EFFECTS OF SEVOFLURANE ANESTHESIA ON EEG PATTERNS AND HEMODYNAMICS

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

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ABBREVIATIONS

ASA	Anesthetic risk group (the American Society of Anesthesiologists)
BIS	Bispectral index
BPM	Beats per minute
BS	Burst suppression
BSR	Burst suppression ratio
CBF	Cerebral blood flow
CH	Controlled hyperventilation
CI	Confidence interval
CNS	Central nervous system
CO	Cardiac output
CO_2	Carbon dioxide
CV	Controlled ventilation
D	Delta
DS	Delta slow, < 2 Hz
DSM	Delta slow, monophasic
DSMS	Delta slow, monophasic with spikes
DSP	Delta with spikes
ECT	Electroconvulsive therapy
ED	Effective dose
EEG	Electroencephalogram
EPSP	Excitatory postsynaptic potential
ET	End–tidal
$ETCO_2$	End–tidal carbon dioxide
ETsevo	End–tidal sevoflurane concentration
FFT	Fast Fourier transformation
FiO_2	Fraction of inspired oxygen
GABA	Gamma–aminobutyric acid
GM	Grand mal, epileptic seizure with tonic–clonic convulsions and characteristic EEG
HR	Heart rate
ISPS	Inhibitory postsynaptic potential
kPa	kiloPascal
LTL	Laparoscopic tubal ligation
LTP	Long term potentiation
MAC	Minimum alveolar concentration
MAP	Mean arterial pressure
MV	Minute ventilation
P	Power
$PaCO_2$	Arterial carbon dioxide tension
PED	Periodic epileptiform discharges
PS	Polyspikes
PSP	Postsynaptic potential
PSR	Polyspikes, rhythmic
PVR	Peripheral vascular resistance
S	Suppression
SB	Spontaneous breathing
SBS	Burst suppression with spikes

SD	Standard deviation
SpO_2	Peripheral blood oxygen saturation
SSP	Suppression with spikes
SV	Stroke volume
THIP	Tetrahydroxyisoxazolopyridine
VCRII	Vital capacity rapid inhalation induction of anesthesia
VF	Ventilatory frequency

INTRODUCTION

Anesthetic adequacy has been assessed from autonomic and movement responses, with efforts concentrated on maintaining cardiovascular stability along with immobility. However, movement response in a non–paralyzed subject during anesthesia has been shown to represent a spinal response (1, 2). Immobility is easily achieved with neuromuscular blocking drugs. When such drugs are used, neither immobility nor cardiovascular stability – which results from areflexia in the autonomous nervous system system – can be deemed to represent depression or the presence of such cortical functions as consciousness and recall. Amount of sedation, i.e., the sleep–component in balanced anesthesia, has been beyond the scope of monitoring possibilities. The new empiric EEG index, the bispectral index (BIS), is a processed, multivariate EEG derivative (3). It has been suggested as a means of monitoring the anesthetic effect on humans (4) and improving patient outcome after anesthesia (5).

Neuroexcitatory movements have been reported in association with many general anesthetics. Perioperative convulsions may result in an increase in cerebral metabolism, in blood flow and in intracranial pressure, which is dangerous to patients at risk for cerebral ischemia or intracranial hypertension. Use of proconvulsant drugs during anesthesia may aggravate preexisting epilepsy. Ictal or postictal state (= epileptic seizure or the state immediately after seizure) may delay emergence from anesthesia, and cause postoperative confusion and risk of hypoventilation and physical injury to the patient.

Sevoflurane has been suggested as a suitable agent for anesthetic induction for both adults and children. Sevoflurane inhalation induction has also been reported to maintain hemodynamic stability (6). The present study was designed to examine the effects of sevoflurane on EEG and hemodynamics during both induction and maintenance of anesthesia in elective surgical patients. This was accomplished by BIS monitoring during anesthesia and surgery, and by time–domain analysis of EEG during induction of anesthesia, with special reference to EEG and hemodynamic interrelations during sevoflurane inhalation induction.

REVIEW OF THE LITERATURE

ELECTROENCEPHALOGRAPHY

Electrical signals generated in the brain can be recorded from the scalp by means of electroencephalography (EEG). Electrical currents on the cortex were first described by Caton in animals (7). Hans Berger began the era of human EEG research in 1929 by his report of electric potentials recorded from the scalp (8). Four years later, he published the first report on the effect of an anesthetic agent on the human EEG (9). Eccles proposed that EEG activity arises from postsynaptic potentials (PSPs) (10). Later, it was shown that both excitatory (EPSP) and inhibitory postsynaptic potentials (ISPS) contribute to this potential (11). With ongoing research, evidence accumulated supporting the idea of EEG originating from the sum of all the excitatory and inhibitory postsynaptic potentials which create extracellular current flow (12). EEG signals are mainly generated by cortical pyramidal cells, cortical glial and granular cells may also contribute to some extent. When PSPs appear and disappear, the EEG scalp voltage changes. Normally, millions of PSPs are firing asynchronously in different cortical regions, together creating a complex composite signal. Therefore, the normal EEG of activated cortical areas is desynchronized (3). Idling cortical areas show repetitive waveforms, mostly with a thalamic pacemaker (13). The aggregate current flow is scattered and decreased on the way to the scalp, especially, as the high resistance of the skull decreases the current flow.

Time domain EEG is the normal clinical presentation of the EEG, where voltage changes (amplitudes) are presented over time. Changes in frequency (repetition rate of the waveform) and amplitude of the EEG may be characterized by means of power spectral analysis. The power spectrum of the EEG is calculated from selected segments (epochs) of time domain EEG using fast Fourier transformation (FFT), a mathematical method, which can be used to decompose EEG into its component sine waves. Theoretically, under ideal conditions, the information content of the waveform is not changed by this transformation, and an inverse Fourier transformation gives the original, complex waveform of the EEG. The decomposed sine wave information can be presented as a distribution of power over frequency, and distinctive figures can be calculated to describe this distribution. Spectral edge frequency 95 refers to the frequency below which 95% of the power of such distribution is found (14, 15). This kind of univariate descriptors of the EEG appear inadequate to describe the behavior of EEG during anesthesia both in terms of anesthetic adequacy (15) and also when trying to identify untoward anesthetic effects, such as spikes (pointed waveforms standing out from the background and a duration of 20–70 ms), all of which are lost (16). Therefore, techniques other than Fourier transformation are required to detect epileptiform EEG. Time domain visual analysis, although cumbersome, is the gold standard. Automated EEG analyzing systems for spike detection have been developed, as well (17, 18).

Even though the EEG was the first electronic monitoring technique in the operating room (19), its use in clinical anesthesia monitoring until recently has been sparse.

EFFECTS OF GENERAL ANESTHETICS ON EEG

The changes in average frequency and amplitude of the EEG show certain similarities with increasing doses of most inhalation anesthetics. Low doses cause an increase in the power of the beta range (Table 1), especially in the frontal regions, and a decrease in the alpha range, and the amplitudes are small. At this stage, also the eye movement artifact ceases.

Increasing the anesthetic dose to a surgical level induces in EEG an average decrease in frequency towards the theta and delta range while the amplitudes increase. With some general anesthetic agents such as isoflurane, sevoflurane, and propofol, a further rise in dose will induce a special EEG pattern, burst suppression. This is a pattern in which high amplitude activity alternates with low voltage periods, usually not exceeding ± 5 μV. Any further increase in the anesthetic dose results in electrical silence, suppression (amplitude < 5 μV).

Table 1. EEG frequency bands (20).

Band	Range (Hz)
Delta (δ)	< 3,5
Theta (θ)	4–7.5
Alpha (α)	8.0–13.0
Beta (β)	> 13.0

BISPECTRAL INDEX (BIS)

In his thorough review of the BIS, Rampil explains its basic principles of development and the mode of action (3). The bispectral index of EEG is a weighted sum of EEG subparameters, containing time domain, frequency domain, and high order spectral subparameters. It was created after long development in a stepwise fashion. A large EEG database was collected from 1500 adult anesthesia EEG recordings along with concurrent behavioral assessments. Several subparameters were calculated and statistically tested to discover the ones correlating best with important clinical endpoints. These were entered into a composite index, BIS. The recorded EEG is first filtered to exclude artifacts and then divided into 2–s epochs. Epochs containing irreparable noise such as any blink artifact, are rejected. From the time domain version of the epoch, the degree of burst suppression (burst suppression ratio, BSR) is calculated as the sum of intervals of suppression (amplitude < 5 μV, at least 0.5 s long) divided by the epoch length. Additional artifact correction can be applied in the presence of a wandering baseline. The epoch is then converted to the frequency domain after Blackman windowing to reduce distortion from epoch–end artifacts. From the frequency domain version of the same epoch, fast Fourier transformation (FFT) and bispectrum are calculated. Two subparameters are derived: the beta ratio and the bispectral component, which is the degree of bicoherence, i.e., phase coupling between FFT–derived primary frequencies.

The beta ratio is the logarithm ratio of two empirically derived power bands: log ($P_{30–47\ Hz}/P_{11–20\ Hz}$). The bispectral component is the log ratio of the bispectrum (B) activity in two frequency ranges, log ($B_{0.5–47\ Hz}/B_{40–47\ Hz}$). The BIS calculation algorithm weights the beta ratio most heavily when the EEG has features referring to light sedation. The bispectral component is dominant in the algorithm calculation during EEG activation (excitement phase of anesthesia) and during the surgical level of anesthesia. BSR is used to detect deep anesthesia. Because of all the necessary processing, the value represented on the monitor's front panel is the average value for the previous 30-60 s of data.

Balanced anesthesia refers to the state in which unawareness and unresponsiveness (both motor and autonomic nervous system) prevail. The BIS monitors the unawareness component of balanced anesthesia (4, 21), but does not predict hemodynamic response to intubation (22). It is not reliable in predicting movement response to skin incision (23). This is to be expected, if we accept the significance of the autonomous nervous system in creating hemodynamic responses (24) and the spinal cord as the major site determining a reflex movement response to surgical stimuli during anesthesia (1, 2). The BIS gets its data from the EEG, which can detect only cortical events, not spinal or autonomous reflexes. The only

component of balanced anesthesia available for monitoring from the cortical level remains the unawareness reflected by the typical EEG features of drug–induced anesthesia: absence of beta–range, presence of high power delta–range, burst suppression, or suppression. The BIS also includes information on the degree of phase coupling invisible from the unprocessed EEG activity and noticed to increase with increasing depth of anesthesia (25).

HEMODYNAMICS

REGULATION OF HEART RATE AND BLOOD PRESSURE

Heart rate (HR) is controlled mainly by the autonomous nervous system (26). The sympathetic system enhances, and the parasympathetic system inhibits the cardiac pacemaker, the sinoatrial node. Changes in HR usually involve a reciprocal action of the two; HR increases with a decrease in parasympathetic activity and an increase in sympathetic activity. A decrease in HR results from the opposite activity. Due to the rapid breakdown of the neurotransmitter (acetylcholine), the effects of vagal stimulation cease very quickly when stimulation is discontinued. Contrary to this, the effects of sympathetic stimulation decay only gradually when the stimulation stops. The onset of sympathetic stimulation results in steady–state values of the heart rate much more slowly than do the inhibitory effects of vagal stimulation.

The cardiac parasympathetic fibers originate in the medulla oblongata, in the dorsal motor nucleus of the vagus, or in the nucleus ambiguus. The cardiac sympathetic fibers originate in the intermediolateral columns of the upper five or six thoracic and lower one or two cervical segments of the spinal cord. These autonomous pathways are under the control of higher regions of the brain, such as hypothalamic, thalamic, and even cortical regions. In the cerebral cortex, the centers regulating cardiac function are located mostly in the frontal lobe, the orbital cortex, and the motor and premotor cortex. Stimulation of the midline, ventral, or medial nuclei of the thalamus causes tachycardia.

The primary functional efferent unit of the sympathetic and parasympathetic nervous system is a two–neuron motor pathway, which consists of a pre– and a postganglionic neuron. The cell body of the preganglionic neuron is located in the CNS, and the cell body of the postganglionic neuron in the autonomic ganglion. The afferent autonomic neuron forms the afferent limb of the reflex arch.

The baroreceptor reflex leads to an inverse change in heart rate in the case of a sudden change in blood pressure. Baroreceptors are located in the aortic arc and carotid sinuses. Volatile anesthetics attenuate arterial baroreflex function.

Chemical control of the heart rate is minimal, but adrenomedullary secretion of epinephrine and norepinephrine is increased in the type of situation that stimulates the sympathetic nervous system.

Blood pressure is determined mainly by blood volume, peripheral vascular resistance (PVR), and cardiac output (CO), which is the amount of blood pumped by the heart within one minute. Peripheral vascular resistance is the mean blood pressure divided by the CO (mean blood pressure = CO × PVR). The volume of blood ejected from one ventricle with one heartbeat is the stroke volume (SV). Thus, CO can be expressed with the equation CO = HR × SV, and mean blood pressure = HR × SV × PVR. Volatile anesthetics decrease peripheral resistance; sevoflurane is reported to affect the vessels by direct dilatation (27).

MEASUREMENT OF BLOOD PRESSURE

Blood pressure can be measured noninvasively by an oscillometric method. A noncompliant cuff containing an inflatable bag is wrapped around an extremity, usually an arm. The inflatable bag lies between the cuff and the skin directly over the artery to be compressed (usually the axillary artery). The artery is occluded by inflating the bag to a pressure above the systolic arterial pressure. The pressure is then slowly released through a valve, and an electrical pressure transducer detects pressure–changes when arterial flow starts under the cuff as the pressure in the cuff falls to a level allowing arterial flow. This gives the systolic pressure. The oscillation is greatest when blood pressure equals the cuff pressure, which gives the mean arterial pressure. The diastolic pressure is measured when the oscillation stops as the pressure in the cuff falls below the diastolic arterial pressure.

SEVOFLURANE

DEVELOPMENT

Sevoflurane ($CH_2F–O–CH(CF_3)_2$) is a halogenated ether. This general anesthetic inhalation agent was developed in the late 1960s in the USA (28). It was set aside for many years for two disadvantages noted during phase–I trials. These disadvantages were metabolism which releases fluoride ions and reactivity with the soda lime, producing substances nephrotoxic in rats. In 1988 Maruishi Pharmaceuticals (Osaka, Japan) restarted the investigations on sevoflurane. The results of clinical trials were good, and in 1990 sevoflurane was approved for clinical use in Japan. In the same year American studies were initiated again, and in 1992 Abbott Laboratories (Chicago, USA) licensed sevoflurane (28).

CARDIOVASCULAR RESPONSES

Heart rate

The initial human study in 1981 found no significant change in heart rate during 1–hour exposure to 2% to 3% sevoflurane in oxygen (29). A stable heart rate during sevoflurane administration at various concentrations has been found in many human studies since that time (30-32). Contrary to these findings, however, some studies reported increases in heart rate during inhalation induction in pediatric patients (33-35).

In animal studies results differ by species: in swine, heart rate remained unchanged during sevoflurane administration (36), but in dogs a significant increase occurred (37).

Arterial blood pressure

Blood pressure responses to volatile anesthetics are a function of their effects on cardiac output and on vascular resistance. Both of these are influenced by the direct effects of the anesthetic on the heart and vascular smooth muscle, and by the indirect effects of the anesthetic on the autonomous nervous system. Arterial systolic blood pressure declined an average of 17% in an initial human phase–I study during 1–hour exposure to 2% to 3% sevoflurane in oxygen (29). A dose–dependent decrease in blood pressure and peripheral vascular resistance without significant changes in sympathetic nerve activity pointed to a direct effect on vascular smooth muscle (27, 31).

RESPIRATORY EFFECTS

Sevoflurane depresses ventilatory function in a dose–dependent manner, shown by an increase in $PaCO_2$ and lower minute ventilation (38). At 1.1 MAC, sevoflurane produced the same degree of respiratory depression as halothane, and at 1.4 MAC, it produced more profound respiratory depression than halothane (38). Sevoflurane was the anesthetic least irritating to the airway and was considered to be the most suitable for inhalational induction of anesthesia, when compared to enflurane, isoflurane, and halothane (39).

INHALATION INDUCTION

Vital capacity rapid inhalation induction (VCRII) is an induction method introduced especially in connection with sevoflurane (40). In VCRII, the patient exhales to the residual volume and then inhales a high concentration of anesthetic agent to the vital capacity, reducing induction phase time. The non–pungency of sevoflurane makes it suitable for this kind of maneuver. Comparing the VCRII technique with the conventional spontaneous inhalation induction technique, each using 4.5% sevoflurane in nitrous oxide and oxygen, the VCRII required only half the length of the conventional inhalation induction (54 s and 108 s, respectively), and was not associated with cardiovascular instability (41). Excitement was reported to be less with VCRII, which was therefore recommended. Comparing VCRII for sevoflurane and halothane, induction time was shorter with sevoflurane (42).

Children

Sevoflurane has low (0.68) solubility in blood (43), facilitating rapid mask induction, as first described by Haga et al. (44). The induction and intubation with high concentrations of sevoflurane (4% or 6.4%) were investigated in 180 children of ages ranging from one to six yr. In this first study of a high inspired sevoflurane concentration it was noticed that convulsions occurred at an incidence reportedly as high as 6%. A significant increase in HR was observed in another study where the inspired sevoflurane concentrations were increased every five breaths and were 2%, 4%, 6%, and 7% (34). During sevoflurane induction with incremental increases in concentration until a maximum of 7% was delivered, significantly higher average heart rates and systolic blood pressures were seen with sevoflurane than with halothane (45); this study reported excitement but no convulsions with sevoflurane mask induction. With administration of rapid increases of gas concentrations, in increments of 1% up to 7% for sevoflurane, induction was reported to be smooth and rapid but characterized by increases in heart rate and systolic blood pressure up to 20% in the sevoflurane group (35). Heart rate increased during sevoflurane induction in a study by Constant et al., comparing different types of sevoflurane inhalation induction and halothane inhalation induction (46). This EEG study reported no seizure–like activity. Increase in heart rate during sevoflurane induction in children was seen also in the study by Viitanen et al. (47).

Adults

In a comparative study with sevoflurane and isoflurane, 46 volunteers breathed approximately 1.7 MAC equivalents of either vapor (40) and exhibited no significant differences in monitored cardiovascular, respiratory, and electrocardiographic variables. The mean time for induction of anesthesia was significantly shorter with sevoflurane (120 s) than with isoflurane (145 s). Increase in heart rate was observed in a study by Sloan et al. (48), in which 50 patients received a single–breath induction with either 5.0% sevoflurane or 5.0%

isoflurane in a 1:1 N_2O/O_2 mixture; induction times were similar for sevoflurane (75 ± 3 s) and isoflurane (67 ± 4). Sevoflurane patients were less likely to have complications during induction; coughing occurred more frequently with isoflurane. During induction, heart rate increased with both drugs. Sevoflurane was thus concluded to be more suitable than isoflurane for a single–breath induction.

CNS TOXICITY

In two of 13 cats receiving 5% sevoflurane, the cortical EEG showed spikes with isoelectricity, and consequent repetitive peripheral electrical stimulation induced generalized seizures (49). Many reports exist on similar influence in humans. A sevoflurane inhalation induction study in children reported convulsions of 30 s duration at an incidence of 6% (44). In a recent study in healthy volunteers, two out of eight had an EEG–verified seizure during long sevoflurane monoanesthesia (50). In a scoliosis operation under 7% sevoflurane in O_2 in N_2O anesthesia, the EEG was recorded and spike–and–wave seizure activity occurred for 30 s (51). One case report describes tonic and clonic movements during sevoflurane inhalation induction, and because they were sustained for 20 min despite the medication, anesthesia had to be discontinued (52). Several reports have appeared on convulsive movements or epileptiform EEG potentials during sevoflurane inhalation induction with high inspired sevoflurane concentrations (53-55). Pediatric patients with epilepsy had, during sevoflurane inhalation induction, EEG–verified generalized epileptiform discharges without visible signs of seizure (56). Reversal of neuromuscular block at the end of sevoflurane anesthesia revealed generalized tonic clonic convulsive–like movements in one healthy 32–year–old patient (57).

CNS TOXICITY OF INHALATION ANESTHETICS OTHER THAN SEVOFLURANE

Neuroexcitatory movements have been reported in association with most of the anesthetic inhalation agents. Both the proconvulsant properties and the anesthetic effects have been hypothetized to depend on the degree of halogen substitution of the compounds (58).

ENFLURANE

Enflurane is probably the most widely recognized currently used anesthetic agent with convulsive properties. Enflurane has induced EEG–verified, generalized, grand mal–type seizures when given at high concentrations with hyperventilation of the patients (59). Numerous reports of epileptiform EEG during enflurane anesthesia have appeared (60-62), and its proconvulsant effects have been used in epilepsy surgery to detect the epileptic focus (63). Heart rate increases during enflurane–induced epileptic discharge (64).

ISOFLURANE, HALOTHANE, DESFLURANE

Halothane and isoflurane are considered safe in respect to convulsions. Some case reports of convulsive movements during halothane or isoflurane anesthesia exist (65, 66), but lack of EEG verification makes evaluation of the origin of these movements difficult. When EEG was recorded during induction of anesthesia with isoflurane, a seizure was recorded during clinical convulsion (67). No epileptiform EEG was seen during hyperventilation with 1.24 MAC desflurane (68). Fluorinated ether with some anesthetic properties (fluorothyl) was marketed in the 1960s as a proconvulsant drug alternative to electroconvulsive therapy (ECT) (69).

CNS–TOXICITY OF NON–INHALATIONAL ANESTHETIC AGENTS

Ketamine has convulsant properties when given to epileptic patients (70), and generalized transient convulsions were reported in non–epileptic patients given ketamine (71). Both alfentanil (50 µg/kg) and fentanyl (10 µg/kg) activate epileptiform activity in patients with intractable temporal lobe epilepsy, and these opioids have been used to assist in the localization of the epileptogenic focus during surgery (72). Propofol has been reported to induce convulsive movements (73) but also to be suitable in treatment of status epilepticus (74). Similar dose–dependent EEG effects were reported in a study with propofol in patients with or without a history of seizure disorders. Whereas induction of anesthesia with higher doses of propofol (> 1.5 mg/kg) in neurosurgical patients with seizure disorder under good control was safe, one patient in the epileptic group had an EEG–recorded and clinical grand mal seizure after propofol 1 mg/kg; the seizure disappeared, however, after an additional 0.5–mg/kg bolus dose (75).

During electroconvulsive therapy (ECT), seizures were longest with methohexitone–alfentanil and shortest with propofol in a study comparing these medications. The combination of methohexitone with alfentanil was recommended in ECT in preference to propofol to prolong seizure duration (76). A prospective study evaluated the effects of propofol sedation on the incidence of intraoperative seizures during awake craniotomy performed for the management of refractory epilepsy. Thirty patients were randomized to receive propofol or neurolept analgesia along with fentanyl and droperidol, and a higher incidence of intraoperative seizures occurred among the neurolept patients (6 vs. 0) (77).

EPILEPTOGENESIS

EXCITABILITY

The basic disturbance in generalized seizures is considered to be exaggerated cortical excitability (78). Excitability is dependent on the balance between inhibitory and excitatory impulses and the level of synchronization of neural networks. Depending upon whether synaptic activity is of the excitatory or inhibitory type, the postsynaptic neuronal membrane will be depolarized or hyperpolarized. Exitatory postsynaptic potentials (ESPSs) result when a neurotransmitter released from a presynaptic terminal causes a net inward movement of positive ions which depolarizes the cell. Inhibitory postsynaptic potentials (IPSPs) hyperpolarize the postsynaptic membrane by causing a net outward ionic current that increases the negative charge inside the cell (78).

The neuron is activated in a non–refractory phase. Additionally, a sufficient amount of excitatory postsynaptic potentials (EPSP) must accumulate in relation to inhibitory postsynaptic potentials (IPSP), to create an action potential. In a normal neuron population, cells act in different phases, with only part of the population in a refractory phase. Under these circumstances even a powerful excitatory torrent of impulses can activate only part of the population. Conversely, an inhibitory impulse can block neurons despite their phase and thereby synchronize a large population of neurons (79). Hypersynchronization is considered to be the most important single mechanism in creating and spreading CNS irritation (80).

SEIZURE THRESHOLD

Seizure threshold is an individual feature, varying considerably interindividually (81). It is affected by many factors such as age and gender (81), hormones (82), even diet (83).

Seizures take place when neural tissue excitability exceeds the individual seizure threshold. This fact is useful in the diagnostic activation of epileptic foci. In epileptic patients on anticonvulsive therapy, sleep deprivation prior to EEG recording activates epileptiform activity (84). The combination of the short sleep following 24 h of sleep deprivation, with subsequent use of the additional provocative methods of hyperventilation, photostimulation and hydration, was reported to yield new diagnostic information on epileptiform EEG in 50% of the epilepsy patients (85). Other reported seizure–inducing mechanisms include intense emotional stress, fever, hypoglycemia, hypocalcemia, hyponatremia, hypomagnesemia, hypoxia, and hyperbaric states (86), some of which elicit seizures even in a non–epileptic brain.

With ECT, seizure can be induced in anyone. Theophylline prolongs seizure duration in ECT (87), and status epilepticus occurred after electroconvulsive therapy in a patient whit a theophylline level above the accepted therapeutic range (88). Caffeine is also used to facilitate ECT in therapy–resistant patients (89). Antimicrobial treatment with imipenem (90), and immonusuppression with cyclosporin A, especially in connection with hypomagnesemia, (91) have both been reported to relate to an increased risk of seizures. In an experimental animal model, dexmedetomidine, a selective alpha2−agonist agent, decreased the convulsion threshold (92). During presurgical evaluation, 14 patients with medically intractable focal epilepsies underwent magnetoencephalographic recordings to localize the epileptogenic focus, and demonstrated the selective proconvulsant effects of methohexital on their epileptogenic focus (93). Clonidine also increased epileptiform activity in patients with seizure disorders. High–dose dexmedetomidine was found in cats to reduce the seizure threshold during enflurane anesthesia (94).

GAMMA–AMINOBUTYRIC ACID, GABA

GABAergic transmission of impulses in CNS is assumed to inhibit the excitative phenomena (95). This main rule does not always, however, apply, as shown by the convulsive effects of some GABAergic agents. Although sevoflurane and enflurane, like many other volatile agents, have been shown to enhance GABAergic transmission (96, 97), deep enflurane anesthesia combined with hyperventilation is known to elicit seizures (59). In the flurothyl seizure model using adult rats, substantia nigra pars reticulata microinjection of the selective GABA–A–receptor agonist muscimol results in a biphasic dose–response curve: intermediate doses being anticonvulsant, but high doses having proconvulsant effects (98). These changes were age–related. In younger animals, no anticonvulsant effects of muscimol occur, only proconvulsant effects, and at lower doses than in adults. Direct GABA agonist THIP (tetrahydroxyisoxazolopyridine) can be used to induce another animal model of epilepsy, synchronous bilateral spike–and–wave activity (99).

KINDLING

Periodic administration of convulsive agents, even at doses or intensities that initially have no convulsive effect, can lead to a progressive and enduring increase in susceptibility to subsequent convulsive stimulation which is known as the kindling effect. Animal kindling models have been used in research on epilepsy.

Analogous to experimental kindling are prolonged febrile seizures in childhood, or an episode of status epilepticus at any age, which can produce the highly characteristic pattern of hippocampal cell loss and shrinkage that is seen later in life, if patients develop temporal lobe epilepsy. Seizure–induced and presumably excitotoxic pathology includes neuronal loss,

reactive gliosis, aberrant synaptic reorganization of surviving cells, and hippocampal tissue shrinkage that may alter extracellular space and affect ionic homeostasis (100).

The epileptic seizures seen during the alcohol withdrawal syndrome are often similar to those seen in experimental epilepsy models such as kindling models (101). The chronic consumption of alcohol, if consumption is interrupted abruptly, can lead to a withdrawal syndrome, which is a state of hyperexcitability characterized by anxiety, fear, muscular rigidity, and tonic–clonic seizures with epileptiform–type characteristics. A possible correlation may exist between these models (101).

The susceptibility of pediatric patients to developing brain pathology in a kindling–like process may be higher when compared to that of adults. Several factors may contribute to the propensity for the developing brain to undergo seizures and develop epilepsy. Hypersynchrony of neuronal circuits contributes to the seizure potential, and several neurobiological features of the immature brain may support synchronized neuronal firing (102). The immature cerebral cortex and hippocampus have a higher density of synapses than that of adults and also a higher density of gap junctions and of excitatory amino acid receptors (102). Enhanced regenerative responses to injury in the developing brain may also contribute to the formation of abnormal hippocampal connections that support epilepsy. Molecular mechanisms that contribute to enhanced synaptic plasticity in the child's brain can also in certain circumstances contribute to epileptogenesis.

The phenomenon of kindling, in which repeated electrical stimulation of neuronal circuits leads to the development of epileptic seizures, is easily elicited in young animals. Long–term potentiation (LTP), in which repeated synaptic stimulation leads to a reduced threshold for activation of that pathway and enhanced postsynaptic potentials, is much more robust in the immature cerebral cortex and may contribute to kindling and epileptogenesis. Age–related enhancement of N–methyl–D–aspartate–type glutamate receptors, important for the activity–dependent plasticity in the developing brain, appears to participate in LTP. This information suggests that normal developmental features of synaptic development make the immature brain more excitable than the adult brain and may contribute to epileptogenesis (102).

The mechanisms of epileptogenic potential of anesthetic agents are unknown. Theoretically, in experimental circumstances a kindling–like effect may exist, for example with repetitive administration of enflurane and hyperventilation and/or photic stimulation. This, however, has not been researched.

MYOCLONUS

Myoclonus is a frequently reported phenomenon in the context of various anesthetic agents. The term “myoclonus” originates from the Greek *klonos*, which refers to violent movements; and the prefix “myo” originally was meant to distinguish these movements from epileptic clonus (103). In the course of time, myoclonus has been connected with epileptic movements as well, and epileptic myoclonus is now considered to be one category of myoclonus (103). Without EEG recording, the exact nature of clonic movements is unclear. Unfortunately, only a few studies reporting myoclonus during anesthesia include the results of simultaneous EEG recording. Etomidate is reported to produce myoclonus in 45% of the patients during cardioversion (104). A study comparing incidence of myoclonus with different anesthetic agents reported myoclonic responses in 69% of the etomidate patients, of whom 22% had multiple spikes appearing on the EEG (105).

A healthy man developed nonconvulsive seizures and generalized paroxysmal fast activity in his EEG following propofol anesthesia (106). An increase in heart rate and excitatory movements during propofol infusion was reported in four patients (107). A report

of five patients with seizures in association with propofol anesthesia included a female epileptic patient who developed severe status epilepticus (108). The other patients with short–lasting seizures had no previous epilepsy. In a propofol induction study with a pediatric patient population, propofol 3 mg/kg induced spontaneous dystonic and choreiform movements in all seven patients but no EEG abnormalities (109). The safety of intravenous methohexital for brief, unconscious sedation of pediatric hematology/oncology outpatients undergoing painful invasive procedures was evaluated, and myoclonus was observed in 10% (110). A small dose of alfentanil (5 µg/kg i.v.) was reported to decrease myoclonus induced by methohexital anesthesia (105).

AIMS OF THE STUDY

Effects of sevoflurane anesthesia on EEG and hemodynamics was studied. Specific objectives of this thesis were:

1. To determine the sevoflurane requirement for adequate anesthesia during laparoscopic tubal ligation (LTL), with the bispectral index of the EEG and hemodynamic responses as criteria.
2. To evaluate the hemodynamic profiles in adults during sevoflurane inhalation induction produced by different breathing modifications.
3. To examine EEG effects and their hemodynamic correlations with the sevoflurane inhalation induction in adults during spontaneous breathing or controlled hyperventilation.
4. To study the effects of delaying the rapid rise in sevoflurane concentration in adults by allowing the patients to breathe spontaneously for two minutes before starting the hyperventilation.
5. To compare in children the effects of spontaneous breathing and controlled ventilation on EEG and hemodynamics during sevoflurane inhalation induction.
6. To compare the development of EEG features in adults versus children during sevoflurane induction.

PATIENTS AND METHODS

PATIENTS

The total number of patients in the present study was 159. The adult study population comprised 127 females. The pediatric population comprised 32 children, 13 female and 19 male. Adult patients were scheduled for elective surgery in the Women's Hospital, Helsinki University Hospital. Children were scheduled for elective surgery in the Eye–Ear Hospital of Helsinki University Hospital.

Study I was based on 32 ASA physical status I–II females who underwent LTL, and Studies II–IV on 95 ASA I–II patients undergoing elective gynecological surgery. Study V involved 32 ASA I–II children, aged 2–12 years, undergoing elective otolaryngolocical surgery (Table 2).

Table 2. Characteristics of study patients.

Study	Age (years) Mean ± SD	Height (cm) Mean ± SD	Weight (kg) Mean ± SD
I	40 ± 4	168 ± 6	64 ± 8
II	38 ± 8	166 ± 5	62 ± 9
III	39 ± 6	166 ± 6	67 ± 9
IV	38 ± 7	165 ± 6	64 ± 9
V	6 ± 2	117 ± 18	24 ± 10

All studies were approved by the ethics committees of the hospitals (Women's Hospital and Eye-Ear Hospital, Helsinki University Hospital, Helsinki). All adult patients gave their written informed consent before participation, and all the parents of the children included in Study V gave preoperative written informed consent. Two adults in Study I were excluded, one because of high BIS values, and the other due to increased arterial pressure after endotracheal intubation. One child was excluded from Study V because of lack of cooperation.

DESIGNS AND PROTOCOLS OF THE ORIGINAL STUDIES

Study I. The sevoflurane requirement, based on BIS and hemodynamic responses in day–case surgery, was assessed. Knowing that unconsciousness in healthy volunteers (with no surgery) is already achieved at 0.4 MAC, we tested the hypothesis that in surgical patients less than 1 MAC sevoflurane can produce unconsciousness. Anesthesia was induced by VCRII and maintained with sevoflurane in N_2O and O_2 (33%) in 32 women undergoing laparoscopic tubal ligation (LTL). The sevoflurane dose was chosen to produce desired BIS levels within agreeable limits of blood pressure and heart rate. For the first patient, the sevoflurane concentration was adjusted to 1 MAC with an end–tidal concentration (ET) of 0.7%. BIS–values were used to determine the concentration to be used for the next patient. If the BIS values remained below 50 for over 50% of the operation time, the concentration of sevoflurane was reduced so that the ET level fell by 0.1%. When the BIS values were greater than 65 for over 50% of the operation time, ET sevoflurane concentration was increased by 0.1% for the next patient. BIS values between 50 and 65 were considered acceptable; thus when the value remained between these limits for more than 50% of the time, no changes in sevoflurane concentration were made for the subsequent patient. BIS values greater than 75

for over 30 sec were treated with a propofol bolus, and the data collection was discontinued. Hemodynamic responses were deemed excessive if increases in systolic arterial pressure were over 30% and/or the increase from the baseline in heart rate was more than 50%. These patients were treated with additional propofol. The data collection was discontinued, and the next patient underwent deeper anesthesia.

Study II. Occasional hyperdynamic circulatory responses during inhalation induction with high sevoflurane concentration were observed during Study I. To examine this further, HR and blood pressure profiles of 30 adult patients during 8% sevoflurane inhalation induction with either spontaneous breathing or controlled hyperventilation were compared. The anesthetic induction began with the VCRII technique followed by either spontaneous breathing or controlled hyperventilation, during which $ETCO_2$ was maintained below 30 mmHg. A blood sample from the radial artery was drawn immediately prior to intubation for blood–gas analysis. Sevoflurane concentration was maintained at 8% until the endotracheal intubation and was reduced to 1% after that point. Another five patients were studied to evaluate the effect of hyperventilation *per se* on the hemodynamics of an anesthetized patient. These patients were anesthetized with a propofol bolus 3 mg/kg followed by propofol infusion 15 mg/kg/h. Patients were hyperventilated exactly like the patients in the controlled ventilation group. Ventilatory and hemodynamic parameters were recorded at 1–min intervals for nine min after the loss of consciousness, six min before and three min after the tracheal intubation. Differences in ventilation types were compared by measuring VF, MV, and ET–sevoflurane concentrations, and by blood gas analysis. Baseline values for hemodynamic parameters were recorded prior to induction during preoxygenation.

Study III. Hyperdynamic circulatory response observed in Study II was researched further in Study III. Epileptic seizures are known to induce an autonomous nervous system response which increases heart rate and blood pressure. Study II was repeated with additional four–channel EEG recording during the inhalation induction. Time domain analysis of EEG phenomena during mask induction was performed off–line. No propofol group was included. The relationships were calculated between percentage rise in HR and occurrence of epileptiform EEG.

Study IV. The hypothesis was that avoiding a very rapid increase in end–tidal sevoflurane concentration by delaying the onset of hyperventilation would influence the appearance of epileptiform EEG patterns. Patients were hyperventilated after loss of consciousness either immediately or after a two–minute period of spontaneous breathing during sevoflurane mask induction. Sevoflurane concentration was maintained at 8% until endotracheal intubation, and decreased to 1% after that. In both groups an $ETCO_2$ below 4% was the aim. Ventilation types were verified by measuring minute ventilation and by gas analysis of a blood sample from the radial artery. Heart rate and blood pressure profiles were compared. Ventilatory and hemodynamic parameters were recorded at 1–min intervals for eight min after loss of consciousness, five min before and three min after tracheal intubation. Baseline values for hemodynamic parameters were recorded during preoxygenation prior to induction. Four–channel EEG recording was visually analyzed off–line by a neurophysiologist unaware of the induction type.

Study V. The occurrence of epileptiform EEG and coinciding hyperdynamic responses in children during 8% sevoflurane inhalation induction with either spontaneous breathing or controlled ventilation were compared. After they became unresponsive to verbal commands, manually controlled ventilation was started in the controlled ventilation group. End–tidal CO_2 was observed and maintained between 4.3 and 5.3 kPa (= 32 and 40 mmHg). If apnea occurred in the spontaneously breathing group, slow controlled ventilation was started after a 30–s waiting period. In patients who had to be assisted, $ETCO_2$ was allowed to rise to between 6.0 and 6.7 kPa (= 45 and 50 mmHg) to mimic sevoflurane–induced respiratory

depression. Blood pressure and HR profiles were compared. A neurophysiologist unaware of the induction type visually analyzed four–channel EEG recording off–line.

Table 3. Study designs and the main topics.

	Number of patients	Design	Part of the anesthesia studied	Ventilation	EEG monitoring	Other measurements	Main topic
I	32	Prospective	Induction, operation, awakening	Controlled, ventilator	2–channel bipolar, frontal, BIS	HR, blood pressure, interview to detect intraoperative awareness	**BIS vs. MAC**
II	35	Prospective, randomized	Induction	Controlled vs. spontaneous	none	HR, blood pressure, SpO_2, blood–gas analysis, VF, MV, ET–sevo, intubation conditions	**Hemodynamics** during **spontaneous** vs. controlled **hyperventilation**
III	30	Prospective, randomized, double–blind EEG analysis	Induction	Controlled vs. spontaneous	4–channel bipolar, frontotemporal	HR, blood pressure, SpO_2, blood–gas analysis	**Hemodynamics** and **EEG** features in **adults** during **spontaneous** vs. controlled **hyperventilation**
IV	30	Prospective, randomized, double–blind EEG analysis	Induction	Controlled vs. 2 min spontaneous and controlled after 2 min	4–channel bipolar frontotemporal	HR, blood pressure, blood–gas analysis, SpO_2,	Sevoflurane **CNS concentration rising speed** vs. **hyperventilation**–induced **EEG** effects
V	32	Prospective, randomized, double–blind EEG analysis	Induction	Controlled vs. spontaneous	4–channel bipolar frontotemporal	HR, blood pressure, SpO_2,	**Hemodynamics** and **EEG** features in **children** during **spontaneous** vs. **controlled ventilation**

METHODS

PREMEDICATION, MONITORING

All adult patients were premedicated with 5 mg oral diazepam. Children were premedicated with oral midazolam 0.5 mg/kg, maximum dose 15 mg, and oral atropin 0.03 mg/kg, maximum dose 1 mg. Monitoring included heart rate (HR), electrocardiogram, pulse oximetry (SpO_2), end–tidal carbon dioxide ($ET–CO_2$), end–tidal sevoflurane concentration (ET–sevo), and blood pressure. Ventilatory and gas measurements were performed from the ventilatory circuit at the connecting piece close to the face mask. All these data were collected with a Datex–Ohmeda AS/3 Anesthesia Monitor (Datex–Ohmeda Div., Instrumentarium Corp., Helsinki, Finland).

ANESTHESIA

Anesthesia for all adult patients was started with VCRII from a face mask using 8% sevoflurane in N_2O and O_2 in a rebreathing circle system containing a carbon dioxide absorber and primed beforehand with sevoflurane. The patients were asked to exhale forcefully to the residual volume, followed by a vital capacity breath with a face mask placed tightly over the nose and the mouth; they were then asked to hold their breath as long as possible. Thereafter, the patients were allowed to breathe normally until unconscious. Unconsciousness was defined as loss of eyelash reflex and no response to verbal commands. After each became unconscious, ventilation was conducted according to specific study protocols until intubation.

To facilitate intubation and to minimize muscle artifacts affecting the EEG, rocuronium was used in Study I. After intubation, the sevoflurane vaporizer was adjusted to 1% in Studies II, III, and IV and to 2% in Study V. In Study I, sevoflurane was administered according to a specific study protocol after intubation.

In five control patients in Study II, anesthesia was induced with a propofol bolus 3 mg/kg, followed by a propofol infusion 15 mg/kg/h.

In children, anesthesia was induced with a face mask (chosen to fit tightly according to each patient's size) with a Jackson–Rees anesthesia system. The children breathed spontaneously until becoming unconscious. Ventilation was conducted according to the specific study protocol until intubation.

O_2:N_2O was 1:2 in Studies I and V, 1:1 in Studies II, III, and IV. Fresh gas–flow rates were nine l/min in Study I, ten l/min in Studies II, III, and IV and equal to the square root of patient weight in kilograms in Study V.

EEG

EEG data were collected with an Aspect EEG monitor A 1000 (Aspect Medical Systems, Natick, MA, USA) and Zipprep™ EEG electrodes (Aspect Medical Systems). Before electrode placement, the skin was prepared with alcohol and abraded to ensure electrical conductivity. A two–channel bipolar EEG was used to record the BIS during anesthesia and surgery in Study I; four–channel bipolar EEG was recorded during induction of anesthesia in Studies III–V. A four–channel EEG in Studies III–V was recorded from the following electrode pairs: Fp1–left mastoid, Fp2–right mastoid, Fpz–left temporal, and Fpz–right temporal. Prior to EEG recording, an impedance check was performed; impedance below 5 kΩ was considered acceptable. Time domain EEG recordings during induction of anesthesia in adults were classified as delta (D), slow delta (DS), slow delta monophasic (DSM), slow delta monophasic with spikes (DSMS), burst suppression (BS), burst suppression with spikes (SBS), polyspikes (PS), rhythmic polyspikes (PSR), in studies III and IV and periodic epileptiform discharges (PED) in Study IV (Fig. 1).

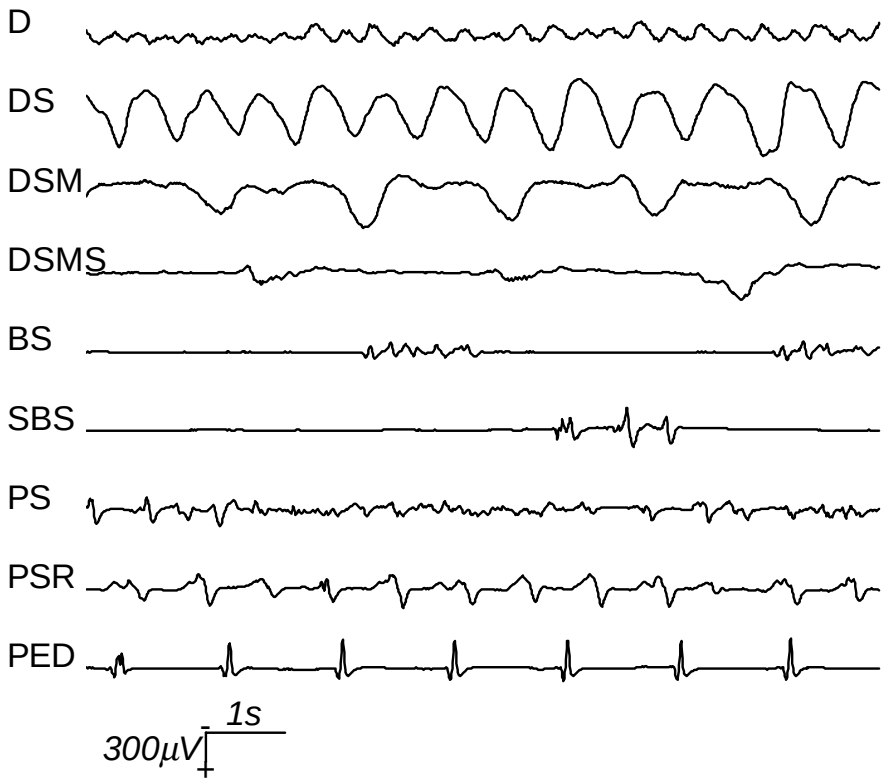

Figure 1. EEG features classified in adults. Delta (D), slow (<2 Hz) delta (DS), slow delta monophasic (DSM), slow delta monophasic with spikes (DSMS), burst suppression (BS), burst suppression with spikes (SBS), polyspikes (PS), rhythmic polyspikes (PSR), and periodic epileptiform discharges (PED).

Similar classification during induction of anesthesia in children was: slow delta (DS), delta (D), delta with spikes (DSP), burst suppression (BS), suppression with spikes (SSP), rhythmic polyspikes (PSR), periodic epileptiform discharges (PED), and suppression (S) (Fig. 2).

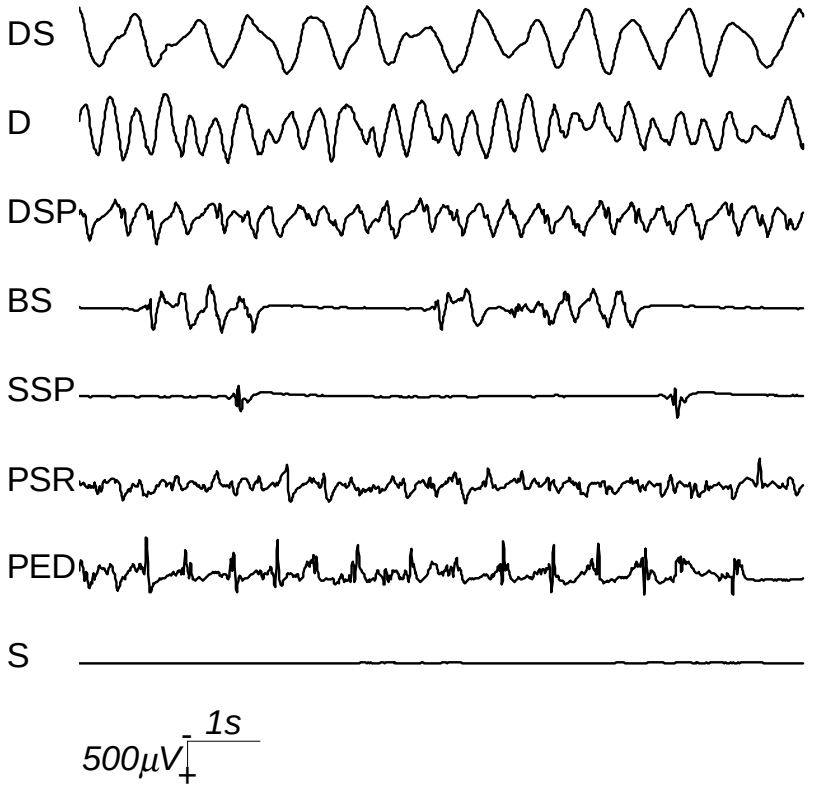

Figure 2. EEG features classified in children.

Occurrence, appearance, and duration of EEG waveforms were calculated. All EEG recordings were visually analyzed and classified by one blinded (= unaware of the induction type of the anesthesia) neurophysiologist familiar with anesthesia EEG.

STATISTICAL ANALYSIS

To calculate the response rates of 50% and 95% in Study I, according to de Jong and Eger (111), a logistic model was applied (112) (S–Plus 4.0, MathSoft Inc, Seattle, WA, USA) to estimate the appropriate doses of sevoflurane. Hemodynamic parameters were analyzed with analysis of variance for repeated measures, followed by paired t–tests for comparisons in changes in MAP and HR within a group, and unpaired t–tests between groups SB and CV as *post hoc* tests (II–V). The Mann–Whitney U–test was used to compare the similarities between the study groups by ASA class in Study II. The occurrence of epileptiform EEG according to induction type was analyzed by Fisher exact test (III–V). The differences in appearance and duration of EEG waveforms between induction types were analyzed with unpaired t–tests. Statistics were analyzed with GB–Stat™ V6.5 (Dynamic Microsystems, Inc, Silver Spring, MD, USA) and with the Statistical Package for the Social Sciences (SPSS),

Windows version 6.0.1 or 9.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant. Parametric data are presented as mean ± SD.

RESULTS

SEVOFLURANE REQUIREMENT IN LTL (AIM 1)

The ET sevoflurane concentrations required to keep BIS values at the 50 to 65 level ranged from 0.7 to 0.9%. The ET sevoflurane concentration required was 0.7% in five patients, 0.8% in 20, and 0.9% in five (Figure 3).

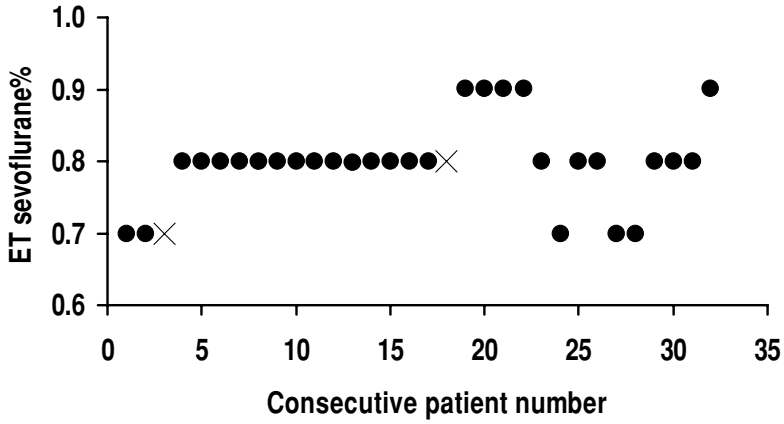

Figure 3. Sevoflurane concentrations required to maintain BIS between 50 and 65 during LTL. X = The two patients excluded from the study.

The ED_{50} for adequate sevoflurane (with N_2O) anesthesia during LTL was 0.7% ET sevoflurane (CI 95% 0.63–0.77). The ED_{95} was 0.83% ET sevoflurane (0.75–0.90). Very low BIS values were recorded immediately after the mask induction, whereas the patients' BIS responses varied somewhat during surgery. The hemodynamic and BIS values recorded during the study are presented in Figure 4.

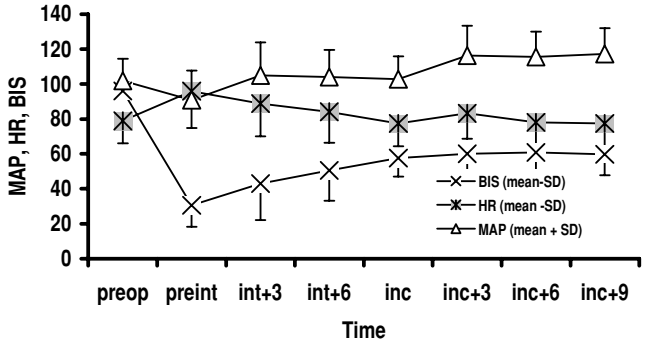

Figure 4. BIS values, heart rate (HR, b.p.m.), and mean arterial pressure (mmHg) preoperatively (preop), before intubation (preint), three and six min after intubation, at skin incision (inc), and until nine min after incision.

HEMODYNAMICS DURING SEVOFLURANE ANESTHESIA (AIM 1)

The hemodynamic profile during BIS–guided anesthesia for LTL is shown in Figure 4. Both heart rate and MAP were stable. An occasional increase in heart rate was observed within the first three min of VCRII induction of anesthesia with sevoflurane.

HEMODYNAMICS DURING SEVOFLURANE INDUCTION (AIMS 2 AND 5)

HEART RATE

In adults, heart rate increased during controlled hyperventilation from the preinduction baseline, and remained at baseline level during spontaneous breathing (Fig. 5a). When controlled hyperventilation was applied after two min of spontaneous breathing in Study IV, heart rate increased more slowly than during induction with immediate onset of hyperventilation. In children, controlled ventilation and spontaneous breathing both increased heart rate (Fig. 5 b).

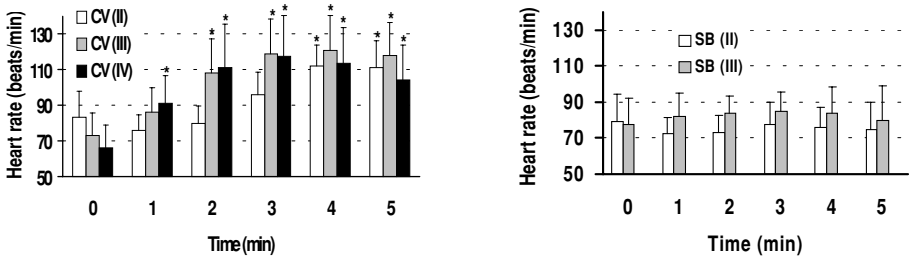

Figure 5 a. Heart rate during 8% sevoflurane induction in adults. Controlled hyperventilation (CV) in Studies II, III, and IV provoked a significant increase in heart rate (left histogram). * $P < 0.001$ within group compared to baseline. 0 = preinduction value. Spontaneous breathing (SB) during 8% sevoflurane induction maintained HR at baseline level.

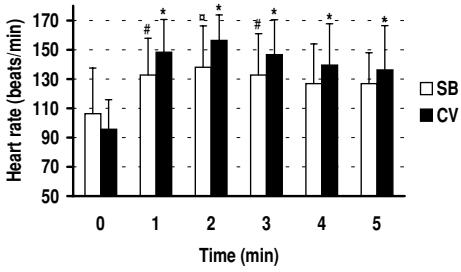

Figure 5 b. In children (V), contrary to adults, spontaneous breathing (SB) also increased heart rate from baseline, although not as much as did controlled ventilation. # $P < 0.05$, ¤ $P < 0.01$, * $P < 0.001$ within group compared to baseline. 0 = preinduction value.

BLOOD PRESSURE

In adults, during controlled hyperventilation blood pressure increased from (III, IV), or remained at baseline level (II). During spontaneous breathing, MAP decreased from baseline level (II, III) (Fig. 6). In children (V), blood pressure increased initially during controlled ventilation and decreased after three min from the beginning of unconsciousness. During spontaneous breathing, blood pressure decreased after four min from the beginning of unconsciousness (Fig 6).

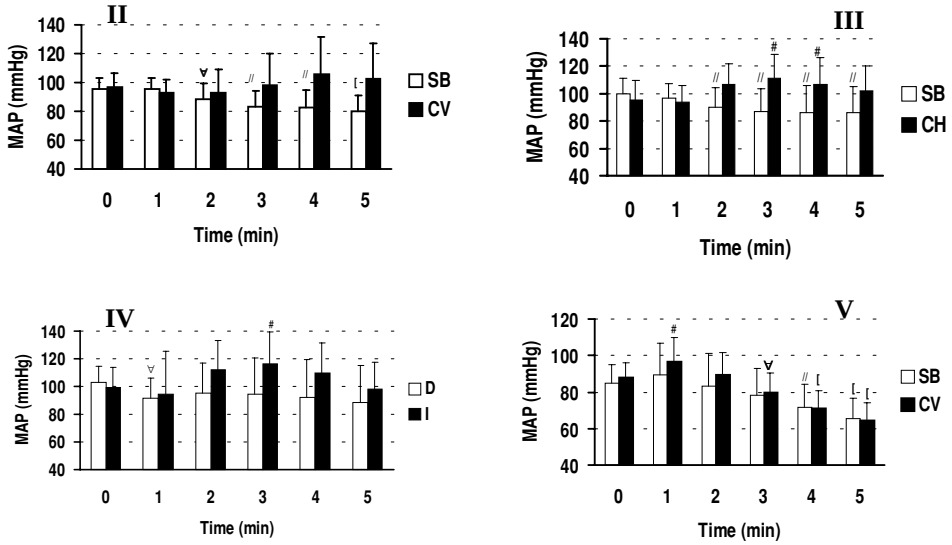

Figure 6. Mean arterial pressure during 8% sevoflurane induction. Controlled hyperventilation (CV, CH) in Studies II and III caused MAP to remain at a higher level than with spontaneous breathing in adults. In children (V), an initial increase in the controlled ventilation group soon turned into a decrease. In Study IV in adults, starting the controlled hyperventilation after two min of spontaneous breathing (D) prevented decrease in blood pressure. Immediate onset of hyperventilation after loss of consciousness (I) increased the blood pressure from the baseline in Study IV. # $P < 0.05$ value higher than baseline. ∀ $P < 0.05$, lower than baseline. // $P < 0.01$, value lower than baseline. [$P < 0.001$, value lower than baseline.

SEVOFLURANE–INDUCED EEG WAVEFORMS DURING INDUCTION (AIMS 3 AND 5)

The evolution of EEG features during anesthetic induction with the 8% sevoflurane–N_2O–O_2 mask started with changes in eye movements: the slowing of saccadic eye movements and cessation of blinks. This was accompanied by an increase in beta (> 13 Hz) range activity. In a few seconds, slowing of the EEG took place. The dominant frequency changed to theta (4 – 8 Hz) and further to delta activity (Figs. 1 and 2). At this point, the EEG recordings began to show epileptiform activity, predominantly in the groups with controlled hyperventilation. Periodic epileptiform EEG features occurred mainly in these groups. Milder,

non–periodic epileptiform EEG features (spikes and polyspikes without rhythmicity) occurred frequently also in the spontaneously breathing groups. In many adult patients breathing spontaneously, monophasic slow delta with or without spikes continued to the end of the study.

SEVOFLURANE–INDUCED EPILEPTIFORM EEG APPEARING ONLY IN ADULTS

Slow monophasic delta with spikes (Fig. 7) occurred in five (33%) patients in the controlled hyperventilation group and in four (27%) in the spontaneous breathing group in Study III (n.s.) and in four (27%) patients in the immediate hyperventilation group and in one (7%) in the delayed hyperventilation group in Study IV ($P < 0.05$).

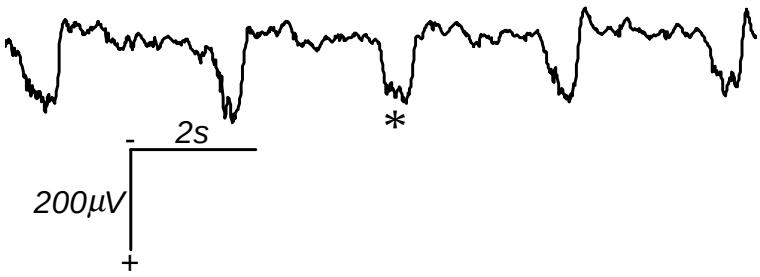

Figure 7. Slow monophasic delta with spikes. Notice the spikes (*) on top of the downward deflecting delta waves.

Polyspikes (Fig. 8) occurred in 13 (87%) patients in the controlled hyperventilation group and in six (40%) in the spontaneously breathing group (III) ($P < 0.05$) and in 14 (93%) patients in both groups in IV (n.s.).

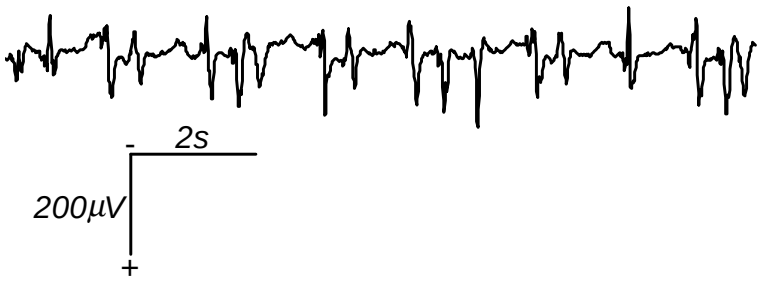

Figure 8. Polyspikes.

Burst suppression with spikes (Fig. 9) was recorded in the controlled hyperventilation group in Study III, in three (20%) patients (n.s. between study groups). In Study IV, two patients (13%) in the immediate hyperventilation group and five (33%) in the delayed hyperventilation group showed burst suppression with spikes (n.s.).

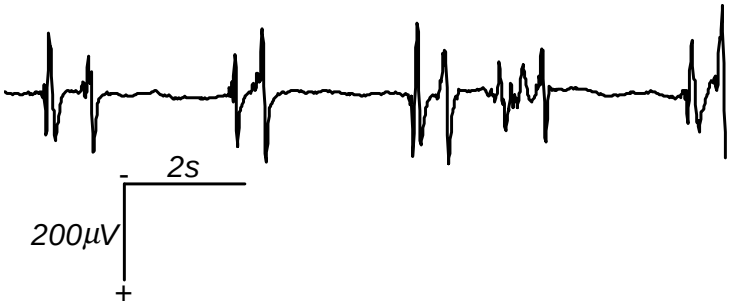

Figure 9. Burst suppression with spikes.

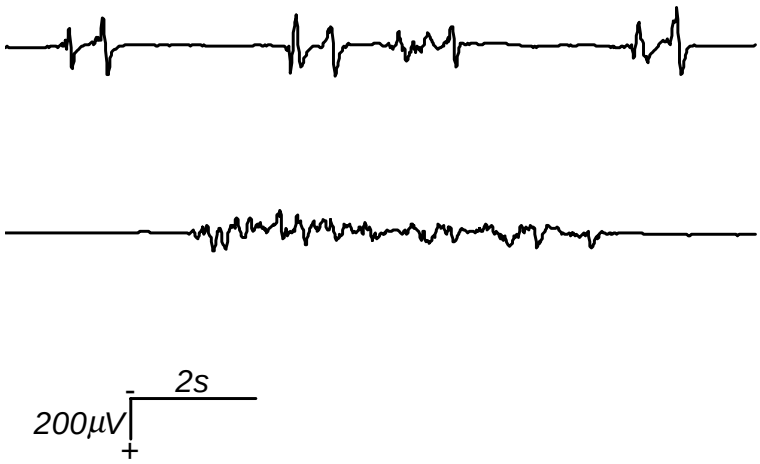

Figure 10. Burst suppression with spikes (upper trace) and burst suppression (lower trace) from the same patient.

SEVOFLURANE–INDUCED EPILEPTIFORM EEG APPEARING ONLY IN CHILDREN

Mild epileptiform EEG (**delta with spikes**) (Fig. 11) were present in 15 patients (94%) in the controlled ventilation group and in 12 (80%) in the spontaneous breathing group (n.s.).

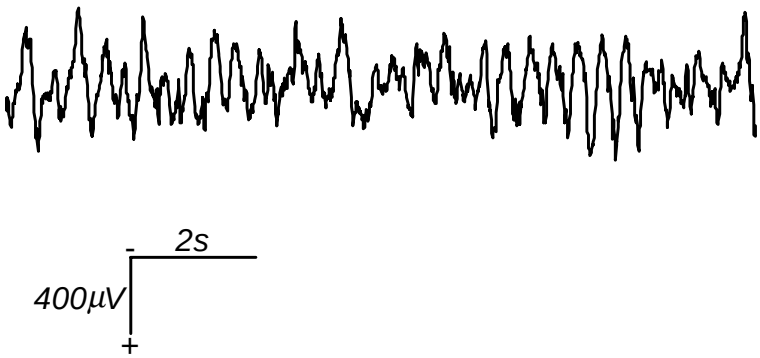

Figure 11. Delta with spikes. Notice the amplitude scale differing from the other EEG traces.

Suppression with spikes (Fig. 12) was present in four patients (25%) in the controlled ventilation group, and in none in the spontaneous breathing group (n.s.).

Figure 12. Suppression with spikes.

SEVOFLURANE–INDUCED EPILEPTIFORM EEG APPEARING BOTH IN ADULTS AND IN CHILDREN

Rhythmic polyspikes (Fig. 13) occurred in 13 (87%) patients in the controlled hyperventilation group and in one (7%) in the spontaneous breathing group in Study III ($P < 0.01$). In that patient, HR increased from 62 to 88 beats/min three min after the beginning of induction. In Study IV, 11 (73%) patients in the immediate hyperventilation group and six (40%) in the delayed hyperventilation group showed rhythmic polyspikes. In children, seven patients (44%) in the controlled ventilation group and three (20%) in the spontaneous breathing group showed periods of rhythmic polyspikes in their EEGs (n.s.).

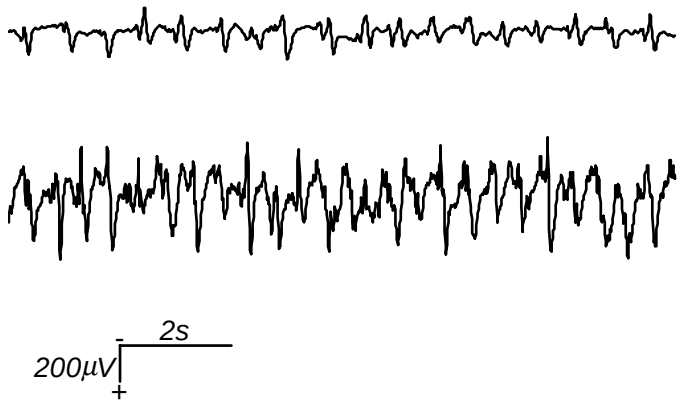

Figure 13. Rhythmic polyspikes. Upper trace from an adult patient, lower from a child.

Periodic epileptiform discharges (**PED**) (Fig. 14) appeared in Study III in ten patients (66%) in the controlled hyperventilation group and in one (7%) in the spontaneous breathing group ($P < 0.01$). In that study they were not classified separately, but were included in the PSR group. PED appeared in ten patients (66%) in the immediate hyperventilation group and in five (33%) in the delayed hyperventilation group in Study IV ($P = 0.07$). In children (Study V), PED appeared in seven patients (44%) in the controlled ventilation group, and in none in the spontaneous breathing group ($P < 0.01$).

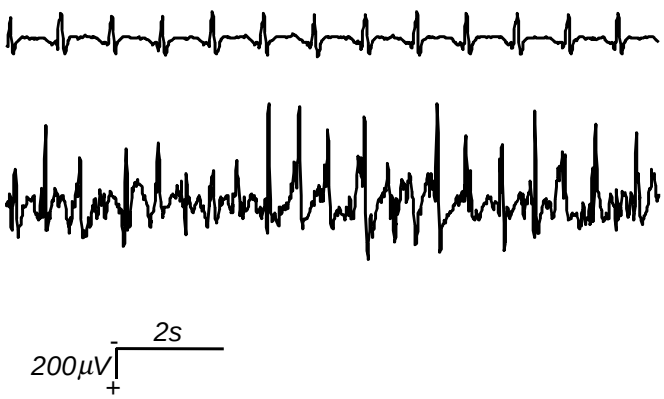

Figure 14. Periodic epileptiform discharges. Upper trace from an adult patient, lower from a child.

HEMODYNAMIC RESPONSE IN CONNECTION WITH EPILEPTIFORM EEG (AIMS 3 AND 5)

In adults, the incidence of epileptiform EEG was high and heart rate and blood pressure both increased from the baseline level in the ventilated groups (Table 4). In the spontaneously breathing adult group, the incidence of epileptiform EEG was low, and heart rate remained at the baseline level while the blood pressure decreased.

In children, the incidence of epileptiform EEG was high, and heart rate increased from the baseline in the ventilated group. Blood pressure reached its peak at one min, but decreased after three min. In the spontaneously breathing pediatric group, the incidence of epileptiform EEG was moderate and so was the increase in heart rate. Blood pressure decreased after four min.

Table 4. *P* = differences within each group compared to the baseline.

Study	Ventilation type	Combined incidence of PSR, PED and SSP (%)	Highest change in heart rate (%)	Highest change in blood pressure (%)
III	Ventilated	87	+ 55 (P<0.001)	+ 17 (P<0.05)
IV	Ventilated	73	+ 77 (P<0.001)	+ 16 (P<0.05)
V	Ventilated	88	+ 63 (P<0.001)	– 27 (P<0.001)
III	Spontaneous	7	+ 9 (n.s.)	– 15 (P<0.01)
V	Spontaneous	20	+ 30 (P<0.01)	– 22 (P<0.001)

THE EFFECTS OF DELAYING THE RAPID RISE IN SEVOFLURANE CONCENTRATION (AIM 4)

Incidence of epileptiform EEG was moderate (40%) with the delayed onset of hyperventilation. This was accompanied by an increase in heart rate of 26% ($P<0.05$) and a blood pressure level remaining at baseline. This hemodynamic response was clearly less than with the immediate onset of hyperventilation (Table 4, Study IV), but the hemodynamic parameter values (as well as the incidence of epileptiform EEG) were higher than with spontaneous breathing throughout the whole induction (Table 4, Study III, spontaneous group).

DIFFERENCES BETWEEN ADULTS AND CHILDREN (AIM 6)

In general, with a similar sevoflurane anesthetic induction and a similar EEG recording technique, amplitudes were much higher in children. The order of the appearance of delta differed between adults and children: in adults after beta the frequency gradually slowed to delta below 4 Hz, and further to delta below 2 Hz. In children delta appeared in reverse order: first after beta a sudden change to slow 0.5 to 2 Hz delta typically took place, and after that the frequency gradually increased to 2 to 4 Hz. Burst suppression was the deepest anesthesia level reached in adults; no adult patient showed suppression in the EEG during five or six min induction, whereas in children suppression was detected in 61%. Besides plain beta, theta, and delta, waveforms occurring in both adults and children during 8% sevoflurane induction were rhythmic polyspikes, periodic epileptiform discharges, and burst suppression (Fig. 15).

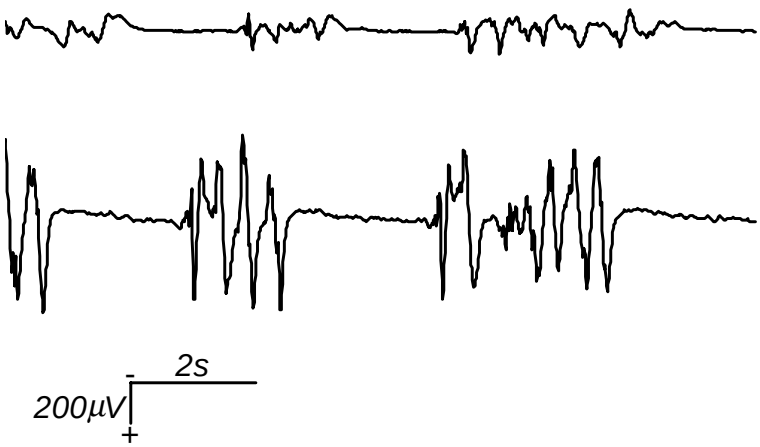

Figure 15. Burst suppression. Upper trace from an adult patient, lower from a child. Notice the typical amplitude difference.

In children, three different types of interictal epileptiform EEG patterns were detected. These were suppression with spikes, rhythmic polyspikes, and periodic epileptiform discharges. Interictal epileptiform EEG patterns were present in 88% of the children

undergoing controlled ventilation and in 20% of those with spontaneous breathing ($P < 0.001$). Suppression was common in children: 11 (69%) in the controlled ventilation group and 8 (53%) in the spontaneous breathing group developed suppression (n.s.). Suppressions occurred mostly after PED or other irritative waveforms, but exceptions were noted, such as suppression straight after delta.

In adults, two different interictal epileptiform EEG patterns occurred: rhythmic polyspikes and periodic epileptiform discharges. In all, interictal epileptiform EEG was seen in 14 (93%) patients in the controlled hyperventilation group and in one (7%) in the spontaneous breathing group in Study III ($P < 0.001$). In Study IV, the total incidence of interictal epileptiform EEG was 11 (73%), and six (40%) with immediate and delayed onset of hyperventilation (n.s.).

Two 8−min EEG recordings from adults and two 6−min EEG records from children are shown in Figures 16–19.

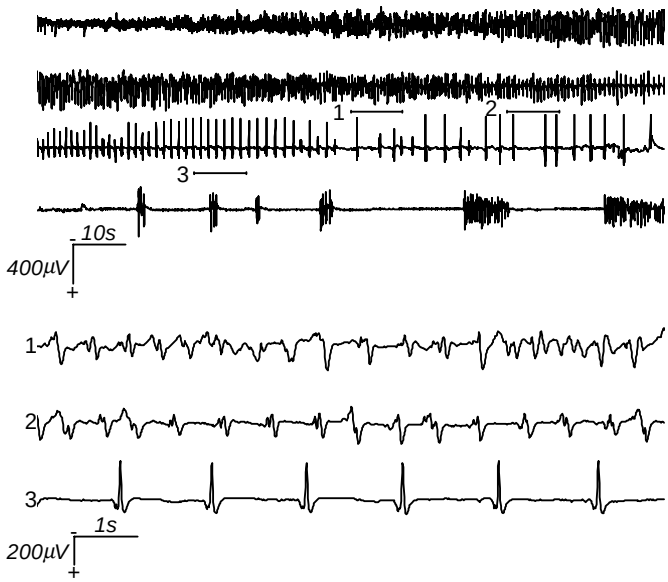

Figure 16. EEG during 8% sevoflurane induction in an adult. Eight min of EEG is presented in four 2–min sections. Three 10–s samples are indicated with horizontal bars. 1. Polyspikes. 2. Rhythmic polyspikes. 3. Periodic epileptiform discharges.

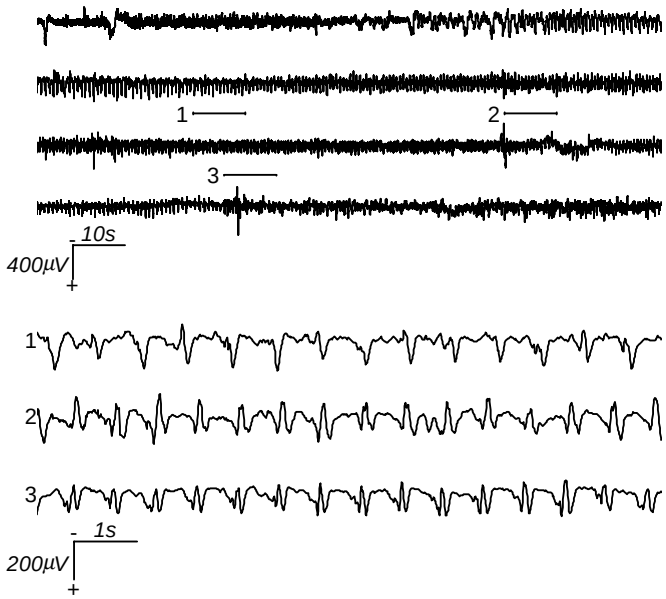

Figure 17. EEG during 8% sevoflurane induction in an adult. Eight min of EEG is presented in four 2–min sections. Three 10–s samples are indicated with horizontal bars. 1. Rhythmic polyspikes. 2 and 3. Periodic epileptiform discharges.

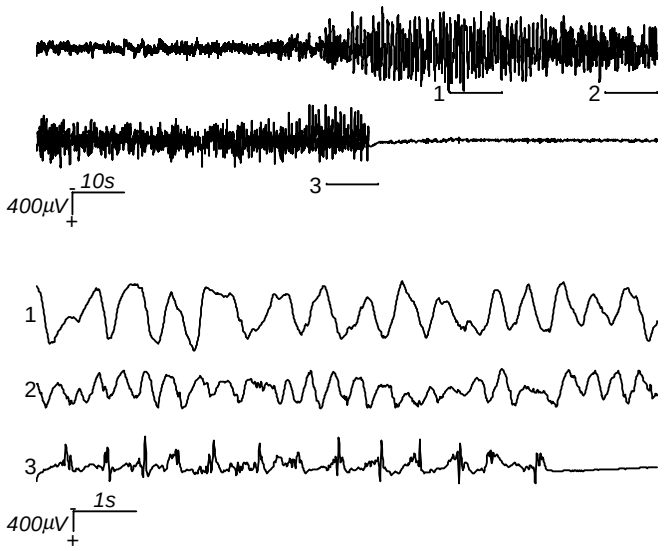

Figure 18. EEG during 8% sevoflurane induction in a pediatric patient. Six min of EEG is presented in two 3–min sections. Three 10–s samples are indicated with horizontal bars. 1. Slow (< 2 Hz) delta. 2. Delta (2–4 Hz). 3. Periodic epileptiform discharges and the beginning of suppression.

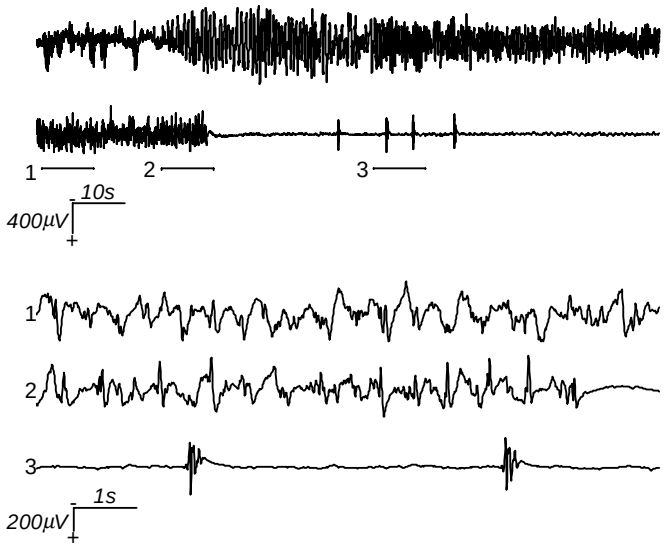

Figure 19. EEG during 8% sevoflurane induction in a pediatric patient. Six min of EEG is presented in two 3–min sections. Three 10–s samples are indicated with horizontal bars. Delta with spikes turning into rhythmic polyspikes. 2. Periodic epileptiform discharges and the beginning of suppression with spikes. 3. Suppression with spikes.

JERKING MOVEMENTS DURING SEVOFLURANE INDUCTION

Two patients in the controlled hyperventilation group in Study II had jerking movements of the shoulders and upper arms at three to five minutes after the start of inhalation anesthesia. Similar movements were seen in four patients with controlled hyperventilation in Study III. Three of these expressed jerking movements of the shoulders, biceps, or arms, and bilateral plantar flexion was seen in one patient. Movements began at one to two min after the first inhalation of sevoflurane, and were associated with slow delta EEG activity with or without spikes. Polyspikes or rhythmic polyspikes were seen later on in all the patients experiencing movement. Two patients with immediate onset of hyperventilation presented jerking movements in Study IV. One of these patients had twitches in all extremities, with slow monophasic delta with spikes turning into polyspikes in the EEG, and the other had twitches in the shoulders while the EEG showed slow monophasic delta with spikes. In both these patients, EEG shortly proceeded into periodic epileptiform discharges. None of the children showed jerking movements during sevoflurane inhalation induction (Study V).

DISCUSSION

METHODOLOGY

ANESTHETIC TECHNIQUE

Benzodiazepine premedication was used in all studies according to the clinical practice of the Women's Hospital and the Eye-Ear Hospital of the Helsinki University Hospital, where the studies were performed. This, however, may have obscured the EEG effects of 8% sevoflurane inhalation induction in Studies III, IV, and V. Omitting premedication from a group of patients might have been informative, but would possibly have led to an increased risk for epileptic events.

The VCRII method (= single–breath method) used in all adults was in line with the recommendations of the manufacturer of sevoflurane, modified only with hyperventilation in the hyperventilated groups in Studies II, III and IV (113). Moderate hyperventilation is common clinical practice in the induction phase of anesthesia. Its purpose may be to ensure good preoxygenation prior to intubation, and to lower CO_2 level moderately to compensate for the inevitable period without ventilation required to intubate the patient. Some anesthesiologists hyperventilate the patient to speed up the induction phase.

ANESTHETIC ADEQUACY

Anesthetic adequacy in Study I was evaluated by use of the BIS, which is designed to monitor the hypnotic effect of anesthetics (114). The BIS monitor is reported to be reliable in detecting unconsciousness, especially at the conventional clinical level of anesthesia (115). During very light levels of anesthesia, other monitoring means, such as the auditory evoked potentials, may be superior for the detection of unawareness (116). Adequacy of analgesia was monitored indirectly as absence of excessive hemodynamic responses. Anesthesia in Study I was considered to be adequate when unconsciousness (BIS < 65) was reached, and unnecessary deep levels (BIS < 50) were avoided to ensure quick recovery from day–case surgery. An earlier report suggested that BIS values below 75 result in only a small possibility of free (explicit) recall (21). Contrary to that, implicit memory formation has been reported to be significant still at BIS levels between 40 and 60 in trauma patients anesthetized with etomidate, isoflurane, and fentanyl (117). However, the significance of implicit memory formation during anesthesia is unclear, and its possible consequences are unknown (118). No testing for implicit memory formation was performed in our study.

EEG

The same equipment and the same montage was used for the EEG recording in adults and in children. The quality of EEG records was good; eyeblinks and EMG artifacts ceased early on nor, during the induction phase of the anesthesia, had surgical interference (diathermia) yet begun. Sevoflurane induction studies were double−blind in regard to the EEG analyses.

Most of the children developed apnea during spontaneous breathing. Although they were ventilated distinctly less than was the controlled ventilation group, EEG features may have been affected by this interference.

EEG was recorded from the frontotemporal regions in Studies III to V. In two of eight healthy volunteers undergoing a study trial under 2 MAC sevoflurane anesthesia, epileptiform

EEG was found in the frontal leads simultaneously with an EEG discharge in the occipitotemporal region (50). Multichannel EEG covering the whole skull might have revealed local EEG events in Studies III to IV. Our EEG recording system (Aspect A 1000 EEG Monitor, Aspect Medical System) is designed to collect data with EEG electrodes (Zipprep, Aspect Medical Systems) which can be used in non–hairy regions only. Therefore, no occipital or parietal EEG was included.

HEMODYNAMIC MONITORING

Heart rate and blood pressure were not monitored blinded, but automatically with an AS/3 Anesthesia Monitor (Datex–Ohmeda Division, Instrumentarium, Helsinki, Finland). Heart rate was calculated automatically from the ECG lead II. Blood pressure measurements were non–invasive, with the cuff adjusted to patient size, as appropriate.

HEMODYNAMICS AND SEVOFLURANE

DURING LTL UNDER SEVOFLURANE ANESTHESIA (AIM 1)

Anesthesia with sevoflurane and nitrous oxide as sole anesthetics provided hemodynamically sufficiently stable anesthesia. However, BIS does not predict intraoperative hemodynamic responses (4). BIS–monitoring in our study demonstrated that hyperdynamic circulatory responses, which are mediated by the autonomic nervous system, are poor indicators of impending intraoperative awareness. In our patients, the largest hyperdynamic response was measured in the presence of a low BIS, and the highest BIS during a modest hyperdynamic response (Study I). We measured high arterial pressures in one patient after endotracheal intubation. It is possible that the 3–min induction time was not sufficient to prevent the circulatory response to intubation in this patient, even though a BIS value around 40 suggested that the patient was unconscious.

It is a common misunderstanding that rising arterial pressure and/or heart rate are tokens of impending awareness. Although this can occasionally be the case, these are far more frequently autonomic reflexes not related to awareness, and best blocked with opioids and antihypertensive drugs. In an animal experiment, a 2.5–fold higher concentration of isoflurane was required to prevent cardiovascular response to noxious stimuli when delivered selectively to the brain, compared to the concentration required when delivered to the whole body (24). This implies that the action of isoflurane in the brain has little to do with such a response. Clinically meaningful concentrations of isoflurane were unable to prevent cardiovascular responses in humans to noxious stimuli (119). BIS seems to be a reliable and easy method for selective monitoring of the sleep component of anesthesia, whereas specific monitoring of analgesic adequacy during anesthesia is yet to come. Inadequate analgesia can often be indirectly identified from cardiovascular instability, but this is inaccurate and can be misleading. In our study, 1 MAC sevoflurane in 66% N_2O in O_2 was sufficient to keep BIS values below 65 and to prevent explicit memory and provide satisfactory hemodynamics during laparoscopic tubal ligation in 95% of the patients.

DURING SEVOFLURANE INDUCTION (AIMS 2 AND 5)

Induction of anesthesia with 8% sevoflurane in N_2O in O_2 with controlled hyperventilation produced a marked hyperdynamic circulatory response both in adults and in children. Previously, hyperdynamic circulatory responses during sevoflurane induction have been reported in children (34, 35). Rapid increases in isoflurane (120) and desflurane (31)

concentrations have been shown to increase heart rates and blood pressures. Inhaled induction of anesthesia with enflurane also increased heart rate (121). With enflurane, desflurane, or isoflurane, airway irritation has been offered as an explanation for the hyperdynamic responses observed (120-122). Airway irritation is not likely, however, to contribute to sevoflurane–induced hyperdynamic response, as sevoflurane is non–pungent and has been found to be the least irritant anesthetic to the airways when compared to halothane, enflurane, or isoflurane (39).

Heart rate increased after loss of consciousness, which excludes anxiety from the list of possible explanations for this increase. Induction was initiated by the VCRII method, providing rapid loss of consciousness: 51 ± 17 s in adults (Study IV) and 41 ± 9 in children (Study V). Increase in heart rate after these time–points is very unlikely to be result from anxiety.

Pain–induced sympathetic stimulation is one common cause of increasing heart rate during surgery. The induction phase studied in this thesis was, however, pain–free, as no manipulation other than mask ventilation occurred.

Controlled hyperventilation was used in Studies II, III, and IV. Hyperventilation during anesthesia as such does not increase heart rate or blood pressure, whether or not hypocapnia is present (123, 124). Instead, hypercapnia increases heart rate in various types of anesthesia (125).

In a majority of patients, epileptic seizures increase heart rate (126-128). The acceleration of heart rate is greater in patients under 25 years old than in those over that age (126). Ictal tachycardia has been suggested to depend on the volume of cerebral structures recruited into a seizure (129). A similar hyperdynamic response occurs during electrically induced seizures (130). During anesthesia, both epileptic discharges (64) and electroencephalic transients (131, 132) have been found to increase heart rate.

During controlled hyperventilation with sevoflurane, blood pressure increased either non–significantly or only initially, decreasing sooner than heart rate. This can be due to the direct vasodilatory effect of sevoflurane (27). With increasing tissue concentrations of sevoflurane, direct vasodilatory action may have dominated the central sympathetic stimulation.

With spontaneous breathing, heart rate remained at the baseline level in adults but increased in children. Blood pressure decreased from the baseline in adults, but an initial increase occurred in children. This has been seen in other studies as well (34, 35).

In adults, controlled hyperventilation during 8% sevoflurane induction in N_2O and O_2 provokes hyperdynamic circulatory responses. Spontaneous breathing during similar sevoflurane induction maintained heart rates at the baseline level but decreased blood pressures.

CONNECTION OF HEMODYNAMICS AND EPILEPTIFORM EEG (AIM 3)

The hyperdynamic response was in proportion to the incidence of epileptiform EEG (Table 4). Rhythmic and periodic epileptiform EEG patterns were seen in patients with a hyperdynamic circulatory response but polyspikes appearing without rhythmicity in adults were not connected to such a response. Increase in hemodynamic variables refers to the seizure–like nature of rhythmic and periodic patterns (133). Anesthesia induction with 8% sevoflurane in N_2O and O_2 elicited epileptiform EEG patterns in adults during both controlled hyperventilation and spontaneous breathing. The incidence of epileptiform EEG was significantly higher with controlled hyperventilation, and rhythmic polyspikes (PSR) and

periodic epileptiform discharges (PED) coincided with hyperdynamic circulatory responses in adults.

HYPERVENTILATION (AIM 4)

Awake hyperventilation induces slow waves in the EEG (134). Hyperventilation–induced EEG changes are not directly related to reduced cerebral blood flow (CBF) (135) or hypoxia (134) but more likely to metabolic changes. Hyperventilation reduces serum potassium concentration, which is directly proportional to arterial carbon dioxide tension (136). Serum calcium concentration also decreases during hyperventilation (137). These electrolyte disturbances could have had an epileptogenic effect and contributed to the abundant epileptiform EEG found in our studies.

Hyperventilation during anesthesia with 1% halothane causes a greater reduction in CBF than does awake hyperventilation (138). However, absolute CBF during anesthesia was greater than awake, because anesthesia increased normocapnic CBF. Sevoflurane has been reported to preserve CBF better than isoflurane during hypocapnia (139). Time–mean middle cerebral artery flow velocity was unchanged when awake and during 1.2 MAC sevoflurane N_2O anesthesia. The cerebrovascular CO_2–reactivity and autoregulation were well maintained during 1.2 MAC sevoflurane with and without 60% nitrous oxide (140). Therefore, hypocapnia is not likely to produce greater vasoconstriction during inhalation anesthesia than when awake. Increased normocapnic CBF during inhalation anesthesia results in greater absolute values in CBF during hypocapnia under anesthesia than during awake hypocapnia. Therefore, reduced CBF to the extent of deficient oxygen supply to the brain is not a feasible explanatory mechanism for the epileptiform EEG in Studies III to V.

However, hyperventilation is commonly used in the diagnostic activation of epileptic phenomena during epilepsy diagnostics, especially in the activation of absence seizures. It is therefore probable that hyperventilation has epileptogenic properties additive to those of sevoflurane itself. This could explain the finding in Study IV, where hyperventilation increased the incidence of periodic and rhythmic epileptiform EEG patterns also when started after a delay of two min, when compared to the incidence of these patterns during spontaneous breathing in Study III. Delaying the onset of hyperventilation by two minutes decreased the incidence of PED by 50% ($P = 0.07$).

DEVELOPMENT OF EEG PATTERNS DURING SEVOFLURANE INDUCTION (AIM 6)

Blinks ceased early in the beginning of induction, and EMG artifact was seldom present. These are distinct advantages compared with awake EEG recording. Development of delta during sevoflurane inhalation induction in children has a different pattern from that of adults. Typically slower (< 2Hz) delta developed first after a short period (few seconds) of beta activity and then turned into 2 to 4 Hz delta. Sevoflurane inhalation induction in adults at a high inspired concentration produced the opposite order of appearance of delta: first, faster 2 to 4 Hz delta appeared and gradually slowed to < 2 Hz delta. Burst suppression occurred more often in children (29%) than in adults (in 17%). Suppression, which was not observed in adults during sevoflurane mask induction, occurred in most children (61%). Suppression often occurred without preceding burst suppression.

The EEG events during similar sevoflurane induction differed between adults and children in the order of the development of delta patterns. The incidence of EEG suppression was over 50% in children whereas none of the adult patients developed suppression. In children, amplitudes of EEG were higher.

NITROUS OXIDE

Nitrous oxide is known to activate the EEG during burst suppression (141), but the effect on interictal spikes during anesthesia is insignificant even in epileptic patients (142). The role of N_2O in eliciting the epileptiform EEG observed is, therefore, assumed to be insignificant. In addition, the presence of N_2O may attenuate brain CO_2 reactivity. Hyperventilation during isoflurane anesthesia with N_2O has been reported to attenuate CO_2 reactivity when compared to a MAC–equivalent anesthesia with isoflurane in oxygen (143). However, since nitrous oxide was used in all the original studies included in this thesis, the effect on EEG of sevoflurane inhalation induction omitting N_2O remains speculative.

PERIODIC EPILEPTIFORM DISCHARGES

PED has been recorded preceding generalized seizure under deep sevoflurane anesthesia (51). It resembles very much the spike–and–wave activity recorded by Rosén et al. (59) preceding generalized seizure of grand mal type under deep enflurane anesthesia and hyperventilation. Sevoflurane induces spikes with isoelectricity in the EEG in cats (49, 144) resembling the PED found in our study. The incidence of spikes in cats increased with increasing concentrations of sevoflurane, and during 5% sevoflurane anesthesia, peripheral electrical stimulation induced GM seizure in cats (49). Thus, this EEG waveform can be the final step before generalized seizure with convulsions. To study sevoflurane–induced PED further, cats could serve as a suitable animal model. A subject of interest would be the possibility of creating in cats a kindling model with repetitive sevoflurane administrations.

Sevoflurane is a GABAergic agent (145). In general, enhancement of GABA functions results in an anticonvulsant effect (146). However, GABAergic activity can be excitatory when the GABA synapse inhibits an inhibitory cell, the result being disinhibitory (147). Inhibitory interneurons of the hippocampus are synchronized by each other (148). Excessive activation of GABA–A receptors in the limbic structures can produce an occurrence of synchronous GABA–mediated potentials (149). These may initiate seizures in rats (150). GABA may also influence in a proconvulsant manner by synchronizing excitatory circuits (151). Systemic administration of GABA–agonists resulted in a marked exacerbation of spike–and–wave discharge duration in a genetic *petit mal* model (152). Fariello and Golden describe an experimental spike–and–wave model in rats induced by intraperitoneal administration of direct GABA–agonist THIP (tetrahydroxyisoxazolopyridine) (99). Enflurane is also a GABAergic agent (153), yet well known for its ability to induce seizures (59).

On the other hand, the identical waveform repetition and regular intercomplex interval typical of sevoflurane–induced PED are rarely seen in EEG recordings except during *petit mal* (absence) seizures. In the absence status epilepticus, a typical spike–and–wave complex appears at 3 Hz rate (154). In Creutzfeld–Jacob disease, herpes simplex encephalitis, and hepatic encephalopathy, the EEG shows periodic discharges of various frequencies (155-157).

Most of the numerous case reports and correspondence communications on sevoflurane–induced epileptiform EEG or convulsions have in common the high sevoflurane concentration during the adverse effect (44, 50-56). The spike–generating EEG effect of high sevoflurane concentration was compared with isoflurane in a study of a population of patients with refractory epilepsy. This property was more prominent with sevoflurane than with isoflurane, but in this special patient group, also high–dose isoflurane increased spike frequency compared with that of awake recordings (158).

JERKING MOVEMENTS DURING SEVOFLURANE INDUCTION

Jerking movements were observed during the early phase of 8% sevoflurane induction in eight out of 90 adult patients and in none of the children. These movements were twitching of the arms and shoulders in six patients, twitching of all extremities in one patient, and plantar flexion in one. These movements lasted approximately 30 seconds and subsided spontaneously. Slow delta with or without spikes was seen in the EEG during these movements and PS, PSR, or PED was seen later in the EEG in these patients. The EEG montage used in the original studies included in this thesis did not contain channels recording directly over the motor cortex, which may in part explain the absence of spikes during movements in some of the patients.

Myoclonus can be divided into those types which are fragments of epilepsy and those which are nonepileptic. Epileptic myoclonus is viewed as the effect of an isolated spike on neurons of the motor system (159). Nonepileptic myoclonus may represent a dyskinetic disturbance caused by the breakdown of the motor control systems of the cerebellum (160). Prominent spiking as in our patients is also seen in connection with myoclonic movements due to hypoclycemia, acute cerebral anoxia, and toxic–metabolic states (160). Myoclonus is associated with massive spike discharges and bursts of bilateral or generalized synchronous polyspikes in patients with primary generalized epilepsy (160).

SUMMARY

While studying the effects of sevoflurane anesthesia on hemodynamics, using the bispectral index (BIS) as a determinant of anesthetic adequacy in day–case anesthesia, unanticipated hyperdynamic circulatory episodes were noted during the induction phase. The induction phase was further investigated in four consecutive studies using time domain analysis of EEG and hemodynamic variables. Altogether, 159 subjects, of whom 127 were adult females, and 32 were children aged 2–12 years, were included.

In the first study, the sevoflurane requirement was evaluated by use of BIS and hemodynamic responses during laparoscopic tubal ligation (LTL). In the following studies, time domain visual EEG analysis, non–invasive arterial pressure monitoring, and heart rate from electrocardiography were used to investigate the effects of sevoflurane on EEG and hemodynamics during induction of anesthesia. A classification of EEG patterns was developed for adults and children.

BIS is an EEG–derived empiric measure of cortical hypnosis. Minimal alveolar concentration (MAC) is a measure of spinal unresponsiveness during anesthesia. When a BIS level of 65 served as a predetermined optimal level of cortical hypnosis during LTL, the ED_{95} of sevoflurane in 66% N_2O and O_2 was approximately 1 MAC. This provided anesthesia with satisfactory hemodynamics and no evidence of awareness.

During induction with 8% sevoflurane in N_2O and O_2, a hyperdynamic circulatory response in adults occurred during controlled hyperventilation but not when the patients were allowed to breathe spontaneously, or when they were hyperventilated with N_2O and O_2 during propofol induction.

Epileptiform EEG was frequently present in adults during 8% sevoflurane induction with controlled hyperventilation, and to a lesser extent, during induction with spontaneous breathing. Hyperdynamic responses coincided with interictal epileptiform EEG, which occurred mostly during controlled hyperventilation.

Factors generating epileptiform EEG were a rapid rise in sevoflurane CNS concentration and patient hyperventilation. The highest increases in heart rates in adults were associated with periodic epileptiform discharges (PED) and rhythmic polyspikes (PSR).

In children, interictal epileptiform EEG (PED, PSR, and suppression with spikes, SSP) was present during sevoflurane induction in 88% with controlled ventilation and in 20% having spontaneous breathing. Apnea occurred in 93% of the children during induction with spontaneous breathing.

EEG features during similar sevoflurane inductions differed between adults and children, some patterns appearing only in adults and some only in children. Amplitudes were higher in children; the order of the appearance of delta differed between adults and children. Suppression was common in children but was not observed in adults.

CONCLUSIONS

The following conclusions can be drawn from the studies:

1. 1 MAC sevoflurane in 66% N_2O in O_2 was sufficient to keep BIS values below 65 and to prevent explicit memory and provide satisfactory hemodynamics during laparoscopic tubal ligation in 95% of the patients.
2. Controlled hyperventilation during 8% sevoflurane induction in N_2O and O_2 provoked hyperdynamic circulatory responses in adults. Spontaneous breathing during similar sevoflurane induction maintained heart rates at the baseline level but decreased blood pressures.
3. Anesthesia induction with 8% sevoflurane in N_2O and O_2 elicited epileptiform EEG patterns in adults both during controlled hyperventilation and during spontaneous breathing. The incidence of epileptiform EEG was significantly higher with controlled hyperventilation, and rhythmic polyspikes (PSR) and periodic epileptiform discharges (PED) coincided with hyperdynamic circulatory responses in adults.
4. Delaying the onset of hyperventilation by two minutes decreased the incidence of PED by 50% ($P = 0.07$).
5. During sevoflurane induction in children, the incidence of interictal epileptiform EEG (PSR, PED, and suppression with spikes, SSP) was higher with controlled ventilation than with spontaneous breathing (88% and 20%, respectively). In the ventilated children, heart rate was significantly higher at two minutes.
6. The EEG events during similar sevoflurane induction differed between adults and children in the order of the development of delta patterns. The incidence of EEG suppression was over 50% in children, whereas none of the adult patients developed suppression. EEG amplitudes were higher in children.

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I consider myself fortunate to have had the privilege to do research under the supervision of Docent Arvi Yli-Hankala. He is a scientist of visionary and creative thinking, enthusiasm, true interest in this topic, and the ability to work very hard. I admire his insight into the mystery of anesthesia. Not only have I learned the basic research skills from him, but also some of his broad–minded manner of approaching various problems, research and others, have changed my thinking. Thanks to him, I've had this exceptionally succinct and consistent research project to carry out as my thesis. On top of it all, working with him has been fun.

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