Anesthesiology 2004; 101:1283–90

Comparative Evaluation of the Datex-Ohmeda S/5 Entropy Module and the Bispectral Index® Monitor during Propofol–Remifentanil Anesthesia

Gunter N. Schmidt, M.D., Petra Bischoff, M.D.,† Thomas Standl, M.D.,‡ Angelika Hellstern, M.D.,§ Olaf Teuber, M.D.,‖ Jochen Schulte am Esch, M.D.#*

Background: **Different analytical concepts were introduced to quantify the changes of the electroencephalogram. The Datex-Ohmeda S/5 Entropy Module (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland) was the first commercial monitor based on the entropy generating two indices, the state entropy (SE) and the response entropy (RE). The aim of the current study was to compare the accuracy of SE and RE with the Bispectral Index® monitor (BIS®; Aspect Medical Systems, Newton, MA) during propofol–remifentanil anesthesia.**

Methods: **The authors investigated 20 female patients during minor gynecologic surgery. SE, RE, BIS, mean arterial blood pressure, heart rate, and sedation level were recorded every 20 s during stepwise increase (target-controlled infusion, 0.5 μg/ml) of propofol until the patients lost response. Five minutes after loss of response, remifentanil infusion (0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was started. Spearman correlation coefficient and prediction probability were calculated for sedation levels with SE, RE, BIS, mean arterial blood pressure, and heart rate. The ability of the investigated parameters to distinguish between the anesthesia steps awake *versus* loss of response, awake *versus* anesthesia, anesthesia *versus* first reaction, and anesthesia *versus* extubation was analyzed with the prediction probability.**

Results: **SE correlates best with sedation levels, but no significant differences of the prediction probability values among SE, RE, and BIS were found. The prediction probability for all investigated steps of anesthesia did not show significant differences among SE, RE, and BIS. SE, RE, and BIS were superior to mean arterial blood pressure and heart rate.**

Conclusion: **SE, RE, and BIS revealed similar information about the level of sedation and allowed the authors to distinguish between different steps of anesthesia. Both monitors provided useful additional information for the anesthesiologist.**

ELECTROENCEPHALOGRAPHY has been introduced in anesthesiology to monitor the hypnotic state of patients. Different analytical concepts have been presented to quantify the changes of the electroencephalogram during the past decades. A big advantage was the fast-Fourier transformation, which allowed calculation of the linear information of the electroencephalography. In recent years, higher-order statistics have been used to describe changes of the electroencephalography. One method is bispectral analysis, which is based on the correlation of the phase between different frequency components of the electroencephalogram.[1] In 1992, the Bispectral Index® monitor (BIS®; Aspect Medical Systems, Newton, MA), a commercial electroencephalographic monitor system, became available, based on the bispectral analysis. Another concept to quantify electroencephalography is the calculation of the entropy, describing the irregularity, complexity, or unpredictability characteristics of a signal. A signal in which sequential values are generated by a random number of generators has high entropy. A regular and well-ordered signal has an entropy value of zero. Bruhn *et al.*[2,3] demonstrated the usefulness of the Shannon entropy and the approximate entropy to describe the electroencephalographic changes during desflurane anesthesia. The Datex-Ohmeda S/5 Entropy Module (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland) is the first commercial monitor based on the spectral entropy.[4] The Datex-Ohmeda S/5 Entropy Module generates two indices, the state entropy (SE) and the response entropy (RE). The SE is computed over the frequency range from 0.8 to 32 Hz, the RE is calculated over the frequency range from 0.8 to 47 Hz. According to the manufacturer, the RE includes additional information about the electromyographic activity (activity higher than 32 Hz) of the face muscles.[4] The SE (range from 91 to 0) and the RE (range from 100 to 0) are normalized in such a way that the RE becomes equal to the SE when there is no electromyographic activity. In a recent study, Vakkuri *et al.*[5] found a faster reaction of RE during emergence than SE and BIS.

The aim of the current study was to give a first impression of the new Datex-Ohmeda S/5 Entropy Module during propofol–remifentanil anesthesia. In detail, we were interested in whether the Datex-Ohmeda S/5 Entropy Module is as reliable or better or worse than the BIS® monitor in reflecting changes during increasing propofol and remifentanil infusions and sedation levels. Moreover, we were interested in the ability to differentiate between the anesthesia steps awake *versus* loss of response, awake *versus* anesthesia, anesthesia *versus* first reaction, and anesthesia *versus* extubation and the nuances of anesthetic steps loss of response *versus* first reaction. In addition, we analyzed the correlation of SE, RE, and BIS from awake throughout extubation during anesthesia with propofol and remifentanil.

* Anesthesia Fellow, † Associate Professor in Anesthesiology, ‡ Professor in Anesthesiology, § Anesthesia Fellow, ‖ Research Fellow, # Professor in Anesthesiology and Chairman.

Received from the Department of Anesthesiology, University Hospital Hamburg-Eppendorf, Hamburg, Germany. Submitted for publication April 6, 2004. Accepted for publication July 21, 2004. Support was provided solely from institutional and/or departmental sources. Drs. Schmidt and Bischoff contributed equally to this article.

Address reprint requests to Dr. Schmidt: Department of Anesthesiology, University Hospital Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. Address electronic mail to: guschmid@uke.uni-hamburg.de.

Table 1. Modified Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
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
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Materials and Methods

After institutional review board (Ethik-Kommission der Arztekammer Hamburg, Hamburg, Germany) approval and written informed consent, 20 elective patients were included in the study. Selection criteria were age 18 to 75 yr, American Society of Anesthesiologists physical status classification I or II, and minor gynecologic surgery.

After premedication with 7.5 mg oral midazolam (30 min before induction), anesthesia was induced with a 0.5-μg/ml target-controlled infusion (Diprifusor, Graseby 3500; Graseby Medical Limited, Hertfordshire, Watford, United Kingdom) of propofol followed by a stepwise increase (0.5 μg/ml) until the patient lost response. Every propofol concentration level was maintained over 1 min. Loss of response was detected by the Modified Observer's Assessment of Alertness/Sedation Scale (MOAAS; table 1).[6] Loss of response was defined by MOAAS values less than 1. MOAAS was tested every 20 s until each target-controlled concentration was reached.

After loss of response, 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil (Graseby 3400; Graseby Medical Limited) was started. Five minutes after the start of remifentanil infusion, cisatracurium (0.1 mg/kg) was given to facilitate tracheal intubation. Anesthesia was maintained with the target-controlled concentration obtained for loss of response added with 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil until skin incision. After skin incision, anesthesia was maintained by the anesthesiologist according to clinical signs. At the end of surgery, propofol and remifentanil infusions were stopped simultaneously. MOAAS was tested every 20 s until extubation. Extubation criteria were sufficient spontaneous breathing and spontaneous eye opening.

We defined five different anesthetic steps: awake, loss of response, steady state anesthesia (target-controlled concentration obtained for loss of response added with 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil) before surgical incision, first reaction (any reaction such as movement, coughing, or eye opening during emergence after stop of propofol–remifentanil infusion; MOAAS was tested every 20 s), and extubation. Comparisons were performed for the anesthesia steps awake *versus* loss of response, awake *versus* anesthesia, anesthesia *versus* first reaction, and anesthesia *versus* extubation. Moreover, we were interested in the differentiation between the anesthesia steps anesthesia loss of response *versus* first reaction.

The electroencephalogram was registered for BIS with BIS® sensor XP electrodes (Aspect Medical Systems) over the temporal-frontal area of the forehead. The BIS (version 4.0) was calculated by the BIS® module (Datex-Ohmeda Division, Instrumentarium Corp.). Electrode impedance was kept below 10 kΩ. The BIS was calculated with a smoothing rate of 30 s. The Entropy Sensor (Datex-Ohmeda Division, Instrumentarium Corp.) was placed over the temporal-frontal area of the forehead after a careful preparation of the skin. The position of the BIS® sensor XP or the Entropy Sensor over the left or right forehead was decided by flipping a coin. After the sensor application, an impedance check was performed automatically. Electrode impedance was also kept below 7.5 kΩ. SE and RE were calculated by the Datex-Ohmeda S/5 Entropy Module.

Heart rate (HR), noninvasive mean arterial blood pressure (MAP), and oxygen saturation were measured and registered at every point of measurement (AS/3; Datex-Ohmeda Division, Instrumentarium Corp.). End-expiratory carbon dioxide concentrations (ET_{CO_2}) were maintained between 35 and 40 mmHg during the whole observation time. All data (SE, RE, BIS, HR, and MAP) were recorded on-line at a 5-s data sampling rate and stored by the Datex-Ohmeda S/5 Collect software (Datex-Ohmeda Division, Instrumentarium Corp.).

Statistical Analysis

Data Range. For SE, RE, BIS, MAP, and HR, the 95, 90, 75, 50, 25, 10, and 5% percentiles were calculated for every change in the MOAAS, at 1, 2, 3, 4, and 5 min after the start of remifentanil infusion, and for the investigated steps (one value for each patient).

Correlations. Comparison of MOAAS with SE, RE, BIS, MAP, and HR was performed with the Spearman correlation coefficient. Moreover, correlations between SE, RE, and BIS were evaluated by nonparametric Spearman rank correlation coefficient for all data pairs from awake through extubation.

Prediction Probability. Comparison of MOAAS scores (first value after reaching a new MOAAS level for every patient) with SE, RE, BIS, MAP, and HR was performed with prediction probability (P_K).[7] The accuracy to distinguish between the anesthetic steps awake *versus* loss of response, awake *versus* anesthesia, anesthesia *versus* first reaction, and anesthesia *versus* extubation were analyzed with P_K. Therefore, we were comparing one value per patient for SE, RE, BIS, MAP, and HR for every step. Moreover, we analyzed P_K for loss of response *versus* first reaction. P_K was calculated using the P_KMACRO as described by Smith *et al.*[7] The jackknife method was used to compute the standard error of the

estimate. A value of $P_K = 0.5$ means that the parameter predicts the steps not better than a 50:50 chance. A value of $P_K = 1.0$ means that the parameter predicts the steps correctly 100% of the time. To compare the parameters to distinguish all steps, we calculated

$$P_{K\,all} = P_{K\,awake\ vs.\ loss\ of\ response} * P_{K\,awake\ vs.\ anesthesia} * P_{K\,anesthesia\ vs.\ first\ reaction} * P_{K\,anesthesia\ vs.\ extubation},$$

All steps were weighed equally. A parameter that distinguishes all steps of anesthesia perfectly with $P_K = 1.0$ results in $P_{Kall} = 1.0 * 1.0 * 1.0 * 1.0 = 1.0$, and a parameter predicting all steps with $P_K = 0.5$ results in $P_{Kall} = 0.5 * 0.5 * 0.5 * 0.5 = 0.0625$. Comparisons of the P_K values were performed with the P_KDMACRO.[7]

Power Calculation. A power calculation, based on differences in P_K, was performed to estimate the sample size. We considered that a difference of less than 0.05 in P_K would not be of clinical importance. The *t* statistic was then calculated as the quotient between the chosen difference in clinical importance and the standard error of the estimate. With these characteristics and testing with a statistical significance of $P < 0.01$, 20 patients should be included in the study.[8]

Logistic Regression. For SE and BIS, the logistic regression was calculated for the probability of loss of response, anesthesia, first reaction, and extubation. The Hill coefficients were calculated to describe the steepness of those relations.[9]

Separation Measures. Changes of RE, BIS, MAP, and HR after the start of remifentanil infusion were tested with the Friedman test for repeated measurements. In case of significant "overall" effects, changes were evaluated in detail *a posteriori* by the Wilcoxon test. The Bonferroni correction was performed to account for multiple testing.

Statistical analyses were performed using the SPSS package (version 9; SPSS, Chicago, IL), SigmaPlot (version 8.0; SPSS), P_KMACRO, and P_KDMACRO.[7] A *P* value less than 0.05 was considered statistically significant.

Results

Data evaluation was performed in 20 female patients (age, 51 ± 14 [SD] years; weight, 71 ± 16 kg; height, 166 ± 6 cm). The duration of surgery was 68 ± 36 min, without unusual perturbations such as blood loss or hypothermia. Patients were extubated after the stop of propofol–remifentanil infusion and at a calculated propofol plasma concentration of 1.2 ± 0.3 μg/ml, without any complications. In no patient did the electrode strips have to be replaced because the electrode impedance was above 10 kΩ for BIS or 7.5 kΩ for SE and RE.

SE, RE, and BIS decreased after induction of anesthesia and increased during emergence (fig. 1). Increasing sedation (from MOAAS = 5 to MOAAS = 0) was associated

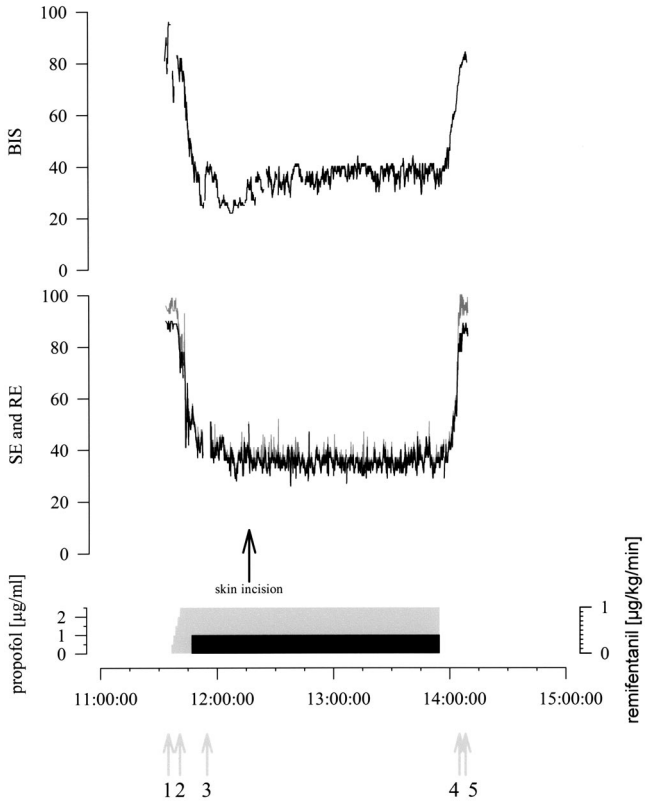

Fig. 1. Example of a 56-yr-old woman. State entropy (SE, *middle*, *black*), response entropy (RE, *middle*, *gray*) and Bispectral Index (BIS, *top*) during anesthesia with propofol and remifentanil. The *gray arrows* mark the investigated steps awake (*1*), loss of response (*2*), anesthesia (*3*), first reaction (*4*), and extubation (*5*).

with decreases for median SE from 89 to 51, median RE from 97 to 55, and median BIS from 94 to 58 as shown in figure 2. SE correlated best with MOAAS ($r = 0.82$, $P_K = 0.89$), but differences of P_K values were not statistically significant (table 2). Correlation coefficients and P_K values for the sedation levels were higher for SE, RE, and BIS than for MAP and HR (table 2).

The start of remifentanil infusion resulted in statistically significant decreases for SE, RE, BIS, MAP, and HR (fig. 3 and table 3). The first effects were found for MAP and HR (second minute), followed by BIS (third minute) and SE and RE (fourth minute).

Changes of SE, RE, BIS, MAP, and HR during the investigated steps are shown in figure 4. Only BIS was able to distinguish each evaluated step with $P_K > 0.90$ (table 4), resulting in $P_{Kall} = 0.9$. SE and RE showed a high prediction probability ($P_K > 0.9$) for the steps awake *versus* loss of response, awake *versus* anesthesia, and anesthesia *versus* extubation (table 4) and a lower prediction probability ($P_K > 0.8$) for the step anesthesia *versus* first reaction. P_K values for SE, RE, and BIS were without any significant differences ($P < 0.05$). The 95% possibility for *loss of response* was 80 for BIS and 81 for SE. The 95% possibility for the *first reaction* was 72 for BIS and 79 for SE (fig. 5 and Table 5). P_{Kall} was higher for BIS, SE, RE

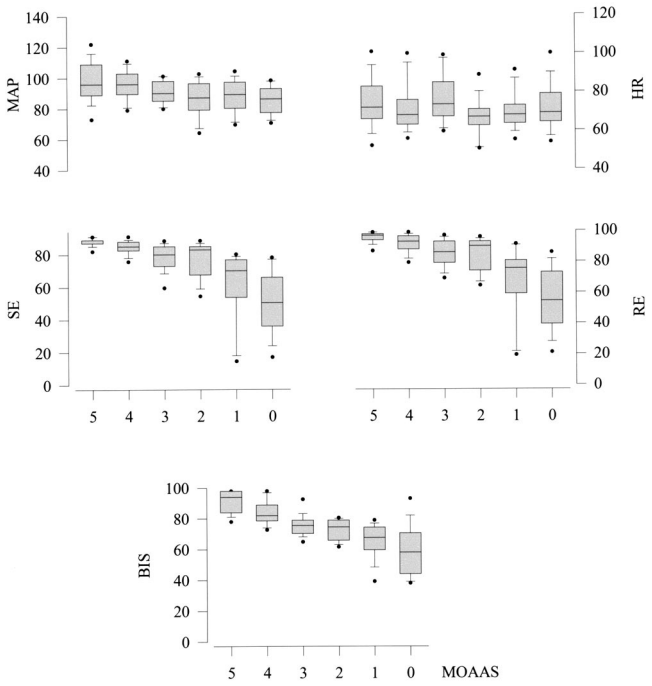

Fig. 2. Modified Observer's Assessment of Alertness/Sedation Scale (MOAAS). Mean arterial pressure (MAP), heart rate (HR), state entropy (SE), response entropy (RE), and Bispectral Index (BIS) during different sedation levels (MOAAS 5 to 0). To demonstrate the scatter of the data, 95, 90, 75, 50, 25, 10, and 5% percentiles are represented.

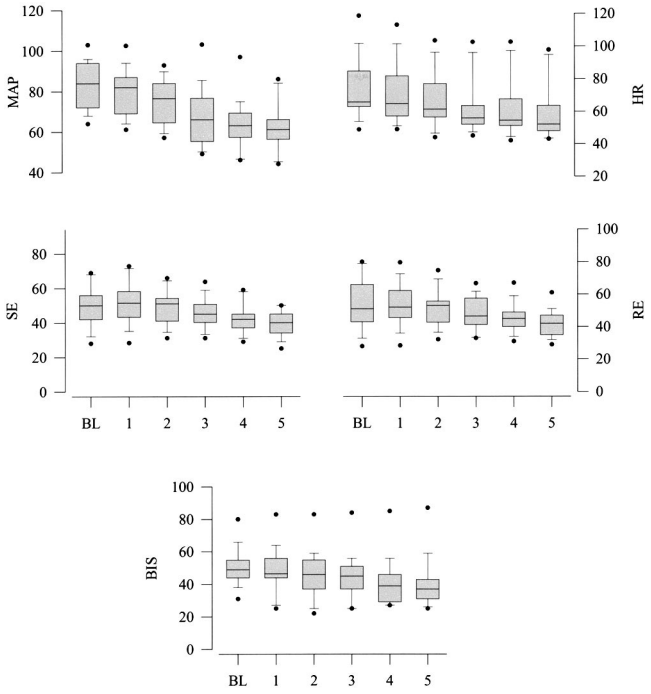

Fig. 3. Remifentanil effects. Mean arterial pressure (MAP), heart rate (HR), state entropy (SE), response entropy (RE) and Bispectral Index (BIS) during target-controlled infusion of propofol (3.1 ± 0.9 [SD] μg/ml) obtained for loss of response (BL) and their changes 1, 2, 3, 4, and 5 min after start of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil. To demonstrate the scatter of the data, 95, 90, 75, 50, 25, 10, and 5% percentiles are represented.

than for MAP and HR. However, SE, RE and BIS were not able to distinguish accurately between *loss of response versus. first reaction* (Table 4 and fig. 6).

Because of the different algorithms of entropy (SE and RE) and BIS, we were interested in the correlation of both parameters. A high correlation coefficient (SE: $r = -0.83$, $P < 0.001$; RE: $r = -0.84$, $P < 0.001$) of both was found (fig. 7). BIS values between 100 and 85 indicating awake patients[10] were indicated in 88% of data pairs by SE values between 91 to 80. BIS values of 65–40 (recommended for general anesthesia)[10] were associated in 84% with SE values of 59 to 30. Details are given in figure 8.

Table 2. Spearman Correlation Coefficient and Prediction Probability for the Modified Observer's Alertness/Sedation Scale

	MOAAS			
	Spearman		Prediction Probability	
	r	P Value	P_K	SEE
BIS	0.79	0.00	0.87	0.01
SE	0.82	0.00	0.89	0.01
RE	0.80	0.00	0.88	0.01
MAP	0.42	0.00	0.69	0.02*†‡
HR	0.11	0.01	0.55	0.02*†‡

* *vs.* Bispectral Index (BIS) ($P < 0.01$). † *vs.* state entropy (SE) ($P < 0.01$). ‡ *vs.* response entropy (RE) ($P < 0.01$).

HR = heart rate; MAP = mean arterial blood pressure; MOAAS = Modified Observer's Alertness/Sedation Scale; P_K = prediction probability; SEE = standard error of the estimate.

Discussion

An accepted standard for the measurement of depth of anesthesia is still missing. In the current study, we used three ways to estimate the status of the Datex-Ohmeda S/5 Entropy Module, a new designed electroencephalographic system, to monitor depth of anesthesia.[4] First, we tested the Datex-Ohmeda S/5 Entropy Module in comparison with different sedation levels. Second, we were interested in changes of the Datex-Ohmeda S/5 Entropy Module after the application of remifentanil. Third, we investigated the ability of the Datex-Ohmeda S/5 Entropy Module to differentiate between different steps of anesthesia.

One strategy to test a depth-of-anesthesia monitor is comparison with patient's clinically observed level of sedation.[8] Therefore, we studied SE, RE, BIS, MAP, and HR during different sedation levels. We used the MOAAS because it provides a good correlation with different degrees of sedation and has been tested in many other studies.[8] In the current study, decreases in sedation level were associated with decreases in SE, RE, and BIS. In contrast, changes in MAP and HR did not correlate well with changes in MOAAS. SE correlated best with

Table 3. Remifentanil Effects

	Friedman				Wilcoxon									
					First Minute		Second Minute		Third Minute		Fourth Minute		Fifth Minute	
	n	χ^2	*df*	P Value	*Z*	P Value	*Z*	P Value	*Z*	P Value	*Z*	P Value	*Z*	P Value
BIS	16	22	5	0.000	−1.5	>0.05	−2.3	>0.05	−2.7	0.030*	−3.1	0.010*	−2.9	0.017*
SE	17	32	5	0.000	−0.5	>0.05	−0.7	>0.05	−2.4	>0.05	−3.1	0.011*	−3.0	0.014*
RE	17	30	5	0.000	−0.7	>0.05	−0.7	>0.05	−2.0	>0.05	−2.8	0.022*	−2.9	0.021*
MAP	19	69	5	0.000	−2.0	>0.05	−3.5	0.003*	−3.6	0.002*	−3.8	0.001*	−3.8	0.001*
HR	18	65	5	0.000	−0.6	>0.05	−3.0	0.015*	−3.7	0.001*	−3.1	0.009*	−3.7	0.001*

* *vs.* 1 min before start of remifentanil infusion ($P < 0.05$).

BIS = Bispectral Index; HR = heart rate; MAP = mean arterial blood pressure; RE = response entropy; SE = state entropy.

MOAAS, but P_K values were without any statistically significant difference among SE, RE, and BIS.

Interestingly, in the current study, SE, RE, BIS, MAP, and HR decreased statistically significantly after the start of remifentanil infusion. No investigations regarding the effects of remifentanil on SE and RE have been published until now. The reaction of BIS on remifentanil infusion has been described controversially. Guignard *et al.*[11] obtained similar BIS values during administration of 4.0 μg/ml propofol effect site concentration combined with remifentanil effect site concentrations of 0, 2, 4, 8, and 16 ng/ml before laryngoscopy, whereas quantitative BIS responses to noxious stimuli (laryngoscopy and intubation) were attenuated in relation to increasing remifentanil applications. These findings indicate that BIS is not a reliable indicator for prediction of responses to painful events, even if BIS changes are related to analgesic components, quantitatively. Explaining the unsatisfying indication of the analgesic power by the BIS, Guignard *et al.*[11] hypothesized that these components are mediated in subcortical brain structures and at the level of spinal cord, which cannot be detected by electroencephalographic registration from the surface of the scalp. In contrast, the current study showed that BIS changed significantly from a median of 49 to a median of 37 in response to remifentanil infusion. Besides a pronounced analgesic effect, all opioids also provide dosage-related sedative effects. Without propofol, remifentanil infusion resulted in high-amplitude electroencephalographic slowing and delta waves. This might be the reason for the correlation of increasing remifentanil dosages (0.01–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) with decreasing BIS values during lower plasma concentrations of propofol (2 μg/ml).[12] The responses of BIS to remifentanil might not be simply remifentanil dosage related. Moreover, BIS also depends on the existence of the hypnotic power from propofol, quantitatively.

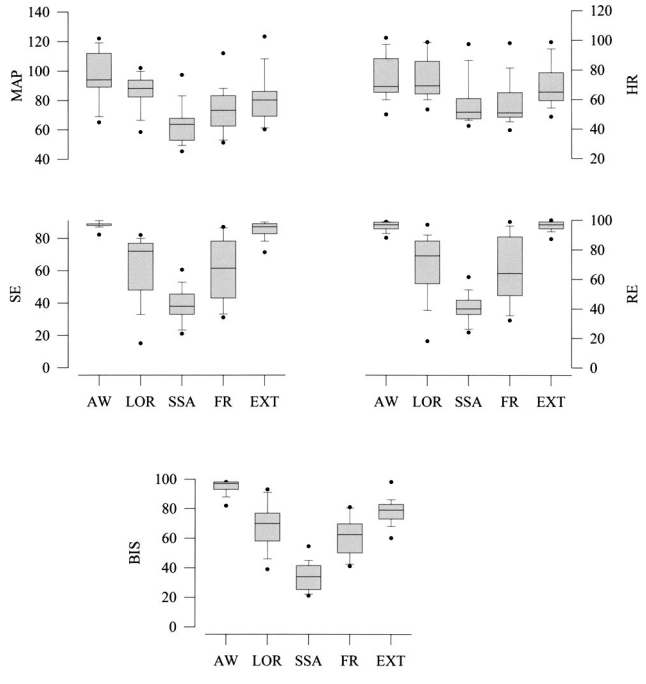

Fig. 4. Investigated anesthetic steps. Mean arterial pressure (MAP), heart rate (HR), state entropy (SE), response entropy (RE), and Bispectral Index (BIS) during the investigated steps: awake (AW), loss of response (LOR), steady state anesthesia (SSA), first reaction (FR) and extubation (EXT). To demonstrate the scatter of the data, 95, 90, 75, 50, 25, 10, and 5% percentiles are represented.

A depth-of-anesthesia monitor should distinguish accurately between different steps of anesthesia such as awake, loss of response, and first reaction during emergence. Therefore, not only statistically significant differences should be recommended. It must be demanded that, for an accurate index, values indicating different steps should not overlap.[13] In the current study, we used the prediction probability (P_K), presented by Smith *et al.*,[7] to detect the accuracy of the parameters to distinguish between the investigated steps of anesthesia. A P_K value of 0.5 means that the parameter distinguishes between the two steps by chance (50:50). A P_K value of 1.0 indicates a correct distinction with no overlap. In the current study, the awake patients were represented by median SE values of 89 (median RE = 97), whereas the median SE for the state of anesthesia was 38 (median RE = 40). SE and RE showed a high prediction probability ($P_K > 0.9$) for the steps awake *versus* loss of response, awake *versus* anesthesia, and anesthesia *versus* extubation. The P_K values of SE and RE were lower

Table 4. Prediction Probability for the Investigated Steps of Anesthesia

	Awake *vs.* Loss of Response		Awake *vs.* Anesthesia		Anesthesia *vs.* First Reaction		Anesthesia *vs.* Extubation			Loss of Response *vs.* First Reaction	
	P_K	SEE	P_K	SEE	P_K	SEE	P_K	SEE	$P_{K\,all}$	P_K	SEE
BIS	**0.98**	0.02	**1.00**	0.00	**0.91**	0.05	**1.00**	0.00	**0.90**	0.66	0.09
SE	**1.00**	0.00	**1.00**	0.00	0.82	0.07	**1.00**	0.00	0.82	0.56	0.10
RE	**0.97**	0.03	**1.00**	0.00	0.85	0.07	**1.00**	0.00	0.82	0.56	0.10
MAP	0.70	0.09*†‡	**0.94**	0.04	0.70	0.09	0.81	0.07	0.37	0.81	0.07
HR	0.50	0.10*†‡	0.87	0.07	0.54	0.10*†‡	0.80	0.08	0.19	0.82	0.07

Boldface numbers indicate P_K values greater than 0.9.

* *vs.* Bispectral Index (BIS) ($P < 0.01$). † *vs.* state entropy (SE) ($P < 0.01$). ‡ *vs.* response entropy (RE) ($P < 0.01$).

HR = heart rate; MAP = mean arterial blood pressure; P_K = prediction probability; SEE = standard error of the estimate.

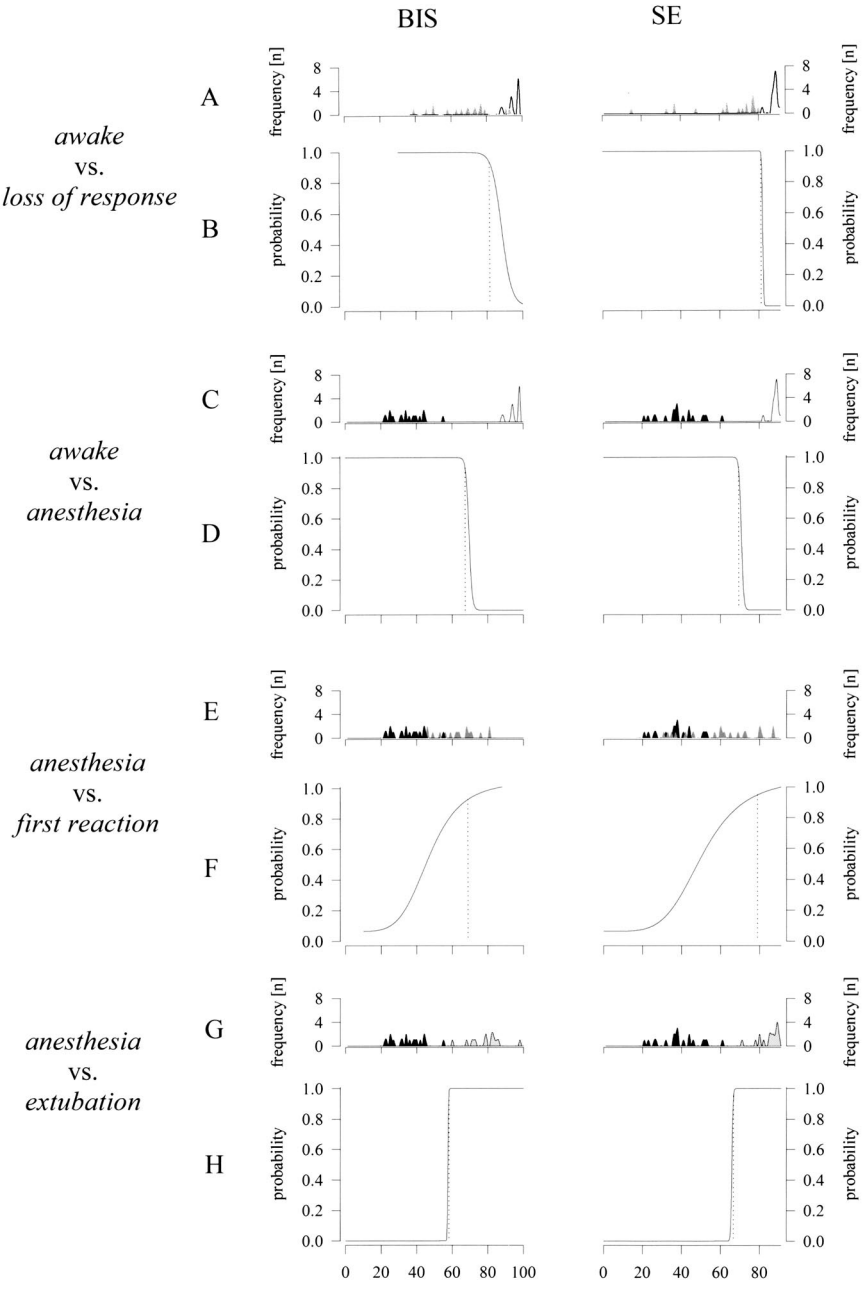

Fig. 5. Logistic regression curve. Shown are the probabilities for loss of response (*B*) and first reaction (*D*) as a function of state entropy (SE, *right*) and Bispectral Index (BIS, *left*). *Dotted lines* indicate the 95% probability. The distributions between awake (*white*) and loss of response (*gray*, *A*) and between anesthesia (*black*) and first response (*dark gray*, *C*) are presented.

Table 5. Probability Curve

	Min	Max	EV_{50}	Hill Slope
BIS				
Awake *vs.* loss of response	0.0	1.0	88	33
Awake *vs.* anesthesia	0.0	1.0	70	83
Anesthesia *vs.* first reaction	0.1	1.0	47	−5
Anesthesia *vs.* extubation	0.0	1.0	57	411
SE				
Awake *vs.* loss of response	0.0	1.0	82	415
Awake *vs.* anesthesia	0.0	1.0	71	129
Anesthesia *vs.* first reaction	0.1	1.1	51	−5
Anesthesia *vs.* extubation	0.0	1.0	66	243

BIS = Bispectral Index; EV_{50} = median effective value, expected to cause a defined effect on 50%; Hill slope = slope of the curve at its midpoint; max = top of the curve; min = bottom of the curve; SE = state entropy.

($P_K < 0.9$) to distinguish between anesthesia *versus* first reaction. One reason might be that the step first reaction (*e.g.*, coughing or moving spontaneously or after stimulation with MOAAS) is not necessarily related to the cortex activity but rather to subcortical activation. However, for the anesthesiologist, it is important to detect and predict the first reaction. The P_K values of SE and RE were similar and with no significant differences compared with BIS. The BIS is the most evaluated parameter derived from the spontaneous electroencephalogram, but its status as a depth of anesthesia monitor is still controversial.[13,14] In a recent study, we underlined the potency of BIS to distinguish between patients who were awake and anesthetized with propofol and remifentanil. For the 25 patients observed, no overlap in the data were found between the awake and anesthetized states.[15] During emergence, BIS was not able to distinguish the first reaction during conditions without any external stimulation from the anesthetized state. We hypothesized that this was due to the well-known delay of BIS of 60 s.[16] Interestingly, in the current study, BIS was able to distinguish between all investigated conditions, including steady state anesthesia *versus* first reaction, accurately ($P_K > 0.9$). The reason for the better

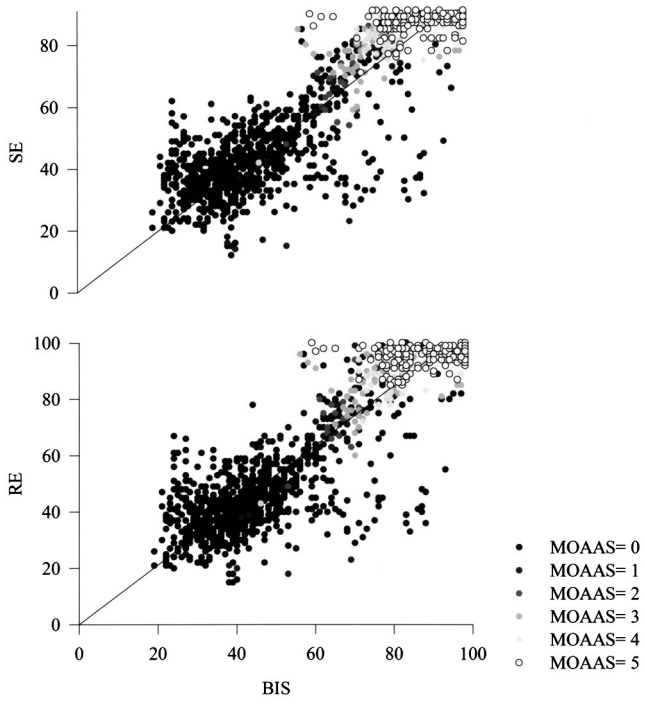

Fig. 7. Comparison of state entropy (SE), response entropy (RE), and Bispectral Index (BIS). Shown are all data pairs from awake through extubation (the *filling of the circle* indicates the Modified Observer's Assessment of Alertness/Sedation Scale [MOAAS]).

differentiation in the current study may be due to stimuli (MOAAS) during the emergence period. In the current study, we found a limitation of the Datex-Ohmeda Entropy Module and the BIS® monitor. SE, RE, and BIS were not able to distinguish between the nuances of anesthesia when patients only lost response to MOAAS *versus* the first reaction during emergence. In accord with our data, for example, an SE value of 80 is not able to predict whether the patient shows a response or not.

The SE, based on electroencephalography, ranges in values from 91 to 0, and the RE, based on electroen-

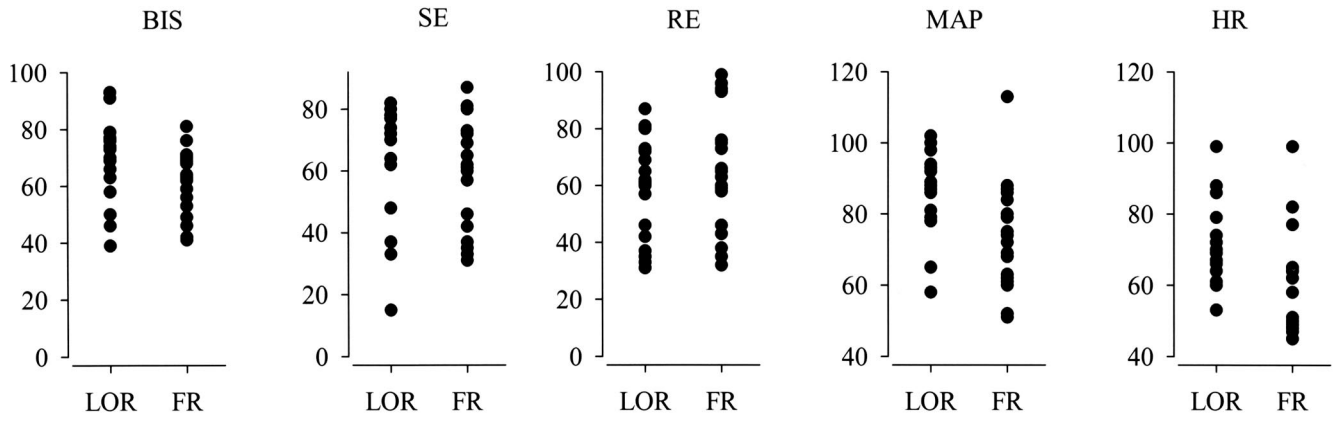

Fig. 6. Overlap during the nuances of anesthesia loss of response (LOR) *versus* first reaction (FR). Bispectral Index (BIS), state entropy (SE), response entropy (RE), mean arterial pressure (MAP), and heart rate (HR) during the steps loss of response (*right*) and first reaction (*left*). Shown are the same data as in figure 5. Each *spot* represents one patient.

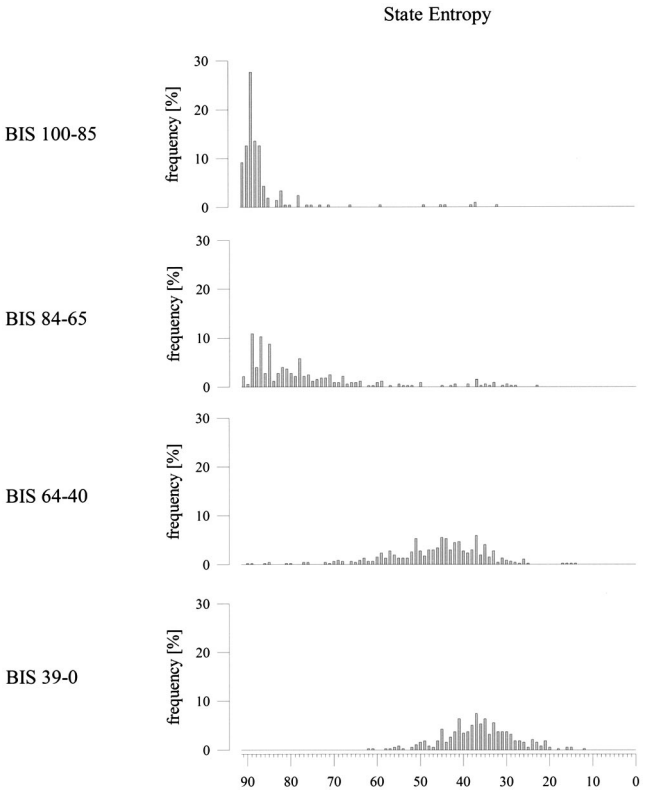

Fig. 8. Bispectral Index (BIS) and the corresponding state entropy. Shown are BIS values recommended for awake (100–85),[10] sedation (84–65),[10] general anesthesia (64–40),[10] and increasing burst suppression (39–0)[10] and the incidence (%) of the state entropy values (91–0).

cephalography and electromyography, ranges in values from 100 to 0.[4] The advantage of RE should be the possibility of a faster reaction to changes such as arousal.[4] Vakkuri *et al.*[5] demonstrated that RE indicates emergence from anesthesia 11 s earlier than SE and 12.4 s earlier than BIS. In the current study, no advantage of RE over SE was found. Differences between SE and RE to distinguish between the investigated steps of anesthesia were without any statistically significant effect. In the study of Vakkuri *et al.*,[5] the patients were tested only for loss of consciousness, defined as inability to respond to verbal command ("squeeze my hand"), and recovery of consciousness was determined to have taken place when the patient again responded purposefully to verbal command ("squeeze my hand"). Therefore, the testing scales in these studies were different.

In summary, SE, RE, and BIS were similar and reliable indices to detect different sedation levels and to distinguish between the investigated steps of anesthesia. We also showed that RE, SE, and BIS did not differentiate between different nuances of anesthesia (loss of response *vs.* first reaction). However, SE, RE, and BIS were superior to MAP and HR to distinguish between different steps of anesthesia with propofol and remifentanil and provided additional information for the anesthesiologist.

References

1. Rampil IJ: A primer for EEG signal processing in anesthesia. ANESTHESIOLOGY 1998; 89:980–1002
2. Bruhn J, Lehmann LE, Ropcke H, Bouillon TW, Hoeft A: Shannon entropy applied to the measurement of the electroencephalographic effects of desflurane. ANESTHESIOLOGY 2001; 95:30–5
3. Bruhn J, Ropcke H, Hoeft A: Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. ANESTHESIOLOGY 2000; 92:715–26
4. Viertiö-Oja H, Maja V, Sarkela M, Talja P, Tenkanen N, Tolvanen-Laakso H, Paloheimo M, Vakkuri A, Yli-Hankala A, Merilainen P: Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. Acta Anaesthesiol Scand 2004; 48:154–61
5. Vakkuri A, Yli-Hankala A, Talja P, Mustola S, Tolvanen-Laakso H, Sampson T, Viertiö-Oja H: Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. Acta Anaesthesiol Scand 2004; 48:145–53
6. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244–51
7. Smith WD, Dutton RC, Smith NT: Measuring the performance of anesthetic depth indicators. ANESTHESIOLOGY 1996; 84:38–51
8. Struys MM, Jensen EW, Smith W, Smith NT, Rampil I, Dumortier FJ, Mestach C, Mortier EP: Performance of the ARX-derived auditory evoked potential index as an indicator of anesthetic depth: A comparison with bispectral index and hemodynamic measures during propofol administration. ANESTHESIOLOGY 2002; 96:803–16
9. Hill A: The possible effect of the aggregation of the molecules of hemoglobin on its dissociation curves. J Physiol 1910; 40:IV–VII
10. Johansen JW, Sebel PS: Development and clinical application of electroencephalographic bispectrum monitoring. ANESTHESIOLOGY 2000; 93:1336–44
11. Guignard B, Menigaux C, Dupont X, Fletcher D, Chauvin M: The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation. Anesth Analg 2000; 90:161–7
12. Strachan AN, Edwards ND: Randomized placebo-controlled trial to assess the effect of remifentanil and propofol on bispectral index and sedation. Br J Anaesth 2000; 84:489–90
13. Drummond JC: Monitoring depth of anesthesia: With emphasis on the application of the Bispectral Index and the middle latency auditory evoked response to the prevention of recall. ANESTHESIOLOGY 2000; 93:876–82
14. Messner M, Beese U, Romstock J, Dinkel M, Tschaikowsky K: The bispectral index declines during neuromuscular block in fully awake persons. Anesth Analg 2003; 97:488–91
15. Schmidt GN, Bischoff P, Standl T, Jensen K, Voigt M, Schulte am Esch J: Narcotrend and Bispectral Index® monitor are superior to classic electroencephalographic parameters for the assessment of anesthetic states during propofol–remifentanil anesthesia. ANESTHESIOLOGY 2003; 99:1072–7
16. Baker GW, Sleigh JW, Smith P: Electroencephalographic indices related to hypnosis and amnesia during propofol anaesthesia for cardioversion. Anaesth Intensive Care 2000; 28:386–91