The impact of age on bispectral index values and EEG bispectrum during anaesthesia with desflurane and halothane in children

O. Tirel13, E. Wodey13 *, R. Harris4, J. Y. Bansard2, C. Ecoffey1 and L. Senhadji2

1Department of Anaesthesiology and Surgical Intensive Care 2, Hospital Pontchaillou, Rennes, France. 2INSERM U 642, LTSI (Laboratoire Traitement du Signal et de l’Image), University of Rennes 1, Rennes, France. 3Groupe de Recherche Cardio-vasculaire (EA 3194), University of Rennes 1, Rennes, France. 4Department of Anaesthesia, St George’s Hospital, London, UK

*Corresponding author: Service d’Anesthésie–Réanimation Chirurgicale 2, Centre Hospitalier Regional et Universitaire, 2 rue Henri le Guilloux, 35033 Rennes Cedex 9, France. E-mail: eric.wodey@chu-rennes.fr

Background. The relationship between end-tidal sevoflurane concentration, bispectral index (BIS) and the EEG bispectrum in children appears to be age dependent. The aim of this study was to quantify the BIS values at 1 MAC (minimum alveolar concentration) for desflurane and halothane, and explore the relationship with age for these anaesthetic agents in children.

Methods. ECG, EEG and BIS were recorded continuously in 90 children aged 6–170 months requiring anaesthesia for elective surgery. Fifty children were anaesthetized with desflurane, and 40 children with halothane. Recordings were performed through to a steady state of 2 MAC, and thereafter at 1 and 0.5 MAC, respectively. The bispectrum of the EEG was estimated using MATLAB software. A multiple correspondence analysis (MCA) was used.

Results. At a steady state of 1 MAC, BIS values were significantly higher with halothane 62 (43–80) than desflurane 34 (18–64). BIS values were significantly correlated with age in both groups: DES (r²=0.57; P<0.01) and HALO (r²=0.48; P<0.01). Changes in position in the structured model of the MCA (dependent on the pattern of the EEG bispectrum) were different for the two volatile anaesthetic agents.

Conclusions. In children, BIS values are linked to age irrespective of the volatile anaesthetic agent used. The difference in BIS values for different agents at the same MAC can be explained by the specific effect on the EEG bispectrum induced by each anaesthetic agent, bringing into question the ability of the EEG bispectrum to accurately determine the depth of anaesthesia.

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(minimum alveolar concentration). The relationship between other volatile anaesthetic agents and BIS, the EEG bispectrum and age has not yet been fully explored. The aim of this study was to explore the relationship between age and the BIS values at 1 MAC of desflurane and halothane in children.

Methods
After approval from the Human Studies Committee, 90 ASA I or II children aged 6–170 months requiring elective surgery were recruited into our observational study with parental consent. We excluded any children with central neurological disease and those taking medication acting on the central nervous system. No children were premedicated. EEG leads (3M Red Dot Silver/Silver Chloride model 2269T, 3M Health Care, St Paul, USA) were placed adjacent to the paediatric BIS leads (Aspect Medical Systems, Newton, IL, USA).

Anaesthesia was induced with sevoflurane 8% in oxygen in the first 50 children. After obtaining i.v. access, all children were intubated without the use of neuromuscular blocking agents. Immediately after intubation, we switched the anaesthetic agent to desflurane. The lungs were then ventilated. Anaesthetic gas and carbon dioxide concentrations were measured continuously in order to ensure normocapnoea. All applied MAC values were corrected for age. In order to achieve both a washout and a steady state at the effect site of 2 MAC of desflurane (EEG signal stationary), the expired concentration of desflurane was maintained at 2 MAC for 10 min with high fresh gas flows at 10 litre min \(^{-1}\) (group DES). For the following 40 children (group HALO), the conduct of anaesthesia was identical except that we used halothane for induction (3.5 vol%) and subsequent maintenance at 2 MAC until a steady state at the effect-site level was obtained (EEG signal stationary).

After starting recording for analysis (T0), the end-tidal concentrations were decreased to 1 MAC corrected for age for both anaesthetic agents. Recordings continued until steady state at 1 MAC was achieved (10 min, T10). We then further decreased the end-tidal anaesthetic agent concentration to 0.5 MAC and continued recording until steady state at this concentration was achieved (T20). At the end of this period in the group HALO, anaesthetic agent was switched to sevoflurane at 1 MAC.

All recordings were obtained in the absence of any surgical stimulation. No additional drugs were administered during this period. ECG, raw EEG (PowerLab\textsuperscript{TM}, ADInstruments, Castle Hill, NSW, Australia) and BIS (Aspect Xp\textsuperscript{TM}) were recorded continuously and mathematically processed as described previously.\textsuperscript{2} The EEG bispectrum for each child under desflurane or halothane anaesthesia was calculated and divided into 36 blocks of frequencies coupling every 20 s throughout the study period and denoted MatBis. An individual value for each of the 36 4\*4 Hz blocks was derived, this corresponding to the mean of the bispectrum for each block. Thus, each child is represented by 36 descriptors evolving over the time of recording. More details were described in our previous work.\textsuperscript{2}

For statistical analysis, we used a multiple correspondence analysis (MCA) derived from previous published recordings of 100 children anaesthetized with sevoflurane at 1 MAC.\textsuperscript{2} In order to explore the effect of change in desflurane and halothane concentrations on the EEG bispectrum, the change in position in the structured model of the MCA during the decrease of anaesthetic agent concentration was analysed for each group of children. This change in position within the structured model of the MCA was determined by changes in the MatBis (i.e. EEG bispectrum) during the decrease from 2 to 0.5 MAC as explained in the appendix of our previous article.\textsuperscript{2} In addition, any correlation between age and BIS values obtained at 1 MAC for each anaesthetic agent was evaluated by means of a Spearman test. A Wilcoxon test was used to establish significant changes in parameters at various points during the decrease in anaesthetics agents. All results are described as median (range). A P-value <0.05 was considered significant. All statistical analyses were performed with the BI\textsuperscript{10} LOGINSERM 1979/1987 software.

Results
We obtained complete recordings in all children except for two children in group HALO (because of protocol violations). No differences are seen between groups in terms of age and weight (Table 1).

At steady state of 1 MAC (T10), BIS values were significantly higher with halothane 62 (43–80) compared with desflurane 34 (18–64) (Fig. 1). BIS values were also significantly correlated to age in both groups at this MAC: DES \((r^2=0.57; P<0.01)\) and HALO \((r^2=0.48; P<0.01)\) (Fig. 2).

In group DES, as end-tidal concentration of desflurane decreased from 2 to 1 MAC and subsequently to 0.5 MAC, children’s position in the structured model of the MCA changed in a similar manner to those seen with sevoflurane anaesthesia, reported in our previous article.\textsuperscript{2} In contrast, in group HALO, children’s position in the structured model at 2 MAC, and change in position during the concentration decrease was entirely different (Fig. 3). When halothane 0.5 MAC was replaced by 1 MAC sevoflurane, children’s position in the MCA returned to the position that we found in children with sevoflurane anaesthesia alone.

<table>
<thead>
<tr>
<th>Table 1: Children’s characteristics and clinical variables at 1 MAC of desflurane (DES) and halothane (HALO). Data are median (range)</th>
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<tr>
<td><strong>DES</strong> ((n=50))</td>
</tr>
<tr>
<td>Age (months)</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Sex ratio (MF)</td>
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<td>End-tidal volatile anaesthetic (%)</td>
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<td>MBP (mm Hg)</td>
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An example of the shape of the EEG bispectrum obtained with sevoflurane, desflurane and halothane at 2, 1 and 0.5 MAC respectively is presented in Figure 4.

**Discussion**

We have found, as previously reported with sevoflurane, that BIS measured at desflurane or halothane 1 MAC is strongly related to the age of children. In addition, BIS values under 1 MAC halothane anaesthesia were found to be distinctly higher, 62 (43–80), than those under 1 MAC desflurane, 34 (18–64), or as previously found with 1 MAC sevoflurane anaesthesia,2 40 (20–60), irrespective of the age of children (Fig. 2).

We have previously demonstrated, using a MCA, that one of the main components used to derive the BIS value, the EEG bispectrum, is itself dependent on age at 1 MAC sevoflurane in children above 1 yr.2 This could explain the inverse correlation of BIS values with age above 1 yr at 1 MAC of sevoflurane.2,3 However, Davidson and colleagues4 have recently reported that in infants less than 1 yr, pre-awakening BIS values show a tendency to be lower than those obtained in children above 1 yr. This correlates with the finding that target BIS values of 40–60 in infants less than 6 months can be achieved with very low concentrations of sevoflurane.7 Overall, these results mean that in clinical practice, if sevoflurane is titrated towards specific BIS levels in children above 1 yr of age, there will be a tendency to use levels greater than 1 MAC (but diminishing as age increases). In contrast, in children less than 1 yr, sevoflurane concentration could be titrated down to a very low level against the BIS, resulting in levels of less than 1% (much less than 0.5 MAC) in this population. This clinical practice is generally not acceptable, especially if a neuromuscular blocking agent is used.7

In this study, we have found that the same relationship exists for desflurane as for sevoflurane in children greater than 1 yr. In contrast with halothane, although a relationship exists between age and BIS at 1 MAC, it appears different to that with the other two anaesthetic agents. In a study of 40 children older than 2 yr, Davidson and colleagues4...
have demonstrated that BIS values obtained under halothane [56.5 (8.1)] were higher than those under isoflurane [35.9 (8.5)] at 1 MAC. Similarly, results reported by Edwards and colleagues\(^6\) showed mean BIS values approximately 15 points higher with halothane than with sevoflurane in children. Our results using the EEG bispectrum could help to explain the difference in BIS values. Constant and colleagues\(^8\) have reported that the effects of sevoflurane

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**Fig 2** Relationship between BIS values at 1 MAC and age using three different volatile agents.

**Fig 3** Change in children’s position in the structured model of the multiple correspondence analysis during decrease in concentration of the three volatile anaesthetic agents. Each point represents 1 min. Larger dots represent steady state. The units of axes F1 and F2 are arbitrary.
and halothane on the EEG in children show different patterns of depression. In our study, sevoflurane and halothane show different patterns in the EEG bispectrum corresponding to their respective frequencies of coupling. For example, at 1 MAC the position of children under halothane anaesthesia is on the left side of the structured model of MCA, corresponding to high frequencies of coupling. In contrast, with sevoflurane, children are positioned on the right side, reflecting the dominance of lower frequencies (Fig. 3) (see also Fig. 3b in ref. 2). Thus, we suggest that the difference between BIS values found using sevoflurane and halothane is not dependent on the depth of anaesthesia, but it is attributable to the different pharmacological effect on EEG frequencies. Indeed, in the switch that we made from 0.5 MAC halothane to 1 MAC sevoflurane at the end of recording in group HALO, we were able to reproduce exactly the pattern of the EEG bispectrum that we obtained in children in group SEVO at 1 MAC. This further supports the notion that the EEG bispectrum is mainly agent dependent.

Some authors have suggested that the definition of MAC (movement to stimulus) may not truly reflect consciousness and the depth of anaesthesia or EEG activity. Thus, the differences shown in the BIS values between halothane and sevoflurane at 1 MAC could be attributed to the fact that movements and MAC are determined more by spinal motor reflexes than 'true' hypnotic effect. BIS monitoring is based on the potential links between the depth of anaesthesia and changes in the EEG, especially the EEG bispectrum. Using the up-and-down technique, Taylor and Lerman9 found that the relationship between 1 MAC of desflurane and age ranged from 9.92 (±0.44%) in infants 6–12 months to 7.98 (±0.43%) in children 5–12 yr. Using a similar technique, 1 MAC of sevoflurane was found to be 3.2% in infants 6–12 months and 2.5% in children 1–12 yr.10 Thus, equipotent concentrations of desflurane are approximately three times those of sevoflurane in children. Despite the criticism of the ability of MAC to reflect the true depth of anaesthesia, we found that the pattern of the EEG bispectrum for both sevoflurane and desflurane at three different equipotent concentrations, 2, 1 and 0.5 MAC, were very similar in terms of their respective positions in the structured model of the MCA. These results therefore add evidence to the validity of the currently accepted MAC levels in determining equipotent effect on EEG with sevoflurane and desflurane. During this study, it was possible to intubate all children without neuromuscular blocking agent or opiate at 2 MAC of halothane or sevoflurane without difficulty (no movement, haemodynamic response, cough or laryngospasm) indicating a similarly profound clinical depth of anaesthesia for both agents. However, it was noticeable that the pattern of the EEG bispectrum at 2 MAC of halothane did not correspond to the pattern with 2 MAC of sevoflurane, but to the pattern with 0.5 MAC of sevoflurane. At 0.5 MAC of sevoflurane (and 0.5 MAC of desflurane), the slightest stimulation of children resulted in signs of wakening, levels of anaesthesia at which it was certainly not possible to intubate. Thus, the ability of the EEG bispectrum to determine the depth of anaesthesia in children may well be fundamentally flawed. Indeed, another recent study using sevoflurane anaesthesia also suggests similar problems with this modality.11

In our previous study using sevoflurane,2 we suggested that it may be possible to improve the accuracy of BIS at deeper levels of anaesthesia in children, and make it independent of age, using an additional frequency of
coupling. We found that changes in the position of children along axis F2 of the MCA model appeared to be more related to the depth of anaesthesia than changes along axis F1 (the axis to which BIS and age were related). This relationship may remain valid for desflurane but in the light of our results with halothane this is by no means a universal reliable indicator of the depth of anaesthesia. In fact, halothane shows an inverse relationship with axis F2 (Fig. 3). Hence, if the depth of anaesthesia is to be assessed using frequencies of coupling of the EEG bispectrum, it is at least necessary to specify the agent used.

In conclusion, BIS values were linked to the age of children irrespective of the volatile anaesthetic agent used. 1 MAC of desflurane, together with 1 MAC of sevoflurane, showed BIS values lower than 1 MAC of halothane at all ages. These differences can be explained by the specific effect on the mechanisms underlying EEG generation induced by each anaesthetic agent, bringing into question the ability of the EEG bispectrum to accurately determine the depth of anaesthesia in children.

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