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The Influence of Remifentanil on the Dynamic Relationship between Sevoflurane and Surrogate Anesthetic Effect Measures Derived from the EEG

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Background: **The authors modeled the influence of remifentanil on the dynamics of sevoflurane using three parameters derived from the electroencephalogram: 95% spectral edge frequency (SEF), canonical univariate parameter (CUP), and Bispectral Index (BIS).**

Methods: **Thirty-six patients with American Society of Anesthesiologists physical status class I or II were recruited, of which 12 received a target remifentanil concentration of 0 ng/ml, eight 2 ng/ml, eight 4 ng/ml, and another eight 8 ng/ml. Next (before surgery), several step-wise changes in the end-tidal sevoflurane concentration ($F_{ET,sevo}$) were performed. A data acquisition system simultaneously recorded $F_{ET,sevo}$, the raw electroencephalogram, BIS, and SEF. The authors used a combination of an effect compartment and an inhibitory sigmoid E_{MAX} model to describe the relation between $F_{ET,sevo}$ and BIS, SEF, and CUP. Model parameters ($t_{1/2}k_{e0}$, E_{MAX}, E_{MIN}, C_{50}, γ, CUP weight factors) were estimated using the population data analysis program NONMEM. Significant remifentanil model parameter dependencies ($P < 0.01$) were determined.**

Results: **Determined from SEF, remifentanil had no effect on $t_{1/2}k_{e0}$ (1.91 ± 0.26 min [mean ± standard error]) but caused an increase in C_{50} (baseline = 1.48 ± 0.12%; 80% increase at 8 ng/ml) and decrease in E_{MIN} (baseline = 10.8 ± 0.6 Hz; 80% reduction at 8 ng/ml). Determined from CUP, remifentanil caused a dose-dependent decrease in $t_{1/2}k_{e0}$ (baseline = 4.31 ± 1.00 min; 60% decrease at 8 ng/ml), with no effect on C_{50} (baseline = 0.88 ± 0.13%). Determined from BIS, remifentanil caused a dose-dependent decrease in $t_{1/2}k_{e0}$ (baseline value = 3.11 ± 0.32 min; 40% decrease at 8 ng/ml), without affecting C_{50} (baseline = 1.12 ± 0.05%). Median R^2 values of the pooled data set were 0.815 for SEF, 0.933 for CUP ($P < 0.01$ *vs.* SEF), and 0.952 for BIS ($P < 0.01$ *vs.* SEF and CUP). Addition of remifentanil increased the R^2 values for CUP only.**

Conclusions: **Remifentanil accelerates sevoflurane blood–brain equilibration without affecting its hypnotic potency as determined from BIS and CUP. In terms of R^2, the authors' pharmacodynamic model describes the anesthetic–BIS relation best.**

GENERAL anesthetics have their intended effect within the central nervous system, producing a state of reversible coma or anesthesia, possibly at the thalamus.[1,2] Because we have no knowledge on the anesthetic concentrations at the effect site(s) within the central nervous system, we use surrogate measures of drug effect derived from the electroencephalogram to get an indication of the temporal effect and potency of anesthetics. For opioids and anesthetic agents, a hysteresis between arterial or end-tidal concentration and electroencephalographic effect has been observed, which is well-described by a pharmacokinetic–pharmacodynamic (PK-PD) model consisting of a part that describes the lag between end-tidal (or arterial) and effect-site concentration and an inhibitory sigmoid E_{MAX} model that translates the effect-site concentration into electroencephalographic effect.[3–6] For example, using this PK-PD model, we previously analyzed the relation between end-tidal concentrations of the inhalational anesthetics isoflurane and sevoflurane and two electroencephalogram-derived parameters (Bispectral Index [BIS] and 95% spectral edge frequency [SEF]).[6] The PK-PD model was well able to describe the data, showing no difference in the lag between end-tidal and effect-site concentrations of both anesthetics (equilibration half-life ranging from 2.3 to 3.5 min) and an isoflurane:sevoflurane potency ratio of 2:1.

In clinical practice, anesthetics are often combined with opioids, which may change the dynamics and steady-state anesthetic–effect relation (and consequently change the parameters of the proposed PK-PD model). For example, the addition of low-dose remifentanil is known to reduce the anesthetic concentration needed to prevent movement in response to a noxious stimulus by more than 50%.[7] Therefore, we studied the effect of four target concentrations of remifentanil on the dynamic relation between end-tidal concentrations of sevoflurane and three parameters derived from the electroencephalogram: SEF,[6] canonical univariate parameter (CUP),[8–11] and BIS.[6,12,13] Electroencephalographic data were obtained in a study period before intubation and surgery. In some subjects, we continued the electroencephalographic data acquisition during surgery. Using the model parameters derived from the study phase, we predicted SEF, CUP, and BIS and quantified how close measurements and predictions were. This part of the study allowed the determination of one or more electroencephalogram-derived measures able to adequately predict changes in the electroencephalogram during anesthesia.

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Materials and Methods

Patients

Thirty-six patients with American Society of Anesthesiologists physical status class I or II, aged 19–60 yr, participated in the protocol, after approval was obtained from the local Medical Ethics Committee (Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands). All patients were scheduled to undergo elective abdominal surgery. Twelve patients received sevoflurane without remifentanil. Part of this data set was reported previously.[6] Twenty-four patients were randomly assigned to receive remifentanil at blood target concentrations of 2, 4, or 8 ng/ml.

Patient exclusion criteria were as follows: weight greater than 25% above ideal body weight; use of medication acting on the central nervous system; and history of esophageal reflux, neurologic, cardiac, pulmonary, hepatic, or renal disease. Patients were included in the study after written informed consent was obtained. They were instructed to fast for at least 6 h before the study and received no premedication.

Study Design

Before induction of anesthesia, intravenous and arterial catheters were inserted for drug administration and drug sampling. Next, remifentanil infusion was started using a target-controlled infusion device (see next section). After reaching the predicted target concentration at the simulated effect site (*i.e.*, brain), step-wise changes in end-tidal sevoflurane concentration were performed (inhaled gas mixture was sevoflurane in nitrogen and 30% oxygen). When consciousness was lost (tested by response to eyelash reflex), a nondepolarizing muscle relaxant was administered, and the lungs of the patients were artificially ventilated (by machine) *via* the mask. During the study, the end-tidal carbon dioxide concentration (P_{CO_2}) was kept between 35 and 40 mmHg. The end-tidal sevoflurane concentration ($F_{ET,sevo}$) sequence was chosen somewhat arbitrarily and involved increases and decreases in end-tidal sevoflurane concentration of 1–2.5% for 10–20 min each. At least three transitions were performed in each patient. When time permitted, additional transitions were performed. Subsequently, the study period ended, the trachea of the patient was intubated, and surgery started.

In 14 patients (13 with remifentanil infusion), data acquisition continued until the end of surgery. During surgery (abdominal hysterectomies or hemicolectomies), the target remifentanil concentration was maintained at the value of the study period, and only the end-tidal sevoflurane concentration was allowed to change. The resident and anesthesiologist in charge of the case during surgery (none of the authors) were unaware of the goals of the study. They were aware of the BIS values and were encouraged to steer the anesthetic depth taking into account all available parameters (*e.g.,* cardiovascular, BIS, and others).

Apparatus

The target-controlled infusion system consisted of a Palm-top computer (Psion 3c, London, United Kingdom), programmed with the pharmacokinetic data set of Minto *et al.*,[4] to control a syringe pump (Becton Dickinson, St. Etienne, France).[5] The electroencephalogram was recorded using an Aspect A-1000 electroencephalographic monitor (software version 3.22; Aspect Medical Systems, Newton, MA). Electrodes (Zipprep; Aspect Medical Systems) were placed on the scalp according to the international 10/20 system for electrode placement at Fp1-A1 and Fp2-A2 for bipolar recordings of the electroencephalogram. Electrode impedances were checked to be less than 2 kΩ before data acquisition started. SEF and BIS were computed by the Aspect monitor. CUP was determined as described later. Bispectral and spectral edge smoothing rates were 15 s and "off," respectively (these were the smallest possible values). Raw and processed electroencephalographic data and serial data (inspired and expired concentrations of the anesthetic, oxygen, and carbon dioxide) from a Datex Capnomac monitor (Datex, Helsinki, Finland) were collected by the Data-logger program (Aspect Medical Systems) using a four-channel communications adapter (QS-100D; Quatech, Akron, OH) and were stored on disk for off-line data analysis.

Determination of Remifentanil Blood Concentration

Directly after the remifentanil target was reached (*i.e.*, before sevoflurane inhalation), 5–10 min after the start of sevoflurane inhalation, 10–15 min later, and at the end of the study period, blood samples were obtained from the arterial catheter. To prevent metabolism of remifentanil in blood samples by aspecific esterases, samples, collected in heparinized tubes, were mixed with citric acid. Forthwith, the tubes were placed in a sample storage box containing dry ice and subsequently were stored in a freezer (−18°C). The procedure for remifentanil concentration determination was published elsewhere.[14] In short, it is based on tandem mass spectrometry detection. Quantification was linear between 0.1 and 50 ng/ml, and accuracy was between 93 and 98%.

The four measured remifentanil values were averaged. This mean value was used in the data analysis when the coefficient of variation was 30% or less. Otherwise, the electroencephalographic data were discarded.

Data Analysis

The $F_{ET,sevo}$ and anesthetic effect parameter data were analyzed with the pharmacodynamic model as described by Olofsen and Dahan,[6] and model parameter values were estimated with NONMEM version V, level 1.1 (a

data analysis program for nonlinear mixed effects modeling; University of California, San Francisco, CA),[15] using a population approach. In brief, the pharmacodynamic model consisted of a hypothetical effect compartment combined with a sigmoid E_{MAX} model described by the equations

$$\frac{dC_e(t)}{dt} = k_{e0} \cdot [C_{ET}(t) - C_e(t)] \quad (1)$$

and

$$E = E_{MAX} + (E_{MIN} - E_{MAX}) \cdot \frac{C_e^{\gamma}(t)}{C_{50}^{\gamma} + C_e^{\gamma}(t)} \quad (2)$$

where k_{e0} is a rate constant determining the speed of equilibration (we estimated the effect-site equilibration half-time $t_{1/2}k_{e0} = \ln 2/k_{e0}$), C_e is the effect-site concentration, E is the effect measure (SEF, CUP, or BIS), E_{MAX} and E_{MIN} are maximal and minimal effect values, C_{50} is the concentration that results in 50% inhibition, and γ is a steepness parameter. For C_{ET}, we substituted $F_{ET,sevo}$. To make the NONMEM analysis feasible, the number of samples per individual was reduced by averaging them such that the sampling period was 25 s (compare Rehberg *et al.*[16]). The average number of data points per patient was approximately 90. Plots of the individual Bayesian parameter value estimates *versus* the actual remifentanil concentration suggested that a suitable function for including remifentanil dependence was an exponential:

$$\Theta = \Theta_0 \cdot e^{-\Theta_r \cdot C_{rem}} \quad (3)$$

where θ_0 is the value of any of the above PK-PD model parameters when remifentanil concentration is zero and θ_r quantifies the decrease (or increase) when remifentanil is present. Moreover, such a remifentanil dependence was also incorporated for the SD of the residual intraindividual variability (σ_ε).

In agreement with our previous study,[6] we discarded corrupted initial SEF data related to artifacts, such as eye movements.

Canonical Univariate Parameter

Recently, the spectral entropy of the electroencephalogram was introduced as a (surrogate) measure reflecting depth of anesthesia.[17–19] It is defined as:

$$SEN = -\sum_k p_k \log p_k \quad (4)$$

where p_k is the normalized power in frequency bin k. This is motivated by the fact that when anesthesia deepens, the power becomes more concentrated in a (lower) frequency band, and hence, entropy decreases. Apart from this, spectral entropy has no theoretical meaning, and it might be that a generalization better describes the effect of anesthetics. Generalizations include the Rényi and Tsallis entropies and the CUP.[8–11,20,21] The latter has already been introduced in the anesthetic literature and can be defined as[8–11]:

$$CUP = a_0 + \sum_k a_k \log p_k \quad (5)$$

The weights a_k offer considerable flexibility compared with the fixed "weights" p_k in equation 4 (or one additional parameter q of the Rényi and Tsallis entropies). To be able to estimate intersubject variability of the a_k, the number of frequency bands was limited so that the bands cover the traditional δ (1–4 Hz), θ (5–8 Hz), α (9–12 Hz), β_1 (13–32 Hz), and β_2 (33–64 Hz) bands. The powers p_k were calculated as the median of 50 normalized power spectra in the corresponding bands, obtained from 25 one-second left- and right-lead electroencephalographic epochs. No further artifact rejection was applied.

We have the "measured" CUP given by equation 5, and we have the predicted CUP given by equation 2. Note that both sides contain parameters to be estimated; E_{MAX} and E_{MIN} are not identifiable and were fixed to 1 and 0, respectively. The remaining parameters cannot be well-estimated using least squares analysis directly because the values of $a_0 = 1$, $a_k = 0$, and high $t_{1/2}k_{e0}$, high C_{50}, and high γ provide a perfect fit but the meaningless solution of CUP = 1. This can be circumvented by maximizing the coefficient of determination instead:

$$R^2 = 1 - \frac{\Sigma(E_i - \hat{E}_i)^2}{\Sigma(E_i - \bar{E})^2} = 1 - \frac{\Sigma(E_i - \hat{E}_i)^2}{N \cdot \sigma^2} \quad (6)$$

where $\hat{E}_i$ is the prediction of effect parameter E_i, and $\bar{E}$; is the mean of E. Note that the denominator equals N times the (biased) variance of E, with N representing the number of measurements. The "pseudomodel" is written as[22]:

$$0 = \frac{E_{ij} - \hat{E}_{ij}}{\sigma_j} + \varepsilon_{ij} \quad (7)$$

where σ_j is the SD of E (of subject j), and ε is a normally distributed random variable with mean zero. This approach enables the maximization of the coefficient of determination and the estimation of the parameters in both equations 5 and 2 as well as their intersubject variability using NONMEM.

Prediction of Electroencephalographic Parameters during Surgery

In the 14 patients in which data were acquired beyond the study period, the parameters SEF, CUP, and BIS during surgery were predicted using the empirical Bayesian model parameter values from the study period.

Table 1. Patient Characteristics

C_{REM} Target (ng/ml)	n	F/M	Age (yr)	Weight (kg)	Height (cm)
0	12	8/4	42 ± 11	69 ± 14	175 ± 8
2	8	6/2	44 ± 8	62 ± 8	167 ± 9
4	8	6/2	43 ± 11	68 ± 8	169 ± 7
8	7	6/1	38 ± 15	78 ± 10	172 ± 9

Values are mean ± SD.
n = number of subjects.

Statistical Analysis

Spectral edge frequency, CUP, and BIS R^2 values and dependencies on remifentanil concentration were compared using Kruskal-Wallis tests.

The significance of the remifentanil dependence of the parameter values of the PK-PD model was assessed by exploring the possibilities of free or fixed $\theta_r = 0$ in the set. Initially, all θ_r were free; iteratively, the one with the highest coefficient of variation was fixed to zero. The final set was the one for which, when a fixed θ_r was set free, the fit would not become better, and when a free θ_r was fixed, the fit would become worse, relative to the fit with all θ_r fixed (degrees of freedom = number of free θ_r). *P* values were determined from the likelihood ratio test with values less than 0.01 considered significant.

Results

Patient data are summarized in table 1. All patients completed the protocol without side effects. Data from one subject (target concentration = 8 ng/ml) were discarded due to inconsistencies in the blood remifentanil concentrations (coefficient of variation > 30%). Average ± SD (mean coefficient of variation) remifentanil concentrations were 1.70 ± 0.31 ng/ml (20%), 4.30 ± 1.13 ng/ml (15.6%), and 7.50 ± 0.84 ng/ml (13.3%) for targets 2, 4, and 8 ng/ml, respectively.

Figure 1 shows the changes in SEF, BIS, and CUP on changes in end-tidal sevoflurane concentration and data fits of two patients at target remifentanil concentrations of 2 ng/ml (left) and 8 ng/ml (right). Their mean measured remifentanil concentrations were 2.1 ng/ml (coefficient of variation = 15%) and 7.8 ng/ml (6%), respectively. The R^2 values are given in the legend of the figure. For all three electroencephalographic measures, inspection of the individual data fits showed that the inhibitory sigmoid E_{MAX} model adequately described the end-tidal sevoflurane electroencephalographic data. Individual R^2 values are given in figure 2; median R^2 values and range are given in table 2. The distribution of R^2 was skewed more strongly toward lower values for SEF compared with CUP and BIS (fig. 2). Overall, R^2 values were best for BIS ($P < 0.01$ *vs.* CUP and SEF), followed by CUP ($P < 0.01$ *vs.* SEF), and worst for SEF (table 2). Remifentanil caused a small but significant increase in R^2 for CUP only ($P = 0.001$), although a trend was observed for BIS ($P = 0.08$).

Individual Bayesian parameter estimates against the measured remifentanil concentration are shown in figure 3. The parameter values of the exponential function fitted through the data are given in table 3, and the calculated parameter values of the sigmoid E_{MAX} model at four remifentanil concentrations (0, 2, 4, and 8 ng/ml) are shown in table 4. When considering the SEF, remifentanil had no effect on the equilibration half-life of sevoflurane ($t_{1/2}k_{e0}$ = 1.91 ± 0.26 min [population value ± standard error]) but caused a significant increase in C_{50} by 80%, from 1.48 ± 0.12% at 0 ng/ml to 2.66% at 8 ng/ml remifentanil. The influence of remifentanil on model parameters derived from CUP and BIS were comparable. Determined from CUP, remifentanil caused a dose-dependent decrease in $t_{1/2}k_{e0}$ by 60% from 4.31 ± 1.00 min (0 ng/ml) to 1.68 min (8 ng/ml), with no effect on C_{50} (baseline = 0.88 ± 0.13%). CUP weight factors were not dependent on remifentanil (fig. 4 and table 3). Determined from BIS, remifentanil caused a significant dose-dependent decrease in $t_{1/2}k_{e0}$ by 40% from 3.11 ± 0.32 min (0 ng/ml) to 1.87 min (8 ng/ml) and γ (from 32.4 ± 0.37 to 2.18), without affecting C_{50} (baseline = 1.12 ± 0.05%). For SEF, CUP, and BIS, remifentanil caused a dose-dependent decrease in σ_ε (table 4).

Individual and mean SEF, BIS, and CUP *versus* effect-site sevoflurane concentration relations are plotted in figure 5. It shows the dependency of SEF_{MIN} values on the remifentanil concentration (see also fig. 3) and the plateau in BIS (values ~30) at high sevoflurane concentrations. The different shapes of the sevoflurane BIS curves are due to differences in parameter γ (equation 2) and not in C_{50} (see also tables 3 and 4).

Study during Surgery

Fourteen patients (10 women, 4 men; mean age, 43.5 ± 9.9 yr) participated in this part of the study. Mean duration of surgery was 123 ± 68 min. Predictions of SEF, CUP, and BIS values during surgery, based on the Bayesian parameter estimates derived from the study period, were variable and, with few exceptions, poor (fig. 2 and table 2). Among patients, the observed deviations from the measured electroencephalographic data showed no consistent pattern. There were no significant differences in R^2 values for SEF, BIS, and CUP (table 2). Good examples of SEF, BIS, and CUP during the study and surgical period are given in figure 6. The lines through the data are the predicted electroencephalographic values. The R^2 values indicate relative good prediction for CUP and BIS (R^2 values 0.749 and 0.688 for CUP and BIS, respectively) and poor prediction for SEF (R^2 = 0.371).

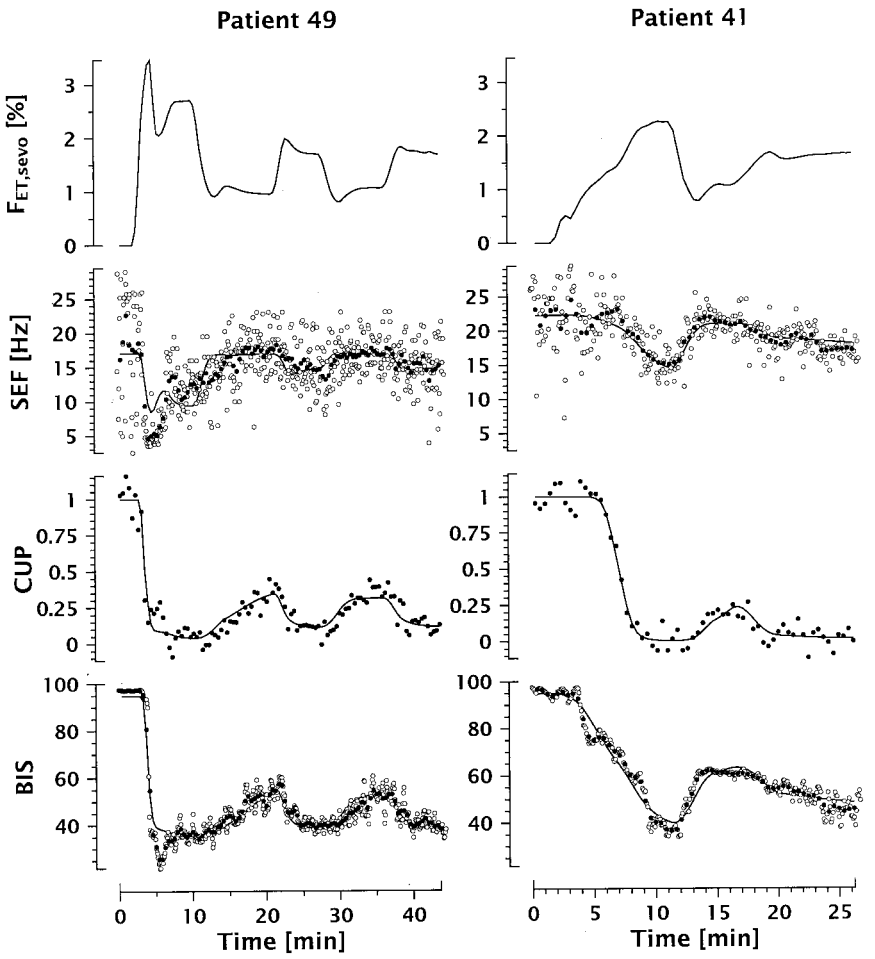

Fig. 1. Two examples of data fits at remifentanil target concentrations of 2 ng/ml (*left*) and 8 ng/ml (*right*). Panels from top to bottom: end-tidal sevoflurane concentration ($F_{ET,sevo}$), 95% spectral edge frequency (SEF), canonical univariate parameter (CUP), and Bispectral Index (BIS). For SEF and BIS, the open symbols are measured values, and the closed symbols are the averaged data points used in the data analysis. For CUP, the closed symbols are the estimated CUP values. The lines through the data are the model fits. R^2 values for patient 49: SEF 0.648, CUP 0.910, BIS 0.960; and for patient 41: SEF 0.818, CUP 0.979, BIS 0.968.

Discussion

In this study, we modeled the influence of remifentanil on the dynamics of sevoflurane using three surrogate effect measures derived from the electroencephalogram: SEF, CUP, and BIS. Overall, the changes in sevoflurane-induced electroencephalographic effects and pharmacodynamics caused by remifentanil were not marked. The principal effects of remifentanil were to decrease the mean values of $t_{1/2}k_{e0}$ (CUP and BIS) and γ (SEF and BIS), and to decrease the variability of CUP and BIS.

The SEF is derived from spectral analysis of the electroencephalogram. Spectral analysis transforms a set of measurements to a set of numbers in the frequency domain (*i.e.*, the power spectrum). The SEF is the highest frequency in the electroencephalogram, determined by the 95% percentile of the power spectral density. In contrast to the SEF, which is chosen in an *ad hoc* manner, the CUP is designed to maximize the correlation between electroencephalographic effect and drug effect-site concentration using a statistical method that searches for the best combination of powers in the frequency spectrum of the electroencephalogram while estimating the parameters of the pharmacodynamic model.[8–10] The CUP has been used previously to assess the effects of propofol, benzodiazepines, and opioids on the electroencephalogram.[8–11] The CUP correlated more accurately (in terms of the signal-to-noise ratio or R^2) and consistently with predicted electroencephalographic effect compared with the SEF. The BIS is partly based on the bispectral analysis of the electroencephalogram.[12,13] In contrast to SEF, the BIS is based on a combination of time domain, frequency domain, and second-order spectral parameters and retains information about the interdependence of frequencies. The parameter derived from this analysis is optimized using a patient database to correlate with the level of hypnosis or sedation (as defined by a sedation score) giving the BIS (see Rosow and Manberg[23] and references cited therein).The index ranges from 100 (awake) to 0 (isoelectric electroencephalogram).

Our analysis shows that R^2 values were greatest for BIS, with values approaching 1, followed by CUP and SEF (table 2). It has been suggested that a value of R^2 close to 1 indicates that the changes in electroencephalographic effect may be entirely explained by changes in anesthetic concentration at its postulated effect site.[9] Despite the fact that the CUP is designed to maximize the correlation between electroencephalographic effect and

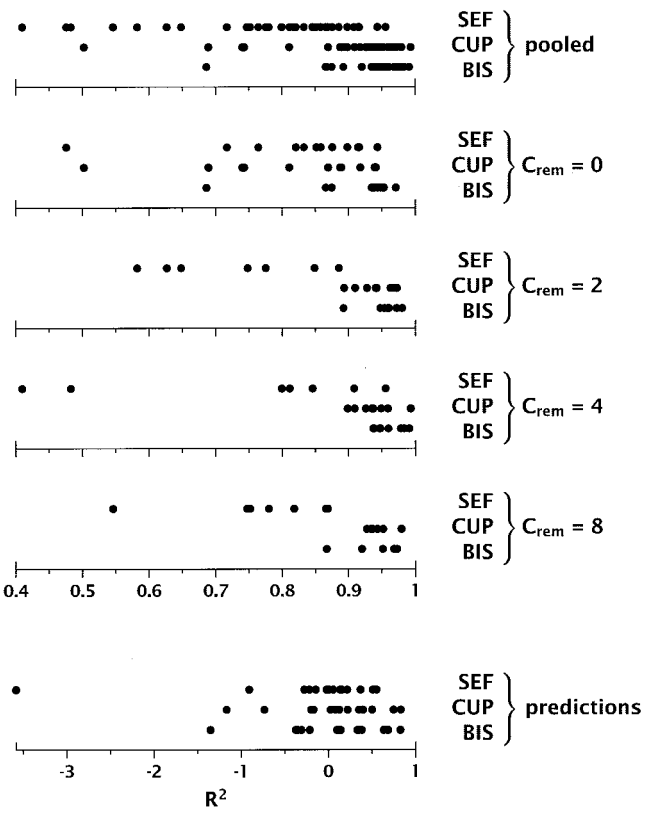

Fig. 2. R^2 values of the individual data fits for 95% spectral edge frequency (SEF), canonical univariate parameter (CUP), and Bispectral Index (BIS). From top to bottom: R^2 values of all data fits (pooled), R^2 values data fits at 0, 2, 4, and 8 ng/ml remifentanil target concentrations, and R^2 values of the predictions during surgery. Note the difference in R^2 axis for the studies and the predictions.

anesthetic effect-site concentration,[8–11] the better performance of BIS relative to CUP is not completely unexpected, taking into account the linkage of BIS to a database of anesthetized patients and close correlation of BIS to hypnotic–sedative end points of anesthesia.[23] Furthermore, there are some methodologic issues that favor greater R^2 for BIS than for CUP. The algorithm in the A1000 monitor, which calculates the BIS, does so after artifact rejection. The absence of a similar artifact rejection algorithm for CUP and SEF, despite the smoothing approach (which does reduce artifact effects on CUP), may at least partly be the cause of the lesser performance of CUP and SEF relative to BIS (see also Bruhn[24]). Taking into account all of the above, it is reasonable to assume that BIS reflects the sevoflurane concentration at the effect site more reliably than the other two parameters we investigated.

After reaching the target remifentanil concentration at the simulated effect site, we applied multiple steps in and out of end-tidal sevoflurane concentration (figs. 1 and 6). The use of "fixed-size" forcing functions to unravel the steady-state and dynamic characteristics of the anesthetic electroencephalographic relation has recently been criticized by Rampil[25] as being suboptimal compared with other input functions, such as a pseudorandom binary sequence. For the proposed PK-PD model, the estimated population parameters of the group receiving no remifentanil, we constructed *a posteriori* an optimal binary sequence by maximizing the determinant of the information matrix.[26,27] Our analysis indicated that the information gained by the optimal input function (which deviated only minimally from our step input function) is negligible relative to our approach.

We applied an exponential function (equation 3) to assess the remifentanil dependency on individual model parameters. This approach seemed adequate. The remifentanil-induced increase in SEF C_{50} seemed to be due to a reduction in SEF_{MIN} rather than to a true decrease in anesthetic potency with increasing concentrations of remifentanil (fig. 3). Theoretically, because SEF_{MIN} is not well-estimated from our data, exploration at higher end-tidal sevoflurane concentrations would be required. However, at end-tidal sevoflurane concentrations greater than 3%, burst suppression is likely to occur. Possibly, alternative parameterization of the model would result in more interpretable parameters.

The remifentanil dose range that we studied (0–9 ng/ml blood concentration) spans concentrations commonly used in clinical practice. Over this dose range, there was no effect by remifentanil on baseline parameters (SEF_{MAX} and BIS_{MAX}) and the potency of sevoflurane (C_{50}). Three previous studies, which modeled the effect of just remifentanil on CUP, SEF, or both, observed C_{50} values of 11.2, 11.7, and 14.8 ng/ml and γ values of 4.3, 2.5, and 2.8, respectively.[4,9,28] This indicates that no change in electroencephalographic parameter occurred over the dose range that we studied and hence explains the absence of effect of remifentanil on BIS_{MAX} and SEF_{MAX} in our study. The absence of an effect of remifentanil on C_{50} of sevoflurane stands in contrast with the synergistic effect of opioids and anesthetics on suppression of somatic responses (such as the minimum alveolar concentration).[7,29] Our findings are in agreement with the observation that (low-dose) opioids do not affect the awakening concentrations of inhalational anesthetics.[30,31] It is possible that different anesthesia outcome parameters (hypnosis–sedation *vs.* suppression of somatic responses) are differently affected by opioids. However, it may be that our chosen electroencephalographic parameters are not sensitive to changes in arousal level from (clinically relevant) doses of opioids and the combination of opioids and anesthetics.[32]

The hysteresis between measured sevoflurane concentration and electroencephalographic effect (expressed by parameter $t_{1/2}k_{e0}$) may be related to the following factors[6]: (1) end-expiratory gas sampling and processing; (2) the end-tidal–to–arterial sevoflurane concentration gradient; (3) cardiac output dependent delivery of sevoflurane to the brain compartment; (4) sevoflurane wash-in and wash-out into and out of the brain compart-

Table 2. R^2 Values

	SEF	CUP	BIS
Target Remifentanil Concentration			
0–8 ng/ml	0.815 (0.410–0.956)	0.933 (0.502–0.993)*	0.952 (0.686–0.991)†
0 ng/ml	0.855 (0.477–0.943)	0.840 (0.502–0.941)	0.939 (0.686–0.953)
2 ng/ml	0.648 (0.582–0.886)	0.937 (0.893–0.973)	0.960 (0.893–0.980)
4 ng/ml	0.806 (0.410–0.956)	0.936 (0.898–0.993)	0.960 (0.937–0.991)
8 ng/ml	0.780 (0.546–0.869)	0.943 (0.928–0.979)	0.968 (0.867–0.973)
Opioid Effect on R^2	$P = 0.41$	$P = 0.001$	$P = 0.08$
Prediction	0.033 (−3.583 to 0.554)	0.178 (−0.733 to 0.749)	0.240 (−1.354 to 0.827)

Values are median (range).

* $P < 0.01$ *versus* spectral edge frequency (SEF); † $P < 0.01$ *versus* SEF and canonical univariate parameter (CUP) (all statistics by Kruskal-Wallis test).

BIS = Bispectral Index.

ment (this factor depends on brain volume, brain blood flow and blood-brain partition coefficient); (5) cortical and subcortical neuronal dynamics; and (6) computation time of electroencephalographic parameter. Remifentanil may have an effect on factors 2–5. Although an effect on factors 2 and 3 results in slower sevoflurane blood–brain equilibration (and hence an increase in $t_{1/2}k_{e0}$; see Olofsen and Dahan[6] for an explanation), an increase in brain blood flow (factor 4) accelerates anesthetic blood–brain equilibration (and consequently causes a reduced $t_{1/2}k_{e0}$). An increase in brain blood flow by remifentanil may be due to an increase in arterial P_{CO_2} (*i.e.*, respiratory acidosis). As estimated from the end-tidal carbon dioxide concentration, we maintained strict normocapnia in our study. We believe that an effect of P_{CO_2} on brain blood flow and thus $t_{1/2}k_{e0}$ was of minor importance. A more important cause for the reduced $t_{1/2}k_{e0}$ may be a direct vasodilatatory effect of remifentanil on brain vessels. A recent positron-emission tomography scan study showed an increase in regional brain blood flow by low-dose remifentanil in structures known to participate in the modulation of vigilance and alertness.[33] An effect of opioids on factor 5 remains unknown. However, it may be that the opioid we used sensitized the receptors at which sevoflurane has its effect or the thalamic–cortical generators of the electroencephalogram. This then may have caused the sevoflurane-related changes in the electroencephalogram to occur more rapidly (without affecting the C_{50} of sevoflurane). This process may occur predominantly in certain electroencephalographic frequencies and thus is seen with the CUP and BIS and not with the SEF. In agreement with our observation,

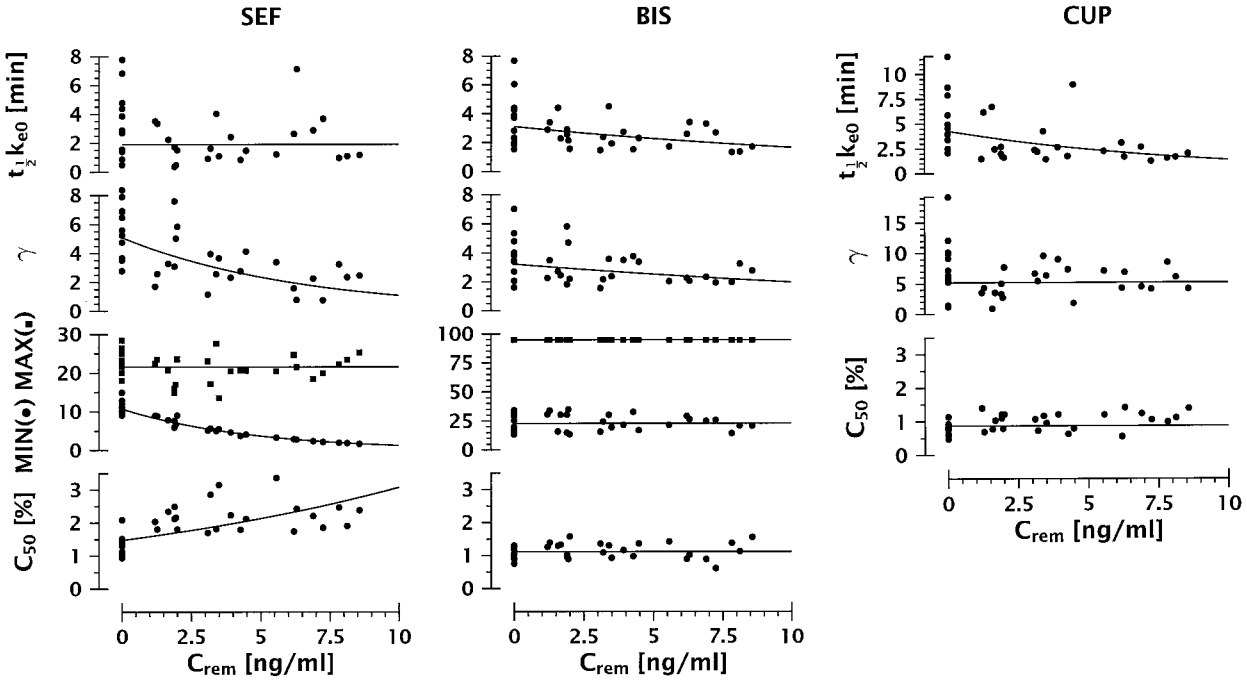

Fig. 3. Individual Bayesian parameter estimates *versus* measured remifentanil concentrations for 95% spectral edge frequency (SEF), Bispectral Index (BIS), and canonical univariate parameter (CUP). Maximum SEF (units Hz) and BIS values are represented by closed squares; minimum SEF (units Hz) and BIS values are represented by closed circles. Remifentanil dependency is demonstrated by fitting the data to equation 3.

Table 3. Model Parameter Value Estimates Describing Remifentanil Dependence for SEF, BIS, and CUP Using Equation 3*

	$t_{1/2}k_{e0}$ (min)	γ	C_{50} (ET%)	MAX	MIN	a_0	a_δ	a_θ	a_α	a_{β_1}	a_{β_2}
95% SEF†											
Θ_0	1.91	5.11	1.48	21.6	10.8						
SE	0.26	0.65	0.12	0.6	0.6						
Θ_r	—	0.154	−0.0734	—	0.211						
SE	—	0.031	0.0239	—	0.138						
%CV	76	51	28	17	18						
CUP											
Θ_0	4.31	5.22	0.88			0.22	−0.041	−0.065	−0.24	−0.093	0.15
SE	1.00	0.86	0.13			0.03	0.02	0.03	0.02	0.04	0.02
Θ_r	0.11	—	0.05			—	—	—	—	—	—
SE	0.03	—	0.02			—	—	—	—	—	—
%CV	51	61	29			14	9	13	12	20	10
BIS											
Θ_0	3.11	3.24	1.12	94.9	23.0						
SE	0.32	0.37	0.05	0.6	2.7						
Θ_r	0.0636	0.0493	—	—	—						
SE	0.0237	0.0204	—	—	—						
%CV	39	36	21	—	36						

* $\Theta = \Theta_0 \cdot e^{-\Theta_r \cdot C_{rem}}$

† Units for SEF_{MAX} and SEF_{MIN} are hertz.

SEF = spectral edge frequency; BIS = Bispectral Index; CUP = canonical univariate parameter; SE = standard error; CV = coefficient of variation.

Gentilini *et al.*[34] recently observed that alfentanil accelerates isoflurane blood–brain equilibration (as determined from BIS), which indicates that the opioid–anesthetic interaction on $t_{1/2}k_{e0}$ is a general observation applicable to all μ opioids and inhalational anesthetics with a similar mode of action. The faster anesthetic blood–brain equilibration during opioid infusion makes a faster automated or manual control of anesthetic depth possible, despite no change in hypnotic potency.

We calculated our CUP weight factors using classic electroencephalographic bands (δ, θ, α, β_1, and β_2). This approach is different from earlier calculations of CUP weight factors for opioids, midazolam, and propofol, which used 3-Hz bins.[8–11] Our lesser discriminative approach was chosen to be able to estimate intersubject variability of the weight factors. These differences in methods hamper the comparison of sevoflurane *versus* midazolam and propofol weight factors. A rough comparison (by averaging over the bins of the corresponding bands) shows qualitative differences among the weight factors of these three agents. This suggests that weight factors for sevoflurane are not generally applicable to other classes of anesthetics and sedatives with possibly different modes of action.[9] Our observation of sevoflurane-induced negative weight factors in the α and β_1

Table 4. Model Parameter Value Estimates of SEF, CUP, and BIS Derived from Equation 3 at Three Remifentanil Concentrations (C_{REM})

C_{REM} (ng/ml)	$t_{1/2}k_{e0}$ (min)	γ	MAX	MIN	C_{50} (ET%)	σ_ϵ
95% SEF*						
0	1.91	5.11	21.6	10.8	1.48	1.50
2	1.91	3.76	21.6	7.08	1.71	1.34
4	1.91	2.76	21.6	4.64	1.99	1.21
8	1.91	1.49	21.6	2.00	2.66	0.97
CUP†						
0	4.31	5.20			0.88	0.40
2	3.44	5.20			0.88	0.23
4	2.71	5.20			0.88	0.23
8	1.68	5.20			0.88	0.23
BIS						
0	3.11	3.24	94.9	23.0	1.12	4.67
2	2.74	2.94	94.9	23.0	1.12	4.21
4	2.41	2.66	94.9	23.0	1.12	3.78
8	1.87	2.18	94.9	23.0	1.12	3.07

* Units for SEF_{MAX}, SEF_{MIN}, and σ_ϵ are hertz. † Because weight factors were independent of remifentanil concentration, they are not listed.

SEF = spectral edge frequency; CUP = canonical univariate parameter; BIS = Bispectral Index.

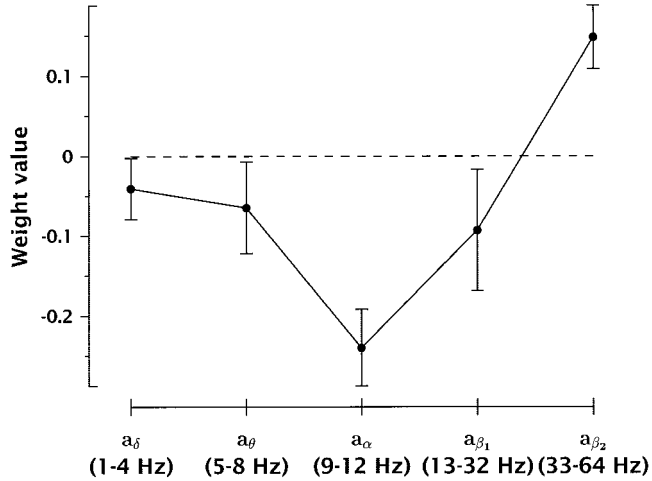

Fig. 4. Values of the sevoflurane weight factors of the canonical univariate parameter for each of the given frequency bands. The values are the population values ± standard error. The sevoflurane weight factors are independent of the remifentanil concentration.

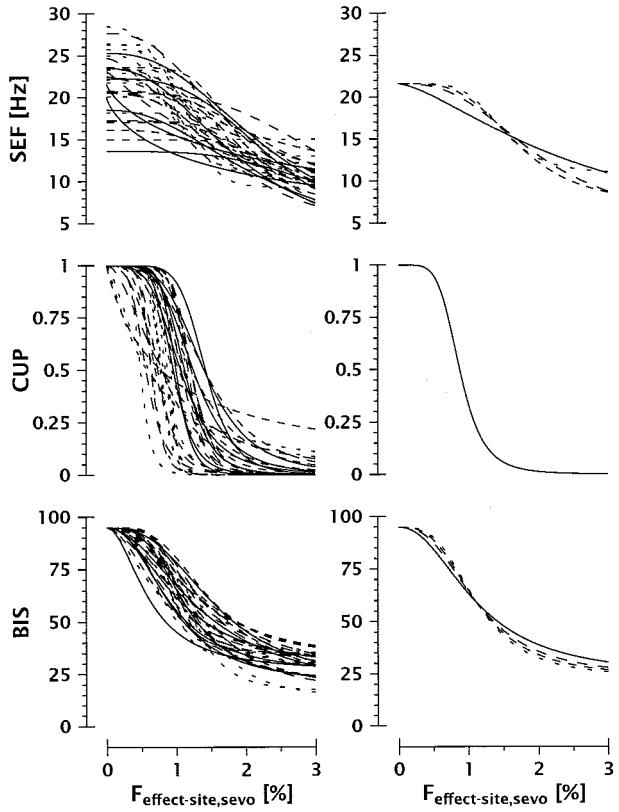

Fig. 5. The individual (*left*) and population (*right*) effect-site sevoflurane concentration–95% spectral edge frequency (SEF) (*top*), –Bispectral Index (BIS) (*middle*), and –canonical univariate parameter (CUP) (*bottom*) relations. The different target remifentanil concentrations are represented by different curves: - - - 0 ng/ml; – – – 2 ng/ml; — — — 4 ng/ml; — 8 ng/ml.

bands and positive weight factors in the β_2 band, information equivalent to the β ratio in the BIS (= log ($Power_{30\text{-}47\ Hz}$)/($Power_{11\text{-}20\ Hz}$)),[13] indicates that the CUP is well able to distinguish wakefulness (high CUP values) from unconsciousness (low CUP values) and *vice versa*, rather than detect subtle changes in the arousal level. A preliminary report from Rehberg *et al.*[35] about the comparison of the CUP weight factors of three volatile anesthetics shows roughly similar weight factors for sevoflurane compared with those observed in our study. However, their data indicate a weight factor with a positive value (0.2–0.3) over the 0.5- to 3-Hz range, whereas we observed a weight factor with a negative value (−0.04) over the 1- to 4-Hz range. We have no explanation for this small difference in study outcomes apart from evident differences in experimental conditions, such as propofol induction in the study of Rehberg *et al.*[35] or the incomplete removal of eye blinks in the awake state in our study.

§ $R^2 = 1$ indicates a perfect model fit; $R^2 = 0$ indicates that the model fit is not better than the mean of the data; $R^2 < 0$ indicates a bias on top of the model fit not better than the mean of the data.

Prediction of the electroencephalographic effect during surgery using the Bayesian model estimates obtained during the study period was poor, with no difference between SEF, CUP, and BIS. R^2 values were generally reduced by approximately 50% during surgery. Moreover, the range of R^2 values included negative numbers.§ The major cause of the poor predictive value of our model parameters during surgery is that although the model parameters were obtained in a relatively quiet period before surgery, they were put to the test in a period with variable noxious stimulation. Evidently, the fixed remifentanil concentrations were insufficient to

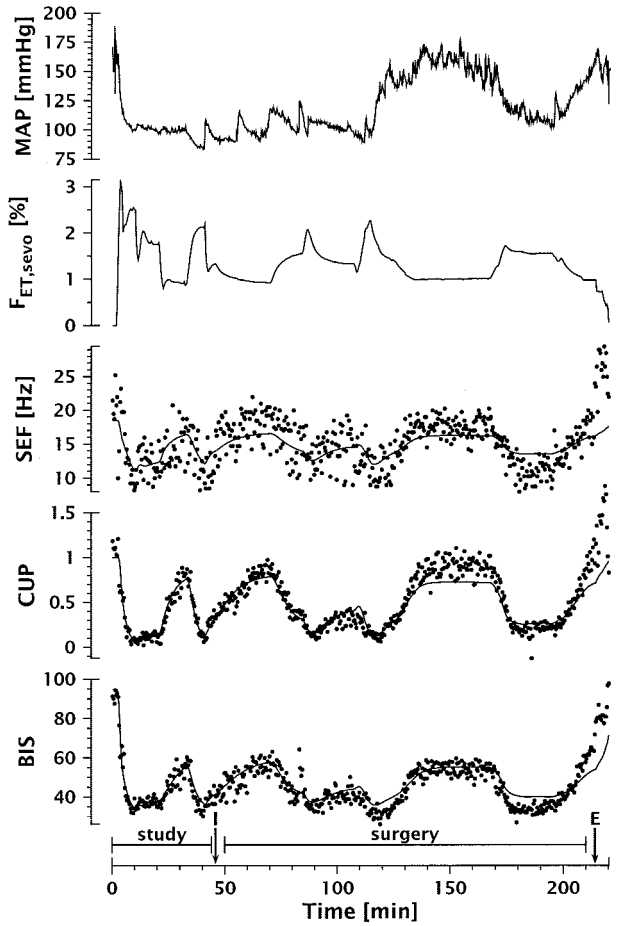

Fig. 6. The effect of sevoflurane (*second panel*) on electroencephalogram-derived parameters (95% spectral edge frequency [SEF], canonical univariate parameter [CUP], and Bispectral Index [BIS]) during a 40-min study period and during abdominal gynecologic surgery, lasting 150 min, in a 45-yr-old patient. During the study period and surgery, the remifentanil target concentration was kept constant at 4 ng/ml. At t = 46 min (I), the patient underwent intubation (after muscle relaxant was administered); at t = 50 min, surgery started; at t = 210 min, surgery ended; and at t = 214 min, the patient underwent extubation (E). The line through the electroencephalographic data is the model prediction derived from the Bayesian parameter estimates obtained during the study period. Prediction of the changes in electroencephalographic effect during surgery were good for CUP and BIS (R^2 0.749 and 0.688 for CUP and BIS, respectively) but poor for SEF (R^2 0.371). On top, the mean arterial pressure (MAP) is shown.

dampen the central response to all noxious stimuli occurring during surgery (an example is given in fig. 6). Recently, Röpcke *et al.*[36] demonstrated in the absence of opioid infusion a rightward shift of the desflurane–BIS and SEF relation due to surgical stimulation, indicating that noxious stimulation affects the level of cortical electrical activity (loss of δ activity and increased α and β activity).[37,38] Our findings and those of Röpcke *et al.*[36] suggest that anesthetic concentration–dependent prediction of anesthetic depth during surgery may only be possible when adequate analgesic treatment prevents transient noxious stimulation and excitatory arousal reactions (as observed in the electroencephalogram) or measures of noxious stimulation and stress (*e.g.*, derived from cardiovascular parameters) are taken into account. An improved prediction of anesthetic electroencephalographic effect during surgery, for example, for automated control of anesthetic depth, requires individual assessment of the anesthetic concentration–effect relation and possibly a recursive parameter estimation procedure (*i.e.*, updating parameter estimates as new data become available). Taking into account our findings from the study period, the BIS seems to be the best of the three electroencephalographic parameters we studied for steering anesthetic–hypnotic depth during surgery.

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