Spectral Entropy and Bispectral Index as Measures of the Electroencephalographic Effects of Sevoflurane

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Background: Recently, entropy algorithms have been proposed as electroencephalographic measures of anesthetic drug effects. Datex-Ohmeda (Helsinki, Finland) introduced the Entropy Module, a new electroencephalographic monitor designed for measuring depth of anesthesia. The monitor calculates a state entropy (SE) computed over the frequency range of 0.8–32 Hz and a response entropy (RE) computed over the frequency range of 0.8–47 Hz. The authors investigated the dose–response relation of SE and RE during sevoflurane anesthesia in comparison with the Bispectral Index (BIS).

Methods: Sixteen patients were studied without surgical stimulus. Anesthesia was induced by sevoflurane inhalation with a tight-fitting facemask. Sevoflurane concentrations were increased and subsequently decreased and increased two to four times until the measurement was stopped and patients were intubated for surgery. The performances of SE, RE, and BIS to predict the estimated sevoflurane effect site concentration, obtained by simultaneous pharmacokinetic and pharmacodynamic modeling, were compared by calculating the correlation coefficients and the prediction probability.

Results: State entropy, RE, and BIS values decreased continuously over the observed concentration range of sevoflurane. Correlation coefficients were slightly but not significantly better for entropy parameters (0.87 ± 0.09 and 0.86 ± 0.10 for SE and RE, respectively) than for BIS (0.85 ± 0.12). Calculating the prediction probability confirmed these results with a prediction probability of 0.84 ± 0.05 and 0.82 ± 0.06 for SE and RE, respectively, and 0.80 ± 0.06 for BIS.

Conclusion: State entropy and RE seem to be useful electroencephalographic measures of sevoflurane drug effect.

THE electroencephalogram is increasingly used to measure anesthetic drug effect on the central nervous system. Because analyzing the real-time raw electroencephalographic signal during anesthesia is difficult, several electroencephalographic monitors have been developed to extract and process information and to present the content in a continuous index from 0 to 100. Zero represents the deepest level of anesthesia (isoelectric encephalographic line), and 100 represents the awake state of a patient. The use of electroencephalographic monitors has been proven to decrease drug consumption during anesthesia[1,2] and to lead to a faster recovery from anesthesia.[1,3] Recently, the use of the Bispectral Index® (BIS®) monitor (Aspect Medical Systems, Newton, MA) has been shown to decrease the incidence of intraoperative awareness.[4,5]

In this study, we investigated the dose–response relation of the new Entropy Module (Datex-Ohmeda, Helsinki, Finland) during sevoflurane anesthesia in comparison with the BIS® monitor. The BIS® monitor uses different algorithms to calculate the BIS during the different stages of anesthesia, *e.g.*, burst suppression[6] and frequency power calculation[7] as well as bispectral analysis,[8] whereas the Entropy Module measures depth of anesthesia by calculating the Shannon entropy[9] of the power spectrum called the *spectral entropy*. The Entropy Module calculates two different spectral entropy indicators: the state entropy (SE), computed over the frequency range of 0.8–32 Hz, reflecting the electroencephalographic-dominant part of the spectrum, and the response entropy (RE), computed over the frequency range of 0.8–47 Hz, including both the electroencephalographic- and electromyographic-dominant parts of the recorded spectrum.

The correlation among the three electroencephalographic parameters (SE, RE, and BIS) and estimated effect site concentrations of sevoflurane was investigated by simultaneous pharmacokinetic and pharmacodynamic modeling. In addition, the ability of the electroencephalographic monitors to differentiate between different effect site concentrations of sevoflurane was investigated by calculating the prediction probability.

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Materials and Methods

After approval by the Institutional Review Board (University of Bonn, Bonn, Germany), written informed consent was obtained from 16 patients aged 29 ± 8 yr (12 men and 4 women) scheduled to undergo minor surgery in general anesthesia. All participants had an American Society of Anesthesiologists physical status classification of I or II. Patients with a history of any disabling central nervous or cerebrovascular disease and patients who had received central nervous system–active drugs were excluded from the study.

Study Design

After arrival in the induction room, an intravenous line was inserted into a large forearm vein, and standard monitors were applied. The electroencephalogram was recorded continuously using the Aspect A-2000 BIS® monitor (version XP) and the Entropy Module. After the skin of the forehead had been prepared with 70% isopropanol, the BIS® (BIS-XP sensor) and Entropy electrodes were positioned as recommended by the manufacturers.

Anesthesia was induced by sevoflurane inhalation only with a tight-fitting facemask and a 4-l airflow of 100% oxygen. As spontaneous breathing diminished, patients were manually assisted and, with cessation of spontaneous breathing, were mechanically ventilated *via* the facemask to an end-tidal carbon dioxide of 35 mmHg. Sevoflurane concentration was initially increased until end-tidal concentrations of 5 vol% were achieved. Subsequently, sevoflurane concentrations were decreased and increased systematically two to four times to end-tidal sevoflurane concentrations between 1 and 4 vol%. Measurements were stopped thereafter, and patients were intubated for surgery.

Study Measurements

Study data were automatically recorded in intervals of 5 s. BIS values were recorded and transferred to computer hard disk for off-line analysis using the software program HyperTerminal (Microsoft, Redmond, VA). Entropy values (SE and RE) as well as inspiratory and expiratory gas concentrations, measured by an infrared spectrophotometric analyzer (Julian; Dräger, Lübeck, Germany), were recorded with the Datex-Ohmeda software S/5 Collect (version 4.0) onto the computer hard disk. The smoothing time period for the BIS® monitor was set to 15 s.

Calculation of Spectral Entropy

The concept of spectral entropy as described by the manufacturer††[10] is based on the Shannon entropy. If Shannon entropy is applied to the power spectrum of a signal, spectral entropy is obtained.[11] This concept is implemented in the Entropy Module. The power spectrum is first calculated for the different frequency ranges and then normalized so the sum of all spectral components equals to one with

$$Q(f) = \frac{P(f)}{\sum_f P(f)}, \qquad (1)$$

where Q(f) is the sum of the normalized power spectral components over the considered frequency range and

P(f) is the power spectrum. In a second step, the normalized power spectrum components are transformed by the Shannon function H(f): f(x) = log (1/x) to obtain transformed components:

$$H(f) = Q(f) * \log\left(\frac{1}{Q(f)}\right). \qquad (2)$$

In a final step, the transformed components are added, and the result is normalized to range between 1 (maximum irregularity) and 0 (complete regularity) by dividing the sum with the factor log (N), where N is equal to the total number of frequency components:

$$E = \frac{\sum_f H(f)}{\log(N)}. \qquad (3)$$

To optimize between time and frequency resolution, different sets of window durations are used within the Entropy Module so that each frequency component is obtained from a time window that is optimal for that particular frequency. The shortest time window is 1.92 s, used for frequencies between 32 and 47 Hz, and the longest time window is 60.12 s, used only for frequencies below 2 Hz.

Consistent with this concept, the Entropy Module calculates two different entropies derived from the time–frequency spectral entropy. One is the SE, computed over the frequency range from 0.8 to 32 Hz, with time windows ranging from 15 to 60 s and ranges on a scale from 0 to 91. The second is the RE, computed over a frequency range from 0.8 to 47 Hz, including both the electroencephalographic- and electromyographic-dominant parts of the spectrum, with time windows as short as 1.92 s for frequencies between 32 and 47 Hz and ranges on a scale from 0 to 100. A more detailed description of the Entropy Module algorithm has been published by Viertio-Oja.[10]

State entropy and RE are calculated using equations 1–3 across the entire range of anesthetic depth, except during burst suppression. Entropy values RE and SE are in principle computed in the same way as they are calculated at lighter levels of anesthesia. The part of the signal that contains a suppressed electroencephalogram is treated as a perfectly regular signal with zero entropy, whereas the entropy associated with the bursts is computed as described previously (equations 1–3).[10]

Calculations and Statistical Analysis

Sevoflurane effect site concentrations were obtained by simultaneous pharmacokinetic and pharmacodynamic modeling.[12] To eliminate the hysteresis between end-tidal concentrations of sevoflurane and electroencephalographic parameter values (SE, RE, BIS), an effect site was introduced into the model:

$$C_{eff}(t) = C_{et}(t) + [(C_{eff}(t-1) - C_{et}(t)] \cdot e^{-k_{e0}}, \qquad (4)$$

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†† Available at: www.datex-ohmeda.com/entropy/downloads/Entropy_algorithm.pdf. Accessed July 1, 2004.

where C_{et} is the end-tidal concentration, C_{eff} is the effect site concentration, $C_{eff}(t-1)$ is the calculated effect site concentration of the previous data point (in our study, one data point was obtained every 5 s), and k_{e0} is the first-order rate constant determining the efflux from the effect site. The relation between estimated effect site concentrations and electroencephalographic parameter values was modeled with a fractional sigmoid E_{max} model (Hill equation[13]):

$$E = E_0 + (E_{max} - E_0) * [C_{eff}^y/(EC_{50}^y + C_{eff}^y)], \quad (5)$$

where E_0 is the measured encephalographic parameter value (SE, RE, BIS) in the absence of the drug (= baseline or awake state), E_{max} is the encephalographic parameter value corresponding to maximum drug effect, EC_{50} is the concentration that causes 50% of the maximum effect, and γ describes the slope of the concentration–response relation. The computations were performed on a spreadsheet using the Excel 2000 software program (Microsoft). Parameters were optimized with the Solver tool within Excel using nonlinear regression with ordinary least squares. Our aim was to maximize the correlation between the measured drug effect (SE, RE, or BIS) and the predicted drug effect. We chose the coefficient of determination[14] (R^2) as an objective function:

$$R^2 = 1 - \frac{SSE}{SST} = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y}_i)^2}. \quad (6)$$

The sum of squared errors (SSE) represents the sum of squares of the differences between observed measurements y_i for a given time and the corresponding model prediction, $\hat{y}_i$. The total sum of squares (SST) stands for the sum of squares of the differences between each actual measurement and the average of all the measurements, $\bar{y}_i$. Because SST is independent of the model parameters, maximizing R^2 is equivalent to minimizing SSE, *i.e.*, it is equivalent to nonlinear regression with ordinary least squares.

Because the classic fractional E_{max} model did not adequately display the data where burst suppression occurred, we discharged epochs with burst suppression before fitting the hysteresis with the E_{max} model. In a second step, the individually fitted k_{e0} for each patient derived from the E_{max} model was then used to calculate the sevoflurane effect site concentration (equation 4). The correlation between effect site concentrations and SE, RE, and BIS was then investigated with the model-independent prediction probability (P_K),[15] including all epochs (*i.e.*, also the epochs where burst suppression occurred). Given two randomly selected data points with distinct anesthetic drug concentration, the P_K value

describes the probability that the encephalographic parameter correctly predicts which of the data points is the one with the higher (or lower) anesthetic drug concentration. As a nonparametric measure, the P_K value is independent of scale units and does not require knowledge of underlying distributions or efforts to linearize or to otherwise transform scales. Furthermore, P_K can be computed for any degree of coarseness or fineness of the scales. Therefore, P_K fully uses the available data without imposing additional arbitrary constraints. Prediction probability P_K has been defined as

$$P_K = \frac{(P_c + 0.5 * P_{tx})}{(P_c + P_d + P_{tx})}, \quad (7)$$

where P_c, P_d, and P_{tx} are the respective probabilities that two data points drawn at random, independently and with replacement, from the population are a concordance, a discordance, or an x-only tie. A P_K value of 1 means that the values of the predicting variable (SE/RE or BIS value) always correctly predict the value of the variable to be predicted (*e.g.*, estimated sevoflurane effect site concentration). A P_K value of 0.5 means that the values of the indicator predict no better than by chance
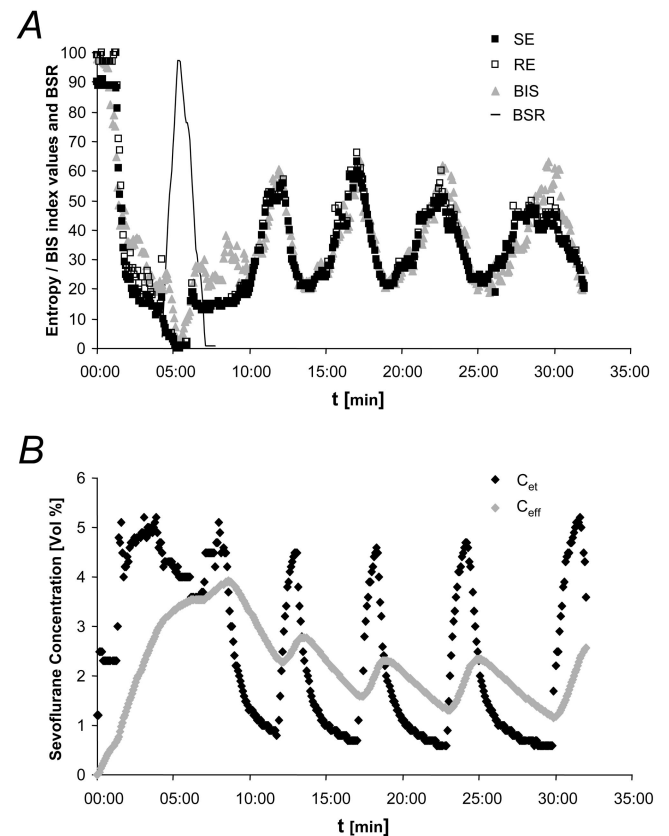
Fig. 1. (*A*) Time course of state entropy (SE), response entropy (RE), Bispectral Index (BIS), and burst suppression ratio (BSR) of patient 1. Each symbol represents an electroencephalographic parameter of a 5-s epoch. (*B*) End-tidal sevoflurane concentration (C_{et}) and calculated effect site concentration (C_{eff}) during the same time course in the same patient.
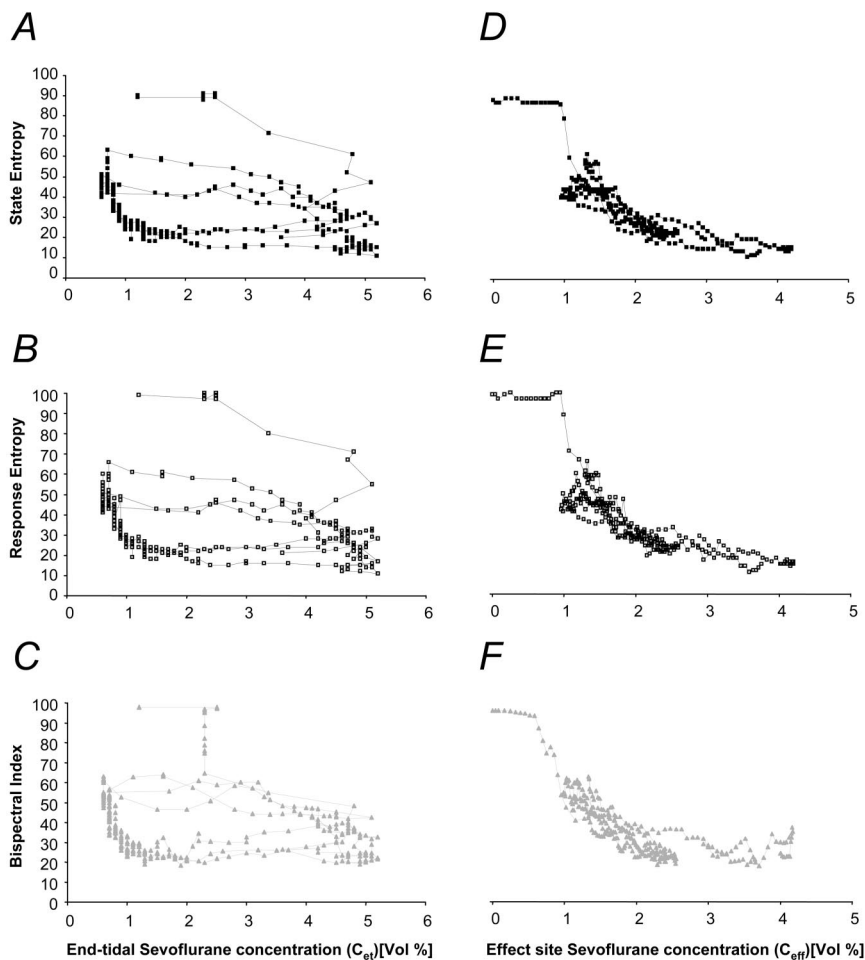
Fig. 2. Relation between state entropy, response entropy, and Bispectral Index and the end-tidal sevoflurane concentration (*A–C*) and the effect site sevoflurane concentration (*D–F*) for the same patient as in figure 1. Each symbol represents the electroencephalographic parameter of a 5-s epoch. C_{eff} = calculated effect site concentration; C_{et} = end-tidal sevoflurane concentration.

only. The P_K values were calculated on a spreadsheet using the Excel 2000 software program. Because sevoflurane concentration increases as BIS, RE, and SE decrease, the actual P_K value we measure is $1 - P_K$.

Statistical analysis was performed using Sigma Stat 2.03 and Sigma Plot 2000 computer software (SPSS Inc., Erkrath, Germany). Statistical calculations were performed by Student *t* test or Wilcoxon test where appropriate. All tests were two tailed, with a statistical significance defined as $P < 0.05$; data are presented as mean and SD.

Results

The mean duration of measurements was 28.5 ± 8 min. During this time, 342 ± 96 artifact-free 5-s epochs per patient were included in the data analysis.

Figures 1A and B show the time course of the measurement of patient 1 where increasing sevoflurane concentrations were correlated with decreasing entropy and BIS values and *vice versa*. Plotting the end-tidal gas concentration of sevoflurane (C_{et}) against SE/RE and BIS values revealed a hysteresis (figs. 2A–C). Simultaneous pharmacokinetic and pharmacodynamic modeling

(equations 4 and 5) of the hysteresis revealed nearly identical results for k_{e0}, E_0, E_{max}, EC_{50}, and γ between SE/RE and BIS (table 1). The k_{e0} values were used to calculate the estimated effect site concentration (C_{eff}) of sevoflurane. Plotting C_{eff} against SE/RE and BIS led to a collapse of the hysteresis (figs. 2D–F).

The correlation of SE/RE and estimated sevoflurane effect site concentration proved to be slightly but not significantly better ($R^2 = 0.87 \pm 0.09$ and 0.86 ± 0.10 for SE and RE, respectively) than for BIS ($R^2 = 0.85 \pm 0.12$). Individual R^2 values are shown in figure 3A for

Table 1. Pharmacokinetic and Pharmacodynamic Parameters

Parameter	SE ± SD	RE ± SD	BIS ± SD
k_{e0}, min^{-1}	0.33 ± 0.21	0.32 ± 0.20	0.31 ± 0.16
E_0	81.91 ± 17.56	89.91 ± 09.70	86.65 ± 17.71
E_{max}	29.33 ± 20.93	23.67 ± 22.84	32.62 ± 22.04
EC_{50}, vol%	1.60 ± 0.51	1.55 ± 0.51	1.45 ± 0.59
γ	3.94 ± 3.74	3.83 ± 3.17	3.64 ± 2.96

BIS = Bispectral Index; E_0 = measured encephalographic parameter value (SE, RE, BIS) in the absence of the drug; EC_{50} = concentration that causes 50% of the maximum effect; E_{max} = encephalographic parameter value corresponding to maximum drug effect; γ = describes the slope of the concentration–response relation; k_{e0} = first-order rate constant determining the efflux from the effect site; RE = response entropy; SE = state entropy.
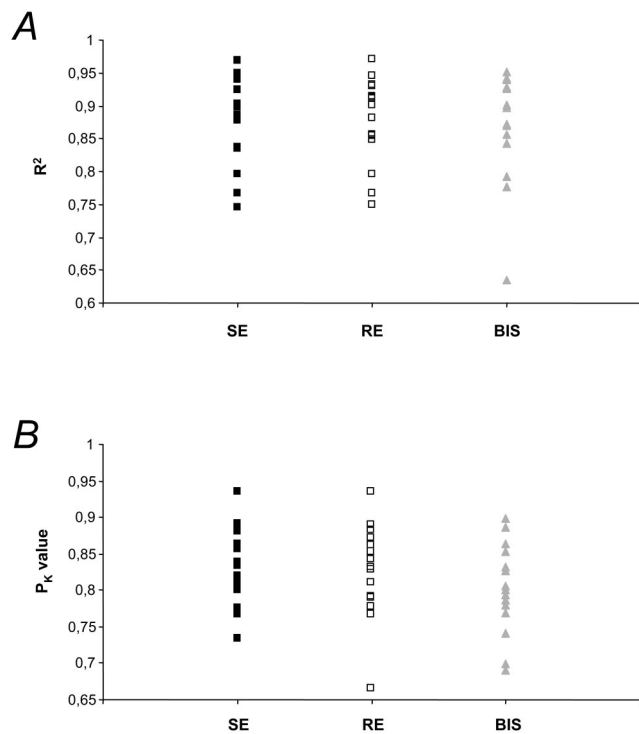
Fig. 3. Correlation coefficient (R^2) values (*A*) and prediction probability (P_K) values (*B*) of all patients (n = 16) for state entropy (SE), response entropy (RE), and Bispectral Index (BIS).
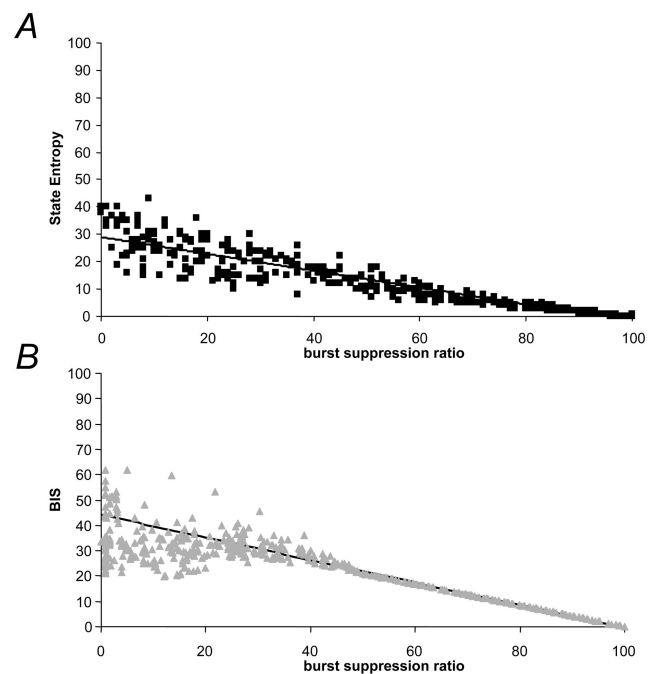

Fig. 4. (*A*) Relation between state entropy and burst suppression as measured by the Entropy Module for all patients (n = 9). A linear fit (y = a − x/b) for all state entropy data points was superimposed (*bold line*) on the pooled data with a = 29.0 and b = 3.25 (R^2 = 0.88). (*B*) Relation between Bispectral Index (BIS) and burst suppression as measured by the BIS® monitor for all patients (n = 9), with a linear fit for all data points (with a burst suppression ratio > 40%) superimposed on the pooled data (a = 44.1 and b = 2.25; R^2 = 0.99).

each patient. Because fitting using the E_{max} model did not incorporate data with burst suppression, we used the model-independent prediction probability (P_K) to evaluate SE/RE and BIS including all data (*i.e.*, also data where burst suppression occurred). In figure 3B, the performance of SE, RE, and BIS to correctly differentiate between different effect site concentrations of sevoflurane expressed by P_K is shown. SE and RE were slightly but not significantly better (0.84 ± 0.05 and 0.82 ± 0.06 for SE and RE, respectively) than BIS (0.80 ± 0.06) in differentiating between different effect site concentrations over the entire range of data points.

Burst suppression occurred in 9 of 16 patients and exceeded a burst suppression ratio (BSR) greater than 40% in seven measurements. Entropy (SE and RE) correlated linearly over the entire burst suppression range in all measurements (R^2 = 0.96 ± 0.02 fitted by the equation Entropy = a − BSR/b yielding the following values: a = 27.6 ± 9.2 and b = 3.97 ± 1.72). The fit of the pooled data is shown superimposed on the data in figure 4A and yielded the following values: a = 29.0 and b = 3.25 (R^2 = 0.88). No correlation could be found between BIS and a BSR of less than 40% (fig. 4B). Increasing BSR greater than 40% leads to a linear correlation with BIS = a − BSR/b yielding the following values: a = 44.1 ± 2.0 and b = 2.25 ± 0.13, with little to no interindividual differences (R^2 = 0.99 ± 0.01). Fitting the pooled data for BSR greater than 40% yielded

identical results, with a = 44.1 and b = 2.25, shown superimposed on the data in figure 4B.

Plotting SE and RE over BIS revealed a sigmoidal correlation between entropy parameters and the Bispectral Index (figs. 5A and B).

Plotting RE over SE shows a linear correlation with RE = 1.05 * SE + 0.31 (R^2 = 0.98) (fig. 6).

In figure 7, we show the sigmoidal correlation between SE (A) and BIS (B) and estimated sevoflurane effect site concentrations. RE also revealed a sigmoidal correlation similar to SE (data not shown).

Discussion

In this study, we demonstrated a close correlation of SE and RE with sevoflurane effect site concentrations. SE and RE detected increasing and decreasing sevoflurane concentrations equally well as the BIS® monitor as judged by the correlation coefficient (R^2) and the prediction probability (P_K). We could also show that different approaches of electroencephalographic analysis lead to nearly identical pharmacokinetic and pharmacodynamic parameters for k_{e0}, γ, and EC_{50}.

Our intention was to investigate the two monitors over the entire range of levels of anesthesia including burst suppression. Unfortunately, the E_{max} model used for
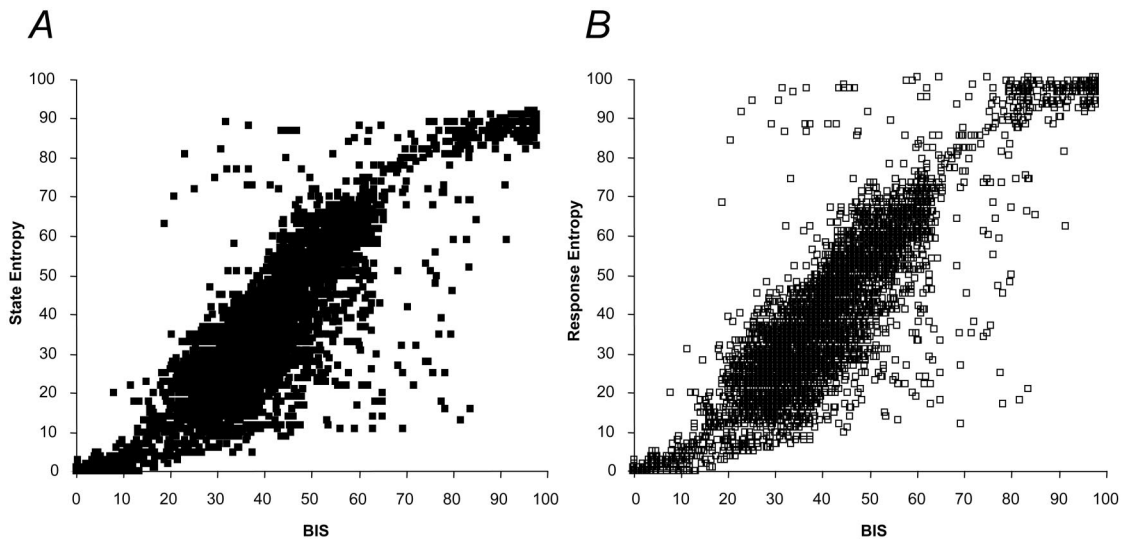
A

B

Fig. 5. Relation between state entropy (*A*) and response entropy (*B*) and Bispectral Index (BIS) over the entire spectrum of their indices representing all patients (n = 16) with 5,359 data pairs.

simultaneous pharmacokinetic and pharmacodynamic modeling was unable to fit the entire data range including burst suppression. A more sophisticated model incorporating two successive sigmoidal curves[16] was necessary. We therefore calculated the R^2 value for each measurement and excluded epochs if burst suppression occurred. Realizing the shortcomings of this approach, leading to a loss of important information regarding the ability of the two monitors to predict burst suppression, we used the model-independent calculation of the prediction probability to evaluate the performance of the monitors over the entire range of observed anesthetic depth, thereby including all epochs of each measurement. However, we used the individually fitted k_{e0} values derived from the E_{max} model to calculate the effect site concentration necessary for the computation of the prediction probability. It has been shown previously that results obtained by prediction probability were confirmed by calculating R^2.[17] We could demonstrate that

both approaches show satisfying correlations for both monitors.

Interestingly, different approaches of calculating drug effects on the electroencephalogram lead to similar results. The P_K values show that both algorithms are equally sophisticated in predicting calculated effect site concentrations of sevoflurane. Comparing the almost identical pharmacokinetic and pharmacodynamic results seems even more astonishing because the BIS integrates several disparate descriptors of the electroencephalo-
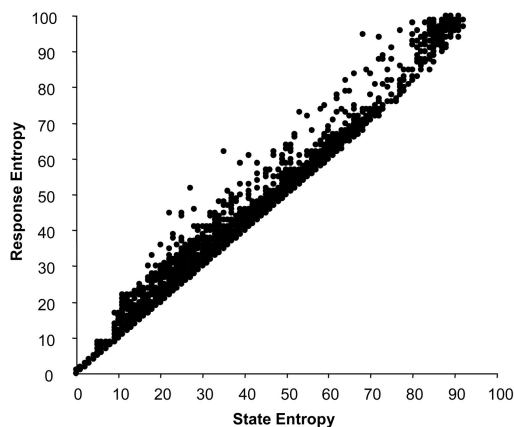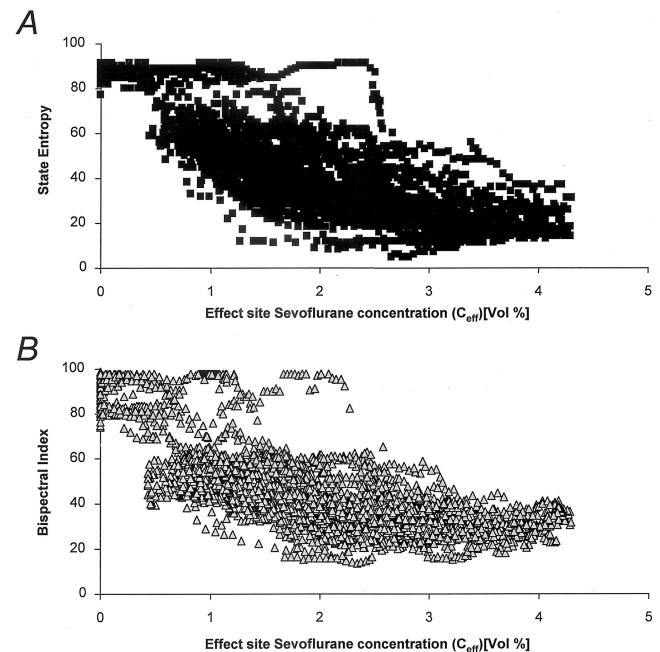
A

B

Fig. 7. Relation between state entropy (*A*) and Bispectral Index (*B*) and the calculated effect site sevoflurane concentration (C_{eff}) for all patients (n = 16). Data where burst suppression occurred were discharged before C_{eff} calculation and are not displayed in the figure (see Materials and Methods).

Fig. 6. Relation between response entropy and state entropy for all patients (n = 16) with 5,359 data pairs.

gram into a univariate variable,[6-8] whereas the Entropy Module uses the same algorithm over the entire range of anesthesia.[10]

Pharmacokinetic and pharmacodynamic parameters have been published previously for BIS values after sevoflurane anesthesia.[18-20] Olofsen *et al.*[18,19] reported $t_{1/2}k_{e0}$ values of 3.5 ± 2.0 and 3.11 ± 0.32 min measured during sevoflurane anesthesia in combination with 70% nitrogen. When converting their $t_{1/2}k_{e0}$ values to k_{e0} ($t_{1/2}k_{e0} = \ln^2/k_{e0}$), their calculated k_{e0} values were 0.20 and 0.22 min^{-1},[18,19] which is 30% less than our measured k_{e0} value. Rehberg *et al.*[20] reported a k_{e0} of 0.29 ± 0.04 for sevoflurane in the absence of nitrogen. Olofsen *et al.*[19] discussed several factors influencing k_{e0}. They showed that remifentanil leads to a dose-dependent decrease in $t_{1/2}k_{e0}$ (increase in k_{e0}). Besides physiologic factors, the time delay due to electroencephalographic parameter calculation by the monitor has a crucial influence on k_{e0}. During propofol anesthesia, calculated k_{e0} values differed up to 100% depending on very short calculation time windows of 2 s[20] or calculation time windows of 30 s using the BIS® monitor.[21] Kreuer *et al.*[21] reported higher k_{e0} values for propofol when estimated using the Narcotrend monitor (MonitorTechnik, Bad Bramstedt, Germany) compared with the BIS® monitor (calculation time windows of 20 and 30 s, respectively). Accordingly, Olofsen and Dahan[18] reported different $t_{1/2}k_{e0}$ values during sevoflurane anesthesia between BIS and spectral edge frequency. Because spectral edge frequency can be calculated immediately without a delay of 30 s, $t_{1/2}k_{e0}$ values were faster compared with BIS $t_{1/2}k_{e0}$ values.[18] The ideal encephalographic monitor would compute an index without a time delay, resulting in smaller $t_{1/2}k_{e0}$ values. We found no significant differences between our calculated k_{e0} values for SE, RE, and BIS.

We further investigated the relation between entropy values and BIS by plotting all data points of SE and RE over BIS (fig. 5). We demonstrate that entropy values and BIS show a close correlation within the index range of 30–70. Because the original mathematical scale of the entropy values ranges between 0 and 1 and the most interesting range of adequate hypnosis and sedation lies between 0.5 and 1.0, a transformation from the original continuous entropy scale to an integer scale of 0–100 has been performed by a nonlinear transformation,[10] leading to the close correlation of entropy and BIS values within the index range of 30–70. This transformation is defined by a particular monotonous spline function transforming the original values between 0.5 and 1 to new values between 30 and 100. The slope of the spline function is steepest between 30 and 80, leading to an enhanced resolution. Below 30 and above 80, the slope becomes shallower. This could explain the sigmoidal correlation between both entropy parameters and BIS. The difference between entropy and BIS for index values less than 30, however, could also originate in different

algorithms of incorporating burst suppression ratios into their corresponding index as shown in figures 4A and B and expressed by the different slope factors b (b = 3.25 for SE and 2.25 for BIS).

During burst suppression, SE equaled RE (data not shown), explained by the fact that the electromyogram equaled zero. In the awake state, an SE value of 91 equals an RE value of 100 because of the additional amount of electromyographic activity calculated by RE in the frequency range between 32 and 47 Hz. It is claimed that RE is able to detect upcoming arousal by detecting muscle activity and that RE is faster to respond to changing electroencephalographic and electromyographic signals because of shorter time windows for signal interpretation (as short as 1.92 s; see Materials and Methods). To prove that RE shows advantages in revealing electromyographic activation and in addition leading to a faster response to upcoming arousal of the patient, further investigations are needed with a different experimental setting including lighter levels of anesthesia and surgical stimuli. The high correlation between RE and SE (fig. 6) does not support the idea that RE actually reveals unique information.

We conclude that the Entropy Module is a useful monitor for measuring the electroencephalographic effects of increasing and decreasing sevoflurane concentrations over the entire range of observed anesthetic depth. Sevoflurane electroencephalographic effects were detected equally well by the Entropy Module and by the BIS® monitor.

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