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Remifentanil Modifies the Relation of Electroencephalographic Spectral Changes and Clinical Endpoints in Propofol Anesthesia

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Background: **Depth-of-anesthesia monitoring with the electroencephalogram has become widely used in anesthesia practice. Generally, the methods presented are based on the spectral changes of the electroencephalogram. In this study, the authors evaluate the influence of remifentanil on the relation of timely occurrence of clinical endpoints and the spectral behavior of the electroencephalogram.**

Methods: **Twenty-seven patients scheduled to undergo a surgical procedure were randomly assigned to three groups. Patients blindly received equal volumes of saline or remifentanil (7.5 or 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$) 1 min before induction of anesthesia with infusion of propofol (30 $mg \cdot kg^{-1} \cdot h^{-1}$). The occurrence of loss of counting, loss of obeying verbal command, and loss of reaction to tetanic stimulation was assessed. The electroencephalogram was recorded from electrode Fz referenced to the common average, and an iterative algorithm was applied to solve the underlying frequency progression pattern. The positions of the clinical endpoints on the pattern were analyzed.**

Results: **The administration of remifentanil during induction of anesthesia with propofol led to an earlier occurrence of the clinical endpoints on the frequency progression pattern. A significant difference ($P < 0.05$) was observed between the saline and high-dose patient groups in all three endpoints. The effect of remifentanil was proportional to the infusion rate.**

Conclusions: **The infusion of remifentanil during propofol anesthesia significantly modifies the mutual relations of the electroencephalographic spectral characteristics and the endpoints in a predictable and quantifiable manner. This finding suggests that the electroencephalographic phenomena and the endpoints may not be identical but rather to some extent separate manifestations of hypnotic drug effect.**

MEASURING the depth of anesthesia using the electroencephalogram has become widely used in hospitals all over the world. A number of electroencephalogram-based depth-of-anesthesia indicators (*e.g.*, the Bispectral Index [A-2000 BIS® monitor; Aspect Medical Systems Inc., Newton, MA],[1] the spectral edge frequency 95% and median power frequency,[2] the Narcotrend index [Narcotrend®; Schiller AG, Baar, Switzerland],[3] the Patient State Index [PSI®; Hospira, Lake Forrest, IL],[4] the spectral entropy[5]), have been proposed to express the suppressive effect of anesthetics on the central nervous system. Regardless of the practical usefulness of these indices at different levels of anesthesia, there is still debate over their accuracy, especially in predicting clinical endpoints in the presence of opioids.

The depth-of-anesthesia monitors greatly rely on the spectral features of the electroencephalogram.[6] However, little work has been published in the fundamental neurophysiologic level considering the relation between the electroencephalographic features and hypnotic endpoints in detail (see, *e.g.*, Koskinen *et al.*,[7] Kuizenga *et al.*,[8] John and Prichep[9]). Use of the electroencephalogram is based on the systematic and rather smooth progression of the spectral characteristics associated with a deepening level of anesthesia. First, there is an increase of α and β power; then, an increase of δ activity and a decrease of α and β activity; and finally, a decrease of δ activity.[7,8,10] The timing of this biphasic behavior of activity is slightly different between the frequency bands.[7,10,11] The progression rate of the biphasic activity from high to low frequencies has recently been shown to anticipate the occurrence time of the loss of obeying verbal command (LVC).[7,12]

The reliable use of processed electroencephalographic features as a measure of the level of hypnosis requires that the features be related with clinical endpoints. This relation can be challenged by the coadministration of opioids that can have synergistic hypnotic effects.[13–15] Remifentanil, for example, reduces propofol requirements and hence accelerates the hypnotic onset of propofol.[16] Controversial results, however, have been reported. Some studies suggest that the depth-of-anesthesia indices are insensitive to the addition of opioids,[17–19] whereas others report a hypnotic response[20,21] that may cause the performance of the indicators to deteriorate.[22]

In this article, an advanced signal processing methodology[11] is applied to study the effects of remifentanil–propofol interaction on the electroencephalogram and the occurrence of clinical endpoints. We test the hypothesis that remifentanil infusion has an influence on the relation between the electroencephalographic spectral contents and clinical endpoints, namely the loss of counting (LC), the LVC, and the loss of reaction to tetanic stimulation (LRT).

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Table 1. Demographic Data

	All (n = 27)	R0 (n = 9)	R1 (n = 9)	R2 (n = 9)
Age, yr	38 ± 10.2	37 ± 11.7	36 ± 7.8	42 ± 10.7
Weight, kg	72.1 ± 13	72.9 ± 14	70.4 ± 12	73.1 ± 15
Height, cm	171 ± 10	173 ± 13	170 ± 9	171 ± 9
ASA physical status I/II, n	23/4	8/1	7/2	8/1

Data are displayed as mean ± SD or observed frequency.
ASA = American Society of Anesthesiologists.

Materials and Methods

Clinical Protocol

The study was approved by the institutional Ethics Committee of South Carelia Central Hospital, Lappeenranta, Finland. Twenty-seven patients (table 1) scheduled to undergo an elective surgical operation gave informed written consent to participate. Patients with cardiovascular or neurologic diseases, diabetes, or a body mass index greater than 30 kg/m^2 and patients taking central nervous system affecting drugs were excluded. Patients were randomly allocated by selection of sealed envelopes to one of three groups (nine each): saline (R0), low-dose remifentanil (R1), and high-dose remifentanil (R2). The study nurse picked up the envelope and prepared the mixture of the "study drug." Patients and the investigating anesthetist (S.M.) were blinded to the identity of the liquid.

The anesthesia monitoring consisted of the electrocardiogram, noninvasive blood pressure, heart rate, end-tidal carbon dioxide, peripheral oxygen saturation, train-of-four, and one-channel electroencephalogram. All of these data were collected using an S/5 monitor (GE Healthcare Finland Oy, Helsinki, Finland). In addition, the electroencephalogram was recorded with an Embla polygraphic recorder (Medcare, Reykjavik, Iceland). The recorder used a sampling rate of 200 Hz and filtered the signals with a band-pass filter of 0.5–90 Hz. The recorder was attached to a laptop computer for on-line monitoring and data storing. The recording was started before the induction of anesthesia and continued for a period covering at least up to 5 min after the tracheal intubation. Although the electroencephalogram was acquired from 17 electrode positions (according to the international 10/20 system[23]), only the electrode montage Fz, referenced to the common average, was used in the analysis. The montage was formed off-line using unipolar recordings. The data of one patient from the R1 group were discarded because of technical problems during the recording.

The patients were premedicated with 0.1 mg/kg oral diazepam 1 h before the induction of anesthesia. At the beginning of the study, all patients received a 0.05-ml/kg bolus and, immediately after that, a 1.5-ml $\cdot kg^{-1} \cdot h^{-1}$ infusion of the "study drug" *via* a syringe pump (Braun perfusor fm; Braun Melsungen, Germany). In the R0 group, the "study drug" was physiologic saline, whereas in the R1 and R2 groups, it was dilution of remifentanil with concentrations of 5 and 20 $\mu g \cdot ml^{-1}$, respectively. Therefore, the administration of remifentanil was 7.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in the R1 group and 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in the R2 group. Anesthesia was induced by intravenous infusion of propofol *via* syringe pump at a rate of 30 mg $\cdot kg^{-1} \cdot h^{-1}$ 1 min after the start of the infusion of the "study drug." From induction onward, lung ventilation was assisted manually *via* facemask with 100% oxygen. When the onset of burst suppression pattern was detected from the electroencephalographic channel of the S/5 monitor, the infusion rate of propofol was decreased to 18 mg $\cdot kg^{-1} \cdot h^{-1}$, and rocuronium (0.6 mg/kg) was given to facilitate tracheal intubation. After the tracheal intubation, patients' lungs were ventilated with 30% oxygen in air. The anesthesia was continued with infusion of propofol (18 mg $\cdot kg^{-1} \cdot h^{-1}$), and the "study drug" (1.5 ml $\cdot kg^{-1} \cdot h^{-1}$) for at least 5 min and thereafter at the discretion of the anesthetist.

During the induction of anesthesia, three endpoints were assessed: LC, LVC, and LRT. LC was assessed by asking the patient to count continuously from start of the infusion of propofol. After LC, LVC was received by asking the patient at 15-s intervals to squeeze the anesthetist's hand. The verbal commands were given by the same investigator (S.M.) for all patients. For LRT, the time at which purposeful somatic movement ceased as a reaction to transcutaneous constant current tetanic stimulation was determined by the anesthesiologist (S.M.). This was performed with tetanic stimulations at 30-s intervals given after LVC. Stimulations consisted of 3-s bursts of 50 Hz and 60 mA applied *via* self-adhesive electrodes to the ulnar nerve at the wrist.

Electroencephalographic Analysis

The detailed signal analysis methods applied to the recorded electroencephalogram are described in the appendix and more thoroughly in our previous work.[11] Generally, the amplitude trend time series representing the electroencephalographic activity in eight different passbands were calculated. The amplitude trends of all patients are presented in figure 1A. The frequency progression time varies between patients due to the inter-individual response to the anesthetic agent, and hence the underlying phenomenon is not very obvious. The amplitude trends are therefore aligned by time scaling to follow a consistent frequency progression pattern (FPP). In time alignment, all eight of the patient's amplitude trends (*e.g.*, signals in different passbands) are used simultaneously to find the single optimal time scale. The time-aligned amplitude trends are given in figure 1B. The proper time scaling has clustered the curves and revealed the unique characteristics of the amplitude trends in the different frequency bands. In figure 1C, the average FPP calculated from the aligned amplitude trends is

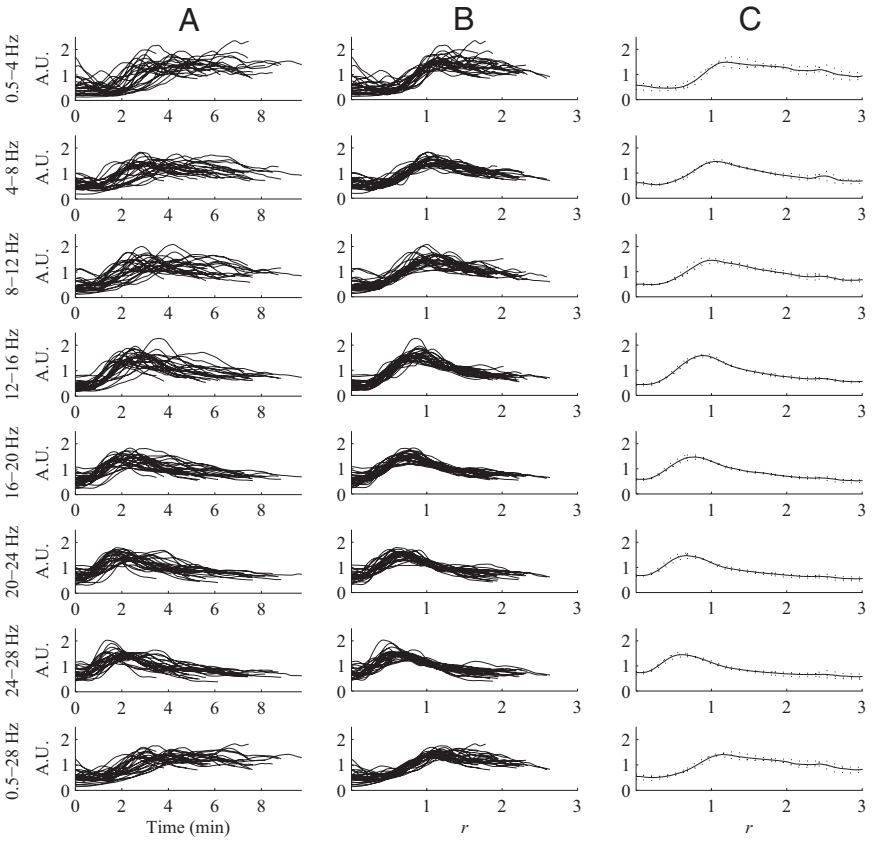

Fig. 1. (*A*) The amplitude trends of the 26 patients. The traces are from the start of the infusion to the onset of burst suppression pattern. The scale is in arbitrary units (A.U.). (*B*) The same traces as in *A* now aligned in time to follow a consistent frequency progression pattern. The trends are presented in *r* scale (see text for explanation). (*C*) The average frequency progression patterns calculated from all aligned amplitude trends (*solid line*) and from the amplitude trends of different groups (*dotted lines*).

illustrated. The FPPs calculated from the aligned amplitude trends of different groups (R0, R1, and R2) are given as well.

The time alignment results in a different time scale for each patient, and therefore the trends can not be given as a function of time in figures 1B and C. Instead, they are presented in *r* scale (see Koskinen *et al.*[7]), in which the value 0 represents the start of induction and 1 represents the instant of the LVC. Because the time alignment results in a unique position of LVC on the FPP for each patient, the median of the R0 group (no remifentanil) LVC points was set to represent the *r* value 1. The *r* scale can therefore be considered as a representation of the phase of the FPP, and $r = 1$ stands for the position in which the LVC occurs without coadministration of opioids.

Statistical Analysis

The group differences in the positions of the clinical endpoints on the FPP, *i.e.*, the *r* scale values at different endpoints, were determined using statistical tests. Because of a rather small sample size, data were not assumed to follow normal distribution (confirmed by the Lilliefors variant of the Kolmogorov-Smirnov test). The comparison was performed with a nonparametric Kruskal-Wallis analysis, with Bonferroni *post hoc* test as necessary. Significance was estimated at $P < 0.05$. Furthermore, the times in which $r = 1$ was reached were compared between groups using the same statistical methods.

The statistical analysis was performed using SPSS 12.0 software (SPSS Inc., Chicago, IL).

Results

Relation of Endpoint Distributions and Frequency Progression Pattern

The positions of clinical endpoints on the FPP are illustrated in figures 2 and 3. In figure 2, the endpoints of all patients on one trace (0.5- to 28-Hz band) of the FPP are given. The distributions of the positions are elucidated with density functions. In figure 3, the positions of the medians of endpoints are presented using traces of all eight passbands. The *r* scale values at different endpoints are illustrated in figure 4. The median *r* scale values at LC for the R0, R1, and R2 groups are 0.80, 0.71, and 0.51, respectively. The respective values at LVC are 1.00, 0.91, and 0.72, and those at LRT are 1.94, 1.17, and 0.85. The results show that remifentanil leads to the earlier occurrence of endpoints on the FPP, *i.e.*, decreases the *r* scale value at different endpoints. The influence of remifentanil is proportional to the infusion rate, which is illustrated in figure 5. In the case of LRT, the decrease of *r* scale values seems to be logarithmic, *i.e.*, rapid with low infusion rates. The *r* scale values at LC and LVC decrease also when the remifentanil infusion rate increases. The decrease in these endpoints seems to

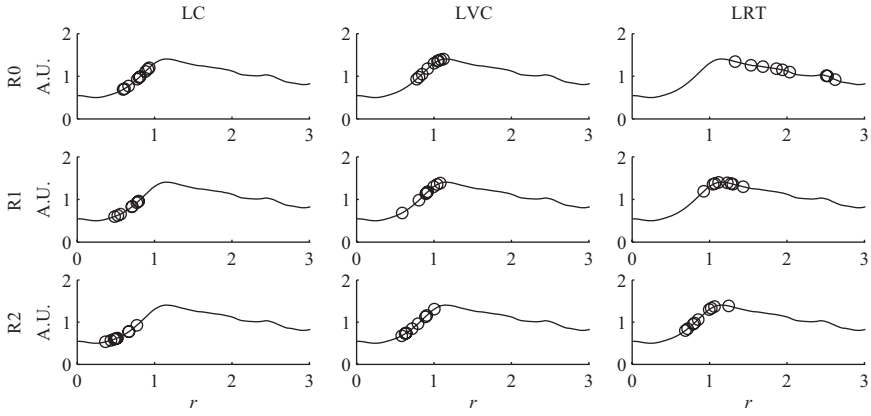

Fig. 2. The positions (○) of clinical endpoints (loss of counting [LC], loss of obeying verbal command [LVC], and loss of reaction to tetanic stimulation [LRT]) on the frequency progression pattern for patient groups R0, R1, and R2. The *solid lines* are the frequency progression pattern on the 0.5- to 28-Hz band. The scale is in arbitrary units (A.U.).

be more or less linearly proportional to the remifentanil infusion rate, however.

Statistical Differences between Remifentanil Groups

The *r* scale values of different endpoints were compared between the groups, and the results are presented in table 2. With the Kruskal-Wallis analysis and Bonferroni *post hoc* test, statistical significance was found only in LRT when the R0 and R1 groups were compared. However, when the R0 and R2 groups were compared, statistical significance was found in all three endpoints.

The effect of remifentanil on the frequency progression phenomenon was examined by analyzing the frequency progression times in different groups. For this, the times from the start of the propofol infusion to $r = 1$ were used (fig. 6). The median times of the R0, R1, and R2 groups at the $r = 1$ point were 2.99, 3.06, and 2.82 min, respectively. No statistically significant difference was found between the groups (table 3). This suggests that remifentanil does not affect significantly the frequency progression time.

Discussion

The effect of remifentanil on the relation of the clinical endpoints and the spectral changes of the electroen-

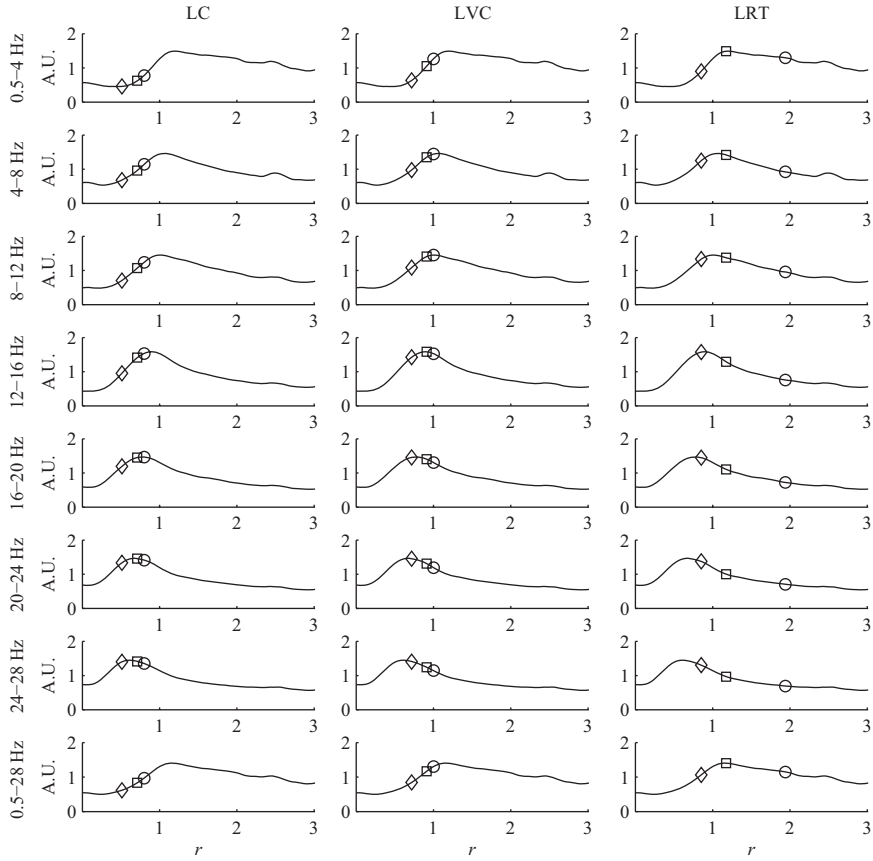

Fig. 3. The positions of the medians of clinical endpoints (loss of counting [LC], loss of obeying verbal command [LVC], and loss of reaction to tetanic stimulation [LRT]) on the frequency progression pattern for patient groups R0 (○), R1 (□), and R2 (◇). The scale is in arbitrary units (A.U.).

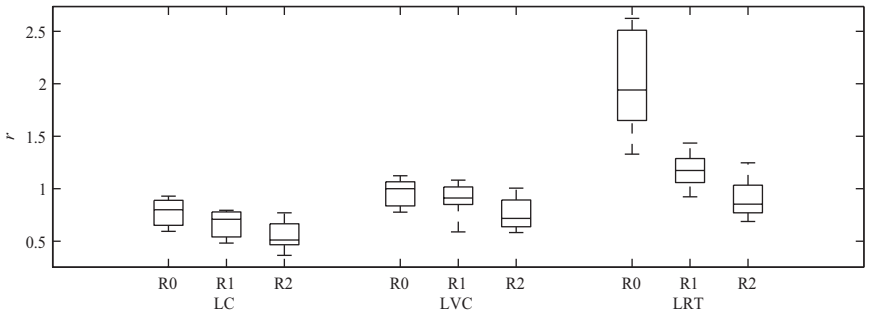

Fig. 4. The *r* scale values at different endpoints (loss of counting [LC], loss of obeying verbal command [LVC], and loss of reaction to tetanic stimulation [LRT]) for patient groups R0, R1, and R2. The five *horizontal lines* in each box plot show the 0th, 25th, 50th, 75th, and 100th percentiles.

cephalogram in propofol-induced anesthesia was studied. The results show that the infusion of remifentanil influences the mutual relations of the electroencephalographic spectral characteristics and the endpoints studied in a predictable and quantifiable manner. The LRT occurred 55% earlier (*r* decreased from 2.01 to 0.91) in the high-dose remifentanil group (R2) than in the saline group (R0). The corresponding values for LVC and LC were 21% and 29%, respectively. This finding suggests that the electroencephalographic phenomena and the endpoints may not be identical but rather to some extent separate manifestations of hypnotic drug effect. However, more studies with a larger data size are required to verify this conclusion.

In the development of monitors, the finding has some importance. Previously, it has been recognized that somatic and hemodynamic reflex responses, such as LRT in this work, are controlled below the level of the cortex in the central nervous system and thus are not directly related to the level of consciousness (*e.g.*, Rampil,[2] Glass *et al.*[24]). Cortical and subcortical measures, such as the electroencephalogram, however, have been assumed to reflect the hypnotic effect, consciousness, memory, or other cortex-related neural functions.[2,9,25] The typical procedure in the development of monitors is to correlate the processed electroencephalographic features with some manual scoring system, such as the Observer's Assessment of Alertness and Sedation scale. The results of this work suggest that a clear distinction should be made between the hypnotic effects on the electroencephalogram and on clinical endpoints. Therefore, the control variables used in depth-of-anesthesia monitors must be selected carefully.

Recently, a number of indices and electroencephalographic measures have been introduced for depth-of-anesthesia monitoring. Basically, they all rely on a major part on the spectral features of electroencephalogram and use the shift of activity from high frequencies to low frequencies as a measure of anesthetic action.[6] The differences mainly concern the details of how this is achieved and how, for example, various artifacts are handled. The research has mainly concentrated on the comparison of different measures in various clinical applications. Because of different measurement conditions and used parameter values, for example, it is often difficult to compare the results of different studies. The results have also sometimes been controversial. For instance, the studies on the influence of remifentanil on electroencephalogram-based depth-of-anesthesia measures show contradictory results, as pointed out in the introduction.

The purpose of this study was to examine in a quantitative manner the uncertainties and inaccuracies of electroencephalogram-based depth-of-anesthesia monitoring related to coadministration of propofol and remifentanil. The problem is approached from a neuroscientific perspective, and therefore the electroencephalographic phenomenon is studied directly, not through indexes, such as BIS® or PSI®. Our purpose was to show the effect of remifentanil on the relation of clinical endpoints and electroencephalographic spectral behavior at a fundamental level. This way, the results are basically applicable to all depth-of-anesthesia measures that are based on spectral changes of the electroencephalogram. The electroencephalographic spectral behavior during induction of anesthesia is described using the FPP, *i.e.*, the activity in eight different passbands. The results we found using the fundamental electroencephalographic activity support the studies performed using indexes. For example, Struys *et al.*[26] found that loss of response

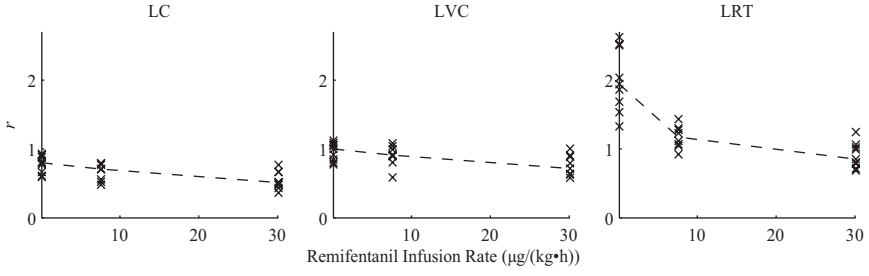

Fig. 5. The *r* scale values at different endpoints as a function of remifentanil infusion rate. The crosses (x) are the *r* scale values of patient groups R0 (0 $\mu g \cdot kg^{-1} \cdot h^{-1}$), R1 (7.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and R2 (30 $\mu g \cdot kg^{-1} \cdot h^{-1}$). The medians of the groups are connected using *dashed lines*. LC = loss of counting; LRT = loss of reaction to tetanic stimulation; LVC = loss of obeying verbal command.

Table 2. *r* Scale Values at Different Endpoints

Group	Mean (95% CI)	Mean Difference (95% CI)	*P* Value
LC			
R0	0.78 (0.68 to 0.87)		0.006*
R1	0.67 (0.56 to 0.77)	0.11 (−0.05 to 0.27)	
R2	0.55 (0.45 to 0.64)	0.23 (0.08 to 0.39)	
LVC			
R0	0.96 (0.86 to 1.06)		0.026*
R1	0.90 (0.77 to 1.03)	0.06 (−0.12 to 0.24)	
R2	0.76 (0.64 to 0.87)	0.21 (0.03 to 0.38)	
LRT			
R0	2.01 (1.65 to 2.36)		<0.001†
R1	1.18 (1.04 to 1.31)	0.85 (0.46 to 1.24)	
R2	0.91 (0.77 to 1.05)	1.10 (0.72 to 1.48)	

Mean difference is calculated compared with R0. *P* values are for Kruskal-Wallis test.

* Significant difference ($P < 0.05$) between the R0 and R2 groups (*post hoc* analysis). † Significant difference ($P < 0.05$) between the R0 and R2 groups and the R0 and R1 groups (*post hoc* analysis).

CI = confidence interval; LC = loss of counting; LRT = loss of reaction to tetanic stimulation; LVC = loss of obeying verbal command.

to verbal command and loss of response to eyelash reflex were reached at higher BIS® and A-Line ARX index (Danmeter A/S, Odense, Denmark) values in a dose-dependent manner when remifentanil was added in propofol anesthesia.

The frequency range investigated in this study (0.5–28 Hz) covers most of the power of the electroencephalogram, and our previous studies[7,11] show that the described biphasic frequency progression phenomena from high to low frequencies can clearly be seen in the presented subbands. The range was sufficient to show the remifentanil-related shift of endpoints. Higher frequencies include considerable electromyographic artifacts that could have deteriorated the smooth amplitude activity waveforms presented. Further studies are needed to examine the potential of frequencies higher than 28 Hz, however.

The effect of remifentanil on certain electroencephalographic parameters, such as approximate entropy and spectral edge frequency 95%, has been reported.[27] The uniform behavior of the FPPs of different groups (fig. 1C) shows, however, that in our study remifentanil does not significantly influence the morphology of the FPP. The finding suggests that remifentanil does not affect the electroencephalographic phenomenon related to the induction of anesthesia, or at least that the phenomenon is strongly dominated by propofol. To further study this proposition, the frequency progression times were examined. Because of the performed time alignment, it was necessary to exclude the possibility that remifentanil, although not changing the morphology of the FPP, affects the frequency progression time. The results presented in figure 6 and table 3 showed that the frequency progression times did not vary significantly between the groups. This could be concluded from the lack of statistical significance, but also from the negligible difference in the means of study groups. This strengthens the proposition that the electroencephalographic frequency progression phenomenon related to the induction of propofol anesthesia is independent of the coadministration of remifentanil.

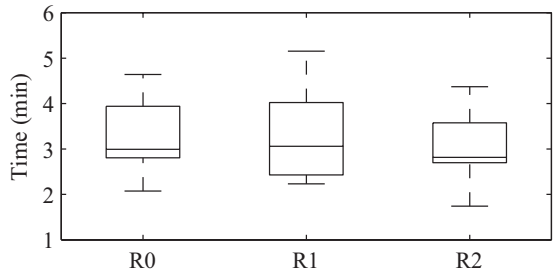

Fig. 6. The times corresponding to $r = 1$ for patient groups R0, R1, and R2. The five *horizontal lines* in each box plot show the 0th, 25th, 50th, 75th, and 100th percentiles.

Table 3. Times from Start of Propofol Infusion to $r = 1$

Group	Mean (95% CI)	Mean Difference (95% CI)	*P* Value
R0	3.32 (2.66 to 3.97)		0.677
R1	3.30 (2.41 to 4.19)	0.01 (−1.13 to 1.16)	
R2	3.05 (2.43 to 3.68)	0.26 (−0.85 to 1.37)	

Mean difference is calculated compared to R0. *P* value is for Kruskal-Wallis test.

CI = confidence interval.

Figures 4 and 5 show that the *r* scale values decrease when remifentanil coadministration is increased. A logarithmic-like decrease of *r* scale values for LRT and a linear-like decrease for LVC and LC were observed. The variation of the R0 group *r* values at LRT seems to be especially large. This finding is supported by the observation that, when only using propofol without opioids, measures from the cerebral cortex, such as BIS®, are poor predictors for LRT.[28] The variation decreases when remifentanil is coadministered with propofol, which means that LRTs are more concentrated in certain positions of FPP. The variation of *r* values at LVC and LC seems to be more or less equal for different groups. Because in this study only three remifentanil infusion rates were used, the results cannot be reliably generalized to other infusion rates. However, knowledge on how the remifentanil infusion rate affects the relation of electroencephalographic indices and clinical endpoints would be valuable for the anesthetist in clinical practice. Therefore, a model for the effect of remifentanil infusion rate should be developed in the future.

Because of drug synergy, nonresponsiveness appears at much lower concentration of propofol in propofol–opioid anesthesia.[15] Therefore, a high dose of opioids associated with a low dose of propofol has become a popular anesthetic technique. It has been suggested that, for example, BIS® should be targeted higher during "opioid-heavy" anesthesia to avoid an unnecessary deep

anesthetic state.[19] The results of this study support this suggestion by showing that remifentanil contributes to the occurrence of clinical endpoints. However, our results also show that remifentanil does not significantly affect the cortical activity seen in the electroencephalogram during induction of anesthesia. This raises the question whether low doses of propofol and high doses of opioid always guarantee an adequate anesthesia by means of higher cortical functions, such as memory. It has been shown that implicit memory is related to the hypnotic electroencephalographic stage in surgical patients.[29] Although the risk of awareness in propofol–remifentanil anesthesia seems to be low,[30] this field warrants further investigation.[31] In this article, only the amount of remifentanil was changed. To further examine this issue, the dosing regimen for propofol should be changed as well.

Some details of the clinical procedure must be taken into account when considering the results of the study. Diazepam premedication probably slightly decreases the propofol dose to attain analgesic and other anesthetic endpoints. Wilder-Smith *et al.*[32] reported a significant decrease in propofol dose to attain analgesic and other anesthetic endpoints after midazolam premedication. Without premedication, higher plasma concentrations of propofol at the analgesic endpoint have been reported.[14] However, in this study, the influence was the same in all groups and did not have significant effect on the expression of electroencephalographic changes. Furthermore, intubation is a significant arousing stimulus and may have an influence on the electroencephalogram. Regardless of this, the effect of intubation and administration of rocuronium on the results are considered to be minor because all of the endpoints were attained before them.

In conclusion, this study shows that coadministration of remifentanil during induction of propofol anesthesia has an effect on the occurrence of clinical endpoints but does not modify the electroencephalographic frequency progression. The mutual relation of the electroencephalographic spectral characteristics and the endpoints is thus affected. The effect is proportional to the dose of the opioids and varies between the endpoints. Because the depth-of-anesthesia indices of today rely greatly on the spectral features of the electroencephalogram, coadministration of opioids with anesthetics may have a negative effect on their reliability.

Appendix: Signal Processing Steps Performed in Electroencephalographic Analysis

The electroencephalographic analysis phases are illustrated in figure 7. First, a finite impulse response (FIR) band-pass filter bank consisting of eight filters was applied to the electroencephalogram of each patient. The passbands were 0.5–4, 4–8, 8–12, 12–16, 16–20, 20–24, and 24–28 Hz, where the limits indicate the 3-dB attenuation points. A passband containing the whole frequency range, *i.e.*, 0.5–28 Hz, was included as well. To correct the delay caused by filtering, a number of samples corresponding to the half of the filter order were ignored from the beginning of the filtered signals.

The amplitude trend time series of the eight signals resulting from the band-pass filtering were calculated next. The signals were first converted to absolute values, *i.e.*, the negative values were multiplied by −1, after which their amplitude trends were extracted using an in-place growing FIR–median hybrid filter presented by Wichman *et al.*[33] This filtering method was chosen for its ability to remove transient spikes and short variations robustly when the filter length is properly selected. A 1,500-level median operator was used, which means that the filter embedded 3,000 data samples (15-s signal sequence). The loss of data caused by filtering was prevented by padding 1,500 zeros into the beginning and end of the signal before filtering. The trends were further down-sampled to 1 Hz to reduce the number of samples. The down-sampling was preceded by low-pass FIR filtering to avoid aliasing. The signals still contained step-like noise due to the edge-preserving characteristics of in-place growing FIR–median hybrid filtering. To remove this noise, a Savitzky-Golay filter[34] with a polynomial order of 3 and frame size of 101, corresponding to 100-s signal sequence, was applied. This filter was capable of smoothing the signal without modifying its general trend and also retains the samples at the beginning and end. Finally, the filtered signals were normalized by dividing them by their mean value between the start of the infusion and the onset of burst suppression pattern to reduce the interindividual amplitude variation. The eight amplitude trends of all patients, resulting from the aforementioned signal processing steps, are illustrated in figure 1A.

Because of the interindividual variability in response to the anesthetics, the frequency progression is not consistent in time between patients. Therefore, an iterative algorithm was applied to the amplitude trends to estimate the underlying FPP. The algorithm, described in detail in our previous work,[11] consisted of the following four steps:

1. Initialization of the FPP: The eight amplitude trends of one patient are chosen as the initial FPP.
2. Amplitude trend alignment: The amplitude trends of all patients are aligned by time scaling to match the FPP. The alignment is based on minimizing the mean squared error between the patient's eight amplitude trends and the FPP. All eight amplitude trends are aligned simultaneously, which results in a single optimal time scale for each patient. Only the signals from start of the infusion to the onset of burst suppression pattern are used in the alignment.
3. Determination of the new FPP: The new FPP is determined by calculating the average of the aligned amplitude trends. To gain also the FPP beyond the onset of burst suppression pattern, the new FPP is calculated from the whole amplitude trends.
4. Comparison of the consecutive FPPs: The new FPP is compared with the previous one, and if no significant difference is found, the iteration is stopped. Otherwise, the iteration is continued from step 2.

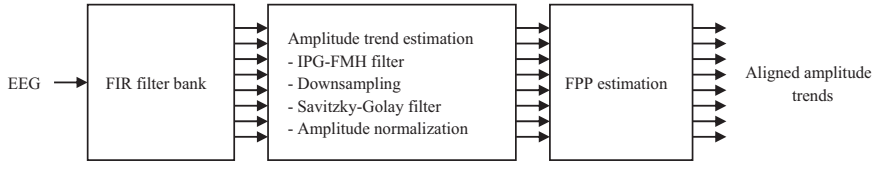

Fig. 7. The signal processing steps performed in the electroencephalographic analysis. EEG = electroencephalogram; FIR = finite impulse response; FPP = frequency progression pattern; IPG-FMH = in-place growing FIR–median hybrid.

With the algorithm, the underlying FPP is revealed, and the best alignment of the amplitude trends of each patient is solved. This way, the occurrence of clinical endpoints can be related to the FPP. The time-aligned amplitude trends of all patients are given in figure 1B.

All the electroencephalographic signal processing was performed with the Matlab® technical computing language (The MathWorks Inc., Natick, MA).

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