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Prefrontal left – dominant hemisphere – gamma and delta oscillators in general anaesthesia with volatile anaesthetics during open thoracic surgery

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Abstract

OBJECTIVES: The main objective was to indicate sufficient general anaesthesia (GA) inhibition for negative experience rejection in GA.
PATIENTS AND METHODS: We investigated the group of patients (n=17, mean age 63.59 years, 9 male – 65.78 years, 8 female – 61.13 years) during GA in open thorax surgery and analyzed EEG signal by power spectrum (pEEG) delta (DR), and gamma rhythms (GR). EEG was performed: OP0 – the day before surgery and in surgery phases OP1–OP5 during GA. Particular GA phases: OP1 = after premedication, OP2 = surgery onset, OP3 = surgery with one-side lung ventilation, OP4 = end of surgery, both sides ventilation, OP5 = end of GA. pEEG registering in the left frontal region Fp_1–A_1 montage in 17 right handed persons.
RESULTS: Mean DR power in OP2 phase is significantly higher than in phase OP5 and mean DR power in OP3 is higher than in OP5. One-lung ventilation did not change minimal alveolar concentration and gases should not accelerate decrease in mean DR power. Higher mean value of GR power in OP0 than in OP3 was statistically significant. Mean GR power in OP3 is statistically significantly lower than in OP4 correlating with the same gases concentration in OP3 and OP4.
CONCLUSION: Our results showed DR power decreased since OP2 till the end of GA it means inhibition represented by power DR fluently decreasing is sufficient for GA depth. GR power decay near the working memory could reduce conscious cognition and unpleasant explicit experience in GA.

ORIGINAL ARTICLE

INTRODUCTION

The 21st century is characteristic with more than a million pages written about human consciousness. Consciousness, namely human, is a multifaceted and ambiguous concept and it focuses on both scientific and philosophical debate. This state of being conscious (awareness) is changed during general anaesthesia (GA) when the primary target must achieve three goals: suppress awareness, install amnesia and analgesia. The anaesthesiologists work every day with the human consciousness and therefore they need the precise data how deep the anaesthesia is (Marchant 2014).

Benefits of pEEG in GA are the measurements and monitoring of the level of consciousness which can help clinicians to formulate the precise type and optimal dosages of anaesthetic or sedative medication for each patient. Time-domain recordings of the electroencephalography (EEG) will deliver an enormous amount of data and requires additional trained personal for continuous EEG signal analysis (Fleming & Smith 1979). In order to decrease the amount of data, computer-processed EEG analysis, such as the power spectrum analysis has been employed for a more practical approach to intra-operative EEG monitoring (Myers *et al.* 1973; Levy *et al.* 1980; Rampil *et al.* 1980). The first observations of the effects of anaesthetic agents on the EEG occurred soon after the development of clinical EEG at the beginning of the 20th century (Rampil 1998).

The use of EEG-based depth of anaesthesia monitors is recommended as an option during any type of general anaesthesia in patients considered at higher risk of adverse outcomes. Our abilities to assess the depth and quality of unconsciousness and the localisation if the effects of volatile anaesthetics during general anaesthesia are not objective and very inaccurate.

We investigate the anaesthesia-induced unconsciousness, using classic and – power spectral analysis (pEEG). Power spectral analysis based on the linear Fourier transform is still a powerful mathematical tool, which can be used effectively to design electroencephalographic parameters indicating the hypnotic component of anaesthesia.

Power spectrum performance

The first step in the process of power spectrum analysis consists of digitizing the primary ('raw') EEG signal at frequent intervals for a certain period of time (e.g. 2–16 s) known as an 'epoch' (Myers *et al.* 1973; Levy *et al.* 1980). For example, an analogue to digital (A/D) signal transformation can be performed at a rate of 64 transformations per second, yielding a 256 sample points A/D conversion during a 4 s epoch of data entry (Myers *et al.* 1973). Next, the data of one epoch are subjected to Fast Fourier Transform (FFT). FFT separates the EEG epochs into a number of component sinusoidal (sine and cosine) waveforms across the entire frequency range (i.e. 0.5–45 Hz), each having a calculated amplitude, frequency and phase whose sum is the original waveform (Levy *et al.* 1980; Pichlmayr *et al.* 1983; John & Prichep 2005). The numerical value of an EEG signal recorded for a certain time series (t) (epoch) can be cal-

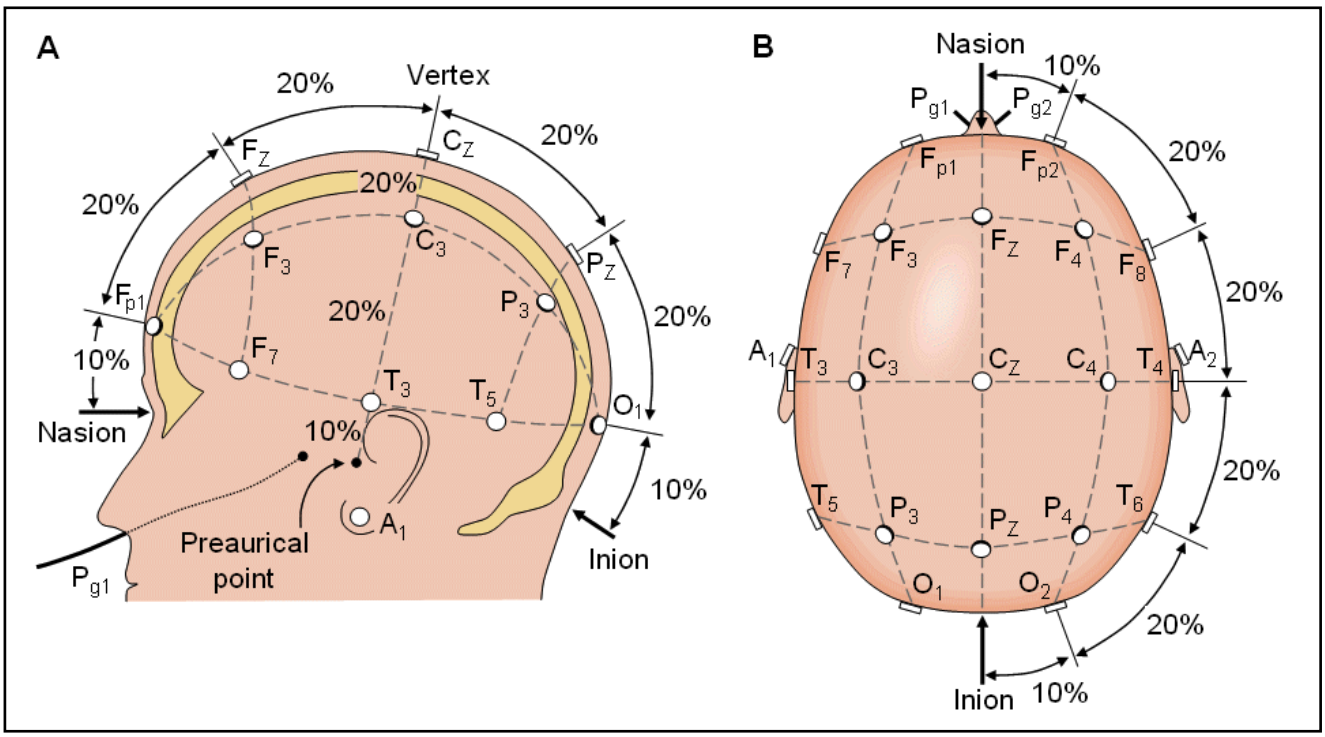

Fig. 1. The international 10–20 system seen from (A) left and (B) above the head. A = Ear lobe, C = central, Pg = nasopharyngeal, P = parietal, F = frontal, Fp = frontal polar, O = occipital (Dvořák 2015).

culated from the amplitude (ai) at each frequency (fi) in the original EEG tracing based on the common used formula (Prichep 2005).

PATIENTS AND METHODS

We examined a group of patients (n=17, mean age 63.59 years, 9 males –mean age 65.78 years, 8 females – mean age 61.13 years) during GA in an open thorax surgery and we analyzed EEG signal by the means of power spectrum and mean frequency of analyzed bands of EEG signal.

EEGs were registered twice: 1. OP0 = the day before surgery, 2. during surgery and GA: OP1 = after premedication, before start of operation with closed eyes, OP2 = surgery onset – skin incision at both sides lung ventilation, OP 3 = surgery in phase with one-side lung ventilation, OP 4 = end of surgery with sewing and both sides ventilation, OP 5 = end of GA, before extubation. Following classic visual evaluation we statistically analyzed EEG signal in the left frontal region Fp_1–A_1 montage in 17 right handed persons.

We prepared wider power spectral analysis of EEG signal registered with colour mapping and then statistic evaluation of the difference in particular reference and laplacian – isoparametric grids of the 10–20 system (Figure 1).

Then we illustrated topographic or Brain Map of EEG activity and the power of the EEG signal in a given frequency band can be displayed in such a manner (Figure 2a, Figure 2b).

Methods of clinical and electrophysiological examination

The recordings were made over a period of one year, and for each EEG a standard 5 minute recording protocol was used. We used different size of EEG caps according to circumference (dimensions) of the head (neurocranium). After the EEG cap application the inion and the nasion were identifying points for correct cap´s position. After an administration of electrically active gel the impedance of particular electrode was improved. Electrode impedances were kept below 5 kΩ (putting an electro technical gel in every electrode and electrodes resistance control) to reduce polarization effects, and standard EEG caps were used with 19 Ag-AgCl electrodes placed according to the international 10–20 system. The recordings were made at a sample rate of 500 Hz using a bipolar and common reference montages (Brainlab, OSG BVBA). For statistic testing of quantitative outcomes (numbers) of the day before surgery we performed 5 minute lasting standard EEG examination for comparing with the samples immediately before anaesthesia, in the course of pre-anaesthesia and within critical stages of surgery under deep general anaesthesia. We randomly extracted 10 short time-windows of each good EEG recordings in the day before operation (reference values for statistic evaluation of EEG sample without artefacts contamination; still many specific problems exists: EEG recording produces a lot of noise) for statistic comparison of EEG samples under the influence of immediate operation stressing condition, pre-anaesthesia and critical stages of GA. Technicians-educated medical doctor-postgraduate student annotated eyes open, eyes closed, hyperventilation events in the day before GA recordings + in the time of surgery maximally stressing nociception time-windows were used for statistic testing in individual case and later for total series testing.

An independent component analysis filter was used to reduce the influence of eye blink artefacts on the described features. After calculating the independent components, each was compared to an electro-oculogram (EOG) channel recorded together with the EEG. If one of the components showed a substantial correlation with the EOG channel (>0.3), it was removed by setting all its values to zero. The remaining components were projected back to their channel space by applying the inverse transform. Other artefacts detection or reduction were performed by means of specific filters and electric alternating current artefacts were elimi-

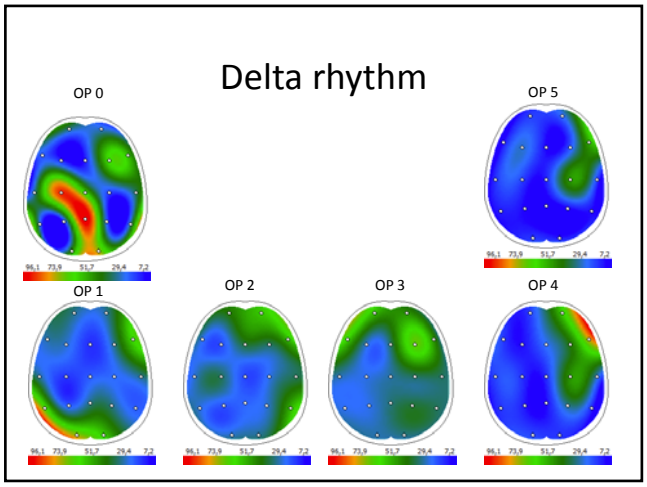

Fig. 2a. Delta rhythm (n=17) during individual stages surgery-GA.

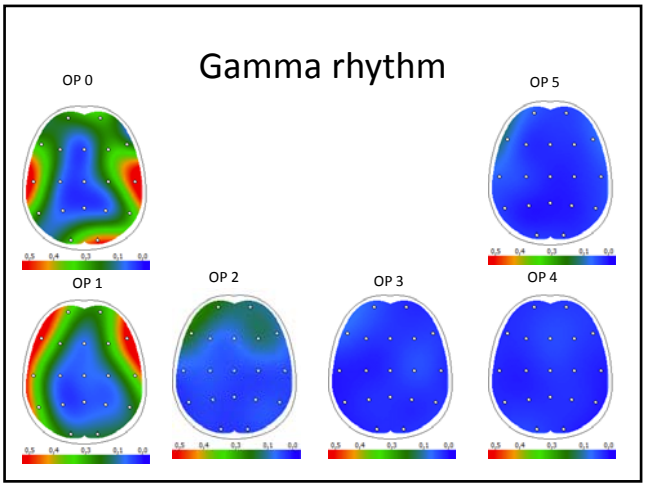

Fig. 2b. Gamma rhythm (n=17) during individual surgery stages-GA.

nated by using of differentiating amplifier inhibiting the alternating current 50 Hz frequency and facilitating the EEG rhythms. Before the EEG sets equipped by differentiating amplifier the primary earth was used with range resistance 2–4 Ω as a basic prerequisite for eliminating alternating current 50 Hz frequency coinciding with gamma rhythm. No other artefact detection or reduction was performed.

RESULTS

The variations of all EEG bands in power spectrum (characterized by the medians of sample in μV^2) during individual stages of the surgery are illustrated in Figure 3.

The frequency changes (characterized by the medians of sample in Hz) during individual surgery stages-GA are depicted in Figure 4.

The power spectra (characterized by the means of sample in μV^2) of delta band are represented in Figure 5 and in Table 1.

Statistic tests of significance of power differences in the particular surgery stages.

Power DR (μV^2)		*p*-value of an appropriate
Differences		one-tailed paired test
OP2–OP5	19.872–7.677 μV^2	0.013599544
OP3–OP5	12.950–7.677 μV^2	0.022788313

Note: The difference between two population means by using data collected in matched pairs (all pairs of surgery stages, i.e. 6×5/2=15 differences) was tested. When the population of differences is normal (Shapiro-Wilk test for normal distribution), null hypothesis is formulated as H_0: $\mu_{OPi} \leq \mu_{OPj}$ and alternative hypothesis, for which we wish to gather supporting evidence is H_1: $\mu_{OPi} > \mu_{OPj}$ ($i,j = 0,1,2,3,4,5$; $i \neq j$), or H_0: $\mu_{OPi} \geq \mu_{OPj}$ and H_1: $\mu_{OPi} < \mu_{OPj}$ respectively. Difference of powers spectra in two particular surgery stages is said to be statistically significant, if the *p*-value of its test (either parametric matched-pairs t-test or nonparametric Wilcoxon signed ranks test) is from interval 0.01–0.05). Difference of powers spectra in two particular surgery stages is said to be statistically highly significant, if the *p*-value of these tests is less than 0.01. If *p*-value of the paired test of difference of powers spectra in two particular surgery stages is greater than 0.05, this difference is not statistically significant.

The changes of delta rhythm frequency (characterized by the medians of sample in Hz) in particular surgery stages-GA are depicted in Figure 6 and illustrated in digits in Table 2.

The means of power spectra and frequency of gamma rhythm are illustrated in Figure 7, Figure 8 and in Table 3.

Statistic tests of significance of different power levels in the particular surgery stages.

Power GR (μV^2)

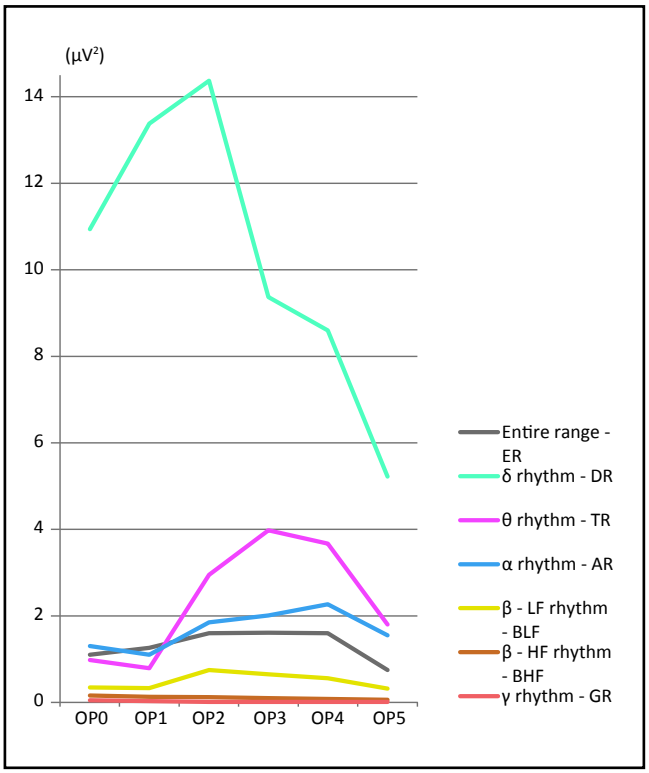

Fig. 3. EEG power spectra (μV^2) during open thorax surgery (all EEG bands) in particular surgery stages-GA.

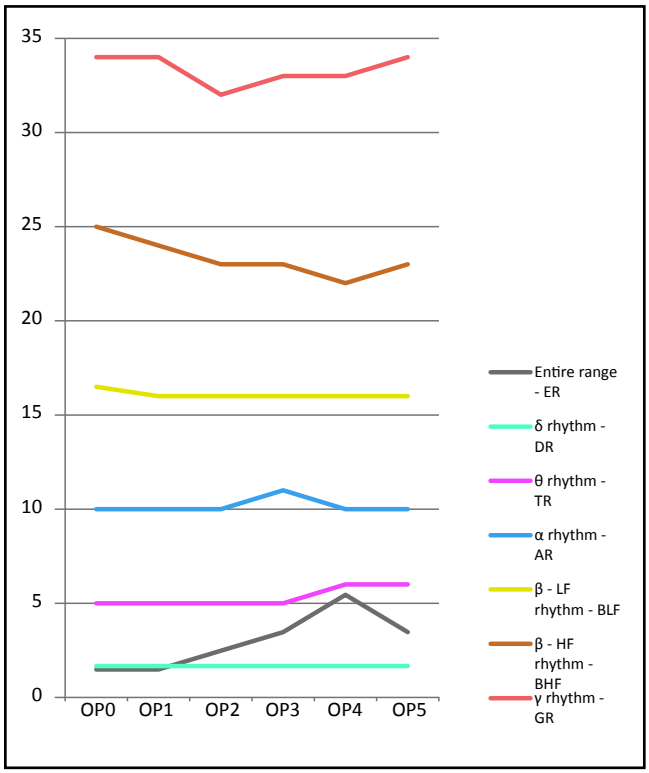

Fig.4. The frequency (Hz) during individual surgery stages-GA (EEG all bands)

Different levels between		*p*-value of Wilcoxon test
OP0–OP2	0.07706–0.01941 μV²	0.0054
OP0–OP3	0.07706–0.00941 μV²	0.0016
OP0–OP4	0.07706–0.01353 μV²	0.0016
OP0–OP5	0.07706–0.01824 μV²	0.0024
OP2–OP3	0.01941–0.00941 μV²	0.00101
OP3–OP5	0.00941–0.01824 μV²	0.00519

Lower power spectrum gamma rhythm in the surgery stage OP3 comparing with the surgery stage OP2 and OP5 is highly statistically significant.

The doses of inhaled anaesthetics are usually referred to their minimum alveolar concentration (MAC): a MAC value of 1 is the dose that prevents movement in 50% of subjects in response to a painful surgical stimulation. At low MAC values (0.1–0.2) anaesthetics produce amnesia, first explicit and then implicit (Eger 1965). Analgesia as a part of the GA was sufficient and patient decreased power spectrum of GR from the 0.01941 in stage OP2 to 0.00941 in stage OP3 (0.00101 $p<0.01$).

Table 4 contains particular MAC values (MAC Fi/ Fe vol %) during surgery stages-GA OP2, OP3, OP4.

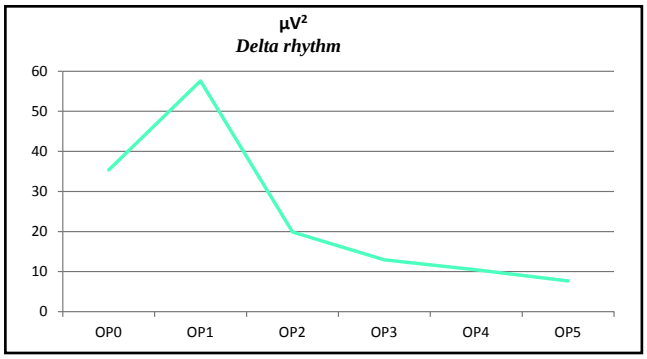

Fig. 5. Delta band power spectrum in the particular surgery stages-GA.

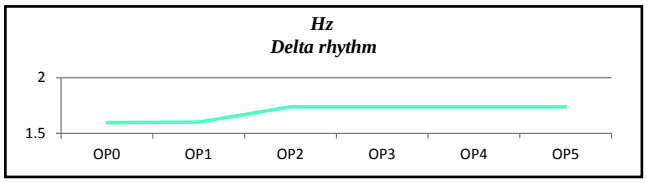

Fig. 6. The changes delta rhythm frequency in particular surgery stages-GA.

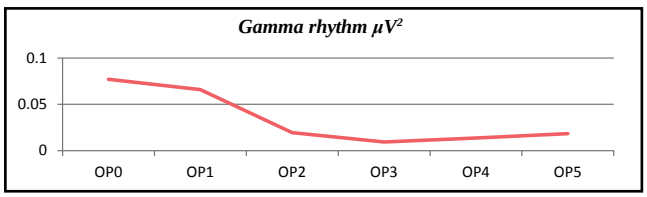

Fig. 7. The power spectrum in particular surgery stages-GA.

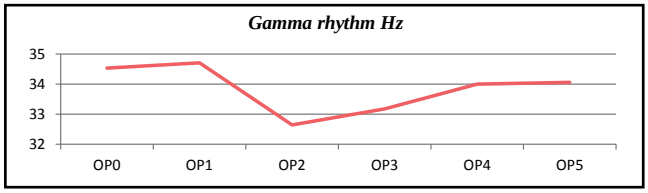

Fig. 8. The frequency of gamma rhythm in particular surgery stages-GA.

Tab. 1. Delta rhythm power spectrum (characterized by the means of sample in μV²) in the particular surgery stages-GA.

Delta rhythm μV²					
OP0	**OP1**	**OP2**	**OP3**	**OP4**	**OP5**
37.0613	57.5935	19.8724	12.9506	10.45	7.67706

Tab. 2. Digital values of delta rhythm frequency medians in particular surgery stages

Delta rhythm Hz					
OP0	**OP1**	**OP2**	**OP3**	**OP4**	**OP5**
1.59688	1.60118	1.73824	1.73824	1.73824	1.73824

Tab. 3. Gamma power and frequency.

	Gamma rhythm					
	OP0	**OP1**	**OP2**	**OP3**	**OP4**	**OP5**
power μV²	0.07706	0.06588	0.01941	0.00941	0.01353	0.01824
frequencies Hz	34.5294	34.7059	32.6471	33.1765	34	34.0588

Tab. 4. contains particular MAC values (MAC Fi/ Fe vol %) during surgery stages-GA OP2, OP3, OP4.

Pacient	**OP 2**	**OP 3**	**OP 4**	**Anaesthetic gas**
	MAC Fi/Fe vol %	**MAC Fi/Fe vol%**	**MAC Fi/Fe vol %**	
1.	1.0	2.0	1.0	Sevofluran
2.	1.0	1.2	1.1	Sevofluran
3.	1.3	1.3	1.2	Sevofluran
4.	1.0	1.2	0.6	Sevofluran
5.	1.7	1.3	1.4	Sevofluran
6.	1.3	1.1	1.0	Sevofluran
7.	0.8	0.9	0.96	Sevofluran
8.	0.8	0.9	0.84	Sevofluran
9.	1.0	1.0	0.9	Sevofluran
10.	0.8 (5.0/5.9)	**1.1 (6.4/7.1)**	0.3 (1.2/0.0)	Desfluran
11.	1.0 (6.5/7.7)	**1.0 (6.2/6.7)**	0.9 (5.3/5.6)	Desfluran
12.	1.0 (6.3/7.8)	**1.0 (6.0/6.6)**	0.7 (4.5/4.9)	Desfluran
13.	0.8 (5.0/6.3)	**1.0 ↑ (5.9/6.4)**	1.0 (6.2/7.1)	Desfluran
14.	1.0 (6.1/8.0)	**1.1 ↑ (6.7/7.4)**	1.1 (6.6/7.1)	Desfluran
15.	0.9 (5.1/6.5)	**1.2 ↑ (6.9/9.6)**	1.2 (6.9/7.4)	Desfluran
16.	0.4 (0.7/0.8)	**0.5 ↑ (1.1/1.3)**	0.7 (1.4/1.7	Desfluran
17.	0.5 (3.0/3.6)	**0.6 ↑ (3.8/4.4)**	0.4 (2.6/3.0)	Desfluran

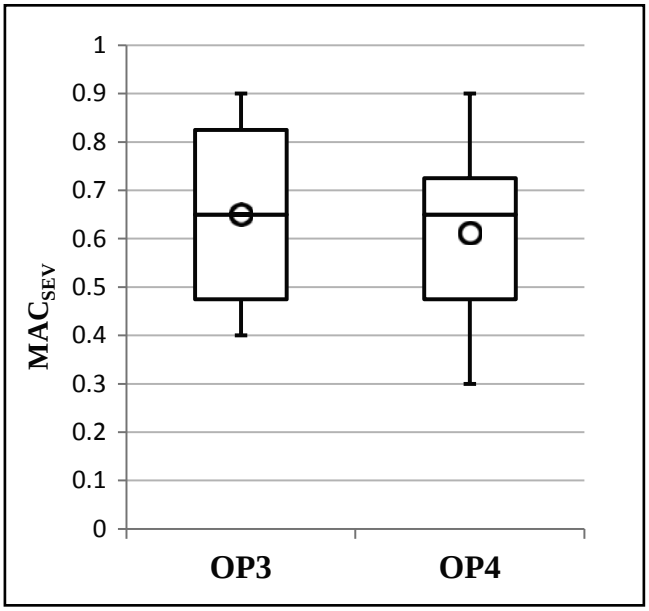

Fig. 9. Comparing MAC_{SEV} values between surgery stages-GA OP3 and OP4.

Statistic comparisons of surgery stages OP3–OP4 by the nonparametric Wilcoxon test did not show a significant difference of the measured value MAC_{SEV}. In stages of surgery OP3–OP4 it was used comparable same amount of sevoflurane (Figure 9).

DISCUSSION

Consciousness correlates with synchronized conformational activities of neuronal dendrite proteins in cortex and other brain regions. Within each protein, conformational states are regulated by endogenous London forces in hydrophobic pockets. By forming exogenous London forces, anaesthetic gases prevent consciousness by impairing endogenous London forces in hydrophobic pockets of dendrite brain proteins (Hameroff 2014).

Loss of consciousness should be considered the essential component of general anaesthesia, ensuring amnesia, inhibiting conscious cognition. Understanding the mechanism of action of anaesthetic gases may answer scientific and philosophical questions regarding consciousness, and vice versa. EEG oscillations are the speech, even the language of the brain that need to be understand and interpreted. In the anaesthetized subject, depression of thalamic gates together with diminished activation of the cortex by the ascending reticular activating system (ARAS) will be indicated by a progressive slowing of the EEG in which the underlying electrical signal will change from low-voltage fast-wave to high-voltage slow-wave pattern. A dose-dependent change in EEG activity along with an increase in anaesthetic depth was clearly demonstrated for many anaesthetics including thiopental (Kiersey *et al.* 1951) and isoflurane (Eger *et al.* 1971). In both studies, increasing doses of the anaesthetic resulted in an increase in EEG amplitude concomitant with a decrease in frequency of the EEG signal. A further increase in cerebro-cortical depression was first indicated by the appearance of burst suppressions followed by a complete loss of electrical discharge have been demonstrated in human patients and animals for a variety of anaesthetic agents including thiopental (Hudson *et al.* 1983), etomidate (Schwilden & Stoeckel 1980), propofol (Schwilden *et al.* 1989; Bergamasco *et al.* 2003), halothane (Pichlmayr & Lips 1980; Otto & Short 1991), isoflurane (Schwender *et al.* 1996), sevoflurane and desflurane (Schwender *et al.* 1998), respectively. A reduction in anaesthetic concentration will reverse EEG slowing.

Strong decrease of power-spectrum delta rhythm (DR) during the course of GA starting in the stage OP1 till the stage OP5-final is commonly known feature and one of the possible interpretations consists of diminishing propofol influence applied as induction to GA, when DR power spectrum increases and this, by the propofol induced delta rhythm lessens common EEG frequency. The conclusion is that the onset of slow oscillations is a neural correlate of propofol-induced loss of consciousness, marking a shift to cortical dynamics in which local neuronal networks remain intact but become functionally isolated in time and space (Lewis *et al.* 2012).

Results obtained by means of LORETA analysis in the same group of patients suggest:

DR was before anaesthesia significantly more active in occipital, parietal and temporal lobe with its maximum set in the superior parietal lobule with slight lateralization to the left. Delta activity increased during the anaesthesia in the depth of limbic lobe slightly exceeding to the surface frontally with right lateralization. Maximum of this activity was found in limbic lobe – cingulate gyrus.

Volatile anaesthetics physically inhibiting oscillation of microtubule associated proteins (MAP) through the hydrophobic pockets oscillation (in femtoseconds frequency) inhibition not in frequency but in power spectrum of the gamma range oscillation and consequently it does not support increase of power spectrum in slower DR e.g. cross coupling GR with DR does not change frequency of DR but DR power spectrum decreases. Such features of cross-coupling interaction between DR versus GR indicates common wave function (Buzsáki & Draguhn, 2004) acting in brain neuropil oscillators. DR dominance means inhibition of lucidity, vigilance, and attention, naturally also cognition and it means pharmacologic induction of transient and reversible unconscious state. Intermittent delta activity was observed as a correlate of confusion and delirium state. By our opinion electromagnetic field - lattice wave function of the brain tissue is a carrier of consciousness lucidity-vigilance, attention, not only conscious, but also subconscious, or unconscious cognition, it is said to be „Aha reflex", psychomotor functions, free-will, and probable intermittent delta waves carrier of reversible confusion-delirium state; and finally, it probable transits all brain

products to the private psychic world – "Qualia" – soul (Drobný & Sániová, 2012).

We concentrate our attention also on the existence of the gamma oscillation in the basic brain neuropil during subconscious cognition – "Aha reflex" after arousal. Remains of GR in the deep stages thoracic surgery-GA indirectly signalize about the readiness to the subconscious cognition which may cause "Aha reflex" and a coherent chain of gamma rhythm associated with awareness of unsuccessfully long-term solution of a problem which from the sub-consciousness suddenly emerges as resolved to aware consciousness (Kandel 2012).

Persistence of GR during GA in posterior part cingulate gyrus (LORETA) means that a cognitive ability in long term memory (LTM) (hippocampus), strongly connected with cingulated gyrus, probably continues in the unconscious level performed by GA (Fischer *et al.* 2015).

Our data suggest a fundamental principle of temporal organization of network connectivity that is maintained during both consciousness and anaesthesia, despite local changes. These findings are consistent with a process of adaptive reconfiguration during GA.

We consider this fact as sufficient prevention Postoperative Cognitive Dysfunction (POCD) from the space and time of surgery (Sániová *et al.* 2012).

CONCLUSION

In dominant fronto-polar area implemented oscillators of GR are entirely inhibited in that neocortical structures during GA, but depicted by LORETA analysis, used also in our group of patients, GR is preserved in cingulate gyrus connected closely with Long Term Memory (LTM) what is the prerequisite for possible subconscious cognition creating "Aha reflex" after arousal. Oscillators of GR dominate over Fp_1–A_1 region near the working memory inhibiting sufficiently on line cognition, what is in controversy with gamma assembly of neurocytes in LTM. It means the on–line unconscious cognition is paralyzed during the whole GA, what we consider a prevention of any sensoric-painful experience in the time of all stages during surgery-GA. One lung ventilation in surgery stage-GA OP3 relating to surgery stage-GA OP4 we consider the probable cause for highly significant GR power spectrum decrease in OP3 relating with gamma power spectrum in OP4. It is valid for dominant fronto-polar region in the right-handed persons. MAC values in surgery stage-GA OP3 and OP4 are not different, therefore we suppose the one-lung ventilation as a possible cause of significant gamma-band power spectrum decrease.

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