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Spectral Entropy as an Electroencephalographic Measure of Anesthetic Drug Effect

A Comparison with Bispectral Index and Processed Midlatency Auditory Evoked Response

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Background: **The authors compared the behavior of two calculations of electroencephalographic spectral entropy, state entropy (SE) and response entropy (RE), with the A-Line® ARX Index (AAI) and the Bispectral Index (BIS) and as measures of anesthetic drug effect. They compared the measures for baseline variability, burst suppression, and prediction probability. They also developed pharmacodynamic models relating SE, RE, AAI, and BIS to the calculated propofol effect-site concentration (Ce_{prop}).**

Methods: **With institutional review board approval, the authors studied 10 patients. All patients received 50 mg/min propofol until either burst suppression greater than 80% or mean arterial pressure less than 50 mmHg was observed. SE, RE, AAI, and BIS were continuously recorded. Ce_{prop} was calculated from the propofol infusion profile. Baseline variability, prediction of burst suppression, prediction probability, and Spearman rank correlation were calculated for SE, RE, AAI, and BIS. The relations between Ce_{prop} and the electroencephalographic measures of drug effect were estimated using nonlinear mixed effect modeling.**

Results: **Baseline variability was lowest when using SE and RE. Burst suppression was most accurately detected by spectral entropy. Prediction probability and individualized Spearman rank correlation were highest for BIS and lowest for SE. Nonlinear mixed effect modeling generated reasonable models relating all four measures to Ce_{prop}.**

Conclusions: **Compared with BIS and AAI, both SE and RE seem to be useful electroencephalographic measures of anesthetic drug effect, with low baseline variability and accurate burst suppression prediction. The ability of the measures to predict Ce_{prop} was best for BIS.**

THE regularity of the background electroencephalogram alters with changing levels of consciousness. Recently, different entropy concepts have been applied to describe the "amount of order" in the electroencephalogram.[1–3] One of these, Shannon entropy, has been shown to be a useful measure of anesthetic drug effect.[3] Shannon entropy measures the predictability of future amplitude values of the electroencephalogram based on the probability distribution of amplitude values already observed in the signal. Unfortunately, Shannon entropy as described is not normalized to the total power of the electroencephalogram. Therefore, its absolute value may vary between individuals because of interindividual differences in signal strength, precluding routine clinical use. To overcome these shortcomings, spectral entropy has been developed. The spectral entropy is obtained by applying the Shannon entropy concept to the power distribution of the Fourier-transformed signal, which has been normalized to unit power. Spectral entropy permits separation of the contributions from different frequency ranges. For example, using spectral entropy, one can separate the high-frequency contribution ($>$ 32 Hz, which is likely electromyographic) from the low-frequency contribution ($<$ 32 Hz, which is likely encephalographic). The detailed spectral entropy algorithm is published elsewhere.[4] Recently, this technology has become commercially availably (M-ENTROPY module; Datex-Ohmeda, Helsinki, Finland). In this device, two spectral entropy indicators are considered, state entropy (SE), calculated over the frequency range (0.8–32 Hz) that is likely dominated by the encephalogram, and response entropy (RE), calculated over the frequency range (0.8–47 Hz) that includes both the electroencephalogram and electromyogram. Sudden appearance of the electromyographic signal data often indicates that the patient is responding to some external stimulus, such as a painful stimulus, *i.e.*, nociception, due to some surgical event.[5,6] Such a response may result in arousal if the level of analgesia is insufficient. In theory, in the nonparalyzed patient's electromyogram can provide a rapid indication of impending arousal.

Processed analysis of the electroencephalogram or midlatency auditory evoked potential (MLAEP) is increasingly applied as a surrogate endpoint for quantification of anesthetic drug effect. Because of the difficulties of analyzing raw waveforms for both electroencephalogram and MLAEP during anesthesia, extraction and presentation of this information necessitates computational analysis of the raw signal. The A-Line® ARX Index (AAI)

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is derived from the MLAEP and has been validated as a measure of anesthetic drug effect during propofol administration.[7]

The most widely adopted electroencephalographic measure of anesthetic drug effect is the Bispectral Index (BIS). The BIS has been extensively studied and validated over the past 10 yr as a measure of anesthetic drug effect.[7]

We evaluated the four electroencephalographic measures of drug effect for stability at baseline (minimal variability in the absence of drug between individuals[8]), accurate detection of burst suppression,[9] prediction probability,[10,11] and correlation with the propofol effect-site concentration. We also developed pharmacodynamic models relating the predicted effect-site propofol concentration to each measure of drug effect.

Materials and Methods

After institutional ethics committee approval (Ghent University Hospital, Gent, Belgium), written informed consent was obtained from 10 patients with American Society of Anesthesiologists physical status I who were aged 18–45 yr and scheduled to undergo ambulatory gynecologic or urologic surgery. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight, neurologic disorder, and recent use of psychoactive medication, including alcohol.

All patients received a continuous infusion of propofol at 50 mg/min (Diprivan 1%; AstraZeneca, London, United Kingdom) using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France). To ensure synchronized data recording, all monitor and infusion data were continuously captured by the computer running RUGLOOP II** *via* multiple RS 232 interfaces. By tracking the infused propofol volume continuously, RUGLOOP II calculated the corresponding effect-site concentration using the three-compartment model enlarged with an effect compartment previously published by Schnider *et al.*[12,13] The calculated effect-site propofol concentration (Ce_{prop}) was computed to yield a time-to-peak effect of 1.6 min after bolus injection,[14] as also published by Schnider *et al.*[12,13] and clinically confirmed by Struys *et al.*[15] Propofol was infused *via* a large left forearm vein. Every patient received approximately 100 ml crystalloid fluid during the study period. No fluid load was given before induction. No patient received preanesthetic medication. No other drugs were given. All patients maintained spontaneous ventilation *via* a facemask delivering 100% O_2. Before starting the drug administration, all patients were asked to close their eyes and relax for 2 min. Thereafter, baseline measures were taken. The operating room was kept silent to avoid noise-related stimulation and artifact.

The propofol infusion was continued until a burst suppression level of 80% or higher was achieved on the BIS® monitor (Aspect Medical Systems, Inc., Newton, MA) or the mean arterial blood pressure decreased below 50 mmHg.

Heart rate, noninvasive blood pressure, oxygen saturation measured by pulse oximetry (Spo_2), and capnography were recorded at 1-min intervals using an S-5 monitor; Datex-Ohmeda). All data were recorded continuously on one computer using RUGLOOP software *via* multiple RS-232 connections. Averaging of the data was performed using 10-s intervals.

Electroencephalographic and MLAEP Data Collection

The SE and RE were calculated using the M-ENTROPY module. The SE value ranges from 91 to 0, and the RE value ranges from 100 to 0. Both entropy values were derived from the frontal electroencephalogram and electromyogram using three electrodes. SE is computed over the frequency range from 0.8 to 32 Hz. It includes the electroencephalogram-dominant part of the spectrum. The time windows for SE are chosen optimally for each particular frequency component and range from 60 s to 15 s. RE is computed over a frequency range from 0.8 to 47 Hz. It includes both the electroencephalogram-dominant and the electromyogram-dominant parts of the spectrum. The time windows for RE are chosen optimally for each frequency, with the longest time window equal to 15.36 s and the shortest time window, applied for frequencies between 32 and 47 Hz, equal to 1.92 s. The RE equals the SE when no electromyographic activity is detected. The description of the full algorithm is described elsewhere.[4]

The AAI (version 1.5) from the MLAEP was calculated using the A-Line® monitor (Danmeter A/S, Odense, Denmark). The AAI value ranges from 100 to 0. The MLAEPs were elicited with a bilateral click stimulus of 70-dB intensity and 2-ms duration. Three electrodes (A-Line® AEP electrodes; Danmeter A/S) were positioned at mid forehead (+), left forehead (reference), and left mastoid (−). The extraction of the MLAEP using a short moving–time average technique together with an ARX model and the calculations of the AAI have been described previously.[16]

The BIS (BIS® version 4.0, XP) was derived from the frontal electroencephalogram and calculated by the A-2000 BIS® monitor using the 4 BIS®-Sensor electrodes (Aspect Medical Systems). The BIS value ranges from 100 to 0. The smoothening time of the BIS® monitor was set at 15 s.

All electroencephalographic data were gathered by computer concurrently with the hemodynamic data and drug infusion information.

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Performance Measures

Baseline Variability. Baseline variability is calculated by computing the coefficient of variation (CV) on the electroencephalographic data points obtained during the first 5 s of the protocol, before any drug has been delivered.

Burst Suppression. The burst suppression ratio (BSR) of the electroencephalogram is measured by all three monitors. For the M-ENTROPY module, burst suppression calculation starts by subtracting a local average from each signal sample to eliminate baseline fluctuations. The signal is then divided into two frequency bands by elliptic filters. Cutoff frequencies of the low-pass and high-pass filters are 20 and 75 Hz, respectively. The low-frequency band is used to detect the burst suppression pattern, and the high-frequency band is used to detect artifacts. An energy operator is applied to estimate signal power in both bands in each 0.05-s epoch. Suppression is detected if the estimated signal power is below a fixed threshold at least for 0.5 s and there is no artifact. The BSR is the percentage of 0.05-s epochs in the past 60 s that were considered suppressed. More detailed information on the burst suppression calculation used in the entropy module is described elsewhere.[17]

For the A-Line® monitor, the raw signal is passed though a preprocessing process to reject artifacts. It then passes through a low-pass filter with a cutoff frequency of 32 Hz, yielding the electroencephalogram signal. The filtered signal then is divided in segments of 500 ms, where the mean value is removed to filter out low frequencies. If a segment has a determined percentage of samples with amplitudes less than 3.4 μV, it is considered as a segment with suppression. The burst suppression is considered as the percentage of segments with suppression during 20 s.

For the BIS® monitor, after preprocessing for artifact detection/correction, the log power of 1-s electroencephalogram epochs in two frequency bands (2–30 and 31–40 Hz) is calculated, and suppression is declared if a weighted sum of these bands is less than a threshold. Hereby, the threshold is adaptive (within a narrow range) based on the statistics of the electroencephalogram. The suppression detection algorithm processes the electroencephalogram in overlapping 1-s epochs offset every 0.5 s. A given 0.5 s of electroencephalogram is determined to be suppressed if suppression was detected for either of the 2 overlapping 1-s epochs that contained it. The suppression ratio is the percentage of 0.5-s epochs in the past 63 s that were considered suppressed.

The relation between the burst suppression and its related electroencephalographic measure (SE, RE, AAI, and BIS) was plotted. For each electroencephalographic measure, a model was fitted to the data using the curve estimation function from SPSS version 12 (SPSS Inc., Chicago, IL). The curve estimation procedure produces curve estimation regression statistics and related plots for different curve estimation regression models, including linear, logarithmic, inverse, quadratic, cubic, power, compound, S-curve, logistic, growth, and exponential. A separate model is produced for each dependent variable together with its regression coefficients, predicted values, residuals, and prediction intervals. After this, the most appropriate regression model can be selected.

Prediction Probability. For each electroencephalographic measure of anesthetic drug effect, we calculated the prediction probability (P_K) developed by Smith *et al.*[10,11] P_K was calculated as the Somers d statistic using SPSS version 12, with the electroencephalographic measure set as the independent variable and the Ce_{prop} as the dependent variable. (We recognize that this is physiologically backward in that the propofol effect-site concentration drives the electroencephalographic response. However, for the purpose of this analysis, the question is how well the observed measure, which is the electroencephalographic response, predicts the unobserved "underlying" state of the patient, which is the Ce_{prop}). The Somers d statistic was then rescaled from the -1 to $+1$ range of the Somers d statistic to the 0 to 1 range of P_K, $P_K = 1 - (1 - |\text{Somers d}|)/2$. Then, a P_K of 1 for the electroencephalographic measure means that this measure always decreases (increases) as the patient reaches higher (lower) drug concentrations according to the effect-site propofol concentration. Alternatively, a P_K value of 0.5 means that the measure is useless for predicting anesthetic drug effect. Individual values were calculated for each measure, and the average, minimum, and maximum P_K values were then tabulated for each electroencephalographic measure of anesthetic drug effect.

Individualized Spearman Rank Correlation. In addition, a nonparametric alternative was investigated. The Spearman rank correlations between Ce_{prop} and SE, RE, AAI, and BIS were individualized in the sense that they were first computed for each patient i separately, say R_i. The reported Spearman rank correlation, R, is a weighted average of the R_i (weighted according to the number of observations for each patient). In this way, R retained its usual interpretation. The confidence intervals on R were obtained by the bootstrap method[18] in which the hierarchical nature of the data was incorporated by resampling within patient. Equality of two correlation coefficients was tested at the 5% level of significance by constructing the 95% confidence intervals of the difference (confidence intervals were also computed with the bootstrap technique). All bootstrap calculations were based on 10,000 simulation runs.

Pharmacodynamic Modeling

The relation between propofol effect-site concentration and the electroencephalographic measures of anes-

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thetic drug effect was analyzed using a sigmoid E_{max} model:

$$\text{Effect} = E_0 + (E_{max} - E_0)\frac{Ce^{\gamma}}{Ce_{50}^{\gamma} + Ce^{\gamma}},$$

where Effect is the electroencephalographic effect being measured (SE, RE, AAI, BIS), E_0 is the baseline measurement when no drug is present, E_{max} is the maximum possible drug effect, C_e is the calculated effect-site concentration of propofol, Ce_{50} is the effect-site concentration associated with 50% maximal drug effect, and γ is the steepness of the concentration-*versus*-response relation. The model parameters were estimated using NONMEM V (GloboMax LLC, Hanover, MD). Interindividual variability was modeled using a log-normal distribution:

$$P_i = P_{TV}e^{-\eta_i},$$

where P_i is the parameter value (E_0, E_{max}, γ, or Ce_{50}) in the ith patient, P_{TV} is the typical value of the parameter in the population, and η is a random variable with a mean of 0 and a variance of ω^2. Individual variability is reported as ω, the SD of η in the log domain, which is approximately the CV in the standard domain. Residual intraindividual variability was modeled using a standard additive error model. Parameters were evaluated by comparing the log-likelihood values (the NONMEM objective function), with improvement of 3.84 in −2LL with the addition of a single parameter considered statistically significant.[19]

Results

The population characteristics were as follows: weight, 62.0 ± 3.8 kg; age, 37.7 ± 16.2 yr; height, 165 ± 6.5 cm; sex, 8 men/2 women. All measured data were included in the analysis. Figures 1 and 2 show the raw data over time for the four electroencephalographic measures of drug effect (SE, RE, AAI, and BIS) and Ce_{prop}. (In fig. 2, the disruption in the continuous increasing Ce_{prop} is due to the inevitable change of the 1% propofol syringe around 600 s.)

Performance Measures

The baseline variability before administration of propofol is shown in table 1. The smallest variability in baseline values as defined by the CV was found for both spectral entropy measures (SE and RE), followed by BIS. AAI had the largest baseline variability.

The correlation between the burst suppression calculation and its related electroencephalographic measures of anesthetic drug effect is observed in figures 3 and 4. As seen in figure 3, for both spectral entropy indicators, a monotonic nonlinear decrease in entropy (quadratic polygonal curve, goodness-of-fit R^2 for SE = 0.72 and for RE = 0.71) was observed with increased levels of burst suppression. Spearman rank correlation coefficients

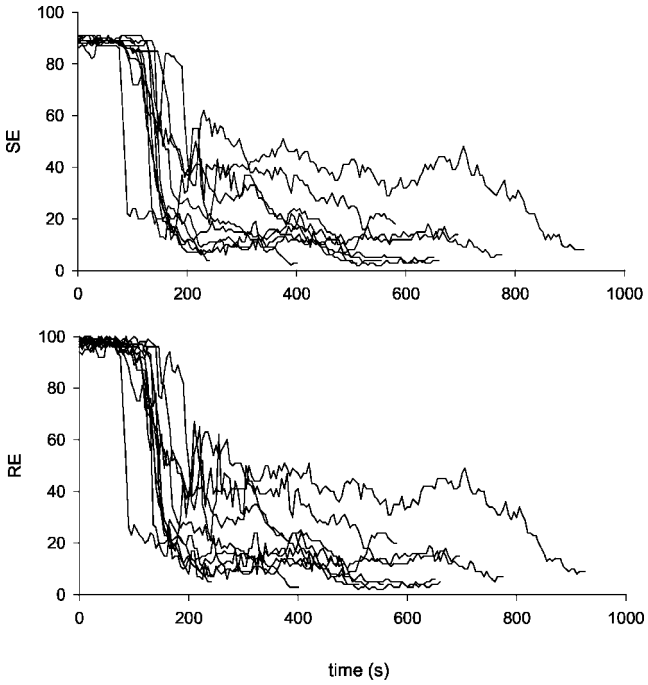

Fig. 1. Individual raw data for state (SE) and response entropy (RE) *versus* time.

were −0.62 and −0.63 for SE and RE, respectively. Figure 4 shows the behavior of the AAI and BIS with increasing levels of BSR. For AAI, no correlation between AAI and the AAI burst suppression could be obtained. For BIS, no accurate correlation could be obtained between BIS and the BSR when all data were included. At a BSR greater than 40, a linear correlation was found.

The P_K values for SE, RE, AAI, and BIS are shown in table 2. The individualized Spearman rank correlations between Ce_{prop} and SE, RE, BIS, and AAI are shown in table 2.

Pharmacodynamic Modeling

Figure 5 shows the behavior of SE and RE *versus* Ce_{prop} for all patients. With increasing Ce_{prop}, both SE and RE decreased monotonically. Similar findings were observed for both AAI and BIS, as seen in figure 6. For the spectral entropy, the difference between RE and SE decreased nonlinearly toward 0 with increasing Ce_{prop} (fig. 7).

The relations of Ce_{prop} to SE and RE are plotted in figure 8. The relations of Ce_{prop} to BIS and AAI are shown in figure 9. The parameter values for each population model including the CV (as a measure of interindividual variability in the standard domain) are found in table 3. The SD for each model (as a measure of the intraindividual variability in the log domain) was 7.1 for SE, 6.8 for RE, 4.8 for AAI, and 4.5 for BIS.

Discussion

In this study, we compared two measures of spectral entropy, SE and RE, with BIS and AAI as a measures of

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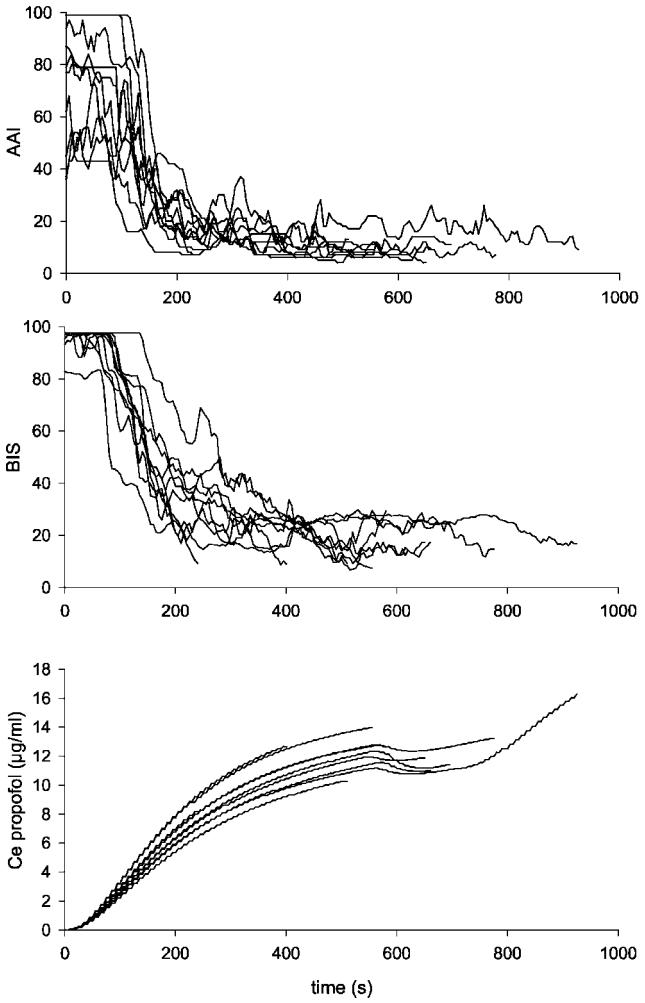

Fig. 2. Individual raw data for Bispectral Index (BIS) and A-Line® ARX Index (AAI) and propofol effect-site concentration (Ce propofol) *versus* time. (The disruption in the continuous increasing Ce propofol is due to the inevitable change of the 1% propofol syringe around 600 s.)

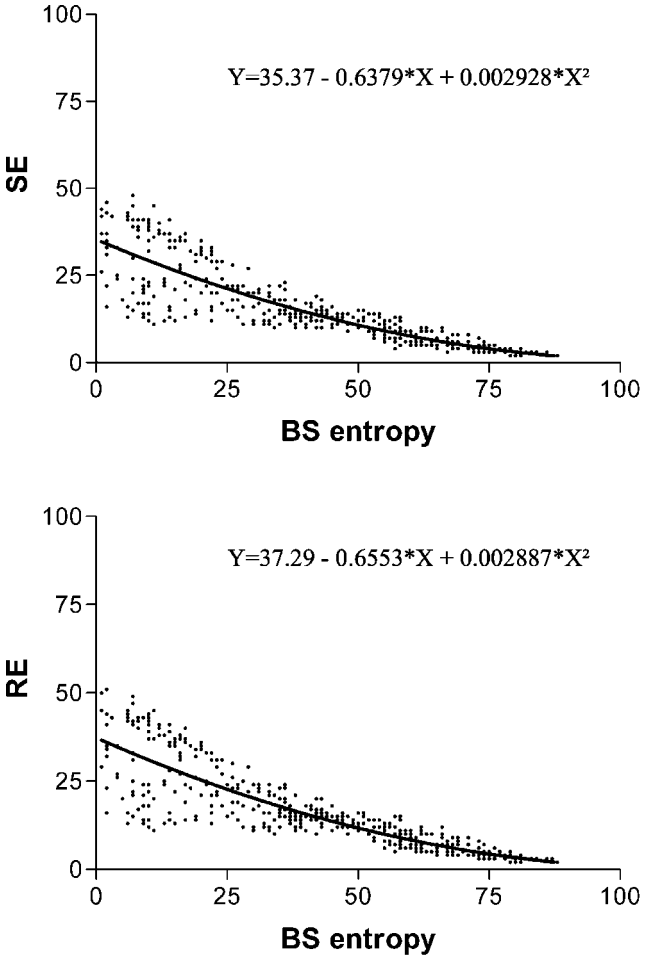

Fig. 3. Behavior of state (SE) (*A*) and response entropy (RE) (*B*) *versus* the burst suppression (BS) ratio as measured by the entropy module for all individual patients (*dots*) and its regression line (*bold line*).

anesthetic drug effect during increasing Ce_{prop}. Also, the stability at baseline and the correlation of burst suppression and its related measures of anesthetic drug effect on the electroencephalogram were tested for the three devices.

Baseline stability was calculated for all measures as seen in table 1. Baseline stability and baseline variation can profoundly affect electroencephalographic-based pharmacodynamic parameter estimation and the usefulness of the processed electroencephalogram or MLAEP as a measure of the arousal state of the central nervous system (depth of anesthesia).[8] Therefore, variation and stability at baseline were measured within our study population by calculating a CV on the data before administering any drug in stable conditions. Both spectral entropy measures showed the highest baseline stability among patients followed by BIS. High levels of baseline variation were found for the AAI. Baseline variation might decrease the predictive ability of the univariate parameter, as stated by Bruhn *et al.*[8]

Table 1. Baseline Stability Defined as the Coefficient of Variation of All Measures

	SE	RE	AAI	BIS
Mean ± SD	89.2 ± 1.4	97.5 ± 1.9	73.0 ± 23.1	95.6 ± 4.6
Coefficient of variation	1.610	1.955	31.697	4.801

AAI = A-Line® ARX Index; BIS = Bispectral Index; RE = response entropy of the spectral entropy; SE = state entropy of the spectral entropy.

Burst suppression represents a benign pattern frequently seen in healthy brain at deep levels of the hypnotic component of anesthesia. It can be identified in the raw electroencephalogram and is composed of episodes of electrical quiescence (the suppression) alternated with high-frequency, high-amplitude electrical activity (the bursts). Increasing anesthetic drug concentration causes increased duration of the suppression periods. Burst suppression patterns of the electroencephalogram are classically quantified as BSR defined as the percentage duration of suppression/duration of the epoch.[8,20,21]

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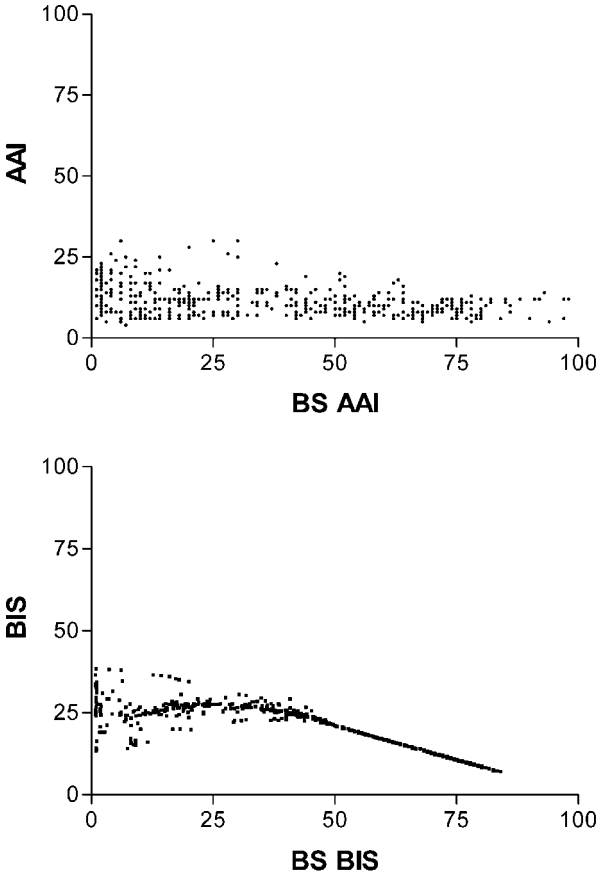

Fig. 4. Behavior of Bispectral Index (BIS) (*A*) and A-Line® ARX Index (AAI) (*B*) *versus* the burst suppression (BS) ratio as measured by the BIS® or AAI monitor (*A* and *B*, respectively) for all individual patients (*dots*).

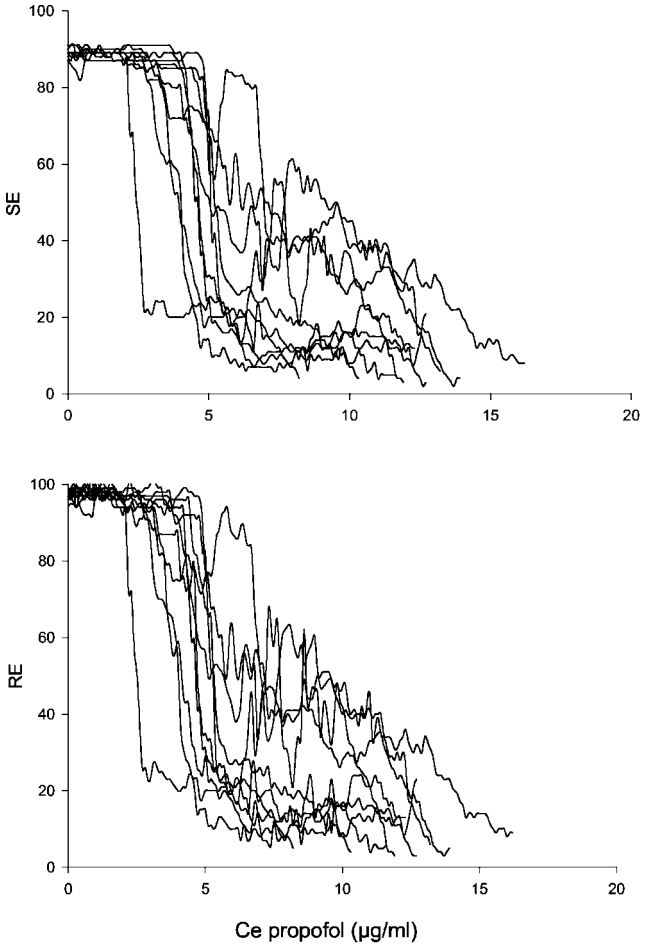

Fig. 5. Individual raw data for state (SE) and response entropy (RE) *versus* propofol effect-site concentration (Ce propofol).

Because the detection of burst suppression represents an important electroencephalographic component to measure deep levels of anesthesia, its correlation to its univariate parameter is important and must be investigated. Figure 3 shows the correlation between SE and RE and its BSR. As the suppression part of the burst suppression is classified as highly regular, the spectral entropy algorithm correctly classifies increasing burst suppression as increasing anesthetic drug effect. As a result, a clear correlation between BSR and SE or RE was found. For MLAEP, it has been published previously that MLAEP lacks accuracy in detecting deepening of the hypnotic–anesthetic level because of a flat MLAEP signal after loss of consciousness.[16] Because AAI is derived from the MLAEP, no BSR was calculated on the original evoked potential signal. As a result, no correlation between AAI and BSR was found. It might be argued that the detection of electroencephalographic burst suppression beside the MLAEP-derived AAI might solve the problem of lack of accuracy at deep levels of anesthesia, which might be revealed in further studies. For BIS, the onset of burst suppression was not correctly detected by BIS as long as BSR was less than 40%, although burst suppression is a part of the BIS® algorithm. Above a BSR of 40, a linear correlation was found between BIS and BSR, as seen in

Table 2. Spearman Rank Correlation Coefficients and Prediction Probability for Each Electroencephalographic Measure of Anesthetic Drug Effect *vs.* Propofol Effect-site Concentration

	SE	RE	AAI	BIS
P_K, median (minimum–maximum)	0.86 (0.60–0.96)	0.89 (0.67–0.96)	0.87 (0.81–0.99)	0.91 (0.72–0.94)
Individualized Spearman rank correlation, mean ± SD (95% CI)	−0.841 ± 0.014 (−0.864, −0.808)*	−0.860 ± 0.013 (−0.882, −0.831)	−0.869 ± 0.010 (−0.883, −0.844)	−0.891 ± 0.011 (−0.907, −0.865)

* $P < 0.05$ between Bispectral Index (BIS) and other measures.

AAI = A-Line® ARX Index; CI = confidence interval; P_K = prediction probability; RE = response entropy of the spectral entropy; SE = state entropy of the spectral entropy.

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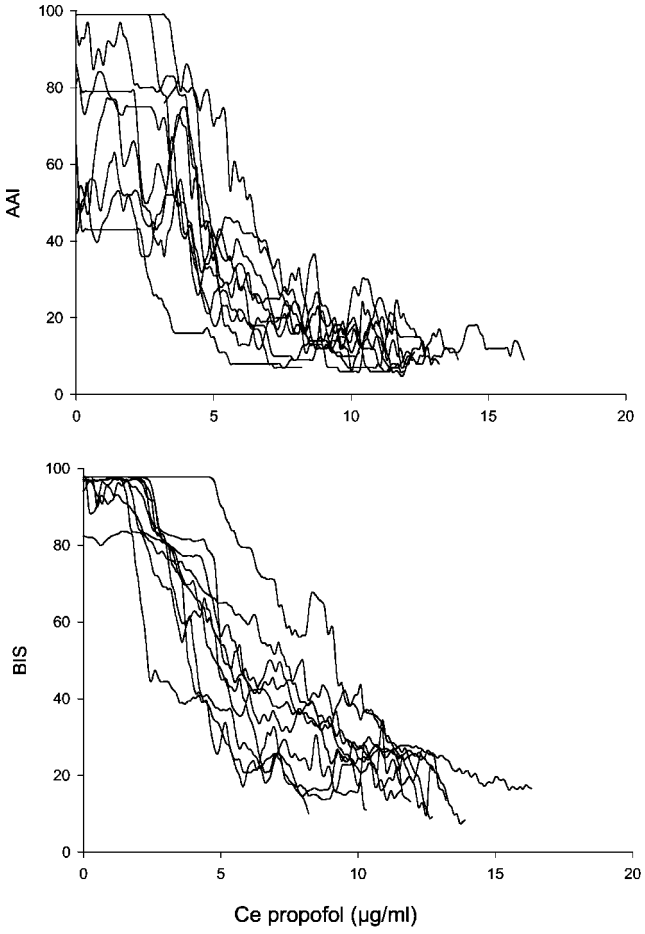

Fig. 6. Individual raw data for Bispectral Index (BIS) and A-Line® ARX Index (AAI) *versus* propofol effect-site concentration (Ce propofol).

figure 8. Others have also found that onset of propofol-induced burst suppression may be correctly detected as deepening of anesthesia by approximate entropy, another form of entropy calculation, but not by BIS.[22] The

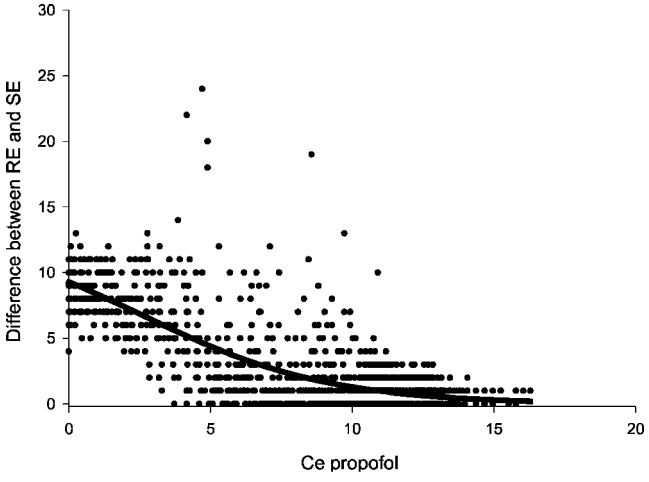

Fig. 7. Difference between response (RE) and state entropy (SE) *versus* the propofol effect-site concentration (Ce propofol) and its regression analysis.

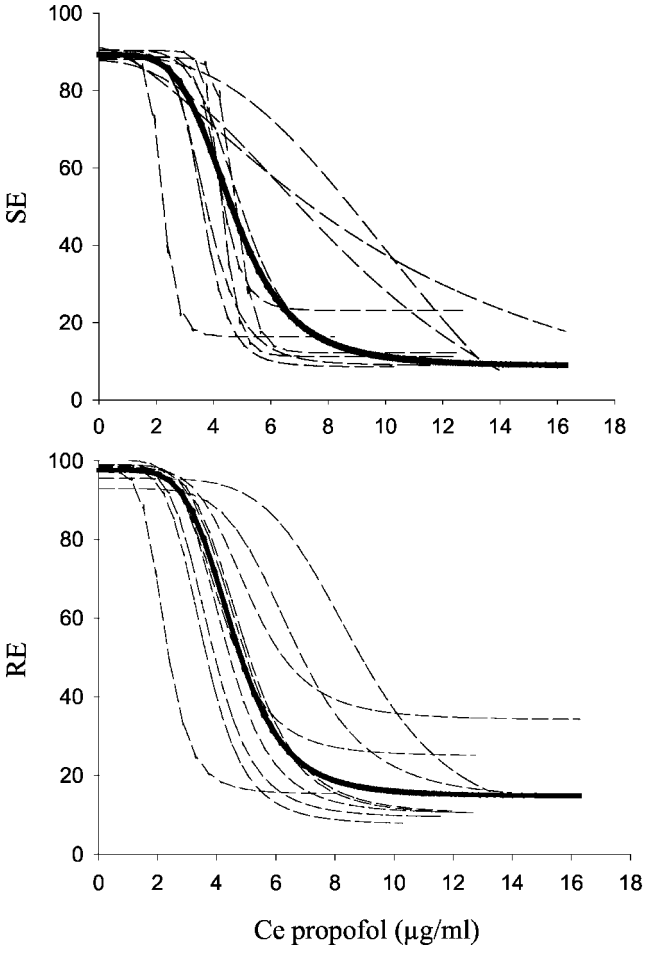

Fig. 8. The relation between propofol effect-site concentration and the state (SE) and response entropy (RE) modeled using nonlinear mixed effect modeling. The individual patients are represented as *dotted lines*, and the typical population curve is plotted as a *straight line*.

same authors found also that BSR is the only determinant for BIS values below 30.[21]

When studying performance accuracy, the question is how well the observed measure, which is the electroencephalographic response, predicts the unobserved "underlying" state of the patient, which is represented by the propofol effect-site concentration. Therefore, P_K was calculated for SE, RE, AAI, and BIS. P_K, a rescaled variant of the $d_{y,x}$ measure of association of Kim, generalizes nonparametric receiver operating characteristics curve area to a polytomous ordinal patient state. It shows the correlation between the value of the electroencephalographic measure of anesthetic drug effect and the calculated effect-site concentration of propofol, taking into account both desired performance and the limitations of the data.[10,11] That is, given two randomly selected electroencephalographic-derived data points with distinct anesthetic drug concentration, P_K is the probability that the indicator describes correctly which of the data points is the one with the higher (or lower) anesthetic drug concentration.[2] To avoid an overwhelming influ-

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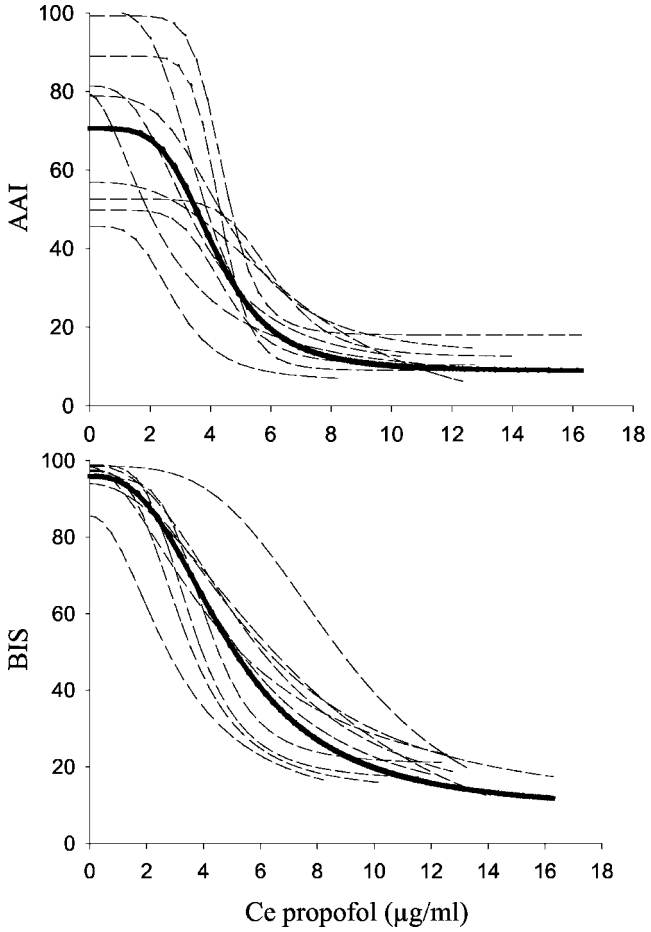

Fig. 9. The relation between propofol effect-site concentration and the Bispectral Index (BIS) and A-Line® ARX Index (AAI) modeled using nonlinear mixed effect modeling. The individual patients are represented as *dotted lines*, and the typical population curve is plotted as a *straight line*.

ence of patient individual variability on the P_K calculation, estimation was performed on an individual patient basis. Although all four measures tended to have similar median P_K values, the range between the minimum and maximum observed was more wider for both entropy measures than for AAI and BIS. Alternatively, a nonparametric approach was used to measure the performance of SE, RE, AAI, and BIS using the individualized Spearman rank correlation. The individualized Spearman rank correlation between the four electroencephalographic measures of drug effect and Ce_{prop}, as shown in table 2, revealed similar findings as P_K. Even more, a significantly lower value for SE compared with BIS was found.

Table 3. Typical Values and Coefficient of Variation for Each Electroencephalographic Measure of Anesthetic Drug Effect

	SE	RE	AAI	BIS
Ce_{50}	4.68 (36%)	4.55 (35%)	4.15 (31%)	4.92 (34%)
E_0	89.3 (24%)	97.6 (3%)	70.6 (28%)	95.9 (4%)
E_{max}	−80.6 (28%)	−82.9 (11%)	−61.8 (31%)	−87.5 (11%)
γ	4.59 (39%)	5.33 (0%)	4.26 (51%)	2.69 (32%)

AAI = A-Line® ARX Index; BIS = Bispectral Index; Ce_{50} = the effect site concentration associated with 50% maximal drug effect; E_0 = the baseline measurement when no drug is present; E_{max} = the maximum possible drug effect; γ = the steepness of the concentration-*vs.*-response relation; SE = state entropy of the spectral entropy; RE = response entropy of the spectral entropy.

Figures 5 and 6 show the raw data for each patient for each electroencephalographic measure of anesthetic drug effect during increasing Ce_{prop}. Figure 7 shows the difference between SE and RE in relation to Ce_{prop}. Previously, using the ABM-2 monitor (Datex-Ohmeda), Struys *et al.*[6] demonstrated that frontal electromyographic activity decreases with increasing propofol drug concentrations and *vice versa*. However, at higher drug concentration, the frontal electromyogram disappeared, making it useless for measuring excessive levels of anesthesia. As seen in figure 7, the difference between RE and SE approached zero in a concentration-dependent manner. It has also been reported that electromyographic activity can be used to detect pending arousal during anesthesia.[5] Because no arousal stimuli were included in the study protocol, this must be investigated in further research.

Figures 8 and 9 show the pharmacodynamic modeling for all measures *versus* Ce_{prop}. Previously, the relation between measures of anesthetic drug effect and Ce_{prop} was observed following a sigmoid E_{max} model.[2,3,6,23,24] Therefore, in our study, the relation between the measures of anesthetic drug effect and Ce_{prop} was also modeled using a sigmoid E_{max} model, and the model parameters were estimated using a population approach. In NONMEM, the parameters in the individual are weighted in a Bayesian manner toward the mean for the population, based on the variance of the individual parameters.[19] The results for each measures of anesthetic drug effect are shown in figures 8 and 9. As shown in table 3, the typical values for each measures of anesthetic drug effect revealed that for both RE as SE, steeper regression curves were seen than for both BIS and AAI, indicating a less graded response in most patients. The measures of individual variability were smaller for BIS and AAI than for SE and RE.

Although the use of a sigmoid E_{max} model is classically proposed in the literature,[2,3,6,23,24] one might criticize this approach. For the entropy of electroencephalography, Steyn-Ross *et al.*[25] discovered that the entropy might decrease discontinuously at the moment of induction into unconsciousness. They even concluded that this discontinuous step change in cortical entropy suggests that the cortical phase transition is analogous to a first-order thermodynamic transition in which the comatose–quiescent state is strongly ordered, whereas the active cortical state is relatively disordered. Recently, Bruhn *et al.*[26] found that two successive sigmoidal curves (instead of one) were useful in describing the pharmacodynamic behavior of two computerized electroencephalographic measures during isoflurane anes-

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thesia. Although examination of our raw data suggests that a single sigmoidal relation is adequate for the range of concentrations studied in this experiment, we cannot rule out the possibility that studies exploring a larger range of concentrations may necessitate different models to accurately characterize the relation between effect-site propofol concentration and electroencephalographic response.

In conclusion, when comparing the performance of two spectral entropies, SE and RE, with AAI and BIS as measures of anesthetic drug effect, it was found that baseline variability was lowest when using SE and RE, followed by BIS. AAI showed high baseline variability. Correlation between the burst suppression calculation and both RE and SE were observed. For BIS, suppression ratio values greater than 40% are linearly correlated with BIS values. For values less than 40%, no correlation with BIS was found. No correlation was obtained between the burst suppression calculation and the AAI. Although all within acceptable range, prediction probability and individualized Spearman rank correlation were highest for BIS and lowest for SE. Population pharmacodynamic modeling of each measure *versus* Ce_{prop} using a sigmoid E_{max} model revealed that for both RE as SE, steeper curves were seen than for both BIS and AAI, indicating an less graded response in most patients. The measures of intraindividual variability were smaller for BIS and AAI than for SE and RE.

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