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Effect of Remifentanil on the Nonlinear Electroencephalographic Entropy Parameters in Propofol Anesthesia

Jukka Kortelainen, *Student Member, IEEE*, Miika Koskinen, Seppo Mustola, Tapio Seppänen

***Abstract*—Nonlinear electroencephalographic entropy parameters have been proposed for the assessment of depth of anesthesia. The influence of remifentanil, a commonly used intraoperative opioid, on these parameters, namely approximate entropy (ApEn), sample entropy (SampEn), and permutation entropy (PeEn), during induction of propofol anesthesia was studied. Remifentanil was shown to reduce the propofol-induced changes in ApEn and SampEn throughout the transition from awake to burst suppression state. Coadministration of opioids therefore challenges the reliability of these parameters as indicators of depth of anesthesia. No consistent influence on PeEn was observed. However, this may have been due to strong interindividual variation in PeEn values.**

I. Introduction

OVER the last years, the assessment of depth of anesthesia using electroencephalogram (EEG) has taken its place in the operating rooms and intensive care units around the world. Increasing concentrations of anesthetics in the blood produce a continuum of EEG changes that can be related to the depth of anesthesia. With propofol, the changes roughly obey the following pattern: an increase of high frequency activity followed by an increase of low frequency and a decrease of high frequency activity [1], [2]. In very deep anesthesia, the burst suppression pattern (BSP) begins. The frequency progression preceding the BSP reflects on the quantitative spectral parameters of EEG, such as spectral edge frequency [3] and spectral entropy [4], which have therefore been used as indicators of depth of anesthesia.

Recently, nonlinear EEG entropy measures have been proposed for the assessment of depth of anesthesia. Compared with linear methods, they have been suggested to detect additional information and quantify thereby better the irregularity of a dynamical system [5]. One of these parameters is approximate entropy (ApEn) [6], which is a complexity measure shown to give a monotonic response to the induction of propofol anesthesia in certain conditions [7]. The shortcomings of ApEn algorithm have led to the development of a closely related parameter, sample entropy (SampEn) [8], [9]. Furthermore, the latest invention, permutation entropy (PeEn), is a complexity measure developed especially for the analysis of noisy chaotic time series [10]. In recent studies, PeEn has shown promising results as an indicator of depth of anesthesia [5], [11].

Remifentanil is a short-acting opioid, often coadministered with propofol for its synergistic hypnotic and analgesic effects [12]. The changes it produces to EEG when administered solely are characteristic of μ-receptor agonists consisting of decreasing frequency and increasing amplitude [13]. The propofol-induced basic frequency progression pattern mentioned above has shown to be robust against coadministration of remifentanil [14]. However, the opioid affects the detailed spectral content of EEG by reducing the propofol-induced changes throughout the transition from awake to burst suppression state [15].

In this paper, the influence of remifentanil on the nonlinear EEG entropy parameters, namely ApEn, SampEn, and PeEn, during induction of propofol anesthesia is studied. The purpose is to test if the opioid affects these measures as it does the spectral parameters. The influence is analyzed from the beginning of propofol infusion to the onset of BSP. The data acquisition procedure and the performed signal processing steps, including the explanation of the applied nonlinear entropy parameters are described in Section II. Section III presents the results. In Section IV, the conclusions and discussion of the study are given.

II. Materials and Methods

A. Patients and Data Acquisition

For the complete details regarding the clinical protocol, the reader is referred to our previous publication [14]. In short, twenty-seven patients scheduled for an elective surgical operation were randomly divided into three groups of nine persons. All patients were anesthetized using intravenous fixed rate propofol infusion. The infusion was continued until the BSP was detected from the anesthesia monitor. During the induction, the patients received either saline (group R0), low dose of remifentanil (group R1), or high dose of remifentanil (group R2). The remifentanil/saline infusion was started one minute before the propofol infusion. The end-point loss of obeying verbal command (LVC) was observed during the infusion. EEG

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J. Kortelainen is with the Department of Electrical and Information Engineering, BOX 4500, FIN-90014 University of Oulu, Finland (e-mail: jukka.kortelainen@ee.oulu.fi).

M. Koskinen is with the Advanced Magnetic Imaging Centre and Brain Research Unit, Helsinki University of Technology, Finland.

S. Mustola is with the Department of Anesthesia, South Carelia Central Hospital, Lappeenranta, Finland.

T. Seppänen is with the Department of Electrical and Information Engineering, University of Oulu, Finland.

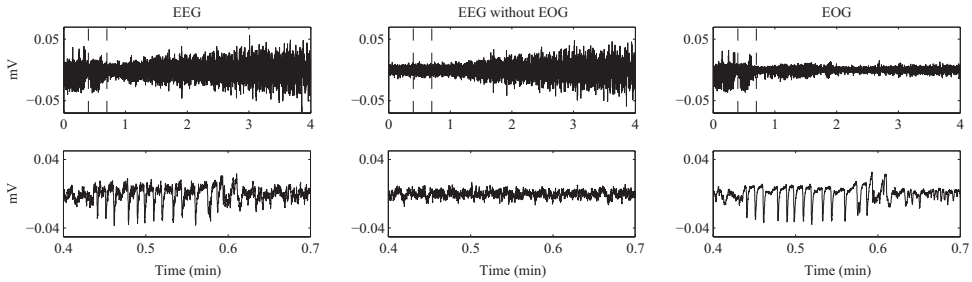

Fig. 1. An example of electroencephalogram (EEG) and the effect of electro-oculographic (EOG) artifact removal. The signals in the upper row are presented from the beginning of propofol infusion. The vertical dashed lines delimit the signal sequences presented in the lower row.

was recorded with an Embla polygraphic recorder (Medcare, Reykjavik, Iceland) from 17 different electrode locations according to the international 10/20 system using a sampling rate of 200 Hz and bandwidth of 0.5-90 Hz. Since the modern depth of anesthesia monitoring is based on the analysis of frontal EEG, only the montage Fz with the common average reference was used in the analysis.

B. Data Preprocessing

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

Data preprocessing consisted of removal of electro-oculographic (EOG) artifact, downsampling, and bandpass filtering. The EOG artifact was removed from the signals utilizing the Automatic Artifact Removal toolbox for Matlab (available at http://www.cs.tut.fi/~gomezher/projects/eeg/aar.htm). The recordings from 17 channels were first decomposed into spatial components using second order blind identification [16]. After removing the components that could be related to electro-oculographic activity, the data were reconstructed. The effect of EOG artifact removal is illustrated in Fig. 1. Next, the data were downsampled to 100 Hz. This sampling rate was preferred as the parameters used in the calculation of entropy measures have been validate using it [11]. Finally, to exclude the high frequency electromyographic artifact, a finite impulse response bandpass filter with a frequency range from 0.5 Hz to 25 Hz was applied to the signals.

C. Approximate Entropy

ApEn is a regularity statistic quantifying the unpredictability of fluctuations in a time series. Let there be a time series $\mathbf{S}_L = s(1), s(2),\ldots, s(L)$. For this sequence, we form m-dimensional subsequence vectors $\mathbf{x}_1, \mathbf{x}_2,\ldots, \mathbf{x}_{L-m+1}$ so that $\mathbf{x}_i = s(i), s(i+1),\ldots, s(i+m-1)$. These vectors are used to define

$$C_{i,m}(r) = \frac{n_{i,m}(r)}{L-m+1}, \tag{1}$$

where $n_{i,\mathrm{m}}(r)$ is the number of $\mathbf{x}_j$, such that $\mathrm{d}[\mathbf{x}_i, \mathbf{x}_j] \le r$. The measure $\mathrm{d}[\mathbf{x}_i, \mathbf{x}_j]$ is defined as the maximum absolute difference of the corresponding scalar components of vectors $\mathbf{x}_i$ and $\mathbf{x}_j$. The threshold value r is usually calculated as

$$r = k\sigma, \tag{2}$$

where σ is the standard deviation of $\mathbf{S}_L$ and k is a predefined constant. Now, ApEn is

$$\mathrm{ApEn} = \Phi_m(r) - \Phi_{m+1}(r), \tag{3}$$

where

$$\Phi_m(r) = (L-m+1)^{-1} \sum_{i=1}^{L-m+1} \ln C_{i,m}(r). \tag{4}$$

ApEn was calculated from the preprocessed signals using 10 s time windows (L = 1000) and two sample subsequence vectors (m = 2). The overlap of the consecutive sequences was 900 samples. In addition, the parameter was calculated using three different k values: 0.05, 0.1, and 0.2. These values were selected based on the previous studies [7], [11].

D. Sample Entropy

ApEn has proven to be highly dependent on the record length and lack relative consistency [8], which has led to the development of a more robust measure, SampEn. Compared to ApEn, SampEn has two computational differences. Firstly, to remove self-matches, $n_{i,m}(r)$ is defined as the number of $\mathbf{x}_j$, such that $\mathrm{d}[\mathbf{x}_i, \mathbf{x}_j] \le r$ and $i \ne j$. As this easily leads to $n_{i,m}(r) = 0$ and further to ln(0), SampEn is calculated as

$$\mathrm{SampEn} = \ln\left[\frac{\Psi_m(r)}{\Psi_{m+1}(r)}\right], \tag{5}$$

where

$$\Psi_m(r) = (L-m+1)^{-1} \sum_{i=1}^{L-m+1} C_{i,m}(r). \tag{6}$$

Secondly, when $n_{i,m}(r)$ is determined for Ψ_m, the last subsequence vector, i.e. $\mathbf{x}_{L-m+1}$, is not included. This is done to make the number of subsequence vector comparisons equal when calculating Ψ_m and Ψ_{m+1}.

SampEn was determined from the preprocessed signals with the same time window size, overlap, m, and k values as used in the calculation of ApEn.

E. Permutation Entropy

PeEn is a measure utilizing ordinal time series analysis. It transforms a given time series into a series of ordinal

patterns, each describing the order relation between a fixed number of consecutive samples. Let there be a time series $\mathbf{S}_L$ and subsequence vectors $\mathbf{x}_i$ as defined in Section II-C. Based on the order relation between the m samples in vectors $\mathbf{x}_i$, a probability distribution $\mathbf{P}_J = p(1), p(2),\ldots, p(J)$ describing the occurrence each pattern is formed. J is the number of distinct patterns and thus $J \leq m!$. Now, PeEn is

$$\mathrm{PeEn} = \frac{H_m}{\ln(m!)}, \tag{7}$$

where

$$H_m = -\sum_{j=1}^{J} p_j \ln p_j, \tag{8}$$

i.e. the Shannon entropy of the probability distribution $\mathbf{P}_J$.

PeEn was calculated from the preprocessed EEGs using six sample subsequence vectors (m = 6), as this value was shown to be suitable for data of this kind [11].

F. Time Normalization

Due to the interindividual variability in response to the anesthetic agent, the EEG changes do not occur consistently in time between patients during induction of anesthesia. To minimize this error, we have presented a method which can be used for the normalization of the parameters, in this case the nonlinear entropy measures, in time [17]. The method is based on the calculation of EEG activity in eight different frequency bands for each patient and minimizing the mean squared error between the activity trends of different patients by linear time-scaling. This approach produces patient-specific time-scaling factors by which the analyzed parameters can be normalized in time. Since the method results in a new time-scale for each patient, the parameters cannot be expressed as a function of absolute time anymore. Therefore, a relative time scale r is used. The r value can be considered to represent the phase of EEG changes occurring during induction of propofol anesthesia. In r scale, the start of propofol infusion (r = 0) and LVC (r = 1) work as the points of reference. Since the occurrence of LVC is affected by remifentanil, r = 1 was defined by using only the group R0 end-points. In this paper, low r values ($0 < r < 1$) are referred to as 'light anesthesia' and high r values ($1 < r < 2$) as 'deep anesthesia'.

III. Results

Fig. 2 illustrates the nonlinear EEG entropy parameters determined for each group as a function of r. Since the BSP generally occurs approximately when r = 2 [18], the analysis was restricted to that value. The group differences in parameter values calculated separately during light and deep anesthesia are given in Table I.

The propofol-induced changes in ApEn and SampEn are reduced by remifentanil throughout the transition from awake to BSP. In the curves with negative slope, the decrease during deep anesthesia and slight increase during

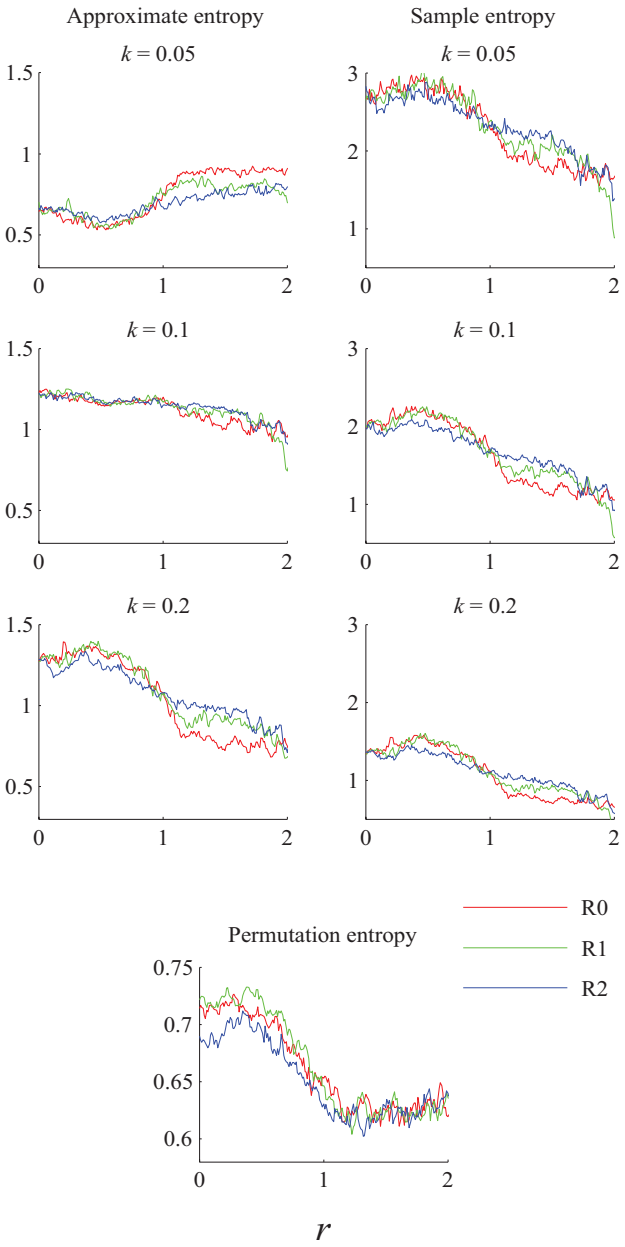

Fig. 2. The nonlinear electroencephalographic entropy parameters during induction of propofol anesthesia in groups R0, R1, and R2. Due to the time normalization, the parameters are presented as a function of relative time r (see text for details). The curves are created by choosing the group's median value at every point in r scale.

light anesthesia are clearly suppressed in the remifentanil groups in a dose-dependent manner. For example, compared to group R0, SampEn is 20% higher during deep anesthesia and 7.1% lower during light anesthesia in group R2 when k = 0.2. In the curves with positive slope (ApEn, k = 0.05), the effect is similar but reversed: remifentanil results in lower values during deep anesthesia and slightly higher values during light anesthesia. The values of group R2 are 15% lower during deep anesthesia and 5.7% higher during light anesthesia, compared to the values of group R0. Overall, the coadministration of opioids seems to reduce the total propofol-induced variation in ApEn and SampEn. The

TABLE I
COMPARISON OF MEDIAN CURVES OF ENTROPY PARAMETERS

	Light anesthesia ($0 < r < 1$)		Deep anesthesia ($1 < r < 2$)	
	R1	R2	R1	R2
ApEn				
$k = 0.05$	3.7 ± 1.1	5.7 ± 0.9	–9.1 ± 0.8	–15 ± 0.6
$k = 0.1$	0.7 ± 0.4	0.3 ± 0.4	2.6 ± 1.1	4.4 ± 0.9
$k = 0.2$	0.4 ± 0.6	–4.9 ± 0.5	12.1 ± 1.7	19.2 ± 1.8
SampEn				
$k = 0.05$	–0.4 ± 0.9	–4.3 ± 0.8	5.7 ± 2.1	11.1 ± 1.9
$k = 0.1$	–0.7 ± 0.7	–6.3 ± 0.6	8.5 ± 2.4	16.7 ± 2.3
$k = 0.2$	–0.5 ± 0.9	–7.1 ± 0.8	10.1 ± 2.5	20 ± 2.4
PeEn	1.4 ± 0.2	–2.3 ± 0.3	–0.6 ± 0.3	–1 ± 0.4

The values of median curves given in Fig. 2 are compared between groups separately during light and deep anesthesia. Data are expressed as a percentual difference compared to the group R0 median curve values at the same points in r scale and displayed as mean ± 95% confidence interval.

ApEn = approximate entropy; SampEn = sample entropy; PeEn = permutation entropy.

behavior of ApEn during induction process depends significantly on k: switching the value from 0.05 to 0.2 changes the trend of the parameter from slightly increasing to decreasing. The trend of SampEn is not similarly affected by the value of k.

Remifentanil does not seem to have a consistent dose-dependent influence on PeEn, as the R0 curve is located between the R1 and R2 curves. However, already in the beginning PeEn differs markedly between groups, implying a strong natural interindividual variation in the values of this parameter. The effect of remifentanil could probably be shown with a larger study group.

IV. CONCLUSIONS AND DISCUSSION

The effect of remifentanil on the nonlinear EEG entropy parameters during induction of propofol anesthesia was studied. The opioid was shown to reduce the propofol-induced changes in ApEn and SampEn throughout the transition from awake to burst suppression state. Coadministration of opioids therefore challenges the reliability of these parameters as indicators of depth of anesthesia. No consistent influence on PeEn was observed. However, this may have been due to strong interindividual variation in PeEn values.

The results of this study are in line with our previous findings. Recently, we have shown that remifentanil significantly changes the spectral content of EEG during induction of propofol anesthesia [15]. These changes reflected on the quantitative spectral parameters used in the depth of anesthesia estimation. In this paper, we illustrate that the opioid affects also the nonlinear EEG entropy measures. The influence is similar in all cases: remifentanil suppresses the propofol-induced EEG changes. Since the whole idea of the depth of anesthesia assessment is indeed to measure the changes in EEG, coadministration of remifentanil can be considered to complicate the reliable use of the signal for this purpose.

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