Effect of age on the comparability of bispectral and state entropy indices during the maintenance of propofol–sufentanil anaesthesia

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Editor’s key points
- This study analyses the agreement between the bispectral index (BIS) and spectral entropy index values during anaesthesia.
- The agreement between BIS and state entropy indices is moderate and deteriorates as patients’ age increases.
- Electrode position is crucial.
- This study cannot determine which index is best adapted for elderly patients.

Background. Manufacturers recommend maintaining anaesthesia at a bispectral index (BIS) or state entropy (SE) index value between 40 and 60.

Methods. We prospectively studied 102 patients receiving propofol–sufentanil anaesthesia administered by anaesthetists blinded to these indices. The main endpoint was crude agreement (P0), defined as the proportion of agreement between BIS and SE index among three categories: <40, between 40 and 60, and >60. Discrepancies in recommendation (DR) were also considered. A DR is type 1 if BIS or SE is <40, while the other is simultaneously >60. A DR is type 2 when BIS and SE index values are on different sides of a threshold (40 or 60) with three subtypes according to the magnitude of their difference. A linear multiple regression was performed to identify covariates that are independently associated with P0.

Results. In total, 12 147 pairs of values were studied. P0 was 59.9 (24.5%) [mean (SD)]. Thirty-three patients presented more than 50% discordant pairs and only seven patients presented more than 95% concordant pairs. Type 1 DR occurred in only 1.1% of all the pairs. The median (inter-quartile range) number of type 2 DR varied from 5 (3–8) to 2 (1–3) according to the degree of difference. Multivariate analysis showed that age (P=0.0004) and electrode position (P=0.0084) were independently associated with P0. An increase in the age of 10 yr decreases P0 by 5%.

Conclusions. The agreement between BIS and SE indices is moderate and deteriorates as patients’ age increases. This study cannot determine which index is best adapted for elderly patients. Additional work comparing both indices with raw EEG traces is warranted.

ClinicalTrials.gov Identifier. NCT00391963.

Keywords: aged; anaesthesia; electroencephalography/methods; intravenous

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Frontal EEG trace can mathematically be transformed into numerical indices to aid in the evaluation of hypnotic depth. Two monitors are particularly in competition: the bispectral index (BIS) monitor (Covidien, Elancourt, France), a commonly used monitor, and entropy monitor, the more recently introduced (GE Healthcare, Helsinki, Finland), with its two parameters: state entropy (SE) and response entropy, with SE being an index of the depth of hypnosis. Both Covidien and GE Healthcare recommend maintaining the BIS and SE values between 40 and 60 during anaesthesia, an interval that ‘ensures adequate hypnotic effect during general anaesthesia while improving the recovery process’ for BIS1 and a ‘clinically meaningful anaesthesia’ with ‘a low probability of consciousness’ for SE index.2 Comparability between these indices must be studied (i) with all anaesthetic agents irrespective of their molecular targets, (ii) in full awareness that an EEG-derived index does not correspond to any firm clinical endpoint as there is no gold standard for defining an adequate anaesthetic depth, and (iii) during the maintenance of anaesthesia. This third consideration is important as the maintenance period of anaesthesia is a challenging period for comparing EEG-derived indices. During induction and emergence, the expected transition between awake and asleep states artificially favours comparability. A previous study has shown a moderate comparability between BIS and SE values in patients receiving sufentanil–sevoflurane–nitrous oxide anaesthesia.3
The aims of this study were (i) to compare BIS and SE values during maintenance of total i.v. anaesthesia, which induces different EEG changes to volatile anaesthetics, especially with spindles at deep anaesthesia levels and (ii) to identify patient characteristics and intraoperative variables that could explain the strength of the concordance.

**Methods**

This study (ClinicalTrials.gov Identifier: NCT00391963) was approved by the Ethics Committee, and written informed consent was obtained from each patient.

**Patients**

One hundred and two patients of ASA physical statuses I–III, aged above 18 yr, and undergoing various elective procedures expected to last at least 1 h (abdominal, gynaecologic, urological, or orthopaedic surgery) were enrolled in this prospective, randomized, single-blinded study. Exclusion criteria were pregnancy, allergy to propofol, a history of any neurological or muscular disorder, treatment with opioids or any psychoactive medication, thyroid disorder, and a surgical procedure performed in the prone or lateral decubitus position that would render the adequate electrode positioning unreliable. Patients receiving local anaesthesia or regional block combined with general anaesthesia were not included in the study.

**Study protocol**

In the operating theatre, an i.v. catheter was inserted into a large forearm vein and standard monitors were applied (S/5™ monitor; GE Healthcare). After the skin of the forehead had carefully been wiped with an alcohol swab and then had waiting with the EEG electrode strips (ZipPrep; Aspect Medical Systems, Natick, MA, USA) were positioned on the forehead in proximity. Both electrodes were on the same side, and their level (above or below) was randomly assigned by tossing a coin. This resulted in two groups: one with the BIS electrode above the entropy electrode and the other with the BIS electrode below the entropy electrode. The BIS and SE plug-in modules were connected to the same S/5™ monitor. The sampling rates for the raw EEG were 400 and 256 Hz for SE and BIS, respectively. The BIS (BIS® version 4.0, XP) was calculated at a smoothing rate of 30 s; the moving average window that was used to calculate SE was 15–60 s. Electrode impedances were considered as acceptable if they were <10 Ω and 7.5 kΩ for BIS and SE values, respectively (as per manufacturers’ recommendations). The monitor display was customized to make the BIS and SE values invisible to the attending anaesthetist.

All the patients received hydroxyzine 100 mg orally 1 h before surgery for premedication. The patients received a standardized anaesthetic protocol. After administration of 100% oxygen, anaesthesia was induced with propofol 2–3 mg kg⁻¹ i.v. and sufentanil 0.2–0.3 μg kg⁻¹ i.v. After the loss of consciousness, oxygen was administered by facemask ventilation, and patients received atracurium 0.5 mg kg⁻¹ i.v. After tracheal intubation, the lungs were mechanically ventilated with a tidal volume of 8–10 ml kg⁻¹, with the ventilatory rate being adjusted to maintain an end-tidal carbon dioxide between 4 and 4.7 kPa.

Anaesthesia was continued with propofol using a target-controlled infusion system (Diprifusor, Zeneca Ltd); sufentanil and atracurium were administered as repeated boluses. Anaesthetists were instructed to guide the titration of general anaesthesia using routine clinical signs and train-of-four monitoring. Volume expansion and vasoactive drugs were administered at the discretion of the attending anaesthetist. Propofol and sufentanil were discontinued at the beginning of skin closure. Residual neuromuscular block was reversed using neostigmine 0.05 mg kg⁻¹ i.v. and atropine 15 μg kg⁻¹ i.v. if necessary.

Finally, all the patients were visited on the first and third postoperative days and interviewed about any memories or recall of intraoperative awareness using a standardized interview procedure.

BIS, BIS-signal quality index (BIS-SQI), and SE values recorded at 1 min intervals were transferred to a computer hard disk using the software program Datex-Ohmeda S/5 Collect (version 4.0) for offline analysis. The beginning of maintenance of anaesthesia was defined as 10 min after tracheal intubation and its end at the discontinuation of propofol and sufentanil induction.

**Statistical analysis and data handling**

For statistical analysis, both BIS and SE values were categorized using values at 40 and 60 as thresholds. The three resultant categories (≤40, between 40 and 60, and >60) indicate for each parameter whether it corresponds to an excessively deep, adequate, or inadequate hypnosis level.

The agreement between BIS and SE indices was quantified for each patient using the proportion P₀, which is the crude proportion of agreement between the two indices among the classes defined by the threshold values. For an agreed pair of BIS and SE measurements (for instance, both between 40 and 60), P₀=1, and for a discordant pair of measurements (for instance, BIS below 40 and SE between 40 and 60), P₀=0. Thereafter, P₀ was defined as the proportion of concordant pairs for each subject.

As defined by the aforementioned maintenance phase, most of these measurements were collected in the presence of surgical stimulation. Comparisons were performed to investigate the relationships between patient characteristics and intraoperative variables and the individual BIS/SE agreement values of P₀. A linear multiple regression (multivariate analysis) was performed to identify a set of covariates that are independently associated with the main outcome, namely P₀. The variables associated with P₀ with P<0.05 in the univariate analysis were considered for the multiple models. Interaction terms were added to the multiple models. To illustrate the impact of age on the agreement, a linear regression plot of the individual values of P₀.
against the patients' ages was graphed for each electrode position group.

Two discrepancies in recommendation (DR) were studied. DR was classified as type 1 if one parameter, BIS or SE, is <40 and the other >60 simultaneously or as type 2 if simultaneous BIS and SE values are on different sides of a threshold (40 or 60) with various degrees of difference between BIS and SE values. In order to investigate the influence of this difference on the judgement outcome, three subtypes of type 2 DR were defined, each with a minimal absolute difference (△), respectively, of 5, 10, and 15. The number of types 1 and 2 DR (NDR) correspond to the sum of all these instances.

Data were expressed as count (%), mean value (standard deviation), or median (25th–75th percentiles). A P-value of less than 0.05 was considered to be statistically significant in all analyses. Data analysis was performed using SAS® (version 8; SAS Institute Inc., Cary, NC, USA).

Results

The patient characteristics and intraoperative characteristics of the patients are reported in Table 1. No patient reported intraoperative recall at the follow-up interviews. No patient was excluded from the analysis.

Of the 16 221 BIS/SE pairs recorded, only 379 (2.3%) exhibited a quality of BIS signal <50, and 467 (2.9%) had a missing SE value. In total, 12 147 pairs belonging to the threshold values of 40 and 60 is presented in Table 2. The BIS tended to be lower than the SE; for instance, the BIS gave values <40 when the SE lay between 40 and 60 in 25% of the cases. In total, 5024 pairs (41.4%) corresponded to instances when BIS and SE values were on different sides of a threshold (40 or 60). Only 136 pairs (1.1%) corresponded to situations where one parameter was <40 and the other one was >60.

The distribution of individual proportions of agreement P0 is presented in Figure 1, and it was centred at 59.9 (24.5%) [mean (so)]. The number of patients with P0<50% was 33 (33%), the number of those with P0<80% was 75 (74%), and the number of those with P0<95% was 95 (94%).

In the univariate analysis, patients' age and the presence of an episode of hypotension during maintenance were strongly prognostic of the BIS/SE agreement, whereas ASA and electrode position were moderately prognostic (Table 3). No other variables reported in Table 1 were significantly associated with P0. The multivariate analysis showed that both age (P=0.0004) and electrode position (P=0.0084) were independently associated with P0 (Table 3). An increase of 10 yr of age was independently associated with a decrease of P0 by 5%.

The proportions of agreement (P0) and patients' age were related linearly in univariate analysis (Fig. 2; P<0.014 regardless of the electrode position).

The NDRs (both crude and expressed per hour of anaesthesia) are reported in Table 4. Type 1 NDR occurred rarely [0 (0–0.65) per hour of anaesthesia], while type 2 NDR occurrences were 3.01 (2.29–4.05), 2.21 (1.20–2.86), and 1.19 (0.50–2.21) per hour of anaesthesia when considering a difference between both indices >5, 10, and 15, respectively.

Table 1 Characteristics of the patients (n=102). *Groups are as follows: BIS electrode below the entropy one (LowB–HighE) and BIS electrode above the entropy one (HighB–LowE). 1Hypotension is defined as requirement of a vasopressor agent. Data are expressed as mean (so) or median (inter-quartile range) or count (%)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Sex, F/M</th>
<th>53 (53)/49 (48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56.8 (16.3)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.7 (13.5)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167 (10)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg m⁻²)</td>
<td>25.9 (4.7)</td>
<td></td>
</tr>
<tr>
<td>ASA physical status, I/II/III</td>
<td>41 (40)/50 (49)/11 (11)</td>
<td></td>
</tr>
<tr>
<td>Surgery: abdominal/orthopaedic/ others</td>
<td>43 (42)/34 (33)/25 (25)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Distribution of BIS and SE according to the threshold values of 40 and 60. Data are expressed as mean numbers of BIS/SE pairs (percentage of all the pairs). BIS, bispectral index; SE, state entropy

<table>
<thead>
<tr>
<th>BIS values</th>
<th>≤40</th>
<th>&gt;40 and ≤60</th>
<th>&gt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE values</td>
<td>≤40</td>
<td>3390 (28.0)</td>
<td>1492 (12.0)</td>
</tr>
<tr>
<td></td>
<td>&gt;40 and ≤60</td>
<td>3092 (25.0)</td>
<td>3178 (26.0)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>62 (0.5)</td>
<td>293 (2.5)</td>
</tr>
<tr>
<td>Totals</td>
<td>6544</td>
<td>4963</td>
<td>640</td>
</tr>
</tbody>
</table>
Discussion

This observational study performed during maintenance of propofol–sufentanil–atracurium anaesthesia demonstrates that the agreement between BIS and SE ($P_0$) deteriorates as the age of the patients increases and that it is worse than that previously described during the maintenance of sufentanil–sevoflurane–nitrous oxide anaesthesia. Indeed, the percentage of patients with $P_0<50$ and $<80\%$ were, respectively, 33 and 74 in this study and 14 and 55 in the previous one. A better agreement was reported by most of the studies comparing BIS and SE values, but they focused on the transition between awake, anaesthetic, and recovery states. Studying such transition periods results in bias since dramatic clinical changes induce acute changes in the monitors’ parameters and consequently favour comparability. However, recently, it has been reported that BIS and SE indices were not able to differentiate consciousness from unconsciousness induced by propofol, sevoflurane, or dexmedetomidine in volunteers receiving each of these drugs in escalating concentrations at 10 min intervals.

![Fig 1](https://academic.oup.com/bja/article-abstract/108/4/638/257289/1)

**Table 1** Proportions of agreement ($P_0$). $P_0$ is the crude proportion of agreement between the two indices. The distribution was centred at 59.9 (24.5\%) [mean (SD)].

![Fig 2](https://academic.oup.com/bja/article-abstract/108/4/638/257289/2)

**Table 2** Linear regression plot of the individual values of crude agreement ($P_0$) against the patients’ ages for each electrode position group ($Y$-axis: agreement expressed as percentage; $X$-axis: age in years). Patients from the group BIS electrode below the entropy electrode are green hollow circles with the dotted regression line. The solid line and blue filled circles represent the group BIS electrode above the entropy electrode.

![Fig 3](https://academic.oup.com/bja/article-abstract/108/4/638/257289/3)

**Table 3** Significant parameters after uni- and multivariate analyses of individual proportions of agreement ($P_0$ expressed as percentage). *ASA value considered as a quantitative variable. †The reference group is ‘Bispectral electrode below the entropy electrode’. ‡The reference group is ‘None’

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference (95% CI)</td>
<td>$P$-value</td>
</tr>
<tr>
<td>Age</td>
<td>−0.6 (−0.9 to −0.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASA*</td>
<td>−7.5 (−14.8 to 0.2)</td>
<td>0.0433</td>
</tr>
<tr>
<td>Electrode position†</td>
<td>10.2 (0.7–19.8)</td>
<td>0.0364</td>
</tr>
<tr>
<td>Hypotension during maintanance‡</td>
<td>−16.1 (−28.0 to −4.1)</td>
<td>0.0092</td>
</tr>
</tbody>
</table>
The most important result of our study is that the agreement between BIS and SE values is better in younger patients than in their elderly counterparts. This result compared well with that of a previous one studying patients aged above 65 yr during repair of femoral neck fractures, in which up to one-quarter of them demonstrated a significant disparity (i.e. low Pearson’s correlation coefficient) between BIS and SE values. Further clinically relevant information came from a study that showed that at loss of consciousness during propofol induction, BIS and SE values were significantly higher in elderly patients than in younger patients.

BIS and SE monitors computerize the EEG without any information on the patients’ age while EEG differs. Age-dependent differences of the awake EEG have been reported by several authors and disputed by others or explained by underlying diseases. Sleep EEG differs between young- and middle-aged healthy men. Ageing not only reduces power in the sleep EEG, but it also causes frequency-specific changes in the brain topography, particularly in the frontal cortical areas, which are close to the BIS and SE sensors. Schultz and colleagues, using a standardized induction of anaesthesia with propofol, demonstrated that older patients had a smaller total power in deep EEG stages compared with younger patients. This was mainly due to smaller amplitudes of delta waves in deep EEG stages. These small delta waves in the elderly may influence BIS and SE differently. Also, EEG transitions with increasing anaesthetic depth are easier to differentiate in younger patients than in older patients. Such EEG modifications could modify the value of an EEG-derived monitor of hypnosis level. However, patients with dementia have a small decrease of 4.8 points in baseline BIS values.

Limitations of the study

This study presents several limitations. First, we chose to blind the attending anaesthetist to the EEG indices, which meant that the general anaesthetic was titrated by clinical signs and haemodynamic values. Secondly, the result of the multiple regression suggested a potential influence of the probe position on the agreement. The probe position could have influenced the results, because the lower sensor is furthest from the brain tissue and the frontal sinuses could limit the signal conduction. Some studies do not report their exact position, while others choose to place the BIS sensor above or below the entropy sensor or each one on one side of the forehead. Ideally, we would have to use a single probe specially designed for this study which could collect the signal for both monitors. Electromyographic and burst-suppression ratio data were displayed by both monitors, but were not included in the analyses. Further studies are needed to evaluate their respective impact on the discrepancy between the methods. This study used only the magnitude of punctual disagreement between the two monitors. Further study using the area under the time curve of disagreement as endpoint could be useful. Finally, we only studied the two devices during the maintenance period of anaesthesia in the presence of surgical stimulus. We could have used another methodology such as that studying the response of both monitors to a change in the hypnotic dose.

Conclusion

Many anaesthetists believe that the BIS and entropy monitors are similar and that there is no scientific evidence that favours one over the other. This study has shown that the percentage of time for which there is agreement between the BIS and SE indices is moderate and that the agreement deteriorates as patients’ age increases. This observational study cannot determine which index is best adapted for elderly patients. Additional work comparing both indices with raw EEG traces is warranted.

Declaration of interest

None declared.

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