# Low S100β Measurements via Jugular Venous Bulb Catheter During Pulsatile Perfusion in Coronary Bypass Grefting Operations

## Koroner Baypas Cerrahisi Sırasında Pulsatil Perfüzyon ile Juguler Venöz Bulb Kateterinden Alınan Kanda Düşük S100β Ölçümleri

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**ABSTRACT**

**Background/Aim:** Although it has been thought that the complications due to non-pulsatile blood flow should decrease with the utilization of pulsatile perfusion during cardiopulmonary bypass (CPB), there is not enough literature about the probable beneficial effects on cerebral perfusion. In this study we aimed to determine whether the utilization of pulsatile or non-pulsatile CPB makes a difference on the cerebral circulation by the measurements of biochemical serum markers and the jugular bulb oxygen saturation ($SjVO_2$) in addition to near- infrared spectroscopy (NIRS).

**Material and Methods:** Eighteen patients scheduled for coronary revascularization on CPB were included in the study. After aortic clamping, non-pulsatile and pulsatile perfusion were both performed for 10-minute periods. S100ß, adrenomedullin (ADM), NSE and $SjVO_2$ measurements were performed 10 minutes before anesthesia, during non-pulsatile perfusion, during pulsatile perfusion and 10 minutes after CPB. Niroxope 401 was used for NIRS measurements.

**Results:** Fourteen patients were male (77.8 %) and four patients were female (22.2 %). The mean age was 59.06±10.40 and the mean ejection fraction was 50.67 ± 13.39 %. There were no statistical differences between the two perfusion regimes with regard to the mean arterial blood pressures (67.26±7.01/68.71±527 mmHg) and the serum hemoglobin levels (8.64±1.32/8.51±1.29 mg/dl). The postoperative neurocognitive dysfunction rate was 27.8 % and the cerebrovascular event rate was 11.1 %. The increasing values of s100β during non-pulsatile perfusion were decreased significantly with pulsatile perfusion. Off-pump NSE levels and ADM levels during pulsatile perfusion and after CPB were statistically higher. There were no statistical differences between the perfusion types for NSE, $SjVO_2$ and NIRS measurements.

**Conclusion:** The decrease in s100β levels during pulsatile perfusion is the striking point of this study. We think that there is a need for more studies with extended patient series to prove that the neurologic complications due to CPB should decrease with pulsatile perfusion.

**Key Words:** Pulsatile Flow, S100 Proteins, Coronary Artery Bypass, Near-Infrared Spectroscopy

**ÖZET**

**Amaç:** Kardiyopulmoner baypas (KPB) sırasında pulsatil perfüzyon kullanımı ile pulsatil olmayan dolaşıma bağlı komplikasyonların azalacağı düşünülse de, pulsatilitenin serebral perfüzyon üzerine olası yararlı etkileri konusunda yeterli literatür bulunmamaktadır. Bu çalışmada, yakın kızılötesi spektroskopi (NIRS) kayıtlarına ek olarak biyokimyasal serum belirteçleri ve juguler bulbus oksijen satürasyonu (SjVO2) ölçümleri yapılarak pulsatil veya pulsatil olmayan KPB kullanımının serebral dolaşım üzerinde fark oluşturup oluşturmadığını göstermeyi amaçladık.

**Yöntem:** KPB ile koroner revaskülarizasyon planlanan 18 hasta çalışmaya dahil edildi. Aorta klemp edildikten sonra, 10 dakikalık periyotlar boyunca non-pulsatil ve pulsatil perfüzyon uygulaması yapıldı. Anesteziden 10 dakika önce, pulsatil olmayan perfüzyon sırasında, pulsatil perfüzyon sırasında ve KPB'den 10 dakika sonra S100ß, adrenomedullin (ADM), NSE ve SjVO2 ölçümleri yapıldı. NIRS ölçümleri için Niroxope 401 kullanıldı.

**Bulgular:** Çalışmaya alınan 14 hasta (% 77,8) erkek ve 4 hasta (% 22,2) kadındı. Ortalama yaş 59.06 ± 10.40 ve ortalama ejeksiyon fraksiyonu % 50.67 ± 13.39 idi. KPB sırasındaki ortalama arteriyel kan basınçları (67.26 ± 7.01 / 68.71 ± 527 mmHg) ve serum hemoglobin seviyeleri (8.64 ± 1.32 / 8.51 ± 1.29 mg / dl) açısından iki perfüzyon rejimi arasında istatistiksel fark yoktu. Postoperatif nörokagnitif disfonksiyon oranı % 27,8 ve serebrovasküler olay oranı % 11,1 idi. Pulsatil olmayan perfüzyon sırasında artan s100β değerlerinin pulsatil perfüzyon ile önemli ölçüde azaldığı görüldü. Pulsatil perfüzyon sırasında ve KPB sonlandırıldıktan sonraki dönem NSE seviyeleri ve ADM seviyeleri istatistiksel olarak daha yüksekti. NSE, SjVO2 ve NIRS ölçümleri için perfüzyon türleri arasında istatistiksel olarak fark yoktu.

Sonuç: Pulsatil perfüzyon sırasında s100β seviyelerindeki düşüş, bu çalışmanın çarpıcı noktasıdır. Pulsatil perfüzyon ile KPB'ye bağlı nörolojik komplikasyonların azalması gerektiğini kanıtlamak için genişletilmiş hasta serileri ile daha fazla çalışmaya ihtiyaç olduğunu düşünüyoruz.

**Anahtar Sözcükler:** Pulsatilite, S100 Proteinler, Koroner Arter Baypas, Yakın Kızılötesi Spektroskopi (NIRS)

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## INTRODUCTION

Among peripheral tissues, brain is the most important organ and the most vulnerable one to ischemia during cardiopulmonary bypass (CBP), and it needs to be well protected (1). Neurological complications that may develop after cardiac surgery are especially due to embolization and hypoperfusion (2). As a result of changes in cerebral blood flow during CPB, despite the cerebral autoregulatory system, it was found that there was a decrease in neurocognitive functions after pump up to 6 months (3). Neurological complications that may develop after cardiac surgery are classified into two groups according to ACC-AHA (American College of Cardiology and American Heart Asssosiation) classification (1-4). While stroke-like events are called as type-1, neurocognitive complications are called type-2. Diagnostic methods are limited in the detection of type 2 complications. In order to detect neurological complications, serum markers such as S100ß, Neuron Specific Enolase (NSE) and adrenomedullin (ADM) were used (5-16).

Although normal circulation physiology has a pulsatile character, standard cardiopulmonary bypass has a non-pulsatile character. It is possible for many heart lung machines to be used to generate pulsatile flows but a fully physiological pulsatility cannot be accomplished with these systems (2, 17). It has been reported that tissue oxygenation and oxygen utilization by tissues increase with pulsatile perfusion and that systemic vascular resistance increase is prevented by maintaining reflex vasomotor control close to normal (18). However, the idea suggesting that pulsatile perfusion may increase the hemolysis rate and publications stating that this technique does not have significant physiological benefits have hindered the proliferation of this technique (2,19,20). Although the publications pointing the impact of pulsatile perfusion on cerebral, renal and gastrointestinal systems are limited in number and include differing conclusions, the general conviction is that the brain functions, cerebral metabolism and blood flow distribution are better with pulsatile CPB (21).

NIRS is fundamentally a regional cerebral oximetry technique. With this optical method, which has come into use in many cardiovascular units, the concentrations of some light-absorbing compounds such as oxygenated hemoglobin (HbO2), deoxygenated hemoglobin (Hb), and oxidized cytochrome oxidase (CtOx) in the cerebral tissue are measured and information on the saturation of cerebral oxygenation ($RSO_2$) and CBF is acquired (22-28).

In our study, we aimed to investigate the effects of pulsatile or non-pulsatile usage of CPB on cerebral circulation by using serum markers related to neurological dysfunctions and CBF measurement methods such as invasive jugular venous oxygen saturation ($SjVO_2$) and non-invasive regional cerebral oxygen saturation ($RSO_2$).

## MATERIALS and METHODS

*Participants*

An 18-weeks study was planned after the approval of Gazi University Ethics Committee (22.12.2008 - 415) was received. Coronary artery disease patients between the ages 18 and 70 who had signed the informed consent form and whose left ventricular ejection fractions were 30% and over were included in the study. Patients with liver disease, renal function disorder (creatinine > 2,0 mg/dl), severe anemia (hemoglobin < 10 mg/dl), reoperations, emergency surgery, psychiatric disease, carotid artery disease, cerebrovascular disease and cardiopulmonary resuscitation history were not included in the study. Patients whose CPB duration was less than 20 minutes or more than 120 minutes and patients who refused the recording of NIRS data were also excluded from the study. Approval of Gazi University Ethics Committee (22. 12.2008 , 415) was received.

*Anesthesia and Premedication*

Etomidate 0.3 mg/kg i.v. was administered after remifentanil infusion for anesthesia induction. Following intubation, 2% sevoflurane was started, and anesthesia was maintained. For blood serum measurements, 18 G catheter was placed retrogradely via the right internal jugular vein so as to position the catheter tip in the jugular bulb. The ventilation of the patient was regulated so as to make 6ml/kg tidal volume, a total of 4l/min in 40% $O_2$ air and to keep $EtCO_2$ in the interval between 30 mmHg and 35 mmHg. In the arterial blood gas analysis, $SO_2$ values were kept over 95% and this value was kept over 99% during CPB.

*Surgery, CPB and Postoperative Follow-up*

After median sternotomy, LIMA artery flap and saphenous vein grafts were harvested for CABG. CPB was instituted after anticoagulation and aortic-atrial cannulation. The total pump blood flows of the patients were adjusted as 2,4 $l/m^2$/min and hemodilution was maintained by decreasing the hematocrit value to 26%. Pump flow was adjusted to keep it between 60-70 mmHg during CPB. After the CPB was started, following aortic cross-clamping, antegrade hypothermic (8 ° C) 15 ml/kg blood cardioplegia was given. Cardioplegia was repeated every 20 minutes with a dosage of 5 ml/kg. All patients were put under alpha-stat ph follow-up regimen and nasopharyngeal body temperature was lowered to 30° C.

Pulsatile pump flow control was activated by using an internal ECG simulator during total bypass with a module in the roller pump we used. ECG frequency and flow ratio were adjusted independently of each other. For every ECG cycle, pump utilization percentage and continuous basal flow were chosen, and flow characteristics were determined. Heart rate was adjusted as 60 rpm for pulsatile mode, adjustments were made to make the pulse width 40-50% and the basal flow amount 35-50%. Proximal anastomoses were done with side clamping aorta. After coronary revascularizations the patients who were observed to have appropriate blood pressures and heart rhythms were weaned from CPB.

*$SjVO_2$ Measurements and Collection of Serum Samples*

A total of 5ml blood was collected from retrograde jugular vein catheter for the basal values of $SjVO_2$, s100ß, NSE and ADM at the 10th minute (t1) after anesthesia. 10 minutes after the aortic clamping during non-pulsatile CPB (t2), a total of 5ml blood was collected from the jugular vein catheter again for blood gas analysis and s100ß, NSE and ADM measurements and pulsatile CPB was started. At the 10th minute after pulsatile CPB was started (t3), blood tests were repeated and NIRS measurement records were continued. After weaning off the pump, recording the NIRS data was continued for 10 minutes and the blood tests were repeated at the 10th minute (t4).

*NIRS Record and Analysis*

After the patients were transferred to the operating table, the probe of NIRS device was placed to the parietofrontal region noninvasively. Continuous recording was done with intervals of 10msn beginning before the anesthesia. By using a previously prepared software package in the biophotonics laboratory, analysis was done in MATLAB program. Mean oxyhemoglobin and deoxyhemoglobin changes were calculated in the time intervals between markers.

*Biochemical Tests*

The blood samples were centrifuged at 800-1000 RPM for 10 minutes and serums were separated. The serums obtained were put in two separate Eppendorf tubes for each patient and they were kept at -70 ºC until the study date. After all the samples were collected, the measurements were done on the same day. Serum S100B levels were analyzed by Enzyme-Linked Immunosorbent Assay (ELISA) method using ready kits (BioVendor, Evropska, Czech Republic). Serum NSE levels were analyzed by Enzyme-Linked Immunosorbent Assay (ELISA) method using ready kits (Epitope Diagnostics, Inc., San Diego, USA). Serum Adrenomedullin levels were analyzed by Enzyme-Linked Immunosorbent Assay (ELISA) method using ready kits (USCNLIFE SCIENCE, CHINA).

*Statistical Analyses*

Statistical Analyses were carried out with SPSS (Version 15.0, SPSS Inc., Chicago, IL) computer program. The results were considered in 95% confidence interval with significance $p < 0.05$. Variance analysis was done in repeated measurements to investigate the differences between the mean values of hemoglobin, NIRS, S100β, NSE, ADM and $SjO_2$. To detect the measurement times that contained statistical differences, Friedman multiple comparison test was used. Willcoxon test was used for the analysis of preoperative and postoperative mini-mental values. Spearman and Pearson correlation coefficients were used to detect the factors effective on the mean values of mini-mental, NIRS, S100β, NSE, ADM and $SjVO_2$.

## RESULTS

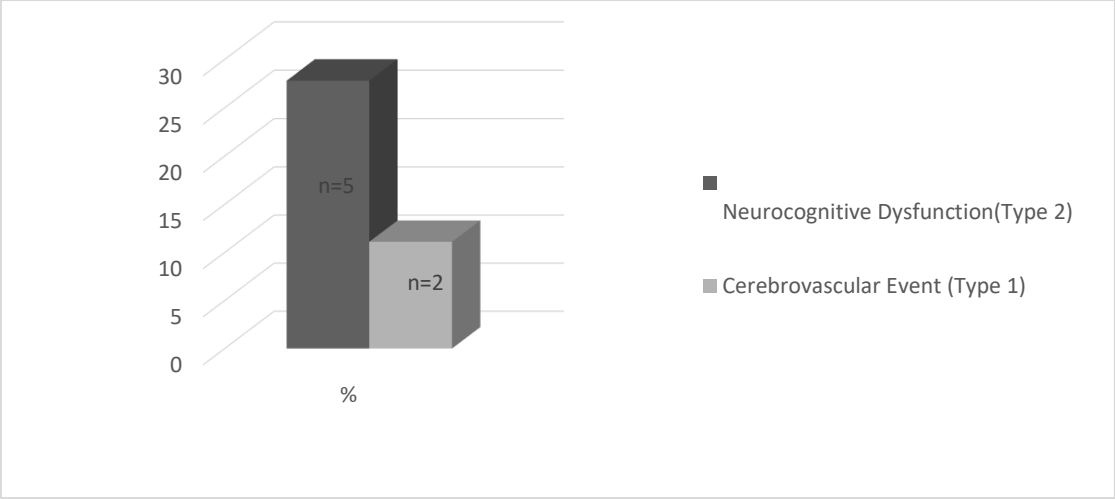
*Biochemical Tests Results*

77.8% of the patients were males and 22.2% were females. Among the preoperative accompanying diseases, hypertension (89.9%) and diabetes (50%) were observed most frequently. 72.2% of the patients had > 10 pack-year smoking history. The mean age of the patients was calculated as 59.06 ± 10,40. While the preoperative mean body weight was 81 ± 11.87 kg., the mean body surface was calculated to be 1.91 ± 0,15 $m^2$. Preoperative mean ejection fraction was 50.67 % ± 13.39. The surgery types that were executed included 5.6% (n=1) single vessel bypass, 27.8% (n = 5) 2 vessels bypass, 44.4% (n = 8) 3 vessels bypass, 16.7% (n = 3) 4 vessels bypass and 5.6% (n = 1) 5 vessels bypass. The mean perfusion flow was calculated as 4617.50 ± 366.25 ml/kg-min, the mean perfusion duration was calculated to be 108.00 ± 29.97 minutes and the mean aortic clamping duration was calculated to be 59,78 ± 23,88 minutes.

While the mean blood pressure of the patients was 67.26 ± 7.01 mmHg during pulsatile perfusion, it was measured to be 68.71 ± 5.27 mmHg during non-pulsatile perfusion.

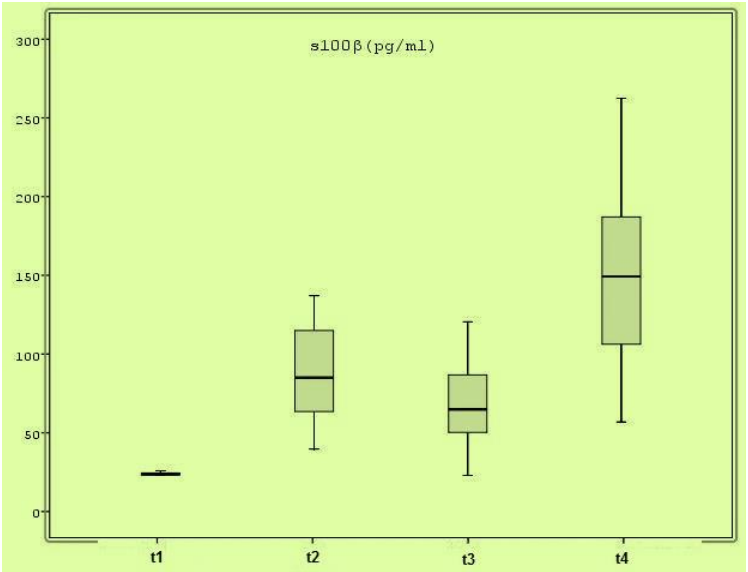
Atrial fibrillation in 7 patients (38,9%), pulmonary complications in 5 patients (27,8%), infection in 4 patients (22,2%), temporary liver function tests disorder in 3 patients (16,7%), low heart output in 3 patients (16,7%), skin reaction in 1 patient (5,6%), extended tube drainage in 1 patient (5,6%), sternal dehiscence in 1 patient (5,6%) and cholestatic jaundice in 1 patient (5,6%) were observed as postoperative complications.

Neurological Complications were observed in 7 patients (38,9%) While neurocognitive dysfunction which is in the 2nd group among cerebral complications, was observed with a ratio of 27.8%, cerebrovascular accident which is in the 1st group was observed with a ratio of %11.1 (Graphic 1).




**Graphic 1:** Neurological Complications

S100β averages were statistically different between all measurements ($p < 0.05$) (Table 1). Pulsatile CPB 10th minute (t3) S100β mean values were correlated with aortic clamp time ($p = 0.03$ / $r = 0.511$) ($p < 0.05$). There was a strong correlation with aortic clamp time and 10th minute after CPB weaning (t4) S100β mean values ($p = 0.003$ / $r = 0664$) ($p < 0.01$). There were also correlations with CPB time, and non-pulsatile pump 10th min (t3) and pulsatile pump 10th min (t4) S100B mean values ($p < 0.05$). There was a strong correlation between CPB time and t4 S100β mean values. ($p < 0.01$) (Graphic 2).




**Graphic 2**: Minimum, maximum and average values for S100β values and 50% of patients

There were statistically significant differences between 10th minutes after CPB weaning (t4) NSE mean values with t1 ($p < 0.001$), t2 ($p < 0.001$), t3 ($p < 0.05$) NSE mean values (Table 1).

**Table 1 :** S100β, NSE,ve ADM mean values of the patients

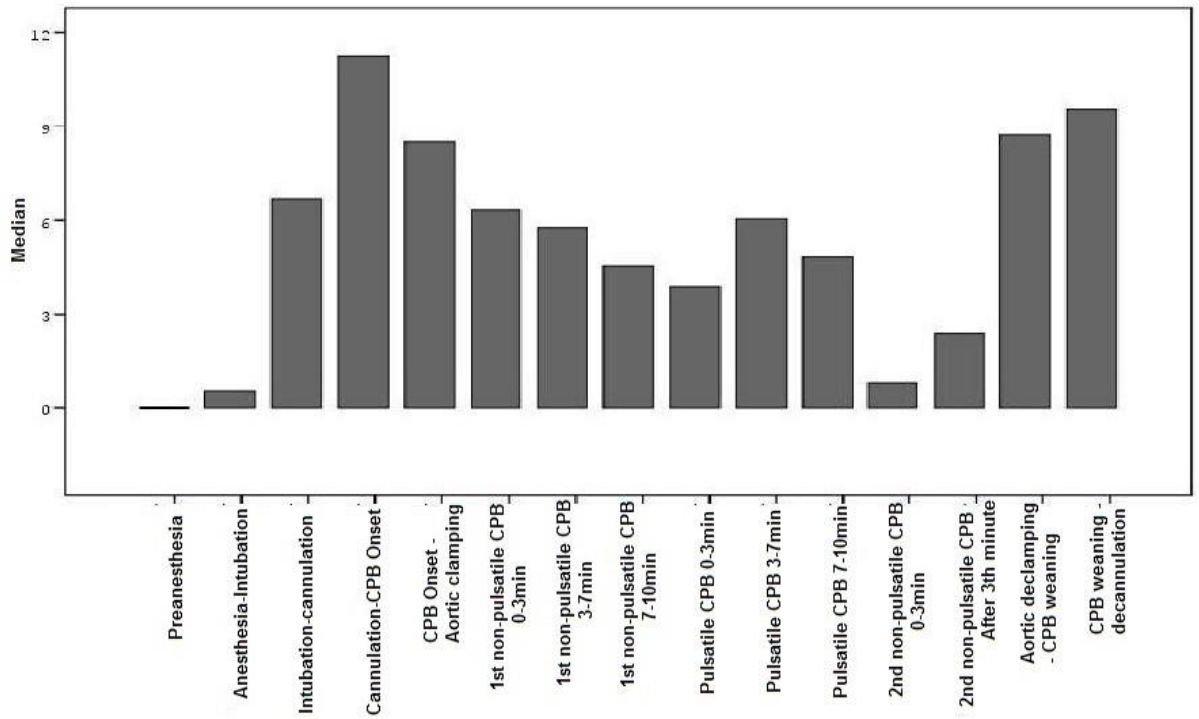
| | S100β (pg/ml) | NSE (ng/ ml) | ADM (pg/ml) |
|---|---|---|---|
| T1 | 23.99 ± 0.84 | 12.48 ± 3.95 | 665.99 ± 39 |
| T2 | 90.22 ± 32.59 | 13.15 ± 4.91 | 652.06 ± 29 |
| T3 | 67.97 ± 29.59 | 15.75 ± 5.82 | 778.78 ± 24 |
| T4 | 150.49 ± 66.10 | 25.71 ± 6.94 | 844.44 ± 26 |

There was a statistically significant difference between t2 ADM mean values and t3 ADM averages ($p < 0.01$) (Table 1). T3 ADM averages and t4 ADM averages were statistically significant difference ($p < 0.05$). There were no correlations between adrenomedullin levels and aortic clamping and perfusion time.

No statistical difference was found for the jugular venous oxygen saturation for all times. Jugular venous oxygen saturation was less than 50% in only 3 patients 10 minutes after anesthesia (t1). There was no correlation between perfusion time and SjVO2 values. Jugular bulb venous oxygen saturation averages at all times in patients with cerebral complications. Although the number of patients who developed neurological complications was 2, the rate was not considered statistically significant.

*NIRS Mesurements*

There was a statistically significant difference between preanesthesia period and intubation-cannulation period for fNIRS-HbO2 ($p < 0.05$). There was a statistically significant difference between preanesthesia period and CPB weaning-deacannulation period for fNIRS-HbO2 ($p < 0.05$). There was a statistically significant difference in mean change of fNIRS-HbO2 between intubation - cannulation period and preanesthesia, pulsatile, 2nd non-pulsatile periods ($p < 0.05$). There was a statistically significant difference in mean change of fNIRS-HbO2 between pulsatile period and intubation-cannulation, CPB weaning-deacannulation period ($p < 0.05$). There was a statistically significant difference in mean change of fNIRS-HbO2 between 2nd non-pulsatile period and intubation-cannulation, CPB weaning- deacannulation periods ($p < 0.05$). There was a statistically significant difference in mean change of fNIRS-HbO2 between CPB weaning-deacannulation period and preanesthesia, pulsatile, 2nd non-pulsatile periods ($p < 0.05$) (Graphic 3).




**Graphic 3 :** NIRS HbO2 changes during operation (mMol / lt)

## DISCUSSION

As a result of the developments in anesthesia, surgery and perfusion regimes, surgeries of older and more complicated patients have become possible, but the frequency of neurologic complications is still high (1,2,29-32).

The utilization of pulsatile flow during CPB has gained popularity especially in the 1980s but it has lost this popularity later. This was mainly due to studies like that of Wesolowski's suggesting that pulsatile circulation did not have an additional advantage.

In these studies, the flow velocities were maintained between 130 ml/kg-min and 200 ml/kg-min. However, the difference between pulsatile and non-pulsatile flow patterns becomes important mainly in flow velocities under 100 ml/kg-min. (33,34). Another reason for pulsatile flow to lose popularity is the concern that it may cause hemolysis. Mechanical trauma on blood is not only due to the flow type but it is also associated with the type of the oxygenator and pump head. (35).

In more recent studies, less mortality and low cardiac output syndrome requiring less medical and mechanical support were observed with pulsatile flow but no increase in hemolysis or decrease in shaped blood cell count was detected (36). In another article, the use of pulsatile perfusion in patients with a high risk of myocardial ischemia and infarction, carotid artery stenosis, chronic renal and hepatic insufficiency and patients with severe arterial hypertension has been reported to be useful. (37).

There are many studies investigating the correlation between the increase in the serum levels of NSE, S100ß and ADM after CPB and neurocognitive function disorders (5-15). NSE is known that this enzyme increases after many cerebrovascular pathologies due to neuron death. In a study, serum NSE levels that start to increase with CPB start to decrease after reaching a peak especially towards the end of the warming period and descend to normal levels on the 2nd day after the operation in neurologically healthy patients (11). In another study, it has been demonstrated that the decrease clearance of NSE values after CPB is 20 hours. This value has been reported as 2 hours for S100 (28). In our study, there were statistically significant differences between 10th minutes after CPB weaning (t4) NSE mean values with t1, t2, t3 NSE mean values as expected. It has been argued that increasing NSE levels during CPB were not only due to cerebral damage but that the serum NSE levels could also increase as a result of hemolysis that developed during CPB (12).

Adrenomedullin, is a peptide impacting the autoregulatory system by causing vasodilatation in the arterioles in the cerebral system without affecting the systemic blood pressure (39,40). According to Serrano et al., when it is given directly from the outside, it binds to receptors in the blood vessels, vasodilatation occurs, perfusion increases and finally damage increases. In our study, no correlation was observed between ADM mean values and aortic clamping and perfusion durations. This statistically significant rise during pulsatile CPB when compared to non-pulsatile CPB can be interpreted as being one of the positive effects of pulsatile CPB on neurological complications.

S100β an astro-glial protein is secreted by degenerated astrocytes. In cases where blood-brain barrier is deteriorated, its concentration in the peripheral circulation increases (13). In our study, statistically the most significant difference between pulsatile and non-pulsatile perfusion was observed in S100β values. The S100β values which were calculated to have a mean value of 23.99 pg/ml after anesthesia displayed statistical increase and reached a mean of 90.22 pg/ml at the 10th minute of non-pulsatile CPB. At the end of the pulsatile CPB, although the CPB duration and aortic clamping duration were prolonged, a statistically significant decrease was observed in S100β values and the mean values were calculated to be 67.97 pg/ml. After pump removal, a statistically significant increase was observed again, and the mean value was calculated to be 150.49 pg/ml. Although there was no difference between the mean blood pressures and serum hemoglobin concentrations during non-pulsatile and pulsatile CPB in our study, we think that observing the mean values of S100β to be statistically significantly low during pulsatile perfusion is important. In some previous studies, it has been claimed that high S100β values were due to pump aspirator and extracranial proteins (13). However, this decrease observed during pulsatile CPB in our study is hard to explain with contamination because the blood drawn from our patients were taken from the jugular venous bulb catheter where contamination is minimum and there was very little pump aspirator use with patients in this study.

In our study, in the patients with neurological complications, no correlation was observed between the aortic clamping duration and perfusion duration due to the insufficiency of the number of patients. All patients except two with neurologic complications were discharged from the ICU within the first 2 days. In one of the patients who had orientation deterioration, agitation and temporary delirium status were observed in the intensive care unit. Temporary renal insufficiency and pulmonary complications developed in these patients. Due to all these factors they could be discharged from the ICU after 5 and 7 days and had prolonged hospital stays.

In our study, it was detected that the most significant changes occurred with mechanical ventilation start after the intubation of the patient and with the removal of the aortic clamp and pump removal. It is an expected result to observe a significant fNIRS-$HbO_2$ increase by making the patient have 100% oxygen respiration in comparison to the period in which the patient has respiration with mask. Decrease in these values that started with CPB continues until the end of CPB and it decreases to almost basal level in the 2nd non-pulsatile period after pulsatile CPB.

In a study similar to ours, which was carried out by using only NIRS, it was claimed that pulsatility did not change cerebral oxygenation (41). Unlike our study, $CtO_2$ levels were also considered in this study.

In this study, we aimed to compare pulsatile and non-pulsatile perfusions, which are two alternative methods causing change between the dynamics of CPB by using current technology, for neurological complications with parameters based on devices and laboratory. The findings we obtained demonstrated that positive benefits on neurological complications could be obtained with pulsatile perfusion. However, studies with wider perspectives are needed to illuminate this subject.

**Conflict of interest**

No conflict of interest was declared by the authors.

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