Performance of entropy and Bispectral Index as measures of anaesthesia effect in children of different ages

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Background. Entropy and Bispectral Index (BIS) have been promoted as EEG-based anaesthesia depth monitors. The EEG changes with brain maturation, but there are limited published data describing the characteristics of entropy in children, and some data suggest that BIS is less reliable in young children. The aim of this study was to compare the performance of entropy as a measure of anaesthetic effect in different age groups. The performance of entropy was compared with BIS.

Methods. Fifty-four children receiving a standard sevoflurane anaesthetic for cardiac catheter studies were enrolled. The entropy and BIS were recorded pre-awakening and at 1.5%, 2% and 2.5% steady-state end-tidal sevoflurane concentrations. For analysis children were divided into four age groups: 0 – 1 yr, 1 – 2 yr, 2 – 4 yr and 4 – 12 yr.

Results. The pre-awakening values were obtained in 46 children. The median pre-awakening values for entropy and BIS varied significantly across ages with the values being lowest in the 0 – 1 yr age group (response entropy: 45 vs 84, 87 and 89, \(P=0.003\); state entropy: 36 vs 78, 74 and 77, \(P=0.009\); BIS: 56 vs 78, 76.5 and 72, \(P=0.02\)). Values were recorded at all three sevoflurane concentrations in 48 children. Compared with older groups, the 0 – 1 yr age group had the least significant difference in BIS and entropy when compared among different sevoflurane concentrations. The calculated sevoflurane concentrations to achieve mid-scale values of entropy and BIS were highest in the 1 – 2yr age group, lower in the 0 – 1 yr age group and progressively lower in the 2 – 4 and 4 – 12 yr age groups.

Conclusions. For both entropy and BIS the measure of anaesthetic effect was significantly different for children aged < 1 yr compared with older children. There was no difference in performance of entropy and BIS. Both should be used cautiously in small children.


Keywords: anaesthesia, paediatric; anaesthetics volatile, sevoflurane; monitoring, bispectral index; monitoring, entropy

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Anaesthesia depth monitors using the processed EEG have been studied extensively in adults. Their validity and utility in children are less certain. The Bispectral Index (BIS) monitor is the most widely studied. In older children the BIS correlates with some measures of anaesthesia effect, but interpatient variability limits its ability to be used to predict awakening.1 6–8 When compared with older children, BIS in infants has poorer correlation with concentration of volatile anaesthetic and lower values at awakening.14

The entropy monitor is another recently developed anaesthesia depth monitor. It measures the degree of entropy, or disorder, in the EEG.9 Entropy falls with increasing concentration of anaesthetic. The entropy monitor has two outputs: response entropy which uses a higher frequency range that includes more EMG signal and a fast response

Declaration of interest. Datex-Ohmeda provided the sensors and the entropy monitor on loan for this study. Datex-Ohmeda had no role in the design, data collection, analysis or writing of this study.
Entropy and BIS in children

Time, and state entropy which uses lower frequencies providing a more stable value but with a slower response time. A relationship between entropy and anaesthesia has been demonstrated in adults. It has been only partially assessed in children.  

The normal EEG changes with age. The frequency of the awake dominant background activity increases with age. This may particularly influence the performance of monitors such as BIS that specifically include analysis of power-frequency relationships in their algorithm. As entropy relies on a different derivative of the EEG, it is possible that the age-related limitations found with BIS, may not be seen with entropy.

The aim of this prospective blinded physiological study was to compare entropy, as a measure of anaesthetic effect, across different age groups. Two measures of anaesthetic effect were assessed. The first is the value at a defined and relevant point of arousal, i.e. the value displayed immediately prior to awakening (pre-awakening). This value was compared between age groups. The second measure of anaesthetic effect is whether the entropy values change with changes in concentration of anaesthetic agent. The significance of this change was assessed in each age group.  

The BIS was recorded concurrently and the same analysis was performed on the data obtained, enabling a direct comparison of performance of entropy and BIS across age groups.

Methods

This was a prospective blinded physiological study of 54 children. The inclusion criteria were children aged between 1 month and 12 yr undergoing anaesthesia for cardiac catheterization. Children were excluded if they had any neurological disease, history of seizures, allergy to adhesives or any contraindication to the anaesthesia protocol. The protocol was approval by the Hospital Research Ethics Committee and parents gave written informed consent. Patients were enrolled between November 2003 and December 2004.

All patients received acetaminophen premedication and, if the anaesthetist deemed it necessary, they also received oral midazolam 0.5 mg kg⁻¹. Anaesthesia was induced using inhalation of sevoflurane, with or without nitrous oxide. The trachea was intubated in all cases (atracurium 0.5 mg kg⁻¹ was used to aid intubation when necessary) and the children’s lungs were mechanically ventilated. Anaesthesia was maintained with sevoflurane in an air-oxygen mix. No opioids were given. Local anaesthesia infiltration was used prior to cannulation of the femoral vessels by the cardiologist.

After induction of anaesthesia, the entropy sensors were attached to the child’s forehead according to the manufacturer’s instructions. The BIS sensors were placed above the entropy sensors as described in a previous paper. An A-2000 XP BIS module (Aspect Medical Systems, Newton, MA, USA) and an entropy module (Datex-Ohmeda, Helsinki, Finland) were used to record the BIS, response entropy and state entropy values. Both modules were combined in a Datex-Ohmeda S/5 monitor. The data were downloaded from the monitor to a laptop computer using the Datex-Ohmeda S/5 Collect program.

Once all catheters had been successfully placed in the femoral vessels, the anaesthetist aimed for predetermined steady-state concentrations of sevoflurane. The anaesthetist sequentially aimed for end-tidal sevoflurane concentrations of 1.5%, 2.0% and 2.5%. The order for all children was determined by randomization performed prior to commencement of the study. For each age group Stata 7 (StataCorp, College Station, TX, USA) was used to allocate study numbers randomly to one of the six possible order groups. An equal number were allocated to each order group. As age groups were not expected to be exactly equal, a minimal excess of study numbers was generated. Successfully enrolled patients were sequentially allocated study numbers in each age group. The order of sevoflurane concentration for each study number was kept in a sealed envelope that was opened by the anaesthetist immediately before aiming for the first concentration. Sevoflurane concentration was measured using a Draeger Julian gas bench. If the child received muscle relaxants to aid tracheal intubation, the anaesthetist waited until the atracurium had worn off before aiming for the sevoflurane end-tidal concentrations. The muscle relaxant was considered to have worn off if there were more than three responses to the train-of-four stimuli using a nerve stimulator. Each end-tidal sevoflurane concentration was maintained for 10 min to allow equilibrium to be established. After 10 min, response entropy, state entropy and BIS were recorded at 10-s intervals for 1 min and averaged. The anaesthetist was given the option to abandon the protocol if the level of anaesthesia was judged to be excessive or inadequate. Ventilation settings were at the discretion of the anaesthetist. During this period the child had no surgical stimulation. The data were collected when the cardiologists were taking pressure readings or passing a cardiac catheter through an established femoral sheath. No dilatation of vessels occurred during this period.

After the final recording the anaesthetic continued with sevoflurane (the concentration was at the discretion of the anaesthetist). On completion of the cardiac catheter study, the children were extubated while deeply anaesthetized and breathing spontaneously. Oxygen 100% was delivered via a face-mask. After cessation of sevoflurane, the child was not physically handled until awakening. Awakening was defined as onset of continuous purposeful movement, phonation or eye-opening. The pre-awakening data were recorded at the moment of awakening. As the monitors generate data from the previous time epochs of EEG, the value at the moment of awakening actually represents EEG activity immediately prior to awakening (pre-awakening). At all times the anaesthetist was blinded to the BIS and entropy values.

For analysis, the patients were divided into four age groups: 0–1 yr, 1–2 yr, 2–4 yr and 4–12 yr.
values for response entropy, state entropy and BIS were compared separately between the age groups using Kruskal–Wallis one-way analysis of variance (ANOVA) on ranks. BIS, response entropy and state entropy values for the three sevoflurane concentrations were compared separately within each age group using Friedman repeated measures analysis on ranks. Sigma Stat 3.0 (SPSS, Chicago, IL, USA) was used for this statistical analysis. As a secondary outcome, the relationship between sevoflurane concentration and BIS response entropy or state entropy was determined across age groups. Only children who had not received midazolam premedication were included in this analysis. A linear regression with robust standard errors was performed for each age group. The sevoflurane concentrations for the midpoint of each scale were determined from the regression equations. SevoBIS50 was set as the concentration where BIS was 50, SevoRe50 was set as the concentration where response entropy was 50 and SevoSE45.5 was set as the concentration where state entropy was 45.5. The predicted standard error for this value was also determined. Stata 7 (StataCorp, College Station, TX, USA) was used for this analysis.

For justification of numbers the primary outcome measure was defined as the pre-awakening value. A difference of 15 points between age groups was taken as clinically significant and is within the range of values described in a previous similar study. Previous studies have also found a standard deviation of ~10 points for pre-awakening values. With α=0.05 and power of 0.8 at least 11 children were needed in each group. Fifty-four patients were enrolled, assuming that at least 11 children would be included in each group with an unpredictable age distribution and possible protocol violations.

Results
Fifty-four children were recruited to the study. All data for four children were excluded because of protocol violations. No data were collected for two children because of software failure, and two were excluded because of changes in the planned procedure requiring changes in the anaesthesia (use of transoesophageal echocardiography). Analyses were conducted on the remaining 50 children. Their characteristics are shown in Table 1. Contrary to the planned protocol, two patients received propofol at induction. These data were not rejected, as the time from propofol administration to the first data recording time-points for these two cases was 42 min and 62 min, respectively.

Of the 50 children, there were 46 complete datasets for pre-awakening. Pre-awakening data for four patients were missing because of unexpectedly long procedures extending beyond the time resources of the research staff. Pre-awakening data are shown in Figure 1. Median pre-awakening values for all children (and for the subgroup who did not receive midazolam) are listed in Table 2. The pre-awakening values varied significantly across age groups for BIS (P=0.02), response entropy (P=0.003) and state entropy (P=0.009). The median values were lower in infants (age 0–1yr) than in older children (age >1 yr). Differences were similar when comparing the subgroups that did not receive midazolam.

Forty-eight of the 50 children had BIS recordings at all three sevoflurane concentrations and 47 had entropy readings at all sevoflurane concentrations. One patient had no BIS and entropy recordings because of cardiovascular instability precluding sevoflurane changes. One patient had an incomplete set of entropy data as the entropy monitor could not interpret the signal at end-tidal sevoflurane concentrations of 1.5% and 2.0%. The reasons for this were unclear. One patient had an incomplete set of BIS and entropy recordings at sevoflurane 2% because the procedure finished before the final concentration equilibrium was achieved. The complete datasets for each age group demonstrating changes in BIS, response entropy and state entropy with changing sevoflurane concentration are shown in Figures 2–4. The spread of values was greatest in children aged 0–1 yr and was greater in entropy than in BIS.

The older age groups had more significant differences in BIS and entropy when compared among different sevoflurane concentrations. For children aged 0–1 yr the median BIS and state entropy values were significantly different among the three sevoflurane concentrations (P=0.02, P=0.05), but the median response entropy did not vary significantly (P=0.1). For children aged 1–2 yr the median BIS, response entropy and state entropy values were all significantly different among the three sevoflurane concentrations (P=0.07, P=0.006, P=0.002). For children aged 2–4 yr and 4–12 yr the

<p>| Table 1 Patient data for age, weight, time from induction to first reading and duration of anaesthesia. Data are given as mean (range) or mean (SD) |</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>0-1 yr (n=8)</th>
<th>1-2 yr (n=10)</th>
<th>2-4 yr (n=18)</th>
<th>4-12 yr (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>6.6 (0.2–1.0)</td>
<td>1.4 (1.1–1.9)</td>
<td>3.0 (2.1–4.0)</td>
<td>7.4 (4.4–12.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>6.9 (2.0)</td>
<td>10.5 (1.3)</td>
<td>12.7 (2.6)</td>
<td>24.8 (10.9)</td>
</tr>
<tr>
<td>Gender</td>
<td>3 M, 5 F</td>
<td>6 M, 4 F</td>
<td>10 M, 8 F</td>
<td>7 M, 7 F</td>
</tr>
<tr>
<td>Sedative premedication</td>
<td>Yes 1</td>
<td>Yes 1</td>
<td>Yes 6</td>
<td>Yes 4</td>
</tr>
<tr>
<td>Induction agent</td>
<td>Sevoflurane 8</td>
<td>Sevoflurane 9</td>
<td>Sevoflurane 17</td>
<td>Sevoflurane 14</td>
</tr>
<tr>
<td>Propofol</td>
<td>Propofol 1</td>
<td>Propofol 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from induction to first reading (min)</td>
<td>47 (12)</td>
<td>45 (8)</td>
<td>41 (23)</td>
<td>43 (15)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>137 (52)</td>
<td>115 (25)</td>
<td>119 (29)</td>
<td>133 (57)</td>
</tr>
</tbody>
</table>
median BIS, response entropy and state entropy values were also all significantly different among the three sevoflurane concentrations ($P < 0.001$ for all comparisons).

SevoBIS50, SevoRE50 and SevoSE45.5 for each age group are shown in Figure 5. The values are greatest in children

<table>
<thead>
<tr>
<th>Age group</th>
<th>BIS (IQR)</th>
<th>Response entropy (IQR)</th>
<th>State entropy (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td>0–1 yr ($n=7$)</td>
<td>56 (43.8–65.2)</td>
<td>45 (33–62.5)</td>
</tr>
<tr>
<td></td>
<td>1–2 yr ($n=9$)</td>
<td>78 (68.8–82.3)</td>
<td>84 (79.8–93.3)</td>
</tr>
<tr>
<td></td>
<td>2–4 yr ($n=16$)</td>
<td>76.5 (68.5–82)</td>
<td>87 (79.5–92.5)</td>
</tr>
<tr>
<td></td>
<td>4–12 yr ($n=14$)</td>
<td>72 (66.3–76.5)</td>
<td>89 (82.5–95.8)</td>
</tr>
<tr>
<td>$P$-value</td>
<td>0.02</td>
<td>0.003</td>
<td>0.009</td>
</tr>
<tr>
<td>Children not receiving midazolam premedication</td>
<td>0–1 yr ($n=7$)</td>
<td>56 (43.8–65.2)</td>
<td>45 (33–62.5)</td>
</tr>
<tr>
<td></td>
<td>1–2 yr ($n=8$)</td>
<td>78.5 (69.5–82.5)</td>
<td>83.5 (79.5–93.5)</td>
</tr>
<tr>
<td></td>
<td>2–4 yr ($n=11$)</td>
<td>76 (63.3–82)</td>
<td>82 (76–91.8)</td>
</tr>
<tr>
<td></td>
<td>4–12 yr ($n=10$)</td>
<td>73.5 (66–77)</td>
<td>88.5 (84–96)</td>
</tr>
<tr>
<td>$P$-value</td>
<td>0.02</td>
<td>0.005</td>
<td>0.01</td>
</tr>
</tbody>
</table>
aged 1–2 yr and decline as age increases. The values for children aged 0–1 yr are also less than those for children aged 1–2 yr.

**Discussion**

In this study we have demonstrated that the pre-awakening values varied significantly across age groups and were lowest in children aged 0–1 yr. This was apparent for both entropy and BIS. Entropy and BIS values change with changes in sevoflurane concentration for children aged >1 yr. The changes in BIS and entropy with changing sevoflurane concentration were less definite for children aged <1 yr. There was also a greater spread of values in this younger age group.

This was the first study to demonstrate a relationship between sevoflurane concentration and entropy in children. A relationship for BIS has been demonstrated previously in older children. A previous study (using lower concentrations of sevoflurane) found no relationship between BIS and sevoflurane concentration in children aged <1 yr. In our study the relationship was also less certain in the younger children. However, the comparison in the youngest age group was limited by both the greater variance and the smaller number of children enrolled.

Our findings were consistent with previous studies that have demonstrated lower pre-awakening BIS values in children aged 0–1 yr. This phenomenon was also seen with entropy. This may imply that the inability of EEG monitoring to predict awakening in small children is more a function of the nature of their arousal and consciousness rather than inherent changes in the EEG with maturation. It has been reported previously that infants have an abrupt transition from unconsciousness, or deep sedation, to arousal, thus suggesting a possibly more binary nature to their consciousness.

Anaesthesia depth monitors aim to quantify some aspects of anaesthesia effect. The aspect of particular interest is consciousness and memory formation, often referred to as the hypnotic component. However, depth of hypnosis remains an artificial construct incorporating hierarchies of a number of related clinical and physiological phenomena (types of memory formation, responsiveness to a variety of stimuli). Hypnotic depth is not a unique measure and there is no single definition of depth of hypnosis. To indicate hypnotic depth, a monitor could provide a variety of information: the brain concentration of a drug, the degree of arousal, the probability that a patient exists in a certain state (i.e. awake or unconscious) or the likelihood of a patient moving to another plane of consciousness (e.g. awakening). The algorithms for currently available depth monitors do not specifically measure any one of these phenomena; indeed, it is unlikely that some aspects of hypnotic depth are directly measurable. Instead, depth monitors have been developed to use components of the EEG, which in some circumstances have an association with some measures of anaesthesia depth, to provide a number useful for guiding anaesthesia delivery.

It is problematic to assess the validity of an anaesthesia depth monitor when there is no simple definition of anaesthesia depth, or depth of hypnosis. In this study we first examined the ability of the monitor to detect changing brain concentrations of anaesthetic in states of unchanging arousal. Secondly, we assessed the change with age in the value that was associated with awakening. This is only a limited assessment of the anaesthesia depth monitors. If a depth monitor is better regarded as an anaesthesia delivery guide, rather than a device measuring an abstract construct, then the most important test of a monitor is its ability to improve anaesthesia delivery and relevant patient outcome parameters. It is also particularly difficult to assess anaesthesia depth monitors in small children, where the frequently used outcome measures of ability to follow command and memory formation cannot be used.

In this study some patients received midazolam as premedication and a greater proportion of children in the older groups received midazolam. The effect of oral midazolam premedication on BIS is uncertain. One study in children age 10–18 yr found no large effects on BIS at awakening or at set sevoflurane concentrations. The same authors reported no effect on intraoperative BIS but a lower BIS on awakening in children aged 10–18 yr. Rodriguez and colleagues reported the opposite: a lower value pre-awakening in those who had received midazolam. However, this result is confounded by the increased use of sedation in younger children. Because of the uncertainty in the effect of midazolam premedication we excluded children who had received midazolam when comparing absolute values across age groups. We also separately compared pre-awakening values in the subgroup of children who did not receive midazolam. When comparing intrapatient changes in BIS or entropy with sevoflurane change, the effect of midazolam would be constant, and so all children were included in this analysis.

To accommodate the entropy sensor, in this study we placed the BIS sensor slightly higher than recommended by the manufacturer. A previous study has demonstrated that this introduces minimal bias.

This study was not primarily designed to compare absolute values of BIS or entropy at specific concentrations of sevoflurane across age groups. We performed this analysis as a secondary outcome. Given this limitation, the results are still of interest. To compare age groups the concentration for the midpoint of the scales was calculated. For BIS and response entropy this was taken to be a value of 50 while for state entropy it was set at 45.5. The linear regression assumed that the values were in the linear portion of the concentration–effect relationship. A review of previous data suggests that this is a valid assumption. There was not a sufficient spread of values to create a sigmoid $E_{\text{max}}$ pharmacodynamic model. Given that BIS and entropy are scales, rather than physiological measures, a
sigmoid $E_{\text{max}}$ pharmacodynamic model is probably also inappropriate.

The calculated concentration of sevoflurane for the mid-point on the entropy and BIS scales was greatest in the 1–2 yr age group with a progressive decrease with increasing age. It was also lower in children aged 0–1 yr. This finding is at odds with the data relating minimal alveolar concentration (MAC) to age. In children the MAC of sevoflurane changes little with decreasing age until the 0–6 months age group (when it rises significantly).\textsuperscript{21} This age-related discrepancy between MAC and EEG suppression has been demonstrated previously.\textsuperscript{22,23} The effects of anaesthetic agents on MAC and EEG suppression are probably anatomically distinct. MAC and EEG-based anaesthesia depth monitors are different measures of different aspects of anaesthesia effect. However, they are related. As concentration increases both will change. It is possible that the indirect relationship between the two differs with brain maturation. If EEG activity is more closely related to amnesia and consciousness than MAC, then the more active EEG relative to MAC in young children may have implications when considering the appropriate MAC fraction of sevoflurane required for the reliable production of amnesia and unconsciousness in young children during anaesthesia.

In conclusion, this study has demonstrated that BIS and entropy have similar performance characteristics in children. Both need to be used with caution in children aged <1 yr.

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