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Volatile anaesthetics reduce serum S100 β concentrations in patients undergoing elective cardiac surgery

Wojciech Dabrowski¹, Ziemowit Rzecki¹, Jaroslaw Wosko¹,
Jadwiga Biernacka¹, Edyta Kotlinska¹, Marek Czajkowski²

¹Department of Anaesthesiology, Intensive Therapy, Medical University of Lublin, Poland;

²Department of Cardiac Surgery, Medical University of Lublin, Poland

Abstract

Background: The effect of volatile anaesthetics on plasma S100 β protein has not been well-documented in cardiac surgery patients. The aim of the study was to analyse the effect of sevoflurane or isoflurane anaesthesia on plasma S100 β concentration in patients undergoing elective, uncomplicated coronary artery bypass graft surgery.

Methods: One hundred thirty seven patients were prospectively randomized and allocated into three groups: A – patients, who didn't receive volatile anaesthetics, B – who received sevoflurane and C – who received isoflurane. S100 β was measured during anaesthesia and postoperative days 1 and 2.

Results: In all patients, S100 β increased during anaesthesia and at the postoperative day 1 and 2. In group A, S100 β increased during anaesthesia and postoperative days 1 and 2 but in groups B and C only during anaesthesia. Plasma S100 β concentrations were significantly higher in group A than in group B and C.

Conclusions: 1) cardiac surgery resulted in S100 β elevation, 2) isoflurane and sevoflurane significantly reduced plasma S100 β concentrations.

Key words: extracorporeal circulation, CABG, S100 β , sevoflurane, isoflurane

List of abbreviations

BMI	body mass index
BSA	body surface area
CABG	coronary artery bypass grafting
ECC	extracorporeal circulation
ISO	isoflurane (Isoflurane, Baxter, USA)
PICU	Postoperative Intensive Care Unit
SEV	sevoflurane (Sevorane, ABBOTT, GB)
TP	time point

Neuropsychological disorders can arise in patients who have undergone cardiopulmonary bypass graft surgery (CABG). Different forms of neuropsychological disorders occur in 50 - 80% of patients after extracorporeal circulation (ECC) and persist longer than six months in 20 - 30% of these patients [1]. An early diagnosis of neuropsychological disorders is difficult and mainly based on S100 β measurements.

S100 β protein is a sensitive marker of brain injury, particularly brain ischaemia. S100 β is an acidic binding protein present in glial and Schwann cells. It plays a crucial role

in many intracellular functions, such as cell energy modulation, cell growth, intracellular calcium homeostasis, glial proliferation and neuronal differentiation. Moreover, S100 β controls intracellular signal transduction and intercellular communication. The normal plasma S100 β concentration ranges from 0.02 to 0.2 $\mu\text{g litre}^{-1}$; levels higher than 0.5 $\mu\text{g litre}^{-1}$ are considered pathological [2-4]. An elevation in plasma S100 β concentration results from an increase in blood-brain barrier permeability after ischemia. Several studies have demonstrated the significant role of S100 β elevation in the diagnosis of postoperative central nervous system dysfunction in patients undergoing coronary artery bypass graft surgery (CABG) [3-6]. Notably, various techniques and pharmacological methods of neurological protection have been used during CABG. Some of these have been well-documented, but others remain controversial. The use of volatile anaesthetics is still a subject of clinical and experimental study.

There are many reports documenting the neuroprotective effect of volatile anaesthetics [7-9]. The inhalation of volatile anaesthetics inhibits glutamate release, inhibits calcium/calmodulin-dependent protein kinase II activity, reduces intracellular calcium influx, decreases the sensitivity of apoptosis-inducing proteins and stabilizes cerebral blood flow [8-12]. Importantly, most of the studies describe such neuroprotective effects both before and during general brain ischemia following brain trauma. Only Kanbak and colleagues [7,13] showed the profitable effects of volatile anaesthetics in patients after CABG. They presented that isoflurane anaesthesia reduced plasma S100 β concentrations and improved the neuropsychological disorders in cardiac surgery patients. Nevertheless, they compared the volatile vs. propofol anaesthesia [7], as well as isoflurane vs. sevoflurane or desflurane anaesthesia [13]. Thus, there are no data analyzing the differences in plasma S100 β concentration during sevoflurane (SEV) and isoflurane (ISO) inhalation as opposed to the midazolam-fentanyl anaesthesia. Therefore, the purpose of the present study

was to analyse changes in plasma S100 β concentration during SEV or ISO anaesthesia in patients undergoing elective coronary artery bypass graft surgery with extracorporeal circulation (ECC).

Patients and methods

The study was approved by the Committee of Bioethics of the Medical University of Lublin and informed consent was obtained from all patients. The study was performed in Cardiac Surgery Department of University Hospital of Lublin; Poland from 2006 to 2007. Patients scheduled for elective CABG due to stable angina pectoris were examined. The exclusion criteria included: any neurological disease or history of neurological disorders, head surgery and severe head trauma, jugular artery stenosis, any chronic respiratory disease, serious endocrine diseases, unstable angina pectoris, chronic renal failure and a EuroScore higher than 8. Additionally, patients with complicated post ECC and/or postoperative serious haemodynamic disorders were excluded. The mini-mental status examination (MMSE) and computed tomography were used for diagnosis of neuropsychological disorders.

One day before surgery, all patients received oral lorazepam (Lorafen, Polfa, PI) (2 mg). One hour before the induction of anaesthesia all of them received intramuscular morphine hydrochloride (Morphicum hydrochloricum, Polfa, PI) (0.1 mg/kg body wt) with midazolam (Midanium Polfa, PI) (0.01 mg/kg body wt).

Before the induction of anaesthesia all patients were routinely monitored with electrocardiography (leads II, III, V5, aVF, aVR and eVL), arterial, central venous pressure and pulmonary arterial pressure measurements.

The induction of anaesthesia was performed with fentanyl (Fentanyl, Polfa, PI) (0.01-0.02 mg/kg body wt), midazolam (0.05-0.1 mg/kg body wt) and etomidate (Hypnomidat, Janssen, G) (0.1-0.5 mg/kg). Muscle relaxation was induced by injecting a single

dose (0.08-0.1 mg/kg body wt) of pancuronium (Pavulon, Organon-Teknica, F). After orotracheal intubation, mechanical ventilation with a mixture of air and oxygen (60% and 40%, respectively) was provided. All the patients were ventilated using intermittent positive pressure ventilation (IPPV) with the following ventilation parameters monitored: tidal volume (6 - 7 ml/kg body wt) and respiratory rate (9/min). The parameters were adjusted to achieve normocapnia, controlled by gas analysis. The anaesthesia was maintained throughout the procedure using the midazolam-fentanyl infusion. Moreover, some patients received fractionated doses of inhaled isoflurane (Forane, Baxter, USA) at the dose of 0.5 - 1% vol or sevoflurane (Sevorane, ABBOTT, GB) at the dose of 0.5 - 1% vol. Volatile anaesthetics were used until the onset of ECC and their doses were dependent on the patient's haemodynamic status. The intra-operative hypertension was treated with volatile anaesthetic or anaesthesia deepening. In patients not responding to anaesthesia deepening single intravenous doses of urapidil were used (Ebrantil, Altana, D). Tachycardia was treated with beta blockers. During the volatile anaesthetic administration, hypotension was corrected with single doses of phenylephrine hydrochloride (phenylephrine Baxter, USA).

After the induction of anaesthesia and before surgery, the Swan-Ganz catheter (ARROW, USA) was inserted via the left internal jugular vein. The thermodilution technique with a 10 ml bolus of ice-cold saline was used for cardiac output measurements. In addition, pulmonary and systemic haemodynamic parameters were measured during surgery and the early postoperative period.

Before ECC, heparinum sulfuricum (Heparin, Polfa, Pl) was used at a dose of 3 mg/kg body wt; the activated clotting time was controlled up to 400 s. For ECC, standard cannulation of the ascending aorta and inferior vena cava was performed through the right atrium. During ECC, circulation and ventilation were maintained with the heart-lung machine S III (Stöckert, Germany). The machine

priming fluid consisted of: 1000 ml of Ringer's solution (Ringer, Polfa, Pl), 500 ml of a 6% solution of hydroxyethylated starch (HAES, Fresenius-Kabi, G), 250 ml of 20% mannitol (Mannitol, Fresenius-Kabi, G), 20 ml of sodium hydroxycarbonate (Natrium bicarbonatum, Polfarma Pl) and 75 mg of heparinum sulfuricum. Cardiopulmonary bypass was instituted at a pulsatile flow rate of 2.4l/min/m² of body surface area (BSA). After traditional aortic clamping, myocardial viability was preserved with antegrade hyperkalemic blood cardioplegia. During ECC, mean arterial pressure, haematocrit, gasometric parameters, lactate, sodium and potassium levels were measured. In all cases, the disconnection of the heart-lung machine was uneventful and intra-aortal counterpulsation was not necessary. After the completion of ECC, some patients received an infusion of dopamine hydrochloride (Dopamine, Polfa, Pl) or dobutamine hydrochloride (Dobutrex, Hexal, G) in doses adjusted to their clinical condition (3 - 15 μ g/kg/min or 3 - 9 μ g/kg/min, respectively). The effect of heparin was reversed by an adequate dose of protamine.

After surgery, patients were sent to the Postoperative Intensive Care Unit. All of them were ventilated using synchronized intermittent mandatory ventilation (SIMV) with pressure support. Patients were subsequently evaluated for extubation until the sixth hour after surgery.

After the induction of anaesthesia and until the beginning of ECC, 500 ml of gelatin preparations (Gelafundin Braun, G) were infused. After ECC, none of the patients required intensive fluid therapy. Insufficiency of intravascular fluids in the early postoperative period was supplemented with gelatin preparations or electrolyte fluids (PWE Polfa, Pl and Ringer, Polfa Pl), and haemodynamic and hematologic parameters were monitored.

According to the volatile anaesthetics administered, patients were randomly assigned to three groups by a concealed envelope method: A) patients who did not receive any volatile anaesthetics, B) those receiving isoflu-

rane at a dose of 0.5 – 1% vol., C) those receiving sevoflurane at a dose of 0.5 – 1% vol.

The observations were conducted at 5 time-points (TP): 1) after the induction of anaesthesia and before surgery, 2) 10 minutes after disconnection of the heart-lung machine, 3) after completion of the procedure and before sending the patient to the postoperative intensive care unit (PICU), 4) on the morning of postoperative day 1, 5) on the morning of postoperative day 2. The first time-point measurement was regarded as a baseline value.

Mini-Mental State Examination test was performed one day prior to surgery and on the third postoperative day. According to MMSE, neuropsychological status was defined in points (from 1 to 30). Mini-Mental State Examination test lower than 9 point was considered as serious postoperative neuropsychological disorders, values between 10 and 23 were considered as mean, moderate cognitive disorders, values higher than 24 points were considered as normal. The computer tomography was performed in all cases with any suspicions of severe postoperative neuropsychological pathology.

Blood samples were collected from the radial artery and immediately centrifuged (2500 r/min), and the resulting plasma was frozen at -20°C. Next, the refrozen samples were centrifuged again (50000 r/min). Immunoassay methods were used to measure S100 β . The samples were incubated in microplate wells pre-coated with mouse antibodies for 2 hours (anti-S100 β conjugated with HRP, BSA and 0.5% ProClin). Two monoclonal antibodies were used for β -chain detection (Sangtec® S100 β ELISA, Biokom – DiSorin, Avenue, USA). Samples were washed with wash buffer. Next, the tetramethylbenzidine chromogen was added and the reaction was allowed to proceed for 15 minutes. The enzyme reaction was stopped by the addition of the kit's stop solution, and the absorbance was measured spectrophotometrically at 450 nm. The absorbance was proportional to the concentration of S100 β protein. The lower limit for detection in the assay was 0.01 μ g/l.

Means and standard deviations (SD) were calculated. The incidence of neuropsychological disorders was measured as a percentage of patients affected. Categorical variables were compared using the χ^2 and Fisher exact test, χ^2 with Yates correction were applicable. The Student's unpaired t-test was used for variables with normal distribution. For variables with non-normal distribution the Wilcoxon signed-rank test and the Kruskal-Wallis ANOVA test for initial detection of differences. The Dunnett's multiple comparison post-hoc test and Spearman's rank correlation tests were used for inter-point and inter-group comparisons. Additionally, the Spearman's rank correlation test was used for overall analysis. $P < 0.05$ was considered significant. A preliminary estimate of sample size was based on an expected 10% reduction in plasma S100 β concentration in group B and C. With a type I error of 0.05 and type II error of 0.2, the required sample size was 24 - 28 patients in each group. The dropout rate was estimated at 10%, thus minimum 31 patients should be randomly assigned to group A, B and C, respectively. The sample size was determined by Statistica 9 program software.

Results

One hundred and seventy-three adult patients were examined. Sixty patients were assigned to group A, 59 to group B and 54 to group C. Thirty-six cases were excluded due to serious postoperative haemodynamic disorders or/and postoperative bleeding requiring reoperation (14, 11 and 11 cases in group A, B and C, respectively). Serious postoperative neuropsychological dysfunctions were noted in 17 patients: 9 in group A, 3 in group B and 5 in group C.

Finally, one hundred and thirty-seven consecutive patients (89 male and 48 female) aged 65 ± 6.42 undergoing elective CABG with normovolemic haemodilution were examined. Forty nine patients were in group A, 43 in group B and 45 in group C. The mean duration of anaesthesia was 259 ± 33.55 min.

Table 1: Demographic data

Groups	VALUES	AGE	TIME OF				BMI	BSA	temp.
			ANAESTH	SURGERY	ECC	AC			
All patients	mean	65	259	202	114	60	26.99	1.95	34.39
	SD	6.42	33.55	29	30.78	20.44	3.75	0.19	0.83
A	mean	66	260	200	115	61	26.26	1.92	34.46
	SD	5.86	28.05	20.61	30.08	20.79	3.96	0.19	0.83
B	mean	65	254	201	112	60	26.51	1.93	34.39
	SD	7.26	35.61	33.59	33.23	21.81	3.01	0.16	0.77
C	mean	66	262	207	114	59	28.25	1.99	34.3
	SD	6.32	37.53	30.18	30.11	19.35	3.93	0.2	0.89

(Table 1), similar in all groups. Likewise, the mean durations of surgery, ECC and aorta clamping were 202 ± 29 min., 114 ± 30.78 min., and 60 ± 20.44 min., respectively (Table 1). The highest BMI was in group C; the lowest values were in group A. There were significant differences in BMI between groups A and B ($P < 0.05$) as well as between groups A and C ($P < 0.05$). In eighty cases, the postoperative course was without serious complications, diuresis was within the normal range, and patients were discharged in good general condition. The postoperative neuropsychological disorders were noted in 17 cases (12.41%). In group A such pathologies were noted in 9 cases (18.36%) – the most serious complication – stroke – was noted in five of them. In group B and C the neuropsychological dysfunctions were noted in 3 and 5 cases (6.98% and 11.11%, respectively). There were no significant differences between group A and B ($\chi^2 = 2.62$, $p = 0.1055$, χ^2 with Yates correction = 0.71 for $p = 0.1908$) as well as between group A and C ($\chi^2 = 0.97$, $p = 0.3236$, χ^2 with Yates correction = 0.49 for $p = 0.4857$).

After ECC, none of the patients required aggressive fluid therapy. Twenty-seven patients did not require catecholamine infusions; 19 received dopamine and 91 received dobutamine infusions in doses dependent

upon their clinical status ($5 - 15 \mu\text{g}/\text{mg}$ body wt/min).

Extracorporeal circulation resulted in an increase in plasma S100 β concentration at TP 2, 3, 4 and 5 ($P < 0.001$; $P < 0.001$; $P < 0.001$ and $P < 0.01$; respectively) (Figure 1). In group A, S100 β increased from TP 2 to 5, but in groups B and C, S100 β only at TP 2 and 3 (Table 2). Significantly higher plasma S100 β concentrations were observed in group A compared to groups B and C (Table 2). There were no differences in plasma S100 β concentrations between groups B and C. Nevertheless, the lowest plasma S100 β concentration was observed in group B (Table 2).

Discussion

Our results demonstrated that extracorporeal circulation resulted in an increase in plasma S100 β concentration. The main finding of the present study was that volatile anaesthetics significantly decreased plasma S100 β concentrations in patients after cardiac surgery. SEV strongly reduced S100 β levels in comparison with isoflurane, but the differences were not statistically significant. The use of volatile anaesthetics didn't statistically reduce the occurrence of postoperative neuropsychological disorders, however the most dan-

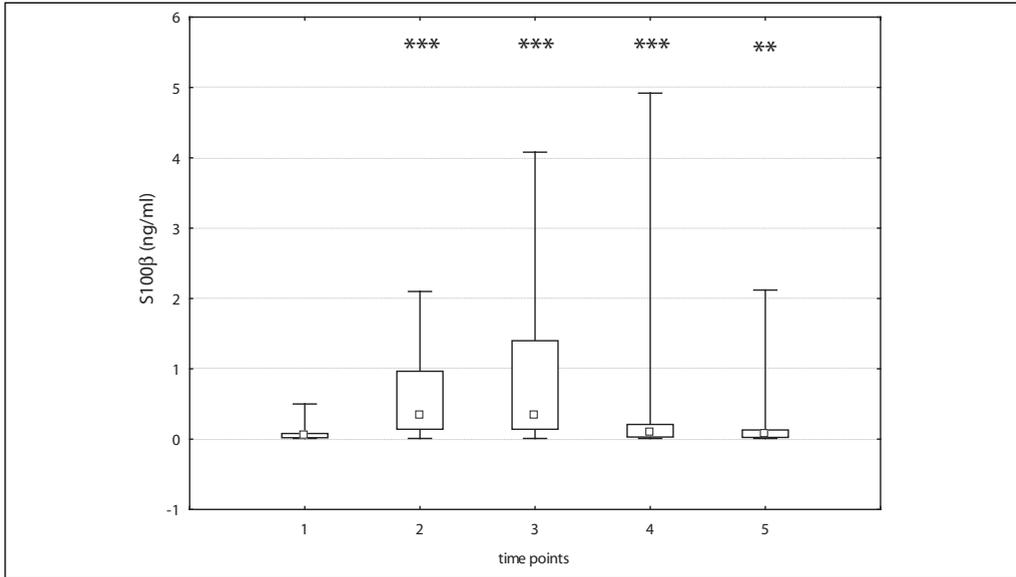


Figure 1: Changes in plasma S100 β concentration in studied patients – the Wilcoxon test. (** $P < 0.01$, *** $P < 0.001$ in comparison with the baseline value, \square Median \square 25% - 75% \square Min. - Max.). TP: 1) after the induction of anaesthesia and before surgery, 2) 10 minutes after disconnection of the heart-lung machine, 3) after completion of the procedure and before sending the patient to the postoperative intensive care unit (PICU), 4) on the morning of postoperative day 1, 5) on the morning of postoperative day 2. The first TP was regarded as a baseline value.

Table 2: Changes in plasma S100 β concentration in group A, B and C (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with baseline value (TP 1); Wilcoxon test) and intergroups differences (Mann-Whitney U-test).

GROUPS	VALUE	TIME-POINTS				
		1	2	3	4	5
Group A	quartile 1	0.03	0.42	0.58	0.09	0.07
	median	0.08	1.16***	0.74***	0.19**	0.14**
	quartile 3	0.1	1.45	2.69	0.48	0.3
Group B	quartile 1	0.02	0.12	0.14	0.02	0.01
	median	0.05	0.28***	0.18***	0.06	0.06
	quartile 3	0.07	0.45	0.50	0.10	0.09
Group C	quartile 1	0.02	0.09	0.08	0.02	0.01
	median	0.04	0.16***	0.19***	0.04	0.04
	quartile 3	0.07	0.56	0.9	0.16	0.09
<i>DIFFERENCES BETWEEN GROUPS A, B AND C AT CONSECUTIVE TIME-POINTS</i>						
group A : group B	P = 0.0768	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001
group A : group C	P = 0.0917	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001
group B : group C	P = 0.7770	P = 0.4490	P = 0.4191	P = 0.8891	P = 0.7706	P = 0.7706

gerous neurological complication – stroke was only noted in patients, who didn't receive SEV or ISO anaesthesia.

Changes in plasma S100 β protein levels have been well-documented in patients undergoing CABG [3,5,6,7,14,15]. Moreover, S100 β is strongly correlated with postoperative neurological disorders after cardiac surgery [3,5,16]. The diagnostic power of S100 β depends on where in the body measurements are taken. The increase in S100 β immediately after completion of ECC results from brain injury as well as from extracerebral tissue damage. Andreas and colleagues [17,18] found high concentrations of S100 β in the cardiotomy suction reservoir and in the wound blood itself after ECC. They observed high S100 β concentrations in mediastinal fat and sternal bone marrow. Moreover, S100 β was found in the pericardium and cardiac tissue [15,19]. Therefore, it seems that an increase in plasma S100 β concentration just after ECC indicated not only brain injury but also damage to many tissues. The postoperative S100 β elevation was much more sensitive for brain injury in cardiac surgery patients [3,5,14,15,20]. Several studies documented that increased S100 β in the early postoperative period significantly predicted neuropsychological disorders [3,5,14,15,20]; this elevation resulted from an increase in brain-blood-barrier permeability [3,4,21,22]. Importantly, the opening of the brain-blood barrier was biphasic after ischemic events [23]. The first phase was over by five hours after ischemia; the second phase lasted from 24 to 47 hours after ischemia. In the present study, the highest plasma S100 β concentrations were noted 10 min after ECC completion and after surgery, but before sending the patient to the PICU, i.e., about two hours after ECC. Moreover, significantly higher S100 β levels were observed 24 and 48 hours after ECC. The first increase might have resulted from brain injury as well as extracerebral tissue damage; however, at time-points 3, 4 and 5 higher S100 β levels resulted from only brain injury.

Interestingly, plasma S100 β was significantly higher in group A than in groups B and C for time-points 2 through 5. These results implicate that volatile anaesthetics significantly decrease brain injury in patients undergoing ECC. The mechanisms by which volatile anaesthetic agents potentially protect the central nervous system remain unclear. Potentiation of GABAergic neurotransmission, antagonism of glutamatergic neurotransmission and inhibited reactive oxygen species seem to be primary among the neuroprotective and precondition effects of volatile anaesthetics [24-26]. Moreover, inhaled anaesthetics modulate intracellular Ca²⁺ homeostasis, reduce the expression of the apoptosis-inducing protein Bax, diminish cerebral metabolic requirements and stabilize cerebral blood flow [11,12,27].

Sevoflurane is a pleasant-smelling volatile anaesthetic with well-documented cardioprotective effects [28,29]. Inhalation of SEV significantly reduces ischaemia-reperfusion injury, stabilizes mitochondrial KATP channels, decreases cystolic and mitochondrial loading, and suppresses neutrophil-endothelium interaction [29,30]. Moreover, SEV stabilizes cerebral blood flow, induces dose-related cerebral metabolic depression, and stabilizes cell membranes in brain tissue [31-34]. The actions of ISO are similar. Additionally, the inhalation of ISO significantly reduces cerebral lactate acidosis during ischaemia [34,35]. Several studies have shown the neuroprotective effects of SEV or ISO anaesthesia in patients after brain injury [7,8,36-38]. It is difficult, however, to precisely define the effect of such volatile anaesthetics on the release of S100 β protein from brain cells. Kanbak and colleagues [7], who analysed changes in plasma S100 β in cardiac surgery patients, observed lower concentrations during isoflurane anaesthesia as compared to propofol anaesthesia. Moreover, they observed better neuropsychological outcome after isoflurane compared with sevoflurane and desflurane anaesthesia [13]. In the present study, plasma S100 β protein levels were significantly lower in patients anaesthetized with volatile agents.

Furthermore, the differences were already noted 10 min after the onset of ECC. Therefore, we can assume that volatile anaesthetics reduce the release of S100 β from the brain and extracerebral tissues.

One important limitation of the present study was the small number of patients with adverse neurological outcomes. The effect of sevoflurane and isoflurane anaesthesia on plasma S100 β concentrations was analyzed in patients without as well as with postoperative neuropsychological complications. These volatile anaesthetics significantly reduced plasma S100 β protein, however they didn't reduce the occurrence of postoperative neuropsychological disorders. Nevertheless, the most serious postoperative neuropsychological complication – stroke – was noted only in patients, who didn't receive volatile anaesthetics. Several studies demonstrated that brain injury resulted in prolonged increases in plasma S100 β protein [3,5,14,15]. The small number of participants with neuropsychological disorders made impossible a precisely analysis of the effect of volatile anaesthetics on neuropsychological outcome. Moreover, it is worth stressing that S100 β is only one of many markers of brain injury. Volatile anaesthetics were used only before ECC: no patients inhaled SEV or ISO after ECC. Therefore, only the preconditional effect of such anaesthetics was examined. Based on our findings, we cannot conclusively prove that volatile anaesthetics have neuroprotective effects in cardiac surgery patients. However, significantly reduced plasma S100 β concentration implies that inhalation of SEV or ISO is advantageous for the central nervous system in patients undergoing ECC. Thus, further studies are necessary to elucidate the neuroprotective effects of volatile anaesthetics in cardiac surgery patients.

In conclusion, ECC increases the plasma S100 β concentration. The inhalation of SEV or ISO significantly reduces the levels of this protein. Moreover, the reduction in plasma S100 β concentration is similar during SEV and ISO anaesthesia.

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Correspondence address:

Wojciech Dabrowski, M.D., Ph.D.
Department of Anaesthesiology and
Intensive Therapy
Medical University of Lublin
Jaczewskiego 8
20-954 Lublin
Poland
w.dabrowski5@yahoo.com