

Spectral Entropy as a Measure of Hypnosis in Children

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Background: **The Datex-Ohmeda S/5 Entropy Module (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland), using time-frequency balanced Spectral Entropy, is a novel tool for monitoring the hypnotic state during anesthesia. The Entropy Module produces two values, State Entropy (SE) and Response Entropy (RE), and in adults, it has been shown to measure reliably the hypnotic effects of various drugs. In children, Spectral Entropy has been only preliminary studied. The authors' aim was to study Spectral Entropy as a marker of hypnotic state during general anesthesia in infants and children.**

Methods: **Twenty infants (aged 1 month–1 yr) and 40 children (aged 1–15 yr) were anesthetized for surgery using standardized sevoflurane-nitrous oxide–based anesthesia. The relationships between SE, RE, or Bispectral Index (BIS) and (1) a modified Observer's Assessment of Alertness/Sedation Scale, (2) non–steady state end-tidal concentration of sevoflurane, (3) steady state end-tidal concentration of sevoflurane, and (4) hemodynamic values were calculated using prediction probability, nonlinear regression, and correlation coefficients, as appropriate. The performances of SE, RE, and BIS were compared.**

Results: **The prediction probability values (± SEM) of SE, RE, and BIS *versus* the modified Observer's Assessment of Alertness/Sedation Scale in the induction phase were 0.83 ± 0.06, 0.88 ± 0.06, and 0.87 ± 0.08 for children and 0.76 ± 0.08, 0.79 ± 0.08, and 0.73 ± 0.10 for infants; values in the emergence phase were 0.68 ± 0.05, 0.74 ± 0.04, and 0.64 ± 0.05 for children and 0.64 ± 0.07, 0.69 ± 0.06, and 0.72 ± 0.06 for infants, respectively. SE, RE, and BIS values were inversely proportionally related to the end-tidal concentration of sevoflurane for children, but for infants, the correlation was much less clear. No significant correlations were found between SE, RE, or BIS values and the hemodynamic values.**

Conclusions: **Spectral Entropy may be a useful tool for measuring the level of hypnosis in anesthetized children and seems to perform as well as BIS. In infants, the clinical usefulness of both these electroencephalogram-derived methods must be evaluated in further controlled studies.**

SEVERAL methods have been introduced to reflect the hypnotic state during anesthesia induced by anesthetic or sedative drugs. These include certain physiologic signs,[1] various clinical scales,[2,3] and methods based on the electroencephalogram.[4] In adults, electroencephalogram-derived indices, such as evoked potential features,[5] the Bispectral Index,[4,6,7] and the Spectral Entropy,[8] have been shown to be indicators of the depth of hypnosis during anesthesia. Benefits of monitoring the level of hypnosis during anesthesia include, *e.g.*, faster recovery,[9–11] reduced need for anesthetics,[10–12] and better individual guidance of anesthesia.[7,13]

The Datex-Ohmeda S/5 Entropy Module (M-Entropy; Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland), using Spectral Entropy, is a novel tool for monitoring the depth of hypnosis. It measures the regularity of the electroencephalogram signal according to an algorithm published previously,[14] providing two values of entropy, the State Entropy (SE) and the Response Entropy (RE). The Entropy Module measures the depth of hypnosis by calculating the spectral entropy of the electroencephalographic power spectrum.[15,16] SE, with a scale of 0–91, is computed over the electroencephalogram-dominant frequency range of 0.8–32 Hz, whereas RE, with a scale 0–100, is computed over the electromyographic-dominant frequency of 0.8–47 Hz. When there is no electromyographic activity present, SE and RE show the same number. The recommended range for adequate anesthesia for both Spectral Entropy parameters is from 40 to 60, and zero-values are associated with a completely suppressed electroencephalogram. Spectral Entropy has been validated to measure the depth of hypnosis in adult patients receiving inhaled or intravenous anesthesia.[8,17–19]

In pediatric patients, electroencephalogram-derived monitors, such as BIS,[9,20–22] and auditory evoked potentials[23,24] have been studied for the measurement of the depth of hypnosis during anesthesia. BIS has been validated in older children,[20–22] but there are conflicting data about the validation of BIS in infants.[7,9,21,25–27] Until now, Spectral Entropy has been only preliminarily studied in pediatric patients.[25,28]

The aim of our study was to evaluate whether Spectral Entropy reliably measures the depth of hypnosis in infants and children during sevoflurane-based general anesthesia. The level of hypnosis was assessed with a modified responsiveness category of the Observer's Assessment of Alertness/Sedation Scale (mOAA/S).[2,3] We hypothesized that there should be, first, a correlation between SE or RE values and the mOAA/S and, second, a correlation between SE or RE values and the end-tidal concentration of sevoflurane. Secondarily, we also com-

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pared the performance of Spectral Entropy with BIS in children of various ages.

Materials and Methods

Patients and Study Design

After institutional ethics committee approval (Hospital for Children and Adolescents, Helsinki University, Helsinki, Finland) and written informed consent of parents were obtained, 20 infants and 40 children were studied. All patients had an American Society of Anesthesiologists physical status classification of I or II and were scheduled to undergo elective surgery during general anesthesia. The inclusion criteria were an age between 1 month and 15 yr and an elective surgical operation with an estimated duration between 0.5 and 5 h, which required general anesthesia without regional anesthetics. Children were excluded if they had a disease or medication affecting the central nervous system or if the surgery affected the head or the neck of the child.

Anesthetic Regimen

Premedication with 0.3 mg/kg oral midazolam (maximum 15 mg) was administered approximately 45 min before the estimated induction of anesthesia. All patients received a standardized anesthetic regimen. Mask induction was performed using an open circuit at high fresh gas flow (4-8 l/min): The patients breathed 5% sevoflurane in a mixture of 70% nitrous oxide in oxygen *via* a tight-fitting facemask until the loss of eyelash reflex. Thereafter, sevoflurane was decreased to the age-corrected 1 minimal alveolar concentration in oxygen.[29] Simultaneously, a peripheral venous catheter was inserted, followed by 2 μg/kg intravenous fentanyl and 0.5 mg/kg rocuronium to facilitate tracheal intubation. When spontaneous breathing diminished, patients were manually ventilated to ensure normocapnia. The patients were intubated 2 min after the loss of eyelash reflex. Thereafter, controlled ventilation was started to maintain the end-tidal carbon dioxide at 35–40 mmHg (ADU S/5 and S/5 Anesthesia Monitor; Datex-Ohmeda Division, Instrumentarium Corp.). After intubation, anesthesia was maintained with 70% N_2O in O_2 and sevoflurane, which was adjusted to maintain the heart rate and mean arterial blood pressure within 20% of the baseline values obtained before the anesthetic induction. In addition, 1 μg/kg fentanyl and 0.2 mg/kg rocuronium were given as needed.

At the end of surgery, 15 mg/kg intravenous acetaminophen was given to all patients, and 1 mg/kg ketoprofen was given to patients older than 6 months for postoperative pain treatment. The ulnar nerve near the wrist was stimulated with a peripheral nerve stimulator (Fisher and Paykel Healthcare, Auckland, New Zealand) using train-of-four and tetanic stimulation. The combination of 40 μg/kg intravenous glycopyrrolate and 10 μg/kg neostigmine was administered when needed (*i.e.*, when a fade in the train-of-four stimulation was observed visually) for reversal of residual neuromuscular blockade.

At the end of surgery, the inhalational agents nitrous oxide and sevoflurane were discontinued without any tapering, and the patient was extubated when sufficient spontaneous breathing had returned. Thereafter, the patient was transferred to the postanesthesia care unit. In case of postoperative pain, 0.1 mg/kg morphine was given repeatedly when needed.

In addition to Spectral Entropy and BIS values, end-tidal sevoflurane and nitrous oxide concentrations, electrocardiogram, heart rate, noninvasive blood pressure (measured at 5-min intervals), capnogram, pulse oximetry saturation, and temperature (S/5 Anesthesia Monitor) were monitored continuously during anesthesia and collected with 5-s intervals on a laptop computer (Toshiba Satellite; Toshiba Corp., Tokyo, Japan).

Electroencephalogram Acquisition

The anesthesiologist in charge was blinded to Spectral Entropy and BIS monitoring throughout the study period, and an independent study nurse supervised recording of all the data. Before the anesthesia induction, a disposable adult Entropy Sensor (Datex-Ohmeda Division, Instrumentarium Corp.) and a disposable adult BIS® Sensor (Aspect Medical Systems, Newton, MA) were placed in the immediate vicinity of each other on the forehead according to the manufacturers' instructions, following as closely as possible the recommended placement in adults. The skin was carefully wiped with an alcohol swab and then allowed to dry. The Entropy Sensor was placed lower and the BIS® Sensor was placed higher on the forehead, and the distal leads of the sensors were placed on the opposite temples. Electrode impedances were considered acceptable if they were below 7.5 kΩ and 10 kΩ for Spectral Entropy and BIS, respectively. Impedances were checked at the start and the end of the recording and whenever unreliable tracking of the electroencephalogram parameters was suspected, and corrective actions were performed if the acceptable impedance levels were exceeded. Spectral Entropy and BIS indices were measured with an M-Entropy and a BIS® Module (BIS® XP, version 3.2; Aspect Medical Systems) of the S/5 Anesthesia Monitor. The

Table 1. Patient Demographics

	Infants	Children
Number of patients	20	40
Male/female	12/8	21/19
Age, yr	0.5 ± 0.2 (0.1–0.9)	8.5 ± 4.7 (1.3–15.9)
Weight, kg	7.9 ± 1.9 (4.6–11.3)	32.8 ± 17.4 (9.4–80.0)

Data are presented as number of patients, mean ± SD (range) where appropriate.

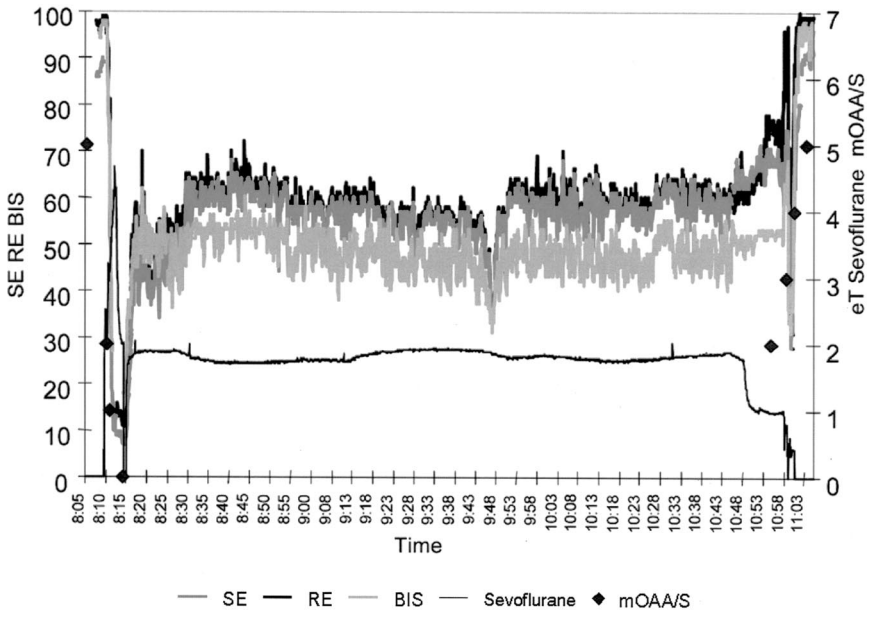

Fig. 1. The graph presents the registration of a child (14-yr-old girl) with the following parameters: State Entropy (SE), Response Entropy (RE), and Bispectral Index (BIS) values; end-tidal sevoflurane concentrations; and scores of the modified Observer's Assessment of Alertness/Sedation Scale (mOAA/S).

sampling rate for the raw electroencephalogram was 400 Hz for Entropy and 256 Hz for BIS; the smoothing window for BIS was 15 s. Spectral Entropy and BIS indices together with all other measured parameters were collected to a laptop computer (Toshiba Satellite) using the S/5 Collect software (Datex-Ohmeda Division, Instrumentarium Corp.). Entropy and BIS measurement were started in the operating room before induction to obtain the baseline values and continued until the patient was awake in the postanesthesia care unit.

Study Measurements

The attending anesthesiologist estimated the level of consciousness by using a modified responsiveness category of the Observer's Assessment of Alertness/Sedation Scale (OAA/S),[2,3] rated from 0 to 5, where 5 = responds readily to name spoken in normal tone, 4 = lethargic response to name spoken in normal tone, 3 = responds only after name is called loudly and/or repeatedly or eyelash reflex is present, 2 = loss of eyelash reflex, 1 = no purposeful response to train-of-four stimulation or to mild painful stimulus (*e.g.*, venous cannulation), and 0 = no purposeful response to 50-Hz stimulation or to painful stimulus (*e.g.*, surgery). The mOAA/S estimation started before induction and was continued until the return of normal, fully awake level of consciousness in the postanesthesia care unit. The analyses of the relation between Spectral Entropy and BIS *versus* the mOAA/S were divided into two periods: (1) the induction phase: the period from the beginning of the anesthetic induction until the administration of rocuronium; and (2) the emergence phase: from the termination of the surgery to the return of normal consciousness. The mOAA/S was assessed every 30 s during the induction phase and every 2 min during the emergence phase. A standardized verbal stimulus (the patient's name) was given at 30-s intervals in the operating room and postanesthesia care unit until the patient was awake (defined as eye opening, purposeful movement, or phonation as appropriate for age).

The relations between SE, RE, and BIS *versus* end-tidal concentrations of sevoflurane were analyzed from the start of anesthesia induction to the extubation of the patient. The end-tidal sevoflurane measurements were performed at 5-s intervals. If the end-tidal concentration had been stable, *i.e.*, end-tidal concentration of sevoflurane within ±0.1% for 5 min, the following measurements after this steady 5 min were included in the steady state concentration of sevoflurane analysis until the concentration changed more than ±0.1%. The steady state end-tidal concentrations of sevoflurane were analyzed retrospectively. Otherwise, these 5-s interval measure-

Table 2. Prediction Probabilities for the Modified Observer's Assessment of Alertness/Sedation Scale in Infants and Children

	mOAA/S	
	Infants	Children
Induction phase		
SE	0.76 ± 0.08	0.83 ± 0.06
RE	0.79 ± 0.08*	0.88 ± 0.06*
BIS	0.73 ± 0.10	0.87 ± 0.08
Emergence phase		
SE	0.64 ± 0.07	0.68 ± 0.05
RE	0.69 ± 0.06	0.74 ± 0.04
BIS	0.72 ± 0.06	0.64 ± 0.05

Data are presented as mean ± SEM.

* Prediction probability (Pk) Response Entropy (RE) children > Pk RE infants ($P = 0.01$).

BIS = Bispectral Index; mOAA/S = modified Observer's Assessment of Alertness/Sedation Scale; SE = Spectral Entropy.

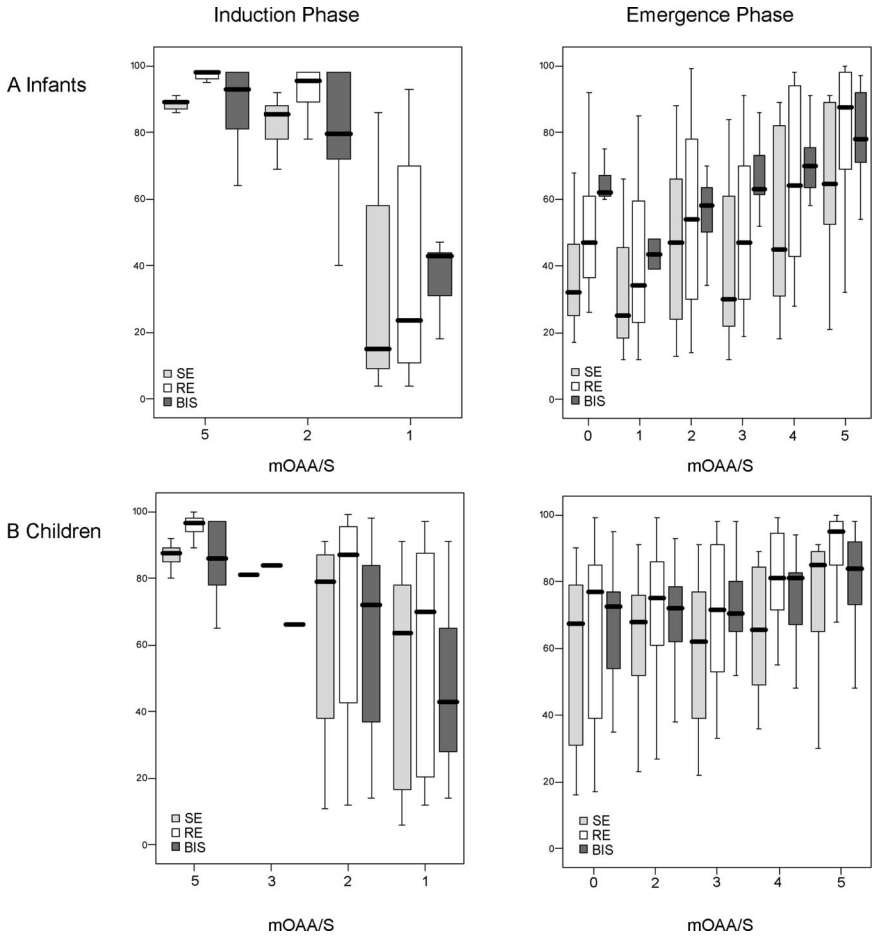

Fig. 2. Box plot analysis demonstrates the relation between the modified Observer's Assessment of Alertness/Sedation Scale (mOAA/S) and State Entropy, Response Entropy, and Bispectral Index during the induction phase and during the emergence phase in infants (*A*) and children (*B*). The mOAA/S scores 4 and 3 were not encountered in infants and the score 4 was not encountered in children in the induction phase. The box plots and whiskers show the mOAA/S values of State Entropy (*light gray boxes*), Response Entropy (*white boxes*), and Bispectral Index (*dark gray boxes*). The *bold black line* within each box indicates the median, the *bottom and the top of the box* indicate 25% and 75% ranges of the group, with the *distance between the top and the bottom* being the interquartile range. The *whiskers* indicate the range of the group.

ments were included in the non–steady state end-tidal concentration of sevoflurane analysis.

The correlations between different electroencephalogram devices (SE, RE, and BIS) and between electroencephalogram values *versus* hemodynamic values (heart rate and mean arterial pressure) were analyzed from the start of anesthesia induction to the extubation of the patient.

Statistical Analysis

The patients were stratified to two groups based on age: infants, 1 month–1 yr; and children, 1–15 yr. The relation between SE, RE, and BIS (ratio scale variables) *versus* mOAA/S (ordinal scale variable) were analyzed with prediction probability (Pk).[30] Pk values were calculated using PKMACRO software (written in Microsoft Excel; Microsoft Corp., Redmond, WA). Both per-subject and overall group relations were considered. The Pk values for different electroencephalographic indices were compared using the Wilcoxon rank sum test with Bonferroni correction, and comparisons of Pk values between the two different age groups were performed using the Mann–Whitney test.

To determine the pharmacodynamic relation between the quantitative electroencephalogram variables (SE, RE, and BIS) and end-tidal sevoflurane concentration, a nonlinear regression fit was performed. This was done separately for infants and children and for steady state as well as non–steady state conditions. The following model was used for the regression fit:

$$E = E_0 - \frac{E_{max} \cdot C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}},$$

where E is the recorded value of SE, RE, or BIS and C is the end-tidal sevoflurane concentration. E_0 is the value at a drug concentration of 0, whereas E_{max} is the maximum value for E. EC_{50} is the drug concentration corresponding to a half-maximal effect of SE, RE, and BIS. Gamma (γ) is a measure to describe the steepness of the drug concentration–effect relation (the Hill coefficient).[31]

The data were fitted to the model using a nonlinear least squares fit routine available in a commercial mathematical software package (Matlab, version 6.5, Release 13; The Mathworks Inc., Matick, MA). E_0 and E_{max} were specified as 100 for BIS and RE and as 91 for SE.[14] The results of the fit were the estimated values of EC_{50} and γ together with their 95% confidence intervals and plotted curves of the equations with these values, as well as 95% confidence intervals for predicted values of SE, RE, and

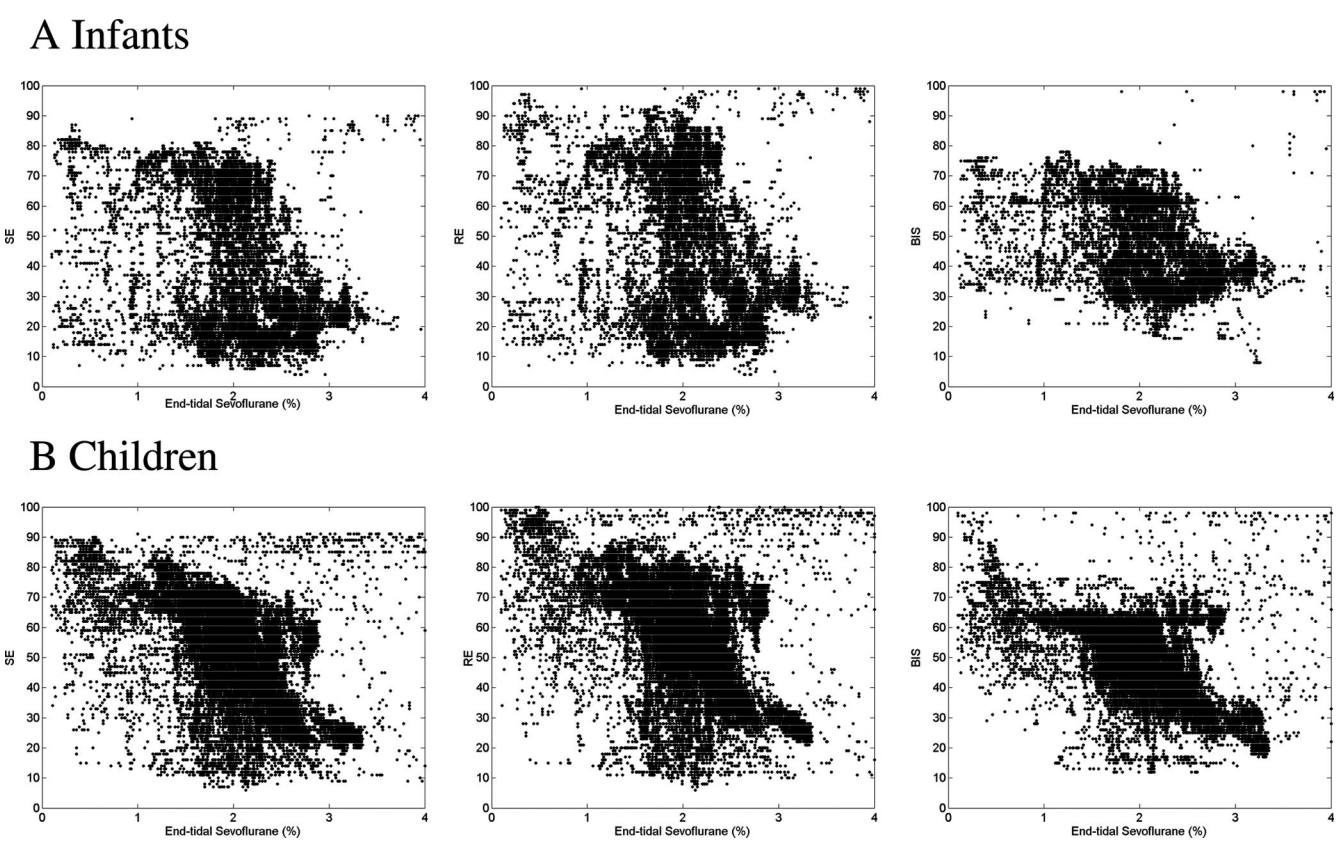

Fig. 3. Plot of the relation between State Entropy (SE), Response Entropy (RE), and Bispectral Index (BIS) values *versus* the end-tidal sevoflurane concentration in infants (*A*) and children (*B*).

BIS when new observations of drug concentrations would be obtained.

The correlations between the different electroencephalographic indices (SE, RE, and BIS) were calculated by mean correlation coefficients, as were also the relations between SE, RE, and BIS *versus* heart rate and mean arterial pressure. These comparisons were made with the Wilcoxon test (pairwise nonparametric). Correlation coefficients were calculated with SPSS V11.01 (SPSS Inc., Chicago, IL).

A *P* value smaller than 0.05 was considered statistically significant. Because we were mainly conducting exploratory analysis to find out the performance of Spectral Entropy in children, which has not been done before, we did not perform a power analysis.

Results

The demographic data of the study are shown in table 1. A representative patient case with relevant data is shown in figure 1. In total, two infants and four children were omitted from different analyses. One infant and two child cases were omitted because of partly missing BIS data, two child cases were omitted because of partly missing mOAA/S data, and one infant case was omitted because of partly missing BIS and mOAA/S data.

The Pk values of SE, RE, and BIS *versus* mOAA/S are shown in table 2. The Pk value of RE in children was significantly higher when compared with RE in infants. Overall, the Pk values were higher among children than among infants, and the Pk values were higher during the induction phase than during the emergence phase. The box plots of SE, RE, and BIS *versus* mOAA/S are shown in figure 2.

The relationships between SE, RE, and BIS *versus* end-tidal concentration of sevoflurane, as used in the pooled analyses for infants and children, are shown in figure 3. The results of the analysis of the nonlinear regression relation between SE, RE, and BIS *versus* non–steady state and steady state end-tidal sevoflurane concentration are presented graphically in figures 4 and 5. The numerical values of the drug concentration corresponding to a half-maximal effect of SE, RE, and BIS (EC_{50}) and the steepness of the relation between the drug concentration–effect relation (the Hill coefficient, γ) for both age groups and both sevoflurane end-tidal concentrations are shown in tables 3 and 4.

The mean correlation coefficients between the various electroencephalogram indices (SE, RE, and BIS) are shown in table 5. The mean correlation coefficients between SE, RE, and BIS *versus* heart rate and mean arterial pressure are shown in table 6. There were no significant correlations between SE, RE, or BIS and the heart rate or mean arterial pressure values.

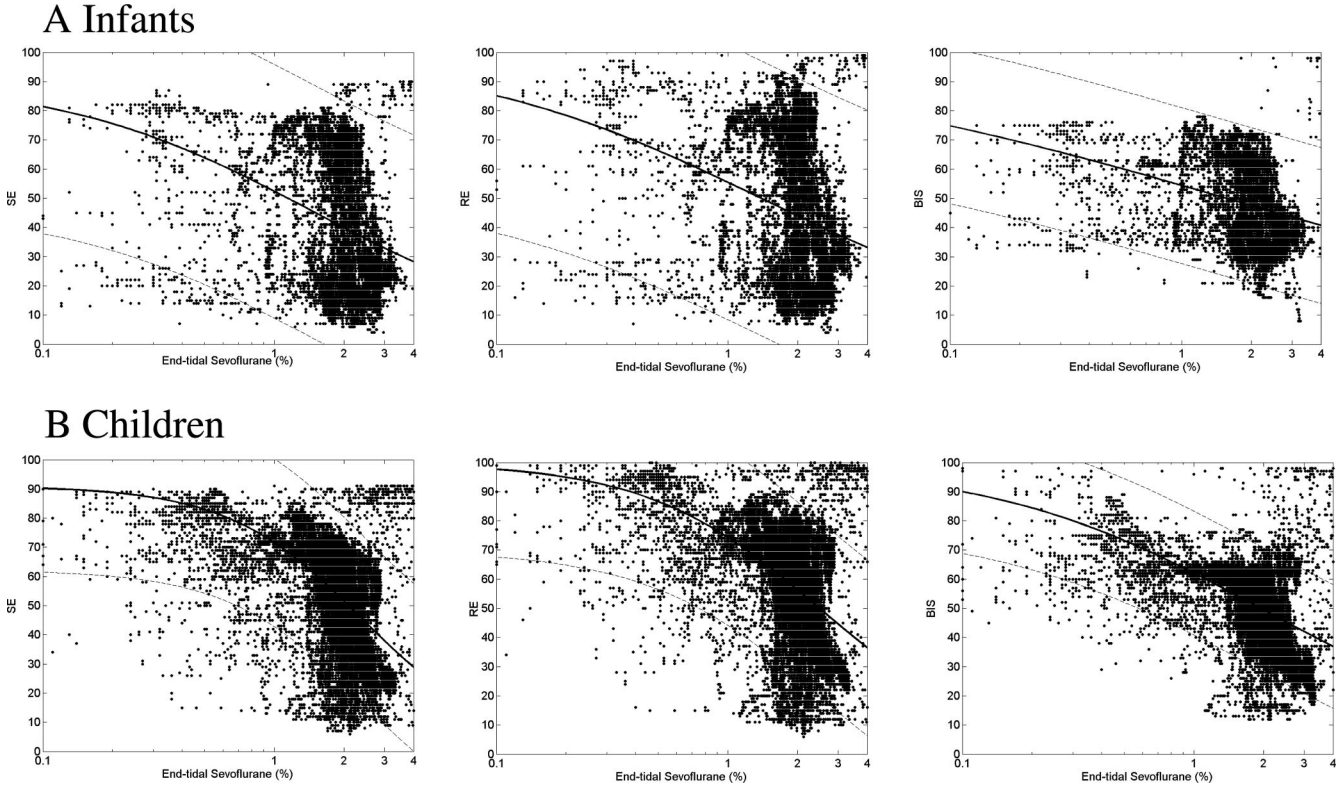

Fig. 4. Logarithmic plot of the relation between State Entropy (SE), Response Entropy (RE), and Bispectral Index (BIS) values *versus* the end-tidal sevoflurane concentration at non–steady state in infants (*A*) and children (*B*). The *continuous line* indicates the predicted values, and the *dotted line* indicates confidence intervals for the predicted values.

Discussion

The current study shows that the Spectral Entropy indices (both SE and RE) reflected the level of hypnosis during sevoflurane–nitrous oxide anesthesia in children as judged primarily by Pk and by the pharmacodynamic regression analysis. However, these correlations were relatively low in infants. Overall, in both children and in infants, Spectral Entropy performed as well as BIS.

The Pk values were better for children than for infants and also better during induction than during emergence. The Pk values of both age groups were lower than those of the adult studies.[8,17–19] This finding was most evident in infants, making the clinical usefulness of Spectral Entropy in the younger age group less obvious or even questionable. Interestingly, this is the case also with BIS.[7,9,21,25–27]

As shown by the box plot graph (fig. 2), there is a significant overlap in all of the electroencephalogram-derived indices (SE, RE, and BIS) when compared with each level of hypnosis as estimated by the behavioral scale (mOAA/S). This is caused by the large interindividual variation of SE, RE, and BIS values during different stages of hypnosis, which was most evident in infants. Especially in infants, the relatively rapid wash-in of sevoflurane seems to produce a phenomenon with "on–off" behavior during the anesthetic induction.

The nonlinear regression analysis (figs. 4 and 5) demonstrates a pharmacodynamic correlation between SE, RE, and BIS *versus* both non–steady state and steady state end-tidal concentration of sevoflurane, which can be assumed from the raw plots of end-tidal sevoflurane *versus* the electroencephalographic indices (fig. 3). In children, there is a gradual relation visible, and fitting the classic E_{max} model seems to be justified. However, in infants, this is much less convincing. A curve-fitting algorithm always gives some results, but the plots for the infants' data show that the practical validity of the fitted curve is poor. This is clearly seen as wide confidence intervals for the estimated values of EC_{50} and γ (tables 3 and 4). In fact, the individual curves for infants are much steeper than the rather shallow curve calculated over the whole population suggests. This effect, obtained when using a pooled data approach, is well established.[32,33] In this study, the relatively small amount of available data points at the level higher than 95% of the E_{max} decreased the reliability of the estimated parameters EC_{50} and γ, as has been previously suggested.[34]

There are only a few studies in children using Spectral Entropy, *i.e.*, only one publication[25] and a congress poster have been presented.[28] The published study of 23 patients by Davidson and coworkers[25] consisted of infants, toddlers, and children undergoing general anesthesia based on isoflurane–nitrous oxide and supplemental peripheral nerve blockade. They found a strong correla-

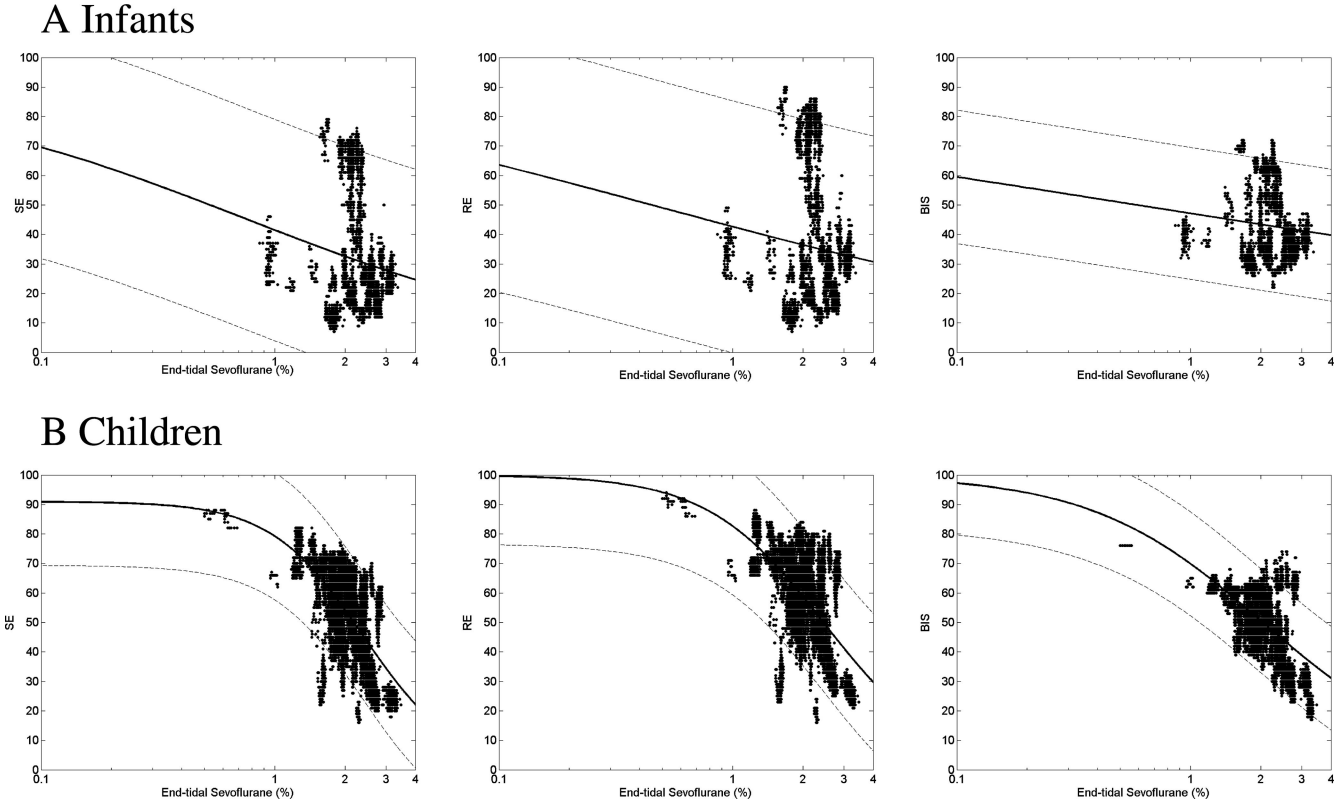

Fig. 5. Logarithmic plot of the relation between State Entropy (SE), Response Entropy (RE), and Bispectral Index (BIS) values *versus* the end-tidal sevoflurane concentration at steady state in infants (*A*) and children (*B*). The *continuous line* indicates the predicted values, and the *dotted line* indicates confidence intervals for predicted values.

tion between BIS and Spectral Entropy for toddlers and children, but the correlation was less for infants. The Spectral Entropy indices were higher before anesthesia induction and after emergence than during anesthesia for toddlers and children, but this was not as apparent in infants. The abstract by Arnaout *et al.*[28] presented 53 children aged 2–12 yr undergoing ear, nose, and throat surgery during general anesthesia based on sevoflurane–nitrous oxide. They found that Spectral Entropy indices and BIS were closely correlated with each other, although during deep anesthesia, the Spectral Entropy values were lower than the BIS value. Arnaout *et al.* stated that Spectral Entropy indices seem to follow the depth of hypnosis in children anesthetized with sevoflurane. These findings are in line with our findings.

There was no correlation between SE, RE, or BIS *versus* heart rate or mean arterial pressure (table 6). Therefore, hemodynamic parameters do not seem to reflect the level of hypnosis, which has been shown previously also in pediatric patients.[22]

The BIS has been validated in older children,[20–22] but there are conflicting data about the performance of BIS

Table 3. Estimations of EC_{50} and γ for Infants and Children with Their 95% Confidence Intervals during Non–Steady State End-tidal Concentration of Sevoflurane

	EC_{50}	γ
Infants		
SE	1.47 (1.44–1.55)	0.80 (0.76–0.83)
RE	1.39 (1.35–1.43)	0.66 (0.63–0.70)
BIS	1.56 (1.52–1.59)	0.40 (0.38–0.42)
Children		
SE	2.40 (2.39–2.41)	1.49 (1.47–1.52)
RE	2.49 (2.47–2.50)	1.16 (1.14–1.19)
BIS	1.95 (1.94–1.96)	0.74 (0.73–0.76)

Data are presented as mean (95% confidence interval).

BIS = Bispectral Index; EC_{50} = drug concentration corresponding to half-maximal effect of SE, RE, and BIS; RE = Response Entropy; SE = Spectral Entropy; γ = a measure to describe the steepness of the drug concentration–effect relation (the Hill coefficient).

Table 4. Estimations of EC_{50} and γ for Infants and Children with Their 95% Confidence Intervals during Steady State End-tidal Concentration of Sevoflurane

	EC_{50}	γ
Infants		
SE	0.74 (0.62–0.86)	0.59 (0.50–0.67)
RE	0.45 (0.27–0.62)	0.37 (0.28–0.46)
BIS	0.59 (0.42–0.76)	0.22 (0.17–0.26)
Children		
SE	2.39 (2.38–2.40)	2.19 (2.16–2.22)
RE	2.45 (2.44–2.46)	1.75 (1.71–1.78)
BIS	2.04 (2.03–2.05)	1.18 (1.16–1.20)

Data are presented as mean (95% confidence interval).

BIS = Bispectral Index; EC_{50} = drug concentration corresponding to half-maximal effect of SE, RE, and BIS; RE = Response Entropy; SE = Spectral Entropy; γ = a measure to describe the steepness of the drug concentration–effect relation (the Hill coefficient).

Table 5. Correlation Coefficients between State Entropy, Response Entropy, and Bispectral Index in Infants and Children

	Infants	Children
SE *vs.* RE	0.98 ± 0.01 (0.97–0.98)	0.97 ± 0.00 (0.97–0.98)
SE *vs.* BIS	0.73 ± 0.02 (0.68–0.78)	0.76 ± 0.04 (0.68–0.84)
RE *vs.* BIS	0.76 ± 0.02 (0.70–0.80)	0.80 ± 0.03 (0.74–0.86)

Data are presented as mean ± SEM (95% confidence interval).
BIS = Bispectral Index; RE = Response Entropy; SE = Spectral Entropy.

in infants.[7,9,21,25–27] Especially, the greater the number of infants is in proportion to children in a BIS study, the poorer the correlations are among the youngest patients.[7,9,21,25] Therefore, when analyzing all of these BIS studies, it is obvious that the validation results are valid for older children, but not in infants younger than 6–12 months. Our BIS results are similar to those of previous investigations, *i.e.*, the performance of BIS is better in children than in infants.

Recently, a depth-of-hypnosis monitor based on auditory evoked potential (Alaris Auditory Evoked Potential Index; Danmeter A/S, Odense, Denmark)[24] was preliminarily evaluated in preschool children receiving sevoflurane anesthesia.[21] This method was able to differentiate reliably between awake and anesthetic states during sevoflurane facemask induction. However, there was considerable variation in individual Alaris Auditory Evoked Potential Index values as well as overlap between different clinical conditions.

The different computing times between BIS and Spectral Entropy may have some influence on the results of our study but also on the clinical usefulness of these depth-of-hypnosis devices, because the faster computing of Spectral Entropy may reflect the rapid changes of anesthetic concentrations more accurately.

Adults and pediatric patients differ not only in respect to body size, but also in respect to pharmacokinetics, cooperation, and methodologic properties. Watcha,[26] Constant,[35] and Constant *et al.*[36] have emphasized age-related differences in the electroencephalogram and the pharmacodynamic effects of anesthetics on the electroencephalogram. There is only a limited amount of data on the effects of anesthetic agents on the electroencephalogram of children of different ages. Well-known differences in the electroencephalograms of infants and teenagers exist, *e.g.*, the frequency of posterior basic rhythm; the quality of spindles, vertex waves, and K complexes; and the electroencephalogram changes during drowsiness.[37] The maturation and synapse formation of the brain continues after birth, which makes the applicability of the depth-of-hypnosis devices in this age group especially challenging.

It is obvious that the differences in electroencephalographic profiles between age groups pose special requirements to all electroencephalogram-derived methods. Denman *et al.*[20] have already highlighted the problems of validating the BIS monitor in pediatric patients. These include at least the following: the lack of an accepted standard for sedation or sleep, problems distinguishing purposeful from nonpurposeful responses, and ethical problems in the study design. Because children encounter all the same problems of inadequate general anesthesia as adults do, the indications for studying these electroencephalographic devices originally designed for adults are justified. Based on our results, the validity and clinical usefulness of Spectral Entropy and BIS in the pediatric population is not as obvious as in adults. However, the reason for this cannot be concluded from our or any of the previous studies. One can suspect physiologic differences between children and adults as a cause of the observed low performance, but methodologic problems and limitations in study design may have an effect as well.

In our study, the BIS® Sensor was placed above the Entropy Sensor, slightly higher on the forehead than recommended by the manufacturer. Similar placement of sensors was applied also by Davidson *et al.*[25] They had compared the BIS values recorded with optimal *versus* higher-than-recommended sensor positioning and concluded that there was a clinically insignificant, small but consistent bias: When the BIS® Sensor was attached above the optimal location, the readings tended to be lower. We found that BIS values could be reliably interpreted, but a true comparison of Spectral Entropy and

Table 6. Correlation Coefficients of State Entropy, Response Entropy, and Bispectral Index *versus* Hemodynamic Values in Infants and Children

	HR	MAP
Infants		
SE	−0.01 ± 0.07 (−0.15 to 0.14)	0.09 ± 0.07 (−0.05 to 0.23)
RE	−0.01 ± 0.07 (−0.15 to 0.14)	0.11 ± 0.07 (−0.04 to 0.26)
BIS	0.01 ± 0.07 (−0.13 to 0.16)	0.06 ± 0.07 (−0.08 to 0.21)
Children		
SE	−0.13 ± 0.06 (−0.25 to 0.00)	0.00 ± 0.06 (−0.12 to 0.12)
RE	−0.12 ± 0.06 (−0.24 to 0.01)	0.02 ± 0.06 (−0.10 to 0.13)
BIS	−0.06 ± 0.06 (−0.17 to 0.06)	0.06 ± 0.06 (−0.06 to 0.18)

Data are presented as mean ± SEM (95% confidence interval).
BIS = Bispectral Index; HR = heart rate; MAP = mean arterial pressure; RE = Response Entropy; SE = Spectral Entropy.

BIS cannot be concluded from our study. In the adult Spectral Entropy sensor, two of the three electroencephalogram electrodes can be placed in the exact recommended location also in children, because only the distance and the location of the "ground" electrode are fixed in relation to the first electrode on the forehead.

The shortcoming of the current study is the lack of one generally accepted and validated scoring system that would work reliably and detect all of the various levels of sedation and anesthesia in infants and children. Unlike in adults, a relatively slow induction period enabling a precise transition from a clinical state to another is a challenging task in a patient population ranging from 1 month to 15 yr of age. Therefore, in contrast to adult studies, during induction it was not possible to correlate numerous different levels of OAA/S measurements with changing values of SE, RE, and BIS. The OAA/S was originally introduced by Chernik *et al.*[2] The OAA/S consists of several components associated with good validity and reliability and high interrater scores in adult patients. We decided to use a modification of the responsiveness category of the OAA/S, which provides the major contribution to the total OAA/S and has been widely used as a modified OAA/S. Malviya *et al.*[3] have presented the University of Michigan Sedation Scale to pediatric patients. They compared the University of Michigan Sedation Scale with the OAA/S and found that both scales worked reliably in pediatric patients during sedation. The second shortcoming of the current study was the use of a neuromuscular blocking agent, which may prevent the potential responses of the patients. However, to avoid the possibility of analyzing unreliable mOAA/S data, only the periods without the effect of rocuronium during induction and emergence were included. Apart from the intubation dose of rocuronium, most of our patients (17 of 20 infants and 35 of 40 children) did not receive an additional dose of the muscle relaxant. We tried to implement a clinically relevant anesthetic regimen appropriate for pediatric patients and exclude known confounding factors, such as regional anesthesia.[27] Nitrous oxide is still commonly used by pediatric anesthesiologists together with sevoflurane and should not have a major effect on our results.

Although investigating the effect of muscle relaxants was not our study objective, it is interesting in the context of RE that includes also electromyographic activity from the frontal muscle. Noxious stimuli may cause electromyographic responses to some extent and produce an increase in RE values in the absence of profound neuromuscular blockade, thus possibly enabling the use of SE − RE difference as a marker of analgesia.

The impact of using steady state *versus* non–steady state end-tidal concentration of sevoflurane as a variable of depth of hypnosis is unclear. Both steady state and non–steady state concentrations have been widely used in studies on the level of hypnosis.[20–22,24] One might argue that steady state concentrations are more reliable; however, obtaining this kind of value is more difficult especially during constantly changing surgical stimuli, causing rapid change of the level of anesthesia and hypnosis.

Whether the immature brain and electroencephalogram, methodologic study problems, or both are behind the questionable usefulness of all the electroencephalogram-derived depth-of-hypnosis monitors in the younger age groups remains unresolved. More studies are warranted. Attention should be paid to study design in general and the infant age group.

Spectral Entropy may be a useful tool for measuring the hypnotic effects of sevoflurane combined with nitrous oxide in children's central nervous systems. Spectral Entropy seems to behave similarly to the BIS. In infants, the clinical usefulness of both of these electroencephalogram-derived methods is questionable and must be evaluated by further controlled studies.

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