

Surgical Stimulation Shifts EEG Concentration–Response Relationship of Desflurane

Heiko Röpcke, M.D., Benno Rehberg, M.D.,* Michael Koenen-Bergmann, M.D.,† Thomas Bouillon, M.D.,† Jörgen Bruhn, M.D.,† Andreas Hoeft, M.D., Ph.D.‡*

Background: **Anesthesiologists routinely increase the delivered anesthetic concentration before surgical stimulation in anticipation of increased anesthetic requirement to achieve certain goals (*e.g.*, amnesia, unconsciousness, and immobility). Electroencephalographic monitoring is one method of determining indirectly anesthetic effect on the brain. The present study investigated the effect of surgical stimuli on the concentration–response relation of desflurane-induced electroencephalographic changes.**

Methods: **The electroencephalographic activity was recorded from 24 female patients who received only desflurane after a single induction dose of propofol. Twelve patients served as a control group before surgical stimulation. The other 12 patients, all undergoing lower abdominal surgery, were investigated between opening and closure of the peritoneum. Desflurane vaporizer settings were randomly increased and decreased between 0.5 and 1.6 minimum alveolar concentration as long as anesthesia was considered adequate. Spectral edge frequency 95, median power frequency, and Bispectral Index were calculated. Desflurane effect-site concentrations and the concentration–effect curves for spectral edge frequency 95, median power frequency, and Bispectral Index were determined by simultaneous pharmacokinetic and pharmacodynamic modeling.**

Results: **Surgical stimulation shifted the desflurane concentration–electroencephalographic effect curves for spectral edge frequency 95, median power frequency, and Bispectral Index toward higher desflurane concentrations. In the unstimulated group, 2.2 ± 0.74 vol% desflurane were necessary to achieve a Bispectral Index of 50, whereas during surgery, 6.8 ± 0.98 vol% (mean ± SE) were required.**

Conclusions: **During surgery, higher concentrations of the volatile anesthetic are required to achieve a desired level of cortical electrical activity and, presumably, anesthesia.**

ALL general anesthetics are known to change electroencephalographic patterns from low-voltage fast waves in conscious humans to high-voltage slow waves in the anesthetized state. Processed univariate electroencephalographic parameters,[1] such as spectral edge frequency, median power frequency, or Bispectral Index, have been related to clinical signs of anesthesia and the corresponding plasma, end-expiratory, or effect-site concentrations.[2–4]

It is likely that noxious stimulation influences the relation between drug concentration and electroencephalographic effects. The classic, excitatory electroencephalographic arousal reaction to transient noxious stimulation consists of a loss of low-frequency (δ) activity and increased high-frequency (α, β) activity.[5,6] This can be reversed by increasing the anesthetic concentration. Therefore, in a clinical setting where there is topic painful stimulation, higher anesthetic concentrations should be required during noxious stimulation to maintain the same anesthetic level and electroencephalographic effect.

Despite the obvious relevance of noxious stimulation for the scientific understanding of anesthetic depth, there are only a few studies that have investigated the effect of surgery *per se* on the intraoperative electroencephalogram.[5,8–11] To our knowledge, studies systematically describing the influence of noxious stimulation on the concentration dependence of processed electroencephalographic parameters are lacking completely. The aim of this study was to investigate the effect of surgical stimulation on the electroencephalographic effects of desflurane.

Methods

Patients and Anesthesia

After approval by the Institutional Review Board (Ethics Committee of the University of Bonn, Bonn, Germany), written informed consent was obtained from 24 female patients with American Society of Anesthesiologists physical status I or II. The demographic data are given in table 1. Not included were patients with apparent neurologic deficit, hypothyroidism or hyperthyroidism, pregnancy, or patients who had received central nervous system active drugs. The patients received 7.5 mg oral midazolam 2 h before surgery. Anesthesia was induced with 2 mg/kg propofol. Vecuronium was administered for neuromuscular block, and no anticholinergic agent was used. As soon as the trachea had been intubated, anesthesia was maintained with desflurane as the sole anesthetic agent. End-tidal desflurane concentrations were measured breath by breath with a Capnomac anesthetic gas analyzer (Datex, Copenhagen, Denmark). Nitrous oxide and opioids were not used. The patients' lungs were ventilated with oxygen and air (fractional inspired oxygen tension, 0.4). End-tidal carbon dioxide tension was measured and kept constant at 35 mmHg. Esophageal temperature was monitored continuously to

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* Staff Anesthesiologist, † Resident in Anesthesia, ‡ Professor of Anesthesiology and Chair.

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Address reprint requests to Dr. Röpcke: Department of Anesthesiology and Intensive Care Medicine, University of Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany. Address electronic mail to: roepcke@mailer.meb.uni-bonn.de. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

Table 1. Demographic Data

	Patients without Surgical Stimulation (n = 12)	Patients with Surgical Stimulation (n = 12)
Gender	12 F	12 F
Age (yr)	37 ± 17	38 ± 11
Weight (kg)	75 ± 13	69 ± 11
Height (cm)	174 ± 12	169 ± 8
ASA classification (n)		
I	5	8
II	7	4

ASA = American Society of Anesthesiologists.

ensure normothermia. Blood pressure and heart rate were measured oscillometrically at 3-min intervals. A 45-min waiting period was allowed for the effects of the induction dose of propofol to dissipate and for transition to pure desflurane anesthesia. During the waiting period, the patients were anesthetized with 1.0 minimum alveolar concentration (MAC) end-tidal desflurane. The attending anesthesiologist was allowed to increase or decrease desflurane concentrations to maintain clinically adequate depth of anesthesia.

For determination of desflurane electroencephalographic effect relation without noxious stimulation, 12 patients were investigated before the start of surgery. To obtain concentration–response curves, the anesthetic concentrations were subsequently decreased and increased. The desflurane concentration applied during the waiting period served as starting point. In half of the patients (randomly assigned), we started the measurements by initially decreasing the desflurane concentration; in the other half of the patients, we initially increased the desflurane concentration. Decreasing the desflurane concentration was realized by turning off the vaporizer. Decreasing the desflurane vaporizer settings was terminated when coughing or moving no longer allowed artifact-free electroencephalographic data collection. To avoid transient cardiovascular stimulation associated with rapid increase in desflurane concentration, the desflurane vaporizer settings were increased in small steps. Desflurane concentrations exceeding 1.6 MAC were not used to avoid a high percentage of burst suppressions.[12] Data were collected for at least 30 min. If more time was available, data collection was prolonged until skin incision (fig. 1).

For determination of desflurane electroencephalographic effect relation during surgical stimulation 12 patients, all undergoing gynecologic laparotomies, were investigated between opening and closure of the peritoneum. After opening of the peritoneum (and at least 45 min after induction of anesthesia), desflurane vaporizer settings were subsequently increased and decreased (fig. 1). Again, in half of the patients (randomly assigned), we started the measurements by initially decreasing the vaporizer settings; in the other half of the patients, by initially increasing the vaporizer settings.

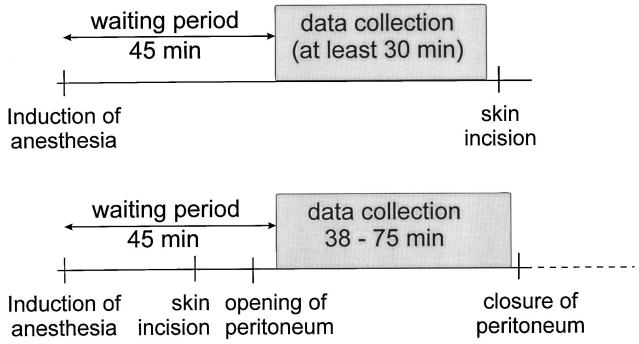

Fig. 1. Timing of data collection. (*Top*) Patients investigated without surgical stimulation. Anesthesia was induced with 2 mg/kg propofol. Thereafter, a 45-min waiting period was allowed for the effects of propofol to dissipate and for transition to pure desflurane anesthesia. The concentration–response curves were obtained before skin incision. (*Bottom*) Patients investigated during surgical stimulation. Again, after induction of anesthesia, a 45-min waiting period was allowed for the effects of propofol to dissipate and for transition to pure desflurane anesthesia. The concentration–response curves were obtained during gynecologic laparotomies between opening and closure of the peritoneum.

Decreasing the desflurane vaporizer settings was terminated if an end-tidal desflurane concentration of 0.5 MAC (= 1.3 · MAC awake[13]) was achieved or if the attending anesthesiologist no longer considered the depth of anesthesia adequate. Inadequate anesthesia was defined by the following criteria:[14]

1. increase in systolic blood pressure by more than 15 mmHg more than normal for that patient, with normal systolic blood pressure defined as the mean of three systolic blood pressure measurements from admission until premedication
2. heart rate exceeding 90 beats/min in the absence of hypovolemia
3. other autonomic signs, such as sweating or flushing
4. somatic responses, such as movements or swallowing

In addition, the anesthesiologist was allowed to terminate decreasing anesthetic concentration if he did not consider the depth of anesthesia adequate. Increasing of desflurane vaporizer settings was terminated when the attending anesthesiologist considered the level of anesthesia too deep or if the end-tidal desflurane concentration of 1.6 MAC was reached. Data collection was terminated at closure of the peritoneum. The patients were visited 1 day after surgery and asked about recall of intraoperative events (explicit memory).

Electroencephalographic Analysis

Before induction of anesthesia, disposable electrodes (Zipprep; Aspect Medical Systems, Natick, MA) were applied to the left and right frontal pole (Fp1 and Fp2, international 10-20 system), with Fpz as the reference plus a ground electrode. Impedance was maintained at a level less than 5 KΩ. One electroencephalographic lead was used for signal analysis with the electroencephalo-

graphic monitor Sirecust 404 (Siemens, Erlangen, Germany). The raw signal was filtered between 0.5 and 32 Hz and divided into epochs of 8.192 s in duration, which were digitized at a rate of 125 Hz. After automatic artifact rejection, the median power frequency (MPF; the frequency less than which 50% of the power lies) and spectral edge frequency 95 (SEF 95; the frequency less than which 95% of the power lies) were calculated for each epoch. A moving average during seven epochs (three forward and three backward) was used for data smoothing. Additionally, we used the Aspect A-1000 EEG Monitor, Version 2.5 (Aspect Medical Systems) to calculate the Bispectral Index (BIS), computed from the bilateral frontal channels. The BIS was internally averaged during 60 s. The electroencephalographic parameters were displayed on the monitor throughout the procedure. The electroencephalogram was recorded for 10 min before induction to obtain a baseline level while the patient was awake. All data were stored on a hard disk.

Statistical Analysis

Simultaneous Pharmacokinetic and Pharmacodynamic Analysis. The program system NONMEM, version 4, with the first order conditional estimation method and η-ε interaction to reduce the influence of model misspecification, was used for all model fits and empirical Bayesian estimation of the individual parameters.[15] To eliminate the hysteresis between end-tidal concentrations and the electroencephalographic parameter values, an effect site was introduced into the model:

$$dC_{eff}/dt = (C_{et} - C_{eff}) \cdot k_{e0} \quad (1)$$

where C_{et} is the end-tidal concentration, C_{eff} the effect-site concentration, and k_{e0} is the first-order rate constant determining the efflux from effect site.

The relation between effect-site concentrations and electroencephalographic parameter values was modeled with a sigmoid E_{max} model:

$$E = E_0 + (E_{max} - E_0) \cdot [C_{eff}^{\gamma}/(EC_{50}^{\gamma} + C_{eff}^{\gamma})] \quad (2)$$

where E_0 is the measured or fitted electroencephalographic parameter value in the absence of the drug (= baseline or awake state), E_{max} is the electroencephalographic parameter value corresponding to maximum drug effect, EC_{50} is the concentration that causes 50% of the maximum effect, and γ describes the slope of the concentration–response relation.[16]

An exponential model was used to describe the interindividual variability for both k_{e0} and all pharmacodynamic parameters:

$$\theta_{(n,i)} = \theta_{(n,m)} \cdot e^{\eta(i)} \quad (3)$$

where n denotes the parameter, i denotes the individual patient number, $\theta_{(n,\,i)}$ refers to the individual value of the respective parameter, $\theta_{(n,\,m)}$ is the population mean of the parameter, and η varies randomly among individuals with mean 0 and diagonal variance–covariance matrix Ω^2.

An additive error model was chosen to model residual variability:

$$DV_{obs} = DV_{exp} + \varepsilon \quad (4)$$

DV_{obs} refers to the observed value of the dependent variable (electroencephalographic parameter value), and DV_{exp} refers to the value predicted based on end-tidal concentration time courses, and the individual pharmacokinetic and pharmacodynamic parameters. ε is a normally distributed random variable with a mean of 0 and a variance of σ^2.

Model Identification

We tried to find an initial model with no covariates. We started with a model with fixed effects (k_{e0}, E_0, EC_{50}, E_{max}, λ, and the error variance σ^2) and then incorporated random effects for each of the parameters. The random effects were added one at a time and were kept in the

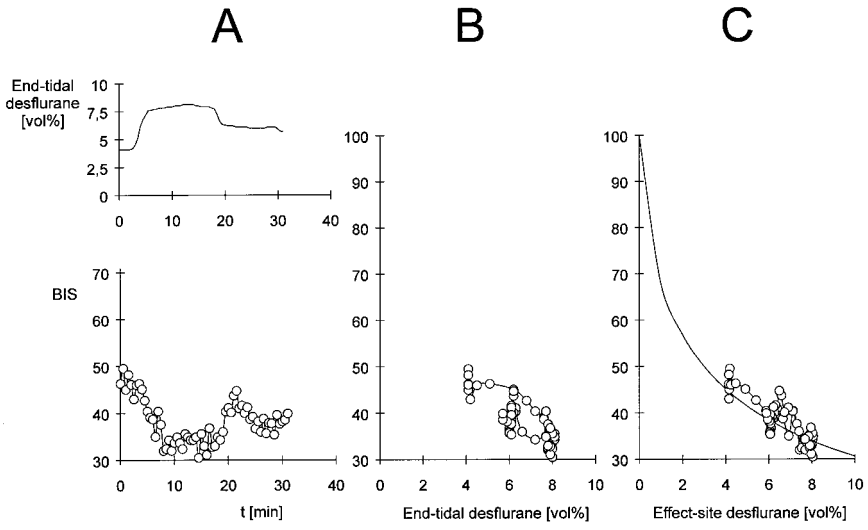

Fig. 2. Determination of the desflurane concentration–electroencephalographic effect relation for a patient without surgical stimulation. (*A*) End-tidal desflurane concentrations and Bispectral Index *versus* time. According to a randomized protocol, desflurane vaporizer settings were increased and decreased. (*B*) End-tidal desflurane concentrations *versus* Bispectral Index. Hysteresis loops were observed. (*C*) Desflurane effect-site concentrations, gained by simultaneous pharmacokinetic and pharmacodynamic analysis, *versus* Bispectral Index. Open circles = Bispectral Index; solid line = pharmacodynamic model.

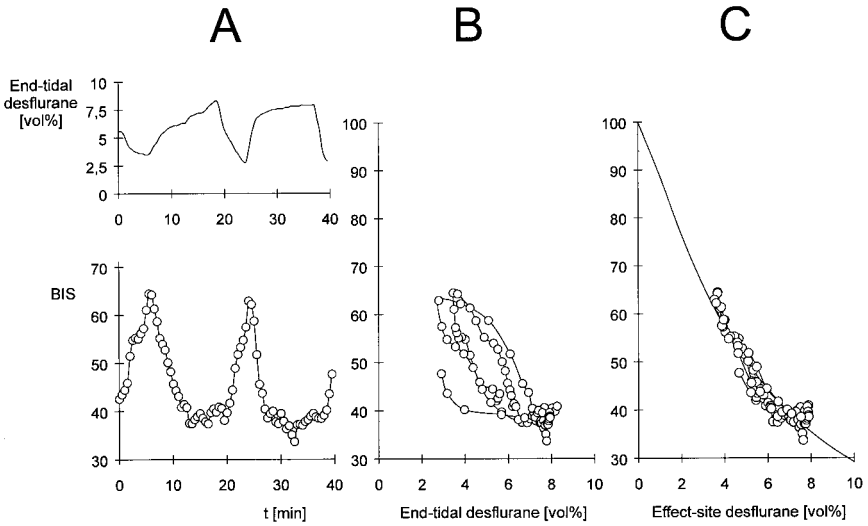

Fig. 3. Determination of desflurane concentration–electroencephalographic effect relation for a patient during surgical stimulation. *(A)* End-tidal desflurane concentrations and Bispectral Index *versus* time. According to a randomized protocol, desflurane vaporizer settings were increased and decreased. (*B*) End-tidal desflurane concentrations *versus* Bispectral Index. An hysteresis loop was observed. (*C*) Desflurane effect-site concentrations, gained by simultaneous pharmacokinetic and pharmacodynamic analysis, *versus* Bispectral Index. Open circles = Bispectral Index; solid line = pharmacodynamic model.

model if they (1) improved the minimum value of the objective function, judged by the likelihood ratio criterion, with $P < 0.05$ and (2) if their 95% confidence intervals excluded the null values.

After a reasonable complete model was found, we refined it by introducing covariates. The initial model served as the null hypothesis for a statistical comparison with models including covariates.

Covariate Analysis

The covariates that were evaluated were patient age and presence or absence of surgical stimulation. Covariates were added one at a time and were kept in the model if they improved the minimum value of the objective function, with $P < 0.05$, and by analysis of the confidence intervals of the estimated parameters.

Patient age was incorporated by using the parameter EC_{50} in an age-dependent manner with

$$\theta_{(EC_{50,i})} = \theta_{(EC_{50,m})} \cdot 10^{\theta_{(age)} \cdot (age(i) - pm_{age})} \quad (5)$$

where $\theta_{(age)}$ is a parameter for age correction, $age_{(i)}$ is the age of the ith patient, and pm_{age} is the population mean of patients' ages.[17]

Whether the presence or absence of surgical stimulation influences the concentration–response curves was investigated by building separate models. The parameters k_{e0}, E_0, E_{max}, EC_{50}, γ, and their variances were allowed to differ between the groups investigated without and during surgical stimulation. Successively, each of these parameters was added one at a time and kept in the model if they significantly improved the minimum value of the objective function and if their confidence intervals excluded the null values.

Results

The investigational protocol was completed in all patients without incident. Periods of burst suppression

Table 2. Improvement in the Objective Function by Introducing Patients' Age and Presence of Surgical Stimulation as Covariates for the Desflurane Concentration–Electroencephalographic Effect Relation in the Initial Models

	Number of Estimated Parameters	Improvement in the Objective Function
SEF 95		
Initial model	10	—
Presence of surgery as a covariate	12	−52.27
Presence of surgery and age as covariates	13	−58.2
MPF		
Initial model	10	—
Presence of surgery as a covariate	11	−11.2
BIS		
Initial model	7	—
Presence of surgery as a covariate	9	−16.89

The search for the final models started with an initial model for each electroencephalographic parameter, built by using the same parameter set for both groups, with and without surgical stimulation. The parameter set contained fixed and random (variances) effect parameters for k_{e0}, E_0, EC_{50}, E_{max}, λ, and the error variance. The initial models served as the null hypothesis for a statistical comparison with models, including covariates. Presence or absence of surgery and patients' age were introduced as covariates and kept in the models if they significantly improved the objective function. Models including presence of surgery as a covariate allowed a shift of the concentration–electroencephalographic effect curve toward higher concentrations by introducing the separate parameter EC_{50} and a greater steepness of the concentration–electroencephalographic effect curves by introducing the separate parameter λ for the patients during surgical stimulation. Age as a covariate was modeled using the EC_{50} in an age-dependent manner. The final estimated models' parameters for spectral edge frequency 95 (SEF 95) are k_{e0}, $\eta_{k_{e0}}$, E_0 during surgery, E_{max}, EC_{50} without surgery, EC_{50} during surgery, γ without surgery, γ during surgery, age correction on EC_{50}, $\eta_{E_{max}}$, $\eta_{EC_{50}}$, η_γ, and σ^2. The final estimated models' parameters for the median power frequency (MPF) are k_{e0}, $\eta_{k_{e0}}$, E_0 during surgery, E_{max}, EC_{50} without surgery, EC_{50} during surgery, γ, $\eta_{E_{max}}$, $\eta_{EC_{50}}$, η_γ, and σ^2. The final estimated models' parameters for the Bispectral Index (BIS) are k_{e0}, $\eta_{k_{e0}}$, EC_{50} without surgery, EC_{50} during surgery, γ without surgery, γ during surgery, $\eta_{EC_{50}}$, η_γ, and σ^2. The minimum value of the objective function is minus twice the logarithm of the likelihood of the data, calculated by the computer program NONMEM.

Table 3. Pharmacokinetic and Pharmacodynamic Parameters for the Concentration–Electroencephalographic Effect Relation

	SEF 95 Parameter	
	Value (θ)	Variance (η)
Pharmacokinetic parameter k_{e0}	0.54 ± 0.08 min^{-1}	0.43 ± 0.21
Pharmacodynamic parameters without surgical stimulation		
E_0	21.7 ± 0.79 Hz*	7.4 ± 1.3*
E_{max}	5.68 ± 1.29 Hz‡	0.26 ± 0.22‡
EC_{50}	2.54 ± 0.49 vol%	0.11 ± 0.05‡
γ	2.20 ± 0.73	0.13 ± 0.05‡
During surgical stimulation		
E_0	17.8 ± 0.69 Hz	—
E_{max}	5.68 ± 1.29 Hz‡	0.26 ± 0.22‡
EC_{50}	5.32 ± 0.31 vol%	0.11 ± 0.05‡
γ	4.21 ± 0.55	0.13 ± 0.05‡
Parameter for age correction $\theta_{(age)}$	−0.0072 ± 0.0032 yr^{-1}‡	—
Error variance (σ^2)	1.17 ± 0.49 Hz^2	

The estimated parameters for the final pharmacokinetic and pharmacodynamic model are those characterized by the mixed-effect model using the computer program NONMEM. Parameters are given as mean ± SEM. The values for EC_{50} are the typical values for a 40-yr-old patient. The EC_{50} for patients' age deviating from 40 yr can be calculated as $EC_{50} \cdot 10^{\theta(age) \cdot (age-40)}$. Thus, a parameter value of −0.0072 for age correction corresponds to a decrease of 15% for each 10 yr.

* Values were taken from baseline measurements. † Parameter values were fixed initially at the respective values, and parameter estimation did not decrease significantly the minimum value of the objective function. ‡ The same parameters were used for both groups, and estimation of separate parameters did not significantly decrease the minimum value of the objective function.

SEF 95 = spectral edge frequency 95; MPF = median power frequency; BIS = Bispectral Index.

were observed in all patients without surgical stimulation when end-tidal desflurane concentrations exceeded 1.5 MAC. During surgery, the period for electroencephalographic data acquisition (between opening and closure of the peritoneum) ranged from 38–75 min. Eighteen percent of the electroencephalographic epochs were rejected because of recognition of electroencephalographic artifacts by the Aspect EEG Monitor, mainly induced by the use of electrosurgical units. None of the patients showed burst suppression patterns during surgery. None of the patients reported recall of intraoperative events when interviewed on the following day.

Figure 2 depicts the relation among the measured end-tidal desflurane concentrations, the calculated effect-site concentrations, and the electroencephalographic parameters for one patient without surgical stimulation; figure 3 depicts the respective desflurane concentrations and electroencephalographic parameters for one patient during surgical stimulation. Hysteresis was identified between end-tidal concentrations and the electroencephalographic parameters and subsequently collapsed by pharmacokinetic and pharmacodynamic modeling.

Using the data from all patients, initial sigmoidal E_{max} models (with no covariates) for SEF 95, MPF, and BIS were built. Table 2 shows the improvement of the objective function by introducing covariates in the respective initial models. The final pharmacokinetic and pharmacodynamic parameter estimation for each electroencephalographic parameter are given in table 3.

To analyze the SEF 95 and desflurane concentration data set, the model finally incorporated a total sum of 13 parameters for the fixed and random effects. The values for E_0 in the group without surgical stimulation were taken from the baseline values from the awake state. Introducing separate parameters for EC_{50} and γ for patients with and without surgical stimulation and using the parameter EC_{50} in an age-dependent manner significantly reduced the value of the objective function.

To analyze the MPF and desflurane concentration data set, the final model incorporated 11 parameters. In contrast to the SEF 95, introducing a separate parameter γ for patients with and without surgical stimulation did not reduce significantly the value of the objective function. Introducing age as a covariate for EC_{50} for MPF improved the fit but did not achieve the desired level of significance.

The model optimally describing the BIS and desflurane concentration–effect relation incorporated nine parameters. The values for E_0 in the group without surgical stimulation did not differ significantly from 100. E_0 during surgical stimulation was initially fixed to 100, and E_{max} was initially fixed to 0 in both groups. Estimation of these parameters did not improve the value of the objective function. For BIS, no age dependence of EC_{50} was found.

Figure 4 displays the individual Bayesian estimates for the individual patients and the models based on the population means for the respective electroencephalographic parameters. Figure 5 depicts the residual errors. The median absolute residual for each electroencephalographic parameter is given in table 4.

Discussion

Our study demonstrated that for up to 8 vol% desflurane, the electroencephalographic parameters SEF 95,

Table 3. Continued

MPF Parameter		BIS Parameter	
Value (θ)	Variance (η)	Value (θ)	Variance (η)
0.53 ± 0.085 min^{-1}	0.28 ± 0.11	0.43 ± 0.09 min^{-1}	0.94 ± 0.41
10.6 ± 0.64 Hz*	4.9 ± 0.9*	100†	—
1.54 ± 0.12 Hz‡	0.10 ± 0.003‡	0†	—
1.86 ± 0.44 vol%	0.16 ± 0.06‡	2.20 ± 0.74 vol%	0.42 ± 0.20‡
5.03 ± 0.95‡	0.34 ± 0.008‡	0.53 ± 0.15	0.39 ± 0.14‡
9.48 ± 2.88 Hz	—	100†	—
1.54 ± 0.12 Hz‡	0.10 ± 0.003‡	0†	—
3.87 ± 0.79 vol%	0.16 ± 0.06‡	6.80 ± 0.98 vol%	0.42 ± 0.02‡
5.03 ± 0.95‡	0.34 ± 0.008‡	0.98 ± 0.14	0.39 ± 0.14‡
—	—	—	—
0.45 ± 0.10 Hz^2		11.0 ± 1.2	

MPF, and BIS were considerably higher if surgical stimulation was present compared with the unstimulated state. Pharmacokinetic and pharmacodynamic analysis showed that surgical stimulation shifted the desflurane concentration–electroencephalographic effect curves toward higher concentrations. In fact, during surgery, concentrations of the volatile anesthetic approximately 2 or 3 times higher were required to maintain a desired level of cortical electrical activity. This result was not unexpected and is indeed consistent with clinical practice. Most anesthesiologists routinely increase volatile anesthetic concentrations anticipating that a surgical stimulus may lead to an arousal reaction.

To the best of our knowledge, there are no studies that systematically investigated the influence of surgical stimulation on the relation of anesthetic concentrations and electroencephalographic effects. In experiments in rats Kissin *et al.*[18] showed that pentobarbital blocked awakening caused by noxious stimulation of different intensities in a dose-related fashion so that more anesthetic was required to block awakening with more intense stimulation. It seems that the nociceptive input to the brain may influence the level of consciousness or at least the level of the electrical activity in the brain. In some studies, laryngoscopy and intubation were used as a model of nociception during anesthesia to investigate the arousal reaction accompanying noxious stimulation and its modulation by anesthetic agents.[19,20] Iselin-Chaves *et al.*[21] applied a painful stimulus, periosteal pressure to the tibia, to anesthetized volunteers to investigate arousal reaction in the electroencephalogram. Other studies focussed on electroencephalographic patterns shortly before arousal after surgery.[22,23] A number of studies investigated the effect of skin incision and start of the surgical procedure on the electroencephalogram.[5,8–11] Some authors reported paradoxical electrophysiologic phenomena such as increases in δ and decreases in α activity after the start of surgery.[8–11] Despite the increasing application of the electroencephalograph for monitoring anesthetic effect,[24,25] it was never systematically investigated under which circumstances or in which subpopulations of patients "paradoxical" arousal reactions may occur. However, in accordance with the study of Wilder-Smith *et al.*[19] and other authors,[20–23] such a pattern could not be observed in any of our patients. Increased parameter values for SEF 95, MPF, and BIS during surgery support a classic, excitatory electroencephalographic arousal reaction comprising a loss of low-frequency (δ) activity and increased high-frequency (α, β) activity.[5,6] An excitatory electroencephalographic arousal reaction resulting from increased nociceptive stimulation is a rational basis for dosing of anesthetics guided by electroencephalographic monitoring.

In contrast to clinical routine, when a combination of various drugs is applied, in this study, desflurane was used as a monoanesthetic. Volatile anesthetics can be used as monoanesthetics during surgical procedures. We did not use more than one anesthetic, thus avoiding an analysis of the interaction of two or more anesthetics on the electroencephalogram, which would require extensive data sampling and analysis. Most studies investigating the cardiovascular,[26] respiratory,[27] electroencephalographic effects,[28] or motor reactions following skin incision[13] used steady-state concentrations of the volatile anesthetic. Studying the effects of volatile anesthetics at steady-state anesthetic concentrations being maintained for 15–30 min, however, may be a difficult task during surgery. Moreover, the maintenance of low anesthetic concentrations over a prolonged period may cause inadequate clinical conditions. Therefore, we preferred to investigate the concentration dependence of volatile anesthetic electroencephalographic effects by variation of the anesthetic concentration (non–steady-state design) and elimination of the hysteresis with an established modeling approach.[29] Because of the pharmacokinetic properties of desflurane,[30] we continued using desflurane with increased vaporizer settings to deepen anesthesia level if the attending anesthesiologist considered the level of anesthesia too low. This allowed us to obtain

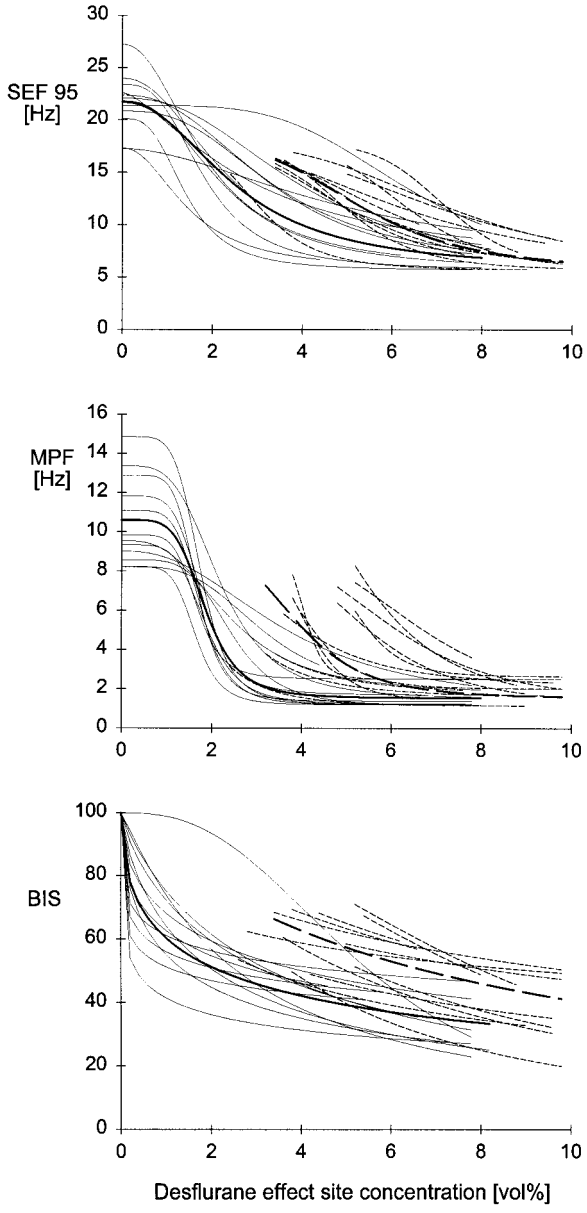

Fig. 4. The desflurane concentration–electroencephalographic effect curves with and without surgical stimulation, stacked as spectral edge frequency 95 (SEF 95; *top*), median power frequency (MPF; *middle*), and Bispectral Index (BIS; *bottom*). Light solid line = individual patients without surgical stimulation; light dashed line = individual patients during surgical stimulation; heavy solid line = model for patients without surgical stimulation; heavy dashed line = model for patients during surgical stimulation.

the entire concentration–effect curve associated with clinically acceptable levels of anesthesia—the therapeutic window. We did not use desflurane concentrations exceeding 1.6 MAC because high concentrations of a volatile anesthetic were known to induce burst suppression patterns in the electroencephalogram.[12] In the presence of burst suppressions, spectral electroencephalographic parameters are invalid.

We used two separate groups of individuals for the comparison of concentration–response curves obtained with and without surgical stimulation. It would have been possible to investigate the patients as their own controls by first obtaining the presurgical concentration–response curves and subsequently obtaining the concentration–response curves during surgery. Using the patients as their own controls might have been advantageous with regard to statistical power. However, we did not want to exclude *a priori* that concentration–response curves may shift over time (acute tolerance).[31] We also did not want to exclude the possibility that our intervention, applying subsequently various anesthetic concentrations associated with light and deep levels of anesthesia, may influence the concentration–response curves (*i.e.*, sensitization).[32] Therefore, we preferred a study design comprising a treatment and a control group, which allows placement of the measurements at equal times after the start of anesthesia in both groups. In addition, we used a randomization sequence, starting in half of the patients with initially decreasing and in the other half with initially increasing anesthetic concentrations.

Decreasing anesthetic concentrations during surgical stimulation may become an ethical problem because the lowest anesthetic concentration that produces unconsciousness in an individual is not known *a priori*. The lowest end-tidal desflurane concentration we applied was 0.5 MAC (= 1.3 · MAC awake[13]), assuming that unconsciousness was maintained in a high percentage of individuals.[33] In addition, criteria for inadequate anesthesia based on autonomic and somatic signs adapted from Ausems *et al.*[14] were used to identify the low end of the therapeutic window. However, clinical signs of adequate depth of anesthesia are known not to be safe in excluding intraoperative awareness.[34] Therefore, the attending anesthesiologist was allowed to terminate decreasing anesthetic concentration if he suspected adequate depth of anesthesia, even if none of these criteria was completely fulfilled, for example, if blood pressure tended to increase but did not reach more than 15 mmHg more than normal.

At concentrations less than 8 vol% desflurane, we observed a considerable rightward shift of the concentration–response curves under surgical stimulation. This is in accordance with investigations of Zbinden *et al.*,[35] who observed that high anesthetic concentrations of up to 1.5 MAC isoflurane did not entirely blunt increases in blood pressure and heart rate after a noxious stimulus. In recently published studies, Antognini and Carstens[36] and Antognini *et al.*[37] found that suppression of the noxious-stimulation effect on the electroencephalogram in goats occurred at approximately 1.0 MAC and that part of this effect was related to anesthetic action in the spinal cord. However, in our study, we could not identify any desflurane concentration at which the increased electroencephalographic activity during surgery was suppressed completely. It is possible that our pharmacodynamic

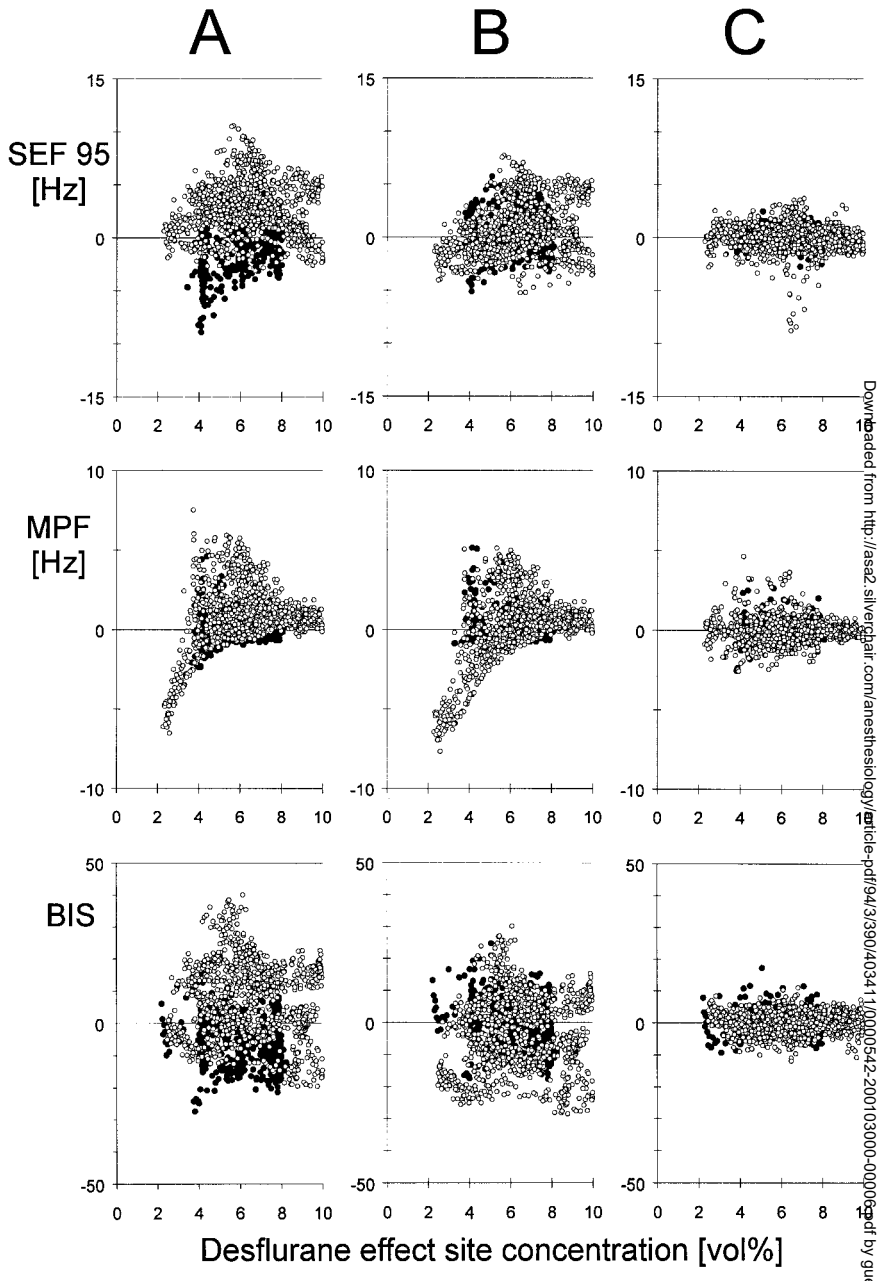

Fig. 5. Graphs of the residual errors, plotted as measured–predicted electroencephalographic parameter value *versus* desflurane concentration, stacked as spectral edge frequency 95 (SEF 95; *top*), median power frequency (MPF; *middle*), and Bispectral Index (BIS; *bottom*). (*A*) Predictions were based on mean pharmacokinetic and pharmacodynamic parameters without surgical stimulation as a covariate. (*B*) Predictions were based on mean pharmacokinetic and pharmacodynamic parameters with surgical stimulation as a covariate. (*C*) Predictions were based on Bayesian estimates of the individual pharmacokinetic and pharmacodynamic parameters and surgical stimulation as a covariate.

modeling failed to identify the desflurane concentration at which concentration–response curves should be regarded as matched. Two concentration–response curves given by sigmoidal E_{max} models only differing in their EC_{50} values will never come into contact at any concentration less than infinite. The question of at which anesthetic concentration the increased electroencephalographic activity during surgery is suppressed completely may be answered more accurately with a steady-state approach.

One part of the inter- and intraindividual variability might have occurred because the level of noxious stimulation might not have remained constant during the data collection in our surgical patients. Quantifying the level of noxious stimulation may indeed be a problem when examining electroencephalographic effects of anesthetics during surgery. We investigated patients undergoing the same type of surgery (gynecologic laparotomies), and we used the same period between opening and closure of the peritoneum to obtain data during surgical stimulation. We expected the intraindividual (over time) variations of the level of surgical stimulation in this period to be rather small,[38] especially in relation to the changes in the dose range of the anesthetic used from 0.5 (rather light anesthesia) to 1.6 MAC (rather deep anesthesia). We considered the median absolute residual (table 4), which reflects one aspect of the influence of inconstant levels of consciousness. The median absolute residual, however, was rather small and not substantially elevated in the group with surgical stimu-

Table 4. Median Absolute Residual for Each Electroencephalographic Parameter

	Median Absolute Residual	
	Without Surgery	During Surgery
SEF 95	0.35 Hz	0.57 Hz
MPF	0.21 Hz	0.32 Hz
BIS	1.9	1.9

The residuals are the differences between the observed electroencephalographic parameters and their predictions based on Bayesian estimates of the individual pharmacokinetic and pharmacodynamic parameters and the individual end-tidal concentration time courses.

SEF 95 = spectral edge frequency 95; MPF = median power frequency; BIS = Bispectral Index.

lation, so we judged the variability in the level of noxious stimulation in our setting to be of minor importance.

Several anesthetics possess electroencephalographic activating properties when administered in low doses. Such a biphasic relation between drug concentration and electroencephalographic effect was found for thiopental,[39] propofol,[40] midazolam,[41] and the volatile anesthetic sevoflurane,[2] but not for opioids.[3] At low anesthetic concentrations, MPF or SEF 95 were found to be slightly elevated compared with preanesthetic values. BIS values could not exceed 100, even if drugs with electroencephalographic activating properties were administered. There is no reason to believe that desflurane behaves differently from sevoflurane in this respect. However, because of its irritating effects on airways with coughing and moving (the patients in our study were intubated) and an increased number of electroencephalographic artifacts, we failed to obtain enough valid data in the group without surgical stimulation below 0.4 MAC desflurane. Therefore, we could not decide whether desflurane possesses electroencephalographic activating properties at low concentrations.

In our setting, we could not model a clear concentration dependence of the cardiovascular parameters for the volatile anesthetic desflurane, perhaps because of its hemodynamic properties. Desflurane decreases dose-dependent blood pressure and heart rate.[26] In particular, rapid increases in desflurane concentrations, as used in our study, are known to increase arterial blood pressure or heart rate transiently.[42] Repetitive rapid increases in desflurane concentration (as used in our study) blunt this transient cardiovascular stimulation.[43]

It is well known that noxious stimulation causes autonomic (*e.g.*, increases in blood pressure and heart rate, sweating, and tearing) and somatic reactions (*e.g.*, movements) and arousal.[7] Because anesthesiologists anticipate a rise in stimulation and concomitant reactions with the commencement of surgery, they routinely increase the dose or concentration of the chosen anesthetic before skin incision, without waiting for emerging signs of inadequate anesthesia.[44] The present study showed that noxious stimulation also affects the level of cortical electrical activity measured by univariate electroencephalographic parameters. The correlation between electroencephalographic parameters and level of sedation or unconsciousness[45] implies that noxious stimulation may decrease the level of sedation. Compared with the unstimulated state, surgery leads to a rightward shift of the concentration–response curve. Therefore, increased anesthetic concentrations are necessary to maintain a desired level of the chosen electroencephalographic parameter in the presence of surgical stimulation.

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