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Epileptiform EEG patterns during different techniques of induction of general anaesthesia with sevoflurane and propofol: a randomised trial

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Abstract

Background: The aim of the study was to assess the influence of volatile induction of general anaesthesia with sevoflurane using two different techniques and intravenous anaesthesia with propofol on the possible presence of epileptiform electroencephalograph patterns during the induction of general anaesthesia.

Methods: Sixty patients (age 18–70 years) were recruited. Exclusion criteria included a history of epilepsy, neurological or neurosurgical diseases, pre-existing EPs (epileptiform patterns) in initial EEG recordings, medication interfering with EEG patterns. Patients were randomly allocated into three different groups, namely: A (sevoflurane, increasing concentrations technique); B (sevoflurane, vital capacity technique); and C (intravenous propofol).

The clinical and instrumental monitoring included arterial blood pressure, heart rate, standard electrocardiography II, arterial oxygen saturation, facial electromyography, fraction of inspired sevoflurane, fraction of expired sevoflurane, minimum alveolar concentration of sevoflurane, and BIS.

Results: Neurophysiological analysis of EEGs showed different EPs: polyspikes (PS), rhythmic polyspikes (PSR), and periodic epileptiform discharges (PED). EPs ($P < 0.05$) were observed in group A (56%) and group B (37%), but not in group C. One patient in group B presented clinical seizures. No significant differences in the vital parameters and anaesthesia parameters between groups was observed, regardless of the presence of EPs, which were associated with both low and more likely high (falsely indicating awakening from anaesthesia) BIS scores.

Conclusion: Our study shows that the BIS score variations do not identify epileptiform activity, which was associated with both low and high scores. In addition, the sevoflurane concentration reached either sedative or toxic concentrations.

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Key words: anaesthetics, volatile, sevoflurane; anaesthetics, intravenous, propofol; anaesthesia, monitoring, bispectral index; electroencephalogram, epileptiform patterns

Both sevoflurane and propofol are considered safe and potent anaesthetics and are widely used for the induction and conduction of general anaesthesia [1–3]. During all stages of general anaesthesia, both agents may induce seizure-like movements or seizures (clinically manifested events and confirming an electroencephalographic pattern) accompanied by haemodynamic instability [4, 5]. Thus, their potential proconvulsant activity should be verified and assessed [6, 7]. Convulsions during sevoflurane anaesthesia were observed with an incidence of only 5% [5], while subclinical activity in the EEGs (without clinically manifested events) during the induction of general anaesthesia with sevoflurane has been demonstrated in 20% of children [4] and in 47% of adults breathing spontaneously; these incidence rates increase with controlled hyperventilation to 88% and hypocapnia with 100% [5].

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The most widely used instrumental method for evaluating cerebral activity is electroencephalography (EEG). EEG is a technique that records the spontaneous electrical activity of the brain from the scalp and correlates it with the underlying brain function [8]. Due to difficulties of interpreting EEG patterns, even by experienced anaesthesiologists, raw EEG data without additional automatic analysis and classification is not widely used in monitoring the depth of general anaesthesia during the daily clinical routine.

The Bispectral index (BIS) is a quantitative electroencephalographic (EEG) indicator that is most commonly used to assess and monitor the hypnotic component of general anaesthesia [9]. BIS analysis serves as an addition to raw EEG analysis, and transforms the EEG signal to a digital score derived from a sensor to generate a number between 0 and 100 to control the depth of anaesthesia: values between 40 and 60 are thought to reflect a level of unconsciousness suitable for surgery, those between 60 and 80 indicate sedation, while values over 80 indicate that the patient is awake [10, 11].

There is more and more evidence suggesting that the BIS score varies during the presence of epileptiform patterns on the EEG [12] under volatile anaesthesia with sevoflurane. The BIS score is reported to abnormally increase [13] or decrease [14] in the presence of haemodynamic fluctuations characteristic of seizures [15] during both induction [16] of and recovery [17–21] from general anaesthesia. Therefore, we tried to identify whether observing variations in the BIS score might be useful in order to identify EPs on the EEG during the induction of general anaesthesia using both intravenous and inhalational techniques.

Therefore, we conducted a randomised, prospective study to assess the influence of the volatile induction of general anaesthesia with sevoflurane using two different techniques, as well as of the intravenous induction of general anaesthesia using propofol, on the possible presence of epileptiform electroencephalograph (EEG) patterns.

METHODS

A prospective and randomised clinical study was duly conducted. A total of 60 patients who were scheduled to undergo elective orthopaedic surgery and met the inclusion criteria were asked to participate in the study. The individuals were aged between 18 and 70 years with an American Society of Anesthesiologists (ASA) score of I-II and were enrolled after obtaining their written informed consent. Ethical approval for this study (NN-6501-196/06) was provided by the Ethical Committee of Medical University of Silesia on 19 December 2006.

The exclusion criteria were as follows: a history of epilepsy; medical treatment that could interfere with the EEG (e.g., tranquilizers, antiepileptic drugs); pregnancy; drug or alcohol abuse; a history of neurological disease or a neurosurgical operation that would impair EEG or BIS monitoring; a history of pulmonary disease, or the presence of signs predicting difficult mask ventilation or intubation. To exclude any pre-existing epileptic EEG patterns, standard 30-minute initial EEG recordings were performed in all the patients participating in the study. The initial EEG was recorded in a dark quiet room for 5 min as a baseline, followed by three eye opening and closing sequences of 10 seconds each and photostimulation lasting 10 min (flash stimuli at frequencies of 3/6/9/12 Hz alpha, 15/18/21/24 Hz beta). Next, another baseline reading was obtained and the patients were asked to achieve a state of hyperventilation by taking 20 forceful breaths per min for five min. Finally, another baseline reading was obtained.

The 60 patients included in the study were randomly assigned to one of the three groups (A, B, or C) using blind random allocation via sealed envelopes.

INDUCTION OF ANAESTHESIA

Before the induction of anaesthesia, none of the patients received any medication on the day of surgery. Directly before surgery, the patients were preoxygenated for 5 min with 100% oxygen. Next, Ringer's solution was intravenously administered (10 mL kg^{-1}). The patients in group A were anaesthetised with sevoflurane using the increasing concentrations technique. The patients breathed spontaneously via the face mask while the sevoflurane concentration in the inhaled gas was doubled every 10 breaths starting from 0.3 vol.% in a sequence 0.3–0.6–1.2–2.4–4.8–8 vol.% until a minimum alveolar concentration (MAC) of 2 was obtained in the exhalation gas. The patients in group B were anaesthetised with 8% sevoflurane and 92% oxygen using the vital capacity technique. The anaesthetic circuit was prefilled with 8% sevoflurane. The patients were asked to exhale to the residual volume. Next, the patients were instructed to perform a vital-capacity breath with a face mask applied tightly to their faces. Then, the patients were encouraged to hold their breaths as long as possible. Thereafter, the patients were asked to breathe spontaneously. In group C, the patients were preoxygenated with 100% oxygen following which propofol was intravenously administered at a single dose of 2.5 mL kg^{-1}, after which it was infused with an infusion speed of 4 mg kg^{-1} h^{-1}. Assisted ventilation was initiated in all the groups after loss of consciousness (LOC) when hypoventilation appeared, and the ciliary reflex disappeared. When the minimum MAC of 2% was achieved for sevoflurane in patients from groups A and B, or 5 min after the bolus of propofol with subsequent propofol infusion in patients in group C, the patients in all the groups were paralysed with a standard intravenous dose

Table 1. Group characteristics

	Group A		Group B		Group C		*P*-value
	mean	SD	mean	SD	mean	SD	
Age [years]	42.9	14.5	39.1	13.2	42.6	15.0	0.664
Weight [kg]	74.9	15.5	76.5	16.9	75.3	15.3	0.950
Height [cm]	168.1	10.6	173.5	10.8	169.9	10.1	0.302
Female: Male	6:10		4:15		6:14		

of 0.08–0.1 mg kg^{-1} cisatracurium; after 45 s, a laryngeal mask (LMA) was applied. CO_2 was maintained at 35–45 mm Hg as hyperventilation may trigger epileptiform activity before and during the induction of general anaesthesia. After LMA placement, the sevoflurane concentration was maintained at level 1 MAC (age-adjusted MAC equivalent using Eger's formula) [22].

Throughout the induction of anaesthesia and the surgery, standard monitoring procedures were utilised to pay close attention to the vital parameters, such as: non-invasive arterial pressure (BP); systolic arterial pressure (SAP); diastolic arterial pressure (DAP); heart rate (HR); standard electrocardiography (ECG) II; arterial oxygen saturation (SaO_2); fraction of inspired oxygen in the gas mixture (FiO_2); facial electromyography (fEMG); fraction of inspired sevoflurane (FiAA); fraction of expired sevoflurane (FeAA); exhaled carbon dioxide concentration ($etCO_2$); minimum alveolar concentration of sevoflurane (MAC); and depth of anaesthesia with the Bispectral Index Score (BIS) (Aspect Medical Systems, Norwood, USA).

ELECTROENCEPHALOGRAPHY AND BISPECTRAL INDEX ANALYSIS

The data were collected and digitised at 10-second intervals using the S5/Collect (Datex-Ohmeda Division by Instrumentarium Corporation) and Bispectrum Analyzer for BIS (BSA for BIS version 3.22B2 for A-2000 — S. Hagihira) installed on a notebook computer. Four EEG channels were recorded using electrode positions with $Ag/AgCl_2$ cup electrodes (Spes Medica, Genova, Italy) attached to the scalp with EC2 Electrode Cream (Grass Technologies). Electrodes (Aspect Medical Systems, Natick, USA) were positioned on both temporal bones laterally to the eyes, on both mastoid bones, on Fp1, Fp2 (international 10–20 electrode system), Fpz and the ground electrode in the centre of the forehead between the eyebrows. A four channel EEG was recorded from the following electrode pairs: Fp1 — left mastoid, Fp2 — right mastoid; Fpz — left temporal and Fpz — right temporal (according to the suggestion of Prof. Ville Jäntti) [4]. The impedance was set below 1 kW, and the electrodes were attached to module S/5 E-EEG of the S/5 anaesthetic monitor (GE Healthcare). The BIS score was derived from a sensor (Aspect Medical Systems, Norwood, USA) positioned diagonally on the patients' foreheads according to the producer's instructions.

Data recording started 5 min prior to the induction of general anaesthesia and continued throughout the induction until the patient was paralysed with an intravenous neuromuscular blocking drug (NMBD). As NMBDs are reported to decrease the BIS value [23], the moment of administration of NMBD constituted the end of the induction of anaesthesia in all the experimental groups. The EEGs recorded before and during the general anaesthesia induction were analysed offline by a neurophysiologist (Jäntti) with expertise in anaesthetic EEGs, the recording technique, and t®he anaesthetic agent used. Although neurophysiological analysis of EEGs may show different patterns, only polyspikes (PS), rhythmic polyspikes (PSR), and periodic epileptiform discharges (PED) were considered to be of the epileptiform type [4, 5].

STATISTICAL ANALYSIS

Data were collected in MS Excel 2010 (Microsoft®, USA) spreadsheets while statistical calculations were performed with the Statistica 10.0 statistical package (StatSoft, Tulsa, USA) and the R software environment. The results are presented as mean values ± standard deviation. The distribution of variables was evaluated using the Shapiro-Wilk test, while the homogeneity of variances was assessed by the Levene test. Quantitative variables were compared using the parametric Student's t-test and a one-way analysis of variances with Games-Howell post-hoc tests. Nominal data were compared with the c^2-test. Results with a P-value less than 0.05 were considered statistically significant.

RESULTS

Out of the 60 patients randomly allocated to one of the three groups, 16 patients in group A, 19 in group B, and 20 in group C were included in the further analysis. Four patients from group A and one from group B were excluded due to possible artefacts in their EEG signals (possible resulting from asymmetric cup electrode placement

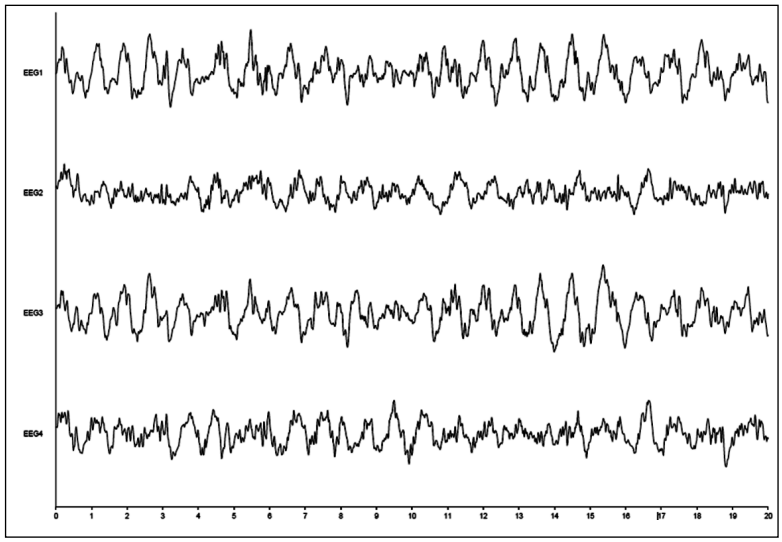

Figure 1. Pattern of polyspike (PS)-type EEG recording (EEG 1: Fp1 — left mastoid, EEG2: Fp2 — right mastoid, EEG 3: Fpz — F7, EEG 4: Fpz — F8) Male: Aged 46, Group B

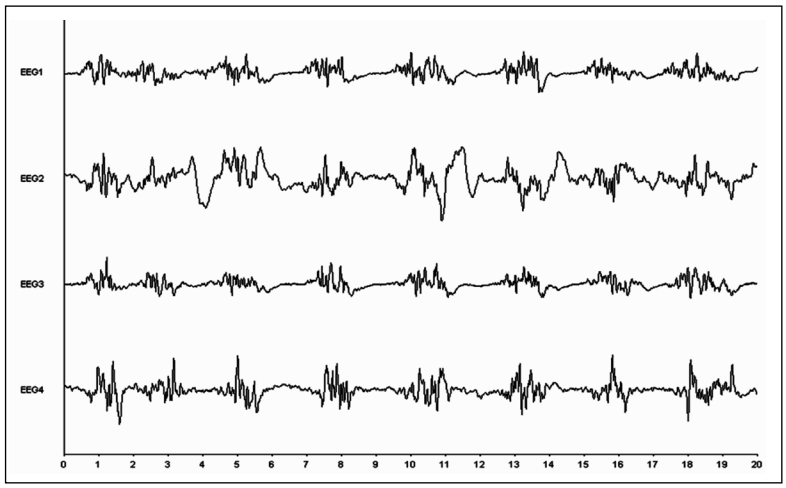

Figure 2. Pattern of rhythmic polyspike (PSR)-type EEG recording (EEG 1: Fp1 — left mastoid, EEG2: Fp2 — right mastoid, EEG 3: Fpz — F7, EEG 4: Fpz — F8); Female: Aged 70, Group A

or muscle artefacts). There were no significant differences in age, body weight, or height of the included patients ($P < 0.05$; Table 1).

Neurophysiological assessment of EEGs during general anaesthesia induction showed different patterns (Figs 1–5). Altogether, epileptiform EEG patterns manifested in 16 of the 35 patients anaesthetised with sevoflurane regardless of the anaesthetic technique. No epileptiform EEG patterns were observed in group C patients (Table 2).

The number of patients with episodes of epileptiform EEG patterns in groups A and C, and B and C, was significantly different (A vs. C: $P = 0.0002$, B vs. C: $P = 0.0065$); however, the difference between groups A and B was not significantly different ($P = 0.5347$). There was also no statistically significant difference between groups A and B in the number of particular patterns. However, it is worth mentioning that all types of epileptiform patterns appeared in the EEGs of patients anaesthetised using the increasing concentration technique (group A), whereas only polyspikes were observed in patients anaesthetised using the vital capacity technique (group B) (PS: 31% vs. 37%, $P = 0.9260$, PSR: 19% vs. 0%, $P = 0.1638$, and PED: 25% vs. 0%, $P = 0.0683$) (Table 2).

In order to assess if the presence of epileptiform EEG patterns depends on a certain depth of anaesthesia and sevoflurane concentration, we compared BIS scores, the

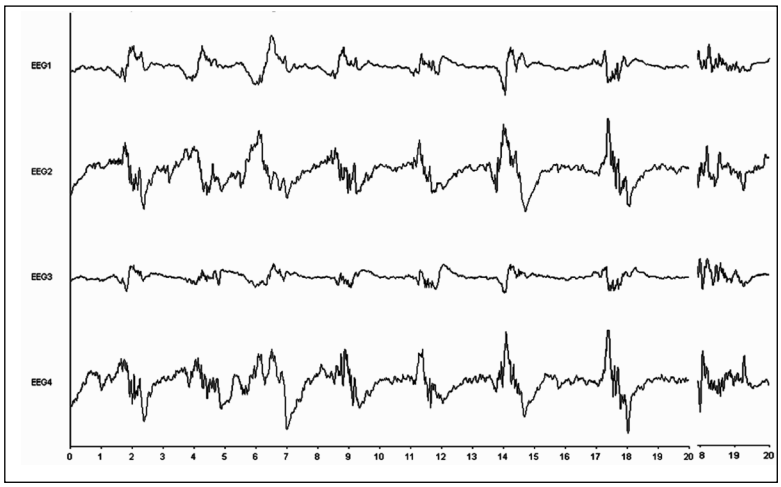

Figure 3. Pattern of periodic epileptiform discharge (PED)-type EEG recording (EEG 1: Fp1 — left mastoid, EEG2: Fp2 — right mastoid, EEG 3: Fpz — F7, EEG 4: Fpz — F8); Female: Aged 60, Group A

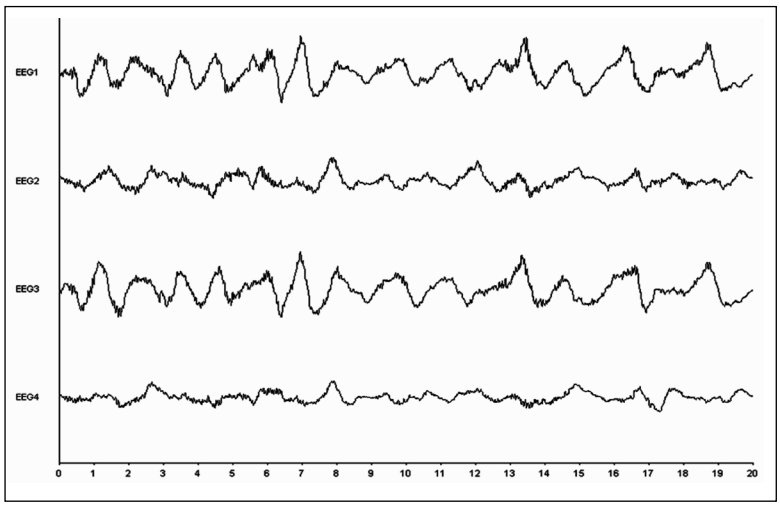

Figure 4. Pattern of slow delta (SD)-type EEG recording (EEG 1: Fp1 — left mastoid, EEG2: Fp2 — right mastoid, EEG 3: Fpz — F7, EEG 4: Fpz — F8) Male: Aged 41, Group A

inspiratory concentration of sevoflurane (FiAA), the expiratory concentration of sevoflurane (FeAA), the minimum alveolar concentration of sevoflurane (MAC), the presence of epileptiform EEG patterns, and the time up to the first epileptiform EEG pattern in the EEG recording. The time intervals from the start of volatile induction of general anaesthesia of general anaesthesia (VIGA) to the very first epileptiform pattern in the EEG were significantly different between groups A and B (O–EF time) (group A: 626 ± 241 seconds vs. group B: 209 ± 195 seconds; $P = 0.0043$); moreover, the last instant with a BIS score > 90 (clinically, loss of consciousness [LOC]) until the very first EP in the EEG was also significantly different (LOC–EF time) (group A: 325 ± 254 seconds vs. group B: 52 ± 60 seconds; $P = 0.0015$).

The mean time interval from the start of induction of the anaesthesia (O) until the very first epileptiform EEG pattern, as well as from the last moment with BIS > 90 (clinically, LOC) to the very first epileptiform EEG pattern, were significantly different between groups A and B (Table 3). The exemplary sequence of events for the patients from group B is presented in Figure 6.

Additionally, the time range when EPs are bound to appear was calculated and the vital parameters in both the groups were compared and analysed at three points in time, namely: 1) before the induction of anaesthesia; 2) before the presence of the first EP in the EEGs in the A-EP and B-EP group, and the mean time to the potential presence of the first EP in the EEGs in the A-nEP and B-nEP groups; 3) during the presence of the first EP in the EEGs in the A-EP and B-EP

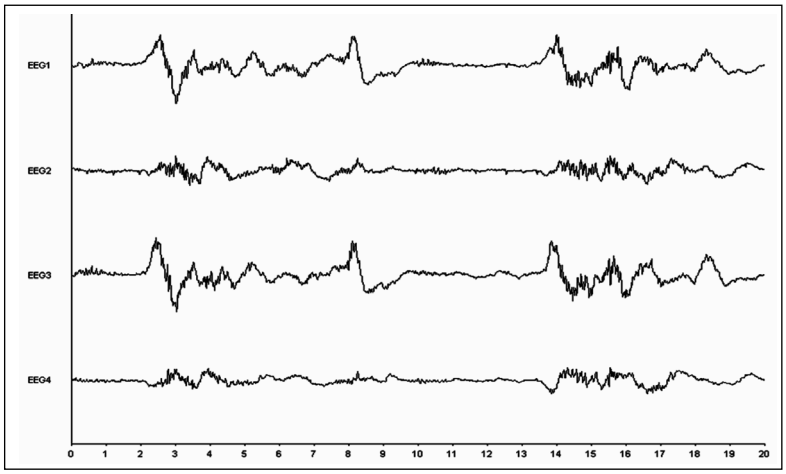

Figure 5. Pattern of slow delta type and burst suppression EEG recording (EEG 1: Fp1 — left mastoid, EEG2: Fp2 — right mastoid, EEG 3: Fpz — F7, EEG 4: Fpz — F8); Male: Aged 41, Group A

Table 2. EEG recordings with epileptiform pattern episodes

	Group A		Group B		Group C		Chi-sq	multiple comparisons — *P*-value		
	n	%	n	%	n	%	P	A vs B	A vs. C	B vs. C
PS or/and PSR or/and PED	9	56%	7	37%	0	0%	0.0001*	0.5347	0.0002*	0.0065*
PS	5	31%	7	37%	0	0%	0.0016*	0.9260	0.0230*	0.0065*
PSR	3	19%	0	0%	0	0%	0.0198*	0.1638	0.1507	
PED	4	25%	0	0%	0	0%	0.0048*	0.0683	0.0608	

*$P < 0.05$

Table 3. Time intervals to the first EEG epileptiform pattern

	Group A		Group B		*P*-value
	mean	SD	mean	SD	
O–EF time [min]	10.26	4.01	3.29	2.75	0.0043*
LOC–EF time [min]	4.85	3.74	0.52	0.60	0.0015*

O — onset; LOC — the last moment with BIS score representing clinical loss of consciousness > 90; EF — time of appearance of the first epileptiform pattern in the EEG; *$P < 0.05$

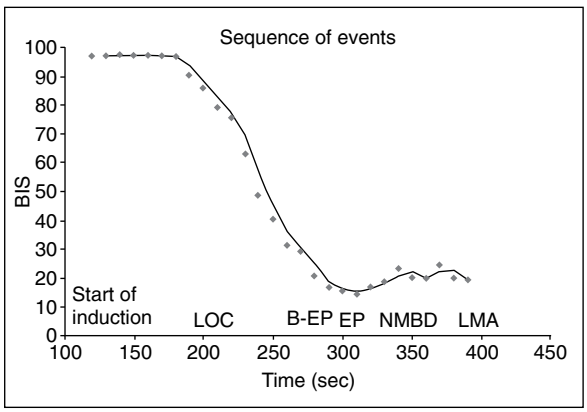

Figure 6. Sequence of events during anaesthesia in the exemplary patient from group B. LOC — loss of consciousness; B-EP — mean time to the first epileptiform pattern in group B; EP — epileptiform pattern episode; NMBD — neuromuscular blocking drug; LMA — laryngeal mask placement

groups and during the mean time interval to the potential presence of the first EP in the EEGs in the A-nEP and B-nEP groups (Table 4). The BIS values in the above-mentioned time points (onset of the induction; 10 s before EP appearance; EP appearance) are presented in the accompanying graphs (Fig. 7, 8A, B).

Two patients in group A, and one patient in group B had higher BIS values (increase in mean BIS values over 15 BIS points) when EPs appeared in comparison with mean BIS values before EPs appeared. Similarly, 1 patient in group A, and 2 patients in group B had lower mean BIS values (decrease in BIS value over 15 BIS points) when EPs appeared in comparison with mean BIS values before EPs appeared.

We observed no statistically significant difference in the BIS, HR, SAP, DAP, MAP, fEMG, FeAA, FiAA, and MAC of

Table 4. Bispectral Index Score

Patients with EEG epileptiform patterns	Group A+B (EP)			Group A (A-EP)			Group B (B-EP)		
	mean	from	to	mean	from	to	mean	from	To
BIS at the first EEG epileptiform pattern	42.1	11	97.4	32.5	14	45	54.5	11	97.4
Minimal BIS before the appearance of epileptiform potentials	48.9	14	97.1	27.8	14	45	76.1	17.3	97.1
Patients without EEG epileptiform patterns	**Group A+B (nEP)**			**Group A (nEP)**			**Group B (nEP)**		
	mean	from	to	mean	from	to	mean	from	To
Minimal BIS before the calculated, assumed appearance of epileptiform potentials	10.0	1.3	23.9	11.2	1.7	19.9	9.3	1.3	23.9

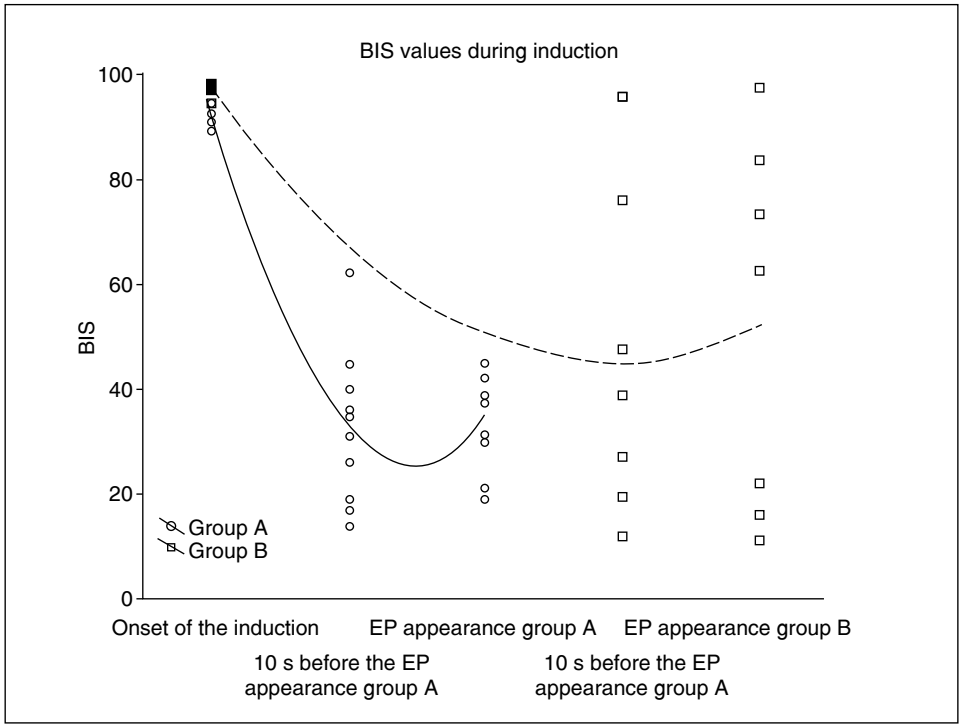

Figure 7. BIS values approximation in time for patients in groups A and B

sevoflurane between the studied groups during any of the analysed stages of VIGA (Table 5).

For example, in group B, a representative male patient, aged 32 years, showed spike activity on EEG patterns after 200 seconds from the beginning of the induction of VIGA, without any clinical manifestation of body movements when the BIS score indicated a still awake state whereas clinically, the patient had already lost consciousness (parameters during the occurrence of first epileptiform pattern were as follows: BIS: 95; MAC: 3.54; fEMG: 0.9; FiAA: 7.27%; FeAA: 7.27%; HR: 74 per min; SAP: 139 mm Hg; DAP: 75 mm Hg; MAP: 100 mm Hg). Another male patient aged 18 years from the same group displayed spike activity after 180 seconds without any clinical manifestation of body movements, when the BIS score indicated a state of nearly toxic concentrations of sevoflurane (parameters at the occurrence of the first epileptiform pattern were as follows BIS: 17; MAC: 2.11; fEMG: 0.3 microV; FiAA: 7.22%; FeAA: 4.33%; HR: 100 per min; SBP: 129 mm Hg; DBP: 70 mm Hg; MAP: 96 mm Hg). During the volatile induction of general anaesthesia in one male patient aged 23 years from group B, there was the manifestation of convulsions following tonic-clonic generalized seizures that resolved after the administration of cisatracurium and LMA installation. Further EEG pattern analysis revealed the development of slow delta waves following polyspikes (parameters at the occurrence of the first epileptiform pattern were as follows BIS: 79; MAC: 1.82; fEMG: 0.8; FiAA: 7.89%; FeAA: 3.75%; HR: 125 per min; SAP: 155 mm Hg; DAP: 86 mm Hg; MAP: 114 mm Hg).

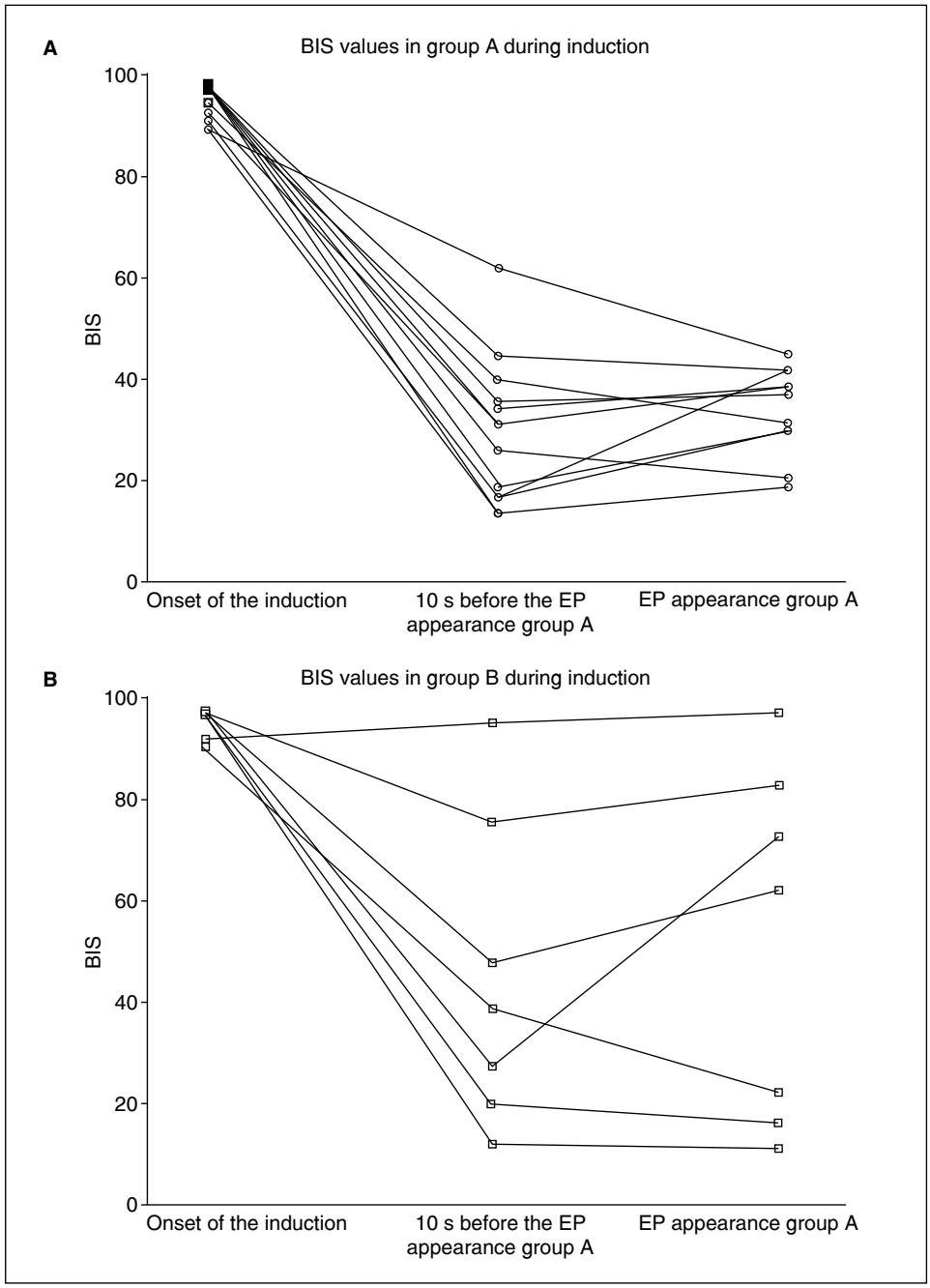

Figure 8. A — BIS values during induction in all patients from group A; **B** — BIS values during induction in all patients from group B

DISCUSSION

Numerous studies have reported potential epileptogenic activity associated with sevoflurane and propofol during all stages of general anaesthesia. Several factors must be considered before drawing conclusions regarding the epileptiform activity induced by propofol. Since EEG analysis was not performed by many authors reporting epileptiform activity after propofol infusion, the presence of epileptiform activity could not be explicitly proven [24–26]. The patients who were given propofol received various drugs during the different stages of anaesthesia [27–30], were given drugs associated with epileptogenic activity (such as fentanyl [31, 32]), had been diagnosed earlier as epileptic [33–37], or had other neurological pathologies [28, 38].

There have been a few reports on the effect of propofol on the EEG patterns in monoanaesthesia [39, 40]. Wang *et al.* [41] found that the sedative dose of propofol (0.5–1 mg kg^{-1}) induced sharp waves in neurosurgical patients with a history of epilepsy (40%), as well as in the control group without epilepsy (33%); this is consistent with some reports indicating

Table 5. BIS, HR, SAP, DAP, MAP, fEMG, FeAA, FiAA and MAC of patients from group A and B before volatile induction of general anaesthesia (stage 1) before presence of first epileptiform pattern. Before presence of first epileptiform pattern (stage 2). During presence of epileptiform pattern (stage 3) as well as before (stage 2) and during (stage 3) presence of EP in patients from group A-EP and B-EP. Mean time from onset of induction [O] to NMBD administration (stage 4)

	A-EP	B-EP	A-nEP	B-nEP	*P*-value
Stage 1.	**Parameters before volatile induction of general anaesthesia**				
BIS	94.91 ± 3.35	97.16 ± 1.16	97.13 ± 1.39	97.02 ± 1.43	0.171
HR [beats min^{-1}]	78.33 ± 9.43	81.14 ± 17.28	66.17 ± 12.75	79.40 ± 17.84	0.257
SAP [mm Hg]	149.42 ± 26.98	138.09 ± 11.72	143.18 ± 9.92	148.54 ± 34.76	0.731
DAP [mm Hg]	87.90 ± 15.41	70.51 ± 10.17	82.44 ± 3.26	84.08 ± 17.70	0.105
MAP [mm Hg]	112.25 ± 17.92	97.33 ± 9.09	104.91 ± 5.36	108.11 ± 23.27	0.197
fEMG	7.60 ± 4.59	13.53 ± 11.57	7.27 ± 6.56	8.41 ± 5.42	0.802
Stage 2.	**Parameters before presence of first EP**		**Parameters before presence of EP in patients from group A-EP and B-EP**		
BIS	42.44 ± 17.82	56.20 ± 31.04	48.47 ± 8.20	58.57 ± 4.62	0.068
HR [beats min^{-1}]	77.56 ± 15.26	90.71 ± 19.87	77.83 ± 20.00	85.90 ± 17.12	0.428
SAP [mm Hg]	135.59 ± 21.05	138.86 ± 10.99	139.05 ± 26.97	145.97 ± 37.95	0.988
DAP [mm Hg]	77.38 ± 17.52	72.82 ± 8.51	81.51 ± 11.31	80.14 ± 16.05	0.582
MAP [mm Hg]	102.18 ± 17.69	101.16 ± 6.62	104.23 ± 17.27	104.60 ± 21.82	0.920
fEMG	1.11 ± 2.21	0.79 ± 0.61	0.82 ± 0.49	0.80 ± 1.11	0.596
FeAA [%]	5.05 ± 0.95	4.69 ± 1.33	4.80 ± 0.52	4.83 ± 0.81	0.699
FiAA [%]	6.59 ± 0.85	6.50 ± 0.91	6.59 ± 0.85	6.96 ± 0.84	0.684
MAC	2.45 ± 0.46	2.29 ± 0.65	2.34 ± 0.26	2.35 ± 0.40	0.702
Stage 3.	**Parameters during presence of EP**		**Parameters during presence of EP in patients from group A-EP and B-EP**		
BIS	27.58 ± 7.59	30.48 ± 12.00	30.32 ± 6.50	27.58 ± 7.74	0.771
HR [beats min^{-1}]	79.00 ± 22.32	92.00 ± 23.93	78.50 ± 15.57	79.70 ± 17.83	0.981
SAP [mm Hg]	134.20 ± 27.13	122.89 ± 25.73	129.50 ± 14.22	131.06 ± 26.23	0.113
DAP [mm Hg]	79.37 ± 17.21	63.11 ± 13.43	80.69 ± 11.71	78.77 ± 16.70	0.897
MAP [mm Hg]	100.24 ± 21.41	89.42 ± 18.42	97.14 ± 10.80	98.10 ± 18.60	0.147
fEMG	0.19 ± 0.12	0.59 ± 0.41	0.40 ± 0.59	0.29 ± 0.57	0.645
FeAA [%]	4.46 ± 0.67	4.85 ± 0.90	5.16 ± 1.09	4.94 ± 0.95	0.204
FiAA [%]	6.06 ± 0.91	6.75 ± 0.68	5.51 ± 1.51	6.63 ± 0.67	0.908
MAC	2.28 ± 0.22	2.36 ± 0.44	2.50 ± 0.56	2.41 ± 0.46	0.664
Stage 4.					
Mean time from onset of induction [O] to NMBD administration [seconds]	573.90 ± 77.40A	270.00 ± 49.57ABC	605.00 ± 139.01B	345.00 ± 102.88C	*P* = 0.0003A *P* = 0.0006B *P* = 0.001C

EP: epileptic pattern; NMBD: neuromuscular-blocking drug; other abbreviations in the text

the epileptiform activity-inducing effect of propofol [26]. After an additional bolus (1.5 mg kg^{-1}, resulting in an overall dose of 2–2.5 mg kg^{-1}), the EPs in EEG recordings disappeared in most of the patients in both the above-mentioned groups from the study by Wang *et al.* [41]. This finding was confirmed by Ebrahim *et al.* [42], who used a single dose of propofol (2 mg kg^{-1}) in 17 patients with multidrug resistant epilepsy with a similar result. Borgeat *et al.* [43], who registered EEGs and videos on-line to compare a single dose of propofol (3 mg kg^{-1}; group A) with single doses of propofol (5 mg kg^{-1}; group B) or thiopental (5–7 mg kg^{-1}; group C) for the induction of anaesthesia in 6–12-year-old children, recorded no epileptiform activity and observed only movements of a subcortical origin, similar to Borgeat *et al.* [43], who compared sedation with propofol on MRI in 25 children with epilepsy and 25 children with learning difficulties with the same observation. Our findings are consistent with the reports on children (confirming no epileptiform activity associated with propofol at a dose of 2.5 mg kg^{-1}) and contribute to the discussion of the influence of propofol on EEG patterns.

There are some studies showing a correlation between EEG patterns and the rate of induction of general anaesthesia with sevoflurane [4], as well as its concentration in the ventilation gas mixture [9].

In our study, epileptiform activity appeared in 16 out of 35 patients anaesthetised with sevoflurane. This is similar to a study by Jääskeläinen *et al.* [39], in which epileptiform activity was recorded during the maintenance of anaesthesia only in a group of patients anaesthetised with sevoflurane at MAC levels 1 and 1.5 or 2; no epileptiform activity was found in the propofol group at an effective plasma concentration 50 (EC_{50}). Yli-Hankala *et al.* [4], who premedicated patients with oral diazepam and anaesthetised them with O_2-N_2O-sevoflurane, and found epileptiform activity in 7 out of 15 patients (47%) during mask induction of general anaesthesia, similar to our study observation where EP appeared in 45.7% of patients during the volatile induction of general anaesthesia with O_2-sevoflurane, regardless of the technique used. Hisada *et al.* [44] analysed the EEG patterns of patients with temporal epilepsy who were anaesthetised with O_2-N_2O-sevoflurane, and found an increased paroxysmal activity at 1.5 MAC. Kurita *et al.* [45] observed spike activity in the EEG patterns compared with basal activity when inducing anaesthesia in patients with epilepsy using fentanyl (5 mg kg^{-1} and sevoflurane 0.5 MAC (vs. 1.5 MAC during normoventilation). Fentanyl has been proved to trigger epileptiform activity in patients with epilepsy [31], while sevoflurane prolongs the fentanyl activity duration up to 1 h.

Kaisti *et al.* [14] studied EEG patterns in volunteers anaesthetised with sevoflurane 7% with oxygen, and found different EPs in 25% of their subjects. The authors observed that the heart rate and blood pressure increased to values characteristic of an epileptic seizure, while the positron emission tomography scan showed decreased regional cerebral blood flow in the brain; thus, they concluded that sevoflurane is an epileptogenic agent [14].

In our study, we used two alternative techniques of inducing general anaesthesia to investigate several factors. We chose the increasing concentration technique as the slowest induction procedure with the lowest inhaled sevoflurane concentration, and the vital capacity technique as the fastest technique with the highest possible inhaled concentration of sevoflurane. Julliac *et al.* [12] examined 40 patients (18–50 years old) who were administered general anaesthesia with 8 vol. % sevoflurane-O_2 using four different techniques. They observed EPs in 12 out of 40 patients included in their study (30%); however, they hyperventilated patients in only one group (5 of 10 with EP). Moreover, they used an anaesthetic circuit that had previously been filled with the ventilation gas mixture. Thus, they observed EPs in 3 out of 10 patients when the end-tidal sevoflurane concentration was maintained at 4%, and in 1 out 10 patients when the end-tidal sevoflurane concentration was 2% (together 4 out of 20 patients, 20%). Hyperventilation had earlier been proven to show an epileptic effect in a study by Vakkuri *et al.* [13], who reported that epileptiform activity was noted in 3 out of 10 patients (30%) in the vital capacity group. In our study, the increasing concentration technique group used a ventilation circuit that was not prefilled with sevoflurane, and its concentration was doubled every 10 breaths; hence, the induction appeared to be slower than in the vital capacity group while epileptiform activity was observed in 9 out of 16 patients (56%).

Contrary to above-mentioned findings from studies concerning adults by Julliac *et al.* [12] and Vakkuri *et al.* [13], different conclusions were drawn in studies involving volatile induction of general anaesthesia in children. Kreuzer *et al.* [46] anaesthetised children premedicated with midazolam using 8% sevoflurane for 3 min or 6% sevoflurane for 5 min in 100% O_2 via a face mask. They concluded that epileptiform potentials tended to appear later in the course of the induction with 6% than that with 8% sevoflurane, which is similar to our findings. Additionally, in their study [46], the time from the start of sevoflurane administration until the loss of consciousness was similar in children anaesthetised with 8% and 6% sevoflurane. The above-mentioned study's conclusion confirms the hypothesis proposed by Julliac *et al.* [12], according to which EEG patterns develop in the same way but at different rates, producing the same clinical manifestations despite the technique used. Moreover, in our findings, despite the technique of volatile induction of general anaesthesia used, EPs appear at a similar rate, while the mean values of the clinical parameters are comparable at the same stages.

Gibert *et al.* [47] aimed to determine if the minimum alveolar concentration (MAC) of sevoflurane under steady-state conditions (in 100% oxygen; in 50% oxygen and 50% nitrous oxide; and in 100% oxygen with a bolus of alfentanil) was associated with the occurrence of major epileptiform signs (defined as rhythmic polyspikes or epileptiform discharges) in children premedicated with hydroxyzine. In the study by Gibert *et al.* [47], the major epileptiform signs of sevoflurane calculated in 100% O_2 corresponded to a surgical MAC of 1.75 (the median sevoflurane concentration causing major epileptiform signs was 4.3%).The authors reported a moderate effect of nitrous oxide and alfentanil in raising the threshold of the signs of a major epileptiform. In our study, we observed EPs (we also considered polyspikes as EPs) at MAC 2.28 ± 0.22 in group A (FeAA: 4.46 ± 0.67%; FiAA: 6.06 ± 0.91%) and at MAC 2.36 ± 0.44 in group B (FeAA: 4.85 ± 0.90%; FiAA: 6.75 ± 0.68%). Moreover, we also observed a phenomenon that in group A, all types of EPs appeared, whereas only polyspikes were recorded in group B despite the fact that the mean BIS, FiAA, FeAA,

and MAC were comparable upon and at their occurrence regardless of the technique of volatile induction of general anaesthesia used.

Schultz *et al.* [48] anaesthetized 70 children aged 7–96 months, premedicated with midazolam using 8% sevoflurane in 100% oxygen via a face mask and immediately reduced the sevoflurane concentration to 4% after loss of consciousness (LOC) to investigate whether a brief exposure to a high inhaled sevoflurane concentration would affect the incidence of epileptiform EEG activity. The authors observed epileptiform EEG patterns without motor manifestations in 14 children (20%) despite premedication with midazolam. In group B from our study, in which the technique of induction of general anaesthesia was similar to the technique in the above-mentioned study, epileptiform patterns appeared in 7 adult patients (37%) without premedication, which could have increased the rate of the presence of EPs in our own study.

Contrary to the findings from the study of Julliac *et al.* [12], our study shows a significantly longer time interval between the onset of induction of general anaesthesia and the appearance of the very first epileptiform pattern when the increasing concentrations technique was used compared with the vital capacity technique. In the study of Julliac *et al.* [12], EEG patterns evolved in the same way but at different rates, probably due to the fact that all their patients were anaesthetised with 8% sevoflurane using either tidal volume or the vital capacity technique when the anaesthetic circuit had already been prefilled with 8% sevoflurane. Therefore, all patients were exposed to a high inhaled concentration of sevoflurane which led to the development to EPs regardless of group allocation.

However, the difference in the number of patients who had EPs between the groups was not statistically significant. Therefore, we hypothesise that, if a certain sevoflurane concentration in the brain is reached, epileptiform potentials may appear on the EEG, irrespective of how this sevoflurane concentration in the brain was reached in adult patients. It is assumed that sevoflurane has an epileptogenic effect when it reaches an appropriate concentration in the limbic system to trigger epileptiform activity. Further, it is hypothesized that sevoflurane acts by one of the following actions: its effect on GABA-related receptors and ionic channels [49]; its excitation of a group of neurons having a natural propensity to react to the excitation by going into an oscillatory seizure state [50]; it sensitizes the cortex inducing an electrical seizure by the increased GABA inhibition [51]; it involves the specific prolongation of GABA-mediated inhibitory postsynaptic potentials favouring the onset of an electrical seizure from a small residual excitatory activity [50]; or changes the permeability of potassium and chloride channels lengthening the duration of the postsynaptic potentials, consequently rendering GABA activity excitatory instead of inhibitory [52]. Although in our study, exposure to a high concentration of sevoflurane in the inhaled ventilation mixture lead to the presence of EPs in patient EEGs in groups A and B, we did not find any direct influence of the concentration of FeAA of sevoflurane on the development of epileptiform patterns on the EEGs using different techniques of volatile induction of general anaesthesia in adult patients. Therefore, based on our study findings we suggest that further studies should be directed towards the identification of either different isoforms of GABA-related receptors or pathological neuronal connections/ion channels that may possibly predispose an individual to the development of EPs after exposure to a specific concentration of sevoflurane during volatile induction of general anaesthesia in adult patients, as well as in children where the FeAA of sevoflurane directly influences the rate of occurrence of EPs in their EEGs [48].

As electroencephalographic on-line monitoring is still rarely used in anaesthesiological practice, we tried to introduce a novel approach to indirectly predict epileptiform activity using BIS analysis. The sequence of changes in EEG patterns is very similar during anaesthesia regardless of sevoflurane or propofol administration. Alpha oscillations (around 10 Hz) are observed in conscious patients with closed eyes: during shallow anaesthesia, the amplitude decreases and frequency increases, while the use of a higher concentration of anaesthetics causes an increase in the amplitude and a decrease in EEG frequency. A 'burst and suppression' appears during deep anaesthesia, namely high-frequency, large-amplitude waves (bursts), alternate with flat traces (suppression). This pattern indicates very deep anaesthesia. Beyond this state, flat traces become dominant while, eventually, waveforms become absent [53]. Additionally, in individual cases, epileptiform patterns may appear in the EEG. Bispectral analysis quantifies the phase relations between the frequency components of EEG signals [54]. The BIS analysis is an EEG recording transformed into the digital form and is detected from the sensor, which is easier and faster for application than the EEG cup bipolar electrodes attached to the scalp. In our study, we found no correlation between the BIS score and the epileptiform activity in 16 patients anaesthetised with sevoflurane. Surprisingly, the EPs appeared at a wide range of BIS scores (11–97) which did not necessarily reflect the patients' clinical status. Given that there is more and more evidence indicating that the BIS score may not reflect the actual depth of anaesthesia during the appearance of EPs on the patients' EEGs, we also decided to analyse the end-tidal concentration of sevoflurane, minimum alveolar concentration of sevoflurane and haemodynamic parameters during the three stages of VIGA: before volatile

induction, before the presence of the first epileptic pattern, and during presence of the first epileptic pattern. Surprisingly, despite the different techniques of VIGA used, we observed no statistically significant differences in the mean values of haemodynamic parameters at the above-mentioned stages, as well as the BIS score, MAC, FiAA, FeAA of sevoflurane, regardless of the presence or absence of EPs in the patients' EEGs.

The main limitation of our study is the lack of video-monitoring of patients to assess delayed neurological evaluation of possible seizures and other episodes. The anaesthesiologists responsible for the patient were supposed to note the appearance of potential seizures or myoclonic episodes on separate sheets. As presented in the results, there was an unexpected course of induction in one case, which was similar to that presented by Pilge *et al.* [16] and Vakkuri *et al.* [5] In these studies, the authors observed convulsions in 5% of the anaesthetised children, whereas in our study, this observation was made in 1 out of 35 adult patients (2.78%).

The other limitation is the lack of a long term follow-up; possible later seizures and neurological complications were not assessed in the study. However, in all the patients, regardless of group allocation, the induction and recovery from general anaesthesia were uncomplicated; patients were discharged to the post-anaesthesia unit with neither neurological deficit nor cognitive dysfunction (9–10 points on the Aldrete scale). Due to the study design, there was a serious risk of multiple muscle artefacts in group B (forced breaths). Although this risk was considered by the neurophysiologist as inherent, only one patient in group B and four in group A were excluded because of artefacts (possible from asymmetric cup electrode placement or muscle artefacts).

The above observations may suggest that EPs appear both while awake and upon near complete suppression of the brain activity as measured by the BIS score, which may not necessarily correspond to clinical signs. This further suggests that epileptiform activity in EEGs cannot be attributed to any specific depth of anaesthesia as measured by the BIS score. This finding is partly consistent with the observations of Kaisti *et al.* [14] on a volunteer sedated with sevoflurane. Särkelä *et al.* [55] found BIS scores above 60 in 34 out of 54 patients with EEG-based EPs. The authors hypothesised that epileptiform activity resulted in false BIS scores. Nevertheless, Julliac *et al.* [12] investigated BIS scores during the induction of anaesthesia with sevoflurane, and showed that BIS scores increased by 20 during EEG epileptiform activity in 5 patients, decreased in 3, and remained unchanged in 4, which is consistent with the findings in our study.

Therefore, reliance on the BIS score for the identification of epileptiform activity during volatile induction of general anaesthesia with sevoflurane may be misleading in adult patients. In individual cases, epileptiform activity may lead to the misinterpretation of BIS scores, especially when it is not accompanied by haemodynamic instability (indicative of the epileptic threshold). The BIS score can be misinterpreted as the anaesthesia not being deep enough since epileptiform activity may falsely elevate the BIS score; as a result, an anaesthesiologist may then attempt to deepen the anaesthesia by administering sevoflurane in a toxic dose. This contradicts the findings in the study by Chinzei *et al.* [56], who claimed that a rapid increase in the BIS score during anaesthesia is a relevant indication of epileptiform activity. Conversely, a decrease in the BIS score upon the appearance of epileptiform activity, as reported by Julliac *et al.* [12], as well as in 3 patients in our study, may be misinterpreted as excessive depth of anaesthesia and result in the anaesthesiologist reducing the dose of the anaesthetic agent and awaking the patient during surgery.

In conclusion, our study findings show that utilising the BIS score variations to detect epileptiform activity during VIGA is controversial. The appearance of EPs is associated with both low and more likely high (falsely indicating awakening from anaesthesia) BIS scores. At the same time, the FeAA of sevoflurane reached sedative or even toxic concentrations. As the BIS score shows aberrant values in the presence of EPs on the EEG, it is safer for anaesthesiologists to rely on raw EEG signals and clinical monitoring and verify the actual depth of anaesthesia, rather than relying on the FeAA of sevoflurane or the BIS score.

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