Anesthesiology 2009; 111:574–83

Effects of Remifentanil on the Spectrum and Quantitative Parameters of Electroencephalogram in Propofol Anesthesia

Jukka Kortelainen, M.Sc., Miika Koskinen, Ph.D.,† Seppo Mustola, M.D., Ph.D.,‡ Tapio Seppänen, Ph.D.§*

Background: **A high dose of opioids associated with a low dose of propofol has become a popular anesthetic technique. However, the influence of opioids on the electroencephalographic phenomenon related to induction of anesthesia and, thereby, on the quantitative parameters used in the depth-of-anesthesia estimation is not well known.**

Methods: **Twenty-seven patients were divided into three groups to receive saline, low-dose remifentanil (7.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) or high-dose remifentanil (30 $\mu g \cdot kg^{-1} \cdot h^{-1}$) during induction of anesthesia with propofol (30 $mg \cdot kg^{-1} \cdot h^{-1}$). Electroencephalogram was recorded from Fz electrode, and its time-frequency properties in the patient groups were analyzed from the induction of anesthesia to the occurrence of burst suppression pattern. The group differences in 14 quantitative spectral parameters used in the depth-of-anesthesia estimation were examined as well.**

Results: **The time-frequency properties of electroencephalogram were different between groups. The high-frequency (greater than 14 Hz) activity during light anesthesia was decreased in remifentanil groups; whereas, increased activity in extended alpha band (7–14 Hz) and decreased activity in delta band (0.5–4 Hz) was observed during deep anesthesia. This resulted in statistically significant changes in all 14 quantitative parameters.**

Conclusions: **The effect of remifentanil on the spectrum and quantitative parameters of electroencephalogram is significant and strongly dependent on the level of anesthesia. Coadministration of opioids therefore challenges the reliability of the spectral properties of electroencephalogram in the depth-of-anesthesia estimation by using a frontal montage. Furthermore, the finding has implications for design of opioid coadministration studies.**

INCREASING concentrations of anesthetics in the blood produce a continuum of electroencephalographic changes. With propofol, the changes obey roughly the following pattern. First, an increase of the high-frequency (greater than 20 Hz) activity; next, a decrease of the high- frequency activity and increase of the middle-frequency (10–20 Hz) activity; finally, a decrease of the middle-frequency activity and an increase of the low-frequency (0.5–5 Hz) activity.[1,2] In very deep anesthesia, the burst suppression pattern (BSP) begins. Potent inhaled GABAergic anesthetics, such as sevoflurane, isoflurane, and desflurane, follow the same electroencephalographic pattern.[3]

Several measures have been developed for the electroencephalogram-based depth-of-anesthesia estimation. These include both simple parameters, such as the spectral edge frequency 95% (SEF95%) and median power frequency (MPF),[4] and more complex commercial indices like Bispectral Index (A-2000 BIS® monitor; Aspect Medical Systems Inc., Newton, MA)[5] or State and Response Entropy (M-entropy® module; GE Healthcare Finland Oy, Helsinki, Finland).[6] Generally, in all these measures, first or higher order spectrum is utilized.[7]

Remifentanil is an opioid that is increasingly used in the operating room and in intensive care.[8,9] It has analgesic and cardiovascular effects similar to those of alfentanil but with a shorter duration of action.[10] The changes remifentanil produces in the electroencephalogram are characteristic of μ-receptor agonists. They consist of decreasing frequency and increasing amplitude, culminating eventually in delta activity at maximal drug effect.[11,12] During the induction of propofol anesthesia, the above-mentioned basic frequency progression pattern has shown to be robust against coadministration of remifentanil.[13] However, there is evidence that addition on remifentanil during steady-state propofol anesthesia affects to some extent, for example, bispectral index and SEF95%, suggesting some unknown contribution of this opioid to the electroencephalogram.[14]

This paper studies the effect of the coadministration of remifentanil on the electroencephalogram phenomenon occurring during the induction of propofol anesthesia. The effects are examined from the beginning of propofol infusion to the onset of BSP. We hypothesize that the opioids result in characteristic changes to the signal's time-frequency properties, even though the basic propofol-induced frequency progression pattern is left untouched. Furthermore, we examine if the possible changes reflect on the quantitative spectral parameters commonly used in the depth-of-anesthesia estimation.

Materials and Methods

Patients and Clinical Protocol

After the study was approved by the institutional Ethics Committee of South Carelia Central Hospital, Lappeenranta, Finland, 27 patients (table 1) scheduled for

* Research Scientist, § Professor, Department of Electrical and Information Engineering, University of Oulu, Finland; † Postdoctoral Researcher, Advanced Magnetic Imaging Centre and Brain Research Unit, Helsinki University of Technology, Helsinki, Finland; ‡ Staff Anesthesiologist, Department of Anesthesia, South Carelia Central Hospital, Lappeenranta, Finland.

Received from the Department of Electrical and Information Engineering, University of Oulu, Oulu, Finland. Submitted for publication November 29, 2008. Accepted for publication May 5, 2009. Funding and equipment for data collection and analysis provided by the Graduate School in Electronics, Telecommunication and Automation, Finland, by the Department of Electrical and Information Engineering, University of Oulu, Oulu, Finland, by the Department of Anesthesia, South Carelia Central Hospital, Lappeenranta, Finland, and by the Academy of Finland (National Centers of Excellence Program 2006–2011), Finland. Supported in part by grants from the Tauno Tönning Foundation, Finland, from the Walter Ahlström Foundation, Finland, and from the Finnish Foundation for Economic and Technology Sciences – KAUTE, Finland.

Address correspondence to Mr. Kortelainen: Department of Electrical and Information Engineering, BOX 4500, FIN-90014 University of Oulu, Finland. jukka.kortelainen@ee.oulu.fi.

Table 1. Demographic Data

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

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

elective surgical procedure gave informed written consent to participate. Patients having cardiovascular or neurologic diseases, diabetes, or a body mass index greater than 30 were excluded as well as the patients using drugs that affect central nervous system. The patients were randomly assigned to one of three groups (9 each): R0, R1, and R2. Depending on the group, patients received saline (R0), low-dose remifentanil (R1, 7.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) or high-dose remifentanil (R2, 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$) during the induction of anesthesia with propofol (30 $mg \cdot kg^{-1} \cdot h^{-1}$). The infusion of propofol started 1 min after the start of the saline/remifentanil infusion. Both drugs were infused at a fixed rate until the BSP was detected from the electroencephalogram channel of S/5 monitor (GE Healthcare Finland). During the induction, loss of obeying verbal command (LVC) was assessed by asking at 15-s intervals the patient to squeeze the anesthesiologist's (SM) hand. After the onset of BSP, propofol infusion rate was decreased to 18 $mg \cdot kg^{-1} \cdot h^{-1}$, by which the BSP was sustained for at least 5 min. Tracheal intubation was facilitated with 0.6 $mg \cdot kg^{-1}$ rocuronium. During the induction process, electroencephalogram was recorded from 17 different electrode locations according to the international 10/20 system[15] with an Embla polygraphic recorder (Medcare, Reykjavik, Iceland). The recorder used a sampling rate of 200 Hz and filtered the signals with a bandpass filter of 0.5–90 Hz. The recording started several minutes before the induction of anesthesia and continued for at least 5 min after the tracheal intubation. To minimize the signal artifact, the patients were told to be quiet and still before the drug infusion began. In the analysis, only the montage Fz with a common average reference was used. This montage was chosen because the modern depth-of-anesthesia monitoring is based on the analysis of frontal electroencephalogram. The data analyzed in this study was also used in our previous publication,[13] to which the reader is referred for complete details regarding the clinical protocol.

Data Preprocessing

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

The electrooculographic artifacts were removed from the recordings by using the Automatic Artifact Removal toolbox for Matlab.‖ First, the electroencephalographic data from 17 channels were decomposed into spatial components by using a blind source separation technique based on second order statistics, *i.e.*, second order blind identification.[16] The components that could be related to electrooculographic activity were then manually detected and left out when the electroencephalographic data were reconstructed from the spatial components.

Spectrograms

After the electrooculographic artifact removal, spectrograms were calculated from the Fz channel of electroencephalograms by using a short-time Fourier transform with a 3-s Hamming window and 2.9-s overlap. This window length was selected experimentally because it compromised the time and frequency resolution appropriately. The window was also long enough for the analysis of the lowest frequencies of interest. An example of a spectrogram with and without electrooculographic artifact is given in figure 1.

To reduce the large difference in the amplitudes of higher and lower frequencies, the spectrograms were amplitude normalized. In this procedure, the values in a specific frequency were divided by the mean value of all patients in that frequency between the start of the propofol infusion and onset of BSP. The effect of amplitude normalization can be seen in figure 1C. The amplitude normalized spectrograms were used only to visualize the changes in the frequency content of electroencephalograms. They were not used when the quantitative spectral parameters were calculated.

To examine the effect of remifentanil on the spectral characteristics of electroencephalograms, the spectrograms of different groups need to be compared. However, due to the interindividual variability in response to the anesthetic agent, the electroencephalographic spectral progression phenomenon varies in time between patients. Because this hinders the comparison, the time scale of the spectrograms was first normalized by using the method presented in our previous study.[17] The method is based on calculation of electroencephalographic activity in eight different frequency bands for each patient and by minimizing the mean squared error between the activity trends of different patients by time scaling. This results in patient-specific time scaling factors that can be applied to the spectrograms. In other words, the spectrograms are normalized in time by using the frequency progression phenomenon of electroencephalogram during the induction process. The method has been applied previously to the dataset used in this study, and the results showed that the time scaling factors do not differ between groups, *i.e.*, remifentanil does not affect the time normalization.[13] The use of the method in this study is therefore reasonable.

‖ Available at: http://www.cs.tut.fi/~gomezher/projects/eeg/aar.htm. Accessed May 6, 2009.

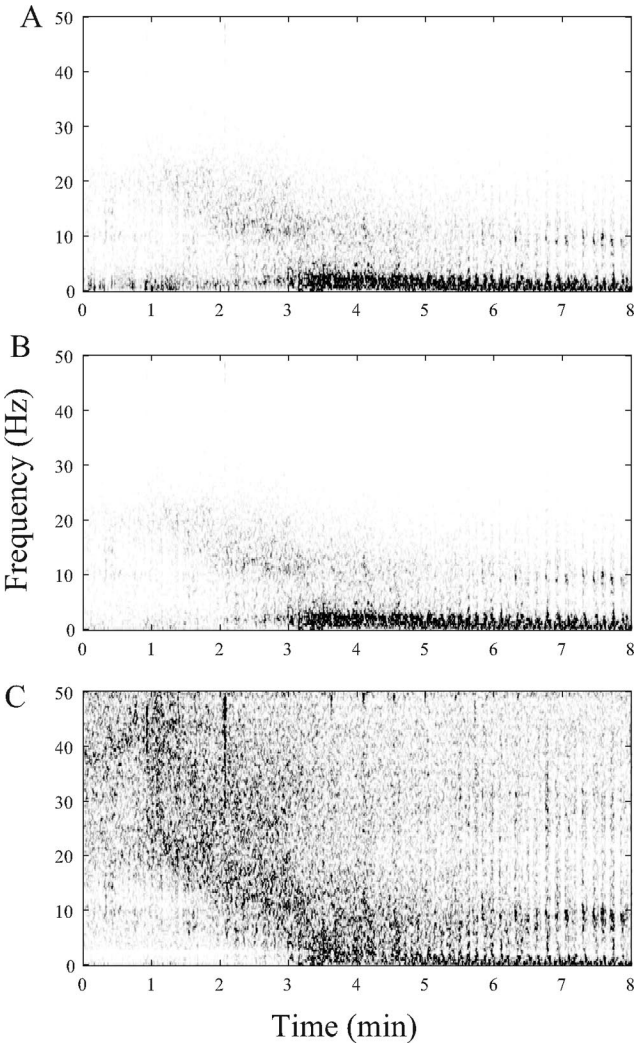

Fig. 1. (*A*) Spectrogram of an electroencephalogram recorded during induction of anesthesia from the beginning of propofol infusion. *Black* and *white* colors represent high and low activity, respectively. Electrooculographic low-frequency artifact can be seen during the first minutes of the recording. The burst suppression pattern occurs approximately after 6-min infusion. (*B*) The same spectrogram as in *A* after electrooculographic artifact removal. (*C*) The same spectrogram as in *B* after amplitude normalization.

After the time normalization, all spectrograms have their own time scale, and they cannot be given as a function of absolute time anymore. Instead, relative time *r* is used. The *r* scale was introduced by Koskinen *et al.*,[18] and its further developed version has been presented recently.[13,19] It can be assumed to describe the phase of the electroencephalographic spectral progression phenomenon during induction of anesthesia. As *r* values are determined from the electroencephalograms recorded during continuous infusion of propofol with a fixed rate, increasing value can be associated with deepening anesthesia. In *r* scale, the start of induction of anesthesia and LVC are used as the points of reference: the values 0 and 1 represent the start of propofol infusion and the position in which the LVC occurs, respectively. The LVC occurs at a different phase of the spectral progression in different groups; therefore, the group R0 positions, *i.e.*, the occurrence of this clinical end point without coadministration of remifentanil, were used. The LVCs of different patients occur also in a slightly different position, and therefore the median of the group R0 LVC points was set to represent the *r* value 1. In this paper, the spectral properties of electroencephalograms are analyzed continuously as a function of *r* and also separately during low *r* values ($0 < r < 1$, defined in this paper as light anesthesia) and high *r* values ($1 < r < 2$, defined in this paper as deep anesthesia). The time-normalization procedure and determination of *r* scale is illustrated in figure 2.

Spectral Parameters

The following 14 spectral parameters were determined as a function of *r* from the time-normalized (not amplitude-normalized) spectrograms: powers in different frequency bands (total, delta, theta, alpha, and beta), relative powers in different frequency bands (delta, theta, alpha, and beta), spectral entropy (SE), relative beta ratio, MPF, spectral edge frequency 90% (SEF90%), and SEF95%. The parameters were chosen on the basis of their common use in the previous research. Because some of the signals were contaminated by high-frequency muscle artifact, the parameters were determined from the spectrum between 0.5 and 25 Hz. Due to the definition of relative beta ratio, higher frequencies were used exceptionally in the calculation of this parameter.

Total spectral, delta, theta, alpha, and beta powers were determined from the spectrograms. The frequency bands were 0.5–25 Hz for total spectral power, 0.5–4 Hz for delta power, 4–8 Hz for theta power, 8–12 Hz for alpha power, and 12–25 Hz for beta power. These parameters were chosen because the electroencephalographic activity in different frequency bands changes during the induction of anesthesia obeying a characteristic pattern.[2,4,20]

Relative delta, theta, alpha, and beta powers were calculated by dividing the power in the corresponding frequency band by the total spectral power. The relative powers represent classic parameters for depth-of-anesthesia estimation and were therefore included in this study.[21,22]

SE is one of the recently proposed measures for the assessment of depth-of-anesthesia. It quantifies the flatness of the power spectrum and is calculated as

$$\mathrm{SE} = \frac{-\sum_{i=f_l}^{f_b} P_n(i)\log P_n(i)}{\log N_f} \quad (1)$$

where f_l is the lower and f_b the higher limit of the used frequency band, and where P_n is the normalized $\left(\sum_{i=f_l}^{f_h} P_n(i) = 1\right)$ power spectrum of the signal. N_f is the number of frequency components in the range $[f_l, f_b]$ and used for the normalization of the values of SE be-

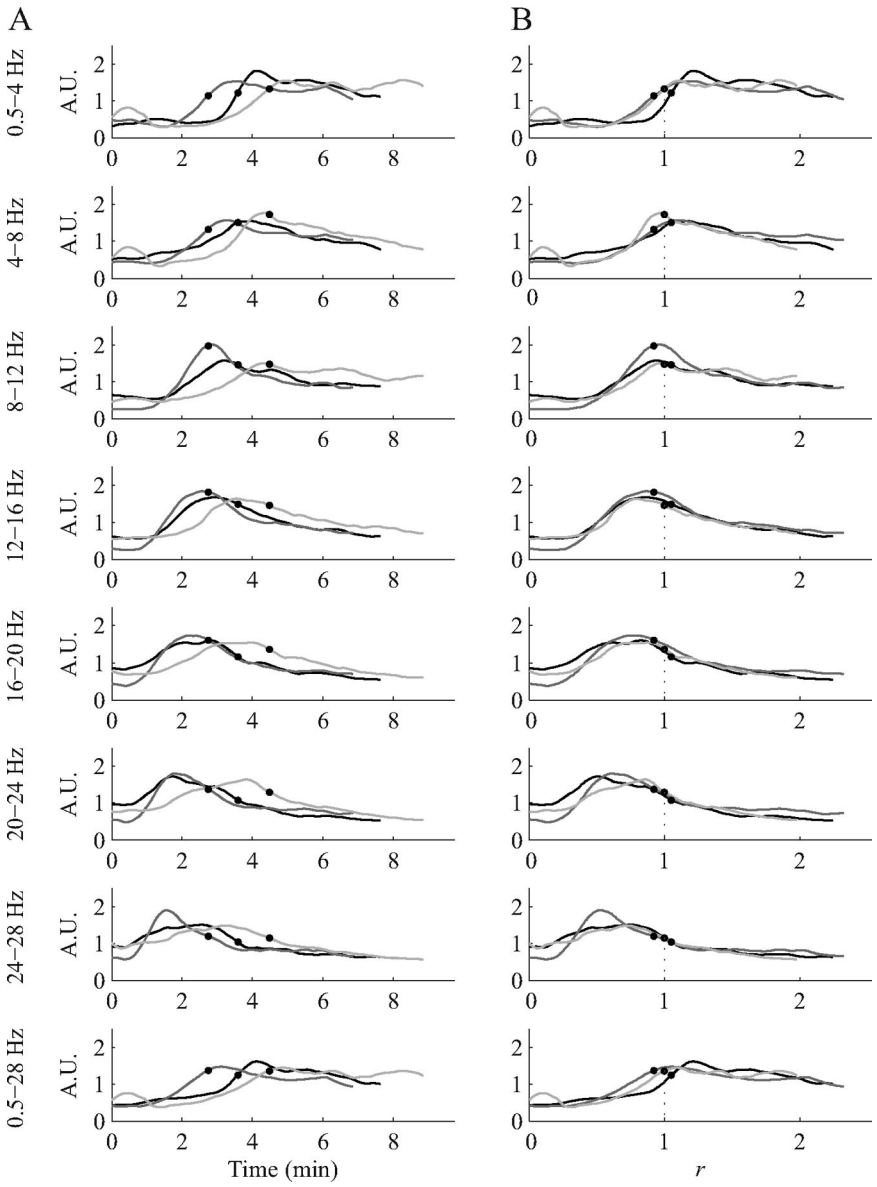

Fig. 2. (*A*) Electroencephalographic activity in eight different frequency bands for three patients. Different *gray* levels are used to represent the data of different patients. The trends are given as a function of time from the beginning of propofol infusion to the onset of burst suppression pattern. Their scale is in arbitrary units (AU). The *dots* on the trends indicate the occurrence of loss of obeying verbal command (LVC). Due to the interindividual variability in response to the anesthetic agent, the spectral progression phenomenon and LVC vary strongly in time between patients. (*B*) The trends after time normalization. The normalization is performed by minimizing the mean squared error between the trends of different patients using patient-specific time scaling factors. Due to the time scaling, the curves and the LVCs have clustered. The curves are given in *r* scale, which is determined by choosing the median of the LVCs to represent *r* = 1. Note that, in practice, the time normalization was performed by using the trends of all 27 patients, and *r* = 1 was determined by using the median of the group R0 LVC points.

tween 0 and 1. In this study, f_l and f_h were 0.5 Hz and 25 Hz, respectively. With an appropriate frequency range, SE has been shown to decrease rather monotonically with increasing depth-of-anesthesia.[23] The parameter has been used in the M-Entropy® module (GE Healthcare Finland Oy).[6]

RBR is a subparameter used in the calculation of Bispectral Index.[4,24] It is the logarithm of the ratio of the electroencephalographic spectral power in 30- to 47-Hz band to the power in 11- to 20-Hz band:

$$\mathrm{RBR} = \log_{10}\frac{P_{30-47\ \mathrm{Hz}}}{P_{11-20\ \mathrm{Hz}}}. \qquad (2)$$

MPF, *SEF90%*, and *SEF95%* represent classic parameters measured during anesthesia and have been under active research.[4,21] Spectral edge frequency X% is the frequency below which X% of the power in the spectrum resides. MPF corresponds to spectral edge frequency 50%.

To reduce noise in data visualization, the underlying trends of the spectral parameters were approximated with curve fitting. Since the parameters were assumed not to follow any specific pattern, the parametric fitting could not be used. Instead, a nonparametric cubic smoothing spline was applied to the data.[25] The spline smoothing is illustrated in figure 3A. Furthermore, the median curves of smoothed spectral parameters were determined for each group as shown in figure 3B.

Statistical Analysis

The group differences in the values of 14 spectral parameters were statistically compared with two approaches. First, the values of each spectral parameter were compared between two specific groups continuously in different *r* values. The comparison was per-

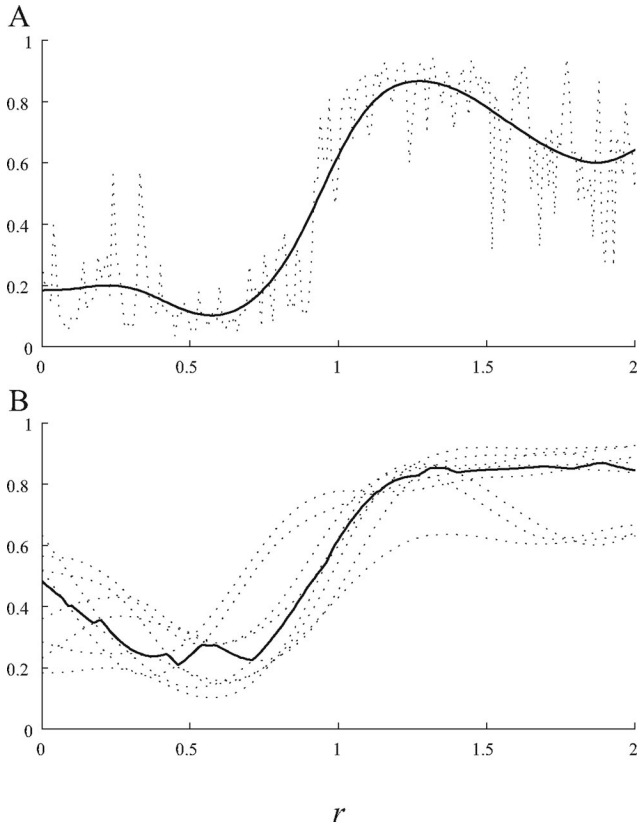

Fig. 3. (*A*) An example of the smoothing of spectral parameters. The underlying trend (*solid line*) of, in this case, the relative delta power (*dashed line*) is approximated by using a nonparametric cubic smoothing spline. (*B*) After smoothing, the median curve (*solid line*) of the specific group is determined. In this example, the median is calculated from the relative delta power curves of group R0 (*dashed lines*). The curves are calculated from the time-normalized spectrograms, due to which they are given as a function of relative time *r*.

formed separately in all r values between 0 and 2 with an interval of 0.01. Since the BSP generally occurs approximately when $r = 2$,[19] the analysis was restricted to that value. The data were not assumed to follow normal distribution, and the comparison was performed with a nonparametric Mann–Whitney U test. $P < 0.05$ was considered statistically significant. Second, the overall effect of remifentanil on the spectral parameters was analyzed separately during light ($0 < r < 1$) and deep ($1 < r < 2$) anesthesia. For this, the spectral parameter median curves (fig. 3B) were used. However, the median curves were determined from the unsmoothed spectral parameter values (no spline smoothing) to avoid statistical bias. The spectral parameter median curves of groups R1 and R2 were compared to group R0 curves with Wilcoxon signed-rank test. The Bonferroni correction was used to adjust for multiple comparisons so that the overall criterion for rejection of the null hypothesis was $P < 0.05$. Thus, because all fourteen spectral parameters were compared between groups R0 and R1 and groups R0 and R2 during light and deep anesthesia, only P values less than 0.05/56 were considered significant.

The statistical analysis was performed with the statistics toolbox for Matlab® (The Mathworks Inc.).

Results

Spectrograms

Figure 4 illustrates the median spectrograms of different groups from $r = 0$ to $r = 2$. The median spectrograms are created by choosing the group's median value at every time-frequency point. The differences between the median spectrograms of two specific groups are given as well. The median spectrograms differ markedly between groups. The following three changes can be clearly related to the increasing dose of remifentanil: (1) decrease of activity in high frequencies (> 14 Hz) during light anesthesia ($0 < r < 1$); (2) increase of activity in extended alpha band (7–14 Hz) during deep anesthesia ($1 < r < 2$); (3) decrease of activity in delta band (0.5–4 Hz) during deep anesthesia ($1 < r < 2$). These changes can be related to the coadministration of remifentanil, as they appear in a dose-dependent manner.

The median spectrogram of group R1 contains relatively strong high-frequency (greater than 30 Hz) activity during very light anesthesia ($r < 0.5$) compared to other groups. Further inspection of the electroencephalograms showed that this activity was electromyographic artifact that occurred most frequently in group R1. Because these artifacts were present also before the drug infusion began, they were considered not to be related to the administration of remifentanil.

Spectral Parameters

The 14 median spectral parameter curves determined for each group from the time-normalized spectrograms are illustrated in figure 5. The figure also shows the results of the statistical comparison of the spectral parameters continuously in different r values. The group differences in spectral parameter median curves analyzed separately during light and deep anesthesia are given in table 2.

The power parameters of different frequency bands follow the changes seen in the spectrograms. In delta band, the activity decreases when the opioids are coadministered. The values of group R0 and R2 are significantly different in deep anesthesia in figure 5. Table 2 shows a decrease of 66%. As a result of the dominant effect of delta activity on total spectral power, the curves of these two parameters resemble each other. In theta and beta bands, the activities do not differ statistically significantly between groups in figure 5, even though the beta activity is clearly suppressed in R1 and R2 during light anesthesia. According to table 2, the decrease is 26% in R1 and 38% in R2. The alpha activity is significantly increased in remifentanil groups during deep anesthesia. As shown in table 2, remifentanil has more than doubled the activity in this band.

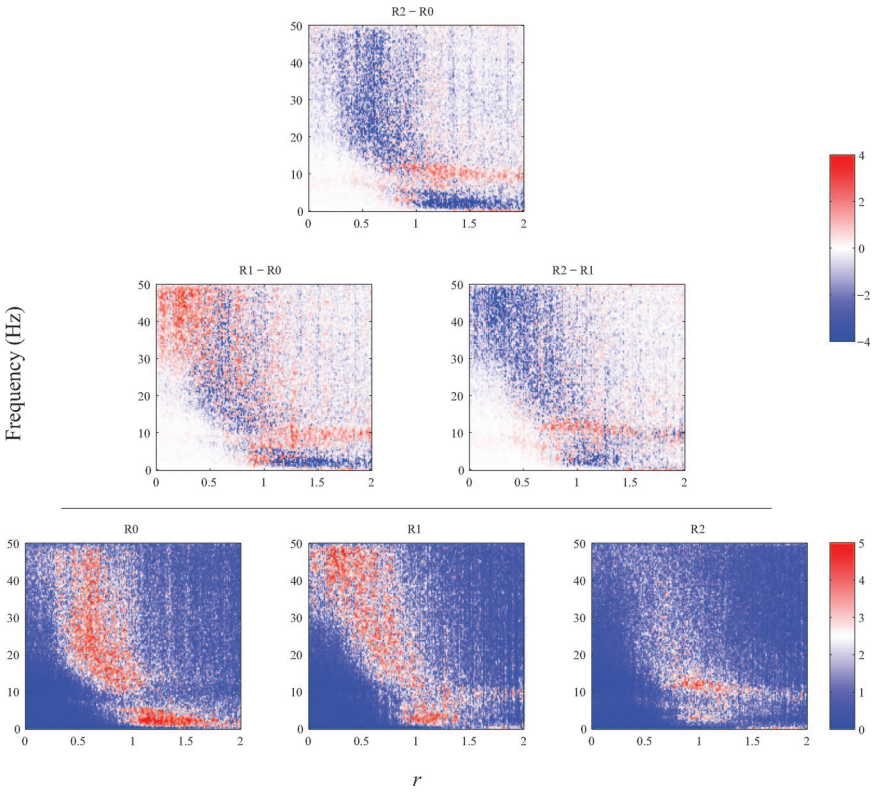

Fig. 4. (*Bottom row*) The median spectrograms of the study groups R0, R1, and R2 calculated from the electroencephalogram during induction of anesthesia. The median spectrograms are calculated by choosing the group's median value at every time-frequency point. (*Top and middle rows*) The difference spectrograms calculated from the median spectrograms of two specific groups. The median spectrograms are determined from the time-normalized spectrograms and therefore given as a function of relative time *r*. The power in spectrograms is given in arbitrary units.

The changes in spectrograms also reflect on the relative powers in different frequency bands, even though the effects in this case are more complex and require a thorough analysis. For example, in figure 5, the theta activity did not differ significantly between groups when the spectral power was analyzed, but it does with the relative power. This can be explained by the fact that, although remifentanil does not affect the theta activity itself, changing the activity in other frequencies influences the relative power parameter. Therefore, due to the lack of delta activity, the relative theta power is significantly higher in remifentanil groups during deep anesthesia. However, this does not explain why the relative theta power is significantly higher in group R2 during very light anesthesia; the delta activity does not differ there between groups. As with the delta power parameter, the high-dose remifentanil group shows significantly lower values for relative delta power during deep anesthesia in figure 5. The values of this parameter have decreased 29% (table 2). Again, due to the presence of strong delta activity, the relative alpha and beta powers are significantly lower in group R0 during deep anesthesia (fig. 5). Naturally, the increased activity in extended alpha band also influences the relative alpha power parameter in remifentanil groups. The total increase of this parameter is 179% and 293% (table 2) in groups R1 and R2, respectively.

In SE, figure 5 shows no significant differences between groups during light anesthesia, although the curve of R2 seems to be slightly decreased. However, during deep anesthesia, the values in R1 and R2 are significantly higher compared to that of R0. For example, in group R2, SE has increased 15% (table 2). This can be explained by the lack of delta activity, due to which the spectrum is more flat in remifentanil groups.

Relative beta ratio was the only parameter in which higher frequencies (greater than 25 Hz) were used. Due to the electromyographic artifact, the values are significantly higher in group R1 during very light anesthesia. The artifact does not explain, however, the decreased values in high-dose remifentanil group after $r = 1$. At that point, the activity in the higher band (30–47 Hz) has ceased, and the lower band (11–20 Hz) activity dominates the values of the parameter. Hence, the lower values in group R2 come from the increased activity in extended alpha band (7–14 Hz) during deep anesthesia. However, as the changes occur only within a narrow range of r (1–1.5), the change reflected on the values in table 2 are moderate.

The parameters MPF, SEF90%, and SEF95% show also differences between study groups. The suppression of high frequencies during light anesthesia results in a significant decrease of SEF90% and SEF95% in high-dose remifentanil group (fig. 5). All three parameters indicate consistently also that the electroencephalographic activity in saline group is in significantly lower frequencies during deep anesthesia. SEF90%, for example, increases from approximately 7 Hz to 12 Hz when the saline is changed to high-dose remifentanil. This corresponds to an increase of more than 50%, as presented in table 2.

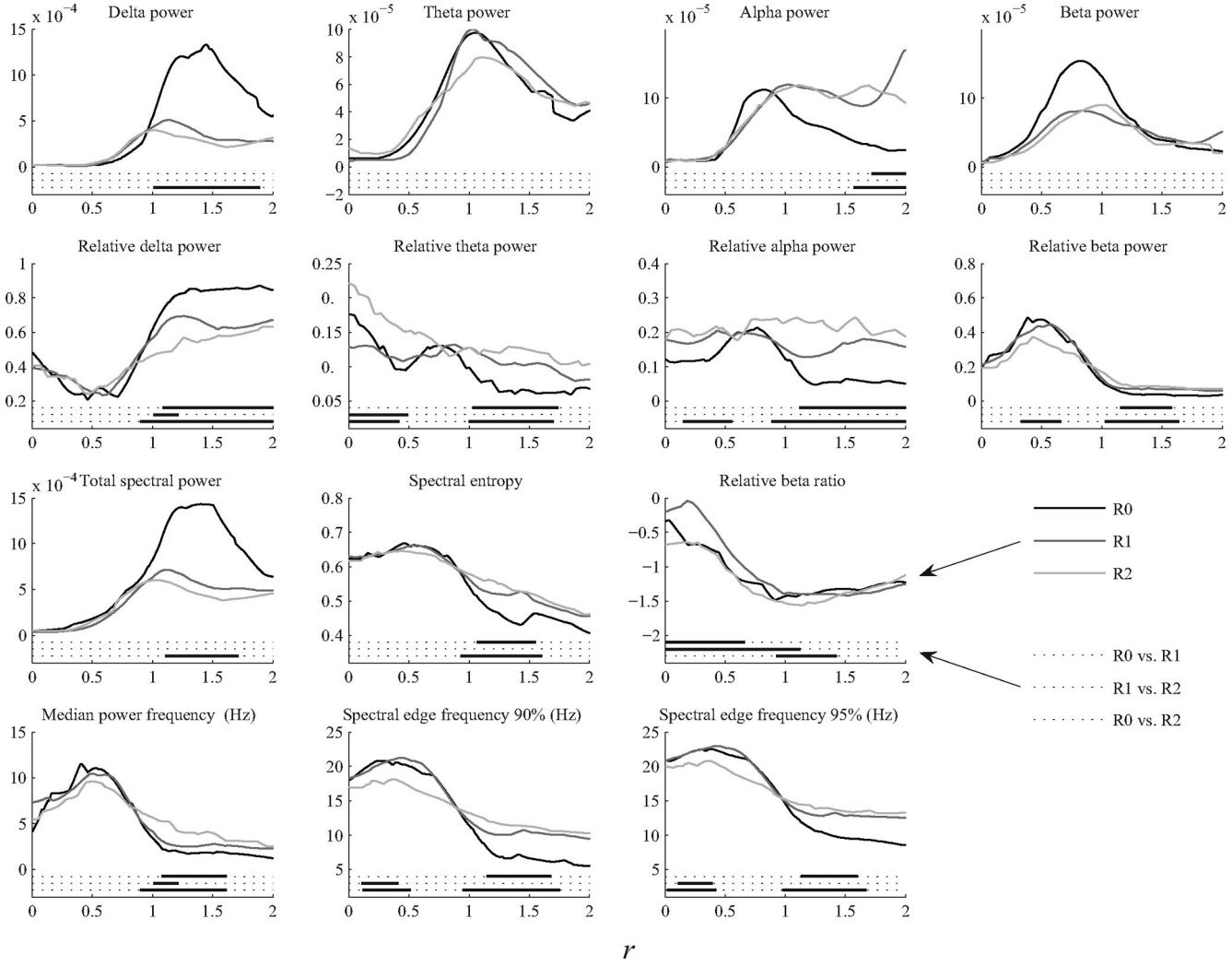

Fig. 5. The 14 median spectral parameter curves of the study groups R0, R1, and R2 calculated from the electroencephalogram during induction of anesthesia. The median curves are created by choosing the group's median value at every point in *r* scale (see fig. 3B). The curves are presented as function of relative time *r*, as they are calculated from the time-normalized spectrograms. The positions in which the values of two specific groups differ significantly ($P < 0.05$) are indicated under the curves.

Discussion

The effect of remifentanil on the time-frequency properties of electroencephalogram during propofol-induced anesthesia was studied. The results show that remifentanil significantly changes the signal's spectral content in a characteristic manner, including decrease of beta activity during light anesthesia as well as decrease of delta and increase of alpha activity during deep anesthesia. The changes were strongly dependent on the level of anesthesia and reflected on the quantitative spectral parameters used in the depth-of-anesthesia estimation. For example, during deep anesthesia, SE and SEF90% were clearly increased by remifentanil; in delta activity, however, a major decrease was observed. Coadministration of opioids therefore challenges the reliability of the spectral properties of electroencephalogram in the depth-of-anesthesia estimation by using a frontal montage, which may have an impact on the indices using these properties.

As mentioned in the introduction, the changes remifentanil solely produces to electroencephalogram, *i.e.*, progression of activity from high to low frequencies, resemble somewhat the propofol-induced changes. This easily leads to the hypothesis that the effects of these two drugs on the electroencephalogram would be synergistic. However, our study shows that instead of increasing the propofol-induced changes, the coadministered remifentanil suppresses some of them (beta activity during light anesthesia and delta activity during deep anesthesia) and induces some of its own (alpha activity during deep anesthesia). According to the quantitative spectral parameters, these changes might lead to an impression of a deeper anesthesia in low *r* values (*e.g.*, lower SEF90% and beta power), but on the other hand a lighter anesthesia in high *r* values (*e.g.*, higher SE and lower delta power).

This study deepens our understanding of the total impact of remifentanil on electroencephalogram-based depth-of-

Table 2. Differences in Spectral Parameter Median Curves

	Light Anesthesia ($0 < r < 1$)		Deep Anesthesia ($1 < r < 2$)	
Spectral Parameter	R1	R2	R1	R2
Total power	–17 (–22 to –11) ↓	–13 (–18 to –9) ↓	–33 (–40 to –27) ↓	–50 (–54 to –46) ↓
Delta power	10 (–2 to 22)	17 (6 to 28)	–47 (–53 to –40) ↓	–66 (–70 to –62) ↓
Theta power	–21 (–28 to –15) ↓	13 (5 to 21)	9 (0 to 18)	–8 (–14 to –1)
Alpha power	12 (1 to 23)	21 (10 to 32)	118 (93 to 143) ↑	114 (96 to 133) ↑
Beta power	–26 (–30 to –21) ↓	–38 (–41 to –35) ↓	–5 (–13 to 3) ↓	–12 (–17 to –7) ↓
Relative delta power	15 (8 to 21)	17 (10 to 23)	–18 (–20 to –16) ↓	–29 (–32 to –27) ↓
Relative theta power	0 (–6 to 7)	28 (21 to 36) ↑	50 (39 to 61) ↑	66 (55 to 78) ↑
Relative alpha power	19 (10 to 29)	43 (31 to 56) ↑	179 (148 to 210) ↑	293 (252 to 334) ↑
Relative beta power	–5 (–9 to 0)	–18 (–23 to –13) ↓	75 (59 to 91) ↑	117 (100 to 134) ↑
SE	–1 (–2 to 0)	–2 (–3 to –1) ↓	11 (9 to 13) ↑	15 (13 to 18) ↑
RBR	–36 (–42 to –29) ↓	17 (11 to 24) ↑	4 (2 to 6)	7 (5 to 9) ↑
MPF	–2 (–8 to 5)	0 (–11 to 11) ↓	19 (11 to 28) ↑	54 (40 to 69) ↑
SEF90%	1 (0 to 2)	–10 (–12 to –9) ↓	47 (37 to 56) ↑	58 (49 to 68) ↑
SEF95%	1 (1 to 2) ↑	–7 (–8 to –6) ↓	20 (16 to 24) ↑	27 (23 to 31) ↑

The spectral parameter median curve values are compared between groups separately during light and deep anesthesia. The median curves were determined for each group from the unsmoothed spectral parameters given as a function of *r*. Data are expressed as a percentage change compared to the group R0 curve values at the same position (same *r* value) and displayed as mean (95% confidence interval).

↑ = curve values are significantly higher compared to group R0 according to Wilcoxon signed-rank test; ↓ = curve values are significantly lower compared to group R0 according to Wilcoxon signed-rank test; MPF = median power frequency; RBR = relative beta ratio; SE = spectral entropy; SEF90% = spectral edge frequency 90%; SEF95% = spectral edge frequency 95%.

anesthesia estimation. In our previous work,[13] we found that the infusion of remifentanil during propofol anesthesia significantly modifies the mutual relations of the electroencephalographic spectral characteristics and the clinical endpoints in a predictable and quantifiable manner. Even though it was shown that the propofol-induced basic frequency progression pattern of electroencephalogram is left untouched, this study shows that also the detailed spectral characteristics are significantly affected by remifentanil and that this phenomenon is strongly dependent on the depth-of-anesthesia. This finding further complicates the reliable usage of spectral properties of electroencephalogram for depth-of-anesthesia estimation when remifentanil is coadministered.

In the literature, the effects of remifentanil on the electroencephalogram during anesthesia have not been presented adequately before. The studies have concentrated on describing the response of the depth-of-anesthesia indices, mostly Bispectral Index, to the coadministration of remifentanil during steady-state anesthesia. The results have been controversial, with some studies suggesting the indices to be affected by the coadministration of opioids,[12,14] and others failing to find an effect.[26,27] One possible explanation for the controversy is that the effect of remifentanil on electroencephalogram is not stable or stationary during different levels of anesthesia. As presented in this paper, the nature of the electroencephalographic changes remifentanil produces seems to be strongly dependent on the phase of the propofol-induced frequency progression pattern. It is likely that the effects of remifentanil differ significantly between two steady-states, making the comparison of the results difficult without an objective control parameter of anesthetic depth. In future, the research should concentrate more on describing the effect of opioids on electroencephalogram throughout the different levels of anesthesia instead of presenting them only for example in a single steady-state condition.

Compared to the previous studies, several improvements were made in this paper. First, the effect of remifentanil on electroencephalogram is presented during the whole process of induction of anesthesia. As a result, the effect of the opioid can be seen in different levels of anesthesia and not only in a single steady-state. Second, instead of examining the effects of remifentanil by using only a few quantitative parameters of electroencephalogram, we illustrate the changes induced in the entire spectrum and how these changes reflect on the parameters. This approach clarifies the underlying spectral phenomenon that causes the changes in the parameters. Third, by applying the time normalization to the spectrograms, we were able to reduce the interindividual variability in response to the anesthetic agent and made the comparison of the data of different patients reasonable as a function of time.

We hypothesize that the effects of remifentanil on the electroencephalogram presented in this study can be generalized to some extent to all drugs with similar pharmacodynamic properties, *i.e.*, μ-receptor agonists. The studies with other opioids (fentanyl, alfentanil, and sufentanil) support this proposition because these drugs have been shown to induce similar electroencephalographic changes with remifentanil during anesthesia.[12,28] However, due to the difference in pharmacokinetic profiles, the beginning and duration of the effect may alter significantly. Furthermore, remifentanil is considered to be a specific μ-receptor agonist; therefore, the electroencephalographic changes induced by the drugs

acting also through other receptor may differ in part from that of remifentanil.

Interestingly, tramadol also induces similar electroencephalographic changes as remifentanil during anesthesia. Tramadol is a centrally acting analgesic occasionally used during operation to prevent postoperative pain. Lately there has been debate about its use during anesthesia. When coadministered with an anesthetic, tramadol has been shown to induce electroencephalographic changes that can be associated with lightening of anesthesia.[29,30] These changes, including decrease of delta activity and increase of alpha activity and SEF95%, are identical to the effects of remifentanil during deep anesthesia reported in this paper. In addition to the affinity for opioid receptors, tramadol appears to have actions on the noradrenergic and serotonergic systems.[31] It has been suggested that the effect on electroencephalogram results from the α-adrenergic activity.[29] However, the changes resemble closely that of remifentanil; we therefore speculate that they are induced by opioid receptor activation. This is supported by the finding that tramadol does not affect electroencephalogram in the presence of remifentanil.[32] The drugs acting through the opioid receptors are known to have synergistic effect with anesthetics to the clinical state of the patients[26,33]; therefore, the electroencephalographic changes tramadol induced may in fact be related to increased clinical sedation.

Findings from the recent studies propose also new directions for future research. An ideal depth-of-anesthesia monitor accurately relates the electroencephalographic recordings to the clinical state of patient. The current indices have been developed to fulfill this task with a single anesthetic agent. However, this paper points out that when coadministered with propofol, the opioids change the electroencephalogram in a rather complex manner that potentially affects the reliability of the indices used in depth-of-anesthesia estimation. One possibility to overcome this problem would be detection of the presence of opioid from the electroencephalogram. This way, the observed changes in the signal could more reliably be related to the clinical state of patient. Based on the results of this study, we can expect this to be possible to some extent. Furthermore, we have studied the effect of remifentanil only from the Fz electrode; this raises the question of whether some other electrode location would be more immune to the coadministration of opioids. It would also be of interest to study whether the effects would be similar with other anesthetics. Recently, several nonlinear measures, such as approximate entropy and permutation entropy, have been proposed for the measurement of depth-of-anesthesia.[34–37] In the future, the effect of remifentanil on these measures should be tested as well.

References

1. Gugino LD, Chabot RJ, Prichep LS, John ER, Formanek V, Aglio LS: Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane. Br J Anaesth 2001; 87:421–8
2. Kortelainen J, Koskinen M, Mustola S, Seppänen T: Time-frequency properties of electroencephalogram during induction of anesthesia. Neurosci Lett 2008; 446:70–4
3. Mahla ME, Black S, Cucchiara RF: Neurologic monitoring, Miller's Anesthesia, 6th edition. Edited by Miller R. Philadelphia, Elsevier, 2005, pp 1511–50
4. Rampil IJ: A primer for EEG signal processing in anesthesia. ANESTHESIOLOGY 1998; 89:980–1002
5. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. ANESTHESIOLOGY 1997; 86:836–47
6. Viertiö-Oja H, Maja V, Särkelä M, Talja P, Tenkanen N, Tolvanen-Laakso H, Paloheimo M, Vakkuri A, Yli-Hankala A, Meriläinen P: Description of the Entropy™ algorithm as applied in the Datex-Ohmeda S/5™ Entropy Module. Acta Anaesthesiol Scand 2004; 48:154–61
7. Voss L, Sleigh J: Monitoring consciousness – The current status of EEG-based depth of anaesthesia monitors. Best Pract Res Clin Anaesthesiol 2007; 21:313–25
8. Zhang Y, Irwin MG, Wong TM: Remifentanil preconditioning protects against ischemic injury in the intact rat heart. ANESTHESIOLOGY 2004; 101:918–23
9. Fodale V, Schifilliti D, Praticò C, Santamaria LB: Remifentanil and the brain. Acta Anaesthesiol Scand 2008; 52:319–26
10. James MK, Vuong A, Grizzle MK, Schuster SV, Shaffer JE: Hemodynamic effects of GI 87084B, an ultra-short acting mu-opioid analgesic, in anesthetized dogs. J Pharmacol Exp Ther 1992; 263:84–91
11. Egan TD, Minto CF, Hermann DJ, Barr J, Muir KT, Shafer SL: Remifentanil *versus* alfentanil: Comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. ANESTHESIOLOGY 1996; 84:821–33
12. Hoffman WE, Cunningham F, James MK, Baughman VL, Albrecht RF: Effects of remifentanil, a new short-acting opioid, on cerebral blood flow, brain electrical activity, and intracranial pressure in dogs anesthetized with isoflurane and nitrous oxide. ANESTHESIOLOGY 1993; 79:107–13
13. Kortelainen J, Koskinen M, Mustola S, Seppänen T: Remifentanil modifies the relation of electroencephalographic spectral changes and clinical endpoints in propofol anesthesia. ANESTHESIOLOGY 2008; 109:198–205
14. Koitabashi T, Johansen JW, Sebel PS: Remifentanil dose/electroencephalogram bispectral response during combined propofol/regional anesthesia. Anesth Analg 2002; 94:1530–3
15. Nuwer MR, Comi G, Emerson R, Fuglsang-Frederiksen A, Guérit JM, Hinrichs H, Ikeda A, Luccas FJ, Rappelsburger P: IFCN standards for digital recording of clinical EEG. International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol 1998; 106:259–61
16. Belouchrani A, Abed-Meraim K, Cardoso J-F, Moulines E: A blind source separation technique using second-order statistics. IEEE Trans Signal Process 1997; 45:434–44
17. Kortelainen J, Koskinen M, Mustola S, Seppänen T: EEG frequency progression during induction of anesthesia – From start of infusion to onset of burst suppression pattern. Conf Proc IEEE Eng Med Biol Soc 2007; 1570–3
18. Koskinen M, Mustola S, Seppänen T: Relation of EEG spectrum progression to loss of responsiveness during induction of anesthesia with propofol. Clin Neurophysiol 2005; 116:2069–76
19. Kortelainen J, Koskinen M, Mustola S, Seppänen T: EEG spectral changes and onset of burst suppression pattern in propofol/remifentanil anesthesia. Conf Proc IEEE Eng Med Biol Soc 2008; 4980–3
20. Kuizenga K, Wierda JM, Kalkman CJ: Biphasic EEG changes in relation to loss of consciousness during induction with thiopental, propofol, etomidate, midazolam or sevoflurane. Br J Anaesth 2001; 86:354–60
21. Mahon P, Greene BR, Greene C, Boylan GB, Shorten GD: Behaviour of spectral entropy, spectral edge frequency 90%, and alpha and beta power parameters during low-dose propofol infusion. Br J Anaesth 2008; 101:213–21
22. Kearse LA Jr, Manberg P, Chamoun N, deBros F, Zaslavsky A: Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia. ANESTHESIOLOGY 1994; 81:1365–70
23. Ferenets R, Vanluchene A, Lipping T, Heyse B, Struys MMRF: Behavior of entropy/complexity measures of the electroencephalogram during propofol-induced sedation: Dose-dependent effects of remifentanil. ANESTHESIOLOGY 2007; 106:696–706
24. Sleigh JW, Steyn-Ross DA, Steyn-Ross ML, Williams ML, Smith P: Comparison of changes in electroencephalographic measures during induction of general anaesthesia – Influence of the gamma frequency band and electromyogram signal. Br J Anaesth 2001; 86:50–8
25. Reinsch C: Smoothing by spline functions. Numer Math 1967; 10:177–83
26. Manyam SC, Gupta DK, Johnson KB, White JL, Pace NL, Westenskow DR, Egan TD: When is a bispectral index of 60 too low? Rational processed electroencephalographic targets are dependent on the sedative-opioid ratio. ANESTHESIOLOGY 2007; 106:472–83
27. Lysakowski C, Dumont L, Pellegrini M, Clergue F, Tassonyi E: Effects of

fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia. Br J Anaesth 2001; 86:523–7

28. Albanèse J, Viviand X, Potie F, Rey M, Alliez B, Martin C: Sufentanil, fentanyl, and alfentanil in head trauma patients – A study on cerebral hemodynamics. Crit Care Med 1999; 27:407–11

29. Vaughan DJ, Shinner G, Thornton C, Brunner MD: Effect of tramadol on electroencephalographic and auditory-evoked response variables during light anaesthesia. Br J Anaesth 2000; 85:705–7

30. Coetzee JF, Maritz JS, du Toit JC: Effect of tramadol on depth of anaesthesia. Br J Anaesth 1996; 76:415–8

31. Dayer P, Desmeules J, Collart L: Pharmacology of tramadol. Drugs 1997; 53:18–24

32. Fodale V, Praticò C, Tescione M, Tanania S, Lucanto T, Santamaria LB: Tramadol does not modify the Bispectral Index during anaesthesia with sevoflurane and remifentanil. Br J Anaesth 2005; 95:212–5

33. Mustola ST, Baer GA, Neuvonen PJ, Toivonen KJ: Requirements of propofol at different end-points without adjuvant and during two different steady infusions of remifentanil. Acta Anaesthesiol Scand 2005; 49:215–21

34. Bruhn J, Röpcke H, Rehberg B, Bouillon T, Hoeft A: Electroencephalogram approximate entropy correctly classifies the occurrence of burst suppression pattern as increasing anesthetic drug effect. ANESTHESIOLOGY 2000; 93:981–5

35. Koskinen M, Seppänen T, Tong S, Mustola S, Thakor NV: Monotonicity of approximate entropy during transition from awareness to unresponsiveness due to propofol anesthetic induction. IEEE Trans Biomed Eng 2006; 53:669–75

36. Li X, Cui S, Voss LJ: Using permutation entropy to measure the electroencephalographic effects of sevoflurane. ANESTHESIOLOGY 2008; 109:448–56

37. Olofsen E, Sleigh JW, Dahan A: Permutation entropy of the electroencephalogram – A measure of anaesthetic drug effect. Br J Anaesth 2008; 101:810–21

ANESTHESIOLOGY REFLECTIONS

Wood, Bickley, and Avertin

To facilitate induction and reduce overall dosage of inhalational anesthetics, Drs. Paul M. Wood (1894–1963) and Robert S. Bickley (1885–1957) investigated preliminary sedation and even "basal anesthesia" of patients with tribromethanol, branded Avertin by Winthrop Chemical Company. By 1936 Anesthesiologist Wood and Surgeon Bickley had popularized American use of this agent by publishing their "Observations on use of tribromethanol (Avertin)" in the *American Journal of Surgery*. When Bickley retired, Wood was forced to "semi-retire" to his wife's family home near West Point, New York, taking with him bottles that he had collected, such as the Avertin one above (courtesy of the Wood Library-Museum). As the bottle label suggests, this "basal anesthetic" was usually administered basally (*i.e., per rectum*), typically to agitated adult and pediatric patients. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.