

# Impact of Bispectral Index Monitoring Versus Clinical Judgment as a Guide for Conduction of Anesthesia on Serum Cortisol Level in Coronary Artery Bypass Graft Surgery

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## Abstract

**Background:** Inadequate depth of anesthesia leads to release of stress hormones. Electroencephalographic monitoring by bispectral index is a guide to assess the depth of anesthesia. The aim of the present study was to measure the serum cortisol levels as an index of stress response in patients who are candidates for coronary artery bypass graft surgery in two groups of patients.

**Methods:** Seventy-six patients who were scheduled for primary elective cardiopulmonary bypass were enrolled in a double-blind randomized study. The patients were divided into two groups. The infusion of anesthetic drugs was guided by bispectral index in group I (n=38), and by clinical judgment in group II (n=38). For all the patients the blood cortisol level was measured four times during operation.

**Results:** Serum cortisol levels decreased during operation in both groups, reaching 67.8% of the baseline in group I and 63.2% of the baseline in group II. There were no significant differences in mean serum cortisol levels between the two groups ( $p < 0.09$ ). Preoperatively, the mean blood cortisol level was 19.94  $\mu\text{g/dl}$  in group I and 16.89  $\mu\text{g/dl}$  in group II which reached to 10.48  $\mu\text{g/dl}$  in group I and 6.42  $\mu\text{g/dl}$  in group II postoperatively. There was no significant difference between two groups regarding bispectral index values.

**Conclusions:** It seems that monitoring of the patients by clinical judgment or bispectral index has equal influences on serum cortisol levels during coronary artery bypass graft surgery.

**Iran J Med Sci 2008; 33(3): 155-159.**

**Keywords** • Depth of anesthesia • stress response • cortisol

## Introduction

**C**ardiopulmonary bypass (CPB) is associated with well described changes in the neurohormonal environment, which are characterized by the activation of the sympathetic axis and a generalized stress endocrine response.<sup>1-5</sup> Cortisol is one of the main components of the endocrine stress reaction.<sup>6</sup> Reducing this hormonal response is beneficial in the

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Submitted: 14 January 2008

Revised: 9 July 2008

Accepted: 3 August 2008

recovery period.<sup>7</sup> Some authors have reported a decline in plasma cortisol levels at the onset of CPB.<sup>1,8</sup> This finding suggests that hemodilution occurs in all patients during CPB surgery.<sup>9</sup> On the other hand, despite the avoidance of cardiopulmonary bypass, off pump coronary artery bypass graft surgery triggers a systemic stress hormone response that is comparable to conventional surgical revascularization.<sup>10</sup>

Anesthetic agents and methods used in such operations have different effects on this response.<sup>7</sup> Inadequate depth of anesthesia during open heart surgery and cardiopulmonary bypass are associated with a significant rise in stress hormones such as cortisol and leptin.<sup>11</sup> Electroencephalographic monitoring may be used to assess the effects of anesthetic drugs on the central nervous system.<sup>12</sup> More specifically, computerized electroencephalogram processing and display technology, such as bispectral index (BIS) monitoring may be a useful tool,<sup>13</sup> to titrate the hypnotic component of anesthesia.<sup>13-18</sup> BIS monitoring may lead to reduced drug consumption, faster recovery from anesthesia,<sup>15</sup> and prevention of untoward side effects of anesthetics such as hemodynamic instability.<sup>19-23</sup>

The aim of the present study was to measure the serum cortisol levels as an index of stress response in patients who are candidates for coronary artery bypass graft (CABG) surgery in two groups of patients. This study also assessed the depth of anesthesia by clinical judgment or BIS monitoring to test correlation between serum cortisol levels and BIS values.

## Patients and Methods

### Study Design

Based on pilot study, 76 patients scheduled to undergo elective CABG surgery were enrolled in a double-blind, prospective randomized study. Patients older than 75 years old with a history of previous cardiac surgery, intravenous treatment for unstable angina, recent (< 3 months) myocardial infarction (MI), left ventricular ejection fraction (LVEF) lesser than 40%, evidence of valvular heart disease, history of hepatic (liver enzymes levels greater than 50% over the normal limits) and renal dysfunction (serum creatinine > 1.5 mg%), or evidence of coexisting endocrine problems (such as diabetes or usage of steroids), and malignant or immunologic diseases were excluded from the study.

The ethics committee at Shiraz University of Medical Sciences was approved the protocol and written informed consents were obtained from all the patients.

### Anesthetic Management

A standardized general anesthesia was achieved by using combination of midazolam 0.1 mg/kg, fentanyl 3 µg/kg, propofol 1 mg/kg, and pancuronium 0.1 mg/kg as a muscle relaxant. Anesthesia was maintained intraoperatively using a mixture of oxygen, air, propofol 100 µgkg<sup>-1</sup>.min<sup>-1</sup> plus fentanyl 0.2 µg.kg<sup>-1</sup>.hr<sup>-1</sup>. All the patients were monitored by standard monitoring systems and the BIS (BIS; Aspect Medical Systems, Newton, MA, USA) electrodes were placed on the forehead according to the manufacture's instruction. Intravenous cannulation and arterial line were inserted by using local anesthetic.

Baseline hemodynamic parameters and BIS were recorded. Central venous pressure was measured by insertion of triple lumen catheter in right internal jugular vein after induction of anesthesia.

The patients were divided by computer generated random numbers into two groups. The patients in control group (n=38) received propofol plus fentanyl by infusion and their needed dosage of drugs were adjusted by hemodynamic data and clinical judgment (blood pressure, heart rate, sweating, movement). Drug infusion rates were adjusted in BIS group (n=38) by 20% increments or decrements of propofol and fentanyl infusion rates. The BIS values were maintained between 40-60 in this group.

An anesthetist and a technician who were blinded to hemodynamic and BIS values collected the data. The BIS were set to be out of vision of anesthetist and only a technician who was not in charge of the patients was aware of the data.

Target perioperative hemodynamic values in both groups were mean arterial pressure greater than 60 mmHg and cardiac output more than 3 l/min guided by non-invasive cardiac output (NICO) monitoring. Target hemodynamic values were generally obtained by optimizing preload followed by the use of inotropic support or vasoconstrictors as needed. Epinephrine was used as the first line inotropic agent, whereas bolus intravenous injections of phenylephrine or norepinephrine infusion were used as vasoconstrictors.

### Cardiopulmonary Bypass Management

A standardized CPB protocol was used for all the patients. Cardiopulmonary bypass was established using double stage cannulation in right atrium and arterial cannula placed in the ascending aorta. Non-pulsatile CPB was conducted under mild core hypothermia (35°C) using a hollow fiber membrane oxygenator (Medtronic Trillium Affinity Nt MN, USA).

The circuit was primed with 1.2 liter ringer solution, 5000 IU sodium heparin, and 50 ml albumin (20%). Intermittent antegrade cold blood cardioplegia (20 °C) delivered through a 12-gauge aortic root cannula was used for myocardial protection.

The cardioplegic mixture consisted of 50% cold ringer solution (1000 ml +20 mEq KCl +40 mEq sodium Bicarbonate + 2 g magnesium sulphate and 1 mg/kg lidocaine) and 50% autologous blood. A dose of 10-15 ml/kg was delivered to induce diastolic cardiac arrest and a maintenance dose of 4 ml/kg was administered after completion of each distal anastomosis.

The left ventricle was vented through the aortic root during aortic cross clamping. Flow was maintained at 2-2.4 l.min<sup>-1</sup>.m<sup>-2</sup> during CPB in order to reach the perfusion pressure between 50 and 80 mmHg.

Alpha stat management of acid-base status was used. Proximal graft anastomoses on the ascending aorta were performed after cross-clamp removal using a partially occlusive clamp.

#### Serum Cortisol Levels Measurement

Blood samples were collected from the radial artery into glass tubes at the onset of anesthesia (T<sub>0</sub>), five minutes after sternotomy (T<sub>1</sub>), 30 minutes after start of CPB (T<sub>2</sub>) and at the end of operation, and before transferring to intensive care unit (ICU) (T<sub>3</sub>).

The BIS values and hemodynamic parameters such as heart rate, mean arterial blood pressure, central venous pressure, systemic vascular resistance, and cardiac output measured by NICO (non-invasive cardiac output that measured these data by analyzing expired CO<sub>2</sub>) were also recorded respectively at those four times, except at T<sub>2</sub> because of effect of CBP on CO<sub>2</sub> measurement.

#### Statistical Analysis

Data are presented as mean ±SD unless otherwise indicated. For statistical analysis *t* test (independent) and Mann-Whitney U test were used. Mann-Whitney test was used for ejection fraction (EF), cortisol levels (T<sub>3</sub>, T<sub>4</sub>), and BIS value. Analysis was performed for the rest of indices by Student's *t* test. For significant

findings Student's *t* test was applied at the endpoint of each measurement. Repeated measure test (independent test) was used when appropriate.

#### Results

Both groups were comparable with respect to age, sex, weight, duration of cardiopulmonary bypass, aortic clamp time, and operation time (table 1).

Both groups had similar extent of revascularization. There were no significant differences in the postoperative duration of mechanical ventilation or time required for the patients to rewarm to systemic (nasopharyngeal) temperature of 37°C. There was no death nor any patient required the use of intra-aortic balloon pump.

BIS was maintained in the range of 40-60 in BIS group. There were no significant differences in mean cortisol levels between the two groups (p=0.09). Preoperatively, mean cortisol levels in group I was 19.94 µg/dl (SD: ±7.93) and in group II was 16.89 µg/dl (SD: ±7.54).

Serum cortisol levels decreased during operation in both groups, reaching 6.41 µg/dl (SD: ±7.32) in group I and 6.20 µg/dl (SD: ±6.88) in group II (p=0.901).

After CPB and surgery, mean serum cortisol levels in both groups changed. Mean serum cortisol level increased by 10.48 µg/dl (SD: ±22.01) in group I and decreased by 6.42 µg/dl (SD: ±7.31) in group II (p=0.328).

Intraoperatively, BIS values were: T<sub>1</sub>=43, T<sub>2</sub>=41, and T<sub>3</sub>=48 for group I, and T<sub>1</sub>=38, T<sub>2</sub>=42, and T<sub>3</sub>=46 for group II, (P<sub>1</sub>=0.13, P<sub>2</sub>=0.91, and P<sub>3</sub>=0.45). There were no significant differences between BIS values in the two groups.

There were no differences in heart rate (figure 1) and mean arterial blood pressure in both groups.

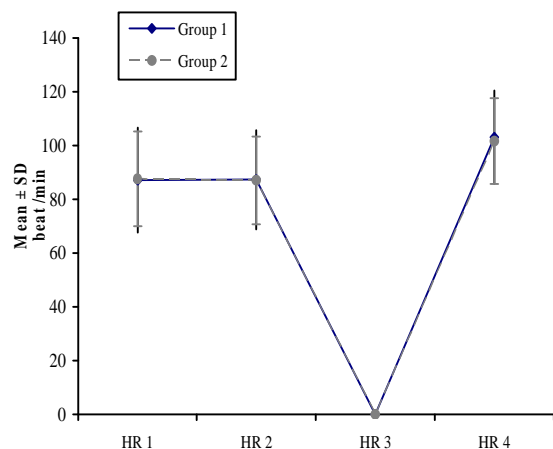
#### Discussion

Stress response to cardiac surgery is influenced by anesthetic technique, patients' age, type of surgery, management of cardiopulmonary bypass, and whether circulatory arrest is used as

**Table 1:** Demographic characteristics and operational variables in the studied patients.

Variable	Group I	Group II	Significance
Age	57.52 ± 11.70	58.05±9.29	NS *
Weight (kg)	67.22 ± 9.08	68.19±12.28	NS
Ejection fraction (%)	51.26±13.89	49.28±10.75	NS
Pump time (min)	70.10±25.13	61.93±27.77	NS
ACT* (min)	42.35±13.89	42.92±17.63	NS
Duration of operation(min)	183.84±55.16	193.88±34.06	NS
Sex (♀)	62.2 %	64.5%	NS
Sex (♂)	37.8%	35.5%	NS

NS= Non Significant, ACT: Aortic clamp time



**Figure 1:** Comparison of heart rate between the two groups in 4 times measurement.

part of the bypass technique.<sup>24</sup> Attenuation of the neuroendocrine stress response, mainly release of catecholamines as a result of noxious stimulation due to intubation, sternotomy and initiation of CPB is an important concern in anesthesia for these patients.<sup>12</sup> Previous studies revealed correlation between BIS and the stress hormones.<sup>12</sup> The present research was designed to study the effects of BIS monitoring on the hormonal/metabolic and cardiovascular responses to the cardiac surgery, and to compare these responses with clinical judgment as a guide for conduction of anesthesia.

Our results showed decrease in serum cortisol levels during operation in both groups. In agreement with our results, several other studies reported these changes in cortisol values during CPB.

Other studies have shown the effect of perioperative hemodilution on the measurement of mediators of the inflammatory response during cardiac surgery.<sup>25</sup> Hemodilution may be only one of several factors affecting hormone and protein levels after the starting of CPB. Therefore, the true levels of the investigated substances may lie between the corrected and non-corrected values.<sup>25</sup>

Although serum cortisol levels in our both groups were decreased, the attenuation of the cortisol levels in BIS group was lesser than control group. However, the differences were not significant statistically.

Previous studies also demonstrated that serum cortisol concentrations decreased compared with baseline values with BIS monitoring. In our study immediately after surgery, serum cortisol levels increased in both groups. This finding is compatible with other studies.<sup>9</sup> Post-operative serum cortisol levels in both groups had not significant differences. Postoperatively, serum cortisol levels increased; however, they were yet lesser than preoperative concentrations.

Other studies have shown a persistent effect of hemodilution up to the second postoperative day in all participants of the study.<sup>25</sup>

Previous reports demonstrated that cortisol measurements were significantly influenced by the perioperative hemodilution of patients who were undergoing cardiac surgery with CPB.<sup>9</sup> Surprisingly, the mean serum cortisol levels in the BIS group were higher than the control group, but this difference was not significant statistically. Systemic hypothermia during CPB has also been shown to attenuate perioperative stress hormone response.<sup>26,27</sup> Because of the influence of hypothermia and hemodilution and other factors on serum cortisol level, it seems that using another index for evaluation of depth of anesthesia is more suitable.

## Conclusion

The present study showed no difference between the two groups regarding serum cortisol level. It seems that clinical assessment exerts enough performance on conduction of anesthesia and parameter such as BIS plays no more roles in this situation.

## Acknowledgements

We wish to express our gratitude and appreciation for the hard work and cooperation of the participants and the staff at Endocrine Research Center of Nemazee Hospital, Shiraz, Iran.

**Conflict of Interest:** None declared

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