

# A Response Surface Model Approach for Continuous Measures of Hypnotic and Analgesic Effect during Sevoflurane–Remifentanil Interaction

## Quantifying the Pharmacodynamic Shift Evoked by Stimulation

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### ABSTRACT

**Background:** The authors studied the interaction between sevoflurane and remifentanil on bispectral index (BIS), state entropy (SE), response entropy (RE), Composite Variability Index, and Surgical Pleth Index, by using a response surface methodology. The authors also studied the influence of stimulation on this interaction.

**Methods:** Forty patients received combined concentrations of remifentanil (0 to 12 ng/ml) and sevoflurane (0.5 to 3.5 vol%) according to a crisscross design (160 concentration pairs). During pseudo–steady-state anesthesia, the pharmacodynamic measures were obtained before and after a series of noxious and nonnoxious stimulations. For the “prestimulation” and “poststimulation” BIS, SE, RE, Composite Variability Index, and Surgical Pleth Index, interaction models were applied to find the best fit, by using NONMEM 7.2.0. (Icon Development Solutions, Hanover, MD).

**Results:** The authors found an additive interaction between sevoflurane and remifentanil on BIS, SE, and RE. For Composite Variability Index, a moderate synergism was found. The comparison of pre- and poststimulation data revealed a shift of  $C50_{SEVO}$  for BIS, SE, and RE, with a consistent increase of 0.3 vol%. The Surgical Pleth Index data did not result in plausible parameter estimates, neither before nor after stimulation.

**Conclusions:** By combining pre- and poststimulation data, interaction models for BIS, SE, and RE demonstrate a consistent influence of “stimulation” on the pharmacodynamic relationship between sevoflurane and remifentanil. Significant population variability exists for Composite Variability Index and Surgical Pleth Index. (**ANESTHESIOLOGY 2014; 120:1390-9**)

TWO important components of general anesthesia are hypnosis and analgesia: The hypnotic component may be defined as probability of tolerance to a nonnoxious stimulus (*e.g.*, name calling or shake and shout), whereas the analgesic component (also called: the balance between nociception and antinociception) may be considered as the probability of tolerance to a noxious stimulus.<sup>1</sup> Tolerance means “the absence of a response” being either a somatic response (*e.g.*, movement, sweating, eye opening), a hemodynamic response (increase in heart rate or blood pressure), or an arousal on the electroencephalogram of the frontal cortex, which is a reflection of a decreased cerebral hypnotic drug effect due to an insufficient analgesic effect. This “component” definition is based on the notion that tolerance to verbal and noxious stimulation will be mediated through different neuronal networks, which are located in the higher cortical *versus* subcortical structures of the brain, respectively.<sup>1</sup> These networks are independently affected by the interaction between a hypnotic and an analgesic drug. As an example of this, Heyse *et al.*<sup>2</sup> showed different response

#### What We Already Know about This Topic

- Continuous neurophysiologically derived measures of hypnotic or analgesic effect are influenced by interaction between hypnotic and analgesic drugs
- The interaction between sevoflurane and remifentanil on nonnoxious and noxious dichotomous effect endpoints was synergistic

#### What This Article Tells Us That Is New

- The opioid effect on electroencephalography-derived variables was very weak
- The effects of sevoflurane and remifentanil on the hypnotic effect measured by bispectral index or entropy were additive, but they acted synergistically on Composite Variability Index
- Painful stimulation increased the  $C50$  of sevoflurane without changing the structural models for bispectral index and entropy; a more complex parameter shift was found for Composite Variability Index

surface models for tolerance to nonnoxious and noxious stimulation.

The first two authors contributed equally to this study and should both be seen as first authors (B.H. and J.H.P.).

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In addition to the dichotomous observations of tolerance to stimulation, several neurophysiology-derived measures of anesthesia effect have been developed to monitor the anesthesia state of the patient in a continuous way. Electroencephalographic measures, such as bispectral index (BIS; Covidien, Boulder, CO), state entropy (SE), and response entropy (RE) (M-Entropy; GE Healthcare, Helsinki, Finland), have a stronger correlation with the hypnotic component than with the analgesic component of anesthesia.<sup>3</sup> More recently, new continuous measures with different neurophysiological background, such as the Surgical Pleth Index (SPI; GE Healthcare) and the Composite Variability Index (CVI; Covidien), attempt to quantify the balance between nociception and antinociception.<sup>4,5</sup> All these continuous surrogate measures of hypnotic or analgesic effect are influenced by the interaction between hypnotic and analgesic drugs and should therefore be studied with this multidrug reality in mind. Eventually, the ultimate goal of continuous monitoring is to effectively counter deviating measurements with an adequate change in the balance between opioids and hypnotics so that better clinical results are obtained. This performance can only be expected if a well-described dose–response relationship exists between the measurements and the applied drug combinations.

To depict this dose–response relationship in the presence of multiple drugs, it is common to use population-derived response surface interaction models.<sup>2</sup> For BIS, SE, RE, CVI, and SPI, the interaction between sevoflurane and remifentanyl on continuous measures has not yet been described.

Therefore, the primary goal of this study was to develop response surface models that best describe the dose–response relationship between the combined administration of sevoflurane and remifentanyl *versus* BIS, SE, RE, CVI, and SPI. Overall, we hypothesized that the nature of the various interactions should be synergistic for the continuous measures as this is in concordance with the interaction on dichotomous clinical endpoints as described by Heyse *et al.*<sup>2</sup> The secondary goal of the study was to investigate whether noxious stimulation significantly affects the model structure or the model parameters.

## Materials and Methods

The data presented in this article were collected during a previous study as published by Heyse *et al.*<sup>2</sup> This study presents the results of a secondary analysis focusing on the continuous measurements of drug effect, whereas the previous study focused on dichotomous endpoints of anesthetic effect (clinical signs of responsiveness). The studied patients, the crisscross study design, and drug administration methods applied in this study have been described elsewhere in detail.<sup>2</sup>

### Subjects

After obtaining Institutional Review Board (Ghent University Hospital Ethics Committee, Gent, Belgium) approval and prospective trial registration at ClinicalTrials.gov

(NCT00522587) and after obtaining written informed consent, 40 patients with American Society of Anesthesiologists status I or II, aged 18 to 60 yr, and scheduled to undergo surgery requiring general anesthesia were included. Exclusion criteria were weight less than 70% or more than 130% of ideal body weight, neurological disorders, diseases involving the cardiovascular system, pulmonary diseases, gastric diseases, endocrine diseases, and recent use of psychoactive medication or use of more than 20 g of alcohol daily. The complete study was executed in a quiet operating room before the start of the surgical procedure.

### Study Design

This study was performed as a randomized, prospective, open-label study. No participant of the study received premedication. After the patients arrived in the operating room, standard monitors (electrocardiogram, noninvasive blood pressure, and hemoglobin oxygen saturation), M-Entropy using a Datex S/5 Anesthesia Monitor (GE Healthcare), and BIS using an Aspect A-2000 monitor (Covidien) were connected, and a large forearm vein was cannulated. Thereafter, the patients were preoxygenated with 6 l/min of O<sub>2</sub> at an F<sub>I</sub> = 1.0 for 5 min using a tight-fitting face mask, which also served to sample exhaled air for end-tidal carbon dioxide measurement. Vital signs and end-tidal sevoflurane concentrations, respiratory data (tidal volume, minute volume, and end-tidal carbon dioxide), and infusion-related data (predicted concentrations and infused volumes) were continuously recorded on a computer hard disk using RUGLOOP II data-recording software (Demed, Temse, Belgium).

### Drug Administration

**Technical Aspects.** Remifentanyl was administered by a target-controlled infusion technique by using RUGLOOP II TCI software (Demed) based on a three-compartment model with an effect-site compartment as published by Minto *et al.*<sup>6,7</sup> Sevoflurane was administered in 50% O<sub>2</sub> and 50% air by using a standard out-of-circle vaporizer and a standard breathing circuit of an ADU anesthesia workstation (Datex/Ohmeda; GE Healthcare).

**Dosing Regimen.** We randomized 40 patients to receive four prespecified combinations of sevoflurane (0.5 to 3.5 vol%) and remifentanyl (0 to 12 ng/ml) according to a modification of the crisscross design proposed by Short *et al.*<sup>8</sup> In half of the patients, remifentanyl was held constant, and sevoflurane was stepwise increased; in the other half, sevoflurane was held constant and remifentanyl was stepwise increased. The dosing schedule is shown in table 1 in the study by Heyse *et al.*<sup>2</sup> No muscle relaxants were administered throughout the study.

### Assessment of Clinical Response

For each concentration step, the clinical response was assessed 12 min after reaching the target concentrations to

allow for plasma effect-site equilibration. The patient was exposed to the following series of stimuli, with increasing intensity: (1) verbal and nonpainful tactile stimuli according to the Modified Observer's Assessment of Alertness/Sedation (OAA/S) score<sup>9</sup>; (2) a tetanic stimulus of the ulnar nerve for 5 s by using the standard neurostimulator; (3) insertion of a laryngeal mask airway (size 3 for women and 4 for men, LMA Unique® [The Surgical Company, Amersfoort, The Netherlands]); and (4) laryngoscopy aiming at full visualization of the vocal cords by using a size-3 curved Macintosh-type blade (HEINE Optotechnik GmbH & Co KG, Herrsching, Germany). All stimuli—including laryngoscopy—were performed by a single anesthesiologist (B.H.) to minimize interindividual variability in stimulation. Between each stimulus, a 1-min delay was maintained to evaluate the somatic responsiveness on each stimulus. If there was no response to a stimulus, the next stimulus was applied 1 min after the response assessment of the previous stimulus.

In this study, we only compared data before OAA/S score (unstimulated state) with data after laryngoscopy (stimulated state). For the data that were obtained in between stimuli, we did not estimate separate models. We could not exclude a bias evoked by influences of the preceding stimulus on the next one. However, by performing simultaneous model estimations on data before and after the sequence of four clinically relevant stimulations, we explore pharmacodynamic differences between a generally “unstimulated” *versus* a “stimulated” anesthesia state.

### Data Acquisition and Management

**BIS, SE, and RE.** The spectral entropy monitor (M-Entropy; GE Healthcare) calculated SE and RE. BIS was simultaneously derived from the frontal electroencephalogram (At-Fpz) by using a quatro BIS™ sensor with four electrodes (Covidien). The smoothing time of the BIS monitor was set at 15 s. All data were recorded electronically using RUGLOOP II software (Demed) with a 5-s time interval.

The median of the recorded values during 1 min before the assessment of the OAA/S score was used for the analysis of the BIS, SE, and RE data.

**CVI.** The raw electroencephalographic signal was captured by the BIS™ monitor with a 128-Hz sample rate and allowed *post hoc* calculation of CVI. The calculation of CVI has been described by Mathews *et al.*<sup>5</sup> The CVI is a composite index that combines the variability in BIS with frontal electromyographic changes over time. A high CVI reflects activation of the frontal electromyography and increased input of sensory information from deep brain structures to the cortex. A low CVI reflects an adequate inhibition of this sensory input and adequate analgesia. The CVI was calculated with a 5-s time interval. The median of the recorded values during 1 min before the assessment of the OAA/S score was used for the analysis. In the case that one or more values were missing during the last minute before

the assessment of OAA/S score due to a technical reason, the CVI was regarded as a missing value and was not taken into account in the analysis.

**SPI.** The SPI is derived from plethysmographic pulse wave characteristics combined with heart rate variability and is a surrogate measure of the orthosympathetic and parasympathetic nervous system response to noxious stimulation. The calculation of SPI has been described by Huiku *et al.*<sup>4</sup> The SPI was calculated with a 1-s time interval. The median of the recorded values during 1 min before the assessment of the OAA/S score was used for the analysis. In the case that there were less than seven values during the last minute before the assessment of OAA/S score, the SPI was regarded as a missing value and was not taken into account in the analysis.

**Data after Stimulation.** A moving median technique was applied on the raw data measured during 1 min after laryngoscopy. For the NONMEM analysis, the highest value of the moving median over several consecutive values was used. By doing so, the effect of single outlier values on the average behavior of each measurement was minimized without losing sensitivity for detecting a relevant response on BIS, SE, RE, CVI, and SPI after stimulation. For measurements that were logged every 5 s (BIS, SE, RE, and CVI), or every second (SPI), we performed the moving median technique over a sequence of respectively five or seven consecutive values. In the case that there were less than five or seven consecutive values during 1 min after application of laryngoscopy, or if laryngoscopy was not applied because the patient was responsive to a previous stimulus (see the study by Heyse *et al.*<sup>2</sup>), the measurement was considered as missing and was not taken into account in the analysis.

### Pharmacodynamic Analysis of the Continuous Variables

For the continuous data, a negative sigmoid  $E_{\max}$  model was used<sup>10</sup>:

$$Effect = E_0 - (E_0 - REST) \cdot \left( \frac{U^\gamma}{1 + U^\gamma} \right) \quad (1)$$

where  $E_0$  is the baseline value in the absence of drug, REST is a nonsuppressible effect (the lowest possible value of the effect variable),  $U$  represents the normalized combined potency of one or more drugs, and  $\gamma$  is the slope parameter reflecting the steepness of the concentration–effect relationship.

The normalized combined potency  $U$  is a function of the drug effect-site concentrations and model parameters, as described in detail in the appendix in the study by Heyse *et al.*<sup>2</sup> The following models were tested:

a. Greco model

$$U = \frac{C_{SEVO}}{C50_{SEVO}} + \frac{C_{REMI}}{C50_{REMI}} + \alpha \cdot \frac{C_{SEVO}}{C50_{SEVO}} \cdot \frac{C_{REMI}}{C50_{REMI}} \quad (2)$$

where  $C_{SEVO}$  is the effect-site concentration of sevoflurane,  $C_{REMI}$  is the effect-site concentration of remifentanyl,  $C50_{SEVO}$  is the effect-site concentration of sevoflurane with 50% effect,  $C50_{REMI}$  is the effect-site concentration of remifentanyl with 50% effect, and  $\alpha$  is a dimensionless interaction parameter.

b. Reduced Greco model without effect of the opioid alone

$$U = \frac{C_{SEVO}}{C50_{SEVO}} \cdot \left( 1 + \frac{C_{REMI}}{C50_{REMI}} \right) \quad (3)$$

c. Minto model<sup>11</sup>

$$U = \frac{\frac{C_{SEVO}}{C50_{SEVO}} + \frac{C_{REMI}}{C50_{REMI}}}{1 - \beta_{U50} \cdot \theta \cdot (1 - \theta)} \quad (4)$$

where  $\beta_{U50}$  is a dimensionless interaction parameter, and  $\theta$  is defined by:

$$\theta = \frac{\frac{C_{SEVO}}{C50_{SEVO}}}{\frac{C_{SEVO}}{C50_{SEVO}} + \frac{C_{REMI}}{C50_{REMI}}} \quad (5)$$

d. Hierarchical model

$$U = \frac{C_{SEVO}}{C50_{SEVO}} \cdot \left( 1 + \left( \frac{C_{REMI}}{C50_{REMI}} \right)^{\gamma_0} \right) \quad (6)$$

where  $\gamma_0$  is the slope parameter reflecting the steepness of the concentration–effect relationship for remifentanyl.

Because each pharmacodynamic endpoint was analyzed separately, the Scaled  $C50_0$  and Fixed  $C50_0$  Hierarchical models are identical.<sup>2</sup>

For BIS, SE, and RE, it was assumed that the measure approaches zero for high concentrations of sevoflurane or remifentanyl, so REST is zero, reducing the model to a fractional  $E_{max}$  model.<sup>10</sup> For CVI and SPI, the nonsuppressible effect REST was modeled as a function of the drug concentrations according to the procedure described by Minto *et al.*<sup>11</sup>:

$$REST = REST_{SEVO} \cdot \theta + REST_{REMI} \cdot (1 - \theta) - \beta_{REST} \cdot \theta \cdot (1 - \theta) \quad (7)$$

where  $REST_{SEVO}$ ,  $REST_{REMI}$ , and  $\beta_{REST}$  are model parameters.

### Parameter Estimation

The model parameters were estimated using NONMEM 7.2.0 (Icon Development Solutions, Hanover, MD), using first-order conditional estimation. Platform was Windows

XP (Microsoft, Redmond, WA) and compiler was G95. For all parameters, interindividual variability was assumed either to be absent or to have a lognormal distribution. It was tested whether a single value for the individual deviation from the typical value ( $\eta$  in NONMEM) could be used for  $C50$  of sevoflurane and remifentanyl, in accordance with the assumption that this value reflects the sensitivity of that individual for hypnotic and opioid drugs. Residual intraindividual variability of the continuous variables was modeled using standard additive or proportional error models.

Parameters were tested for significance by comparing the objective function which is minus two times log-likelihood ( $-2LL$ ). Significance level for hypothesis tests was 0.01 (chi-square test), or a 6.84 difference in the  $-2LL$  adding one parameter for nested models. The goodness-of-fit for the models was also assessed by visual inspection of the predicted *versus* observed plots and the distribution of residuals for each of the continuous endpoints.

Model building was performed starting with the simplest form of each model and expanding the model with parameters and interindividual variability until the decrease of the objective function value was not statistically significant using the chi-square test. In addition, model building was started with the most complex model, reducing the model by fixing parameters to zero. The NONMEM analysis was performed with various values for initial estimates and boundary values. The results were accepted as valid only if both minimization and covariance steps were successful, unless stated otherwise.

To evaluate the final model, a bootstrap analysis was performed, based on 2,000 sets of 40 patients each, randomly selected from the available 40 patients, using a custom program written in c. Results were analyzed in Excel (Microsoft) to obtain nonparametric 95% CIs.

The poststimulation data after laryngoscopy were analyzed by using an identical modeling approach as applied on the prestimulation data. To investigate the effect of the stimulations on the model parameters, we performed a simultaneous fitting of the data before OAA/S (= unstimulated anesthesia state) and after laryngoscopy (= stimulated anesthesia state) in a stepwise model-building process, starting with fixed common parameters for both data sets, followed by testing the addition of parameters for the difference between before OAA/S and after laryngoscopy.

### Statistical Analysis

All model parameters are reported as typical values with relative standard error (in % of the typical value) within parentheses, and clinical data are given as mean and SD or as median and range, when appropriate.

### Results

In total, 40 patients (26 women and 14 men) were included in this study. The demographics are as follows: body weight,

66 ± 11 kg; height, 172 ± 8 cm; and age, 30 ± 11 yr. All patients were classified as American Society of Anesthesiologists status I.

### Data

In total, the data sets contained 159 periods of testing (40 patients with 4 periods per patient minus 1 missing period where no stimulus was given).

### Model Development for BIS

Initially, BIS data were analyzed using the Greco, Reduced Greco, Minto, and Hierarchical models, using a fractional  $E_{\max}$  model (REST = 0). For both the Greco model and the Minto model, the interaction term for C50 did not differ significantly from zero. Similarly, the interaction term for  $\gamma$  in the Minto model did not differ significantly from zero. Consequently, both models yield identical results. The objective function value for the Greco model (808.5) was markedly lower than that for the Reduced Greco model (823.0) and Hierarchical model (822.2), and therefore, the Greco model was considered as the most appropriate method. The additional error model fitted better to the data than the proportional error model, as concluded from the objective function value and diagnostic plots of residuals.

### Final Model for BIS

The final results for this model are shown in table 1. In the final model, interindividual variability was included in C50<sub>REMI</sub> and C50<sub>SEVO</sub> with a common *eta*. The value for C50 for remifentanil (27.3 ng/ml) exceeds the upper range

of concentrations in the study (12 ng/ml), but its precision was satisfactory (relative standard error 12%).

The response surface of the final model is shown in figure 1. Figure 2 depicts the observed BIS values (filled symbols) and predicted BIS (solid line) *versus* the normalized combined potency  $U_{\text{BIS}}$ , which has a sigmoidal  $E_{\max}$  relationship.

### Model Development for SE and RE

The Greco model was found to be the most appropriate model for SE and RE, in accordance with the best model for BIS.

### Final Models for SE and RE

The results of the final models are summarized in table 1. The variability in SE and RE is larger than for the BIS data, as reflected in larger relative standard errors, larger interindividual variability, and larger residual SD.

The response surfaces of the final models for SE and RE are shown in figure 1. Figures 3 and 4 depict the observed (filled symbols) and predicted (solid line) SE and RE *versus* the normalized combined potencies  $U_{\text{SE}}$  and  $U_{\text{RE}}$ , respectively, which also have a sigmoidal  $E_{\max}$  relationship.

### Model Development for CVI

In four patients, the CVI could not be calculated due to missing data. In 17 patients, the CVI could not be calculated from the available electroencephalogram registration in one or more periods. In total, 122 CVI values in 36 patients were available.

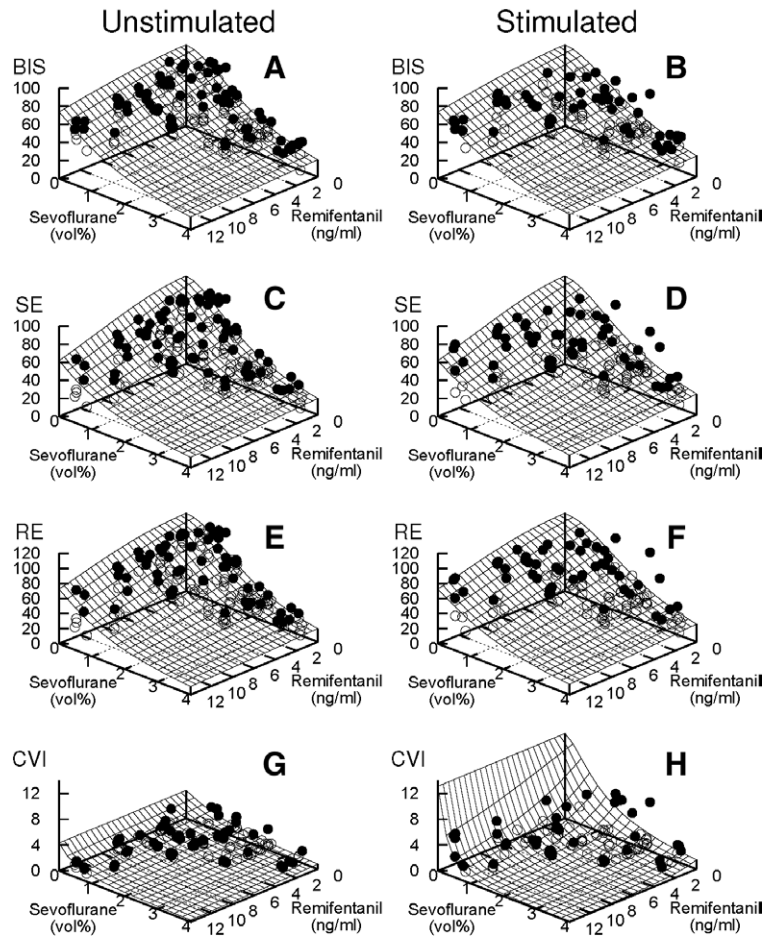
**Table 1.** Population Model Estimates for BIS, SE, RE, and CVI

Interaction Model	BIS	SE	RE	CVI
	Greco/Minto	Greco/Minto	Greco/Minto	Reduced Greco
C50 <sub>REMI</sub> (ng/ml)	27.3 (13%) (20.4–37.7)	16.2 (19%) (11.0–27.9)	18.2 (21%) (12.6–31.9)	7.56 (32%) (4.01–17.7)
C50 <sub>SEVO</sub> (vol%)	1.99 (6%) (1.68–2.23)	1.82 (8%) (1.49–2.11)	1.88 (7%) (1.58–2.14)	1.09 (97%) (0.08–3.28)
$\gamma$	1.88 (10%) (1.53–2.27)	1.87 (9%) (1.54–2.26)	2.08 (8%) (1.76–2.40)	1.16 (29%) (0.77–2.15)
$E_0$	89.5 (4%) (83.5–99.1)	97.1 (5%) (84.3–110)	103 (4%) (95–113)	4.32 (57%) (2.35–19.9)
IIV(C50 <sub>REMI</sub> )	20% (14%) (14–25%)	59% (19%) (33–86%)	67% (19%) (43–99%)	0*
IIV(C50 <sub>SEVO</sub> )	20%†	22% (22%) (8–30%)	25% (19%) (13–34%)	18% (24%) (0–26%)
Residual SD	6.2‡ (9%) (5.0–7.2)	9.5‡ (10%) (7.5–11.1)	9.6‡ (10%) (7.5–11.2)	27%§ (11%) (22–33%)
$\Delta$ C50 <sub>SEVO</sub> (vol%)	0.30 (18%) (0.20–0.41)	0.31 (22%) (0.18–0.46)	0.36 (20%) (0.23–0.52)	

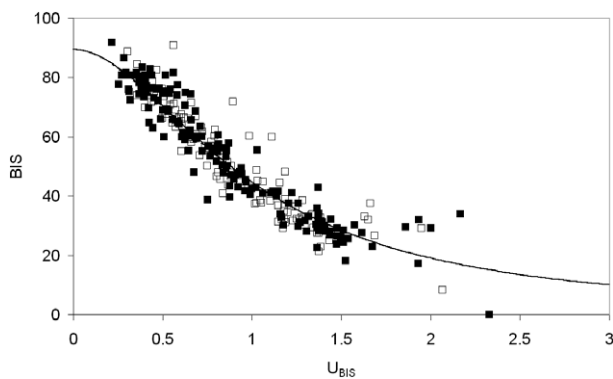
Values are typical values, relative standard error (% of the typical value) and 95% CI obtained by bootstrapping.

\* Not significantly different from zero; † Common value for remifentanil and sevoflurane; ‡ Additive error; § Proportional error; || Could not be estimated (for details, see text).

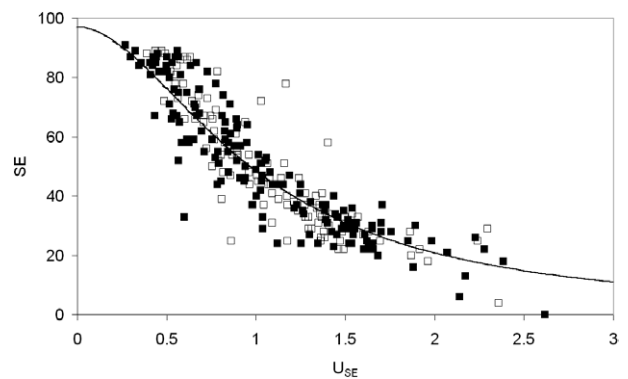
BIS = bispectral index; CVI = Composite Variability Index; C50<sub>REMI</sub> = effect-site concentration of remifentanil with 50% effect; C50<sub>SEVO</sub> = effect-site concentration of sevoflurane with 50% effect;  $\Delta$ C50<sub>SEVO</sub> = increase of C50<sub>SEVO</sub> after laryngoscopy, as obtained in a separate analysis (see text);  $E_0$  = baseline value in the absence of drugs;  $\gamma$  = model parameter reflecting the steepness of the concentration–effect relationship; IIV(C50<sub>REMI</sub>) and IIV(C50<sub>SEVO</sub>) = interindividual variability for C50<sub>REMI</sub> and C50<sub>SEVO</sub>, respectively (calculated as the square root of interindividual variance, multiplied by 100%); Residual SD = SD of the differences between the observed and predicted responses (calculated as the square root of the residual variance); RE = response entropy; SE = state entropy.



**Fig. 1.** Response surface for electroencephalographic endpoints before stimulation (A, C, E, G) and after stimulation (B, D, F, H) was applied: Bispectral index (BIS), state entropy (SE), response entropy (RE), and Composite Variability Index (CVI), as a function of the end-tidal steady-state sevoflurane concentration and the predicted remifentanyl effect-site concentration, calculated from the data listed in table 1. Measured values above the surface are shown as *filled circles* and below the surface as *open circles*.



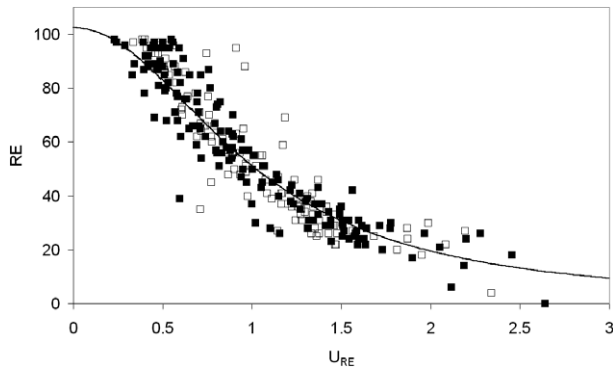
**Fig. 2.** Relationship between the normalized combined potency  $U_{BIS}$  according to the Greco model and the observed bispectral index (BIS) (*squares*,  $n = 159$ ) and predicted BIS (*solid line*; calculated from the data listed in table 1) for unstimulated (*filled symbols*) and stimulated (*open symbols*).



**Fig. 3.** Relationship between the normalized combined potency  $U_{SE}$  according to the Greco model and the observed state entropy (SE) (*squares*,  $n = 159$ ) and predicted SE (*solid line*; calculated from the data listed in table 1) for unstimulated (*filled symbols*) and stimulated (*open symbols*).

For CVI, the objective function value of the Reduced Greco model was lower than for the Greco model and Minto model. The proportional error model fitted better to the data than the additional error model, as concluded from

the objective function value and diagnostic plots of residuals. Using the Hierarchical model, the slope factor  $\gamma$  for remifentanyl (0.289) and  $C50_{SEVO}$  (0.266 vol.%) was very low,  $E_0$  (10.2) was much higher than the highest observed CVI



**Fig. 4.** Relationship between the normalized combined potency  $U_{RE}$  according to the Greco model and the observed response entropy (RE) (squares,  $n = 159$ ) and predicted RE (solid line; calculated from the data listed in table 1) for unstimulated (filled symbols) and stimulated (open symbols).

value, and standard errors were high; therefore, this model was not accepted as a valid model.

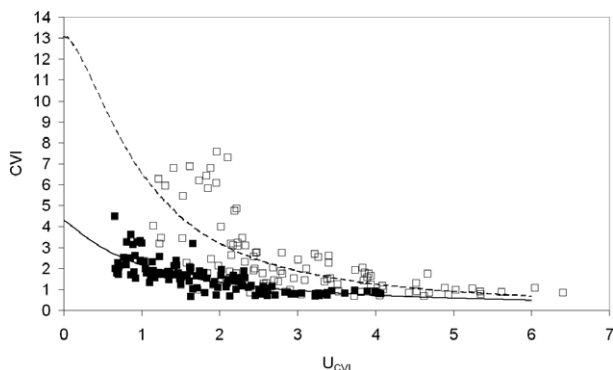
#### Final Model for CVI

The results for the final Reduced Greco model are shown in table 1. The residual error of 27% is large and the CIs for the model parameters are wide, reflecting the poor fit.

The response surface of the final model for CVI is shown in figure 1. Figure 5 depicts the observed (filled symbols) and predicted CVI values (solid line) versus the normalized combined potency  $U_{CVI}$ . The CVI has a sigmoidal  $E_{max}$  relationship with  $U_{CVI}$ , which is comparable in behavior to BIS, SE, and RE.

#### Model Development for SPI

In two patients, the SPI could not be calculated due to missing data. In four patients, the SPI could not be calculated from the available plethysmography data in one or more periods. In total, SPI data from 145 periods in 38 patients were available.



**Fig. 5.** Relationship between the normalized combined potency  $U_{CVI}$  according to the Reduced Greco model and the observed Composite Variability Index (CVI) (squares,  $n = 122$ ) and predicted CVI (lines; calculated from the data listed in table 1) for unstimulated (filled symbols, solid line) and stimulated (open symbols, dashed line).

Modeling of the SPI data did not result in reliable results. Plotting the SPI data against the sevoflurane or remifentanil concentration revealed that the SPI value is hardly affected by sevoflurane or remifentanil, in contrast to the BIS, SE, RE, and CVI (data not shown).

#### Data after Stimulation

The data after stimulation were first analyzed using an identical modeling approach as applied on the unstimulated data. For BIS, SE, and RE, the number of data points was 114 (in 45 periods, laryngoscopy was not applied for ethical or other reasons). The optimal models were identical and the parameters were broadly comparable with the results before the assessment of OAA/S, except for  $C50_{SEVO}$ , which was consistently higher after the series of stimulation (data not shown).

Next, to investigate this effect of stimulation on the model parameters, we performed a simultaneous fitting of the data before OAA/S (= unstimulated anesthesia state) and after laryngoscopy in a model-building process (= stimulated anesthesia state), starting with fixed common parameters for both data sets, followed by adding parameters for the difference between before OAA/S and after laryngoscopy. This analysis revealed that  $C50_{SEVO}$  was significantly higher after laryngoscopy for BIS, SE, and RE, with an average increase of 0.3 vol% sevoflurane (table 1), whereas the other parameters did not change. The response surfaces of the final models for BIS, SE, and RE are shown in figure 1. Figures 2–4 depict the observed values (open symbols) and predicted values (solid line) versus the normalized combined potency  $U$  for BIS, SE, and SE, respectively. Because the baseline values, maximal effect and steepness of the model are not affected by the stimulation, the relationship between  $U$  and predicted value is not affected, and the solid line is identical for unstimulated and stimulated conditions. For each combination of sevoflurane and remifentanil, the value  $U_{BIS}$  (similar for  $U_{SE}$  and  $U_{RE}$ ) after stimulation is lower compared with the unstimulated state as a result of the higher  $C50_{SEVO}$ . Consequently, the predicted BIS after stimulation will be higher than in the unstimulated state, reflecting a reduction of the combined drug effect. In other words, stimulation moves  $U_{BIS}$  to the left, and the predicted BIS upwards along the solid lines of figures 2–4.

In contrast, simultaneous analysis of the CVI data before OAA/S and after laryngoscopy, with parameters fixed to the values from the analysis of the data before OAA/S alone (table 1), resulted in a lower value for  $C50_{REMI}$  (3.09 ng/ml; CI, 1.78 to 4.68 ng/ml), a higher value for  $\gamma$  (1.62; CI, 1.28 to 1.79), and  $E_0$  (13.1; CI, 9.4 to 17.2). Also, the residual SD (46%; CI, 37 to 53%) after stimulation was higher, indicating an even larger variability in the dose–response relationship of CVI compared with the unstimulated condition. Figure 5 depicts the observed values (open symbols) and predicted CVI (dashed line) versus the normalized combined potency  $U_{CVI}$ , respectively. Figure 5 also shows the shift in dose–response relationship of CVI versus  $U_{CVI}$  between the unstimulated

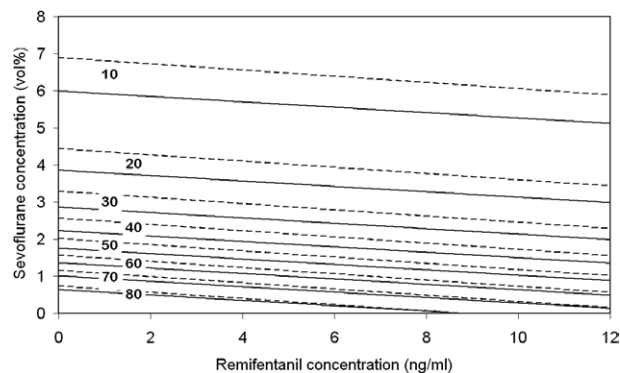
(solid line) and stimulated condition (dashed line). Because the baseline and steepness are affected by the stimulation, the relationship between  $U_{CVI}$  and predicted value is different for the unstimulated and stimulated data. The response surface for CVI after stimulation is shown in figure 1.

The SPI data after stimulation (104 valid SPI values) were analyzed using the same approaches. Similar to the unstimulated data, the SPI values after stimulation were hardly affected by sevoflurane or remifentanyl, and modeling did not result in reliable results (data not shown).

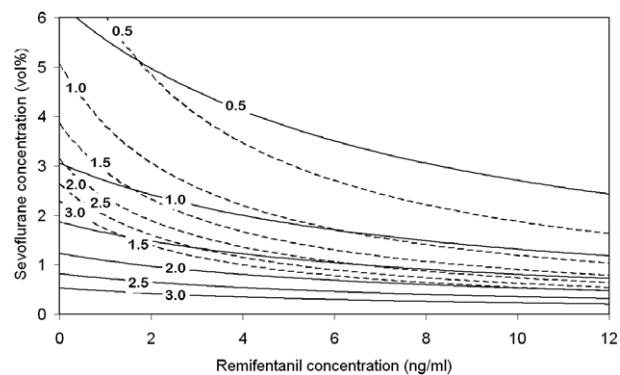
**Isoboles**

In figure 6, the isoboles of BIS values from 10 to 80 are depicted for the unstimulated (solid lines) and stimulated (dashed lines) condition. The additive nature of the interaction results in linear isoboles for the complete range of BIS values. The isoboles are shifted upwards after stimulation, reflecting the increase in  $C50_{SEVO}$ .

In figure 7, the isoboles of CVI values from 0.5 to 3 are depicted for the unstimulated (solid lines) and stimulated (dashed lines) condition.



**Fig. 6.** Isoboles for bispectral index values of 10, 20, 30, 40, 50, 60, 70, and 80 for the unstimulated (solid lines) and stimulated (dashed lines) data, as a function of the end-tidal sevoflurane concentration and the predicted remifentanyl effect-site concentration, calculated from the data listed in table 1.



**Fig. 7.** Isoboles for Composite Variability Index values of 0.5, 1, 1.5, 2, 2.5, and 3 for the unstimulated (solid lines) and stimulated (dashed lines) data, as a function of the end-tidal sevoflurane concentration and the predicted remifentanyl effect-site concentration, calculated from the data listed in table 1.

(dashed lines) condition, showing a synergistic nature of the interaction, as reflected by the Reduced Greco model. For low CVI values, the isoboles of the stimulated condition intersect the isoboles of the unstimulated condition.

For SPI, no isoboles could be depicted, as we could not fit an appropriate response surface model to the data.

**Discussion**

We describe the interaction between sevoflurane and remifentanyl on BIS, SE, RE, CVI, and SPI. Although opioids have a rather weak effect on the electroencephalogram, we found an additive effect of remifentanyl on reduction of BIS, SE, and RE by sevoflurane. The effect on CVI was synergistic. The SPI was not affected by sevoflurane or remifentanyl. The Greco model provided the best fit of the data for BIS, SE, and RE, whereas the reduced Greco model best described CVI. Interestingly, the structural interaction model was not affected by noxious stimulation, but noxious stimulation did increase the  $C50_{SEVO}$  for BIS, SE, and RE by 20%, whereas the  $C50_{REMI}$  did not change. In contrast, for CVI all model parameters changed except  $C50_{SEVO}$ .

The findings on (unstimulated) BIS, SE, and RE are in agreement with that reported in previous literature. Nieuwenhuijs *et al.*<sup>12</sup> presented an interaction model during sevoflurane–alfentanil anesthesia, suggesting additivity for BIS. During propofol anesthesia, Vanluchene *et al.*<sup>3</sup> found that remifentanyl evoked an increase in the threshold for loss of consciousness on BIS, SE, and RE in a dose-dependent way, but no conclusion was drawn on the nature of this interaction. Bouillon *et al.*<sup>13</sup> found additivity for BIS during propofol–remifentanyl anesthesia. Schumacher *et al.*<sup>10</sup> found an additive interaction on BIS for combined propofol and sevoflurane. Conversely, the interaction of sevoflurane and remifentanyl on clinical endpoints of effect, as published by Heyse *et al.*,<sup>2</sup> was not additive but synergistic. Also,  $C50_{REMI}$  was 10-fold higher for BIS, SE, and RE compared with  $C50_{REMI}$  for dichotomous endpoints.<sup>2</sup> Apparently, the opioid effect on the electroencephalogram is weak, despite a strong effect on patient responsiveness. This may explain why electroencephalographic variables are poor predictors of responsiveness to noxious stimuli.

According to the parameter estimates (table 1), BIS is least opioid sensitive, followed by SE, RE, and CVI, whereas BIS, SE, and RE are equally sensitive to sevoflurane, but less than CVI. The slope of the response surfaces is similar for BIS, SE, and RE, but steeper than the slope for CVI (fig. 5). The interaction model for BIS is characterized by the lowest interindividual (table 1: IIV [ $C50_{REMI}$ ]) and residual variability.

Interaction models not only define combined effects of sevoflurane and remifentanyl as a response surface but also allow expression of the potency of a combination of drugs as one dimensionless number. For this purpose, we introduced “U” being units of combined potency related to each of the investigated effects variables. For example,  $U_{BIS}$  is the sum of



the sevoflurane and remifentanil concentration both normalized to the respective  $C50$ 's of the BIS dose–response curve (equations 2 and 4). The potency  $U_{BIS} = 1$  can be achieved by 1.99 vol% of sevoflurane ( $=C50_{SEVO}$ ) or (e.g.) by 1.49 vol% of sevoflurane ( $=0.75 \times C50_{SEVO}$ ) plus 6.8 ng/ml of remifentanil ( $=0.25 \times C50_{REMI}$ ). As  $C50$  is specific for each electroencephalographic variable, one given sevoflurane and remifentanil concentration does not yield identical values of “U” for BIS, SE, RE, or CVI. According to the final models (table 1), 1.5 vol% of sevoflurane combined with 5 ng/ml of remifentanil yields a  $U_{BIS}$ ,  $U_{SE}$ ,  $U_{RE}$ , and  $U_{CVI}$  of 0.94, 1.13, 1.07, and 2.29, respectively.

In concordance with Minto *et al.*,<sup>11</sup> we consider the combination of two drugs as a virtual new drug. “U” can be used as if it was a drug concentration of that virtual new drug on the x-axis of a two-dimensional concentration–response curve (figs. 2–5). With the selected interaction models, the combined potency “U” predicted the effect on BIS, SE, and RE with an error of approximately 10%, which is comparable to that reported in the previous studies.<sup>13</sup>

“U” as a number represents potency of a combination of sevoflurane and remifentanil to suppress the electroencephalographic variable and has similarities with the Noxious Stimulation Response Index.<sup>14</sup> The Noxious Stimulation Response Index is based on the suppression of a response to laryngoscopy, using the Hierarchical interaction model. The  $C50_{REMI}$  (1.16 ng/ml) in this model is much lower than the  $C50_{REMI}$  in the current study (7.5 to 27.3 ng/ml, depending on the type of electroencephalographic variable). This makes Noxious Stimulation Response Index much more opioid sensitive compared with “U,” which is in agreement with the fact that hypnotics have a stronger effect on electroencephalogram than the effects of opioids on electroencephalogram. The clinical utility of any of the “U”s or Noxious Stimulation Response Index to titrate opioids and hypnotics remains to be determined.

The CVI as a potential indicator of nociception behaved similar as dichotomous endpoints in the previous study<sup>2</sup>: the interaction was synergistic. The best fit was found with the reduced Greco model. As expected, the concentration–response curve of CVI was affected by noxious stimulation (figs. 5 and 7), especially due to a substantial increase in baseline effect ( $E_0$ ), probably due to an increase in electromyographic activity. The dose–response curve was rather flat, and a ceiling effect was observed at the level of a CVI of approximately 1 (fig. 5). This explains why a larger increase of the sevoflurane concentration is needed to lower CVI from 1 to 0.5 than that required to lower CVI from 3 to 2.5 (fig. 7). Although noxious stimulation and opioids evoke a greater effect on CVI than on BIS, SE, and RE, CVI may offer lower discriminating capacity compared with BIS, SE, and RE. Even in our best-fitted model, the differences between estimated and observed CVI were high, especially after noxious stimulation (figs. 1 and 5).

The poststimulation data set represents a population that is in a pharmacological pseudosteady state (at similar drug

concentrations as before stimulation), where the applied stimuli may have disrupted the balance between drug concentrations and effect variables. Assuming that noxious stimulation might induce an arousal response on the electroencephalographic variables, we hypothesized that the parameter estimates from the poststimulation data could be different from those of the prestimulation data. We expected larger differences in model estimates for CVI and SPI compared with BIS, SE, and RE, as the arousal response in BIS is already suppressed by rather low remifentanil concentrations.<sup>15</sup>

For all poststimulation response surface models, the structural model with the lowest objective function was identical to the prestimulation model. For BIS, SE, and RE, the model parameters hardly changed, except for  $C50_{SEVO}$  (consistently 0.3 vol% higher after laryngoscopy). This pharmacodynamic shift is consistent for BIS and entropy and it is only little smaller than the difference between  $C50_{SEVO}$  for tolerance of shake and shout and laryngoscopy, found in the previous article (0.53 vol%).<sup>2</sup> Typical accuracy for measuring sevoflurane end-tidal concentrations is  $\pm 0.15$  vol% + 5% of reading. The time between nonstimulation and poststimulation sampling did not exceed 6 min and therefore was assumed to be constant. Therefore, we consider 0.3 vol% (or 14% of 1 minimal alveolar concentration) as clinically relevant. The sevoflurane and remifentanil concentrations mentioned above (1.5 vol% and 5 ng/ml) yield a poststimulation U for BIS, SE, and RE which is approximately 10% lower than the prestimulation U. Therefore, both single-model parameters (e.g.,  $C50$ s) and combined potency U could be used as surrogate measures of stimulus intensity.

For CVI, the changes in the poststimulation model are complex.  $C50_{REMI}$  decreased to 3.09 ng/ml. Gamma and the baseline effect ( $E_0$ ) increased. The increased steepness of the dose–response curve and the larger difference between baseline and maximal effect suggest an improved descriptive capacity for CVI in stimulated compared with unstimulated conditions. However, the residual SD and the standard errors of the parameters indicate a larger variability in the dose–response relationship compared with the unstimulated condition. Our finding is in agreement with the notion that a noxious stimulus is mandatory to measure the balance between nociception and antinociception accurately.

For SPI, we were not able to extract plausible parameter estimates from our data, neither from prestimulation nor from poststimulation observations. Either SPI is hardly affected by sevoflurane and remifentanil or the inter- and intraindividual variability of SPI hides a minimal dose–response relationship. The sympathetic and parasympathetic nerve system may be affected by many confounding factors apart from noxious stimulation and anesthetic drug dosages. The inability to detect any dose–response relationship in steady-state conditions, both with or without noxious stimulation, lowers the expectations for SPI as a guide for titrating sevoflurane and remifentanil anesthesia.

In conclusion, sevoflurane and remifentanyl are additive on BIS and entropy, but they act synergistic on CVI. SPI is not correlated to drug concentrations. Noxious stimulation did not change structural models but increased the C50 of sevoflurane related to BIS and entropy, whereas a more complex parameter shift was found for CVI.

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## Competing Interests

The authors declare no competing interests.

## Correspondence

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