

Evaluation of the EEG-signal during Volatile Anaesthesia: Methodological Approach

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The presence of the EEG patterns showing some similarities with epileptiform activity as well as epileptic EEG discharges and motor seizures observed in some people during anaesthesia conducted with volatile anaesthetics is now well-recognized. Nevertheless the practical as well as theoretical implications indicate for the necessity of better understanding of the nature and mechanism of these patterns. The aim of this study was to verify the usefulness of some methods of the EEG analyses to characterize the atypical forms of EEG. It was shown that the estimation of Higuchi's fractal dimension and mean phase coherence as well as the analysis of time-frequency distributions (spectrograms and scalograms) revealed the quantitative features of atypical patterns and their relationships with the depth of anaesthesia.

Key words: EEG patterns, volatile anaesthetics, Higuchi's fractal dimension, mean phase coherence, time-frequency distributions

1. Introduction

There are several reasons that indicate importance of monitoring of the functional brain states during general anaesthesia using the EEG methodology. The obvious reason is determination of the depth of anaesthesia and subsequent recovery of the brain functions. Another reason stems from the fact that some volatile anaesthetics induce brain states promoting the epileptic EEG discharges and motor seizures.

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Electroencephalographic seizure activating properties of some anaesthetic agents are already well known. Some of them, like short-lasting barbiturates or opioids [1], are used in an attempt of presurgical localization of epileptic foci. However, the problem with volatile anesthetics is more complex. Seizure precipitating properties of volatile anaesthetics was described in patients with epilepsy as well as in non-epileptic patients [2–19]. Hyperdynamic cardiovascular response in adult people and children without history of epilepsy subjected to sevoflurane anaesthesia was reported to be associated with the epileptiform EEG activity and motor jerks such as twitches of arms and shoulders. Hemodynamic variables like heart rate and blood pressure increased strongly in those patients [5, 9, 15, 18].

Detection of the epileptiform EEG patterns may be important for selection of proper anaesthetic in selected groups of patients. The problem has obviously medical as well as theoretical implications. The biological problem refers to the hypothetical interpretation of the spike-wave patterns induced by anaesthesia as epileptiform interictal discharges. Solution of this problem at the first stage of analysis will require appropriate methodology of the EEG recording and analysis.

The purpose of this research is basically methodological. It concentrates on the applicability of different methods of the EEG signal analysis in order to determine objectively different patterns of brain electrical activity during anaesthesia.

2. Materials and Methods

2.1. Patients

The analysis was performed on the EEG records obtained during general anaesthesia. The study was approved by the Ethical Committee of the Medical University of Silesia and written informed consent was obtained from all of patients involved. The data were taken from 12 adult patients of both genders that underwent elective surgery under general anaesthesia, categorized as class I (normal, healthy patients) and II (patients with mild systemic disease) according to the American Society of Anaesthesiologists (ASA) scale. Patients with history of allergic reactions to drugs used in the study, the epileptics and with other previously diagnosed neurological deficits and/or psychiatric disorders, as well as patients receiving neuropsychiatric medication and addicted to any psychoactive substances were excluded from the study. Randomization was performed to assign a patient to one of three groups according to the anaesthetic agent used to maintain anaesthesia. Within the different anaesthesia regimens patients were anaesthetised sequentially with one of three different volatile agents (isoflurane, sevoflurane or desflurane) in order to receive progressive and sequential concentrations of these three anaesthetic agents.

In the morning of the day of surgery the patients did not receive any premedication to avoid its influence on the EEG patterns. In the operating room an i.v. cannula was inserted into the large forearm vein and standard monitors were applied. Continuous

standard monitoring included heart bioelectric activity (ECG), heart rate (HR), non-invasive systemic arterial pressure, respiratory rate, haemoglobin oxygen saturation, and end-tidal concentrations of the volatile anaesthetic agents, oxygen and carbon dioxide. Oxygen saturation was measured by pulse oxymetry and maintained above 95% during the study.

In order to avoid opioid and N₂O effect on central nervous system, analgesia during surgery was achieved by an epidural catheter placed in the lumbar space, via which patients received 20 ml of 0.5% bupivacaine (Marcaine, Astra-Zeneca). In all the patients, anaesthesia was induced intravenously with 2–2.5 mg/kg of propofol (Diprivan, Astra-Zeneca). Before anaesthesia induction oxygen was administered by facemask. Each patient received a muscle-relaxant factor – 0.08–0.10 mg/kg mc of vecuronium (Norcuron, Organon) and 3 min later laryngeal mask was inserted. The lungs were mechanically ventilated to obtain the end-tidal carbon dioxide concentration of 35–37 mmHg. Immediately after the laryngeal mask insertion anaesthesia was maintained with either iso-, sevo- or desflurane delivered in an air-oxygen mixture of carrier gases. The beginning concentration of anaesthetic agent was 0.4 MAC (Minimal Alveolar Concentration is defined as the partial pressure of volatile anaesthetic inhibiting movement reaction for noxious stimulation in 50% of anaesthetized patients). The concentration of 0.4 MAC was maintained for 30 minutes – the waiting period – to eliminate the effect of intravenous induction. Administration of the agent was adjusted in steps of 0.2 MAC beginning from 0.4 MAC until burst suppression (BS) appeared in the EEG. Up to 10 min were allowed for equilibration once a stable end-tidal concentration had been obtained at each step. Then the concentration of anaesthetic agent was subsequently decreased by 0.2 MAC every 5 minutes until the end of surgery, return of consciousness and the laryngeal mask removal. No more neuromuscular blocking agents were given intraoperatively. Emergence from anaesthesia was assessed by measuring the times to spontaneous opening of eyes, the laryngeal mask removal, stating the name, and arrival at the post-anaesthesia care unit. Finally, all the patients were visited in the postanaesthesia care unit and on the first and third postoperative day and interviewed about intraoperative recall.

2.2. EEG Registration

Before induction of anaesthesia the EEG control recording lasting 15 minutes was performed. The EEG signal was obtained from bipolar montage between gold cup electrodes (F3C3, F4C4, P3O1, P4O2 according to the international 10–20 system of electrode placement). For the EEG recordings, the skin of the scalp had been degreased with 70% isopropanol to obtain impedance less than 5 kOhm. Gold EEG electrodes (Grass Technologies) placement was made on the scalp with adhesive paste EC2 (Grass-Telefactor). The EEG monitoring was performed using S/5 Monitor (GE Medical, Finland). Four channel raw EEG was continuously digitized and simultaneously recorded (sampling frequency was 100 Hz for each channel).

2.3. Signal Analysis

The analysis of the volatile anesthetic-induced EEG-signals were performed using visual inspection as well as some quantitative methods.

All signals were visually inspected by the neurophysiologist. The signals were viewed using Viewer ddv designed by P.J. Durka and written by W. Maleński and D. Ircha for the Warsaw Medical Academy, Department of Psychiatry [20]. Two-second EEG segments containing patterns of single isolated spikes or spike with slow waves clearly distinguished from background activity and generated synchronously in several channels (basically in all four channels with frontal predominance) were marked.

The aim of the quantitative analysis was determination of the characteristic features of the volatile anaesthetic-induced EEG using:

1. Fractal dimension;
2. Mean phase coherence;
3. Time-frequency distributions obtained using short-time Fourier transform signal analysis, i. e.: spectrograms;
4. Time-frequency distributions obtained using wavelet analysis, i.e.: scalograms;
5. Time and frequency marginals extracted from scalograms.

Signal analysis using fractal dimension, mean phase coherence and spectrograms was performed for the whole EEG-signal. Whereas wavelet analysis was applied only for the consecutive 20 or 40-second-long windows.

2.4. Fractal Dimension

Fractal dimension was included into the performed analysis because this index ranging from 1 (for a deterministic curves, for example a sinusoid) to 2 (for random time series) reflects the complexity of signal. The largest values of the fractal dimension were found for wake stage, while deepening of anaesthesia corresponded to its lower values [21–24] what proved that this index could be useful for the assessment of anaesthesia stage. Moreover fractal dimension may be useful for detection of episodes of transient synchronization of the neuronal structures.

The fractal dimension of EEG-signal was calculated using Higuchi's algorithm [23, 25] which for a given time series: $X(1), X(2), \dots, X(N)$ constructs k new time series:

$$X_m^k : X(m), X(m+k), \dots, X\left(m + \text{int}\left(\frac{N-m}{k}\right) \cdot k\right) \quad (1)$$

for $m = 1, 2, \dots, k$; where m – initial time, k – time interval. The length, $L_m(k)$, of each curve X_m^k was calculated as:

$$L_m(k) = \frac{1}{k} \left[\sum_{i=1, \text{int}\left(\frac{N-m}{k}\right)}^{\text{int}\left(\frac{N-1}{k}\right)} |X(m+ik) - X(m+(i-1)k)| \right], \quad (2)$$

where N – the total number of samples in the original signal.

$L(k)$ was calculated as the mean of the k values $L_m(k)$ for $m=1, \dots, k$.

For a curve which has the fractal dimension D_f :

$$L(k) \sim k^{-D_f}. \quad (3)$$

The fractal dimension was calculated by means of the least-squares linear best-fitting procedure as the angular coefficient of the linear regression of the graph:

$$\ln L(k) \sim D_f \cdot \ln \frac{1}{k}. \quad (4)$$

Higuchi's fractal dimension was calculated in one second-long windows (100 samples) using FRASTTM software for automatic sleep staging and FRANESTM for monitoring the depth of anaesthesia written by E. Olejarczyk and integrated into SENSATION systems with new wireless sensors [26].

2.5. Mean Phase Coherence

To study the synchronization of EEG activity registered by various electrodes the mean phase coherence was analyzed. This index is defined in a following way:

for a given measured EEG-signal $s(t)$ we define an analytic signal s_a :

$$s_a(t) = s(t) - i \hat{s}(t) = A(t) e^{i\Phi(t)}, \quad (5)$$

where

i – imaginary unit;

$\hat{s}(t)$ – Hilbert transform of measured signal $s(t)$;

$A(t)$ – amplitude of signal $s(t)$;

$\Phi(t) = \arctan(\hat{s}(t)/s(t))$ – phase of signal $s(t)$;

and therefore phase synchronization is defined as locking of phases of two oscillators a and b , i.e.:

$$\Phi_{n,m}(t) = n \cdot \Phi_a(t) - m \cdot \Phi_b(t) = \text{const}. \quad (6)$$

where n and m are integers, $\Phi_a(t)$ and $\Phi_b(t)$ denote the phases of the oscillators, and $\Phi_{n,m}(t)$ is defined as their relative phase.

Since our aim was to estimate the synchronization between time series that are obtained from the same physiological system (i.e. the brain) we consider it most likely to encounter synchronization at a phase locking ratio of $n : m = 1 : 1$ [27] and the mean phase coherence has been defined as:

$$R = \left| \frac{1}{N} \sum_{j=0}^{N-1} e^{i\phi_{1,1}(j\Delta t)} \right| \quad (7)$$

where

i – imaginary unit;

$1/\Delta t$ – the sampling rate of discrete time series;

N – the total number of samples in window;

$\Phi_{1,1}$ – the relative phase of two signals at a phase locking ratio of $n : m = 1 : 1$;

Δt – time between the successive samples j from 1 to $N-1$.

Using the Euler's formula R value turns into:

$$R = \left(\left[\frac{1}{N} \sum_{j=0}^{N-1} \sin(\phi_{1,1}(j\Delta t)) \right]^2 + \left[\frac{1}{N} \sum_{j=0}^{N-1} \cos(\phi_{1,1}(j\Delta t)) \right]^2 \right)^{1/2} \quad (8)$$

The value of R is equal one when phase difference is constant, i. e. synchronization of the signals is perfect. On the other hand if the phases are not synchronized the value of R is equal to zero. Decrease of the mean phase coherence between two signals indicates a partial loss of synchronization between them.

The mean phase coherence was calculated for a pair of frontal channels and a pair of back channels in both brain hemispheres according to the algorithm described in [28, 29] using MATLAB in 2 minute window. The *hilbert* procedure was applied to calculate Hilbert's transform of the signals.

2.6. Time-frequency Distributions

Time-frequency distributions decompose the signal on a basis of elementary signals (the atoms) well localized in time and frequency. Two well-known examples of such decompositions are short-time Fourier transform and wavelet transform.

Spectrogram is the square magnitude of short-time Fourier transform and scalogram is squared magnitude of the wavelet transform.

2.7. Spectrograms

Spectrograms were used to consistent visualization of the temporal nature of the analyzed signals. Spectrogram is a measure of energy of a signal contained in time-frequency domain (t, f) . Graphic representation of spectrogram used in this study is the substitute of three-dimensional plot of energy of the signal frequency content.

Two ways of graphic representation were applied. To illustrate the general features of the power spectral density (energy spectral density) of the corresponding frequency content in the time moment t was represented using dots in greyscale. Power spectral density in these spectrograms was denominated in decibels and calculated using the formula: $P = 10 * \log_{10}(|X(f)|^2) = 20 * \log_{10}(|X(f)|)$, where $X(f)$ denotes the discrete-time Fourier transform of EEG-signal. To illustrate the power spectral density of the corresponding frequency content in a more precise way allowing to explain the quantitative features of spectra it was represented by numeric values in linear scale.

Spectrograms were performed using MATLAB Signal Processing Toolbox. The *specgram* procedure computes the windowed discrete-time Fourier transform of a signal using sliding window. The spectrogram is the magnitude of this function. The sampling frequency 100 Hz and Hann window of one-second length (100 points) were used. The sections overlap by number of samples corresponding to half of the window's length. The frequency vector was in the range from 0 to 50.

2.8. Scalograms

While the short-time Fourier transform decomposes the signal on the basis of elementary signals (sines and cosines), the wavelet transform decomposes the signal using a family of functions generated by translations and dilations of the mother waveform (wavelet). Thus a scalogram is the affine counterpart of the spectrogram.

Scalograms were used to obtain information on the signal features which can not be obtained using spectrograms because of their limitations.

The short-time Fourier transform is not appropriate to analyze a signal which has time-varying frequency components because this transform uses a single analysis window. As a result resolution of the spectrogram is limited. A wide window gives good frequency resolution at cost of poor time resolution. A narrower window gives good time resolution but poor frequency resolution. Therefore it is not possible to obtain good time and frequency resolutions of the spectrogram simultaneously. To avoid this main limitation of spectrogram the wavelet transform (or multiresolution analysis in general) uses short windows at high frequencies and long windows at low frequencies. So, it gives good time resolution for high-frequency events and good frequency resolution for low-frequency events. Therefore both duration and bandwidth of the wavelet change but the wavelet shape remains the same. This partially overcomes the resolution limitation of the short-time Fourier transform and makes the scalograms especially useful for the analysis of short transient activity forms present in the burst suppression region.

The scalograms were calculated using procedures from MATLAB package: Time-Frequency Toolbox [30]. Procedure *tfrscalogram* computes the squared magnitude of continuous wavelet transform for Morlet wavelet.

2.9. Time and Frequency Marginal Distributions

The time marginal corresponds to the instantaneous power of the signal while the frequency marginal corresponds to the energy spectral density. Therefore they were included into the analysis to assess the evolution of these variables during anaesthesia.

The marginal distributions of a time-frequency distribution (tfr) were defined as:

$$\text{time marginal: } m_f(t) = \int_{-\infty}^{+\infty} \text{tfr}(t, f) df \quad (9)$$

$$\text{frequency marginal: } m_t(f) = \int_{-\infty}^{+\infty} \text{tfr}(t, f) dt. \quad (10)$$

The marginals were calculated in burst-suppression region for 32 segments for scalograms. Each of them had length equal 4096 samples (about 40 seconds). Then the segments were stitched together. Thus the analyzed signal was about 22 minutes-long. Procedure *margtfr* from MATLAB package: Time-Frequency Toolbox [30] was used to compute the time and frequency marginals.

3. Results

3.1. Patients' Statistics

The study groups were comparable in demographic data, initial basic life parameters and ASA score. A total of 12 patients were enrolled in this investigation with the study groups being similar in respect of age, weight, height, ASA physical status, and duration of anaesthesia and surgery.

The studied population encompassed 6 (50%) women and 6 (50%) men, aged from 19 to 70 (mean: 48.7 ± 14.1) years. Body mass ranged from 45 to 110 (mean 73.6 ± 12.9) kg, and height from 145 to 189 (mean: 165.3 ± 8.1) cm. All researched groups were compared with regard to the above-specified demographic features ($p > 0.05$). The frequency of occurrence of the selected coexisting illnesses and the mean duration of the operation were similar in all analysed groups ($p > 0.05$). Mean anaesthesia duration was 155 ± 15 minutes.

3.2. Electrophysiological Observations

Three different time regions of anaesthesia state progress can be distinguished: high frequency activity in the beginning of EEG-signal registration when anaesthetic concentration is still low (Fig. 1A), through region in which spike-waves and spike-slow wave patterns start to appear when anaesthetic concentration grows (Fig. 1B) and burst-suppression region with burst forms, spike-waves and spike-slow wave

patterns separated by short time intervals of EEG activity fading when anaesthetic concentration reach the maximal value (Fig. 1C).

EEG-signal evoked by volatile anaesthetics possessed such characteristic forms of activity as burst forms, spike-waves and spike-slow wave patterns (Fig. 2 and Fig. 3) as well as continuous brain activity in the alpha and beta frequency range appearing predominantly in the frontal channels (Fig. 4B).

The continuous activity could be easily distinguished from the artifacts evoked by muscular activity (Fig. 4A). The spectra of continuous activity manifested characteristic frequencies in the alpha and beta range (frequency peak at 10 and 16 Hz) (Fig. 4D) which were absent in the spectra of muscular activity and movement artifacts (Fig. 4C).

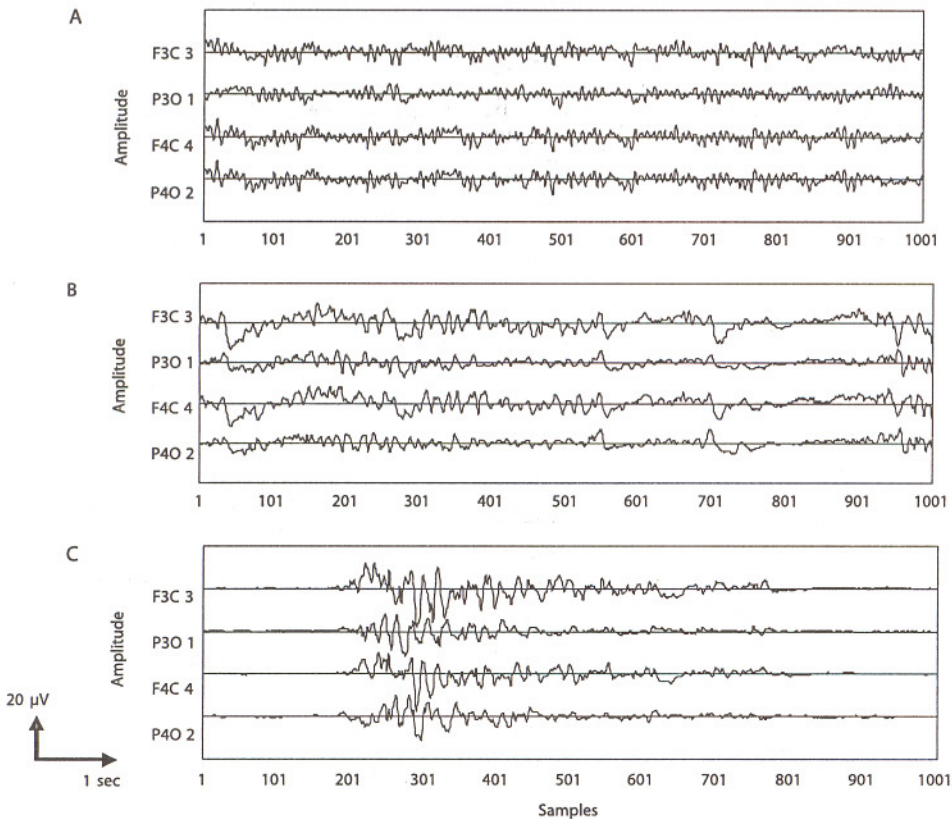


Fig. 1. Example of the original EEG records in symmetrical, anterior (frontal) and posterior (parieto-occipital) derivations from the left and right hemisphere characteristic for three different regions of anaesthesia evolution: A – high frequency activity in the beginning of EEG-signal registration when anaesthetic concentration is still low, B – region in which spike-waves and spike-slow wave patterns start to appear when anaesthetic concentration grows, C – burst-suppression region with burst forms, spike-waves and spike-slow wave patterns separated by short time intervals of EEG activity lack when anaesthetic concentration reaches the maximal value

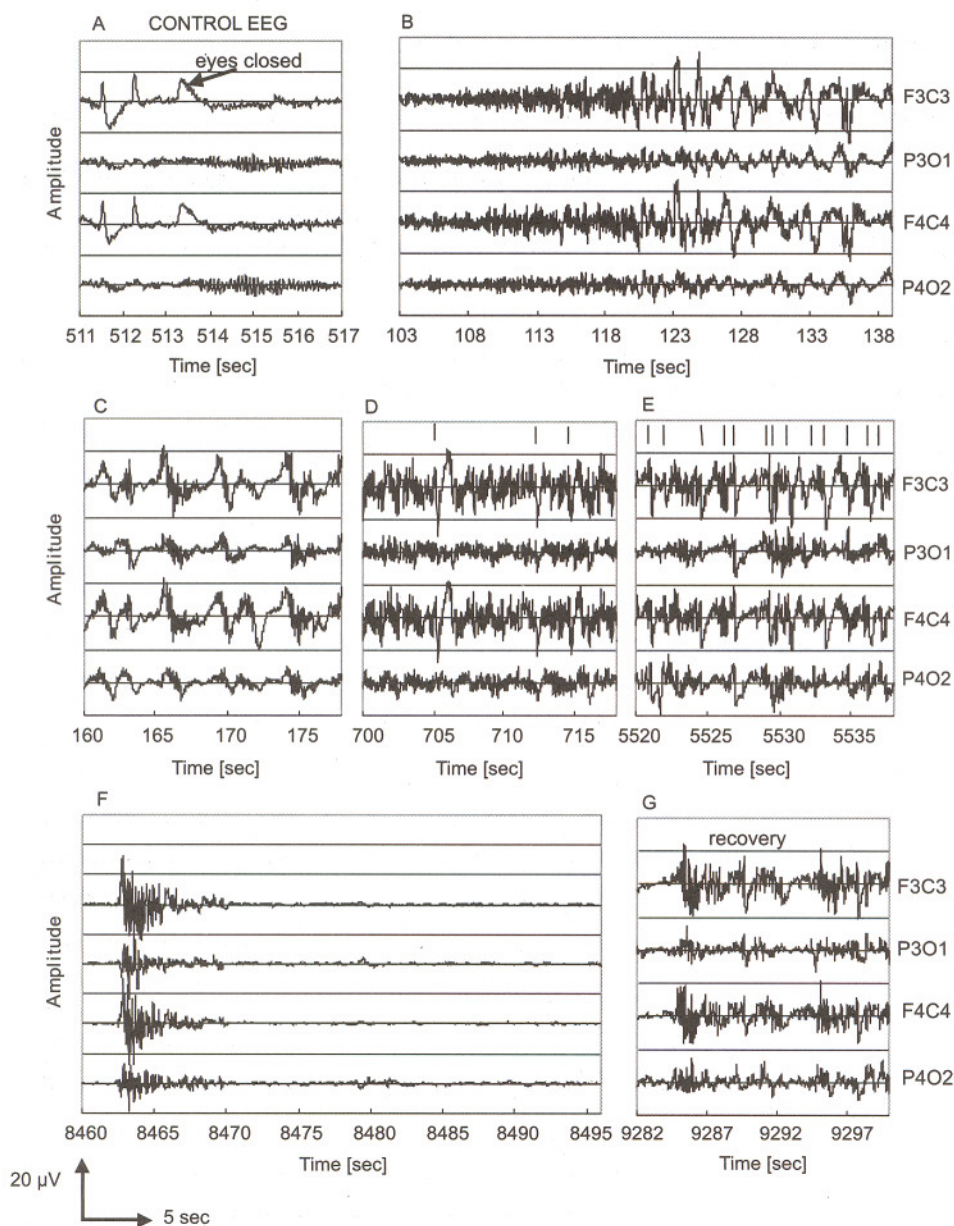


Fig. 2. EEG patterns during the control EEG recording and on different levels of isoflurane anaesthesia: A – EEG record before induction of anaesthesia: a fragment of arrest reaction with the eye movement artifacts and the eyes closed (arrow) with subsequent burst of the alpha waves 10/s in parieto-occipital derivations, B – Initial stage of anaesthesia. There is transient accentuation of the EEG activity within the alpha and beta frequency range (8–30/s) with frontal predominance with subsequent appearance of high voltage slow waves, C – EEG patterns of the third minute after induction of anaesthesia (0.4 MAC) with slow wave with superimposed fast activity in the alpha-beta range, D–E – subsequent transformation of the EEG patterns with deepening level of anaesthesia (from 0.4 to 1.0 MAC) with increased number of spiky waves and generalization in all derivations, F – EEG burst-suppression pattern with 5 Hz frequency waves (> 1.5 MAC), G – Recovery from anaesthesia (less than 1.0 MAC) with the continuous EEG activity often associated with sharp forms appearance

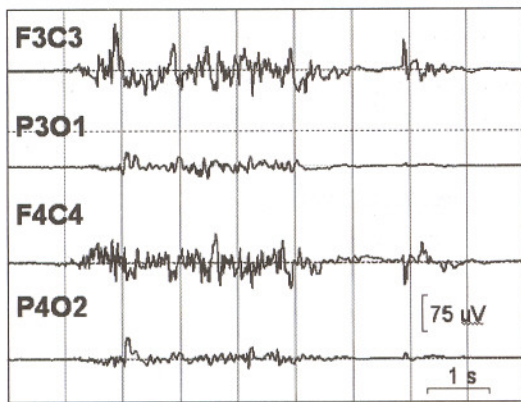


Fig. 3. Example of the original EEG records in symmetrical, anterior (frontal) and posterior (parieto-occipital) derivations from the left and right hemisphere. Isolated burst of the low, medium and high frequency EEG components with subsequent isolated spike, characteristic for the burst – suppression pattern of the brain electrical activity observed on advanced stages of sevoflurane anaesthesia

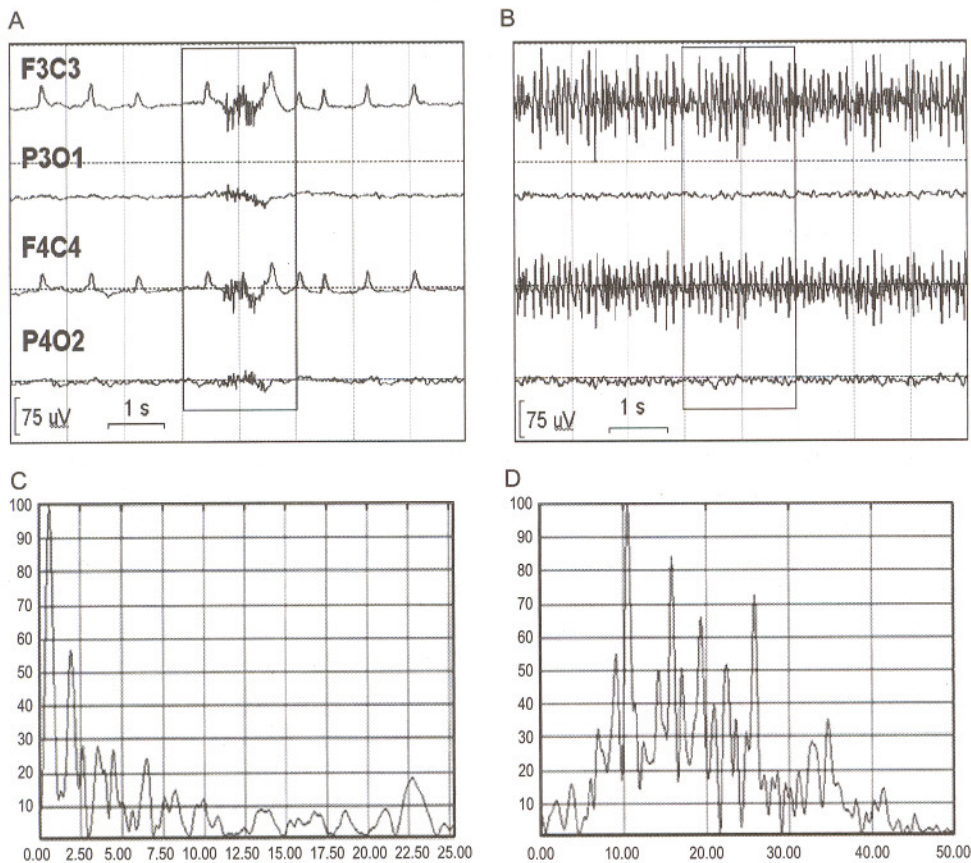


Fig. 4. A – Patterns of muscular activity with the eye movement artifact recorded in the frontal channel. B – Continuous brain activity within the alpha and beta range. C, D – Two-second-long fragments of the records at the F3C3 channel and their spectral analysis – FFT vs. frequency in Hz

Another example was discharge-like activity observed during the burst-suppression period which could be easily distinguished from the ECG artifacts (Fig. 5).

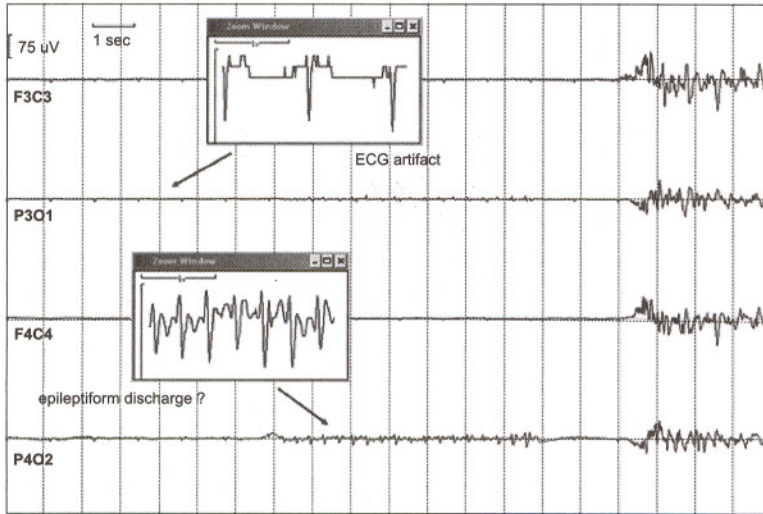


Fig. 5. A discharge-like activity during the burst-suppression EEG pattern and examples of the ECG artifacts

3.3. Spectrograms

For each of the four channels, similar and characteristic time-frequency distribution was observed (Fig. 6). In this Figure contribution of the alpha waves was represented by the bands of orange dots spreading at the level between 9 and 12 Hz. The performed signal analysis showed that the contribution of the alpha waves decreased until the EEG-signal suppression during deep anaesthesia and then increased again when the patient was awaking. During the EEG-signal suppression region a series of narrow segments corresponding to the bursts with high frequency contribution to the spectra separated by the segments of low-frequency contribution were observed. These data shown that the contribution of the alpha waves to the EEG-signal spectrum could be an additional indicator of the consciousness level.

The spectral power calculated as a squared magnitude of the discrete-time Fourier transform for frequencies 5 Hz and 10 Hz manifested some relationship with the concentration of volatile anesthetic (Fig. 7). For the minimal alveolar concentration (MAC) in the range from 0.5 to 1.0 powers for the theta waves (5 Hz) and for the alpha waves (10 Hz) were similar. For MAC greater than 1.0 the relationship was different, i.e. the power for the theta waves was large while this for the alpha waves was small. The minimal alveolar concentration was defined as such concentration of the volatile anaesthetic in the lungs that is needed to prevent movement (motor response) in 50% of subjects in response to surgical (pain) stimulus. If MAC is 1.0, then 1.3 MAC would block response in 95% of the subjects.

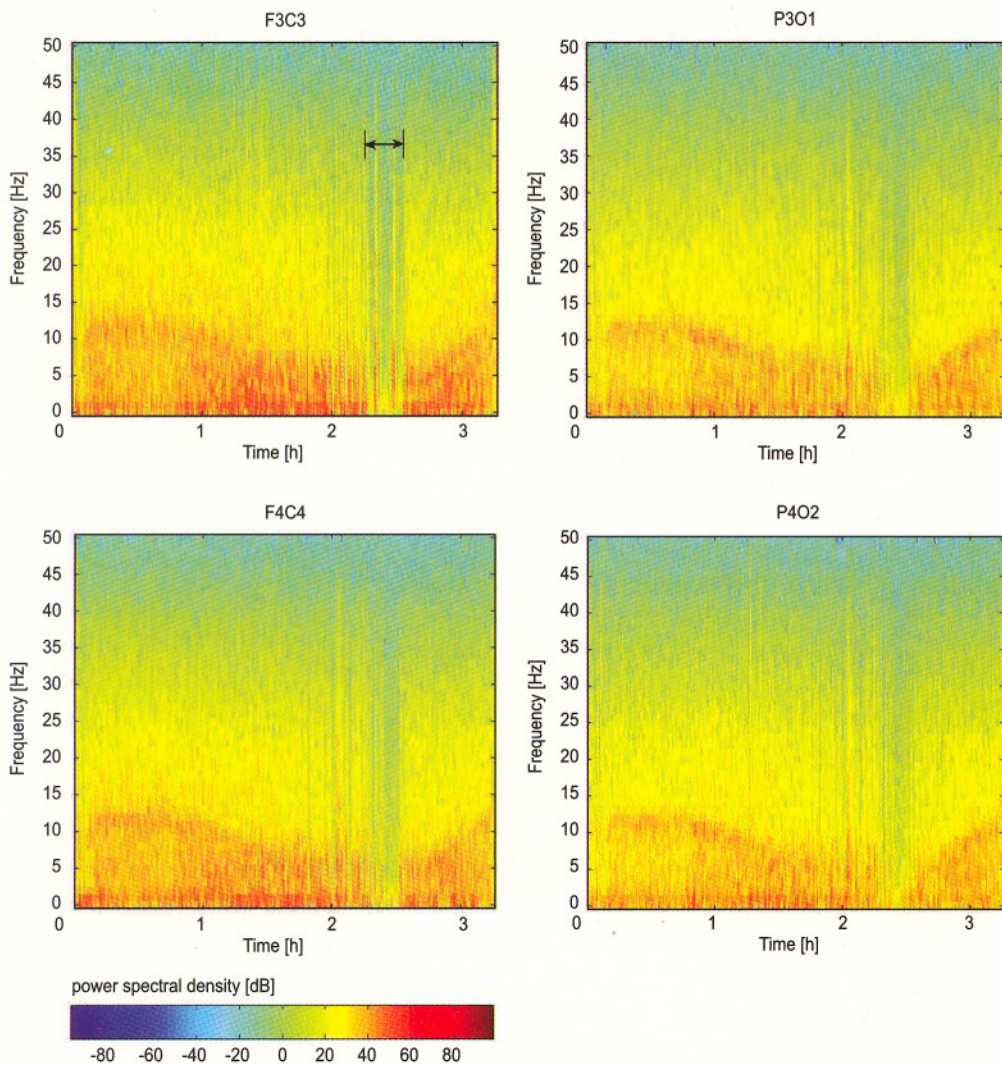


Fig. 6. Spectrograms. Evolution of the frequency spectra of the EEG activity recorded in a patient under isoflurane anaesthesia lasting about 3 hours. It illustrates gradual diminution of the EEG activity mainly within the alpha range, periods of burst suppression and gradual recovery. Each dot of colour scale represents energy of the corresponding frequency content in the time moment t . Arrows denote the burst suppression region

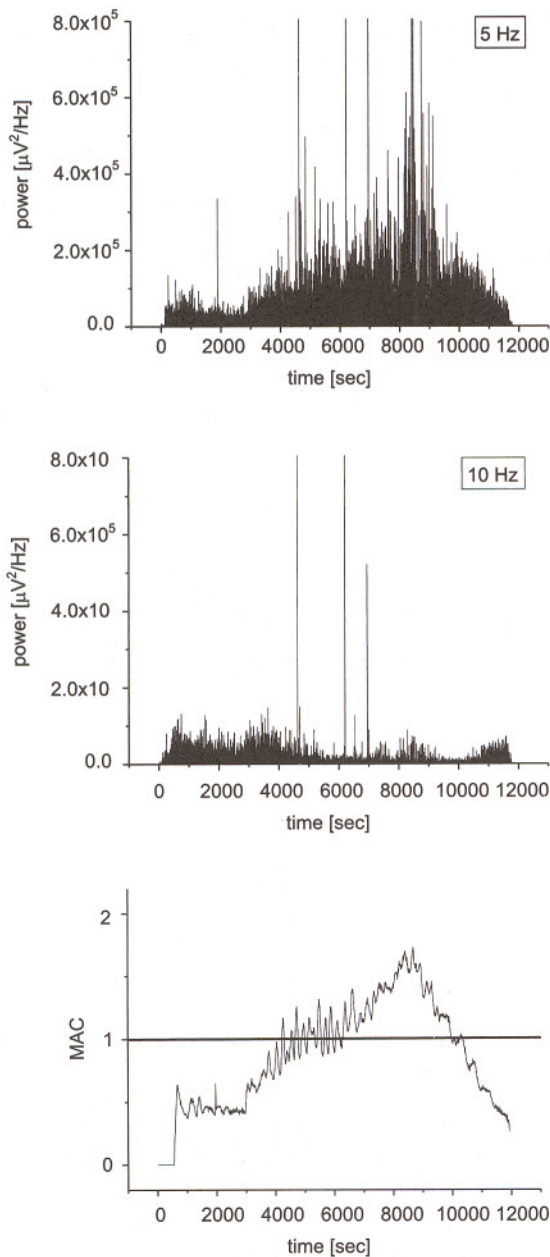


Fig. 7. Relationship between spectral powers for the EEG wave frequencies around 5 Hz and 10 Hz vs. the isoflurane concentration in the course of anaesthesia (3 hours). The whole EEG spectrum for the patient 1 illustrates Fig. 8. The minimal alveolar concentration (MAC) was defined as a concentration of the volatile anaesthetic in the lungs that is needed to prevent movement (motor response) in 50% of subjects in response to surgical (pain) stimulus. If MAC is 1.0, then 1.3 MAC would block response in 95% of subjects

The obtained results shown that two characteristic wave frequencies, 5 and 10 Hz, could be associated with the process of anaesthesia progression. During first hour of the anaesthesia, before the anaesthetic concentration reached value 1, the alpha frequency band (10 Hz) and the theta band (5 Hz) had a similar contribution. After that time interval, before the anaesthetic concentration reached maximal value, the contribution of alpha wave diminished while the contribution of theta wave increased rapidly. The alpha waves suppression evoked by volatile anesthetic permitted to detect

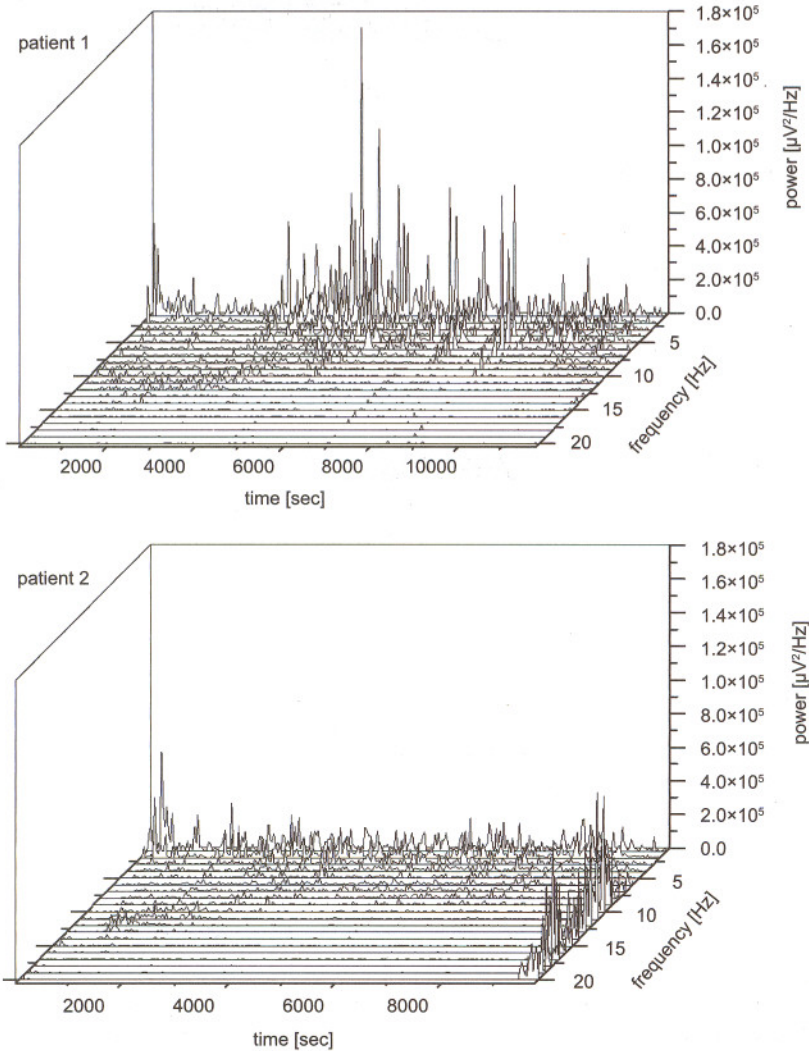


Fig. 8. Comparison of spectral powers for two different volatile anaesthetics: isoflurane (patient 1) and desflurane (patient 2). The graphs illustrate apparent differences between the two functional states created by the two anaesthetics. High content of the fast EEG activity (the beta waves) in the patient 2 (under desflurane anaesthesia), especially during recovery was observed

the theta waves that were dominated by higher frequencies during the awake state. However during the maximal anaesthetic concentration not only the contribution of theta wave was maximal but also some increase in the alpha wave contribution reappeared. This stage of anaesthesia corresponded to the burst suppression region.

It was found that the signal spectral power depended on the kind of volatile anaesthetic (Fig. 8). In the case of patient 2 desflurane evoked the signal with the high power beta waves (12–30 Hz) in the last segment of record displaying some similarity with seizure activity. Therefore further studies aimed at explanation of this case using multi-channel approach and higher statistics of patients are required.

3.4. Fractal Dimension

Before induction of the anaesthesia the fractal dimension was 1.88 ± 0.04 . During first hour of the anaesthesia course when the concentration of anaesthetic was low and nearly constant and the contribution of the alpha and theta waves were comparable the fractal dimension was nearly constant with mean 1.56 ± 0.07 (Fig. 9). In the subsequent time interval when the concentration of anaesthetic increased until the beginning of the EEG-signal suppression region it decreased to 1.23 ± 0.05 . During the burst suppression region the fractal dimension increased to 1.57 ± 0.05 .

Average decrease of fractal dimension between the first hour of the anaesthesia and start of the burst-suppression region for the frontal channels in the group of 12 patients was 0.23 ± 0.07 (Table 1).

Table 1. Percentage decrease of the fractal dimension and mean phase coherence between beginning of the anaesthesia and start of the burst-suppression region for the frontal channels in group of 12 patients

Patient	1	2	3	4	5	6	7	8	9	10	11	12	mean
Higuchi's fractal dimension	21	26	14	12	22	25	17	16	28	27	31	34	23±7
Mean phase coherence	24	33	35	62	24	9	21	29	40	22	13	5	26±15

These data shown that the fractal dimension analysis gave an additional, to the spectral analysis, information concerning the EEG-signal complexity evolution during anaesthesia progression (Fig. 6 and 8). The fractal dimension analysis shown that the EEG-signal with comparable contributions of the alpha and theta waves observed in first hour of the anaesthesia at low and nearly constant concentration of anesthetic was the most complex ($D_f = 1.88 \pm 0.04$). On the other hand in the presence of medium concentration of anesthetic, when the alpha wave contribution was diminished while the theta wave contribution was large, the signal was less complex ($D_f = 1.56 \pm 0.07$). At the burst suppression, at the highest concentration of anesthetic

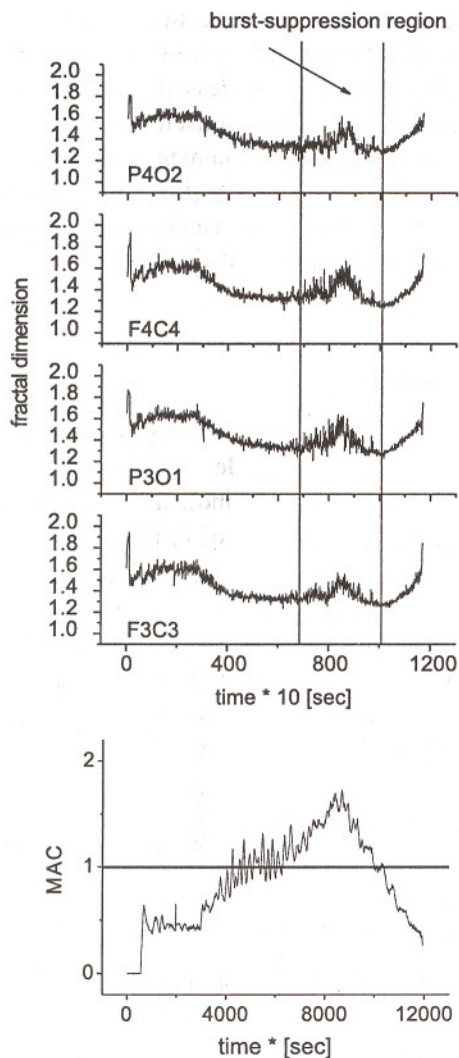


Fig. 9. Evolution of the fractal dimension (D_f) of the EEG-signal in relation with the isoflurane concentration

(more than 1 MAC), the complexity of signal increased again ($D_f = 1.57 \pm 0.05$). It occurred at the presence of alpha wave contribution comparable to that observed in the first hour and a few times larger contribution of the theta wave (Fig. 6).

The above observations may suggest that the contribution of the theta wave had no influence on the signal complexity. However, the structure of EEG-signal at the burst suppression region was different as compared with the structure observed in the preceding parts of the signal. Therefore the corresponding increase of the fractal dimension reflected another phenomena and thereby shown that the spectral analysis

alone did not elevated the differences in the structure of EEG-signal for the alpha and theta waves at burst suppression region while the fractal dimension revealed the increase in the signal complexity. Nevertheless, this increase of the signal complexity may not be considered as increase of the consciousness level.

Generally these results are in good agreement with our previous findings that the awake brain state has the highest value of the fractal dimension while the deepening of the anaesthesia corresponds to the lower value of this index [21–24]. The presence of rare forms like bursts or sharp transients in the EEG-signal were manifested by the fractal dimension increases.

3.5. Mean Phase Coherence

The mean phase coherence was high before the burst suppression region and rapidly decreased with entering this region [Fig. 10]. Mean difference of the mean phase coherence between commencement of the anaesthetic induction and start of the burst-suppression region for the frontal channels in the group of 12 patients was 0.26 ± 0.15 (Table 1).

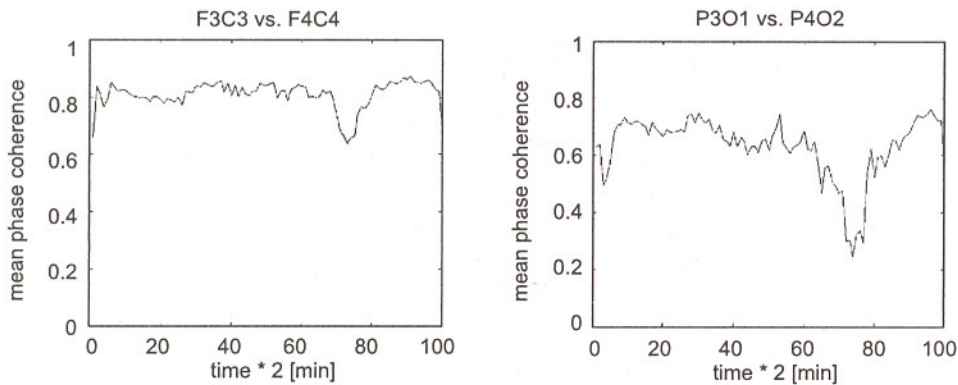


Fig. 10. Changes of the mean phase coherence of the EEG activity between the left and right hemispheres (for F3C3-F4C4 and P3O1-P4O2 channels) in the course of isoflurane anaesthesia

It showed that the loss of consciousness during the anaesthesia before the burst suppression region did not completely dismantle the process of synchronization between the left and right brain hemispheres. On the other hand decreasing of the mean phase coherence between two frontal or two back channels following the deepening of the anaesthesia indicated the loss of synchronization. The bigger synchronization was in the posterior part of the brain.

3.6. Scalograms

The results of EEG-signal analysis performed using scalograms are shown at Fig. 11. Figures 11A and 11B show the EEG activity during the burst-suppression stage of the

isoflurane anaesthesia. The wavelet analysis shown that the contribution of characteristic 5 Hz frequency wave dominated in the burst suppression region (Fig. 11A). The hypothesis about the existence of 5 Hz rhythm generation mechanism in the neuronal network responsible for burst activity could be formulated. The presence of this characteristic frequency is seen particularly in the frontal channels but it does not mean that the generation mechanism must be placed there [31]. In the case of burst with presence of other forms like spike-wave activity contribution of other frequencies to the scalogram were observed (Fig. 11B).

Figure 11C and 11D present the EEG-signal fragments for patient 2 under the desflurane anaesthesia. In the first hour of the anaesthesia a very strong contribution of the 12 Hz component appeared (Fig. 11C). The strength of this contribution was comparable to the contribution of 5 Hz component in the burst suppression region. In the last segment of the EEG-signal the contributions of components for the frequencies about 15 Hz were the strongest (Fig. 11D). This fragment corresponds to high content of the fast EEG activity (beta waves) observed during the recovery presented in Fig. 8.

This data shown that the scalograms revealed the structure of EEG-signal more precisely than the spectrograms [Fig. 6–8].

3.7. Time and Frequency Marginal Distributions

The frequency marginal plots for the region of burst suppression manifested two distinctive frequencies: 5 Hz and 3 Hz (Fig. 12). The 5 Hz waves dominated at the frontal channels. They were present at the posterior channels also, but with much lower spectral energy. This analysis shown the evolution of the dominant 5 Hz frequency waves during the whole burst suppression region.

In the time marginal course a series of distinct spikes was observed (Fig. 13A and B). They corresponded to the signal instantaneous power increases for bursts appearing during the burst-suppression region. The spike-slow wave forms can also give some contribution to these power increases. Distribution of the duration of time segments between the successive bursts was calculated for four channels using the normalized time marginal data for six thresholds: 0.1, 0.15, 0.2, 0.25, 0.3, 0.35. The maximal value of the normalized instantaneous power greater than given threshold was calculated for the short segments corresponding to each spike and then distances between successive maxima were determined. Only the distribution obtained for the threshold 0.1 was presented (Fig. 13C) because the thresholds from 0.15 to 0.25 gave similar results while the higher thresholds resulted in loss of information. This distribution manifested good regularity (Fig. 13C) which corresponded to the regularity of the volatile anaesthetic concentration changes, i. e., to the concentration increase and decrease in the region of EEG-signal suppression (Fig. 9). Therefore this analysis shown that the higher was the anaesthetic concentration the longer were the segments of EEG-signal suppression.

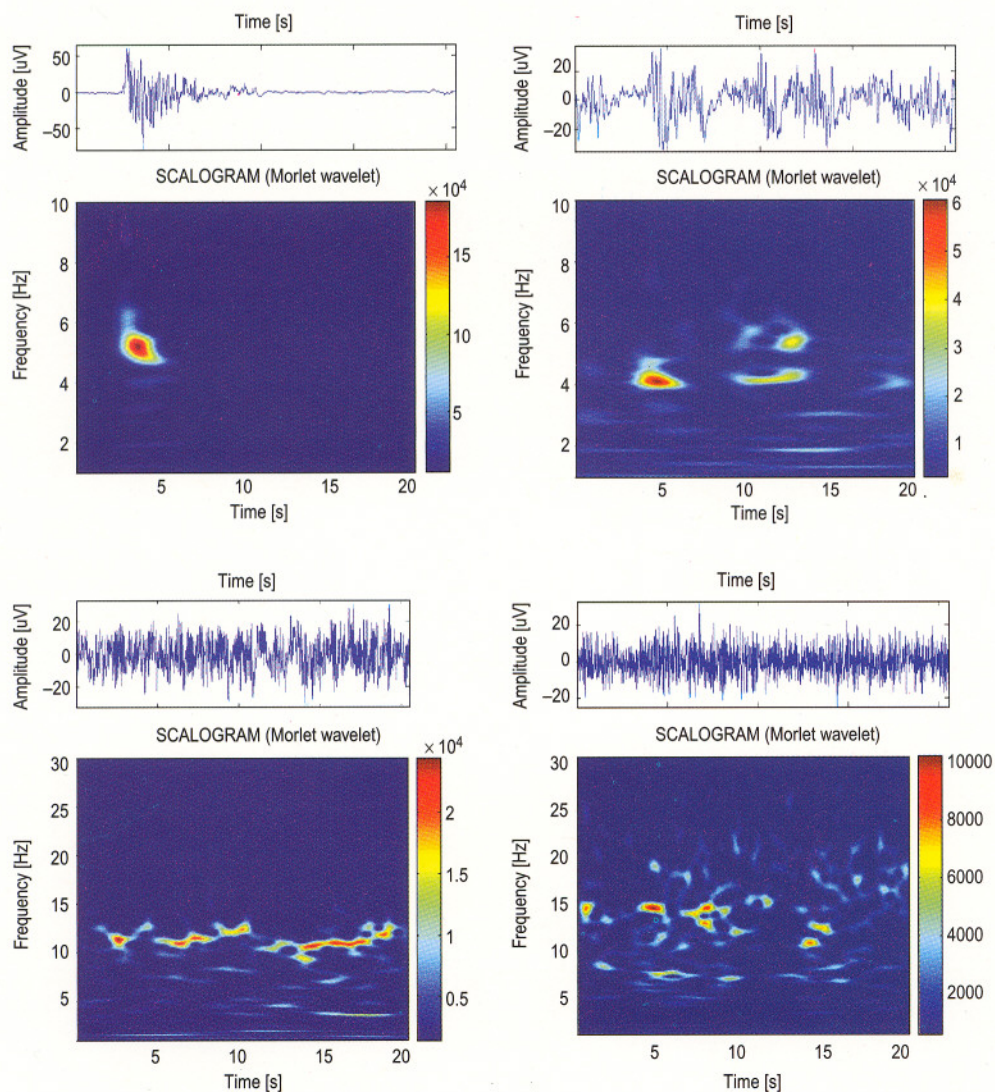


Fig. 11. Four examples of the 20-second EEG-signal fragments with their scalograms: A – The characteristic 5 Hz frequency wave contribution in the burst-suppression region was clearly seen; B – Other frequencies contributed to the scalogram in the case of burst and other forms like spike-slow wave activity presence. C, D – The contribution of beta waves seen mainly in the range from 12 to 15 Hz. Power spectral density of the corresponding frequency content in the time moment t was represented using dots in colour scale

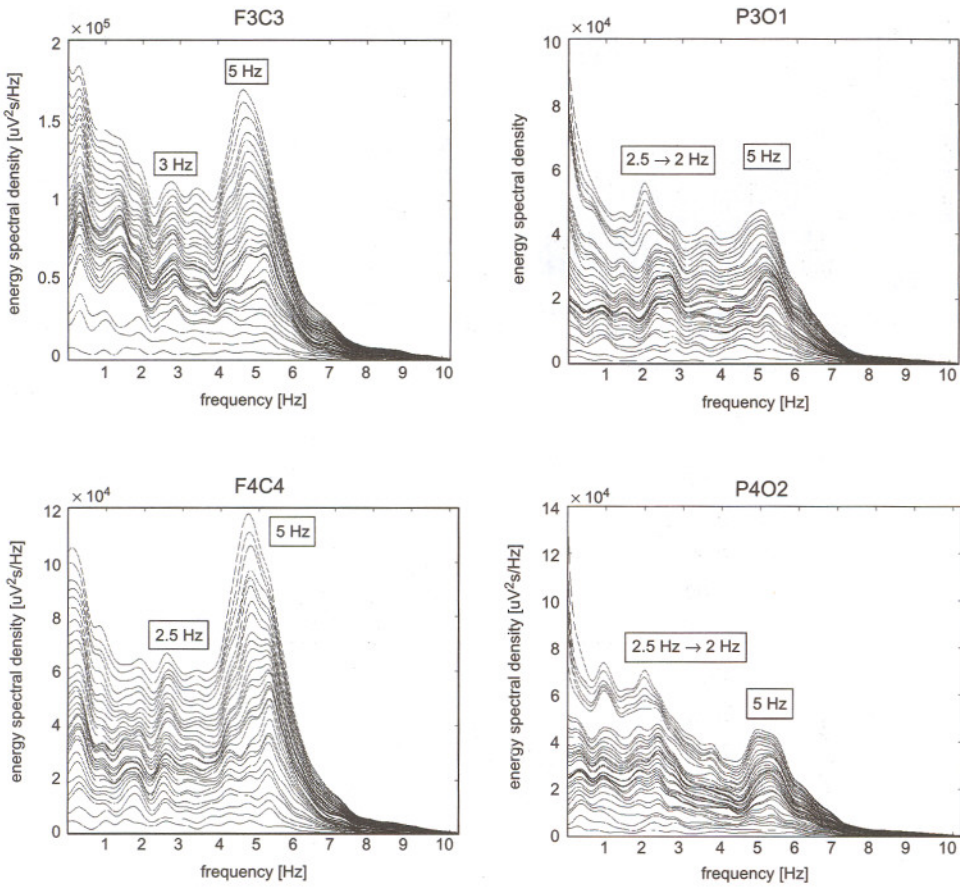


Fig. 12. Frequency marginals corresponding to the energy spectral densities for the same signal as on Fig. 13. This figure illustrates the dominant waves of 5 Hz frequency in the frontal derivations, reflecting the burst form contribution. Lines from bottom to top indicate time from the start to the end of the burst-suppression period lasting about 22 minutes in 32 steps

Moreover, Pearson's correlation coefficient was calculated for every pair of time marginals and for time lag changed from -5 sec to 5 sec every 0.01 sec. Time shift was not observed for channels placed in the opposite hemispheres (F3C3-F4C4 and P3O1-P4O2 channels), but there existed time shift for the posterior channels in reference to the frontal ones. For the left posterior derivation time shift was equal to 0.2 sec in reference to both the frontal channels and for the right posterior derivation the time shift was equal to 0.27 sec in reference to both the frontal channels. This observation could suggest that bursts generator is localized in the frontal lobe.

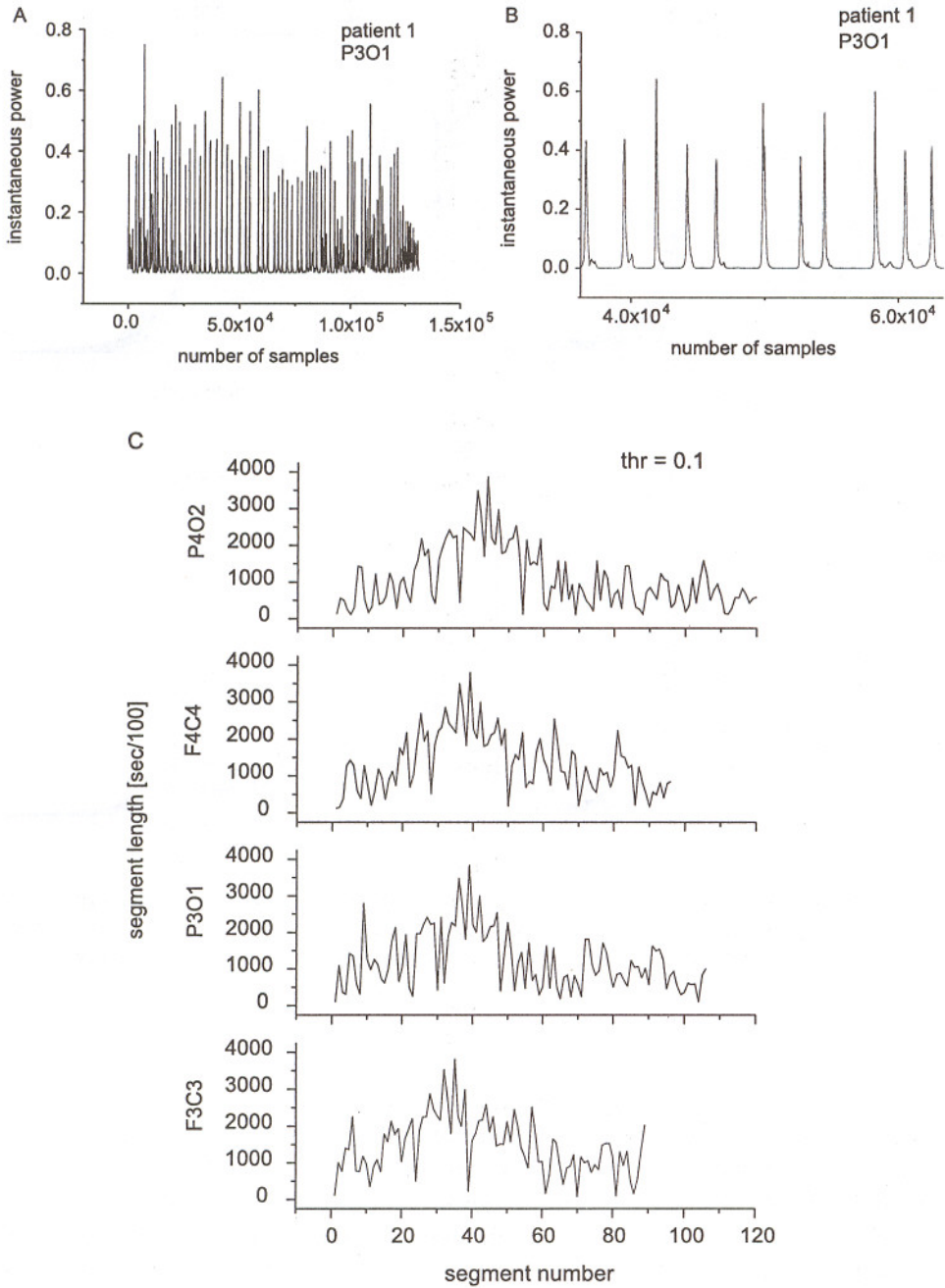


Fig. 13. A – time marginals in the burst-suppression region, B – zoomed fragment. C – the distribution of segments length between the successive spikes for 4 channels and the threshold of time marginal corresponding to instantaneous power of the signal equal 0.1. The instantaneous power was normalized to value 1

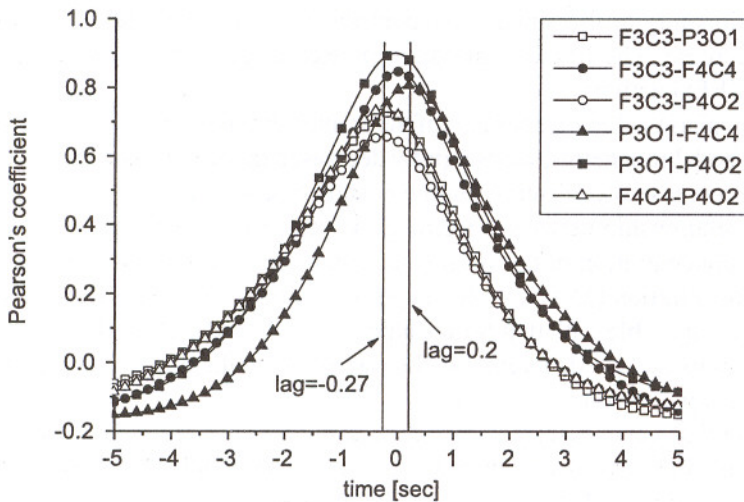


Fig. 14. Correlation of the time marginals in the burst-suppression region for every pair of channels. There was no time shift between the left and right hemisphere (for F3C3-F4C4 and P3O1-P4O2 channels). For the left posterior derivation time shift was equal to 0.2 sec with reference to both the frontal channels and for the right posterior derivation the time shift was equal to 0.27 sec with reference to both the frontal channels was observed

4. Discussion and Conclusions

The EEG patterns observed in this study possessed all characteristic features typical for the functional state evoked by the volatile anaesthetics described in the literature [1, 11, 13, 31–33]. These were slow waves, burst forms, isolated spikes and spike-slow wave patterns and continuous fast EEG activity in the alpha and the beta frequency range appearing predominantly in the frontal channels. In general many patterns of the background EEG activity induced by the volatile anaesthetics have spiky character. That may reflect functional disposition of some cerebral structures resulting in promotion of the development of epileptiform EEG patterns and motor seizures, especially in people with epilepsy. However the comparison of the obtained results with those of the previous studies should be done with caution because some patterns of activity, as for instance bursts, are described in the literature using the same name nevertheless that they manifest different structure [34, 35].

The performed analysis demonstrated the following quantitative features characteristic for the EEG-signal evoked by the volatile anaesthetics:

1. The contribution of the alpha waves in the overall EEG pattern was gradually decreasing with increasing depth of anaesthesia with complete suppression during the deepest anaesthesia. The amount of the alpha activity was increasing again when the patient was awakening.

2. Diminishing of the alpha wave contribution corresponded to the fractal dimension decrease. The fractal dimension increased again in the burst-suppression fragment of EEG activity.

3. Mean phase coherence for pair of the frontal channels and pair of the posterior channels in both brain hemispheres rapidly decreased in the burst-suppression region. The bigger decrease was observed in the posterior part of brain.

4. The relationship between spectral power for waves of frequencies 5 Hz and 10 Hz with concentration of the volatile anaesthetic was observed. For the minimal alveolar concentration (MAC) in the range from 0.5 to 1.0 the power of 5 Hz theta waves was comparable with that for the alpha waves (10 Hz). For MAC greater than 1.0 this relationship was different, i.e. the power of the theta waves was large while power of the alpha activity was small.

5. In the frequency marginals two distinctive frequencies: 5 Hz and 3 Hz were observed. The 5 Hz waves dominated at the frontal channels. They were present at the posterior channels also, but with much lower spectral energy. The dominant 5 Hz waves in the frontal derivations reflected the burst form contribution.

6. Correlations of the time marginals in the burst-suppression region for every pair of channels shown that time shift was not observed for the channels placed in the opposite hemispheres (F3C3-F4C4 and P3O1-P4O2 channels), but there existed time shift for the posterior channels with reference to the frontal ones. For the left posterior derivation time shift was equal to 0.2 sec with reference to both the frontal channels and for the right posterior derivation the time shift was equal to 0.27 sec with reference to both the frontal channels. This observation possibly suggests that the bursts generator is localized in the frontal lobe.

Comparison of the different analysis methods for study of evolution of the EEG activity in the course of anaesthesia was performed. Relationships between spectral power, fractal dimension and mean phase coherence and the concentration of the volatile anaesthetic were observed. Each of used methods gave complementary information about the same signal and permitted to evaluate utility of each of them to study different signal features.

The frequency progression pattern was observed earlier by Lloyd-Thomas et al. [36] who found that increased concentrations of isoflurane produced decreasing of fast and increasing of slow wave component in the EEG-signal. Other authors [37–40] also reported results for the EEG-signal registered from the start of the propofol anesthetic infusion to the onset of the burst suppression pattern but they did not study the time-spectral characteristics during the burst suppression and during the recovery or with other drugs. In our study the EEG-signal was registered continuously from the wake state, through the induction of anaesthesia and all stages including the burst-suppression period to the recovery from anaesthesia. The progression of the EEG-signal spectrum was treated as a whole and demonstrated in form of the spectrogram. For the different volatile anesthetics agents (isoflurane, sevoflurane

or desflurane) we observed similar pattern. The particular role of the alpha waves contribution to the spectrum was underlined also.

Lipping et al. [41] analyzed coherence of the EEG-signal during propofol anaesthesia using standard Matlab function *cohere*. They showed that the beta activity, corresponding to spindles, started several minutes before the onset of burst suppression and slowed down gradually. However this coherence could only be seen between the depth electrodes and the scalp. No studies are performed with other anaesthetics. Koskinen et al. [39, 42] observed systematic phase synchronization changes between the EEG channels in certain frequency bands during induction and recovery from propofol anaesthesia. They applied the same algorithm for mean phase coherence calculation as in our work. However, they had not quantified the relation between phase synchronization and levels of anaesthesia other than induction and recovery. In consequence they had not observed the behavior of coherence for the most interesting fragment of the EEG-signal during anaesthesia which is the burst-suppression region.

The relation between fractal dimension and spectral analysis of the EEG-signals during isoflurane, desflurane and sevoflurane anaesthesia was reported for the first time in our paper. The fractal dimension method regarding spectral methods gives more precise information about transient changes in the signals giving the possibility to determine the exact moment of anaesthetic induction and early warn of undesired events. Unfortunately, neither the spectral methods nor the fractal dimension and mean phase coherence permit to analyze so short transient activity like spike-waves. It seems that the wavelet analysis is especially useful for this purpose.

The wavelet analysis was applied previously to studying of EEG activity during anaesthesia. Sarkela et al. [43] developed the wavelet subband entropy – a novel method for detection and quantification of the epileptiform electroencephalographic activity during sevoflurane anaesthesia. This method is useful in off-line analysis only because of its time-consuming algorithm. Moreover, these authors did not give any information about features of the EEG-signal during anaesthesia. They were concentrated on the epileptiform detection only. The results of our study shown that the wavelet analysis gave additional information about the EEG-signal registered during the anaesthesia evoked by fluorinated inhalation anaesthetics.

The analysis of burst-suppression region shown that in the frequency marginals two distinctive frequencies: 5 Hz and 3 Hz were observed. The 5 Hz waves dominated at the frontal channels. These waves were present at the posterior channels also, but with much lower spectral energy. The dominant 5 Hz waves in the frontal derivations reflected the burst form contribution.

The analysis of correlation between the time marginals shown absence of time shift between the channels placed in the opposite hemispheres (F3C3-F4C4 and P3O1-P4O2 channels). On the contrary, time shift existed for the posterior channels with reference to the frontal ones. For the left posterior derivation with reference to both the frontal channels time shift was equal to 0.2 sec and for the right posterior derivation

with reference to both the frontal channels the time shift was equal to 0.27 sec. This observation could suggest that the bursts generator was localized in the frontal lobe.

Hudetz and Imas [34] observed burst activation by flash stimuli during isoflurane anaesthesia in rats. They reported that spontaneous and flash-induced burst were similar in frequency, latency and spatial distribution. They found maximum power in the frontal cortex but, unlike in our work, with a dominant frequency of 10 Hz.

Further studies aimed at detection of spike-wave form features and their evolution in the course of anaesthesia for different concentrations and different kinds of volatile anaesthetics should be carried out.

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References

1. Ragazzo P.C., Galanopoulou A.S.: Alfentanil-induced activation: a promising tool in the presurgical evaluation of temporal lobe epilepsy patients. *Brain Res. Rev.* 2000, 32, 316–327.
2. Baines D.: Convulsive movements with sevoflurane. *Anaesth. Intensive Care* 1998, 26, 329.
3. Haga S., Shima T., Momose K., Andoh K., Hashimoto Y.: Anesthetic induction of children with high concentrations of sevoflurane. *Masui*, 1992, 41, 1951–1955.
4. Hymes J.A.: Seizure activity during isoflurane anesthesia. *Anesth. Analg.* 1985, 64, 367–368.
5. Jantti V., Yli-Hankala A.: Neurophysiology of anaesthesia. *Clinical Neurophysiology at the Beginning of the 21st Century. Supplements to Clinical Neurophysiology*, 2000, 53.
6. Jantti V., Mustola S., Huotari A., Koskinen M.: The importance of looking at the EEG when presenting univariate variables to describe it. *Br. J. Anaesth.*, 2002, 88(5), 739–746.
7. Kaisti K.K., Jääskeläinen S.K., Rinne J.O., Metsähonkala L., Scheinin H.: Epileptiform discharges during 2 MAC sevoflurane anesthesia in two healthy volunteers. *Anesthesiology* 1999, 91, 1952–1955.
8. Komatsu H., Taie S., Endo S., Fukuda K., Ueki M., Nogaya J., Ogli K.: Electrical Seizures during Sevoflurane Anesthesia in Two Pediatric Patients with Epilepsy. *Anesthesiology* 1994, 81, 1535–1537.
9. Nousiainen U., Mervaala E., Ylinen A., Uusitupa M., Riekkinen P.: The importance of the electrocardiogram in ambulatory electroencephalographic recordings. *Arch. Neurol.* 1989, 46, 1171–1174.
10. Poulton T.J., Ellingson R.J.: Seizure associated with induction of anesthesia with isoflurane. *Anesthesiology* 1984, 61, 471–476.
11. Sato K., Shamoto H., Kato M.: Effect of sevoflurane on electrocorticogram in normal brain, *Journal of neurosurgical anesthesiology* 2002, 14(1), 63–65.
12. Schultz B., Schultz A.: Epileptiform EEG potentials with sevoflurane. *Anaesth Intensive Care* 1998, 26, 329.
13. Schultz A., Schultz B., Grouven U., Beger F., Korsch G.: Sharp transients in the EEG's of non-epileptiform adult patients receiving sevoflurane, *Pharmacy World & Science* 2001, 23(2), 82–85.

14. Terasako K., Ishii S.: Postoperative seizure-like activity following sevoflurane anesthesia. *Acta Anaesthesiol. Scand.* 1996, 40, 953–954.
15. Vakkuri A.: Effects of sevoflurane anesthesia on EEG patterns and hemodynamics. PhD Thesis 2000, Department of Anaesthesia and Intensive Care Medicine, Women's Hospital and surgical Hospital, Helsinki University Hospital, University of Helsinki, Finland.
16. Vakkuri A., Yli-Hankala A., Särkelä M., Lindgren L., Mennander S., Korttila K., Saarnivaara L., Jäntti V.: Sevoflurane mask induction of anaesthesia is associated with epileptiform EEG in children. *Acta Anaesthesiologica Scandinavica* 2001, 45(7), 805–811.
17. Woodforth I., Hicks R., Crawford M., Stephen J., Burke D.: Electroencephalographic evidence of seizure activity under deep sevoflurane anesthesia in a nonepileptic patient. *Anesthesiology* 1997, 87(6), 1579–1582.
18. Yli-Hankala A., Vakkuri A., Särkelä M., Lindgren L., Korttila K., Jäntti V.: Epileptiform electroencephalogram during mask induction of anesthesia with sevoflurane, *Anesthesiology* 1999, 91(6), 1596–1603.
19. Zacharias M.: Convulsive movements with sevoflurane in children. *Anaesth Intensive Care* 1997, 25, 727.
20. Durka P., Maleński W., Ircha D.: Viewer ddv (<http://brain.fuw.edu.pl/~durka/>).
21. Ferenets R., Lipping T., Anier A., Jantti V., Melto S., Hovilehti S.: Comparison of entropy and complexity measures for the assessment of depth of sedation. *IEEE Trans. Biomed. Eng.* 2006. 53(6), 1067–77.
22. Klonowski W., Olejarczyk E., Stepień R., Jalowiecki P., Rudner R.: Monitoring the Depth of Anaesthesia Using Fractal Complexity Method. in: *Complexus Mundi. Emergent Patterns in Nature*, Ed. M.N.Novak, World Scientific, New Jersey, London, Singapore, 2006, 981-256-666-X, 333–342.
23. Olejarczyk E.: Analysis of EEG signals using fractal dimension, PhD Thesis, Institute of Biocybernetics and Biomedical Engineering Polish Academy of Science. Warsaw 2003.
24. Rudner R., Jalowiecki P., Willand M., Klonowski W., Olejarczyk E., Stepień R., Hagihira S.: Fractal dimension – a new EEG-based method of assessing depth of anaesthesia in comparison with BIS during induction and recovery from anaesthesia. *Euroanaesthesia 2005 – 13th Annual Meeting of European Society of Anaesthesiologists and 27th Annual Meeting of the European Academy of Anaesthesiology*, 28–31 May 2005, Vienne, *European Journal of Anaesthesiology* 22, suppl. 34, A–118, 32–33, 2005.
25. Higuchi T.: Approach to an irregular time series on the basis of the fractal theory. *Physica* 1988, D 31, 277–283.
26. Olejarczyk E.: http://www.sensation-eu.org/pdf/SENSATION_2nd_Newsletter.pdf
27. Tass P., Rosenblum M.G., Weule J., Kurths J., Pikovsky A.S., Volkman J., Schnitzler A., Freund H.J.: Detection of n:m phase locking from noisy data: application to magnetoencephalography. *Phys. Rev. Lett.* 1998, 81, 3291–3294.
28. De Clercq: Advanced preprocessing techniques and nonlinear signal analysis applied to scalp electroencephalograms for the prediction of epileptic seizures, PhD Thesis, Katholieke Universiteit Leuven 2005.
29. Mormann F., Lehnertz K., David P., Elger C.E.: Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients 2000, *Physica D* 144, 358–369.
30. Davy M., Roy E.: Time-frequency Toolbox portable ANSI C Package, <http://www.sigproc.eng.cam.ac.uk/~md283/toolbox/Ctfbeng.html>, 2001.
31. Katz A., Marks DA., McCarthy G., Spencer SS.: Does interictal spiking change prior to seizures? *Electroencephalogr. Clin. Neurophysiol.* 1991, 79, 153–156.
32. Cascino G.D., Sharbrough W.: III – Intraoperative electroencephalographic monitoring. In: *Electrodiagnosis in Clinical Neurology*, M.J. Aminoff (Ed.), Churchill Livingstone, 4th Edition, 1999, 211–221.
33. Ermes M., Särkelä M., van Gils M., Vakkuri A., Yli-Hankala A., Jäntti V.: Method for the Automatic Detection of Epileptiform Waveforms in Sevoflurane-induced Anesthesia EEG. *Proc. 28th IEEE EMBS Ann. Intern. Conf.*, New York City, USA, Aug 30-Sept 3, 2006, SuBO1.3, 6343–6346.

34. Hudetz A.G., Imas O.A.: Burst activation of the Cerebral Cortex by Flash Stimuli during Isoflurane Anaesthesia in Rats, *Anesthesiology* 2007, 107, 983–991.
35. Sarkela M., Mustola S., Seppanen T., Koskinen M., Lepola P., Suominen K., Juvonen T., Tolvanen-Laakso H., Jantti V.: Automatic analysis and monitoring of burst suppression in anesthesia, *J. Clin. Monit. Comp.* 2002, 17, 125–134.
36. Lloyd-Thomas A.R., Cole P.V., Prior P.F.: Quantitative EEG and brainstem auditory evoked potentials: comparison of isoflurane with halothane using the cerebral function analysing monitor, *Brit. J. Anaesth.*, 1990, 65, 306–312.
37. 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, 1570–1573.
38. Koskinen M., Mustola S., Seppanen T.: Relation of EEG spectrum progression to loss of responsiveness during induction of anesthesia with propofol. *Clin. Neurophysiol.* 2005, 116, 2069–2076.
39. Koskinen M.: Automatic assessment of functional suppression of the central nervous system due to propofol anesthetic infusion. From EEG phenomena to a quantitative index. PhD Thesis 2006, Faculty of Technology, Department of Electrical and Information Engineering, Infotech Oulu, University of Oulu, Finland.
40. Kuizenga K., Wierda J.M., Kalkman C.J.: Biphasic EEG. changes in relation to loss of consciousness during induction with thiopental, propofol, etomidate, midazolam or sevoflurane. *Br. J. Anaesth.* 2001, 86, 354–360.
41. Lipping T., Ferenets R., Puumala P., Suominen K., Karvonen E., Sonkajarvi E., Alahuhta S.: EEG independent component and coherence analysis from scalp and depth electrodes during propofol anesthesia. *Proc. 25th IEEE EMBS Ann. Intern. Conf.*, Cancun, Mexico, 2003.
42. Koskinen M., Seppanen T., Tuukkanen J., Yli-Hankala A., Jantti V.: Propofol anesthesia induces phase synchronization changes in EEG. *Clin. Neurophysiol.* 2001, 112, 386–392.
43. Sarkela M.O., Ermes M.J., van Gils M.J., Yli-Hankala A.M., Jantti V.H., Vakkuri A.P.: Quantification of epileptiform electroencephalographic activity during sevoflurane mask induction. *Anesthesiology* 2007, 107(6), 928–938.