and neuron-specific enolase levels in patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth. 2013;27(3):510-5.

54. Snyder-Ramos SA, Gruhlke T, Bauer H, Bauer M, Luntz AP, Motsch J, et al. Cerebral and extracerebral release of protein S100B in cardiac surgical patients. Anaesthesia. 2004;59(4):344-9.

55. Motallebzadeh R, Kanagasabay R, Bland M, Kaski JC, Jahangiri M. S100 protein and its relation to cerebral microemboli in on-pump and off-pump coronary artery bypass surgery. Eur J Cardiothorac Surg. 2004;25(3):409-14.

56. Rasmussen LS, Christiansen M, Eliasen K, Sander-Jensen K, Moller JT. Biochemical markers for brain damage after cardiac surgery: time profile and correlation with cognitive dysfunction. Acta Anaesthesiol Scand. 2002;46(5):547-51.

57. Rasmussen LS, Sztuk F, Christiansen M, Elliott MJ. Normothermic versus hypothermic cardiopulmonary bypass during repair of congenital heart disease. J Cardiothorac Vasc Anesth. 2001;15(5):563-6.

58. Reinsfelt B, Westerlind A, Ioanes D, Zetterberg H, Fredén-Lindqvist J, Ricksten SE. Transcranial Doppler microembolic signals and serum marker evidence of brain injury during transcatheter aortic valve implantation. Acta Anaesthesiol Scand. 2012;56(2):240-7.

59. Robson MJ, Alston RP, Deary IJ, Andrews PJ, Souter MJ. Jugular bulb oxyhemoglobin desaturation, S100 beta, and neurologic and cognitive outcomes after coronary artery surgery. Anesth Analg. 2001;93(4):839-45.

60. Schoenburg M, Kraus B, Muehling A, Taborski U, Hofmann H, Erhardt G, et al. The dynamic air bubble trap reduces cerebral microembolism during cardiopulmonary bypass. J Thorac Cardiovasc Surg. 2003;126(5):1455-60.

61. Scholz M, Wimmer-Greinecker G, Kleine P, Dzemali O, Martens S, Moritz A, et al. Cariporide (HOE642) limits S-100B release during cardiac surgery. J Cardiovasc Pharmacol. 2003;41(3):468-73.

62. Shaaban-Ali M, Harmer M, Vaughan RS, Dunne JA, Latto IP, Haaverstad R, et al. Changes in serum S100 beta protein and Mini-Mental State Examination after cold (28 degrees C) and warm (34 degrees C) cardiopulmonary bypass using different blood gas strategies (alpha-stat and pH-stat). Acta Anaesthesiol Scand. 2002;46(1):10-6.

63. Shaaban Ali M, Harmer M, Elliott M, Thomas AL, Kirkham F. A pilot study of evaluation of cerebral function by S100 beta protein and near-infrared spectroscopy during cold and warm cardiopulmonary bypass in infants and children undergoing open-heart surgery. Anaesthesia. 2004;59(1):20-6.

64. Singh SP, Kapoor PM, Chowdhury U, Kiran U. Comparison of S100ß levels, and their correlation with hemodynamic indices in patients undergoing coronary artery bypass grafting with three different anesthetic techniques. Ann Card Anaesth. 2011;14(3):197-202.

65. Janigro D. A response to 'Cerebral and extracerebral release of protein S100B in cardiac surgical patients', Snyder-Ramos SA, Gruhlke T, Bauer H, Bauer M, Luntz AP, Motsch J, Martin E, Vahl CF, Missler U, Wiesmann M and Bottiger BW, Anaesthesia. 2004;59:344-9. Anaesthesia. 2004;59(11):1149-50.

66. Svenmarker S, Engström KG, Karlsson T, Jansson E, Lindholm R, Aberg T. Influence of pericardial suction blood retransfusion on memory function and release of protein S100B. Perfusion. 2004;19(6):337-43.

67. Svenmarker S, Sandström E, Karlsson T, Aberg T. Is there an association between release of protein S100B during cardiopulmonary bypass and memory disturbances? Scand Cardiovasc J. 2002;36(2):117-22.

68. Takayama H, Soltow LO, Chandler WL, Vocelka CR, Aldea GS. Does the type of surgery effect systemic response following cardiopulmonary bypass? J Card Surg. 2007;22(4):307-13.

69. Tamura A, Imamaki M, Shimura H, Niitsuma Y, Miyazaki M. Release of serum S-100 beta protein and neuron-specific enolase after off-pump coronary artery bypass grafting with and without

intracranial and cervical artery stenosis. Ann Thorac Cardiovasc Surg. 2011;17(1):33-8.

70. Ueno T, Iguro Y, Yamamoto H, Sakata R, Kakihana Y, Nakamura K. Serial measurement of serum S-100B protein as a marker of cerebral damage after cardiac surgery. Ann Thorac Surg. 2003;75(6):1892-7.

71. Wimmer-Greinecker G, Matheis G, Brieden M, Dietrich M, Oremek G, Westphal K, et al. Neuropsychological changes after cardiopulmonary bypass for coronary artery bypass grafting. Thorac Cardiovasc Surg. 1998;46(4):207-12.

72. Wimmer-Greinecker G, Matheis G, Martens S, Oremek G, Abdel-Rahman U, Moritz A. Synthetic protein treated versus heparin coated cardiopulmonary bypass surfaces: similar clinical results and minor biochemical differences. Eur J Cardiothorac Surg. 1999;16(2):211-7.

73. Wong CH, Rooney SJ, Bonser RS. S-100 beta release in hypothermic circulatory arrest and coronary artery surgery. Ann Thorac Surg. 1999;67(6):1911-4.

74. Khaladj N, Teebken OE, Hagl C, Wilhelmi MH, Tschan C, Weissenborn K, et al. The role of cerebrospinal fluid S100 and lactate to predict clinically evident spinal cord ischaemia in thoraco-abdominal aortic surgery. Eur J Vasc Endovasc Surg. 2008;36(1):11-9.

75. van Dongen EP, Ter Beek HT, Boezeman EH, Schepens MA, Langemeijer HJ, Aarts LP. Normal serum concentrations of S-100 protein and changes in cerebrospinal fluid concentrations of S-100 protein during and after thoracoabdominal aortic aneurysm surgery: is S-100 protein a biochemical marker of clinical value in detecting spinal cord ischemia? J Vasc Surg. 1998;27(2):344-6.

76. Kunihara T, Shiiya N, Yasuda K. Changes in S100beta protein levels in cerebrospinal fluid after thoracoabdominal aortic operations. J Thorac Cardiovasc Surg. 2001;122(5):1019-20.

77. Shiiya N, Kunihara T, Miyatake T, Matsuzaki K, Yasuda K. Tau protein in the cerebrospinal fluid is a marker of brain injury after aortic surgery. Ann Thorac Surg. 2004;77(6):2034-8.

78. Ashraf S, Bhattacharya K, Tian Y, Watterson K. Cytokine and S100B levels in paediatric patients undergoing corrective cardiac surgery with or without total circulatory arrest. Eur J Cardiothorac Surg. 1999;16(1):32-7.

79. Büttner T, Weyers S, Postert T, Sprengelmeyer R, Kuhn W. S-100 protein: serum marker of focal brain damage after ischemic territorial MCA infarction. Stroke. 1997;28(10):1961-5.

80. Fassbender K, Schmidt R, Schreiner A, Fatar M, Mühlhauser F, Daffertshofer M, et al. Leakage of brain-originated proteins in peripheral blood: temporal profile and diagnostic value in early ischemic stroke. J Neurol Sci. 1997;148(1):101-5.

81. Missler U, Wiesmann M, Friedrich C, Kaps M. S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. Stroke. 1997;28(10):1956-60.

82. Ali MS, Harmer M, Vaughan R. Serum S100 protein as a marker of cerebral damage during cardiac surgery. Br J Anaesth. 2000;85(2):287-98.

83. Motallebzadeh R, Jahangiri M. The effect of the dynamic air bubble trap on cerebral microemboli and S100 beta. J Thorac Cardiovasc Surg. 2004;128(1):154.

84. Vaage J, Anderson R. Biochemical markers of neurologic injury in cardiac surgery: the rise and fall of S100 beta. J Thorac Cardiovasc Surg. 2001;122(5):853-5.

85. Missler U, Orlowski N, Nötzold A, Dibbelt L, Steinmeier E, Wiesmann M. Early elevation of S-100B protein in blood after cardiac surgery is not a predictor of ischemic cerebral injury. Clin Chim Acta. 2002;321(1-2):29-33.

86. Babin-Ebell J, Misoph M, Müllges W, Neukam K, Reese J, Elert O. Intraoperative embolus formation during cardiopulmonary bypass affects the release of S100B. Thorac Cardiovasc Surg. 1999;47(3):166-9.

87. Johnsson P. S100-B in blood: a marker of brain damage or simply a covariate? Scand Cardiovasc J. 2000;34(6):548-9.

88. Svenmarker S, Sandström E, Karlsson T, Jansson E, Häggmark S, Lindholm R, et al. Clinical effects of the heparin coated surface in cardiopulmonary bypass. Eur J Cardiothorac Surg. 1997;11(5):957-64.

89. Oki A, Ohtake H, Okada Y, Kawada T, Takaba T. Simultaneous monitoring of somatosensory evoked potentials and regional cerebral oxygen saturation combined with serial measurement of plasma levels of cerebral specific proteins for the early diagnosis of postoperative brain damage in cardiovascular surgery. J Artif Organs. 2004;7(1):13-8.

90. Baranyi A, Rothenhäusler HB. The impact of S100b and persistent high levels of neuron-specific enolase on cognitive performance in elderly patients after cardiopulmonary bypass. Brain Int. 2013;27(4):417-24.

91. Berns M, Seeberg L, Schmidt M, Kerner T. High-dose propofol triggers short-term neuroprotection and long-term neurodegeneration in primary neuronal cultures from rat embryos. J Int Med Res. 2009;37(3):680-8.

92. Wang KJ, Wu HH, Fang SY, Yang YR, Tseng AC. Serum S-100 beta protein during coronary artery bypass graft surgery with or without cardiopulmonary bypass. Ann Thorac Surg. 2005;80(4):1371-4.

93. Weaver KD, Wiseman DB, Farber M, Ewend MG, Marston W, Keagy BA. Complications of lumbar drainage after thoracoabdominal aortic aneurysm repair. J Vasc Surg. 2001;34(4):623-7.