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Author(s)	Kunihara, Takashi; 國原, 孝; Shiiya, Norihiko et al.
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**Arterio-Jugular Differences in Serum S-100 β Proteins in Patients Receiving
Selective Cerebral Perfusion**

Running Title; S100 β in Selective Cerebral Perfusion

Takashi Kunihara, Norihiko Shiiya, Luo Bin, and Keishu Yasuda

N14, W5, Kita-ku, Sapporo, Japan 060-8648

Department of Cardiovascular Surgery, Hokkaido University School of Medicine,
Sapporo, Japan

Reprint requests to:

Takashi Kunihara

FAX: +81-11-747-0476

E-mail: kunihara@med.hokudai.ac.jp

ABSTRACT

Background: The early increase in serum S100 β after cardiopulmonary bypass (CPB) seems to be derived from an extracerebral source. To exclude contamination, we investigated the arterio-jugular differences in the S100 β levels in patients receiving selective cerebral perfusion (SCP). We also evaluated the brain protective effect of SCP by comparing the arterial S100 β levels with those in patients undergoing coronary artery bypass grafting (CABG).

Methods: We measured arterial and jugular venous levels of S100 β in ten patients undergoing aortic arch repair with SCP for up to 12h postoperatively (SCP-group). We also measured arterial levels of S100 β in nine patients undergoing CABG (CPB-group).

Results: There was no incidence of hospital death or stroke in this series. The arterial levels of S100 β in both groups were comparable and peaked just after CPB was stopped. The arterial and jugular venous levels of S100 β were almost equivalent. The arterio-jugular differences in S100 β levels were negligible, even in our SCP-group patient with postoperative delirium, who had a peak value three-times higher than the other patients.

Conclusions: The arterio-jugular differences in S100 β did not clarify the origin of their increase. Thus, measuring the jugular venous levels of S100 β in patients without postoperative clinical neurological deterioration would be of little benefit. However, SCP seems to protect the brain against S100 β release as well as conventional CPB.

KEY WORDS

S-100 β protein, jugular vein, selective cerebral perfusion, aortic arch aneurysm, extracerebral contamination

INTRODUCTION

Despite recent technical advances in aortic arch surgery, neurological complications are still a major concern. Because of its simplicity, hypothermic circulatory arrest (HCA), with or without retrograde cerebral perfusion, has been widely adopted as an adjunct to prevent ischemic cerebral injury [1, 2]. However, its use is limited by the duration of the procedure, so some surgeons prefer to use selective cerebral perfusion (SCP) when prolonged ischemia is anticipated [3, 4]. A specific, quantitative, and predictive biochemical marker of brain injury would help to clarify the advantages and limitations of these three adjuncts.

S-100 β protein (S100 β), which is found predominantly in glial and Schwann cells, is thought to be a specific biochemical marker for brain injury [5]. However, the early increase in serum S100 β during cardiopulmonary bypass (CPB) is unlikely to be associated with clinically detectable brain injury [6]. Extracerebral contamination [7, 8], increased permeability of the blood-brain barrier (BBB) related to inflammatory responses [9-11], and changes in the rate of elimination through the kidney may explain this discrepancy [12].

Raabe and colleagues found that S100 β levels in the jugular vein were significantly higher than those in the artery in patients with severe head injury [13]. Therefore, measuring the S100 β levels in the jugular vein may help to clarify the origin of S100 β in patients undergoing CPB. However, to our knowledge, no study on the jugular vein levels of S100 β in patients undergoing CPB or SCP has been published.

We investigated the arterio-jugular differences in S100 β levels to exclude extracerebral contamination in patients undergoing SCP. We also evaluated the protective effect of SCP by comparing arterial S100 β levels with those in patients undergoing coronary artery bypass grafting (CABG).

MATERIALS AND METHODS

Patients

Ten patients undergoing reconstruction of the aortic arch or ascending aorta with SCP were enrolled in this study (SCP-group). All patients underwent elective surgical repair at Hokkaido University Hospital during theywar between May, 1999 and May, 2000. We obtained approval from the institutional review board and written

informed consent was given by all patients. The underlying disease were chronic aortic dissection in four patients, one of whom had a pseudoaneurysm, and non-dissection degenerative disease in six patients. The operations performed were replacement of the ascending aorta in one patient, hemiarch replacement in three patients, and total aortic arch replacement in five patients, two of whom underwent one-vessel CABG. Distal anastomosis of the CABG was done during core cooling. One patient underwent re-fixation of a stent graft in the distal arch. Three patients had undergone previous aortic surgery for other lesions; in the thoracoabdominal aorta in one and in the abdominal aorta in two. One patient with an old cerebral infarction resulting in aphasia had also undergone cerebral aneurysm repair (coating procedure) 3 years earlier

As a control, we enrolled ten patients who underwent elective CABG with CPB during the same period (CPB-group). One patient, who had the highest S100 level ($5.17 \mu\text{g/L}$) just after the conclusion of CPB, was excluded following the development of renal insufficiency receiving hemodialysis. The number of distal anastomoses was 3.8 ± 1.1 and a side biting clamp was applied to the ascending aorta in all patients. One patient underwent concomitant left ventricular aneurysmectomy and another patient had

a history of transient ischemic attack.

There were no significant differences between the two groups in age, gender, height, body weight, preoperative serum creatinine (Cr) levels or Cr-clearance levels (Table 1).

Anesthesia, operative methods, and adjuncts.

All patients received standard general anesthesia using neuromuscular blockade and intermittent intravenous fentanyl. All operations were performed through a midline sternal incision. We described our operative methods of aortic arch replacement in detail previously [4]. Briefly, systemic perfusion cooling was done through an arterial return cannula placed in the proximal ascending aorta in four patients, the aortic arch in two, the brachiocephalic artery in one, and the femoral artery in three. When the rectal temperature had dropped to 22°C, selective cerebral perfusion of the three arch vessels was established. All three arch vessels were cannulated directly in three patients, and perfused through a balloon catheter introduced via the aortic arch in two patients. In the other five patients, the brachiocephalic artery and the left common carotid artery were cannulated directly and the left subclavian artery was perfused

through a balloon catheter. The initial total flow for the SCP was 683.3 ± 66.0 ml/min (11.3 ± 1.4 ml/min/kg). The pressures in the bilateral radial arteries and left superficial temporal artery were continuously monitored to keep the latter around 50 mmHg during SCP. We performed open distal aortic anastomosis first, followed by systemic reperfusion through the side branch of the prosthesis, then proximal aortic anastomosis to shorten the duration of myocardial ischemia. Finally we connected the arch vessels to the branches of the prosthesis during the rewarming phase. When concomitant CABG was done, the distal anastomosis was performed during cooling and the proximal anastomosis was performed after the completion of SCP using a side-biting clamp. The autologous saphenous vein was used as the conduits for CABG.

The system for CPB consisted of a heparin-coated circuit (Terumo Co., Tokyo, Japan), a centrifugal pump (Medtronic Bio-Medicus Inc., Eden Prairie, MN), and a membrane oxygenator (Capiiox SX-18™, Terumo Co., Tokyo, Japan). We did not use an arterial filter. This system was primed with lactated Ringer's solution, with 5 mg/kg betamethasone added. The same dose of betamethasone was given intravenously before starting CPB. To prime the circuit for SCP, the initial dilution ratio in the SCP group

was significantly larger than that in the CPB group, at $22.1 \pm 4.4\%$ vs. $15.3 \pm 3.0\%$ ($p=.0063$), but there was no significant difference in the final dilution ratio ($30.1 \pm 11.7\%$ vs. $21.9 \pm 9.9\%$). The alpha-stat strategy was applied during CPB. A cardiotomy sucker and a centrifugal cell-saving device (Cell Saver 5™, HAEMONETICS CO., LTD, Braintree, MA) were used in all patients, but washed red blood cells (RBC) were returned during the operation in only five patients. Postoperative shed mediastinal blood was discarded.

CABG was performed using standard techniques. We used an average of 2.3 ± 0.9 arterial conduits for CABG. The left internal thoracic artery was used in eight patients (concomitantly with the right internal thoracic artery in one), the left radial artery was used in eight patients, and the right gastroepiploic artery was used in four patients. An average of 0.3 ± 0.5 autologous saphenous vein grafts were also used ($n=3$). Instead of betamethasone, we gave 1000mg methylprednisolone in both the CPB circuit and the systemic circulation in five patients. We gave 250mg methylprednisolone to the other four patients.

Measurement of S100β Protein.

Using a percutaneous retrograde approach, a 4Fr oximetric catheter (OPTICATH™, Abbott laboratories, Abbott Park, IL) was placed in the right internal jugular venous bulb through a 5.5Fr sheath in the SCP-group. We collected samples of whole blood from the radial artery or CPB circuit (only at T1-T3), and from the internal jugular vein in the SCP-group at the following seven times: just before and after the initiation of CPB (T0, T1), just before systemic circulatory arrest (T2), 1 hour after the onset of SCP (T3), just after the conclusion of CPB (T4), just after skin closure (T5), and 12h after surgery (T6). In the control, T2 was omitted and T3 was substituted by 1 hour after aortic crossclamping (AXC). Blood samples were centrifuged in an Ependorf centrifuge and the supernatant was separated for immediate freezing at -80°C for later measurements during April and May, 2000. This method of storage would not influence the measurements of S100β (personal communication). The serum levels of S100β were measured in duplicate using a commercially available two-site immunoradiometric assay kit (Sangtec Medical AB, Bromma, Sweden). The minimum detectable level was 0.2 μg/L.

Statistical Analysis.

All values are expressed as means \pm standard deviation (SD). We used the paired *t*-test for statistical analysis of time-related data and the unpaired *t*-test for comparisons between the groups. The Chi-square test was used for comparison of frequencies. All statistical analyses were done by procedures in StatView™ 5.0 for Macintosh (SAS Institute, Inc., Cary, NC). A *P*-value of less than 0.05 was considered significant.

RESULTS

The patients in the SCP-group were all men, ranging in age from 60-80 years old (mean 71.7 ± 5.9 years old) and the control consisted of seven men and two women, ranging in age from 55-86 years old (mean 64.9 ± 9.9 years).

There was no incidence of hospital death or stroke. One 79-year-old man in the SCP-group suffered temporary delirium. All patients, except for one, were weaned off mechanical ventilation within 24 hours after surgery. One patient required mechanical ventilation for two days. There were no complications related to cannulation of the internal jugular vein. There were no significant differences between the two groups in

the mean operative, CPB, or AXC times (Table 1). The mean operative, CPB, AXC, SCP, and HCA times for the patient with postoperative delirium were 454, 242, 50, 88, and 33 min, respectively. There were no significant differences between the two groups in intraoperative blood loss, transfused banked red blood cells (RBC), returned autologous washed RBCs, or the highest postoperative serum Cr level (Table 1). These respective amounts in the patient with postoperative delirium were 390ml, 560ml, 383ml, and 1.6mg/dl.

The arterial S100 β levels increased gradually after T1 and peaked at T4 in both groups (Fig 1). They were significantly higher than the levels at T0, from T2 to T4 in the SCP-group and from T1 to T6 in the CPB-group. The arterial S100 β levels in the SCP-group were slightly higher than those in the CPB-group at all times, but the differences were not significant.

The patient with delirium had the highest arterial S100 β level in the SCP-group at T3 and T4. His jugular venous S100 β level was also slightly higher than his arterial level at T3 and T6. The mean arterial S100 β levels in the other nine patients were almost equivalent to the jugular venous levels throughout the observation period. Thus,

there were no significant differences between them at any time (Fig 3).

DISCUSSION

To our knowledge, this is the first study to evaluate the arterio-jugular differences in S100 β levels in patients undergoing SCP. During SCP and reperfusion, the jugular venous S100 β levels were almost equivalent to the arterial S100 β levels in patients without any postoperative neurological deficit. Even in the patient with postoperative delirium, who had the highest S100 β peak level, the arterio-jugular difference in S100 β was not as great as one might expect. Moreover, the arterial S100 β levels in the SCP-group were comparable with those in the CPB-group.

These findings suggest that the arterio-jugular differences in S100 β levels provide little beneficial information about patients without postoperative irreversible neurological injury after SCP, however, they have been reported to be a useful marker of brain injury in patients with severe head injury [13]. There are two possible explanations for this. First, recirculation equilibrates the concentrations so quickly that even a significant release of S100 β would create only a subtle difference in the

arterio-jugular concentration. Although none of the patient in our series suffered postoperative stroke, it would be interesting to investigate the arterio-jugular differences in S100 β levels in such patients. Second, our method of SCP provides sufficient brain protection that the S100 β release from the brain would be minimal. Since brain metabolism was thoroughly depressed at the lowest rectal temperature of $18.6 \pm 2.2^\circ\text{C}$, the total flow of the SCP of $11.3 \pm 1.4\text{ml/min/kg}$ might be more than adequate for cerebral metabolic demand. Our previous study using near-infrared spectrophotometry and jugular venous oxygen saturation clearly demonstrated this [14]. Recent studies found higher serum S100 β levels in patients with HCA than in those without HCA [15-17]. Therefore, our result reinforces the advantages of SCP. Although Svensson and colleagues reported that the serum S100 β levels in patients given HCA were not different from those in patients given SCP [17], this inconsistency may be explained by the difference in perfusion conditions.

The fact that the patient with postoperative delirium had a three-fold higher S100 β peak level than the other patients supports the possibility that S100 β is a marker of brain injury. Moreover, the result that S100 β leakage during SCP was comparable

with that during CPB suggests that our current technique of SCP protects the brain effectively. Although the arterial S100 β levels in the SCP-group were slightly higher than those in the CPB-group, they were already higher at T0 in the SCP-group than before CPB in the CPB-group. Bhattacharya and associates found slightly increased preoperative serum S100 β levels in patients with acute aortic dissection [15]. None of the patients in this series had acute aortic dissection, although the four patients with chronic aortic dissection had slightly higher arterial S100 β levels than the six patients without aortic dissection in the SCP-group (0.93 ± 0.93 vs. 0.53 ± 0.39 , $p=0.3693$).

The arterial S100 β levels in both groups increased gradually during CPB and peaked just after the conclusion of CPB, followed by a gradual decrease. This trend is similar to findings reported by many researchers [15-20]. The underlying mechanism of this gradual elevation is multifactorial. Reversible injury of the Schwann cells and glial cells increases the permeability of the BBB [9-11], and extracerebral contamination [7, 8] may also play a role. Although S100 β is an unquestionable marker of brain injury [5, 6], it is still unclear why S100 β increases during CPB without neurologic sequelae. Cerebral microemboli were found to be associated with neurocognitive dysfunction [21]

and significantly correlated with the S100 β level [18] after cardiac surgery. Therefore, subclinical brain injury may be responsible for the gradual elevation in S100 β during CPB. This speculation is supported by reports that S100 β release is well correlated with neuropsychological function [8, 22] and is attenuated by arterial line filtration [19].

Second, the increased permeability of BBB, which is related to the inflammatory responses caused by CPB, may accelerate S100 β leakage through the BBB [9-11]. This phenomenon, recognized as postoperative cerebral edema, develops predominately in the white matter of the brain, where most Schwann cells and glial cells are found [6].

Thus, it has been reported that S100 β elevation is correlated with the duration of CPB [16, 18, 20, 22], which may explain why the S100 β value increases gradually during CPB. The contribution of these two factors to gradual S100 β elevation during CPB is confirmed by the reduced S100 β release during off-pump CABG [20]. Third, a high S100 β value was found in blood from a cardiomy reservoir [8]. Thus, as long as blood from a cardiomy reservoir is returned to a patient, the S100 β level will rise gradually during CPB.

The present study has some limitations. First, the data of the patients

undergoing HCA with or without retrograde cerebral perfusion are lacking. Although it is difficult to interpret the data obtained during HCA, those obtained during reperfusion are of great importance. Unfortunately, because we performed SCP routinely for aortic arch repair, we have no concrete comparative data during HCA. Second, steroid doses were not identical in the two groups and varied within the CPB-group. The administration of steroids may attenuate an increase in the permeability of the BBB associated with CPB [23], thereby reducing the leakage of S100 β through the BBB. Our previous studies also showed a large gradient in proinflammatory cytokines (interleukin-8) [24] or S100 β [25] between cerebrospinal fluid and serum in patients undergoing thoracoabdominal aortic surgery and given the same dose of steroids. We must take into account that the patients in the SCP-group were given a higher dose of steroids than those in the CPB-group. In the CPB-group, there was no significant difference in arterial S100 β between the patients given 500mg of methylprednisolone and those given 2000mg of methylprednisolone at any time (data not shown). Furthermore, the larger initial dilution ratio to prime the CPB circuit in the SCP-group might result in smaller differences in the S100 β levels than the true values in the two

groups, although this would affect only the intraoperative data. Third, the etiology and operative procedure were not uniform in the SCP-group. There were many variations in arterial return cannulation, cannulation for SCP, the number of pumps used for SCP, and surgical extension. Retrograde femoral perfusion may be responsible for brain micro-emboli when downstream atherosclerosis exists [4]. When arch vessels were perfused through a balloon from its orifice, patients were exposed to temporal arrest of the cerebral circulation [17]. Moreover, SCP with one pump and SCP with two pumps will have different physiological effects. In our study, the SCP time for hemiarch replacement was naturally shorter than that for total arch replacement (100.2 ± 55.7 min vs. 149.8 ± 36.8 min, $p=0.1353$), therefore, our results warrant further investigation in animal models under uniform conditions. Fourth, the jugular venous S100 β levels were not measured in our CPB-group because our institutional review board did not allow us to perform this invasive and expensive measurement in the CPB-group, only for scientific interest. On the other hand, we routinely insert a jugular venous oximetric catheter for SCP, so this investigation could be performed without additional risk or cost. The arterial S100 β levels in the CPB-group were measured only to disclose the brain

protective effect of SCP, which was considered a secondary purpose of this study. Thus, we deemed our study design to be justified.

In conclusion, the S100 β levels in the jugular vein did not provide evidence of its extracerebral source in patients without postoperative stroke. The fact that there was no difference in S100 β levels in the artery and jugular vein indicates that there was no remarkable ischemic insult in the SCP-group, which is consistent with the clinical outcome. The arterial S100 β levels suggest that the brain protection provided by SCP is comparable to that provided by CPB alone in patients undergoing CABG. Our preliminary results in this small cohort warrant further investigation in a larger series.

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LEGENDS

Table 1. Patient characteristics including operative data

Data are expressed as means \pm standard deviation. See text for abbreviations.

Fig. 1. Comparison of the time course of arterial S-100 β protein levels between patients undergoing selective cerebral perfusion (open circles; SCP-group, n=10) and those undergoing coronary artery bypass grafting (closed circles; CPB-group, n=9). Data are expressed as means \pm standard deviation.

T0, T1: just before and after the initiation of CPB, T2: just before systemic circulatory arrest, T3: 1 hour after the onset of SCP, T4: just after the conclusion of CPB, T5: just after skin closure, T6: 12h after surgery. In the control, T2 was omitted and T3 was substituted by 1 hour after aortic crossclamping.

Fig. 2. Comparison of the time course of serum S-100 β protein levels between a 79-year-old man with postoperative temporal delirium (circles) and nine patients with normal postoperative neurological status (squares) during and after selective cerebral perfusion. Each open circle or square represents a sample from the artery, whereas each closed circle or square represents a sample from the internal jugular vein. Data are

expressed as means \pm standard deviation.

T0, T1: just before and after the initiation of CPB, T2: just before systemic circulatory arrest, T3: 1 hour after the onset of SCP, T4: just after the conclusion of CPB, T5: just after skin closure, T6: 12h after surgery. In the control, T2 was omitted and T3 was substituted by 1 hour after aortic crossclamping.

Table 1.

	SCP-group	CPB-group	p-value
Age (years)	71.7±5.9	64.9±9.9	.0835
Height (cm)	167.3±6.7	163.1±11.0	.3298
Body weight (kg)	60.7±7.7	63.2±15.4	.6569
Operation time (min)	528±208	438±130	.2836
CPB time (min)	227±49	194±48	.1606
AXC time (min)	100±45	119±25	.3029
SCP time (min)	125±52		
HCA time (min)	65±35		
Lowest RT (°C)	18.6±2.2	33.1±0.7	<.0001
Blood loss (ml)	471±314	680±853	.4796
Transfused banked RBC (ml)	824±1246 (n=5)	576±516 (n=8)	.5857
Washed RBC return (ml)	456±909 (n=5)	194±226 (n=3)	.5043
Preoperative Ccr (mg/ml/min)	70.8±21.4	59.0±37.3	.4103

Preoperative Cr (mg/dl)	1.0±0.3	1.0±0.5	.8949
Postoperative highest Cr (mg/dl)	1.3±0.6	1.0±0.4	.3028

CPB, Cardiopulmonary bypass, AXC, Aortic crossclamping, SCP, Selective cerebral perfusion, HCA, Hypothermic circulatory arrest, RT, rectal temperature, Blood loss, Intraoperative blood loss, Transfusion, Intraoperative homologous blood transfusion, Banked RBC, Intraoperative homologous red blood cell transfusion, Washed RBC return, Intraoperative washed autologous red blood cell return, Ccr, Creatinine clearance level, Cr, Serum creatinine level

Arterial S100 β ($\mu\text{g/L}$)

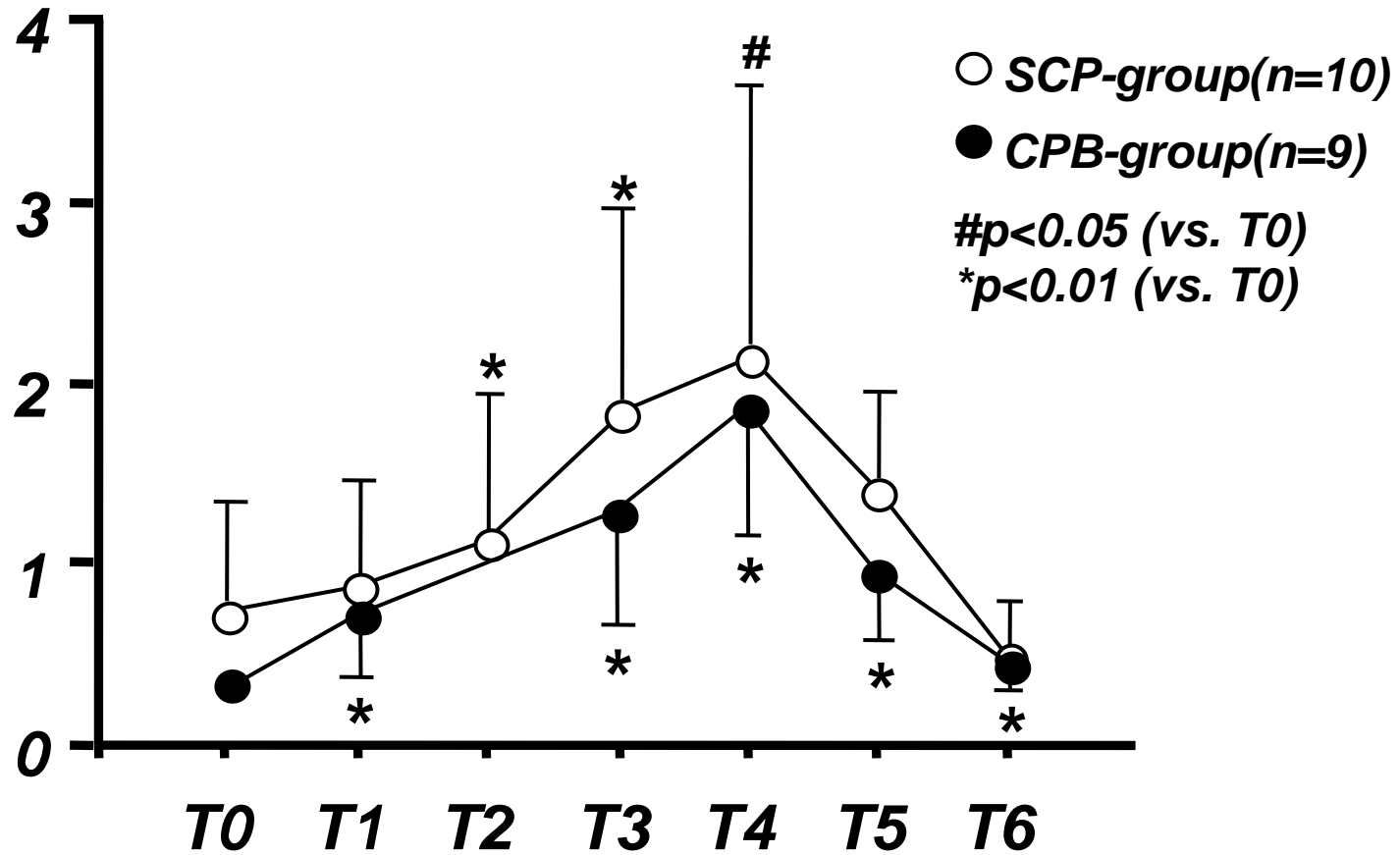


Figure 1

Serum S100 β ($\mu\text{g/L}$)

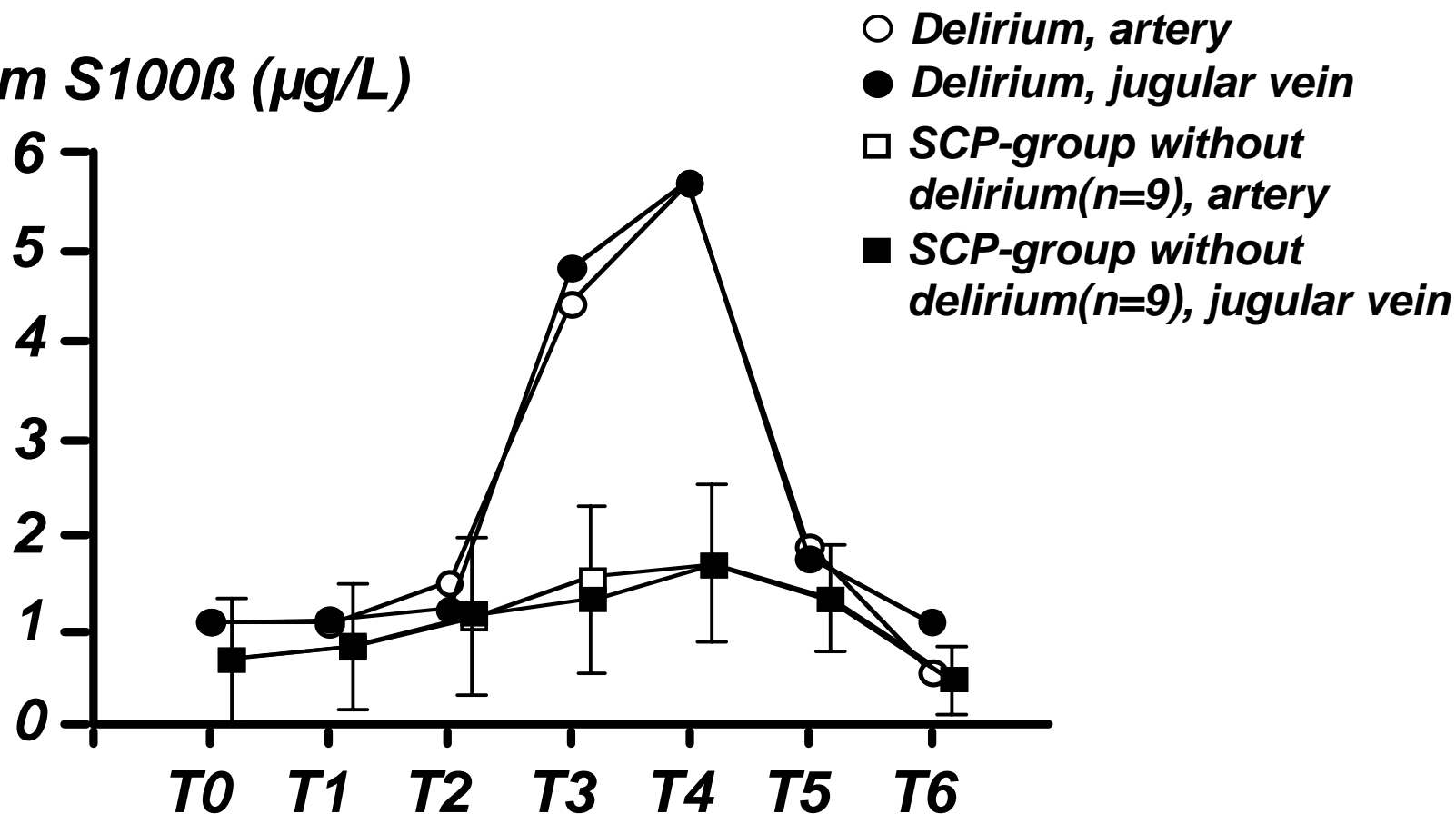


Figure 2