Pulsatil Akım Kardiyopulmoner Bypass Sonrası S100B Protein Salınımını Azaltmıyor

PULSATILE BLOOD FLOW DURING CARDIOPULMONARY BYPASS DOES NOT REDUCE THE RELEASE OF S100B

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Özet

Amaç: S100B proteininin kardiyak operasyon ve kardiyopulmoner bypass sonrası görülebilen serebral hasarın bir göstergesi olduğu düşünülmektedir. Bu çalışmanın amacı serum S100B proteinini kullanarak, kardiyopulmoner bypass sonrasında görülebilen serebral hasara, pulsatil akımlı kardiyopulmoner bypassın etkisini araştırmaktı.

Materyal ve Metod: Elektif koroner bypass ameliyatı planlanan 30 hasta randomize olarak iki gruba ayırıldı (Grup A pulsatil akım, Grup B devamlı akım). Bütün hastalarda pulsatil ve devamlı akım sağlayabilen döner başlıklı pompa kullanıldı. Tüm hastalardan ameliyat öncesi, kardiyopulmoner bypass başlangıcında, aort klempi kaldırılmadan, cilt kapatılırken, ameliyat sonrasında 6. ve 12. saatlerde kan örneği alınarak saklandı. Elde edilen serumlardaki S100B seviyesi immunoluminometrik yöntemle ölçüldü.

Bulgular: Her iki grup yaş, anastomoz sayısı, kardiyopulmoner bypass ve aort klemp zamanı, ventilasyon zamanı ve yoğun bakımda kalış süreleri açısından karşılaştırıldı. Her iki grupta ameliyat sonrası S100B değerleri ameliyat öncesi değerlere göre önemli ölçüde yükseldi ($p < 0.001$). Devamlı akım uygulanan gruptaki S100B değerleri, özellikle aort klempi kaldırıldığında ve cilt insizyonu kapatılırken alınan kan örneklerinde diğer gruba oranla yüksek çıkmasına rağmen (1.7'e karşın 1 ve 2.2'ye karşın 1.74 µg/L; $p > 0.05$), her iki gruptaki S100B seviyeleri arasındaki fark hiçbir dönemde anlamlı bulunamadı.

Sonuç: Kardiyopulmoner bypass sırasında serum S100B değeri anlamlı derecede yükselmektedir. Kardiyopulmoner bypass sırasında uygulanan pulsatil akım devamlı akımla karşılaştırıldığında, pulsatil akımın kardiyopulmoner bypass ve sonrasında S100B salınımına anlamlı etkisi olmadığı görülmüştür. Bu sonuçlar pulsatil akımın serebral hasarı azaltıcı etkisi olmadığını göstermektedir.

Anahtar kelimeler: Serebral koruma, koroner bypass cerrahisi, pulsatil akım, S100B

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Summary

Background: S100B protein has been suggested to be a marker for cerebral injury after cardiac operation and extra-corporeal circulation. The aim of this study was to determine the effect of pulsatile blood flow during cardiopulmonary bypass (CPB) on cerebral injury by using S100B as a marker for cerebral injury.

Methods: Thirty patients with elective coronary artery bypass grafting were randomized into two groups (Group A pulsatile, and Group B non-pulsatile). In all cases a roller pump with a pulsatile and non-pulsatile mode was used for CPB. Serial blood samples (preoperative, beginning of CPB, before aortic cross clamp release, during skin closure and 6 and 12 hours postoperatively) were collected. The serum was analyzed for S100B using immunoluminometric assay.

Results: Both groups were matched for age, number of grafts, and duration of CPB and aortic cross clamping, the time of ventilation and ICU stay. Postoperative levels of S100B were significantly higher in both groups compared to the preoperative levels ($p < 0.001$). Although S100B levels were higher at the time of declamping the aorta and during skin closure in the non-pulsatile group (1.7 vs 1 and 2.2 vs 1.74 µg/L; $p > 0.05$), there was no significant difference in S100B levels between the groups at any time.

Conclusions: Serum levels of S100B increase significantly during CPB. However, pulsatile perfusion does not reduce serum S100B release significantly during CBP compared with non-pulsatile perfusion. These results indicate that pulsatile blood flow does not have a neuroprotective effect.

Keywords: Cerebral protection, coronary bypass surgery, pulsatile flow, S100B

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Introduction

Cerebral injury persists as the predominant co-morbidity after cardiopulmonary bypass (CPB). The reported incidence of stroke after coronary artery bypass grafting (CABG) is 0.8% to 5.2% [1]. The pathogenesis remains unclear, but may involve both surgical and extra-corporeal perfusion techniques [2,3]. Increasing knowledge of cerebral physiology and mechanisms of cellular damage during CPB has resulted in developments in biocompatibility, oxygenator design, and pump technology [2,3]. Although the effect of pulsatile or non-pulsatile flow during cardiopulmonary bypass on cerebral injury was studied in previous investigations [4-6], the effect of these different perfusion techniques on S100B release during CPB is still not known clearly. Only Kusch [7] compared the serum S100B concentration by using pulsatile and non-pulsatile flow during CPB and concluded that, pulsatile flow caused less cerebral damage.

S100B protein has been suggested as a promising marker for cerebral injury during cardiac surgery [8-12]. The S100-ab and -bb isoforms are predominantly present in astroglial or microglial cells and are considered to be highly specific for the brain. S100B protein is normally not present in serum, but appears after stroke, subarachnoidal hemorrhage, head injury, or extra corporeal circulation [8,9,13,14]. The present work is an extension of Kuschs study [7], but we used immunoluminometric assay (Liaison Sangtec 100, AB Sangtec Medical, Bromma, Sweden) to measure S100B release, which is a different and a more sensitive technique.

Material and Methods

Patients

The institutional ethics committee on human research approved the study protocol. Informed consent was obtained from all patients. Thirty patients undergoing elective CABG were randomized for pulsatile or non-pulsatile flow during CPB. Patients with a history of stroke, transient ischemic attack, reversible neurological disorder, carotid artery disease, or other brain disease were excluded. To avoid a possible influence of renal disorder on the elimination of S100B, patients with renal failure (creatinine > 1.6 mg/dL) were also excluded. Clinical variables, such as angina score, associated illness, ejection fraction, number of anastomoses, duration of CPB, duration of aortic cross clamp and ventilation time were registered. All patients underwent neurologic assessment preoperatively and in the intensive care unit after operation by experienced cardiac anesthesiologist or in the ward by experienced neurologist. The assessment started a few hours after the operation and was repeated during the stay in the ward.

The patients were divided into two groups. Both groups consisted of 15 patients, who underwent repeated neurological examination the week before surgery and daily after operation. Blood samples for the analysis of S100B protein were collected from each patient before surgery (1), at the beginning of CPB (2), before aortic cross clamp release (3), skin closure (4), postoperative 6 hours (5), and postoperative 12 hours (6).

Anesthesia and Extra Corporeal Circulation

After premedication, anesthesia was induced with midazolam (70 µg/kg) and fentanyl (10 µg/kg). Muscle relaxation was achieved with pancronium bromide (0.1-0.2 mg/kg). Anesthesia was supported by inhalation of isoflurane 0.5% to 1% (Abbot Laboratories, North Chicago, IL, USA). The extra corporeal circuit consisted of a roller pump (Stöckert Instrumente, Munich, Germany) with a non-pulsatile and pulsatile running mode, a hollow fiber membrane oxygenator (D 708 simplex III, Dideco, Mirandola, Italy). Patients were heparinized before initiation of CPB with 300 IU/kg, and additional doses were given to maintain an ACT of more than 480 seconds. Non-pulsatile extra-corporeal circulation was initiated with a flow of 2.4 to 2.6 L/m^2/min. Flow patterns were changed from non-pulsatile to pulsatile flow by switching the modes of the pump control program. Moderate systemic hypothermia (28°C nasopharyngeally) was used. Cardiac arrest was achieved by infusion of cold blood cardioplegic solution and topical ice-cold infusion. The distal anastomoses were performed during a single period of cross clamping. The proximal anastomoses to the aorta were completed during rewarming period. Extra corporeal circulation was terminated by 37°C. Heparin was neutralized with protamine.

S 100B Assay

All blood samples were centrifuged for five minutes at 3,000 rpm, frozen and stored at -80°C until analyzed. S100B levels were measured with an automated immunoluminometric assay (Liaison Sangtec 100, AB Sangtec Medical, Bromma, Sweden). Liaison Sangtec 100 is a two-site immunoluminometric assay based on paramagnetic particles coated with two monoclonal antibodies and a monoclonal tracer antibody labeled with an isoluminal derivative. The magnetic particles, assay buffer and sample are first incubated and unbound material is removed by a wash cycle. Tracer is added and after a second incubation, unbound material is removed by a second wash cycle. Subsequently, the starter reagents are added, and the S100B concentration is determined by way of the chemiluminescence reaction induced. The light signal measured in RLUs (relative light units) is directly proportional to the amount of S100B in the sample. The Liaison Sangtec 100 measures concentrations between 0.02-30 µg/L with an intra-assay variation of 3.7% for a mean value of 5.4 µg/L (ranging between 6.4 - 2.8% for 0.11-18.4 µg/L).

Statistical Analysis

The data were reported as the mean and ± the standard deviation of the mean. S100B data were compared using 2-way analysis of variance and Student's T-test. P-values < 0.05 were considered significant. SPSS for Windows (Version 7.0; SPSS Inc, Chicago, IL, USA) was used for data analysis.

Results

Clinical Results

There was no operative mortality. The postoperative neurological examinations did not reveal any transient or permanent neurologic deficit in either group. The patient characteristics are shown in Table 1. No patients had any preoperative history of neurologic disease. Both groups were matched for angina score (Canadian Cardiovascular Society Classification of Angina Pectoris), associated illness, ejection

Table 1. Demographic and surgical data.

	Group A (pulsatile) (n = 15)	Group B (non-pulsatile) (n = 15)	*p*
Age (years)	62.5 ± 7.5	60 ± 10	> 0.05
Gender (m/f)	9/6	8/7	> 0.05
No. of anastomoses	3.3 ± 1	2.7 ± 1	> 0.05
CBP (min)	85.5 ± 26	74 ± 24.2	> 0.05
Cross clamp time (min)	48 ± 15	42 ± 17	> 0.05
Ventilation time (hours)	5.4 ± 1	6 ± 2	> 0.05
ICU stay (hours)	19.6 ± 2.1	22 ± 2	> 0.05

CBP = cardiopulmonary bypass; ICU = intensive care unit

Table 2. S 100B Measurements.

	Group A (pulsatile) (n = 15; µg/L)	Group B (non-pulsatile) (n = 15; µg/L)	*p*
Preoperative	0.12 ± 0.03	0.09 ± 0.04	0.38
Beginning of CPB	0.85 ± 0.32	0.35 ± 0.21	0.12
Cross clamp release	1 ± 0.42	1.7 ± 0.54	0.08
Skin closure	1.7 ± 0.35	2.2 ± 0.6	0.20
Postoperative 6 hours	0.43 ± 0.15	0.36 ± 0.08	0.15
Postoperative 12 hours	0.32 ± 0.18	0.3 ± 0.16	0.11

CBP = cardiopulmonary bypass

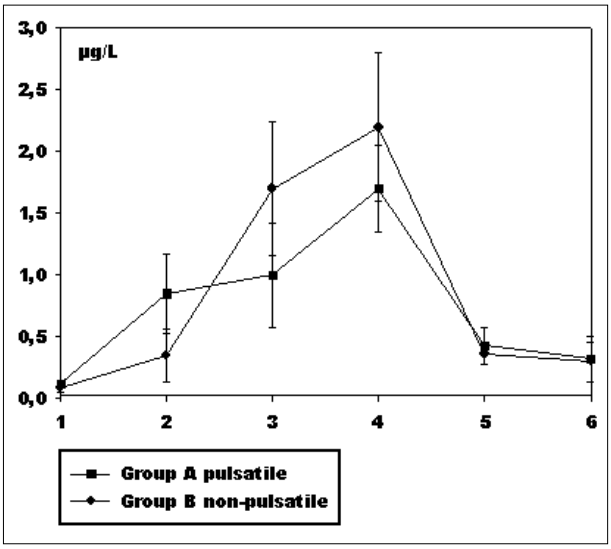

Figure 1. Release of protein S-100B in patients with pulsatile or non-pulsatile flow during CPB.
(The range of 95% of healthy subjects is < 0.12 µg/L)

fraction, gender, age, number of distal anastomoses, total perfusion time, aortic cross clamp time, ventilation time and duration of ICU stay. There were no significant differences between the two groups. All patients were discharged from the ICU on the first postoperative day. Data collection was 100% in all 30 patients.

S 100B Release

The release pattern of S100 B is shown in Table 2 and Figure 1. The mean preoperative levels were similar in both groups [0.12 µg/L (pulsatile) compared with 0.09 µg/L (non-pulsatile)]. S100B levels s increased significantly during CPB ($p < 0.001$). Peak values in both groups were recorded at skin closure, with higher levels in the non-pulsatile group (2.2 ± 0.6 vs 1.7 ± 0.35 µg/L), but this difference did not reach significance ($p > 0.05$). In general, S100B values in group B (non-pulsatile group) seemed a little higher than in group A (pulsatile group); this difference did not reach significance at any time ($p > 0.05$). All postoperative values were significantly higher than the preoperative values. In neither group did the postoperative S100B levels correlate with age, gender, total perfusion time, aortic cross clamp time, ventilation time and time of ICU stay.

Conclusions

Whether pulsatile flow during CPB itself has a beneficial effect on the brain or not is still unclear [4-6]. Although many authors have investigated pulsatile and non-pulsatile flow methods by looking at cerebral metabolism [4] or tissue oxygen saturation [15], there is still no conclusive evidence. Kusch [7] compared the effect of pulsatile versus non-pulsatile flow on serum S100B protein release that has been suggested as a promising marker for cerebral injury during cardiac operation. He presumed that pulsatile flow lowered cerebral destruction and S100B showed a lower increase compared to non-pulsatile flow. The present study was designed to determine whether this relation exists when more sensitive S100B measurements were used.

Since the discovery of S100B protein as a marker for cerebral damage, it has been used in neurologic and trauma patients to prove organic cerebral damage [16]. A number of studies showed elevated S100B levels in patients undergoing cardiac operations using extra corporeal circulation [8,11,17]. Other investigators such as Kumar [18] and Taggart [10] described S100B release during and after CPB even in neurologically asymptomatic patients. Serum S100B levels are measured using a monoclonal immunoradiometric assay or an immunoluminometric assay. The previous report measured S100B by using an immunoradiometric assay, which has a detection limit of 0.2 μg/L at the lowest [7]. In the present study we used an immunoluminometric assay, which is able to measure S100B to a lowest level of 0.02 μg/L. S100B levels were significantly increased ($p < 0.001$) after CPB in both groups but there were no significant differences between the groups at any time. These findings implicate that CPB increases the S100B levels. But pulsatile flow during CPB does not reduce the S100B release compared with non-pulsatile flow, which raises the suspicion that other etiologic factors contribute to the total astroglial damage sustained during CPB. The benefit of pulsatile perfusion is the capability to produce high perfusion pressure without flow stagnation and erythrocyte aggregation. It is also thought that more parts of the capillary bed are perfused by pulsatile flow than by non-pulsatile flow [19]. But it has also been speculated that neurological dysfunction is not the result of a single factor [20]. A possible relationship between micro-embolism and neurological dysfunction has been reported [21-23]. Moody and associates [21] demonstrated the presence of dilatation of small capillaries and arterioles in the brain after operation with CPB, but not after other types of surgical procedures. The capillary dilatations are believed to be the result of lipid micro-emboli. It is understandable that pulsatile perfusion failed to prevent neurological dysfunction if the major cause is attributed to micro-embolism. Moreover, it may be possible that pulsatile perfusion increases the risk of micro- or macro-embolism [24].

The sample size of study may be relatively small to clearly examine the neurological outcome and due to the small study group and wide range, results may be non-significant. There was no transient or permanent neurological deficit in either group. This situation may also contribute to these results. Another point should be mentioned here. The increase in serum S100B during and after conventional CABG may originate from peripheral nerves, extracts of fat, bone marrow, and organs of mesenchymal organs [25]. Furthermore, S100B accumulates in the mediastinum during and after operation [26], and therefore, substantial amounts of S100B are present in blood returned to the bypass circuit from the cardiotomy suckers. This contamination reduces the diagnostic value of S100B measurements during the first hours after operation. However, the biological half-life of S100B is only 25 minutes. The rapid elimination from bloodstream thus makes it very unlikely that any degree of contamination would affect S100B measurements at the postoperative 6th and 12th hours. Kilminster and colleagues [27] studied S100B protein release during and 5 h after the onset of CPB, and neuropsychological tests preoperatively and for 6-8 weeks after surgery in 130 patients undergoing cardiac surgery. They found that less S100B protein release was associated with better neuropsychological performance.

In conclusion, CPB increases serum S100B levels significantly in patients undergoing coronary artery bypass grafting. However, pulsatile perfusion does not reduce serum S100B release compared to non-pulsatile perfusion. Using S100B as a marker for cerebral injury pulsatile flow has no beneficial effect. Further studies are needed to confirm these results.

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