ORIGINAL ARTICLE

S100B protein and neuron-specific enolase as predictors of cognitive dysfunction after coronary artery bypass graft surgery

A prospective observational study

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BACKGROUND Postoperative cognitive dysfunction (POCD) may be related to the systemic inflammatory response and an increase in serum markers of brain injury such as S100B protein and neuron-specific enolase (NSE).

OBJECTIVE The study aims to evaluate the association between POCD and serum levels of S100B and NSE after coronary artery bypass grafting surgery (CABG).

DESIGN Prospective observational study.

SETTING Single university teaching hospital.

PATIENTS We investigated 88 patients undergoing CABG.

MAIN OUTCOMES MEASURES Cognitive function was measured preoperatively, and at the 21st and 180th postoperative days (i.e. 6 months after surgery). S100B protein and NSE serum levels were evaluated preoperatively, after

induction of anaesthesia, at the end of surgery and at 6 and 24 h after surgery.

RESULTS The incidence of POCD was 26.1% at 21 days after surgery and 22.7% at 6 months after surgery. Increased serum levels of S100B protein and NSE were observed postoperatively and may indicate brain damage.

CONCLUSION Although serum levels of S100B protein and NSE are both significantly increased postoperatively, our findings indicate that serum levels of S100B protein may be more accurate than NSE in the detection of POCD after CABG.

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Introduction

Cognitive dysfunction after cardiac surgery is affecting up to 65% of patients at hospital discharge.¹ Even after a few months, the prevalence of postoperative cognitive dysfunction (POCD) is still high affecting up to 40% of patients.¹ POCD comprises a wide range of cognitive functions, including working and long-term memory, information processing, attention and cognitive flexibility, thus affecting quality of life and

increasing mortality.^{2,3} POCD pathogenesis has not been properly clarified, but advanced age, pre-existing cerebrovascular and systemic vascular disease and systemic inflammation have been considered important risk factors.^{2,3} Notably, neuroinflammation may cause neural cell dysfunction or death, leading to increased blood levels of biochemical markers for brain damage.^{4,5}

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S100B protein and neuron-specific enolase (NSE) are well known as potential markers of neural injury.^{5–10,28–36} S100B protein is an acidic calcium-binding protein, which is found in astrocytes and Schwann cells, and physiological serum levels of S100B protein are low. In the early stages of brain injury, glial cells are activated, and S100B is released into the blood after neural damage. Therefore, S100B protein seems to be a potential biochemical marker of POCD. NSE is a glycolytic protein with a serum half-life longer than 20 h. It is primarily located in the cytoplasm of neurons and involved in increasing neuronal chloride levels during onset of neuronal activity.²⁸ However, some other sources of NSE include smooth muscle, adipose tissue, platelets and red blood cells.²⁸

Increased serum levels of NSE may indicate neuronal damage and increased serum levels of S100B protein may reflect either glial damage or astrocytic reactions to neural injury, namely reactive astrogliosis, which can have beneficial or detrimental consequences.^{6,7} Both S100B protein and NSE serum levels have been shown to increase following cardiac surgery.^{5–10} The elevation of serum levels of S100B protein and NSE may help to identify POCD.

The clinical diagnosis of POCD is somewhat difficult, involving application of several cognitive tests and requiring prolonged follow-up after surgery. Moreover, there is still no consensus about which neurocognitive tests should be used, main reference points, and the duration of follow-up. Most previous studies conducted only a general assessment rather than a comprehensive cognitive function assessment after surgery.^{11–14}

The present study aims to evaluate the association between POCD and increased serum levels of S100B protein and NSE after coronary artery bypass grafting surgery (CABG) with cardiopulmonary bypass (CPB).

Methods

Ethics

The study was approved by the Ethical Committee of Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo (ethical committee No 1081/04) on 27 January 2009 (Chairperson Professor E. A. de Castilho) and registered at ClinicalTrials.gov (NCT01550159) on 6 February 2012. Participants received a written and oral explanation of the study and gave written informed consent.

Study population

Adults between 40 and 90 years of age, were considered to be eligible for this prospective observational study.

Exclusion criteria were those who could not read or write; those who did not understand the Portuguese language; those with a history of psychiatric or neurological symptoms (history of stroke, transient ischaemic attacks,

Fig. 1

Patient enrolment flow diagram. This illustrates the flow of all patients screened, excluded and enrolled in the study.

seizures, generalised anxiety, alcoholism or drug addiction); those who had already undergone neurosurgical or cardiac procedures; those who refused to participate in the study and those who had already participated in other studies.

The Mini Mental State Examination is a tool that can be used to systematically and thoroughly assess mental status. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall and language. The maximum score is 30. In our study, the Mini Mental State Examination was used only before surgery for preoperative cognitive impairment screening and those who did not obtain minimum standard scores (≥ 25 points) were also excluded (Fig. 1).

Neurocognitive tests

The postoperative neurocognitive assessment protocol was designed to evaluate general cognitive function and identify patients with postoperative delirium and POCD.

The overall assessment of cognition was carried out using the Telephone Interview Cognitive Status (TICS) at all postoperative evaluation time points, that is, third, seventh, 21st, 90th and 180th postoperative days. TICS consists of a structured interview with 11 items that assess the skills of spatial and temporal orientation, mental

control, memory, general information, language and calculations. This is a standard test for evaluation of neuropsychological function used to perform cognitive screening when face-to-face evaluation is impractical or inefficient, for instance, in epidemiological studies of large populations or patients who are unable to attend clinic return. The TICS was applied face-to-face or, alternatively, by telephone when patients could not return for evaluation.¹⁵

The diagnosis of postoperative delirium employed the Confusion Assessment Method for the ICU (CAM-ICU) on the third and seventh postoperative days. The CAM-ICU is an instrument that assesses acute confusional state, displaying high sensitivity and specificity. This evaluation is performed using simple questions and commands. For the diagnosis of postoperative delirium employing the CAM-ICU, the patient must show changes in mental status (acute changes and/or mental status fluctuation), which are associated with inattention. Patients were considered to present postoperative delirium when the diagnosis was present in at least one of two evaluations.¹⁴

Additionally, a team of experienced psychologists assessed patients before surgery, 21 and 180 days after surgery by applying a validated cognitive test battery: Verbal Learning Test (VLT), Stroop Colour Word Test (SCWT), Trail Making Test (TMT) and Symbol Digit Modalities Test (SDMT). All neuropsychological tests are extensively described elsewhere.^{11–20} In summary, the tests are as follows:

- (1) VLT. The test assesses immediate memory span, learning, susceptibility to interference and recognition memory. It consists of the same 15 nouns read aloud, with a 1 s interval between words, for three consecutive trials (VLT-A1, VLT-A2 and VLT-A3); each trial is followed by a free recall test. A delayed recall of these 15 words (VLT-D) was performed 20 min after the third trial. Instructions were repeated before each trial to minimise forgetting. We evaluated the number of words recalled and the number of errors made for each presentation, adding up the errors related to the repetition of words already recalled (reverberation).¹⁷
- (2) SCWT. The test assesses selective attention, inhibitory ability and mental flexibility. It consists of three main components using four different colours (SCWT-1, SCWT-2 and SCWT-3). For SCWT-1 the patient is shown a colour name word (written in black) and must say/verbalise the colour name word. For SCWT-2 the patient is shown a rectangle filled with colour and the colour name word is also printed in black within the rectangle. The patient must say/verbalise the colour that fills the rectangle. For SCWT-3 the patient is shown a colour name word printed in a colour different from the

colour name word and they must tell the tester the colour of the printing. The name words for the colours all followed the same order as for SCWT-1. In this test, we evaluate the time spent and number of errors (up to 40) in each part.¹⁸

- (3) TMT. The test consists of two parts (TMT-A and TMT-B). In TMT-A, the study participant must draw lines connecting consecutively numbered circles. In TMT-B, the study participant must draw lines connecting circles alternately with letters and numbers in an ordered sequence. The TMT-A involves complex visual and motor speed and the TMT-B evaluates the executive processes. Time spent and number of errors in each part are assessed.¹⁹
- (4) SDMT. The test measures short-term memory, visual-spatial skills and attention. It is a task performed in 180 s and the study participant must write the number referred to each symbol. A target of symbols and their numbers are displayed (110 symbols are provided). Number of hits and number of errors are registered.²⁰

Criteria for postoperative cognitive dysfunction diagnosis

TICS values were used only to evaluate the evolution of general cognition postoperatively and the CAM-ICU was applied in the third and seventh days postoperatively. Notably, both TICS and CAM-ICU were not included in the battery for POCD screening. For the diagnosis of POCD, a composite cognitive index was arbitrarily established by the authors and defined by the occurrence of cognitive impairment in at least two of eight possible cognitive deficits: VLT-A (average VLT-A1, VLT-A2 and VLT-A3), VLT-D, SCWT-1, SCWT-2, SCWT-3, TMT-A, TMT-B and SDMT. The definition of cognitive dysfunction followed the same criteria established by previous studies and considered a reduction greater than or equal to 20% in all tools when compared with the results obtained in the assessment conducted preoperatively.^{14,21}

Assessment of serum levels of S100B protein and neuron-specific enolase

Serum levels of S100B protein and NSE were obtained from venous blood samples (3 ml) collected before surgery, after the anaesthetic induction, immediately after surgery and 6 and 24 h postoperatively. Samples were placed in dry tubes and centrifuged; serum was removed and stored at -80°C until the analysis.

S100B protein was measured by a commercially available S100 ELISA kit (DiaSorin, Gerenzano, Italy). A quantitative monoclonal two-site ELISA microplate assay in which the last antibody added to the reaction system is labelled with peroxidase. After the addition of a peroxidase substrate, the reaction produces a final colour

product read in a spectrophotometer. S100B protein levels were expressed as nanograms per millilitre.⁷

NSE was measured using an electrochemiluminescent assay. It consists of a double-sandwich assay that uses an anti-NSE antibody labelled with ruthenium, which is the luminescent molecule. Reactions and quantification were performed with Elecsys 2010 (Roche Diagnostics Corporation, Indianapolis, Indiana, USA). This assay has no interference with erythrocyte enolase when gross haemolysis is absent. NSE levels were expressed as nanograms per millilitre.⁷ All samples were measured in triplicate and the coefficient of variation was less than 5% for both analyses.

Anaesthetic management

Patients received a single dose of bromazepam 3 mg orally 30 min before surgery. After admission to the operating room, they were monitored using pulse oximetry, five-lead electrocardiogram, and continuous ST segment analysis in a multichannel monitor (Siemens monitor SC 9000 Infinity XL, Munich, Germany). Peripheral venous puncture was obtained in the upper limb with a 14 or 16G catheter. Invasive blood pressure monitoring was performed after radial artery puncture with a 20G catheter, using a pressure transducer, and verifying attainment of the pressure curve. After pre-oxygenation with 100% oxygen, an intravenous administration of $3 \mu\text{g kg}^{-1}$ fentanyl or $0.5 \mu\text{g kg}^{-1}$ sufentanil followed by an injection of 0.2 mg kg^{-1} etomidate, 2 mg kg^{-1} propofol or 0.1 to 0.2 mg kg^{-1} midazolam was performed. Muscle relaxation was obtained with 0.1 to 0.2 mg kg^{-1} pancuronium bromide or 0.1 mg kg^{-1} cisatracurium besylate, followed by manual mask ventilation and tracheal intubation. Mechanical ventilation was performed in a circular valve system with carbon dioxide absorber, according to NBR/ABNT No. 10012 (Brazilian Association of Technical Standards, Sao Paulo, Brazil), as part of a Cicero anaesthetic machine (Dräger, Lubeck, Germany). It was adjusted to a tidal volume of 8 ml kg^{-1} , FiO_2 0.6, I:E ratio of 1:2, mean respiratory rate of 12 breaths min^{-1} , positive end expiratory pressure of $5 \text{ cmH}_2\text{O}$, adjusted to maintain end-tidal carbon dioxide between 30 and 40 mmHg. Anaesthesia was maintained with inhalational isoflurane or sevoflurane adjusted between 0.5 and 1.0 minimum alveolar concentration. During CPB, ventilation was interrupted and hypnosis was maintained by infusion of propofol or midazolam.

After general anaesthesia induction, an oesophageal temperature transducer was applied and bladder catheterisation was performed. Pulmonary artery catheterisation was performed (7.5F catheter with thermal filament – CCO catheter, Edwards Lifesciences, Irvine, California, USA) and the catheter was connected to a Vigilance II monitor (Edwards Lifesciences, Irvine, California, USA).

Cardiopulmonary bypass management

For the CPB pump, a non-heparinised roller circuit (Braille, Sao Jose do Rio Preto, Brazil) was used, filled with Ringer's solution to a total volume of 1500 ml, and maintained near an average flow rate of 3.5 to 4.5 l min^{-1} . Moderate hypothermia between 28 and 32°C was maintained; a membrane type oxygenator was also used. Heparin (500 U kg^{-1}) was applied as an anti-coagulant prior to the establishment of CPB, and protamine was used to reverse the effect of heparin. The antifibrinolytic agent used was epsilon-aminocaproic acid (80 mg kg^{-1}); cardioplegia consisted of a standard cardioplegic solution, added to the mixture of the patient's blood and priming solution contained in the reservoir. At the time of rewarming, inotropic or vasodilators were used as needed by the anaesthesiologist. At the end of the surgery, patients were transferred to a surgical intensive care unit.

Statistical analysis

For the sample size calculation, we considered the estimated profile of sensitivity and specificity of the association between serum levels of NSE or S100B protein and POCD. To estimate sensitivity and specificity of 70%, considering an error of 10%, a confidence interval of 95% and a power of 80%, we estimated a sample of 80 patients was needed.

Numerical variables were given as mean Standard Deviation. Data were submitted to Shapiro–Wilk test for normality evaluation. One-way analysis of variance (ANOVA) or Kruskal–Wallis tests were used for analysis between groups at each time point for parametric and nonparametric continuous data, respectively. When differences were found, Bonferroni's multiple comparison test or Mann–Whitney's test with correction for multiple comparisons were applied. Differences between serum biochemical markers according to general cognitive (TICS), delirium (CAM-ICU) and POCD outcomes were evaluated by two-sample Wilcoxon rank-sum test. For longitudinal analyses regarding POCD, serum markers and time, we used two-way ANOVA. Correlation analyses were performed using Pearson's or Spearman's rank sum correlation. Receiver operating characteristic (ROC) curve analysis was performed for the prediction of outcome related to biochemical markers and calculation of area under the curve (AUC). $P < 0.05$ was considered statistically significant. All confidence intervals were constructed with 95% statistical confidence. Statistical analysis was performed using STATA 12.0 (StataCorp LP, Texas, USA).

Results

From a total of 129 patients, 88 were ultimately included in the study analysis. Clinical, demographic and procedure data are summarised in Table 1. As depicted in Table 2, we observed a significant increase in serum

Table 1 Demographic characteristics of the study population ($n = 88$) and procedure data

Characteristics:	
Age (years)	61.8 (9.2)
Sex (Male – Female) (%)	77 to 23%
BMI	27.1 (3.7)
Active smoking	15 (17%)
Previous myocardial infarction	38 (43%)
Hypertension	79 (90%)
Diabetes	43 (49%)
Dyslipidaemia	61 (69%)
Chronic renal insufficiency	7 (8%)
Hypothyroidism	6 (7%)
Procedure data	
CPB duration (min)	100.5 (23.6)
Anaesthesia duration (min)	424.9 (63.8)
Surgery duration (min)	359.9 (64.9)
Mechanical ventilation after surgery (min)	487.5 (264)
Hospitalisation after surgery (days)	10.0 (4.4)

Data are shown as count n (%) or mean (SD). BMI, Body Mass Index; CPB, cardiopulmonary bypass; $n = 88$ patients.

levels of S100B protein and NSE immediately after surgery ($P < 0.0001$ for S100B protein and $P = 0.011$ for NSE). Additionally, NSE serum levels remained increased at 6 h ($P < 0.0001$) and 24 h ($P = 0.014$) after surgery whereas S100B protein levels partially returned to baseline levels – $P = 0.17$ and $P = 0.18$, respectively for 6 and 24 h after surgery (Table 2). Notably, a significant correlation between both serum biochemical markers was found after anaesthesia induction ($r = 0.23$, $P = 0.029$) and at the end of surgery ($r = 0.30$, $P = 0.004$).

Some 41 patients (46.6%) displayed postoperative delirium as evidenced by the CAM-ICU. Analyses of the correlation of postoperative delirium using the CAM-ICU and serum levels of S100B protein and NSE were not statistically significant ($P > 0.05$) in all time points (data not shown). Additionally, analysis of general cognition using TICS showed some cognitive impairment in 69.8, 50.7, 47.9, 36.8 and 41.0% of patients in the third, seventh, 21st, 90th and 180th postoperative days, respectively. Additionally, we found a significant correlation between serum levels of NSE immediately after surgery and TICS scores in the seventh ($r = 0.25$; $P = 0.04$) and 180th ($r = 0.48$; $P < 0.001$) postoperative days, respectively.

With regard to the overall evaluation of POCD, at the 21st day after surgery, 26.1% of patients had pre-established criteria for POCD diagnosis. At the 180th postoperative day, POCD was observed in 22.7% of patients.

We observed that S100B protein serum levels were significantly increased at the end of surgery in patients displaying POCD 21 days after surgery ($P = 0.017$, Fig. 2). Additionally, patients displaying POCD 180 days after surgery presented higher levels of S100B protein at 24 h after surgery in comparison to patients without POCD ($P = 0.037$, Fig. 2). Comparisons between patients with or without POCD at 21 and 180 days after surgery showed no statistically differences in serum levels of NSE. Notably, two-way ANOVA 21 days after surgery demonstrated a significant interaction between time and POCD regarding S100B protein ($P = 0.034$) but not NSE ($P = 0.353$) serum levels. However, two-way ANOVA 180 days after surgery demonstrated a significant interaction between time and POCD regarding NSE ($P = 0.033$) but not S100B protein ($P = 0.719$) serum levels. ROC curves for S100B protein and NSE are demonstrated in Figs. 3 and 4. Notably, S100B protein serum levels at the end of surgery could significantly predict POCD 21 days after surgery, whereas S100B protein serum levels at 6 and 24 h after surgery could significantly predict POCD 180 days after surgery. NSE serum levels could not predict POCD at any time (Fig. 4). Interestingly, higher serum levels of S100B protein and NSE after induction tended to negatively predict POCD 21 days after surgery (AUC < 0.5 , Fig. 3).

Discussion

Based on our diagnostic criteria, our findings showed that the incidence of POCD 21 days after CABG surgery was around 25% and remained almost unchanged 6 months after surgery. Increased serum levels of S100B protein and NSE, especially immediately after surgery, indicated that anaesthesia and surgery might be significantly related to a level of neural damage that correlates with POCD. However, a weak association between increased serum levels of S100B protein or NSE and POCD was observed. Some cognitive impairment using TICS was observed in more than a half of patients at almost all time points. A high incidence of postoperative delirium was also observed after the first week following surgery.

Despite improvements in surgical and anaesthetic techniques over the last decades, brain injury after cardiac surgery is still highly prevalent.²² The most common form of brain injury after cardiac surgery is called cognitive dysfunction, with clinical manifestations, such as deterioration in memory, attention, motor function and

Table 2 S100B and neuron-specific enolase serum levels ($n = 88$ patients)

Serum Biomarker (ng/ml)	Measurement time points				
	Baseline	Post-anaesthesia	End of surgery	6 h	24 h
S100B	0.33 (0.47)	0.46 (0.65)	1.75 (1.51)*	0.74 (1.68)	0.74 (0.75)
NSE	10.5 (5.9)	7.7 (6.1)	15.4 (12.5)#	16.7 (13.0)*	15.3 (8.7)#

Data are shown as mean (SD). NSE, neuron-specific enolase. * = $P < 0.001$. # = $P < 0.05$ as compared with baseline (one-way ANOVA followed by Bonferroni's multiple comparison test); $n = 88$ patients.

Fig. 2

Biochemical serum markers profile regarding presence ($n = 23$ patients) or absence ($n = 65$ patients) of POCD 21 days after surgery (panel A for S100B protein and panel B for NSE), and presence ($n = 20$ patients) or absence ($n = 68$ patients) of POCD 180 days after surgery (panel C for S100B protein and panel D for NSE). Data are shown as mean SD. * = $P < 0.05$ between groups, two-sample Wilcoxon rank-sum test; two-way ANOVA 21 days after surgery: S100B protein ($P = 0.034$) and NSE ($P = 0.353$); two-way ANOVA 180 days after surgery: S100B protein ($P = 0.719$) and NSE ($P = 0.033$); $n = 88$ patients. ANOVA, analysis of variance; NSE, neuron-specific enolase.

visuospatial ability.²² Cognitive dysfunction is commonly detected after cardiac surgery, regardless of the screening method applied, but the incidence of POCD after cardiac surgery varies considerably, and may be as high as 50 to 70% at 1 week after surgery, declining to 30% after 2 months.²³

Cardiac surgery can induce an activation of the immune system, resulting in a strong systemic inflammatory response, which may cause damage to the central nervous system (CNS). When an excessive CNS inflammatory response occurs, peripherally originating cytokines can cause central neuronal and glial toxicity, thus affecting the function of synaptic connections and causing neuronal and glial toxicity.^{22–24} The occurrence of POCD after cardiac surgery may be related to a combination of several factors often associated with CPB, including embolism, hypoperfusion and inflammatory response.²² However, these events are not exclusive to CPB, since patients submitted to off-pump procedures or

non-cardiac surgeries also display similar events.^{25,26} Notably, there is growing evidence that cerebrovascular risk factors may play a significant role in both early and late POCD.^{22,25,27}

In the present study, we observed that both neuropsychological tools and serum biochemical markers indicated some degree of brain damage. Both serum NSE and S100B protein were significantly elevated after CABG surgery with CPB and might represent substantial neuronal and glial cell damage, respectively. Notably, serum levels of NSE remained high 6 and 24 h after surgery, indicating some differences regarding time profile between both biochemical markers. These findings corroborate previous data indicating that serum levels of NSE remain increased even 36 h after surgery.⁵ Nonetheless, our findings suggest that S100B protein levels tended to return to normal levels 6 h after surgery. Notably, previous reports indicated that the elevation of S100B protein levels is short lived, with a peak serum

Fig. 3

ROC curves for S100B protein (a) and NSE (b) serum levels and POCD detection at 21 days (top row) and 180 days (bottom row) after surgery. NSE, neuron-specific enolase; POCD, postoperative cognitive dysfunction; ROC, receiver operating characteristic.

concentration occurring 30 min postoperatively and returning to basal levels within 18 h after surgery.²⁹

Although previous studies indicated NSE as a reliable biochemical marker of postoperative dysfunction,^{5,9,10} our study failed to demonstrate a solid association between serum NSE and POCD, since only a weak association between NSE levels immediately after surgery and TICS scores in the seventh and 180th postoperative day and a small interaction between time and POCD regarding NSE serum levels were found. Nevertheless, S100B protein serum levels were significantly increased postoperatively in patients displaying POCD as compared with patients without cognitive dysfunction 21 and 180 days after surgery. Additionally, ROC curve analysis demonstrated that S100B serum levels could

significantly predict POCD 21 and 180 days after surgery. Considering our findings, S100B protein seems to be more useful as a biochemical marker of POCD than NSE. Although controversy remains, several authors were able to demonstrate a relationship between the degree of cognitive dysfunction and S100B protein,^{6,9,10,29–33} which is consistent with our present findings. Considering that S100B protein is highly brain specific,²⁸ S100B protein may be a better predictive marker of POCD. Nevertheless, AUC obtained from ROC curves for S100B protein was relatively small in all time points (<0.7), indicating a reasonably weak association with POCD. The lack of a strong association between neural tissue damage markers (both S100B protein and NSE) and POCD has already been demonstrated previously.^{5,21} These contradictory findings may

Fig. 4

POCD prediction performance for S100B protein (left) and NSE (right) serum levels assessed at three different time points after surgery. S100B protein serum levels at the end of surgery could significantly predict POCD 21 days after surgery, whereas S100B protein serum levels at 6 and 24 h after surgery could not significantly predict POCD 180 days after surgery. NSE serum levels could not significantly predict POCD. Horizontal dashed line marks chance performance (0.5). Prediction performance is defined as the AUC of the ROC curve (see Fig. 2). * = $P < 0.05$ compared with chance performance, permutation test. AUC, area under the curve; NSE, neuron-specific enolase; POCD, postoperative cognitive dysfunction.

be related to the variability of POCD criteria, lack of comprehensive evaluation of POCD, short follow-up and/or additional pathophysiological mechanisms, involving extracerebral sources of biochemical markers.^{25,34–36} Of note, although not statistically significant, levels of S100B protein and NSE after anaesthesia induction displayed some negative predictive value for POCD 21 days after surgery. This suggests that patients presenting higher levels of S100B protein and NSE before surgery may present a lower incidence of POCD. Although it deserves future investigation, this finding might point to a neuro-protective role of these compounds (especially S100B protein³⁷) and patients displaying higher levels of these proteins may be protected from brain injury.

Importantly, almost half of the patients experienced an acute state of confusion in the first week after surgery. The high incidence of patients with postoperative delirium after cardiac surgery has been found previously.^{1,5,38,39} The choice of CAM-ICU as a tool for the evaluation of postoperative delirium proved effective and highly sensitive in this setting. An important factor that contributed to the accuracy of CAM-ICU was the application of the test on two occasions in the first week after surgery, especially given the fluctuating nature of postoperative delirium. Indeed, there is evidence that the CAM-ICU should be applied daily in patients at high risk for developing postoperative delirium. With a sensitivity and specificity greater than 90%, the CAM-ICU, if applied daily,⁴⁰ could have identified a higher incidence of delirium.⁴⁰ Notably, in the present study,

we did not find a statistical association between postoperative delirium and increased serum levels of S100B protein and NSE. The reasons for this finding are unclear but may indicate that neural cell damage might not be related or necessary to the generation of delirium states.

Our study has several limitations. Firstly, the overall number of patients in our study who displayed POCD was small, which may be related to the battery of neurocognitive tests used. The prevalence of POCD reported in previous studies varies widely and the conflicting results may be attributable to different diagnostic criteria for POCD.^{38–40} Secondly, neither S100B protein nor NSE is fully specific to the CNS.²⁸ The impact of other sources for those biomarkers needs to be considered when interpreting serum marker concentration.

Conclusion

In summary, this study provides additional evidence that CABG surgery with CPB is associated with high postoperative serum levels of S100B protein and NSE, which may indicate significant neural damage. S100B protein serum levels may be more accurate than NSE in predicting POCD after CABG surgery. Future studies should focus on accurate detection of POCD, validation of new biochemical markers and understanding the mechanisms of POCD.

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