Egyptian Journal of Anaesthesia (2011) **27**, 233–240

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

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Research Article

Bilateral Bispectral Index (BIS)-VISTA monitoring of cerebral hypoperfusion in patients with carotid artery stenosis undergoing coronary artery bypass surgery

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Received 2 June 2011; accepted 25 July 2011
Available online 31 August 2011

KEYWORDS

Bispectral index;
Cardiac surgery;
Cerebral ischemia;
Carotid artery stenosis

Abstract *Background:* Carotid stenosis is a frequent coexisting condition in patients undergoing Coronary Artery Bypass Graft (CABG) surgery. During cardiac surgery, acute hemodynamic changes can cause cerebral ischemia. When acute slowing of the Electroencephalography (EEG) develops because of cerebral ischemia, a profound reduction in Bispectral Index (BIS) is seen, although the depth of anesthesia does not change. We investigated the diagnostic value of bilateral BIS as an indicator of cerebral hypoperfusion during CABG surgery in patients with carotid artery stenosis and the incidence of left-right BIS differences.

Methods: Forty patients scheduled for elective CABG surgery were randomized into two groups according to preoperative Duplex carotid ultrasound; Group with Carotid Artery stenosis (CA-stenosis) ($n = 23$) and Group without stenosis (CA-normal) ($n = 17$). All patients underwent monitoring using bilateral BIS system. We analyzed BIS data at eight stages of the CABG procedure.

Results: Mean BIS values recorded from left and right hemispheres declined significantly in comparison to steady state of anesthesia in both groups (T2), ($p < 0.0001$ for both). In CA-stenosis group only, there were significant interhemispheric differences during AXC apply ($p < 0.01$). Average BIS values of right and left hemispheres and parallel to it, SEF data decreased significantly in both groups during initiation of CPB-T3, during AXC application-T4 and during AXC removal-T6

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Peer review under responsibility of Egyptian Society of Anesthesiologists.
doi:10.1016/j.egja.2011.07.006

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($p < 0.001$). Intergroup comparison showed significant decrease in BIS values in CA-stenosis group when compared to CA-normal group during induction of anesthesia-T1 and during AXC apply-T4 (both $p < 0.001$) and during AXC removal-T6 ($p = 0.04$).

Conclusion: Our findings suggest that an acute decrease in BIS which represent abrupt slowing of the EEG, reflects acute cerebral hypoperfusion particularly when it accompanies acute hypotension, as long as the changes in BIS is not drug induced.

1. Introduction

Carotid stenosis is a frequent coexisting condition in patients undergoing Coronary Artery Bypass Graft (CABG) surgery. Stroke and postoperative cognitive decline, may be related to cerebral hypoperfusion during CABG [1]. During cardiac surgery, haemodynamic changes such as acute hypotension and cardiac arrest can cause cerebral ischemia [2]. When Cerebral Blood Flow (CBF) decreases by more than half, Electroencephalography (EEG) evidence of cerebral ischemia appears as acute slowing of the raw EEG frequency [3] which occurs within seconds of hypotension [4]. When acute slowing of the EEG develops because of cerebral ischaemia, an abrupt and profound reduction in Bispectral Index (BIS) which is a processed EEG parameter, is seen, although the depth of anesthesia does not change [5].

It is widely accepted that BIS values derived from the left or the right forehead will be the same. However, it has not yet been cleared that the two BIS values are the same in patients with unilateral carotid artery disease. Recently, a bilateral two-channel EEG-sensor has been introduced to monitor the BIS on both cerebral hemispheres [6]. In some patients significant left–right differences may occur, whereas no relevant side differences are expected in the majority of patients. Monitoring the bispectral index bilaterally during general anesthesia showed differences of 10 or more arbitrary BIS units for 30 s or more 6% of the time during general anesthesia [7].

One of the most studied potential markers of brain injury is Neuron-Specific Enolase (NSE), which is one of the five isozymes of the glycolytic enzyme, enolase, is used to screen potential brain ischemia during cardiac surgery [8].

The aim of this study was to investigate the diagnostic value of bilateral BIS as an indicator of cerebral hypoperfusion during cardiac surgery patients with carotid artery stenosis and the incidence of left-right BIS differences (primary outcome). Also examine the relation between BIS differences and postoperative outcome (secondary outcome). Until now, to our knowledge no studies were undertaken examining the previously addressed questions.

2. Patients and methods

2.1. Patient enrollment

We prospectively recruited 40 patients undergoing on-pump CABG at a tertiary medical center in Jeddah, Saudi. All patients provided written informed consent and the study was approved by the human subjects committee. Patients were enrolled if they satisfied the following criteria: left ventricular ejection fraction more than 40%, no significant cerebral hemodynamic effects due to sever carotid artery stenosis (>80%), no sever renal impairment (plasma creatinine >2.5 mg/dL) and no severe hepatic disease (liver enzymes >2 times the upper limit of normal). We did not include patients suffering from neurological disorders.

All patients underwent a preoperative Duplex carotid ultrasound using a HDI 5000 Duplex Ultrasound (ATL, Inc., Bothell, WA), which is interpreted by an attending radiologist, who is blind for study aims for determining the degree of carotid stenosis.

Two groups of patients developed; Group with Carotid Artery stenosis (CA-stenosis) ($n = 23$) and Group without Carotid Artery stenosis (CA-normal) ($n = 17$). Thirteen patients had bilateral carotid stenosis. Data collection were performed in a double-blind fashion in which neither the patient nor the medical team were aware about group design.

2.2. Anesthesia and surgical techniques

All preoperative medications were continued preoperatively. One hour preoperatively, 0.1 mg/kg morphine sulfate was given intramuscularly. After reaching the operating theater, the standard monitors were attached to the patients and a continuous cardiac output pulmonary artery catheter (Edwards Lifesciences, Irvine, CA), inserted after induction of anesthesia.

All patients underwent bilateral cortical function monitoring using the BIS-VISTA monitoring system (BISx4TM) with bihemispheric capabilities (bilateral BIS Quattro) (Aspect Medical Systems, Norwood, MA, USA). The BIS Quattro sensors were applied on the right and left sides of the forehead according to the manufacturer's instruction to give a four-channel bilateral reference frontotemporal montage. The sensors were connected to a digital signal converter and then to the portable BIS-VISTA monitor, which displays both a raw EEG waveform and a numerical BIS value.

Induction was done using propofol (1.0 mg/kg), midazolam (0.1 mg/kg), fentanyl (5–10 μg/kg) and rocuronium (0.6 mg/kg) to facilitate tracheal intubation. Maintenance of anesthesia was achieved by infusion of propofol (2–3 mg/kg/h), fentanyl (3 μg/kg/h) and rocruonium (3 μg/kg/h). Ventilatory parameters were adjusted to keep $PaCO_2$ between 35 and 45 mmHg.

Heparin sulfate 4 mg/kg was administered prior to CPB and supplemented as needed to maintain an Activated Clotting Time (ACT) of at least 400 s. CPB was instituted by a roller pump (Stockert S3, Sorin Group, Deutschland, München, Germany) using a membrane oxygenator (Medtronic, USA) with a flow rate of 2.4 l/min/m^2. Antegrade intermittent warm blood cardioplegia was used for myocardial protection. Systemic temperature was allowed to drift to 35 °C. Mean arterial pressure was kept at 60–80 mmHg with the aid of nitroglycrine or noradrenaline and manipulating pump flow. Hematocrit was maintained above 25%. Anesthesia during cardiopulmonary bypass was maintained using propofol infusion at a rate of

2–3 mg/kg/h. We tried to keep BIS value around 40–60 after the anesthetic induction and during steady stat of CPB. After separation from CPB and removal of the aortic cannula, heparin activity was neutralized with protamine sulfate and at the end of surgery, the patient transferred to ICU.

2.3. Bilateral Bispectral Index (BIS) [9]

The *BIS Bilateral* System was designed to record and display four channels of EEG; two from each side of the brain. The system calculates BIS numbers and other variables for the left and right sides of the brain. The Density Spectral Array (DSA) is a traditional EEG power-based display used to convey the frequency and power distribution of the EEG signal over time. The frequency ranges that predominate are depicted via a color spectrum where warmer colors (e.g., red and orange) indicate more dominant frequencies, and cooler colors (blue and green) indicate frequencies that are not as dominant (Fig. 1).

Spectral Edge Frequency (SEF) is an EEG power-based parameter displayed both numerically and graphically (as a white line) in Hertz for both the left and right hemispheres of the brain. It is the frequency below which 95% of the power on that side of the brain resides. Asymmetry (ASYM) indicator is an EEG power-based parameter that quantifies hemispheric differences in relative total power of the EEG. The ASYM indicator is a simplified way of viewing power differences noted in the DSA display between the left and right hemispheres. The ASYM scale begins at 20% to highlight potentially clinically significant asymmetry. The white graph indicates the side with relative greater power. Asymmetry data are also displayed, with the designation "L" or "R"' to indicate the corresponding part of the brain. ASYM of 0 indicates no asymmetry, and R2 denotes 2% asymmetry to the right side. EEG Suppression Ratio (SR) is the percentage of time period where the EEG is considered to be isoelectric.

To acquire high-quality data, only BIS–EEG values with a Signal Quality Index (SQI) greater than 80 and EMG less than 50 were included in the present analysis. Five minutes of artifact-free BIS–EEG was analyzed in each patient separately for the right and left sensors for each time point. We analyzed BIS data at eight stages of the CABG procedure. These stages were chosen because each is a necessary step during the CABG procedure which occur sequentially and thus provided consistent analytic time points. Surgical stages were defined as follows: baseline-before induction of anesthesia-T0; during induction of anesthesia-T1; 15 minutes after induction-T2; CPB initiation-T3; application of the aortic cross clamp (AXC)-T4; at the 30th minute of the CPB-T5; AXC removal-T6; 15 min after cessation of CPB-T7. During periods of aortic cross clamp application and removal, cardiopulmonary bypass flow was reduced by protocol.

2.4. Blood sampling and biochemical assays

Blood samples were collected from the central venous line preoperatively after induction of anesthesia and before skin incision, 6 and 48 h after operation. Whole blood should be collected by venipuncture and the serum is separated by centrifugation ($1500 \times g$ for 10 min). Serum samples should be stored at -20 °C or below until measurement. Serum samples were assayed in duplicate using commercially available high sensitivity immunoassays. The assay utilizes the two-site "sandwich" technique. Samples were assayed for NSE, using (ALPCO Diagnostics, Windham, NH). All assays were performed as per manufacturer's specifications. The normal range was found to be less than 15 ng/ml. The sensitivity of the human NSE ELISA as determined by the 95% confidence limit on 20 duplicate determinations of zero standards is approximately 1.2 ng/ml.

2.5. Hemodynamic and postoperative variables

Heart Rate (HR), Mean Arterial Pressure (MAP), Cardiac Index (CI), Systemic Vascular Resistance Index (SVRI) and Pulmonary Capillary Wedge Pressure (PCWP) were collected at same time points of BIS mentioned above. During CPB, pump flow was considered the CO. Clinical outcome (gross neurological examination), duration of tracheal intubation, ICU stay and postoperative complications among the study patients were documented.

2.6. Statistical analysis

Data were statistically described in terms of mean ± standard deviation (±SD). Normality of data was tested using Kolmogorov Smirnov test. Comparison between the study groups was done using Mann Whitney *U* test for independent samples. Within group comparison between baseline and over time values was done using Freidman's test. Correlation between various variables was done using Spearman rank correlation equation for non normal variables. The presence or absence of a statistically significant correlation between MAP and

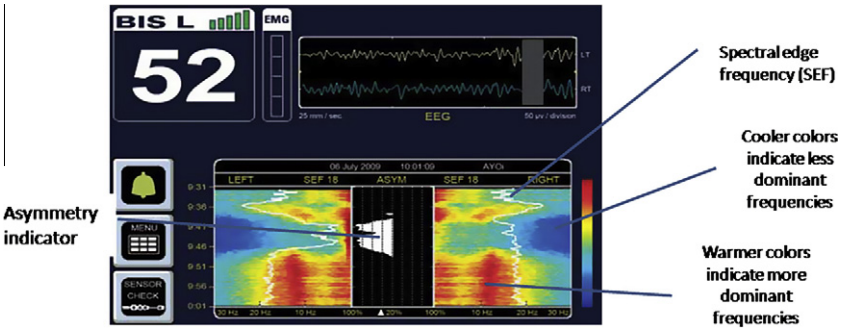

Figure 1 EEG trace and DSA display shows asymmetry indicator shift to Left side.

BIS was taken to show that BIS changes were MAP dependent or not. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results

3.1. Demographic and hemodynamic data

The group with carotid artery stenosis was slightly older than other group. Demographic and perioperative data were comparable between the two groups. The study groups were comparable regarding duration of postoperative mechanical ventilation and postoperative ICU stay (Table 1). No postoperative gross neurological complications were recorded between the study groups.

Hemodynamic data analysis showed no statistical significant differences between both groups at baseline and at all time points during whole surgery. MAP and CI showed a remarkable decrease in both groups during induction of anesthesia but did not reach statistical significance when compared to baseline followed by significant decrease again during initiation of CPB, application of AXC and removal of AXC without statistical significant difference between both groups (Table 2).

3.2. NSE data

The serum levels of neuron-specific enolase (NSE) 6 and 48 h after operation in CA-stenosis group were 13.64 ± 4.50 ng/ml and 8.77 ± 2.31 ng/ml, respectively. Only 6 h postoperatively was significantly higher than that before operation (7.07 ± 2.40 ng/ml, $p < 0.001$). The serum levels of NSE 6 and 48 h after operation in CA-normal group were 8.32 ± 2.30 ng/ml and 7.54 ± 3.24 ng/ml, respectively, both not significantly different from that before operation (6.37 ± 2.31 ng/ml, $p > 0.05$). Intergroup comparison showed that NSE was significantly elevated in the CA-stenosis group compared with CA-normal group at the 6-h time point.

3.3. BIS–EEG analysis

Mean BIS values recorded from left and right hemispheres declined significantly in comparison to steady state of anesthesia (after induction until going on CPB-T2), ($p < 0.0001$ for both), with no significant interhemispheric differences over time in CA-normal group. However in CA-stenosis group there were significant interhemispheric differences only during AXC apply ($p < 0.01$). Again, when compared to steady state of anesthesia, the average BIS values (as mean of right and left hemispheres) and parallel to it, SEF data decreased significantly in both groups during initiation of CPB-T3, during AXC application-T4 and during AXC removal-T6 ($p < 0.001$). Intergroup comparison showed significant decrease in BIS values in CA-stenosis group when compared to CA-normal group during induction of anesthesia-T1 and during AXC apply-T4 (both $p < 0.001$) and during AXC removal-T6 ($p = 0.04$). On the other hand, SEF values decreased significantly in CA-stenosis group in comparison to CA-normal group only at AXC apply ($p < 0.05$). ASYM figure showed different values at different time points but without any significance except in three patients with unilateral sever CA-stenosis. BSR increased significantly during periods of significant decreased BIS (initiation of CPB and AXC apply) in both groups in comparison to steady state time point (T2) ($p < 0.001$) without any significance between both groups. Signal quality index (SQI) was maintained greater than 80 and EMG less than 30 in both groups during the whole procedure (Table 3).

The correlation between the BIS values and MAP was investigated in both groups; there was no correlation between both variables in CA-stenosis group but in CA-normal group, there was negative correlation at time of induction ($r = -0.691$, $p = 0.009$) and there was positive correlation at steady state of anesthesia after induction ($r = 0.694$, $p = 0.009$).

3.4. Data of the three patients who developed significant asymmetry

In CA-stenosis group, three patients with asymptomatic unilateral sever stenosis, left and right BIS values were mostly discordant during the study. *Two patients had unilateral sever right CA-stenosis* and showed marked reduction of right BIS

Table 1 Demographics and perioperative data.

Parameter	CA-stenosis ($n = 23$)	CA-normal ($n = 17$)
Age (years)	58 (10)	54 (8)
Sex (male/female)	21/2	16/1
BSA (m^2)	1.92 (0.16)	1.89 (0.10)
Ejection fraction	55 (2)	56 (2)
Diabetes (n & %)	22 (47%)	16 (54%)
Hypertension (n & %)	21 (76%)	15 (87%)
Baseline hematocrit (%)	39.4 (6.2)	37.4 (5.4)
CPB time (min)	103 (25)	112 (22)
AXC (min)	59 (11.8)	67 (12.5)
Time to extubation (h)	3.8 (1.3)	4.2 (0.8)
ICU stay (days)	2.2 (0.8)	2.2 (0.8)

Values are presented as mean (SD) and ratio for sex. BSA, body surface area; CPB, cardiopulmonary bypass; AXC, aortic cross clamp.

Table 2 Intraoperative hemodynamic data.

CA-stenosis (n = 23) CA-normal (n = 17)	Before induction (T0)	During induction (T1)	15 min after induction (T2)	Going on CPB (T3)	AXC apply (T4)	30 min on CPB (T5)	AXC removal (T6)	15 min post CPB (T7)
HR (beat/min)								
CA-stenosis	68.1(7.4)	69.7(8.1)	72.7(6.4)	65.6(6.8)	0.0	0.0	67.1(7.8)	90.1(5.7)[@]
CA-normal	70.6(6.5)	70.7(5.8)	71.5(6.6)	68.0(4.7)	0.0	0.0	65.6(8.2)	90.6(3.2)[@]
MAP (mmHg)								
CA-stenosis	84.9(5.9)	77.6(5.5)	85.9(21.2)	42.3(6.7)[@]	33.5(5.4)[@]	89.5(7.3)	38.3(4.9)[@]	84.6(6.4)
CA-normal	89.4(5.0)	73.8(7.9)	86.7(6.8)	44.0(4.2)[@]	31.7(6.8)[@]	73.1(4.8)	35.2(4.1)[@]	84.6(8.1)
PCWP(mmHg)								
CA-stenosis	12.4(2.3)	13.2(2.3)	13.1(1.9)	13.2(2.3)	0.0	0.0	11.6(1.6)	11.1(1.7)
CA-normal	12.6(2.2)	12.5(2.5)	11.3(1.9)	12.4(1.9)	0.0	0.0	12.3(1.3)	12.5(1.6)
CVP (mmHg)								
CA-stenosis	11.6(2.4)	11.2(1.6)	11.5(1.6)	11.7(1.6)	0.0	0.0	12.3(1.7)	10.6(1.4)
CA-normal	11.3(1.6)	11.1(1.4)	11.6(1.1)	11.2(1.3)	0.0	0.0	12.5(1.3)	11.9(1.4)
CI ($l/min/m^2$)								
CA-stenosis	2.3(0.4)	2.1(0.5)	2.4(0.5)	1.9(0.1)[@]	1.8(0.12)[@]	2.2(0.2)	2.01(0.2)[@]	4.2(0.7)[@]
CA-normal	2.2(0.3)	2.1(0.4)	2.3(0.3)	1.8(0.15)[@]	1.7(0.13)[@]	2.1(0.19)	2.06(0.2)[@]	4.3(0.6)[@]

Values are presented as mean (SD). HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index.

[@] $p < 0.001$ *vs.* T0.

values and marked shift of Asymmetry indicator graph to left during periods of cerebral hypo perfusion. The maximum changes occurred in one patient upon apply of cross-clamping of the aorta and in the other one, during initiation of CPB. The third patient with left CA-stenosis developed marked reduction of left BIS value and shift of the Asymmetry graph to the right side at same time points. During periods of cerebral ischemia, BIS decreased abruptly and resolved again within few minutes after maintaining high MAP. BIS never reached 0 during these ischemic events. In all the ischemic periods BIS reductions lasted < 3 min. Detailed BIS data of the three patients are shown in Table 4.

4. Discussion

The main results of the present study showed that no significant differences were found between the EEG–BIS values of the right and left hemispheres in each group except during AXC apply in CA-stenosis group. At that time, marked drop of MAP occurred due to slow down of pump flow. When the average BIS values and parallel to it, SEF data compared to steady state of anesthesia (T2), we found that, it decreased significantly in both groups during periods of abrupt reduction of MAP (T3, T4 and T6) ($p < 0.001$). Intergroup comparison showed significant decrease in average BIS values in CA-stenosis group during induction of anesthesia, during AXC apply and during AXC removal. Also, the results of neuron specific enolase (NSE) confirmed our significant BIS values difference between both groups as it was significantly elevated in the CA-stenosis group compared with CA-normal group at the 6-h time point. Finally, all these BIS changes did not lead to any gross neurological complications in both groups postoperatively.

During cardiac surgery, several factors could contribute to decreased BIS value, including deep anesthesia, hypothermia, and cerebral ischemia [10]. We excluded any artifact effect by checking a good contact between BIS sensor and skin, EMG influences, reviewing of SQI, and monitoring of the raw EEG. The SQI and BSR are consistent with the BIS monitor; the better SQI, the lower BSR; the higher is the probability that the signal is artifact-free [11]. In our study, propofol infusion rate did not change during the periods of BIS decrease and there was no other anesthetic given during this time. The effect of hypothermia on the BIS value should be considered [12], but it is not a cause in our patients, because our temperature did not go below 35 °C. Cerebral ischemia during cardiac surgery can occur at the start of CPB due to acute haemodilution which may lead to development of cerebral hypoperfusion because of reduced MAP due to decreased peripheral vascular resistance [13,14]. In our study, we tried to keep hematocrit level above 25% to avoid this effect. Other reasons for cerebral hypoperfusion, the temporally decreased patient's blood pressure during apply and removal of aortic clamp because of the slowing of the bypass pump flow [15].

MAP reduction below the normal limit of cerebral autoregulation could be the likely cause of the decreased BIS values in our subjects, as increasing the pump flow resulted in increased BIS values. In a patient with normal autoregulation, CBF should be maintained at a MAP of 80 mmHg. Chronic hypertension is accompanied by a rightward shift of the autoregulation curve [16], so hypertensive patients with carotid artery disease may be more liable for impaired cerebral autoregulation if they developed low MAP. Yasuhiro et al. [10], described cerebral hypoperfusion detected by BIS monitoring during arteriovenous shunt in chronic uncontrolled hypertensive patient when MAP dropped below the lower limit of autoregulation. Our result in CA-normal group, showed negative correlation between BIS value and MAP at time of induction and another positive correlation at steady state of anesthesia after induction but in CA-stenosis group, there was no such correlation. With a sudden reduction in blood pressure, CBF will decrease for a brief period (1 ± 2 min) before autoregula-

Table 3 BIS data in both groups.

CA-stenosis (n = 23) CA-normal (n = 17)	Before induction (T0)	During Induction (T1)	15 min after induction (T2)	Going on CPB (T3)	AXC apply (T4)	30 min on CPB (T5)	AXC removal (T6)	15 min post CPB (T7)
CA-stenosis								
Rt BIS	84.1(4.6)	37.1(6.8)	48.6(3.9)	27.5(4.1)[@]	21.7(3.1)[@]	48.4(4.9)	31.4(5.7)[@]	59.5(3.7)
Lt BIS	85.7(3.5)	40.1(5.8)	51.04(6.4)	29.2(4.4)[@]	25.6(2.6)[@,#]	46.7(4.4)	32.8(6.3)[@]	57.0(4.7)
CA-normal								
Rt BIS	87.6(2.8)	47.7(5.1)	54.9(3.6)	31.08(3.1)[@]	29.1(1.7)[@]	49.3(5.2)	35.6(4.4)[@]	58.8(5.2)
Lt BIS	85.3(3.4)	45.9(5.4)	52.6(3.2)	28.3(3.1)[@]	28.6(2.2)[@]	48.3(4.9)	34.6(5.3)[@]	59.3(4.2)
Average/BIS								
CA-stenosis	84.8(3.4)	37.6(5.6)	50.3(4.4)	28.3(3.6)[@]	25.1(1.6)[@]	48.1(4.6)	32.1(4.4)[@]	57.2(4.1)
CA-normal	86.5(2.3)	45.8(4.7)[**]	52.8(2.9)	29.6(2.2)[@]	28.8(1.3)[@,**]	49.8(4.9)	35.1(3.1)[*,@]	56.1(4.4)
BSR								
CA-stenosis	0.1(0.4)	0.7(1.2)	0.04(0.2)	3.3(3.7)[@]	3.4(4.7)[@]	0.0(0.0)	0.7(1.4)	0.0(0.0)
CA-normal	0.01(0.0)	0.5(0.7)	0.0(0.0)	1.6(2.2)[@]	2.1(1.4)[@]	0.0(0.0)	0.0(0.0)	0.0(0.0)
EEG/SEF								
CA-stenosis	19.7(2.2)	12.5(1.03)	15.04(1.2)	9.5(0.9)[@]	6.3(0.7)[@]	14.5(0.8)	9.1(1.4)[@]	14.8(1.2)
CA-normal	19.0(2.5)	12.7(1.01)	14.7(1.3)	9.7(1.09)[@]	9.6(1.04)[@,*]	14.4(1.1)	9.08(1.1)[@]	15.1(1.2)
EMG								
CA-stenosis	44.6(4.2)	29.7(3.9)	24.8(2.3)	25.7(2.7)	26.6(2.2)	26.2(2.2)	27.2(2.2)	29.0(2.9)[@]
CA-normal	45.2(4.1)	29.3(3.3)	24.8(2.1)	26.8(2.7)	25.0(2.3)	26.1(2.7)	25.8(2.4)	29.2(2.7)[@]
SQI								
CA-stenosis	88.9(2.6)	93.0(2.3)	97.4(2.04)	99.4(1.5)	97.4(4.2)	96.3(3.3)	97.4(4.2)	97.9(2.4)
CA-normal	88.6(2.3)	92.6(2.5)	97.6(1.8)	98.5(1.8)	97.5(3.5)	96.5(3.1)	97.2(3.2)	98.1(2.3)

Values are presented as mean (SD), ASYM, asymmetry; BSR, burst suppression ratio; EMG, electromyography; DSA, density spectral array; SEF, spectral edge frequency; SQI, signal quality index.

[*] $p < 0.05$.

[**] $p < 0.01$ between both groups.

[#] $p <$ between Rt and Lt BIS within each group.

[@] $p < 0.001$ T3, T4, T5, T6 and T7 *vs.* T2.

tion restores CBF [17]. The decreases in BIS in our patients lasted for no longer than 3 min in most ischemic events, suggesting that cerebral autoregulation restored CBF during hypotension.

EEG changes during cerebral ischemia include progressive slowing of the signal, decrease in high-frequency activity and finally, becoming an isoelectric EEG with prolongation of ischemia [18]. EEG slowing leads to a decrease in the Spectral Edge Frequency (SEF) that might be accompanied by a decrease in BIS, because the changes in BIS correlated well with SEF during surgical levels of anesthesia [19]. Morimoto et al. [19] reported that BSR values >40% are linearly and inversely correlated with BIS values in the range of 30–0. This suggests that a BIS value <30 is an indicator of EEG suppression when BSR is high.

Monitoring cerebral hypoperfusion during cardiac surgery is not an easy tool. Jugular bulb venous oxygen saturation has been used as a sensitive marker for cerebral oxygenation in cardiac surgery [20] but is invasive; transcranial Doppler detect high intensity transient signals detecting microemboli but does not reflect global cerebral hypoperfusion [21]. Near-infrared spectrometry monitors tissue oxygenation but has not been systematically evaluated in cardiac surgery [22]. On the other hand, BIS monitoring devices are widespread, and in addition to adjusting level of anesthesia intraoperatively, they could help to predict cerebral hypoperfusion.

Several possible indications other than monitoring depth of anesthetic have been described for BIS monitoring. It could be used as an indicator of inadequate cerebral perfusion during carotid artery surgery [5]. Many publications confirming our results for BIS value as indicator for cerebral hypoperfusion during periods of hypotension have been reported [23,24]. Erol et al. [25] examined Effects of cerebral hypoperfusion on BIS index: using an animal experiment during hemorrhagic shock. They found that, therapies with different impact on cerebral perfusion resulted in differing changes of BIS values; this suggests that BIS may also have reflected changes of cerebral perfusion. Thomas et al. [11] presented a case of possible cerebral hypoperfusion during beating heart surgery as shown by the bispectral index. A recent study by Hayashida et al. [13] presented a small series of 10 cases of children underwent cardiac surgery in which a reduction of cerebral oxygen saturation was accompanied by simultaneous BIS decreases in five children during acute hypotension at the onset of CPB indicating a reduction in cerebral blood flow, which associated with acute slowing of the raw EEG waveforms. Another work for Hayashida et al. [26] studied 65 children had done congenital heart surgery using hypothermic CPB. During surgery, they measured BIS and regional cerebral hemoglobin oxygen saturation (Sr_{O2}) with near-infrared spectroscopy (NIRS). Cerebral ischaemia was diagnosed if both Sr_{O2} and BIS decreased abruptly when acute hypotension occurred.

Table 4 BIS data of three patients with severe unilateral CA-stenosis.

	Before induction (T0)	During Induction (T1)	15 min after induction (T2)	Going on CPB (T3)	AXC apply (T4)	30 min on CPB (T5)	AXC removal (T6)	15 min post CPB (T7)
Patient # 1								
Rt-BIS	79	32	50	30	31	47	31	57
Lt-BIS	82	25	45	19	18	42	20	56
ASYM	0	R20	L2	**R55**	**R50**	0	**R30**	L8
BSR	0	3	0	12	16	0	4	0
EEG/SEF	23	12	15	9	7	13	7	14
Patient # 2								
Rt-BIS	80	25	48	22	19	39	21	63
Lt-BIS	79	34	49	33	31	40	33	60
ASYM	0	L35	L4	**L45**	**L63**	R2	**L47**	L8
BSR	0	4	0	17	15	0	5	0
EEG/SEF	19	12	14	8	9	15	9	16
Patient # 3								
Rt-BIS	89	22	46	18	21	51	19	67
Lt-BIS	90	35	45	32	29	50	31	65
ASYM	0	L24	L2	**L88**	**L70**	0	**L80**	L8
BSR	0	4	0	7	10	0	3	0
EEG/SEF	18	11	16	9	8	15	8	16

ASYM, asymmetry; BSR, burst suppression ratio; DSA, density spectral array; SEF, spectral edge frequency.Bold figures indicate the corresponding part of the brain (right or left) with marked asymmetry of EEG power to this side.

Changes in the BIS value during cerebral ischemia is probably highly sensitive but without specificity because several factors can induce BIS variations, especially during CPB [23]. The changes in BIS value in our subjects lagged behind the period of cerebral hypoperfusion (reduced MAP) by approximately 60 s. This may be caused by the 30- to 60-s delay inherent in the calculation time of the BIS monitor and the lag time between decreases in cerebral blood flow and neuronal dysfunction [23].

BIS values derived from the left and right forehead of healthy subjects not expected to show significant difference. In our study, the two cerebral hemispheres produced comparable values however we had three patients with unilateral sever CA-stenosis, they showed marked interhemispheric differences during periods of marked reduction of MAP. It is possible that bilateral EEGs could differ for a variety of reasons, such as the underlying disease pathology or anatomical differences. John et al. [27] demonstrated that at deep level of unconsciousness, there is a clear lack of coherence between homologus regions of the two hemispheres with significant uncoupling of interhemispheric relationships. This uncoupling may result in interhemispheric differences in signal processing speed and sampling of the BIS values, which is almost a real-time measure. Niedhart et al. [7] reported that 6% of surgeries recorded the readings that differed bilaterally by 10 or more in BIS units which sustained 30 s or longer. In our study, in case of sever unilateral stenosis, the difference in the right and left BIS values was more than 10, and it continued for 2–3 min. In patients with unilateral severe ICA disease, if the circle of Willis is intact, collateral blood flow from the contralateral side allows brain perfusion to the diseased hemisphere. However, low cerebral perfusion pressure due to reduced MAP may lead to a more reduced CBF towards the diseased hemisphere [28]. Lee et al. [6] reported on two patients with unilateral severe carotid artery stenosis, there were great differences between the BIS values obtained from sensors placed on each side of the forehead. Konstanze et al. [29] investigated the predictive value of bilateral BIS to detect significant differences between delirious and nondelirious patients after cardiac surgery. He concluded that the bilateral BIS index was significantly lower in delirious patients compared to nondelirious. Dahaba et al. [30] used Bilateral BIS monitor as a measure of physiologic sleep in sleep-deprived anesthesiologist, they found that, no significant interhemispheric differences in BIS values obtained from right and left hemisphere overtime; however, in one subject, the left and right BIS values were mostly discordant throughout the recordings.

The key features of the new BIS bilateral system are the ability to display bilateral four channels of continuous real-time EEG data, the availability of a color-based density spectral array (DSA) of processed EEG information and finally an ''Asymmetry indicator'' which compares the total power measured from the two hemispheres and provides a graphic representation when the relative difference is more than 20%. These tools of EEG parameters can alert anesthesiologist to both global and interhemispheric changes.

In conclusion, our work illustrated EEG changes that quickly detected by the new BIS bilateral monitoring system. So our findings suggest that if a change in BIS is not drug induced, an acute decrease in BIS which reflects abrupt slowing of the EEG indicates cerebral hypoperfusion, particularly when it accompanies acute hypotension. Also, carotid stenosis had significant impact on cerebral blood flow during periods of reduced MAP.

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