Original Article

The bilateral bispectral and the composite variability indexes during anesthesia for unilateral surgical procedure

ABSTRACT

Background: The composite variability index (CVI), derived from the bispectral analysis (BIS), has been designed to detect nociception; however, there is no evidence that bilateral BIS and CVI show intrapatient reproducibility or variability.

Methods: We conducted an observational study in patients who underwent for total knee arthroplasty. A BIS Bilateral Sensor was applied and continuously recorded at different points of the anesthesia procedure. Bland–Altman limits of agreement and dispersion for BIS and for CVI were applied.

Results: Forty-nine right-handed patients were studied. There were differences between the right and left BIS values after tracheal intubation (which was higher on the right side) and at surgical stimulus (higher on the left side). The maximum BIS and minimum, mean, and maximum CVI scores were higher on the left side for left-side procedures, but there were no differences in any indexes for the right-side procedures. Except for the baseline measurements, both CVI and BIS scores presented high interpatient variability. Although the right to left bias was < 3% for the BIS index, dispersion was large at different stages of the anesthesia. The right to left bias for the CVI was 3.8% at tracheal intubation and 5.7% during surgical stimulus.

Conclusions: Our results indicate that the large interindividual variability of BIS and CVI limits their usefulness. We found differences between the left and right measurements in a right-handed series of patients during surgical stimuli though they were not clinically relevant.

Key words: Anesthesia; bispectral analysis; composite variability index; knee replacement

Introduction

Widely used in anesthesia, the bispectral index (BIS) is a commercial product that processes electroencephalogram (EEG) signals measured over the forehead. In a *post hoc* secondary analysis, BIS monitoring was associated with a reduction of awareness events[1] although both its clinical effectiveness and its cost-effectiveness depend on the probability of awareness.[2] The measurement of nociception during anesthesia is challenging, and no fully effective clinical method has been established to date. BIS monitoring can neither detect nor predict a possibly inadequate nociception–antinociception balance.[3] Recently, the composite variability index (CVI), derived from the standard deviations of BIS and electromyogram, has been designed to detect low levels of analgesia and indicate inadequate antinociception.[4] According to the manufacturers'

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recommendations, BIS probes can be applied on the left and right sides of the forehead, giving clinically equivalent assessments for the depth of anesthesia.[5] However, it is generally agreed that BIS is not sufficiently reliable to detect ipsilateral or contralateral effects in ischemic episodes.[6,7] Differences in BIS indexes were detected in shunting patients for carotid surgery,[8] either in the presence of unilateral brain lesions[9] or during the anesthesia process.[10,11]

So far, there is no evidence that bilateral BIS and CVI show intrapatient reproducibility or variability. We aimed to determine whether the intrapatient and interpatient variability between the right and left values of BIS and CVI during anesthesia induction, during tracheal intubation, in response to surgical stimuli, and on recovery after the anesthesia in a series of patients scheduled for knee replacement in whom unilateral nociception was induced.

Methods

We conducted a prospective, observational study in a consecutive sample of patients who were undergoing elective surgery for total knee arthroplasty (TKA) under general anesthesia and were included in a controlled trial. Approval was obtained from the hospital's Institutional Review Board, and all patients recruited provided written informed consent.

Eligible participants were all adult patients scheduled for TKA. Exclusion criteria were the presence of neurologic disease, the use of medication acting on the central nervous system, and a history of the following conditions: Uncontrolled diabetic disease, difficult airway management, asthmatic disease, arterial vascular limb surgery or high-risk deep venous thrombosis, and severe cardiac disease. Subjects in whom a patient control analgesia system could not be used were also excluded from the study.

The EEG signal was acquired using a BIS Bilateral Sensor (Aspect Medical Systems) applied to the forehead as recommended by the manufacturer to record a bilateral frontoparietal signal. Bilateral BIS and CVI scores were calculated in real time and recorded from a BIS VISTA monitoring system at 1-s resolution for offline data analysis. Hemodynamic values were computed by a Datex-Ohmeda system monitor (GE, Helsinki, Finland), heart rate from a single-channel electrocardiogram signal, and blood pressure from a noninvasive and inflatable cuff every 5 min. Continuous pulse oximetry and end-tidal CO_2 were also recorded. All the data were extracted from the Datex-Ohmeda patient monitor and recorded on a laptop running Rugloop data collection software provided by Aspect Medical, which computed the synchronization of the information from the BIS VISTA and the Datex- Ohmeda. Clinicians used the Rugloop software to record the induction, intubation, surgical, and extubation points.

For the first 5 min, patients breathed oxygen via a face mask (fresh gas flow 6 L/min), and general anesthesia was induced with propofol 2 mg/kg and fentanyl 3 μg/kg. Tracheal intubation was facilitated with rocuronium 0.6 mg/kg. Anesthesia was maintained with sevoflurane and oxygen in air (FiO_2 0.7). Lungs were ventilated to maintain end-tidal carbon dioxide concentration at 30–35 mmHg. All patients were warmed with a system of heat convection (Warm Touch, Mallinckrodt, St. Louis, MO, USA) to maintain body temperatures between 36°C and 36.5°C.

All the patients started with sevoflurane in a fresh gas flow of 4 L per min for 4 min to reach a 1.3 CAM to keep the BIS value between 40 and 60; after that, fresh gas flow was kept at 1 L per min. Blood pressure was measured every 5 min. If the systolic blood pressure (SBP) was below 90 mmHg and the BIS values were between 40 and 60, a repeated bolus of 5 mg of ephedrine was administered intravenously. If the SBP was below 90 mmHg and the BIS values below 40, the sevoflurane vaporizer was decreased by 0.4%, until a BIS value above 40 was achieved. If the SBP was higher than 165 mmHg and the BIS values were above 60, the sevoflurane vaporizer was increased by 0.4%, until the BIS value fell below 60. If the SBP was above 165 mmHg and the BIS values were in the range of 40–60, a bolus of 1 μg/kg of fentanyl was administered until adequate SBP was achieved. Atropine 1 mg was administered intravenously if the heart rate was below 50 beats per min.

Bilateral BIS and CVI values were continuously recorded on the computer, and the analysis was performed offline. We determined the mean values of each side for 1 min at the following points:

- Baseline, before anesthesia induction
- Before tracheal intubation (considered the anesthesia induction point)
- After tracheal intubation
- At the surgical stimulus point
- Once the patient regained consciousness, before tracheal extubation (considered the anesthesia recovery point).

Patients' and surgical characteristics were also recorded.

As we did not expect the BIS and CVI data to be homogeneous, all quantitative values are expressed as median and interquartile range and were analyzed using the nonparametric Wilcoxon test. A $P < 0.05$ was considered statistically significant.

To compare BIS left-sided versus right-sided, we used the Bland–Altman limits of agreement at the following points: Before anesthesia induction, before tracheal intubation, after tracheal intubation, during the surgical stimulus, and at the end of anesthesia. Bland–Altman limits of agreement for CVI were applied at tracheal intubation and surgical stimulus point because basal (prior anesthesia induction) has to zero value. Dispersion of both BIS and CVI was expressed as the mean right to left difference ±2 standard deviation. The SPSS data manager was used for data analysis.

Results

Forty-nine right-handed patients were studied. Twenty-eight were women (57%). Median age was 74 year old (interquartile 54–86). American Society of Anesthesiologists risk classification I-II and III in 73% and 27% of patients, respectively. Median surgery time was 100 min (inter quartiles 80 to114). Surgery was in the left side in 21 patients, whereas right side was 28 patients.

There were no differences between the right and left BIS values, except for the mean CVI values at the surgical stimulus point were higher on the left side [Table 1].

Table 2 displays the comparisons between right and left BIS and CVI, depending on the side of the surgical stimulus.

Table 1: Median bispectral index and composite variability index values in each phase of anesthesia according to each side of the head monitoring (*n*=49 patients)

	Left	Right
Mean basal BIS	96.5 (93-97)	97 (92-98)
Mean anesthesia induction BIS	30.5 (24-41.5)	33 (24-47)
Mean tracheal intubation BIS	36 (26-49)	37 (27-50)
Mean surgical stimuli BIS	51 (44-57)	49 (45-58)
Mean tracheal extubation BIS	83 (76-89)	85 (79-88)
Mean anesthesia induction CVI	1.47 (0.77-3.04)	2.1 (0.7-3.2)
Mean tracheal intubation CVI	2.18 (1.12-4.23)	2.35 (1.12-4.37)
Mean surgical stimuli CVI	1.62 (1.31-2.5)	1.51 (1.19-1.7)*
Mean tracheal extubation CVI	0 (0-3.85)	0 (0-3.7)

Values are expressed as median (25-75 quartiles). Inter group comparison *$P<0.05$. BIS: Bispectral index; CVI: Composite variability index

There were no differences in any indexes for the right-side procedures; the mean CVI scores were higher on the left index for left-side procedures.

Except for the baseline measurements, both CVI and BIS scores presented high interpatient variability. Although the right to left bias was 2.87% for the BIS index at surgical stimulus, dispersion was large at different stages of the anesthesia [Table 3]. The right to left bias for the CVI was 3.8% at tracheal intubation and 5.7% during surgical stimulus [Table 3].

Discussion

In this series of right-handed patients, BIS and CVI of both hemispheres were equivalent throughout the anesthesia and the surgical procedures. The only discrepancy was the mean CVI values at the surgical stimulus point, higher on the left; no clear explanation for this observation was found, and it had no clinical relevance. Other assessments in bilateral BIS during anesthesia found no differences in values on either side.[12] Moreover, no differences were reported for diverse cranial placements of BIS,[13,14] indicating that variations between stages of anesthesia or during anesthesia are more important than a specific localization of the BIS signal. However, in our series, BIS bias was 4.65% at tracheal intubation and 2.87% during surgical stimuli, indicating some variability in the measurements of both sides. All our patients were right-handed, and none had a history of organic brain disease, dementia, or stroke, so these factors could not have influenced our results. The impact of right-handedness on anesthetic sensitivity has been reported to be negligible.[15] In contrast, Niedhart *et al*.[11] found sustained periods of 30 s or longer during which the BIS readings suggested a different depth of anesthesia.

In relation to surgical stimuli, we observed higher values of CVI in the left index regardless of the side of the procedure. These findings are difficult to explain because the nociceptive stimulus reaches the contralateral spinothalamic projections at the medullary dorsal horn and continues to the

Table 2: Median bispectral index and composite variability index values depending on the side of the surgical stimulus

	Left procedure (*n*=21)		Right procedure (*n*=28)	
	Left index	Right index	Left index	Right index
Mean anesthesia induction BIS	36 (24-42)	36 (25-45)	30 (24-41)	30 (23-49)
Mean trachea intubation BIS	39 (25-48)	42 (28-49)	36 (26-53)	36 (26-53)
Median surgical stimuli BIS	47.6 (43-57.5)	47 (43-54)	52 (46-57)	51 (46-59)
Mean anesthesia induction CVI	1.55 (0.94-3.68)	2.86 (0.82-3.55)	1.4 (0.73-2.98)	1.61 (0.81-3.09)
Mean trachea intubation CVI	3.38 (1.12-4.29)	3.16 (1.4-4.46)	1.98 (1.07-4.1)	1.87 (0.94-3.91)
Median surgical stimuli CVI	1.61 (1.22-2.29)	1.42 (1.13-2.08)*	1.63 (1.33-1.8)	1.5 (1.3-1.8)

Values are expressed as median (25-75 quartiles). *$P<0.01$. BIS: Bispectral index; CVI: Composite variability index

Table 3: Right to left bias of bispectral index and composite variability index at different stages of anesthesia

	Mean bilateral BIS	Mean right-left BIS difference*	Right to left BIS bias (%)	Mean bilateral CVI	Mean right-left CVI difference*	Right to left CVI bias (%)
Basal	95.08	0.42±3.6	0.43	-	-	-
Anesthesia induction	44.85	−0.78±11.4	1.75	-	-	-
Tracheal intubation	43.22	−2.01±11.1	4.65	2.95	−0.112±2.8	3.8
Surgical stimulus	55.21	1.59±7.28	2.87	2.425	0.138±0.96	5.7
Tracheal extubation	86.1	−1.63±11.4	1.89	-	-	-

*Mean±2SD. SD: Standard deviation; BIS: Bispectral index; CVI: Composite variability index

contralateral cortical areas of the brain so that an increase of CVI values on the contralateral side to surgery would be expected. Differences between the two hemispheres were noted during carotid clamping, related to the presence of delta waves irrespective of the side of the hemisphere affected.[16] However, the EEG is unlikely to be a useful measure of anesthesia depth and nociception.[17] Another study reported no significant interhemispheric differences in the BIS index between frontal brain tumor patients and controls managed with propofol at loss of consciousness and during recovery.[18]

When considering the values of BIS and CVI to differentiate nociception, we did not observe changes before and after tracheal intubation. We also noted limited the ability of the two indexes to predict adequate prevention of nociception. BIS is a good predictor of loss and return of consciousness but not of nociception, even though it correlates well with sevoflurane effect side concentration.[19] Ellerkmann *et al*.[4] demonstrated that the CVI was able to predict movement at nociceptive stimulus in young patients under propofol and remifentanil anesthesia; however, in Ellerkmann *et al*.'s study,[4] the CVI values ranged widely. In our series, we used sevoflurane as an anesthetic agent and most patients were elderly (median age of 74), and age-dependent variations have been reported for EEG-derived indexes.[20] What is more, using dilatation changes of the pupillary reflex as a measure of nociception, the minimum alveolar concentration of sevoflurane was influenced by age.[21] Adequate deep anesthesia may explain the lack of differences at surgical stimulus, but it cannot explain the CVIs lack of sensitivity for detecting nociception produced by tracheal intubation. In our study, the anesthesia induction produced changes in the CVI, probably related to mask ventilation and the pain associated with the administration of anesthetic drugs. On the other hand, CVI data before tracheal intubation in our series were similar to those in the Ellerkmann *et al*. study.[4]

In our series, the CVI had a large interpatient variability. Biases were 3.8% at tracheal intubation and 5.7% during surgical stimuli. However, the range of absolute differences was wide, indicating variability in the measurements, as pointed out Crosby and Culley in an editorial,[22] the processed EEG can be a window to evaluate anesthesia depth, but it is limited by its wide interindividual variation.

Our study has several limitations. First, we used sevoflurane to maintain anesthesia, and so our results cannot be extrapolated to other anesthetics, especially intravenous anesthesia. Second, the small number of patients analyzed may influence the interindividual variation of the two indexes. Third, our patients were elderly, so our results do not apply to younger populations. Finally, we explored the laterality of surgical stress; consequently, we cannot extend our results to trunk or abdominal surgery.

To summarize, we found differences between the left and right measurements in a right-handed series of patients during surgical stimuli though they were not clinically relevant; these differences were not influenced by the laterality of the noxious stimulus.

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Conflicts of interest

There are no conflicts of interest.

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