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Correlation of Approximate Entropy, Bispectral Index, and Spectral Edge Frequency 95 (SEF95) with Clinical Signs of "Anesthetic Depth" during Coadministration of Propofol and Remifentanil

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Background: **Several studies relating electroencephalogram parameter values to clinical endpoints using a single (mostly hypnotic) drug at relatively low levels of central nervous system depression (sedation) have been published. However, the usefulness of a parameter derived from the electroencephalogram for clinical anesthesia largely depends on its ability to predict the response to stimuli of different intensity or painfulness under a combination of a hypnotic and an (opioid) analgesic. This study was designed to evaluate the predictive performance of spectral edge frequency 95 (SEF95), BIS, and approximate entropy for the response to increasingly intense stimuli under different concentrations of both propofol and remifentanil in the therapeutic range.**

Methods: **Ten healthy male and ten healthy female volunteers were studied during coadministration of propofol and remifentanil. After having maintained a specific target concentration for 10 min, the depth of sedation–anesthesia was assessed using the responsiveness component of the Observer's Assessment of Alertness/Sedation (OAA/S) rating scale, which was modified by adding insertion of a laryngeal mask and laryngoscopy. The electroencephalogram derived parameters approximate entropy, bispectral index, and SEF95 were recorded just before sedation level was assessed.**

Results: **The prediction probability values for approximate entropy were slightly, but not significantly, better than those for bispectral index, SEF95, and the combination of drug concentrations. A much lower prediction ability was observed for tolerance of airway manipulation than for hypnotic endpoints.**

Conclusion: **Approximate entropy revealed informations on hypnotic and analgesic endpoints using coadministration of propofol and remifentanil comparable to bispectral index, SEF95, and the combination of drug concentrations.**

DESPITE considerable efforts, "depth of anesthesia" is still poorly defined and thus difficult to measure. The anesthetic state consists of at least two components: hypnosis and analgesia. Immobility in response to noxious stimulation is often used as a surrogate for these. To circumvent this vexing problem, anesthesiologists have turned toward more easily quantifiable electroencephalographic changes as a measure of anesthetic depth.[1] Electroencephalographic changes correlate closely with drug concentrations at the effect site, but predominantly describe the hypnotic effect of anesthetic drugs. Several different processing methods have been applied to the "raw" electroencephalogram signal: Spectral edge frequency 95 (SEF95)[2] is directly derived from the power spectrum having undergone Fourier transformation to decompose the electroencephalographic signal into its component sine waves. Bispectral analysis is also based on Fourier spectral analysis, but incorporates the degree of phase coupling between the component waves. The bispectral index (BIS) integrates several disparate descriptors of the electroencephalogram into a univariate variable.[3] The combination of features has been optimized using a large database, including assessment of sedation–hypnotic endpoints.[4] Approximate entropy quantifies the regularity of data time series,[5] *i.e.*, the predictability of the subsequent amplitude value based on the knowledge of the previous amplitude values. Approximate entropy has been shown to correlate strongly with desflurane effect compartment concentrations during desflurane mono-anesthesia[6] and to correlate with the burst suppression ratio after the occurrence of burst suppression patterns at high isoflurane concentrations.[7]

Studies relating electroencephalographic parameter values to clinical endpoints using a single (mostly hypnotic) drug at the level of sedation have been published. However, the clinical usefulness of electroencephalographic derived parameters largely depends on their ability to predict the response to different stimuli in the presence of both a hypnotic and an (opioid) analgesic.[8,9] This study was designed to evaluate the predictive performance of SEF95, BIS, and approximate entropy regarding the response to increasingly intense stimuli in the presence of therapeutic combinations of propofol and remifentanil.

Materials and Methods

Subjects

The study was approved by the Stanford University Institutional Review Board. Written informed consent was obtained from each subject. Ten healthy male and ten healthy female volunteers, (aged: 33.5 yr [20–43 yr],

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Table 1. Responsiveness Scores of a Modified Observer's Assessment of Alertness/Sedation Scale (OAA/S)

Responsiveness	Score
Responds to name spoken in a soft voice	5
Responds only after name is called loudly and/or repeatedly	4
Responds only after shaking and shouting his or her name	3
Responds only after insertion of a laryngeal mask airway	2
Responds only after laryngoscopy	1
Does not respond to laryngoscopy	0

weight: 69.3 kg [50–120 kg], median and range, respectively) were studied. All volunteers received a physical examination, laboratory tests (complete blood cell count, blood chemistries [SMA 20]), and an electrocardiogram.

Study Design

The study was performed as a randomized, prospective, open label study. An electrocardiogram, a pulse oximeter, and a noninvasive blood pressure monitor were attached to volunteers, after they arrived at the operating room. Thereafter, two intravenous cannulae for drug and fluid administration were placed in a forearm vein on each arm. A 20-gauge plastic cannula was inserted into the radial artery of the nondominant hand. Ventilation and P_{ETCO_2} were measured and recorded continuously with an anesthesia monitor (Datex, AS3, Helsinki, Finland). Drugs were administered *via* target-controlled infusion (TCI) with a Harvard infusion pump (Harvard Clinical Technology, Inc., South Natick, MA) driven by STANPUMP (written by, and freely available from Steven L. Shafer, M.D., Department of Anesthesia, Stanford University, Stanford, CA) running on a commercially available laptop computer. The propofol pharmacokinetic parameters were obtained from Schnider *et al.*[10] (median subject). The remifentanil pharmacokinetic parameters were the covariate adjusted set reported by Minto *et al.*[11] The administration schedule was optimized for a single drug pharmacodynamic study (respiratory depression) followed by a pharmacodynamic interaction study (central nervous system depression).

Initially, the volunteers received either propofol or remifentanil alone in a stepwise ascending fashion until their P_{ETCO_2} exceeded 65 mmHg, or apnea periods of more than 60 s occurred. Thereafter, the respective drug concentration in the effect compartment was allowed to fall passively to 1 μg/ml of propofol or 1 ng/ml of remifentanil. As soon as this concentration was maintained for at least 15 min according to the TCI predictions, the volunteer was exposed to a series of stimuli with increasing intensity, specifically: calling his or her name in a soft voice, shouting his or her name, shaking the volunteer and shouting his or her name, insertion of a laryngeal mask airway, laryngoscopy, as shown in table 1. The series was terminated as soon as a response was elicited. Responses were defined as verbal (*e.g.*, "I'm awake"), eye opening, increase in systolic blood pressure greater than 15 mmHg above baseline value, increase in heart rate of 15%, movement, coughing, biting, grimacing, lacrimation, flushing, or sweating. After eliciting a response, the administration of the respective second drug was started. The target concentration for this drug was kept constant throughout the pharmacodynamic interaction study. Thereafter, the concentration of the first drug was stepwise increased again until the volunteer was able to undergo the entire stimulus series, including laryngoscopy, without coughing or movement. The number of steps during stepwise increase and the respective peak concentrations were therefore determined by the sensitivity of the respective individual to the respiratory and central nervous system depressant effects of the drugs, whereas the order of administration and the constant target concentration used for the second drug was allocated to each individual before the experiment using a randomization list. Tables 2 and 3 display the peak concentrations achieved and the allocated constant concentrations for the second drug.

Table 2. Combinations of Propofol and Remifentanil (Changing Propofol (P) Concentrations; Constant Remifentanil (R) Concentrations)

Individual	Peak Concentration P for P + R [μg/ml]	R Concentration [ng/ml]
3	12	0
11	12	0
6	6	1
7	4	2
14	3	2
15	3	2
12	3	3
13	2	3
5	4	4
18	3	4

With the exception of two volunteers (3,11; propofol only), every volunteer received a stepwise increased–decreased infusion of propofol in the presence of a constant concentration of remifentanil. The propofol concentration indicated refers to the highest concentration achieved during the CNS depression–interaction phase (changing concentrations of the first drug and constant concentrations of the respective second drug). The concentration ranges were determined by pharmacodynamic considerations (see Methods). The remifentanil target for one volunteer (15) was erroneously set to 2 ng/ml instead of 1 ng/ml.

After having maintained each target concentration in the central nervous system interaction part for 10 min, the depth of sedation and anesthesia was assessed using the responsiveness component of the Observer's Assessment of Alertness/Sedation (OAA/S) rating scale,[12] which was modified by adding the increasingly intense stimuli described previously. These stimuli were applied at 15-s intervals. All assessments of sedation levels were performed by one investigator (SLS) to minimize interobserver variability. The electroencephalogram parameters were recorded just before sedation level was assessed.

Electroencephalographic Monitoring

Electroencephalographic electrodes (ZipPrep, Aspect Medical Systems, Natick, MA) were placed on the scalp in the following configuration: bipolar frontomastoid montage (Fp1-A1 and Fp2-A2: international 10–20 system of electrode placement). The impedance of each electrode was less than 2kOhm. The bispectral index (version 3.22) and SEF95 (the 95th percentile of the power distribution) were recorded continuously using an Aspect A1000 electroencephalogram monitor (Aspect Medical Systems, Natick, MA). Serial output files consisting of processed electroencephalographic parameters were collected on a personal computer. The raw electroencephalogram was digitized at 128 Hz, 12-bit resolution, and stored on a computer hard disk for subsequent processing. The electroencephalogram approximate entropy was calculated off-line from 2^{10} data points (= 8 s epochs): Approximate entropy quantifies the predictability of subsequent amplitude values of the electroencephalogram, based on the knowledge of the previous amplitude values. The absolute value of the approximate entropy is influenced by three parameters: the length of the epoch (*N*), the number of previous values used for the prediction of the subsequent value (*m*), and a filtering level (*r*). In this study *N* was fixed at 1,024, thus one value of approximate entropy could be calculated for each 8 s epoch of the electroencephalogram. The noise filter *r* was defined as relative fraction of the SD of the 1,024 amplitude values. We used the parameter set $m = 2$ and $r = 0.2 \times$ SD, which was found to exert the best performance for electroencephalogram approximate entropy in a preliminary study.[6]

A step-by-step procedure with an example,[6] a VBasic program[6] and a Fortran program[5] to calculate approximate entropy have been published.

Before calculation of BIS and SEF95 the Aspect monitor applies an automatic artifact detection and removal algorithm to the raw electroencephalogram signals. Therefore, we visually screened the raw electroencephalogram for possible artifacts and excluded artifact-loaded epochs before calculating approximate entropy. Assuming that most artifacts will be generated by eye, lid, and body movements in the awake state, we only performed the visual screening for artifacts in this state, using the non–artifact-screened approximate entropy values in all other states.

The bispectral index, SEF95, and approximate entropy values were calculated by averaging the 60-s interval immediately before assessment. To minimize artifacts, the volunteers were instructed not to open their eyes, talk, or move during the electroencephalogram recording before the sedation level was assessed.

Analysis of Propofol

0.05 ml of 1 M sodium hydroxide solution and 600 μl of a 1:1 mixture of ethyl acetate–heptane containing 150 ng of the internal standard, thymol were added to 0.2 ml of the plasma sample containing propofol and agitated by a vortex shaker for 30 s. The emulsion was centrifuged for 3 min at 3,000 rotations/min (1,400 g) and the upper liquid phase transferred to an autosample vial for analysis. Injections of 2 μl were made in splitless mode with a constant flow of 3 psi of the helium carrier gas at 50°C on a J & W 30 m × 0.32 mm DB-5 capillary column with a 0.25 μm film of phenylmethyl silicone. The gas chromatograph, a Hewlett-Packard Model 5890 II (Hewlett Packard, Palo Alto, CA) was equipped with a 5972A mass selective detector operating in the electron impact mode (70 eV) with selected ion monitoring. The detector monitored the 163.1 m/z fragments for propofol and 135.1 m/z fragment for thymol with a dwell time of 100 ms. The data were processed with HP1034C mass spectrometer control software (Hewlett Packard, Palo Alto, CA).

The interday coefficients of variation (bias) were 10.4% (14.0%) for quality control samples containing 0.1 μg/ml propofol and 4.0% (10.1%) for quality control samples containing 10 μg/ml propofol. The limit of quantitation was 0.1 μg/ml, the assay was linear from 0.1–15 μg/ml propofol.

Analysis of Remifentanil

Blood (2 ml) containing remifentanil and citric acid was spiked with 5 ng of fentanyl in 50 μl acetonitrile (internal standard) and 4 ml of acetonitrile as extraction solvent. The mixture was vortexed and equilibrated at 25°C for at least 30 min. 200 μl of 10% zinc sulfate was added, the tubes were vortexed and centrifuged at 1,650*g* for 15 min. The supernatant was transferred into screw cap culture tubes containing 2 ml of 0.1 M sodium acetate, pH 6.0. Bond Elut Certify SPEs were placed on a Varian Vac Elut vacuum manifold and preconditioned with 2 ml of isopropanol and 2 ml of 0.1 M sodium acetate, pH 6.0. The buffered supernatant (3 ml) was then loaded onto the preconditioned cartridge. The cartridge was rinsed with 1 ml of 1 M acetic acid, dried under vacuum for at least 5 min, rinsed again with 6 ml of isopropanol and dried under full vacuum for at least 5 min. The extracts were then eluted from the cartridge with 4 ml of freshly prepared methylene chloride–isopropanol–sodium hydroxide (78:20:2 v/v/v, prepared with sonication) by gravity filtration. The eluate was evaporated to dryness under nitrogen using a TurboVap LV evaporator (Zymark, Hopkinton, MA). The residues were redissolved in 50 μl ethyl acetate, briefly vortexed and loaded into autosampler vials. Samples were analyzed by GC-MSD (Hewlett-Packard Model 5890 II with a 5972A mass selective detector) (Hewlett Packard, Palo Alto, CA). 5 μl aliquots were injected on a J & W 30 m × 0.32 mm DB-5 capillary column with a 0.25 μM film of phenylmethyl silicone. The MSD was operated in the electron impact mode (70 eV) with selected ion monitoring. The detector monitored the 227.1 m/z frag-

ments for remifentanil and 245.1 m/z fragment for fentanyl with a dwell time of 100 ms. The data were processed with proprietary mass spectrometer control software (HP1034C). The interday coefficients of variation (bias) were 8.5% (5.4%) for quality control samples containing 5 ng/ml remifentanil and 9.3%% (2.4%) for quality control samples containing 20 ng/ml remifentanil. The limit of quantitation was 0.25 ng/ml, the assay was linear from 0.25 ng/ml to 30 ng/ml.

Analysis of Drug Interaction

The drug interaction between remifentanil and propofol was modeled according to Minto *et al.*[13]: First, the drug concentrations were normalized to their respective potencies (C_{50} values):

$$U_{remi} = \frac{C_{remi}}{C_{50,\,remi}}$$

$$U_{prop} = \frac{C_{prop}}{C_{50,\,prop}}$$

where c_{remi} and c_{prop} are the respective concentrations of remifentanil and propofol. Because BIS, approximate entropy, and SEF95 approach 0 at infinite drug concentrations, a fractional E_{max} model was used for the description of the concentration response relationship.

$$E = E_0{}^*\left(1 - \frac{\frac{c}{C_{50}}}{1 + \frac{c}{C_{50}}}\right)$$

Any given (fixed) ratio of the two drugs was considered to behave as a "new" drug with its own (sigmoidal) concentration-response relation.

For an additive interaction, the "effective" concentration is the sum of the individual concentrations normalized to the C_{50}'s of the respective drugs (compare "MAC additivity"). In our case:

$$E = E_0{}^*\left(1 - \frac{U_{prop} + U_{remi}}{1 + U_{prop} + U_{remi}}\right)$$

The "normalized drug concentration" is $U_{remi} + U_{prop}$.

Deviation from a purely additive interaction is modeled by changing the potency of the drug mixture depending on the ratio of the interacting drugs:

$$\theta = U_{prop}/(U_{remi} + U_{prop})$$

By definition, θ ranges from 0 (remifentanil only) to 1 (propofol only). Thus, the concentration–response relationship for any ratio of the two drugs regardless of the type of interaction can be described as:

$$E = E_0{}^*\left(1 - \frac{((U_{remi} + U_{prop})/U_{50(\theta)})^{\gamma}}{1 + ((U_{remi} + U_{prop})/U_{50(\theta)})^{\gamma}}\right)$$

where θ is the ratio of the two drugs, the normalized drug concentration is $U_{remi}+U_{prop}$, γ is the steepness of the concentration-response relation, $U_{50}(\theta)$ is the number of units (U) associated with 50% of maximum effect at ratio θ. $U_{50}(\theta)$ equals 1, if the two drugs are additive, $U_{50}(\theta)$ is less than 1, if the two drugs are synergistic, and $U_{50}(\theta)$ is greater than 1, if the two drugs are infraaditive.

According to Minto *et al.*[13] the equation for potency as a function of θ can be simplified to a quadratic polynomial:

$$U_{50}(\theta) = 1 - \beta_{2,U50}\theta + \beta_{2,U50}\theta^2$$

The parameters γ, $\beta_{2,U50}$, $C_{50,remi}$ and $C_{50,prop}$ were optimized with the Solver tool of Excel (Microsoft, Redmond, WA) maximizing the R^2 value for the correlation between observed OAA/S score and drug effect E.

Statistical Analysis

The efficacy of electroencephalogram parameters to predict depth of sedation and anesthesia was evaluated using prediction probability (P_K), which compares the performance of indicators having different units of measurement. The mathematical basis of P_K was described by Smith *et al.*[14] A P_K value of 1 means that the values of the predicting variable (*e.g.*, anesthetic depth indicator) always correctly predict the value of the variable to be predicted (*e.g.*, true observed anesthetic depth). A P_K value of 0.5 means that the values of the indicator predict no better than a 50–50 chance. For the modified OAA/S score, a P_K value was computed for all sedation assessments combined. Similarly, P_K values for consciousness (modified OAA/S score 5–3) *versus* unconsciousness (modified OAA/S score 2–0) and response to noxious stimulus assessments after loss of consciousness (*i.e.*, modified OAA/S score 2 *vs.* 1 *vs.* 0) were determined.

The jackknife method was used to compute the SE of the estimate, based on the assumption that all assessments were independent. A paired-data jackknife analysis[14,15] was used to evaluate whether the P_K for one variable was different from another one. Bonferroni correction was used to the paired-data jackknife analysis to correct for multiple comparisons. Significance level was set at 0.01.

Results

With increasing sedation, the BIS values decreased from 90 (median) at an OAA/S of 5, to 50 at an OAA/S of 0. The SEF95 decreased from 24 to 12 and the approximate entropy decreased from 1.59 to 0.81 (fig. 1).

The interaction model of Minto *et al.*[13] adequately describes the interaction of propofol and remifentanil concerning the modified OAA/S scale. The parameter of the interaction model are shown in table 4. The values for U_{50} (0.5) of 0.64 for the target concentrations respec-

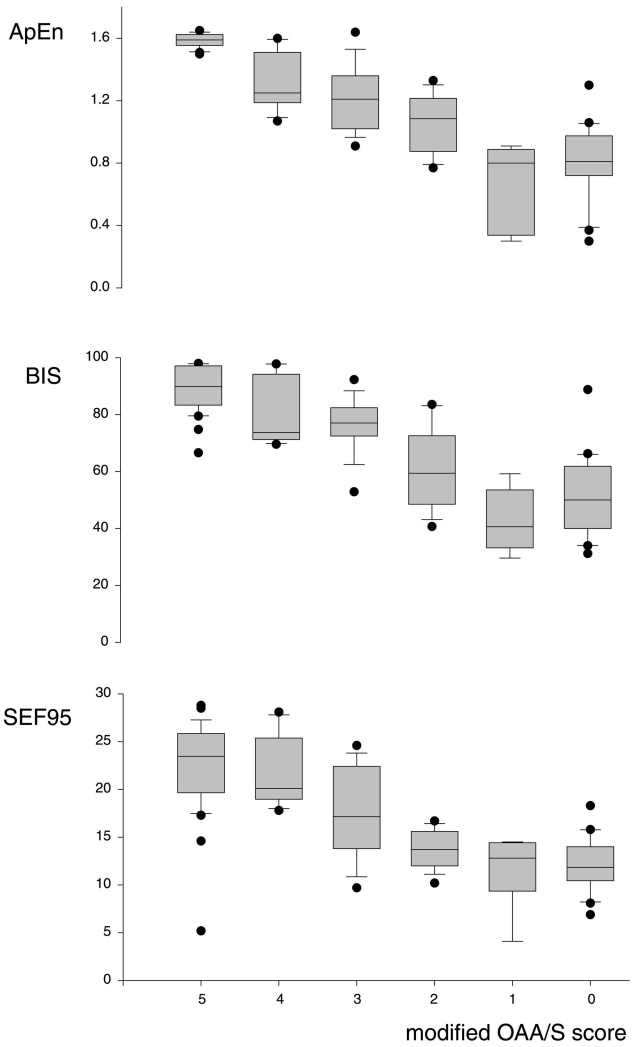

Fig. 1. The median, 10th, 25th, 75th, and 90th percentiles of approximate entropy (ApEn), bispectral index (BIS) and spectral edge frequency 95 (SEF95) related to the modified OAA/S scores are plotted as vertical boxes with error bars.

tively 0.74 for the measured concentrations indicate that the interaction between propofol and remifentanil is synergistic for this endpoint.

The ability of the indicators to predict the modified OAA/S score, consciousness *versus* unconsciousness, and response to increasingly intense stimulus assessments (insertion of laryngeal mask or laryngoscopy) after loss of consciousness as presented by the P_K values is shown in table 5. The prediction probability values for approximate entropy were slightly better than those for bispectral index, SEF95, and the combination of drug concentrations. But none of the differences reached statistical significance. A much lower prediction ability was observed for analgetic endpoints than for hypnotic endpoints.

Discussion

We explored the ability of different electroencephalogram parameters, the measured drug concentrations, and the predicted drug concentrations to predict the response to stimuli of increasing intensity during concomitant administration of propofol and remifentanil. All predictors performed well for the overall assessments ($P_K > 0.83$) and for predicting the hypnotic endpoint consciousness *versus* unconsciousness ($P_K > 0.92$) but less for predicting analgesic endpoints. There was a tendency for approximate entropy to marginally outperform the other indicators.

Approximate entropy was derived from the Kolmogorov-Sinai entropy and quantifies the regularity of data time series.[5] Compared to the multiparameter index bispectral index, which requires Fourier transformation and third order statistics,[1] the algorithm to obtain approximate entropy is simple and straightforward. It is therefore surprising that approximate entropy is at least as useful as the BIS value for prediction of clinical response. Approximate entropy has already been shown to correlate strongly with desflurane effect compartment concentrations[6] and with burst suppression ratio during high isoflurane concentrations.[7] In addition approximate entropy baseline values have been reported to be more artifact resistant and show less intra- and interindividual variations than spectral parameters of the electroencephalogram.[16]

Table 3. Changing Remifentanil (R) Concentrations; Constant Propofol (P) Concentrations

Individual	Peak Concentration R for R + P [ng/ml]	P Concentration [μg/ml]
1	24	0
2	40	0
16	3	1
17	24	1
8	4	2
20	3	2
9	3	3
19	5	3
4	1	4
10	2	4

With the exception of two volunteers (1,2; remifentanil only), every volunteer received a stepwise increased–decreased infusion of remifentanil in the presence of a constant concentration of propofol. The remifentanil concentration indicated refers to the highest concentration achieved during the CNS depression–interaction phase (changing concentrations of the first drug and constant concentrations of the respective second drug). The concentration ranges were determined by pharmacodynamic considerations (see Methods).

Table 4. Parameter Describing the Interaction Model[13] for Remifentanil and Propofol

	Target Drug Concentrations	Measured Drug Concentrations
γ	23.1	12.5
U_{50} (0.5)	0.64	0.74
$C_{50,remi}$ [μg/ml]	2.3	1.64
$C_{50,prop}$ [ng/ml]	25.7	18.6

γ = Steepness factor determining the slope of the concentration–response relationship; U_{50} (0.5) = potency of the drug combination at ratio 0.5 relative to the normalized potency of each drug by itself. Values less than 1 indicate synergy; C_{50} = concentration associated with 50% of the maximum effect.

Table 5. Prediction Probability Scores, Mean (SE)

	P_κ for mod. OAA/S Score	P_κ for (un)consciousness	P_κ for Response to Noxious Stimuli
Approximate entropy	0.89 (0.01)	0.95 (0.01)	0.70 (0.05)
Bispectral index (BIS)	0.85 (0.02)	0.94 (0.02)	0.62 (0.05)
Spectral edge frequency 95 (SEF95)	0.83 (0.02)	0.92 (0.02)	0.63 (0.05)
Target drug concentrations	0.86 (0.02)	0.92 (0.02)	0.71 (0.04)
Measured drug concentrations	0.86 (0.02)	0.93 (0.02)	0.60 (0.05)

P_κ = prediction probability.

To the best of our knowledge only one research group studied the correlation of approximate entropy with clinical endpoints.[17] Unfortunately these results have been questioned due to the use of a nonoptimal algorithm and problems with the study design.[18]

Regarding the prediction of response to "wakeup" stimuli and airway manipulation, we found a higher prediction probability for approximate entropy than for SEF95. We have also found that approximate entropy is essentially equivalent to BIS as predictor of hypnosis and response to airway management. This qualifies approximate entropy as a promising candidate for a future on-line electroencephalogram monitor, with the advantage of a well-defined, published, and nonproprietary algorithm.

Our study differs in two ways from previous studies correlating the OAA/S score with electroencephalogram parameter values. First, we modified the OAA/S score by introducing "airway manipulation" endpoints. In our opinion this more closely reflects daily clinical practice, where 'anesthetic depth' is a fluent continuum from increasing sedation over loss of consciousness to nonresponsiveness to increasingly intense and/or painful stimuli. As expected, the predictive performance of electroencephalogram derived parameters for response to airway manipulation is much lower than for hypnosis, a problem that most likely cannot be solved by a more sophisticated analysis of the electroencephalogram since the neural substrate of the movement response was reported to differ from the cortical generators of the electroencephalogram.[19,20]

Second, we investigated the coadministration of an opioid with a hypnotic drug at variable concentrations. This approach equals the clinical practice of anesthesia, which cannot be said about "single drug studies." However, since the pharmacodynamic profiles of opioids and propofol differ, lower prediction probabilities for the combination than for each single drug using the identical experimental protocol are likely.

However, the predication probabilities are in good concordance with previously reported prediction probabilities from single drug studies.[4,21,22] This underlines the usefulness of electroencephalogram monitoring in daily clinical practice with varying proportions of hypnotic and opioid, which even occur during the course of a single anesthetic (many anesthesiologists aim for initially high opioid and relatively low hypnotic concentrations at the beginning of anesthesia and shift toward low opioid and relatively high hypnotic concentrations when nearing extubation).

The P_K value for the combined drug concentrations differed only slightly from the values for the electroencephalogram-derived parameters. Since predicted concentrations were equally useful, one might argue that the processed electroencephalogram adds little knowledge if the drugs are administered by a TCI device based on a "reasonable" pharmacokinetic parameter set. This assumption disregards the homogeneity of the investigated population (we only studied young healthy volunteers) and the close resemblance to the population from which the pharmacokinetic parameter sets were obtained. It must be kept in mind that pharmacokinetic (and pharmacodynamic) studies at the extremes of age or of high-risk patients are notoriously difficult to find and that these patients very likely display a higher interindividual variability with regard to both pharmacokinetics and pharmacodynamics. This would necessarily translate into lower prediction probability values, even if suitable parameter sets were available. In addition, the parameters of the interaction model were optimized for this specific data set resulting in high P_K values. The P_K values may be lower for the same parameters of the interaction model applied to a different data set.

In conclusion, approximate entropy, BIS, and SEF95, as well as measured and predicted drug concentrations yielded good prediction probabilities with regard to hypnotic drugs, but only marginally acceptable ones with regard to airway manipulation during coadministration of propofol and remifentanil. The prediction probability for APE was slightly, but not significantly, better than that of bispectral index, SEF95, and the combination of drug concentrations. Although drug concentrations performed as well as electroencephalogram parameters in healthy volunteers, further investigations in more diverse groups are necessary to corroborate this finding in the clinical setting.

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