

# Does cardiopulmonary bypass change serum neuron-specific enolase levels?

*Kardiyopulmoner baypas serum nöron spesifik enolaz düzeyini değiştiriyor mu?*

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## ABSTRACT

**Objective:** The effects of cardiopulmonary bypass (CPB) on serum neuron-specific enolase (NSE) levels in patients without cognitive dysfunction and neurological deficit are not yet clarified. This study was designed to see the sole effect of extracorporeal circulation on serum NSE levels in patients without any clinically observed neurological deficit.

**Methods:** Thirty-two consecutive patients undergoing first elective open-heart surgery were included in this prospective study. Neurological status was assessed by clinical examination before surgery, and on the postoperative first and second days. Blood samples were obtained after anesthesia induction before the administration of heparin, within the first hour post CPB, 24 and 48 hours after the end of operation. Each blood sample was assayed for hemoglobin (Hb), hematocrit and NSE levels. The Friedman's Test to compare the serial measurements of NSE and hemoglobin samples and the post-hoc Tukey test for paired comparisons between pre and postoperative values were applied Pearson correlation test was used to examine the correlation between NSE concentration and aortic cross-clamping time and CPB time, age, postoperative hematocrit and hemoglobin levels and the amount of blood products transfusion.

**Results:** There were no significant differences between NSE values at any sampling time: 11.6±8.0 mg/dL, 8.7±4.7 mg/dL, 9.3±5.4 mg/dL and 8.9±5.8 mg/dL, measured preoperatively, at the end of operation, on the first and second post-operative days, respectively. There was no significant correlation between NSE values with any of the compared variables including CPB time.

**Conclusion:** This study demonstrated that the possible damage of CPB on central nervous system and on blood cells did not reach to the extent of causing any significant increase in serum NSE levels in non-complicated patients undergoing open-heart surgery. (*Anadolu Kardiyol Derg 2007; 7: 411-4*)

**Key words:** Cardiopulmonary bypass, neuron specific enolase

## ÖZET

**Amaç:** Kardiyopulmoner baypasın (KPB) nörolojik fonksiyon bozukluğu olmayan hastalardaki etkisi henüz tam olarak açıklığa kavuşturulabilmiş değildir. Bu çalışma, nörolojik hasar bulgusu olmayan hastalarda, sadece ekstrakorporeal dolaşımın serum nöron spesifik enolaz (NSE) düzeyleri üzerine olan etkisini araştırmak için düzenlenmiştir.

**Yöntemler:** Bu prospektif çalışmaya kliniğimizde elektif açık kalp cerrahisi uygulanan ardışık 32 hasta alındı. Hastaların preoperatif ve post-operatif dönem 24. ve 48. saatlerinde nörolojik muayeneleri yapıldı. Anestezi induksiyonu sonrasında, kardiyopulmoner baypas'ın 1., 24. ve 48. saatlerinde kan örnekleri alındı. Tüm kan örneklerinde hemoglobin (Hb) ve NSE düzeylerine bakıldı. Preoperatif ve postoperatif, NSE ve Hb düzeylerinin karşılaştırılması için Friedman's Test ve post-hoc Tukey test kullanıldı. Nöron spesifik enolaz ve kardiyopulmoner baypas süresi, aortik kros-klemp süresi, hasta yaşı, hematokrit ve hemogloblin düzeyleri arasındaki ilişki için Pearson korelasyon testi uygulandı.

**Bulgular:** Operasyondan hemen sonra ve postoperatif 1. günde bakılan serum nöron spesifik enolaz düzeyleri, preoperatif dönemdeki düzeylerine göre daha düşük bulundu, ancak istatistiksel olarak anlamlı bir fark saptanmadı (11.6±8.0 mg/dL, 8.7±4.7 mg/dL, 9.3±5.4 mg/dL ve 8.9±5.8 mg/dL). Serum NSE düzeyleri ile kardiyopulmoner baypas süreleri arasında anlamlı bir korelasyon saptanmadı.

**Sonuç:** Çalışmamızda kardiyopulmoner baypas ile santral sinir sisteminde ve kan hücrelerinde, serum NSE düzeylerini yükseltecek düzeyde olumsuz etkisinin olmadığı görülmüştür. (*Anadolu Kardiyol Derg 2007; 7: 411-4*)

**Anahtar kelimeler:** Kardiyopulmoner baypas, nöron spesifik enolaz

## Introduction

Neurological deficit continues to be a matter of concern in patients undergoing cardiac operations with cardiopulmonary bypass (CPB), which is reported to be permanent in 1% to 5% of cases (1–3). Furthermore, temporary cognitive dysfunction

has been reported to occur in up to 70% of patients undergoing CPB (4).

Neuron-specific enolase (NSE) is a diametric cytoplasmic isoenzyme known as well-established marker of neuronal damage in various neurological disorders (5–12). Few studies have shown the relationship between cognitive impairment and

NSE levels after CPB (13, 14). However, the effects of CPB in patients without cognitive dysfunction and neurological deficit are not yet clarified. This study was designed to establish the sole effect of extracorporeal circulation on serum NSE levels in patients without any clinically observed neurological deficit.

### Methods

Thirty-two consecutive patients undergoing first elective open-heart surgery were included in this prospective study. Exclusion criteria were having a history of cerebral disease and/or any stroke developed in the postoperative course. Patients were asked to volunteer for the study and an informed consent was obtained. Indications for surgery were coronary artery disease in 23, valvular heart disease in eight patients, and atrial septal defect in one. The male/female ratio was 28/4 and median age was 64 years (range 37 to 79 years) (Table 1).

The anesthesia procedure was similar in all patients, and consisted of 5 mg/kg of fentanyl in combination with thiopental 3 to 5 mg/kg at induction. Intubation was performed during pancuronium relaxation and anesthesia was maintained by additional doses of fentanyl and inhalation of enflurane.

In surgery, a median sternotomy was made, heparin was given (3mg/kg), aortic and right atrial venous cannula were inserted, and a standard CPB with moderate systemic hypothermia (28°C of esophageal temperature) was instituted using a Dideco D.708 simplex III hollow-fiber membrane oxygenator and roller pump generating a nonpulsatile flow. An arterial filter was included in the circuit. Mean arterial pressure was maintained above 50 mmHg during cardiopulmonary bypass. For myocardial protection, cold anterograde intermittent blood cardioplegia and topical ice slush were used. In all coronary artery disease patients, left internal mammary artery was used for left anterior descending coronary artery and saphenous vein for the other coronaries. All distal anastomoses were performed under aortic cross-clamping while proximal anastomoses were performed with a site-biting clamp on the ascending aorta. All valvular heart diseases patients had their valves replaced.

Blood samples were obtained after anesthesia induction before the administration of heparin (Pre-CPB), within the first hour (post-CPB), 24 and 48 hours after the end of CPB. Neurological status was assessed by clinical examination before surgery, and on the postoperative first and second days.

Each blood sample was assayed for hemoglobin (Hb), hematocrit and NSE levels. Hemoglobin (Hb) and hematocrit

were measured immediately after sampling. For NSE, samples were centrifuged at 5000 g for 3 min and frozen at -80°C until assayed.

### Statistical analysis

SPSS (10.0) statistical analysis program for Windows (Chicago, IL, USA) was implemented for the analysis. After testing the normality of data distribution, the Friedman's Test for non-parametric repeated measures comparisons was performed to compare the serial measurements of NSE and hemoglobin samples. The post-hoc Tukey multiple comparison test was applied for paired comparisons between the pre and postoperative values.

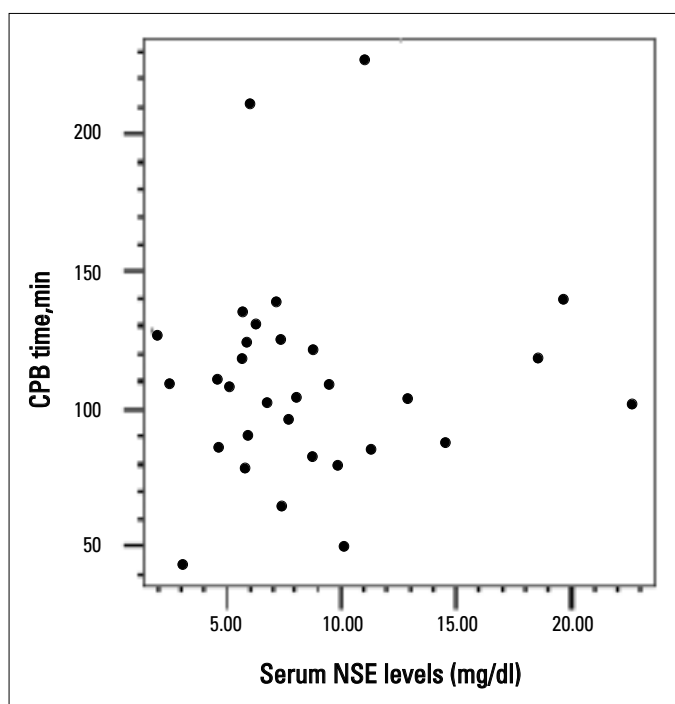
Pearson correlation test was used to examine the correlation between NSE concentration and aortic cross-clamping time, CPB time, age, postoperative hematocrit and hemoglobin levels and the amount of blood products transfusion. Data were expressed as the mean and standard deviation. Statistical significance was assumed at a probability level of less than 0.05.

### Results

The perioperative and postoperative course was uneventful in all patients included in the study except for one case that had major stroke at postoperative period. Preoperative and postoperative values are given in Table 2. The median CPB was 99 minutes (range 43 to 138 minutes). The NSE values, at end of the operation, on the first and second post-operative day were lower when compared with the preoperative values, but the differences were not significant. There was no significant correlation between the end operation NSE values and CPB and cross-clamp times (Fig. 1). Total Hb values measured in post-CPB sampling times were found to be lower than pre-CPB values ( $p < 0.01$ , Table 2); however, no correlation was found between NSE and Hb values (Table 3).

**Table 1. Characteristics and intraoperative data of 35 patients**

|                                  |        |
|----------------------------------|--------|
| Mean age, years                  | 60±10  |
| Male/Female                      | 28/4   |
| Indications for surgery          |        |
| Coronary artery disease, n       | 23     |
| Valvular heart surgery, n        | 8      |
| Atrial septal defect, n          | 1      |
| Mean CPB time, min               | 108±36 |
| Mean cross-clamp time, min       | 64±23  |
| CPB- cardiopulmonary bypass time |        |



**Figure 1. The relationship of cardiopulmonary bypass time and serum NSE levels immediately after operation ( $r=0.053$ ,  $p=0.779$ )**

CPB - cardiopulmonary bypass, NSE - neuron specific enolase

## Discussion

Our study demonstrated that post- cardiopulmonary bypass serum NSE levels remained near pre-operative values in this group of patients without any clinically observed neurological deficit; changes in serum NSE levels did not correlate with serum Hb levels.

Neuron-specific enolase, a dimeric cytoplasmic isoenzyme has been shown to be located in neurons and neuroectodermal tissue. Numerous studies have suggested that NSE may be useful marker in predicting the prognosis after brain damage (12, 15). Marked increases in serum NSE levels were observed during and after CPB operations especially in patients who showed neurocognitive dysfunction in the post-operative period (16, 17). Serum NSE level was shown to reach its peak during CPB at the end of re-warming and started to decrease immediate after the end of operation down to near normal levels by second day after surgery in neurologically intact patients (18). In the present study, we did not observe any significant changes in serum NSE levels before and after surgery. This finding might be attributed in part to the timing of blood sampling where NSE release was not at its peak level and returned to near normal values. In this regard, our data are consistent with previous studies that serum NSE levels are near normal values at 24 hours after surgery (18).

In addition, NSE was also found in platelets and erythrocytes, and hemolysis has an effect on serum NSE levels (19). For these reasons, CPB due not only adverse effects on central nervous system but also its detrimental effects on blood cells causing hemolysis, can increase serum NSE levels in patients undergoing

open-heart surgery. Hemodilution is a widely used method adjuvant to hypothermic CPB for safety measures in cardiac surgery. Lower Hb values in the postoperative period may be attributed to blood loss and hemodilution. Postoperative Hb levels were lower in the present study. However, changes in serum NSE levels did not correlate with changes in Hb levels. This finding may be explained by that the effect of hemolysis on changes of serum Hb levels is not prominent enough to alter serum NSE levels. We did not find significant differences in preoperative serum NSE levels compared to postoperative NSE levels in the postoperative period in present study.

## Conclusion

The data of this study demonstrated that the possible damage of CPB on central nervous system and on blood cells did not reach to the extent of causing any significant increase in serum NSE levels in non-complicated patients undergoing open-heart surgery.

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**Table 2. Changes in NSE and hemoglobin levels after operation**

|                             | NSE, mg/dL | Hb, g/dL  |
|-----------------------------|------------|-----------|
| Preoperative                | 11.6±8.0   | 13.2±1.5* |
| Immediately after operation | 8.7±4.7    | 9.2±1.7   |
| 24 hour after operation     | 9.3±5.4    | 8.5±1.3   |
| 48 hour after operation     | 8.9±5.8    | 8.8±1.4   |
| χ <sup>2</sup>              | 1.91       | 46.57     |
| p                           | 0.59       | <0.001    |

Friedman non-parametric test for repeated measurements  
\*- p<0.01 for Tukey multiple comparisons test, preoperative hemoglobin compared to post-operative hemoglobin levels  
The values are presented as mean±standard deviation  
Hb- hemoglobin, NSE- neuron specific enolase

**Table 3. Correlation of NSE levels with clinical and intraoperative variables**

|  | Age            | CPB time time  | Cross-clamp operation Hb levels | Immediately after operation Hb levels | 24 hours after Hb levels |
|--|----------------|----------------|---------------------------------|---------------------------------------|--------------------------|
| Preoperative NSE<br>r / p value                | -0.009 / 0.962 | -0.094 / 0.616 | 0.153 / 0.411                   | -0.024 / 0.896                        | -0.050 / 0.790           |
| Immediately after operation NSE<br>r / p value | -0.088 / 0.631 | -0.053 / 0.779 | 0.112 / 0.547                   | -0.204 / 0.270                        | -0.003 / 0.988           |
| 24 hour after operation NSE<br>r / p value     | -0.148 / 0.419 | -0.060 / 0.748 | -0.011 / 0.952                  | -0.045 / 0.808                        | -0.190 / 0.307           |
| 48 hour after operation NSE<br>r / p value     | -0.218 / 0.232 | -0.251 / 0.173 | -0.267 / 0.147                  | 0.275 / 0.135                         | 0.054 / 0.773            |

CPB- cardiopulmonary bypass time, Hb - hemoglobin, NSE - neuron specific enolase

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