

# Risk Factors for the Occurrence of Electroencephalogram Abnormalities during Induction of Anesthesia with Sevoflurane in Nonepileptic Patients

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**Background:** The aim of this prospective study was to determine the risk factors of epileptiform discharge during induction with sevoflurane in healthy adult patients.

**Methods:** Forty adult patients with American Society of Anesthesiologists physical status I were randomly allocated to one of four groups. **Group A:** Patients breathed 8% sevoflurane in oxygen (8 l/min) via a prefilled circuit. End-tidal sevoflurane was maintained at 4%. Tracheal intubation was performed at the third minute after cisatracurium injection. **Group B:** The anesthesia protocol was similar, but a vital capacity technique was performed. **Group C:** Patients were anesthetized as in group A but were hyperventilated. **Group D:** Patients were anesthetized as in group A, but end-tidal sevoflurane was maintained at 2%. An electroencephalogram was recorded before and during induction up to 11 min after the start of induction. Statistical analysis was performed with Statview 5.0® (SAS Institute Inc., Cary, NC) for multivariate analysis.

**Results:** Twelve patients experienced epileptiform discharges. Risk factors were female sex (odds ratio, 12.60; 95% confidence interval, 1.46–135), delay to the occurrence of  $\beta$  waves (odds ratio, 0.92; 95% confidence interval, 0.86–0.99), and end-tidal sevoflurane (odds ratio, 8.78; 95% confidence interval, 1.12–69). Epileptiform discharges were not associated with significant hemodynamic or Bispectral Index variations.

**Conclusion:** Induction with sevoflurane may result in epileptiform electroencephalographic activity. Only electroencephalographic monitoring allows the diagnosis. Risk factors are mainly female sex, short delay to onset of anesthesia, and high alveolar sevoflurane concentration. Induction with high sevoflurane concentration is controversial mainly in women.

SEVOFLURANE has a nonpungent odor with minimal respiratory irritability that makes it popular for mask induction in children. It is widely used for the induction and maintenance of anesthesia in pediatrics, and its suitability for mask induction in adults has been confirmed.<sup>1-3</sup> Sevoflurane is well tolerated, and inhalation of high concentrations (7–8%) has been recommended to accelerate the loss of consciousness and decrease the risk of body movement, agitation, breath holding, and coughing.<sup>4,5</sup> However, electroencephalographic abnormalities as well as tremor, clonus, and seizure-like motor

activity have been reported in patients anesthetized with sevoflurane.<sup>6-10</sup> Several risk factors for the occurrence of epileptiform electroencephalogram activity during anesthetic induction with sevoflurane have been proposed,<sup>11-15</sup> such as speed of anesthetic induction,<sup>11,12</sup> high alveolar sevoflurane concentration,<sup>9,12,15</sup> and hyperventilation.<sup>13</sup> It was shown that in nonepileptic patients, the occurrence of epileptiform electroencephalogram increased when high concentrations of sevoflurane were used<sup>9,12,15</sup> and when patients were hyperventilated.<sup>13</sup> Epileptiform discharges were associated with a transient hyperdynamic circulatory response when patients were hyperventilated.<sup>11</sup>

No study has yet explored and compared these hypotheses and tried to determine the main factors responsible for the occurrence of electroencephalographic abnormalities. The purpose of this study, therefore, was to evaluate the risk factors thought to induce electroencephalographic abnormalities during sevoflurane induction in nonepileptic adult patients, *i.e.*, high alveolar sevoflurane concentration, hyperventilation, and speed of anesthetic induction, and to seek whether other factors may be involved.

## Materials and Methods

### Patients and Study Design

After obtaining the approval of the Ethics Committee of the University Hospital of Bordeaux (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Bordeaux, France) and written informed consent from the patients, 40 patients with American Society of Anesthesiologists physical status I undergoing elective ear-nose-throat surgery participated in the study. Excluding criteria were age younger than 18 yr or older than 50 yr; history of cardiac, pulmonary, renal, or neurologic disease; history of malignant hyperthermia; pregnancy; gastroesophageal reflux; heavy smoking; predictive signs of difficult intubation or difficult mask ventilation; and treatment that might interfere with the electroencephalogram.

All patients fasted for at least 8 h before induction of anesthesia and received no premedication. After intravenous line placement and intravenous infusion of lactated Ringer's solution, patients breathed oxygen *via* a face-mask for 3 min. Patients were randomly assigned to one of four groups using blocked random allocation and sealed envelopes. In group A, patients were anesthetized

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**Table 1. Group Characteristics**

	Group A (n = 10)	Group B (n = 10)	Group C (n = 10)	Group D (n = 10)
Sevoflurane alveolar target	4%	4%	4%	2%
Ventilation	Spontaneous	Spontaneous	Manual hyperventilation	Spontaneous
Induction technique	Tidal	Vital capacity	Tidal	Tidal

Manual hyperventilation: Target was end-tidal carbon dioxide  $30 \pm 2$  mmHg. Tidal volume technique: Patients breathed spontaneously during induction and then were manually ventilated after being paralyzed. Vital capacity technique: After deep exhalation to residual volume, patients were told to take a vital capacity breath and to hold their breath for as long as possible. Then they breathed spontaneously and were manually ventilated after being paralyzed.

with 8% sevoflurane and a tidal volume technique; sevoflurane alveolar concentration was maintained at 4%, and patients breathed spontaneously. In group B, patients were anesthetized with 8% sevoflurane with a vital capacity technique; thereafter, they breathed spontaneously, and sevoflurane alveolar concentration was maintained at 4%. In group C, patients were anesthetized with 8% sevoflurane with a tidal volume technique; they were hyperventilated, and sevoflurane alveolar concentration was maintained at 4%. In group D, patients were anesthetized with a tidal volume technique with 8% sevoflurane for 2 min and breathed spontaneously; thereafter, sevoflurane alveolar concentration was maintained at 2% (table 1). In every group, patients were manually ventilated after being paralyzed. In group C, they were hyperventilated, and end-tidal carbon dioxide ( $ET_{CO_2}$ ) was maintained at  $30 \pm 2$  mmHg. In the other groups, patients were normoventilated ( $ET_{CO_2}$  was maintained at  $40 \pm 2$  mmHg). In all groups, anesthesia was induced with 8% sevoflurane *via* the circuit of the Julian anesthesia workstation (Dräger Medical, Lübeck, Germany), which was prefilled with 8% sevoflurane. Fresh gas flow was set at 8 l/min. After loss of eyelash reflex, the vaporizer was set to maintain the sevoflurane alveolar concentration at the predetermined alveolar concentration, and fresh gas flow was set at 6 l/min. Patients received 0.15 mg/kg cisatracurium 6 min after the beginning of anesthesia, and tracheal intubation was performed 3 min later.

Monitoring included electrocardiogram, noninvasive systolic and diastolic arterial pressures, heart rate and pulse oximetry (AS/3; Datex-Ohmeda Div., Instrumentarium Corp., Helsinki, Finland), Bispectral Index (BIS<sup>®</sup> A-2000, XP platform; Aspect Medical System, Natick, MA).  $ET_{CO_2}$ , end-tidal sevoflurane ( $ET_{sevo}$ ), and inspired concentration of sevoflurane were monitored through the gas analyzer of the anesthesia workstation. BIS was measured using a disposable strip electrode (BIS<sup>®</sup> Quatro electrode; Aspect Medical System) placed on the forehead of the patient, and the impedance of the electrodes was confirmed to be less than 2 k $\Omega$ . Systolic arterial pressure, diastolic arterial pressure, heart rate, pulse oximetry,  $ET_{CO_2}$ , inspired fraction of sevoflurane,  $ET_{sevo}$ , and BIS were manually recorded every minute.

#### *Electroencephalographic Recordings*

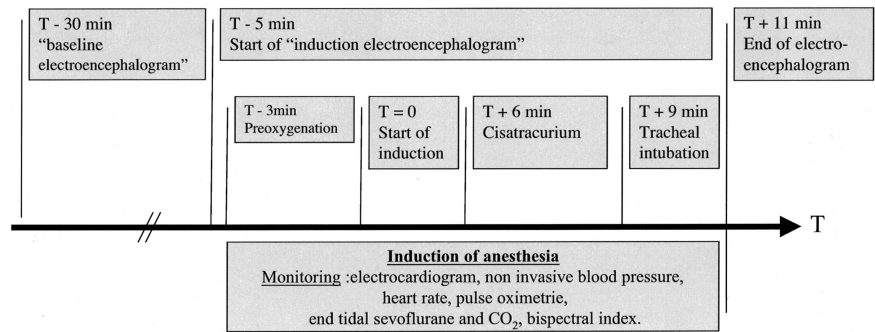
A bipolar electroencephalogram was recorded by eight Ag-AgCl electrodes positioned with collodion according

to the international 10-20 system, referenced to ground over a frontal added electrode. Standard positions were Fp1, Fp2, T3, T4, C3, C4, O1, and O2. Bipolar electroencephalographic montage was used for further analysis. Impedance was kept below 5 k $\Omega$ . The electroencephalogram (Deltamed, Paris, France) was filtered (0.1–70 Hz), amplified, and digitized (sampling rate 256 Hz). Electromyographic data were collected through surface electrodes to detect myoclonic jerk. Bipolar electromyographic recordings were obtained from the right and left median deltoid fasciculus with surface electrodes. The signal was filtered (120 Hz), amplified, and digitized (sampling rate 256 Hz). The electrocardiogram was also recorded with one additional channel. Electroencephalogram-synchronized video acquisition was performed to detect the occurrence of abnormal movements during sevoflurane induction.

On the morning of surgery (7:00 AM), an initial electroencephalographic recording was performed (baseline electroencephalogram) before induction in a quiet room to check basal cerebral activity. This recording lasted 15 min; rest period, reactivity to eye opening, and the effect of 4-min hyperventilation were then tested. Thereafter, “induction electroencephalogram” recording corresponding to sevoflurane-related electroencephalogram was started in the operating room. It began 5 min before sevoflurane induction and continued until 11 min after the start of induction, *i.e.*, 2 min after intubation (fig. 1). The start of induction was indicated verbally by the anesthesiologist and was immediately transcribed with a marker on the electroencephalogram. The neurophysiologist who performed the electroencephalogram was blinded to the result of the randomization.

Electroencephalograms were analyzed off-line by a neurophysiologist familiar with anesthesia electroencephalograms and blinded to the randomization. Electroencephalographic features related to sevoflurane induction were as follows:  $\alpha$ -wave activity related to awake state (7–12 Hz; fig. 2A), fast  $\beta$ -type rhythms corresponding to rapid oscillations (13–20 Hz; fig. 2B), slow  $\theta$ -type rhythms (4–7 Hz; fig. 2C), and high-amplitude  $\delta$ -type rhythms (0.5–4 Hz; fig. 2D). Isoelectric tracing alternating with bursting activity, corresponding to the burst-suppression state, was observed for very deep anesthesia (fig. 2E). Electroencephalographic abnormalities related to epileptic features were classified according to the

**Fig. 1. Diagram of study electroencephalographic recording.** CO<sub>2</sub> = carbon dioxide.



description of Vakkuri *et al.*<sup>13</sup> and Jääskeläinen *et al.*<sup>15</sup> and the recommendations of Constant *et al.*<sup>16</sup>: Spikes and spikes with slow wave complexes, rhythmic polyspikes corresponding to waveforms appearing at regular intervals, and periodic epileptiform discharge, which refers to periodic hypersynchronized complexes occurring bilaterally (figs. 3A and B). All of these electroencephalographic phenomena were considered as epileptiform<sup>15</sup> and were considered as epileptiform discharges. Rhythmic hypersynchronized  $\delta$ -wave activity was also observed bilaterally (fig. 3C) but was considered as normal electroencephalographic activity in the context of sevoflurane anesthesia and was excluded from analysis.<sup>16</sup>

For electroencephalographic analysis, quantitative parameters were as follows: the delay between the start of induction and the first changes in electroencephalographic activity (appearance of  $\beta$ ,  $\theta$ , or  $\delta$  rhythms), the occurrence of burst suppressions, and the duration of the suppression period, *i.e.*, the sum of the electroencephalographic silences.

#### Statistical Analysis

Statistical analysis was performed with Epi Info 6.04 (Centers for Disease Control and Prevention, Atlanta, GA) on a personal computer for descriptive analysis and with Statview 5.0<sup>®</sup> (SAS Institute Inc., Cary, NC) for univariate and multivariate regression analysis. The number of patients required for each group was calculated to demonstrate that a high sevoflurane concentration might be a risk factor of epileptiform electroencephalographic activity. According to the data of Yli-Hankala *et al.*,<sup>12</sup> hyperventilation led to epileptiform electroencephalographic activity (spike or polyspikes) in all patients, whereas only 47% of patients experienced such problems with spontaneous ventilation. We hypothesized that the differences observed with a high sevoflurane concentration should be of the same degree as observed in the event of hyperventilation. With an unexposed:exposed ratio of 1:3, we required 8 and 23 patients exposed to low and high concentrations of sevoflurane, respectively, to demonstrate a difference with a 5%  $\alpha$  risk and 80% power. Ten patients were included per group. Therefore, we had threefold more normally ven-

tilated subjects than hyperventilated ones, thus allowing any eventual difference due to capnia to be demonstrated with the same power and  $\alpha$  risk.

Quantitative variables were nonparametric and were therefore expressed as median [25-75 interquartile]. Qualitative variables were expressed as percentage.

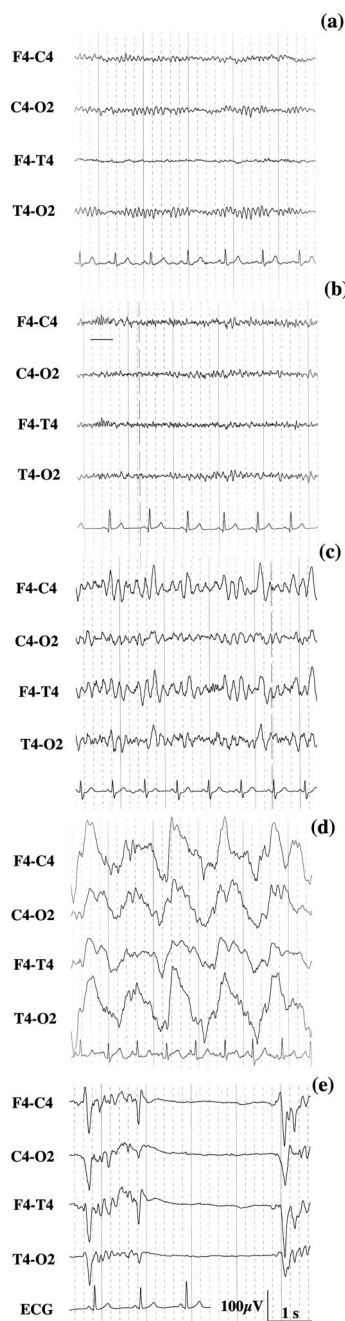
Between-group analysis was performed with the Mann-Whitney test to compare quantitative or ordinal variables for two groups and with the Kruskal-Wallis test to compare three or more groups. The bilateral *P* value was expressed for each result. A *P* value less than 0.05 was considered significant. Qualitative variables were compared with the chi-square test.

Variables found to be associated with epileptiform discharges with a probability of less than 0.25 were included as independent variables in a backward stepwise logistic regression analysis. Results were expressed as odds ratios with 95% confidence intervals.

#### Results

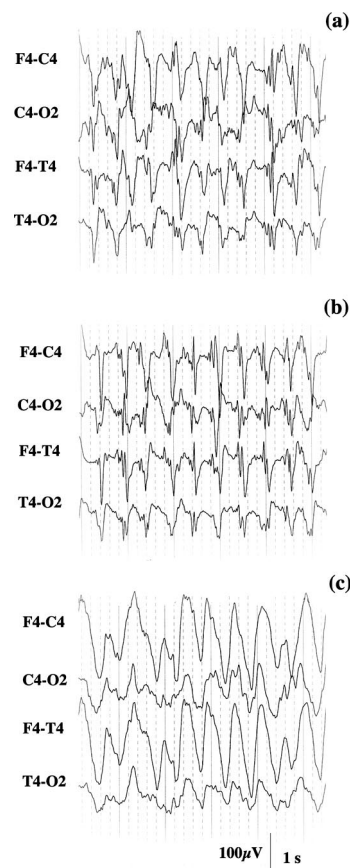
Among the 40 patients included, no significant difference was found between the four groups in terms of age, sex, height, or weight (table 2). Epileptiform discharges as defined above occurred in 12 patients (30%): 3 in group A, 3 in group B, 5 in group C, and 1 in group D. The difference was not significant. In 9 patients, rhythmic hypersynchronized  $\delta$ -wave activity preceded the occurrence of epileptiform discharges. Epileptiform discharges were continuous in 9 patients and discontinuous with short periods of slow activity (2-5 seconds' duration) in the 3 other patients. One episode of slow activity occurred in 2 patients, and four episodes occurred in the other patient. Epileptiform patterns were generalized, but the amplitude of epileptiform discharges was predominant in frontal region in every patient (table 3). The delay to the occurrence of epileptiform discharges was 230 [206-354] s. In 5 patients, epileptiform discharges occurred less than 160 s after the beginning of  $\delta$ -wave onset. The mean epileptiform discharge duration was 225 [74-382] s. However, 3 patients were still experiencing epileptiform discharges at the end of induction, *i.e.*, 11 min after the onset of induction. Episodes of epileptiform





**Fig. 2.** Pattern of electroencephalographic changes during induction of anesthesia with sevoflurane. Electroencephalographic traces of the right hemisphere and electrocardiogram (ECG) are presented (F: frontal, C: central, T: temporal, O: occipital). (A) Electroencephalographic activity during awake state. (B) Beta oscillations are underlined. (C) Slow  $\theta$  activity. (D) Delta oscillations during relatively deep anesthesia. (E) Burst-suppression pattern during deep anesthesia.

discharges were preceded by burst-suppression activity only in 2 patients but were followed by burst-suppression activity in 9 of them. Only 1 patient, in group D, did not experience any burst suppression. In 6 patients, epileptiform discharges disappeared after intubation when the sevoflurane alveolar concentration was decreased but were still present at the end of the study at the 11th minute in 3



**Fig. 3.** Electroencephalographic features related to sevoflurane use. Electroencephalographic traces of the right hemisphere and electrocardiogram are presented (C = central; F = frontal; O = occipital; T = temporal). (A) Polyspike waves. (B) Epileptiform discharges. (C) Slow  $\delta$  rhythms of high amplitude.

patients. They disappeared a few minutes later. For surgical reasons (ear-nose-throat surgery), it was not possible to record the electroencephalogram during the whole period of anesthesia. Nevertheless, all patients had an uncomplicated recovery. Epileptiform discharges were not associated with any significant increase in heart rate and arterial pressure, and a hyperdynamic cardiovascular response was present in only 2 patients. Episodes of epileptiform discharges were associated with slight limb movements in 2 patients as detected by electromyogram and video recording. In one of them, abnormal movements corresponded to sustained and repetitive muscle contractions (mean duration  $1.5 \pm 0.3$  s) of the two upper limbs and persisted for a period of 90 s. In the other patient, movements affected the lower limbs, corresponding to slow complex movements during a short and irreproducible period of 20 s. These movements were not recorded on electromyogram but observed on video. Movements disappeared rapidly whereas epileptiform discharges persisted. During episodes of epileptiform discharges, BIS increased by more than 20 in 5 patients, decreased in 3, and did not change in the others. Epileptiform discharges occurred only in 1 patient in group D. This 34-yr-old woman, 1.60 m, 60 kg, lost consciousness rapidly (delays to  $\beta$ - and  $\delta$ -wave onset were

**Table 2. Patient Demographic Characteristics**

	Group A (n = 10)	Group B (n = 10)	Group C (n = 10)	Group D (n = 10)
Age, yr	26 [21–44]	34 [30–39]	27 [21–34]	32 [30–34]
Sex, M/F	6/4	5/5	4/6	5/5
Height, cm	176 [161–180]	167 [165–175]	170 [160–174]	166 [160–174]
Weight, kg	68 [60–78]	70 [60–76]	59 [55–70]	62 [56–70]

Values are median [interquartile range] or number. Group A: Patients were anesthetized breathing spontaneously 8% sevoflurane *via* a prefilled circuit and 8 l/min fresh gas flow. End-tidal sevoflurane was maintained at 4% for 6 min. Group B: Patients were anesthetized as in group A with vital capacity induction technique. Group C: Patients were anesthetized as in group A but were hyperventilated after loss of consciousness. Group D: Patients were anesthetized as in group A, but after 2 min, end-tidal sevoflurane was maintained at 2%.

40 and 80 s, respectively), probably because she hyperventilated. Epileptiform discharges occurred 340 s after the beginning of induction, lasted 8 s, and were not preceded or followed by burst suppression. At that moment,  $ET_{CO_2}$  was 24 mmHg, and  $ET_{sevo}$  was 2.2%. No hyperdynamic cardiovascular response or BIS variation occurred.

Because no significant difference was found between the groups, we looked for risk factors for the occurrence of epileptiform discharges using univariate analysis. Results are given in table 4. The most important factors were the speed of induction, *i.e.*, the delay to the occurrence of  $\beta$  and  $\delta$  waves,  $ET_{sevo}$ , and female sex. Hypocapnia was not correlated with the occurrence of epileptiform discharges. The following variables were used for multivariate regression: sex, height, weight, age,  $ET_{sevo}$ , delay  $\beta$ , delay  $\delta$ , systolic arterial pressure, and  $ET_{CO_2}$ . Independent risk factors for the occurrence of epileptiform discharges were female sex (odds ratio, 12.60; 95% confidence interval, 1.46–135), delay to the occurrence of  $\beta$  waves (odds ratio, 0.92; 95% confidence interval, 0.86–0.99), and  $ET_{sevo}$  (odds ratio, 8.78; 95% confidence interval, 1.12–69) (table 5).

The delay to the occurrence of  $\beta$  and  $\delta$  waves was not different between patients anesthetized either with the tidal volume technique or with the vital capacity technique (respectively, delay  $\beta$ : 50 [34–63] *vs.* 40 [31–61] s; and delay  $\delta$ : 75 [65–99] *vs.* 71 [62–81] s).

In six patients, BIS decreased abruptly to less than 10 during the 4 first minutes of induction and increased to

values greater than 25 after 1 min without any stimulation. This sharp decrease was not related to a shorter delay to the occurrence of  $\beta$  and  $\delta$  waves or to any electroencephalographic abnormalities.

## Discussion

Three factors were found to be responsible for the occurrence of epileptiform discharges. Two are already known, *i.e.*, a large expired concentration of sevoflurane and the speed of anesthetic induction.<sup>9,10,17</sup> However, to our knowledge, female sex has never been found to be a risk factor for the occurrence of epileptiform discharges during inhalation induction with sevoflurane. Considering the first two factors, two generating mechanisms for the occurrence of epileptiform discharge may be evoked. The first hypothesis is already known: Epileptiform discharges occurred mainly during deep anesthesia. It has been shown that anesthesia maintained with 2 minimum alveolar concentration (MAC) sevoflurane resulted in epileptiform discharges in 50–100% of patients.<sup>9,12,15,17</sup> The occurrence of epileptiform activity is dose dependent, and the threshold is around 1.5 MAC.<sup>15</sup> In our study, epileptiform discharges were preceded by episodes of burst suppression in two patients, but no threshold could be established because the effect site concentration of sevoflurane was not at steady state when epileptiform discharges occurred. However, the

**Table 3. Characteristics of Epileptiform Discharges**

Patient	Group	Sex	Age, yr	$\beta$ Onset, s	$\delta$ Onset, s	Epileptiform Discharges Topography	Epileptiform Discharges Onset, s	Epileptiform Discharges Duration, s	Abnormal Movements
2	D	F	34	40	80	Frontal	340	8	0
8	B	F	39	32	52	Frontal	397	263	0
13	A	F	27	16	69	Frontal	155	369	1
17	C	F	30	14	75	Frontal	474	186	0
18	A	M	24	27	64	Frontal	240	420	0
19	C	F	23	35	62	Frontal	296	306	0
23	B	F	35	70	137	Frontal	480	180	1
25	C	M	29	44	48	Frontal	192	40	0
27	C	F	24	26	65	Frontal	220	420	0
30	C	F	18	29	36	Frontal	218	460	0
36	B	F	27	37	66	Frontal	166	85	0
40	A	F	39	33	51	Frontal	211	36	0
Median [interquartile]	—	—	28 [24–34]	33 [26–40]	65 [51–75]	—	230 [206–354]	225 [74–382]	—

**Table 4. Characteristics of Patients According to Independent Predictors of Epileptiform Discharges**

	Normal Electroencephalogram (n = 28)		Electroencephalogram with Epileptiform Discharges (n = 12)		P Value
ET <sub>sevo</sub> , %	3.9	[2.4–4.2]	4.5	[3.8–4.9]	0.006*
Delay $\beta$ , s	47	[37–66]	33	[26–40]	0.009*
Delay $\delta$ , s	73	[68–84]	65	[51–75]	0.036*
ETCO <sub>2</sub> , mmHg	32	[29–36]	30	[23–32]	0.156
Sex, M/F		18/10		2/10	0.016*
Weight, kg	65	[60–77]	57	[53–71]	0.051
Height, cm	173	[162–177]	163	[159–170]	0.047*
Age, yr	32	[22–42]	28	[24–35]	0.301
SAP baseline, mmHg	129	[120–143]	117	[101–127]	0.016*
HR baseline, beats/min	73	[65–85]	73	[65–83]	0.712

Values are median [interquartile range] or number.

\*  $P < 0.05$  was considered significant.

Delay  $\beta/\delta$  = time between start of induction and occurrence of  $\beta/\delta$  waves; ETco<sub>2</sub> = end-tidal concentration of carbon dioxide; ET<sub>sevo</sub> = end-tidal concentration of sevoflurane; HR = heart rate; SAP = systolic arterial pressure.

mean ET<sub>sevo</sub> at that moment was around 2 MAC (4.3% [4.0–4.7%]). Modeling with Gas Man<sup>®</sup> (MedMan Simulations, Inc., Chestnut Hill, MA) showed that the effect site concentration of sevoflurane was probably higher than 3.5% when severe epileptiform discharges occurred. These results suggest that sevoflurane, like enflurane, may have epileptogenic properties at high alveolar concentration. This epileptogenic potential was not found when desflurane was used at a deep level of anesthesia<sup>17</sup> and seems to be characteristic of sevoflurane. The fact that the epileptiform electroencephalographic activity disappeared after the sevoflurane alveolar concentration decreased favors this hypothesis. The second factor to be considered in the occurrence of epileptiform discharges is a rapid increase in sevoflurane concentration resulting in a shorter delay to the onset of  $\beta$  and  $\delta$  waves: the shorter the delay, the higher the risk of occurrence of epileptiform discharges. Other studies also reported that a rapid increase in sevoflurane concentration induced epileptiform electroencephalogram during normoventilation<sup>17</sup> and hyperventilation.<sup>13</sup> This factor was independent of ET<sub>sevo</sub>; epileptiform discharges occurred in five patients less than 160 s after the beginning of loss of consciousness and in one patient in group D, suggesting that a transient inhomogeneous distribution of sevoflurane in the brain is responsible for generating epileptiform discharges. Sevoflurane has a biphasic effect on the electroencephalogram, *i.e.*, an increase in  $\alpha$  and  $\beta$  activity followed by a decrease in  $\alpha$  and  $\beta$  activity

**Table 5. Risk Factors for Epileptiform Discharges (Multivariate Regression)**

Variable	Odds Ratio (95% CI)	P Value
Sex, male	12.60 (1.46–135)	0.037
Delay $\beta$ , s	0.92 (0.86–0.99)	0.043
ET <sub>sevo</sub> , %	8.78 (1.12–69)	0.039

Only the variables that were considered significant from 95% confidence interval (CI) are listed.

Delay  $\beta$  = time between start of induction and occurrence of  $\beta$  waves; ET<sub>sevo</sub> = end-tidal concentration of sevoflurane.

and an increase in  $\delta$  activity.<sup>18</sup> Beta activity could be considered as the initial cortical reaction to sevoflurane inhalation when the patient is awake, whereas  $\delta$ -wave activity might be a marker for the transitional state between consciousness and unconsciousness.<sup>18</sup> Arousal state transitions are known to promote the occurrence of epileptiform phenomena or seizures in patients with epilepsy.<sup>19,20</sup> During sleep initiation, thalamic activity changes are a response to the characteristic cortical synchronization observed in sleep.<sup>20</sup> Such thalamic neuronal activity changes are related to the action of  $\gamma$ -aminobutyric acid systems from the thalamic reticular nucleus on the thalamocortical neurons, which develop a bursting pattern due to posthyperpolarization.<sup>21,22</sup> This bursting activity could account for the cortical hypersynchronization observed during sleep initiation. Because epileptiform phenomena correspond to pathologic cortical hypersynchronization, electroencephalographic abnormalities could be more frequent during sleep initiation. Therefore, we hypothesize that rapid sevoflurane induction could have induced a too-rapid sleep initiation and thus triggered epileptiform discharges. Sevoflurane has been proven to act on  $\gamma$ -aminobutyric acid transmission and could induce oversynchronization of thalamocortical neurons.<sup>13</sup> To demonstrate the role played by sevoflurane in the occurrence of epileptiform discharge, it would have been interesting to have a control group anesthetized with an alternative technique, *e.g.*, propofol, in the same anesthetic conditions, *i.e.*, high effect site concentration and short delay to the onset of anesthesia. Indeed, rapid changes at the effect site have also been suggested as an explanation for the epileptogenic activity associated with propofol anesthesia.<sup>23,24</sup> Nevertheless, a sharp increase in alveolar desflurane concentration does not result in similar electroencephalographic abnormalities. It has been suggested that proconvulsivant drugs may act to decrease the amplitude of miniature inhibitory postsynaptic currents or elicit greater calcium-induced presynaptic mobilization of excitatory neurotransmitters.<sup>25</sup> A mathematical model



has shown that the trajectory followed by enflurane in response to increasing concentrations has a greater probability of crossing or entering a region where the cortex undergoes a sudden change in behavior to the unstable seizure state compared with isoflurane.<sup>25</sup> Enflurane reduces the inhibitory postsynaptic potential more than isoflurane, resulting in a higher probability of firing.<sup>25</sup> A similar phenomenon might explain the difference between sevoflurane and desflurane in terms of the proconvulsant effect.<sup>17</sup> However, in the absence of a control group, we are unable to say whether sevoflurane among anesthetics has the greatest ability to cause spike activity. The additive effect of hypocapnia underlined by several reports<sup>11,13</sup> was not found to be a risk factor in our patients, whereas the mean  $ET_{CO_2}$  was 30 [28–32] mmHg when epileptiform discharges occurred, and 50% of patients in the hyperventilated group experienced epileptiform discharges. Because epileptiform discharges occurred during induction at different moments [206–354 s], it was difficult to compare  $ET_{CO_2}$  within patients with or without electroencephalographic abnormalities. For this reason,  $ET_{CO_2}$  at the moment epileptiform discharges occurred was compared with the mean  $ET_{CO_2}$  during induction in the other patients. The difference was not significant. Moreover, because of the mask dead space,  $ET_{CO_2}$  measurement was imprecise and underestimated in patients breathing spontaneously. This is a limitation of our study. To investigate the role played by hyperventilation in the occurrence of epileptiform discharges during induction, it would have been preferable to ventilate patients either with normocapnia or with hypocapnia and to measure arterial carbon dioxide. Because there was no control of ventilation, no definitive conclusions can be drawn regarding the role played by hypocapnia in our patients. In addition, hyperventilation may induce seizures during the electroencephalographic diagnosis of epilepsy, but no patient was sensitized to hypocapnia.

The main factor found after multivariate analysis was female sex. Even though sex distribution was equal (20 women and 20 men), epileptiform discharges occurred in 10 women (50%) and only in 2 men (10%). This is the first study to highlight the role of female sex on the convulsant effect of sevoflurane. Prospective studies showing a high percentage of electroencephalographic abnormalities occurring during induction with sevoflurane were all conducted in women,<sup>11–14</sup> except one.<sup>15</sup> Pharmacokinetic and pharmacodynamic effects may be involved. A smaller muscle compartment in female patients cannot account for these pharmacokinetic differences because it is well established that the muscle compartment plays a negligible role during induction. On the other hand, in women, where the alveolar dead space is smaller, the increase in sevoflurane brain concentration might be sharper and the delay to the onset of  $\beta$  and  $\delta$  waves and the equilibrium between alveolar and

brain concentrations might be shorter. However, whereas the delay to the onset of  $\beta$  waves was shorter in our female patients (37 [29–49] vs. 44 [38–63] s), these differences were not statistically significant. The greater sensitivity of women to the convulsant effect of sevoflurane might also be due to pharmacodynamic effects. Several studies have shown a possible hormonal influence on the effect of hypnotic drugs.<sup>26–28</sup> Pregnancy decreases the MAC of isoflurane.<sup>29</sup> In a retrospective data analysis, it was found that nonpregnant women had the same MAC as men except with sevoflurane; MAC values of sevoflurane determined by logistic regression were significantly higher in men.<sup>27</sup> However, in our study, BIS values were not significantly different at any time between men and women. In a study on gender and recovery after general anesthesia, sex differences seemed to be accentuated in younger patients, suggesting a possible female hormone role on the modulation of anesthetic action.<sup>26</sup> The hypothetical role of female hormones in the occurrence of epileptiform discharges is supported by our data. Epileptiform discharges occurred only in women younger than 40 yr (10 of 17 women aged < 40 yr and 0 of 3 women aged > 40 yr). The role of female hormones in seizure activity is still controversial, but clinical studies on seizure and female hormones suggest that high estrogen levels may have a proconvulsant effect. Estrogen increases the availability of  $\gamma$ -aminobutyric acid A receptor subtypes<sup>30</sup> and might therefore modulate the anesthetic action of sevoflurane in women. However, whether female sex is the main risk factor for the occurrence of epileptiform discharges remains unclear, and the reasons are probably multifactorial. The pharmacokinetic and pharmacodynamic hypotheses are not clearly proven by our results, but the fact that epileptiform discharges occurred only in young women suggests a hormonal influence.

Bispectral Index value variations were neither predictive nor diagnostic of the occurrence of epileptiform discharges. No specific BIS variation occurred during epileptiform discharge episodes. BIS increased in five patients, decreased in three patients, and did not change in four, so BIS variations were not predictive of epileptiform discharge occurrence. However, epileptiform discharges have been reported to induce sharp increases in BIS value and a simultaneous discharge activity visible on the raw electroencephalographic display of the monitor.<sup>9</sup> It may be advisable to look at the raw electroencephalographic plot during sevoflurane induction because this is the only way to detect the occurrence of epileptiform discharges.<sup>16,17</sup>

Transient hyperdynamic cardiovascular responses have been reported during inhalation of high sevoflurane concentrations.<sup>11,12,17</sup> Tachycardia has been hypothesized as being due to transient epileptiform activity, because patients with epileptiform phenomena in electroencephalogram tend to have a faster heart rate. Our

results do not support this hypothesis because we did not find any specific heart rate variation during epileptiform discharge episodes. This discrepancy might be due to a deeper level of anesthesia in the other studies. For example, when sevoflurane was maintained at 8% and was associated with 50% nitrous oxide, tachycardia occurred in hyperventilated patients but not in those breathing spontaneously.<sup>11,12</sup>

Recovery was uneventful in every patient, even in the two patients experiencing tremor activity. The deleterious effect of epileptiform discharges is unsure. The question is to know whether epileptiform discharges are of clinical relevance except when measuring something. We did not study cognitive function after sevoflurane anesthesia in our patients. Therefore, we cannot point to the role of epileptiform discharge occurrence on cognition. Cognitive outcome after anesthesia with sevoflurane alone or in association with other drugs has been previously assessed.<sup>31-35</sup> Transient cognitive impairment was observed with sevoflurane alone or in association with other drugs.<sup>31,33,35</sup> Comparison of sevoflurane with other anesthetics revealed either a similar effect or a more prolonged effect on cognitive outcome, but this cognitive impairment was always transient.<sup>35</sup> However, it seems that seizures, especially generalized tonic-clonic seizures, can have a direct adverse effect on cognition<sup>36</sup> and that subclinical epileptiform discharges may explain cognitive impairment.<sup>37,38</sup> Even if epileptiform discharge episodes did not exceed 460 s in our study, we cannot rule out a possible deleterious effect on cognitive function. To clarify this important point, a study on cognition and electroencephalographic follow-up should be initiated.

The current findings indicate that sevoflurane mask induction with a high inspired concentration is potentially epileptogenic mainly in young women. Consequently, it should be recommended to associate opioids to decrease the sevoflurane alveolar concentration needed to perform tracheal intubation in good conditions.<sup>39,40</sup> However, maintaining spontaneous ventilation together with adequate intubation conditions is recommended in patients with predictive signs of difficult intubation. In such patients, induction with sevoflurane is possible. To decrease the risk of epileptiform discharge occurrence, it might be useful to reduce the speed of induction, to increase the alveolar concentration progressively, and to prevent hyperventilation.

In conclusion, induction with high sevoflurane concentrations may trigger epileptiform electroencephalographic activity without motor or cardiovascular manifestations in healthy adult patients. No other symptoms were associated in this series, and only electroencephalographic monitoring allowed the diagnosis. The risk factors for the occurrence of epileptiform discharges during mask induction with sevoflurane were found to be a short delay to the onset of anesthesia, a high alve-

olar sevoflurane concentration, and female sex. In the absence of suspected difficult intubation, the rapid induction of anesthesia with high sevoflurane concentrations requires careful consideration in young women.

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