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Studies on the assessment of the adequacy of anesthesia

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Academic dissertation

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To my family

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Abstract

Beginning in the 1990's, several commercial hypnosis monitoring systems based on the processed electroencephalogram (EEG) have been developed for use during general anesthesia. The assessment of the analgesic component (antinociception) of general anesthesia is an emerging field of research. This study investigated the interaction of hypnosis and antinociception, the association of several physiological variables with the degree of intraoperative nociception, and aspects of Bispectral Index Scale (BIS) monitoring during general anesthesia. In addition, EEG features and heart rate responses during desflurane and sevoflurane anesthesia were compared.

A total of 418 relatively healthy female patients were recruited; 344 were included in the analysis. The skin-electrode impedance values of EEG electrodes and electrocardiography (ECG) electrodes after different skin pretreatment methods were compared in 51 patients. The difference in BIS values obtained with ECG electrodes and EEG electrodes was studied in 26 patients. The difference in BIS values obtained with two sets of EEG electrodes was studied in eight patients. 31 patients were randomized to receive either sevoflurane or desflurane at the highest possible inspired vaporizer concentration (7 % or 18 %). The incidence of epileptiform EEG and the degree of tachycardia during a five-minute study period were compared. 120 ambulatory surgery patients were randomized to receive either sevoflurane–nitrous oxide (N_2O) or isoflurane–N_2O anesthesia. BIS was maintained between 50 and 60 by adjusting the concentration of the volatile agent. The times to home-readiness and to other recovery milestones, and the quality of recovery were compared. 82 patients were randomized to receive a bolus of either propofol or alfentanil in the event of movement during uterine dilatation and curettage. The incidence of recurring movement was compared. The association of heart rate (HR), heart rate variability (HRV), frontal electromyogram (fEMG) power, EEG-, and pulse plethysmography (PPG)-derived variables with surgery-induced movement responses was explored during propofol–N_2O–alfentanil (82 patients, study IV) or sevoflurane anesthesia (26 patients, study V).

ECG electrode impedances after both abrasion paste and alcohol swab skin pretreatment were lower compared to EEG electrodes after alcohol swab ($p \leq 0.001$). ECG electrode impedances after alcohol swab alone were higher than EEG electrode impedances ($p \leq 0.001$). Impedances decreased during anesthesia with all electrode-skin preparation combinations ($p \leq 0.002$). The BIS values registered with ECG electrodes were higher than those registered simultaneously with EEG electrodes (grand average BIS value difference 5.2, 95 % CI [3.5; 7.0], $p < 0.001$ *vs.* 0). The BIS values registered simultaneously with two sets of EEG electrodes were similar (grand average BIS value difference 1.7, 95 % CI [−0.1; 3.4]; $p = 0.061$ *vs.* 0). Epileptiform EEG activity was detected in eight of 15 sevoflurane patients during the rapid increase in the inspired volatile concentration, and in none of the 16 desflurane patients (incidences 0.53 *vs.* 0, $p < 0.001$; difference in incidences 0.53, 95 % CI [0.23; 0.75]). Heart rate increased transiently following the rapid increase in the inhaled desflurane concentration ($[F(5,18) = 16.39, p < 0.001]$). In the sevoflurane group, the increase was slower and more subtle $[F(5,18) = 3.05, p = 0.037]$. No statistically or clinically significant difference in the time to home-readiness between the isoflurane and sevoflurane groups was found (331 min and 347 min, difference −38 min, 95 % CI [−106; 29]). All other early and intermediate recovery parameters were also similar. A propofol bolus of 0.7 mg / kg *i.v.* was more effective than an alfentanil bolus of 0.5 mg *i.v.* in preventing the recurrence of movement

during uterine dilatation and curettage. The incidences of recurring movement were 73 % and 38 % in the alfentanil and propofol groups (difference 35 %, 95 % CI [9 %; 56 %], p = 0.014). According to logistic regression analysis, both the group assignment and the time from the administration of the group drug to the end of the procedure were significantly associated with the probability of recurring movement. HR and several HRV-, fEMG-, PPG-, and EEG-derived variables were associated with surgery-induced movement responses. Movers were discriminated from non-movers mostly by the post-stimulus values *per se* or normalized with respect to the pre-stimulus values. In logistic regression analysis, the best classification performance, evaluated by leave-one-out cross-validation, was achieved with the combination of normalized fEMG power and HR in study IV (overall accuracy 81 %, sensitivity 53 %, specificity 95 %), and with the combination of normalized EEG Response Entropy, R-to-R interval (RRI), and PPG dicrotic notch amplitude in study V (overall accuracy 96 %, sensitivity 90 %, specificity 100 %).

In conclusion, designated EEG electrodes may be superior to ECG electrodes in BIS monitoring. Desflurane may be a safer volatile agent than sevoflurane in patients with a lowered seizure threshold. The tachycardia induced by a rapid increase in the inspired desflurane concentration may present a risk for patients with heart disease. When the administration of isoflurane or sevoflurane is adjusted to maintain BIS values at 50–60 in healthy ambulatory surgery patients, the speed and quality of recovery are similar after both isoflurane–N_2O and sevoflurane–N_2O anesthesia. When anesthesia is maintained by the inhalation of N_2O (67 %) and bolus doses of propofol and alfentanil in healthy unparalyzed patients, movement responses may be best avoided by ensuring a relatively deep hypnotic level with propofol. In the present studies, autonomic and fEMG responses were superior to EEG responses in discriminating movers from non-movers during surgical stimulation. HR / RRI, fEMG, and PPG dicrotic notch amplitude are potential indicators of nociception during anesthesia, but their performance needs to be validated in future studies. Combining information from different sources may improve the discrimination of the level of nociception.

List of original publications

I Seitsonen E, Yli-Hankala A, Korttila K. Are electrocardiogram electrodes acceptable for electroencephalogram bispectral monitoring? Acta Anaesthesiol Scand 2000; 44: 1266–70.

II Vakkuri AP, Seitsonen ER, Jäntti VH, Särkelä M, Korttila KT, Paloheimo MP, Yli-Hankala AM. A rapid increase in the inspired concentration of desflurane is not associated with epileptiform electroencephalogram. Anesth Analg 2005; 101: 396–400.

III Seitsonen ER, Yli-Hankala AM, Korttila KT. Similar recovery from bispectral index-titrated isoflurane and sevoflurane anesthesia after outpatient gynecological surgery. J Clin Anesth 2006; 18: 272–9.

IV Seitsonen ER, Cohen-Laroque ES, van Gils MJ, Korttila KT, Neuvonen PJ, Yli-Hankala AM. Propofol versus alfentanil to prevent movement responses during uterine curettage. Acta Anaesthesiol Scand 2007; 51: 751–8.

V Seitsonen ER, Korhonen IK, van Gils MJ, Huiku M, Lötjönen JM, Korttila KT, Yli-Hankala AM. EEG spectral entropy, heart rate, photoplethysmography and motor responses to skin incision during sevoflurane anesthesia. Acta Anaesthesiol Scand 2005; 49: 284–92.

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Abbreviations

AAI	A-Line Autoregressive Index
ACC	anterior cingulate cortex
AEP	auditory evoked potential
Ag / AgCl	silver / silver-chloride
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (glutamate receptor)
ANOVA	analysis of variance
ANS	autonomic nervous sytem
AOA	adequacy of anesthesia
ApEn	approximate entropy
ASA	American Society of Anesthesiologists
AU	arbitrary units
BIS	Bispectral Index Scale
BSR	burst suppression ratio
CBF	cerebral blood flow
CMR	cerebral metabolic rate
CNS	central nervous system
Corp.	corporation
C_{p50}	effective plasma concentration in 50 % of patients
CSSA	Clinical Signs – Stimulus – Antinociception score
dB	decibels
DC	direct coupling (capacitor-free coupling) between the stages of amplification; direct current; ultraslow potentials
DFT	discrete Fourier transform
Div.	division
DSST	Digit Symbol Substitution Test
$EC_{50/95}$	effective concentration in 50 % or 95 % of patients
ECG	electrocardiography
$ED_{50/95}$	effective dose in 50 % or 95 % of patients
EEG	electroencephalography
e.g.	for example
EMG	electromyography
fEMG	frontal electromyography
EPSP / EPSC	excitatory postsynaptic potential / current
FDA	United States Food and Drug Administration
FFT	fast Fourier transform
GABA	γ-amino butyric acid
h	hours
HBI	heart beat interval
HR	heart rate
HRV	heart rate variability
HF	high frequency; used in HRV analysis of the frequency range 0.15–0.4 Hz
Hz	herz
i.e.	id est; that is
i.m.	intramuscularly
IPSP / IPSC	inhibitory postsynaptic potential / current
i.v.	intravenously
kΩ	kilo-ohms
LC	locus coeruleus

LF	low frequency; used in HRV analysis of the frequency range 0.04–0.15 Hz
LOC	loss of consciousness
MAC	minimum alveolar concentration
MAP	mean arterial pressure
MF	median frequency
µV	microvolts
min	minutes
MLAEP	middle latency auditory evoked potentials
MRF	midbrain reticular formation
NCF	nucleus cuneiformis
NLEO	nonlinear energy operator
NMB	neuromuscular blockade; neuromuscular blocking
NMDA	N-methyl-D-aspartate (glutamate receptor)
NNT	number needed to treat
N_2O	nitrous oxide
NRM	nucleus raphe magnus
NRPG	nucleus reticularis paragigantocellularis
NTS	nucleus tractii solitarii
OAA / S	Observer's Assessment of Alertness / Sedation scale
mOAA / S	modified Observer's Assessment of Alertness / Sedation scale
OR	operating room; odds ratio
P_K	prediction probability
PACU	post-operative care unit
PAG	periaqueductal grey
PBN	parabrachial nucleus
PD	pharmacodynamic
PK	pharmacokinetic
PPG	pulse plethysmography
PSD	power spectral density
PSW	polyspike wave
PTT	pulse transit time
PWR	pulse wave reflex
RE	Response Entropy (in time-frequency balanced spectral entropy)
RMSSD	root of mean squared difference between successive R-to-R intervals
ROC	return of consciousness; Receiver Operating Characteristic
RN	Response index of Nociception
RRI	R-to-R interval; time between two successive beats in ECG
RSA	respiratory sinus arrhythmia
RVM	rostral ventromedial medulla
s	seconds
SD	standard deviation
SD1	SD of the residual against the line y = x in Poincaré analysis
SD2	SD of the residual against the line y' = (–x)+2m, where m is the mean of the variable during the epoch of interest, in Poincaré analysis
SDNN	standard deviation of normal-to-normal intervals
SE	State Entropy (in time-frequency balanced spectral entropy)
SEF95	spectral edge frequency; the frequency below which lies 95 % of the total EEG power
SEP	somatosensory evoked potentials
SSI	Surgical Stress Index
SVmR	skin vasomotor reflex
sVRP	slow ventral root potential
SW	slow wave

TOF	train-of-four neuromuscular stimulation
TSS	total surgical stress
ULF	ultralow frequency; used in HRV analysis of the frequency range < 0.003 Hz
v.	version
VAS	Visual Analog Scale
VLF	very low frquency; used in HRV analysis of the frequency range 0.003–0.04 Hz
VLM	ventrolateral medulla
vs.	versus
ZXF	zero crossing frequency

Introduction

Multiple anesthetic agents, individually variable pharmacokinetic and pharmacodynamic phenomena and the continuously changing intensity of surgical stimulation interact in a complex way to determine the adequacy of general anesthesia. The goal of balanced general anesthesia is to safely provide a state of unconsciousness with lack of memory formation and unresponsiveness to noxious stimuli, thus maintaining good conditions for surgery. In order to maximize patient safety and comfort and to facilitate an uncomplicated recovery it is necessary to avoid both underdosing and overdosing of anesthetic agents. To this end, development of methods for monitoring anesthetic effect with respect to different components of general anesthesia is needed.

The concept of balanced anesthesia, which refers to the achievement of different anesthetic goals by the administration of specific drugs in suitable proportions, originated in the first half of the 20th century. The triad of hypnosis, analgesia (antinociception), and muscle relaxation was first presented by Rees and Gray (Rees and Gray 1950). Different anesthetic end-points result from actions at different sites. The cortex, thalamus, and reticular formation probably participate in producing consciousness and are depressed by anesthetics. The amount of ascending afferent sensory information influences the arousal level of the brain. Analgesic agents are more effective than hypnotic agents in blocking cardiovascular responses. Low concentrations of hypnotics may even be hyperalgesic. Movement is blocked largely via anesthetic action in the spinal cord. Cortical electrical activity is more sensitive to anesthetic agents than subcortical activity. Movement responses to noxious stimulation may occur despite marked cortical electroencephalogram (EEG) depression. If the brain is selectively anesthetized and concentrations in the torso are low, much higher brain anesthetic concentrations are required to produce immobility than when systemic administration is used. The dose-response curve of opioid analgesics for reducing hypnotic requirements is steepest for blocking autonomic responses, somewhat less steep for blocking movement responses, and the most shallow for inducing unconsciousness (Antognini and Carstens 2002).

The interaction of hypnotic agents and opioid analgesics during general anesthesia can be schematically described by a hierarchical model introduced by Bouillon and colleagues. Initially, a noxious stimulus is processed at subcortical levels of the central nervous system (CNS), where opioids attenuate the nociceptive signal. The attenuated signal is then projected to the cortical level, where hypnotic agents act to suppress arousal (Bouillon *et al* 2004).

The incidence of awareness in the general surgical population is 0.1 %–0.2 %, and tends to be greater in patients with neuromuscular blockade during surgery. Recollection of intraoperative events may be delayed beyond the immediate perioperative period, or may fade with time. Intraoperative awareness may lead to sustained psychological symptoms (Sandin *et al* 2000). Beginning in the 1990's, several commercial hypnosis monitoring systems based on processed EEG have been developed, including the Bispectral Index Scale® (Aspect Medical Systems, Inc., MA, USA) and time-frequency balanced spectral entropy (M-Entropy®, GE Healthcare). Consciousness may in itself be more of an on-off phenomenon than a continuous variable. Hypnosis monitors have the potential to improve the quality of anesthesia by decreasing the probability of both unintentional consciousness and overdosing of anesthetics and by improving the recovery profile. The information they provide must be interpreted in the light of the technical basis of the devices, the technical and physiological

sources of error, the prevailing drug concentrations, the physiology of the electrical activity in the brain, consciousness and nociception, and the interactions of the components of anesthesia (Bonhomme and Hans 2004). Monitoring the hypnotic state via processed EEG may alert clinicians to equipment malfunction or other discontinuities in anesthetic delivery earlier than changes in vital signs (Luginbühl and Schnider 2002, Mathews *et al* 2005).

The stress response to surgery comprises the secretion of pituitary and adrenal cortical hormones, the activation of the sympathetic nervous system, and an immunological acute phase reaction with production of cytokines by activated leucocytes, fibroblasts and endothelial cells, and acute phase proteins by the liver. The endocrine response leads to salt and water retention and mobilization of energy substrates via catabolism. The stress response is activated by afferent neural input from the site of injury to the hypothalamus. The magnitude and duration of the stress response is proportional to the extent of the surgical injury. Opioids and especially neuraxial blockade attenuate the stress response, although the neuroendocrine responses to upper abdominal and thoracic surgery have not been abolished reliably by any anesthetic technique. Also, anesthesia has little effect on the cytokine response to surgery (Desborough 2000).

Thus, even in the unconscious anesthetized patient nociception induces several physiological responses, which may have persistent effects post-operatively, leading to hyperdynamic circulation, hypermetabolism, catabolism, immunosuppression, hypercoagulability, and disturbances in pulmonary and gastrointestinal function (Carr and Goudas 1999, Kehlet and Dahl 2003). A multimodal approach to reduce perioperative stress may have several advantageous effects on recovery, with the potential to reduce the risks of cardiac, pulmonary, thromboembolic and infective complications, gastrointestinal and cerebral dysfunction, catabolism and decreased functional capacity (Kehlet 1997, Wilmore 2002).

In addition to autonomic and endocrine reactions, surgical stimulation may elicit motor responses, despite unconsciousness. The assessment of the antinociceptive component of general anesthesia is an emerging field of research. Possible indicators of the nociceptive-antinociceptive balance during anesthesia are the EEG arousal reactions (Wilder-Smith *et al* 1995, Guignard *et al* 2000, Hagihira *et al* 2004b), fEMG activation responses (Viertiö-Oja *et al* 2004), the middle latency auditory evoked potentials (MLAEP) (Nishiyama and Hanaoka 2004, Bonhomme *et al* 2006), the somatosensory evoked potentials (SEP) (Kochs *et al* 1990), changes in the palmar skin electrical conductance (Storm *et al* 2002, Storm *et al* 2005, Gjerstad *et al* 2007), reflex pupillary dilation responses (Larson *et al* 1993, Larson *et al* 1997, Barvais *et al* 2003, Constant *et al* 2006), changes in the superficial skin perfusion (Shimoda *et al* 1998a, Shimoda *et al* 1998b) and changes in the pulse plethysmography (PPG) waveform (Luginbühl *et al* 2002). Recently, an index for the assessment of surgical stress, based on a linear weighted combination of the normalized PPG amplitude and the heart beat interval, has been introduced (Huiku *et al* 2007) and is currently undergoing clinical validation.

The aim of the present study was to investigate the technical constraints and benefit of EEG BIS monitoring in ambulatory surgical patients. In addition, possibilities to monitor the nociceptive-antinociceptive balance during general anesthesia, and the interaction between hypnosis and antinociception were explored in order to contribute to the development of the assessment of the adequacy of anesthesia. Finally, the relationship between hemodynamic responses and EEG changes during the administration of high concentrations of sevoflurane or desflurane was investigated.

Review of the literature

General anesthesia

The idea that general anesthetics act on brain lipids was presented as early as 1847 by von Bibra and Harless. In 1901 Meyer and Overton independently observed that the potency of volatile agents depends on their lipid solubility (Mashour 2006). In 1984 Franks and Lieb discovered that several anesthetic agents inhibited an enzyme, a protein compound, by a competitive mechanism and concluded that general anesthetics bind to specific receptors (Franks and Lieb 1984).

Based on current knowledge, the structurally very different general anesthetics act on ligand-gated (γ-amino butyric acid $(GABA)_A$, glycine, glutamate, nicotinic acetylcholine and serotonin receptors) and voltage-gated K^+, Na^+ and Ca^{++} channels on neuronal membranes. Some non-voltage gated K^+ channels, such as those responsible for maintaining the resting membrane potential, are also sensitive to anesthetics. They may also act directly on cytoplasmic proteins. Metabotropic receptors, which partly bind the same ligands as the ligand-gated ion channels and modulate synaptic transmission, may also be affected by anesthetic agents. In addition to postsynaptic effects, anesthetics can act on presynaptic targets such as the voltage-gated Ca^{++} channels, which regulate transmitter release. In addition, it is possible that anesthetics change the lipid micro-environment of ion channel proteins, and thus their function. Anesthetic action on synaptic transmission is clinically much more important than their effect on axonal conduction. Neurons are not exclusive targets to anesthetic agents. Glia, skeletal and cardiac muscle cells and cells of the endocrine and immune systems are also affected (Urban 2002, Århem *et al* 2003, Mashour *et al* 2005, Hameroff 2006).

Anesthetic effects depend on the connections and feedback in neural networks. A depressant anesthetic action on the molecular level can result in inhibition, excitation, or no effect at higher levels of integration within the CNS. Also, at the subcellular level it is difficult to predict the effect of agonist binding on long second-messenger cascades (Urban 2002). Anesthesia may be associated with both decreased and increased activity of and decreased and increased coherence between neurons (John *et al* 2001, Århem *et al* 2003, Hameroff 2006).

General anesthetics increase the sensitivity of GABA receptors to bind agonist and prolong the inhibitory postsynaptic currents induced by GABA. Conversely, they reduce excitatory postynaptic currents by causing frequent closure or blockade of the opening of the acetylcholine receptor ion channel. Neuronal nicotinic acetylcholine receptors are inhibited by inhaled anesthetics at low concentrations which cause amnesia but not immobility (Campagna *et al* 2003). Whereas propofol, pentobarbital and midazolam decrease the release of noradrenaline and acetylcholine from the rat brain, ketamine, N_2O, and xenon, which are potent N-methyl-D-aspartate (NMDA) receptor inhibitors, increase the release of these neurotransmitters. Ketamine and N_2O stimulate the sympathetic system, whereas xenon is sympatholytic. Ketamine and N_2O increase the cerebral metabolic rate (CMR) and cerebral blood flow (CBF). Xenon also seems to increase CBF (Hirota 2006).

Acetylcholine and glutamate receptor agonists are excitatory at the locus coeruleus (LC), a major noradrenergic nucleus located in the midbrain (pons). Antagonists at these receptors act as hypnotics. GABA, opioid and α_2-receptor agonists are inhibitory when injected to the LC. These agents have sedative properties and reduce the requirements for volatile anesthetics (Rosow 1997). Different anesthetic agents

can act preferentially in specific regions of the central nervous system or on specific subsets of neurons to achieve the anesthetic end-points, despite the interaction between different areas of the central nervous system. The mechanism of general anesthesia may be related to the disruption of the so-called cognitive binding, an integration process thought to occur in the brain within and across sensory modalities. Anesthesia-induced unbinding would occur from the cellular level to the neural network level, with loss of connectivity between different brain structures (John and Prichep 2005, Mashour *et al* 2005, Mashour 2006).

Induction of anesthesia is associated with reduced CBF and CMR both globally and in various specific regions of the cortex, thalamus and brainstem (Urban 2002, Campagna *et al* 2003, John and Prichep 2005). It seems that low doses of anesthetic agents primarily affect sensory and association cortices, whereas with higher doses subcortical structures, notably the thalamus and MRF, are suppressed (Alkire *et al* 2000, Heinke and Schwarzbauer 2002). The thalamus and the brainstem reticular activating system are key structures in the regulation of vigilance. During sedation and transition to unconsciousness, propofol preferentially decreases blood flow in areas linked to the control of consciousness, sensory (especially visual) associative functions and autonomic control (Fiset *et al* 1999).

Episodic memory is lost at lower anesthetic concentrations than those which induce unconsciousness (Glass *et al* 1997, John and Prichep 2005). At low anesthetic concentrations implicit memory formation may be present, while explicit memory is blocked (Antognini and Carstens 2002).

Perceptual tasks are associated with widespread phase-locked EEG γ oscillations. Anesthesia may interrupt the coherent cortico-thalamocortical resonance, as exemplified by the disappearance of the auditory steady-state 40 Hz response (John and Prichep 2005). Loss of consciousness seems to involve disruption of EEG γ band phase synchrony between frontal and posterior brain regions (John *et al* 2001, Hameroff 2006). The processing of fragmentary sensory data may continue, whereas the formation of complex representations is lost (John and Prichep 2005, Mashour *et al* 2005).

The NMDA receptor, which strengthens the synapses between simultaneously active neurons, has been hypothesized to be the ultimate target of all anesthetic agents. States of consciousness would emerge automatically in sufficiently large neural networks containing active NMDA receptors, resulting in coherent neuronal assemblies (Flohr 2006).

Alkire and colleagues suggested that a hyperpolarization block of the thalamus may underlie loss of consciousness, resulting in a burst-firing pattern of thalamocortical cells and high voltage, slow wave cortical electrical activity. Anesthetics may exert direct hyperpolarizing effects on thalamocortical cells, decrease excitatory input (cholinergic, glutamatergic, aminergic), or enhance inhibitory input, interfering with the reticular-thalamic activating system. Subcortical structures may be required for wakefulness, whereas cortical areas may provide the perceptual content of consciousness (Alkire *et al* 2000).

Nociception and anesthesia

In peripheral tissues, noxious stimuli (mechanical, thermal, or chemical) activate nociceptors, which transmit electrical signals along thinly myelinated Aδ- or unmyelinated C-fibers to the dorsal horn of the spinal cord. The primary afferents synapse with either ascending projection neurons or interneurons. A simple spinal reflex arc is formed by a primary afferent, one or more excitatory interneurons, and a motoneuron. Information is conveyed from the spinal nociceptive neurons to the thalamus and to the brainstem via the spinothalamic, spinoreticular, and spinomesencephalic tracts, situated in the anterolateral quarter of the spinal cord. The reticular formation, a key structure in the modulation of arousal, in turn is connected with the thalamus. Also, spinal projections to the periaqueductal gray (PAG) in the mesencephalon, the parabrachial nucleus (PBN) in the pons and to the ventrolateral medulla (VLM) exist (Brooks and Tracey 2005, Tracey 2005). Direct connections between the

spinal cord and the hypothalamus form the spinohypothalamic tract (Giesler *et al* 1994, Brooks and Tracey 2005). The thalamic nuclei project to numerous cortical areas. Roughly, the lateral thalamocortical system is involved in the sensory-discriminative aspect of nociception, whereas the medial system is involved in the affective and motivational integration of nociceptive information (Kalso 2002).

Both visceral and somatic nociceptive input activate the nucleus cuneiformis (NCF), a nucleus of the reticular formation, the adjacent PAG, and areas in the dorsolateral pons, consistent with the LC medially and PBN laterally. The NTS, the nucleus gracilis, and the dorsal reticular nucleus of the medulla, situated in the left dorsolateral medulla, are activated predominantly by visceral nociceptive signals (Dunckley *et al* 2005). Spinal and trigeminal nociceptive input and visceral afferent information converge on the central autonomic network including the insular cortex and the anterior cingulate cortex (ACC), the central nucleus of the amygdala, several areas of the hypothalamus, PAG, PBN, VLM, the nucleus of the solitary tract (NTS) and the raphe nuclei (rostroventromedial medulla, RVM). These areas have numerous interconnections and generate stimulus-specific autonomic, endocrine, motor, and arousal responses. They project to preganglionic sympathetic and parasympathetic neurons, which also receive direct input from nociceptive afferents of the same spinal segment. They also project to the spinal cord dorsal horn and participate in modulating nociceptive processing (Benarroch 2006). The sympathetic and parasympathetic preautonomic neurons are functionally specialized, but may coexist in the same hypothalamic and brainstem nuclei (Buijs *et al* 2003).

Nociceptive input induces an increase in blood pressure, which is mediated by neurons in the rostral ventrolateral medulla (Stornetta *et al* 1989, Allen and Pronych 1997). They project to the sympathetic preganglionic neurons in the intermediolateral nucleus of the thoracic spinal cord and also provide tonic excitation, which serves to maintain resting blood pressure (Morrison *et al* 1988, Stornetta *et al* 1989). The pressor response may be dominant over a simultaneous depressor response (Allen and Pronych 1997). The depressor response, mediated by the ventrolateral PAG, is characteristic of deep somatic or visceral nociception (Keay *et al* 2000).

The brainstem is critically involved in the immediate reactions to noxious stimulation. During tonic stimulation, the autonomic response may habituate (Petrovic *et al* 2004). The neurons in the brainstem reticular formation project to the nucleus facialis, which provides motor innervation to the facial muscles (Sun and Panneton 2005). The neurons in the medial reticular formation, along with the raphe nuclei and nucleus retroambiguus, also project to motoneurons innervating the abdominal muscles (Billig *et al* 2001). The PAG may participate in integrating the somatic and cardiovascular defense reactions. The hypothalamus coordinates complex response patterns effected by other areas of the basal forebrain, the brainstem, and the spinal cord (Saper 2002).

Increased circulating catecholamines are associated with increased arousal (Andrzejowski *et al* 2000). This may be the result of β-receptor activation in the medial septal region of the basal forebrain (Berridge and Foote 1996, Berridge *et al* 1996), but increased clearance or redistribution of anesthetics due to increased cardiac output may also play a role (Andrzejowski *et al* 2000).

The activation of the noradrenergic LC by nociceptive input, as well as sudden noises or other non-noxious stimuli, is associated with increased attention and arousal (Kalso 2002, Leone *et al* 2006). Opioid analgesics inhibit the LC. They stimulate the PAG and nucleus reticularis paragigantocellularis (NRPG). These in turn activate the nucleus raphe magnus (NRM), a key structure in the descending modulation of nociceptive transmission in the dorsal horn (serotonin, encephalin). The LC is also involved in descending modulation (noradrenalin) (Kalso 2002). The descending pain modulatory system causes either inhibition or facilitation of nociceptive processing, depending on circumstances. The PAG, NCF, RVM, PBN, and the dorsal reticular nucleus of the medulla may be involved in the generation and maintenance of central sensitization states and

hyperalgesia (Tracey 2005, Leone *et al* 2006).

The μ opioid receptors are widely distributed in the forebrain, brainstem and the superficial layers of the spinal cord dorsal horn. They are located both pre- and postsynaptically, and in both extrasynaptic and synaptic regions. They may be involved in the modulation of both transmitter release and the firing pattern of postsynaptic neurons, resulting in inhibition of nociceptive neurotransmission (Glaum *et al* 1994, Grudt and Williams 1994, Cheng *et al* 1996, Ding *et al* 1996, Zhang *et al* 1996, Kohno *et al* 2005). The μ opioid agonists preferentially inhibit the calcium channels on small unmyelinated nociceptors (Taddese *et al* 1995). They directly hyperpolarize cells in the substantia gelatinosa by increasing potassium conductance (Yoshimura and North 1983, Grudt and Williams 1994).

In a study on the superficial layer of the rat cervical spinal cord, the relative proportions of μ, δ and κ opioid receptors were 70 %, 23 %, and 7 %. It was estimated that 76 %, 61 %, and 53 % of these were located presynaptically in the afferent fibers (Besse *et al* 1990). Different opioid receptor subtypes may be involved in the modulation of different nociceptive modalitites (Schmauss and Yaksh 1984). Both μ and δ opioid agonists inhibit the responses of spinal cord dorsal horn nociceptive neurons to electrical stimulation of the Aδ-fibers and C-fibers. The responses mediated by C-fibers are more markedly and consistently depressed than those mediated by Aδ-fibers (Wang *et al* 1996).

Opioids depress the slow ventral root potential, which is associated with nociception, especially the late component mediated by metabotropic receptors. Their effects on fast glutamate mediated neurotransmission (AMPA receptors are responsible for the monosynaptic reflex, and NMDA receptors mediate the early component of the slow ventral root potential) in the ventral horn are small. Opioids slightly depress the inhibitory (antinociceptive) dorsal root potential (Feng and Kendig 1995). The spinal cord is an important site for opioid action (Yaksh and Rudy 1977). Opioids also act on supraspinal targets (Vigouret *et al* 1973, Yaksh *et al* 1976, Takagi *et al* 1978, Wagner *et al* 2001). Endogenous opioid peptides participate in mediating the descending inhibition of nociceptive transmission (Budai and Fields 1998). Opioids may also have peripheral antinociceptive effects on local opioid receptors (Stein *et al* 1990a, Stein *et al* 1990b).

Increasing opoid concentrations attenuate the hemodynamic response to tracheal intubation. The same applies to increasing propofol concentrations, although to a lesser degree (Luginbühl *et al* 2006). Rantanen and colleagues found that during anesthesia with propofol titrated to state entropy (SE) 50 and 1 ng / ml (effect-site) remifentanil, a 30 s tetanic electrical stimulus induces a significantly greater RRI decrease than a 5 s stimulus, comparable to that induced by skin incision. At remifentanil concentrations 3 ng / ml and 5 ng / ml the RRI responses to a 30 s tetanic stimulus and skin incision are very small (Rantanen *et al* 2006b). A modest dose of fentanyl decreases the concentration of isoflurane or desflurane, combined with N_2O, required to block adrenergic responses to skin incision by approximately 60 % (Daniel *et al* 1998).

The concentration of inhaled anesthetics required to block cardiovascular responses is much higher than that required to block movement responses to noxious stimulation. Also, more interindividual variability in the level of anesthesia needed to block cardiovascular responses than in that needed to block movement responses exists. In general, the higher the sympathetic activity in the awake state, the greater the change in cardiovascular variables (and plasma noradrenalin levels) at induction of anesthesia (Roizen *et al* 1981). Similarly to movement responses, anesthetic effects at the level of the spinal cord are probably important in mediating the attenuation of cardiovascular responses (Antognini and Berg 1995).

Anesthetic actions in the spinal cord include the suppression of the excitability of motoneurons, either directly or indirectly, and the suppression of the responses of nociceptive neurons, with varying molecular targets. In addition to immobility, antinociception is largely produced at the spinal level but is subject to supraspinal influences. The thalamus and the anterior cingulate cortex appear to be targets

for opioid and N_2O analgesia (Urban 2002).

Increasing isoflurane concentrations in the brain attenuate the noxious-stimulus evoked activity in spinal dorsal horn nociceptive neurons in the presence of relatively low spinal cord isoflurane concentrations, possibly by changing the balance of descending inhibition and facilitation. With high spinal cord isoflurane concentrations, the supraspinal effects are masked by the direct spinal isoflurane effect (Antognini *et al* 1998, Jinks *et al* 1999). Isoflurane depresses the nociception-related slow ventral root potential in the isolated rat spinal cord. At concentrations close to those required for general anesthesia, the monosynaptic reflex is also depressed (Savola *et al* 1991).

Subanesthetic concentrations of propofol are hyperalgesic by heat stimulation (Hofbauer *et al* 2004) and mechanical pressure stimulation (Petersen-Felix *et al* 1996). Subanesthetic concentrations of propofol do not increase the threshold of the nociceptive motor reflex to repeated electrical stimulation. The sedation produced by propofol can influence nociceptive electrophysiological responses (Petersen-Felix *et al* 1996). After loss of consciousness during propofol sedation, noxious stimulation may still activate the insular cortex, involved in autonomic and homeostatic regulation, even though increased activity in the thalamus is lost (Hofbauer *et al* 2004).

Propofol decreases the metabolic activity in both the rat brain and spinal cord (Cavazzuti *et al* 1991). Propofol has a direct depressing effect on the activity of spinal cord dorsal horn nociceptive neurons at noxious mechanical stimulation (Antognini *et al* 2000c). It blunts the EEG and midbrain responses to noxious mechanical stimulation by both a direct brain effect and an indirect spinal effect (Antognini *et al* 2001). In the isolated rat spinal cord, propofol inhibits nociceptive-related neurotransmission at concentrations near the general anesthetic level, acting like a $GABA_A$ agonist (Jewett *et al* 1992).

It has been suggested that the δ opioid receptor (Nadeson and Goodchild 1997) and the glycine receptor (Dong and Xu 2002) are involved in propofol-induced antinociception in the spinal cord in addition to the $GABA_A$ receptor. Propofol seems to have a suppressive effect on the L-type calcium channel, which may play a role in spinal nociceptive and motor circuits (Guertin and Hounsgaard 1999). Spinal neuronal responses to both noxious mechanical and heat stimuli and non-noxious mechanical stimuli are depressed by propofol in rats (Sun *et al* 2004) and cats (Uchida *et al* 1995). In a rat model, propofol attenuated spinal sensitization (O'Connor and Abram 1995). Propofol and alfentanil both have the capacity to depress the sVRP, and subclinical concentrations of propofol significantly enhance the effect of alfentanil (Feng and Kendig 1997).

Propofol does depress nociceptive signal transmission in the spinal cord, but to a significantly lesser extent than sevoflurane (Matute *et al* 2004). In clinically relevant concentrations, the capacity of propofol to depress spinal neuronal activity is less than that of sevoflurane, possibly due to more restricted molecular targets (Grasshoff and Antkowiak 2004). Suppression of spinal cord reflex function by propofol may occur more slowly than suppression of forebrain function, and with doses insufficient to produce unresponsiveness to noxious stimulation (Baars *et al* 2006a, Baars *et al* 2006b). Apparently propofol causes complex dose-dependent effects in different parts of the CNS. These may also vary between different stimulus modalitites.

Surgical nociception may lead to both spinal sensitization and descending inhibition of nociceptive processing. A rebound central sensitization may occur after the cessation of post-operative opioid analgesia in patients who receive nonanalgesic anesthesia. Objective changes in sensory processing after surgery are only weakly correlated with subjective pain intensity or analgesic consumption (Wilder-Smith 2000).

The adequacy of anesthesia

Eger and Sonner argue that the anesthetic state caused by inhaled agents is defined by reversible amnesia and immobility. They hold that unconsciousness cannot be directly measured,

unless it is accepted that the loss of awareness (loss of responses to command) implies unconsciousness. Autonomic reflexes are often functional at clinically relevant anesthetic concentrations and muscle relaxation is not always present. Analgesia, a subjective experience, cannot be verified (Eger and Sonner 2006). A similar view was presented by Antognini and Carstens, who define general anesthesia as a combination of unconsciousness, amnesia, and immobility. In their opinion, analgesia may indirectly contribute to the state of general anesthesia and may be important for patient management, but since no conscious perception is normally present during general anesthesia, analgesia is not an essential component. Likewise, hemodynamic stability may be important for certain patient groups, but is not an essential component of general anesthesia (Antognini and Carstens 2002).

Autonomic, endocrine and motor reflex responses during anesthesia, however, are linked to nociception, which can be defined as the unconscious processing of noxious stimuli during anesthesia. They can be suppressed by analgesic drugs, most commonly opioids, without using exceedingly large doses of hypnotic drugs. Hypnotic drugs are used to achieve loss of consciousness and recall, whereby the patient is unable to respond to or remember a non-noxious (or noxious) stimulus. Muscle relaxation, which may be necessary for certain surgical procedures, is sometimes regarded as a component of balanced anesthesia. It can be achieved with either a sufficient amount of hypnotic and analgesic drugs, or by neuromuscular blocking agents.

Tammisto and colleagues were among the pioneers in establishing the optimal combination of hypnotic and analgetic agents in terms of not only unconsciousness, but also antinociception, *i.e.* tolerance of surgical stimuli (Tammisto *et al* 1980, Tammisto and Aromaa 1982). Tammisto and Olkkola demonstrated the negative linear relationship between the end-tidal enflurane concentration and the level of neuromuscular blockade necessary to produce adequate surgical muscle relaxation during upper abdominal surgery (Tammisto and Olkkola 1995).

Opioids alone do not reliably produce unconsciousness, even at high doses, although increasing opioid doses reduce the requirements for hypnotic agents (Jhaveri *et al* 1997). Unresponsiveness to verbal or other stimuli does not always imply unconsciousness. The level of opioid analgesia affects the level of hypnosis at loss of responsiveness (Jensen *et al* 2004).

The level of hypnosis during surgery is determined by the interaction of hypnotic drugs, analgetic drugs, and the intensity of noxious stimulation (Bouillon *et al* 2004, Hagihira *et al* 2004b). Increasing surgical stimulation shifts the individual dose-response curve toward higher anesthetic concentrations (Heier and Steen 1996). Hagihira and colleagues have advocated the maintenance of unconsciousness during surgery with steady concentrations of hypnotic agents and adjusting the level of antinociception to the changing levels of surgical stimulation (Hagihira *et al* 2004b).

Different anesthetic agents have varying potencies to produce each of the components of anesthesia (Heier and Steen 1996). Kissin concluded that the components of anesthesia, whether produced by a single agent or multiple drugs, represent different pharmacological actions. Ideally, the level of each component should be separately assessed (Kissin 1993).

In unparalyzed patients, the observation of movement responses to surgery is the best clinical measure for detecting impending awareness. Hemodynamic responses do not correlate well with end-tidal concentrations of volatile anesthetic agents, and the relationship between autonomic and movement responses during inhalation anesthesia is poor. Autonomic responses are not only affected by the depth of anesthesia but also by cardiovascular drugs, the circulating blood volume, acid-base status, and cardiac contractility (Heier and Steen 1996). Thus, the correlation between the hypnotic level and somatic and hemodynamic responses during anesthesia is not very good (Gan *et al* 1997, Luginbühl *et al* 2003).

In an effort to improve the objective assessment of the adequacy of anesthesia, several different hypnosis monitoring techniques based on processed EEG have been developed

and are commercially available. Apart from BIS® (Aspect Medical Systems, Inc., MA, USA) and M-Entropy® (GE Healthcare), these include the Patient State Index (PSA®, Hospira Inc., IL, USA), SNAP II® (Everest Biomedical Instruments Company, MO, USA), Narcotrend® (Hannover, Germany), and the Cerebral State Index (CSM®, Danmeter A/S, Odense, Denmark). Earlier EEG monitoring systems included the Anesthesia and Brain Activity Monitor (ABM®, Datex/Instrumentarium Corp., Helsinki, Finland), the Cerebral Function Analysing Monitor (CFAM®) and the Advanced Depth of Anaesthesia Monitor (ADAM®) (Sebel *et al* 1983, Edmonds and Paloheimo 1985, Thomsen *et al* 1989).

The A-Line Autoregressive Index (AAI®, Danmeter A/S, Odense, Denmark) is based on the analysis of the middle latency auditory evoked potential waveforms. The composite AAI index combines information from both MLAEP and the spontaneous EEG. Gajraj and colleagues proposed that the AEP_{Index}, also derived from the morphology of the MLAEP waveform, provides a measure of the overall balance between surgical stimulation, analgesia, and hypnosis (Gajraj *et al* 1999). Recently ocular microtremor, a high-frequency, low-amplitude physiological tremor driven by oculomotor neurons embedded in the brainstem reticular formation, has been suggested to reflect the adequacy of anesthesia (Heaney *et al* 2004).

In general, the curves relating EEG and MLAEP variables to clinical end-points are relatively shallow, with large interindividual variability and suboptimal sensitivity and specificity (Heier and Steen 1996). Schwilden noted that in addition to the strength of association between a monitoring measure and the clinical end-points, the signal-to-noise ratio is important for the applicability of that measure. He suggested that in the future the intensity of surgical stimulation needs to be incorporated into pharmacokinetic (PK)-pharmacodynamic (PD) models to describe the relationship between electrophysiological variables and clinical anesthesia (Schwilden 2006).

Electroencephalography

The physiological basis of the electroencephalogram

The neocortex consists of six neuronal layers or lamina, histologically differentiated according to the dominant cell type. Two prevalent cell types are the large pyramidal cells and the smaller granular cells, the relative density of which varies in different cortical regions. In addition to this laminar arrengement, the cells are organized into vertical functional units or columns. The pyramidal cells have prominent apical dendrites, which extend to the cortical surface. Other cell types also display long dendritic and axonal arborizations (Kahle 1986). The neurons interact via synapses which cover the somata, the dendrites, and the axon hillocks in large numbers (Speckmann and Elger 1999).

Synaptic activity causes alterations in the resting cell membrane potentials: either excitatory (depolarizing, EPSP) or inhibitory (hyperpolarizing, IPSP) postsynaptic potentials. Primary transmembrane ionic currents induce secondary ionic currents along the cell membrane both intra- and extracellularly. Extracellular potentials are called field potentials. The glia cells may amplify the field potentials (Speckmann and Elger 1999). Ionic currents spread from the source neurons throughout an essentially liquid medium to the skin (volume conduction). The spatial and temporal summation of numerous EPSPs or IPSPs result in field potentials large enough to be detected on the surface of the skull (Creutzfeldt *et al* 1966). Conduction through the cerebrospinal fluid, the skull and the scalp leads to weakening and spatial smearing of the regional voltage differences (Rampil 1998). Summation of asynchronous potentials tends to result in a relatively low-amplitude EEG signal, whereas synchronous oscillations are associated with a higher amplitude. Under normal metabolic conditions, the dominant frequency and the amplitude of the EEG signal are inversely correlated (Edmonds *et al* 2004a).

Cortical dendrites are also interconnected via electrical gap junctions, which may partici-

pate in mediating γ frequency synchronization in membrane potentials. Coordinated activity in dendritic proteins may support γ synchrony, thought to be critical for consciousness (Hameroff 2006).

Signal transduction and registration of the electroencephalogram

Electrodes are needed to transduce the biopotentials into voltage changes recordable with electronic equipment. Typically, the gap between the metal conductor of the recording apparatus and the skin is bridged with electrolyte jelly. A continuous exchange of ions takes place at the metal-electrolyte and skin-electrolyte interfaces, with an excess charge in the solution. This results in the formation of an electrical double layer, with a steady DC potential and a certain capacitance. These DC potentials may interfere with the recording of the EEG signal (Kamp and Lopes da Silva 1999). The DC potentials formed at the metal-electrolyte and skin-electrolyte interfaces are connected in series. Ideally, the DC potentials of separate electrodes should be equal. In practice, a certain potential difference, the DC offset voltage, exists between different electrodes. When using similar, good quality electrodes, attached in the same way, the DC offset voltage is relatively small. The DC potential, resistance, and capacitance of the metal-electrolyte interface depend on the metal used, the electrolyte composition, the temperature, and the magnitude and frequency of the current. The stability of the metal-electrolyte interface can be increased by a suitable salt coating. The Ag / AgCl electrode is frequently used for EEG recordings due to its favorable electrical properties.

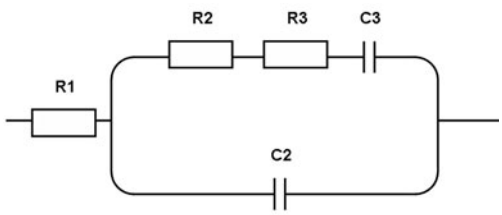

Figure 1. A simplified diagram of the impedance of a metal-electrolyte interface. R1 = electrolyte resistance, R2 = electrical double layer resistance, C2 = electrical double layer capacitance, R3 and C3 = time- and frequency-dependent diffusion impedance. Modified from Kamp and Lopes da Silva 1999.

At the skin-electrolyte interface, the resistance and capacitance are strongly influenced by the width of the epidermis and the magnitude of the current. The dry outermost layer of the skin is a poor conductor. The resistance of the skin-electrolyte junction can be reduced by using a high concentration of NaCl (5 %-10 %), and by scraping off the *stratum corneum* of the skin. Careful preparation of the skin and the use of electrode jelly also serve to reduce electrode movement artifacts. The resistance and capacitance in different parts of the body fluid-skin-electrolyte-electrode complex are components of the impedance (figure 1), which characterizes the relationship between applied voltage and resulting current. The frequency-dependent component of the impedance is inversely proportional to the square root of frequency (Kamp and Lopes da Silva 1999).

The most commonly used method of electrode placement is the International 10–20 System (figure 2) (Report of the committee on methods of clinical examination in electroencephalography 1958), where specific relative distances between bony landmarks (nasion, inion, and preauricular points) are used to make the electrode placement comparable between patients and separate measurements. The electrodes are designated with a number (odd numbers on the left, even numbers on the right) and a letter (or letters) referring to the anatomical area. Either referential or bipolar recording can be used. In the former, all electrodes are referred to a single common electrode, one common electrode on each side of the head, or the electrically combined activity of two or more electrodes. The particular choice of reference influences the resulting signal. For example, temporal cortical activity may be reflected on the earlobe reference. Bipolar recordings measure voltage between specified electrode pairs. A voltage, which is negative at input one (active electrode in referential montage) relative

to input two, is presented as an upward deflection of the EEG tracing. If a transient signal is similar in both recording electrodes, it may be cancelled out. The electrode pairs, which the amplifier compares, are channels that together comprise the montage. In general, the differential voltage increases as the distance between the two electrodes increases (Reilly 1999). The ground electrode provides a return path for mains leakage current (Kamp and Lopes da Silva 1999).

In order to avoid significant signal attenuation at the amplifier, the electrode impedance must be sufficiently small compared to the amplifier input impedance and the cable impedance. The optimal amplifier input impedance in EEG recordings is around 10 megaohms. Differential amplifiers are designed to measure the voltage difference between input terminals and reject the common mode potential present in both terminals. External electrical sources cause an alternating common mode potential, which depends on the impedance of the ground electrode, between the electrodes and the earth. For this mains power interference (or high frequency signal from electrical devices) to be effectively attenuated the difference between the electrode impedances must be as small as possible and the amplifier input impedance must be large. An unbalance in the impedances of the recording electrodes restricts the accuracy of measurement (Kamp and Lopes da Silva 1999). Generally the impedance of EEG electrodes should be less than 5 kΩ. The appearance of mains power interference in the recording may be a sign of deteriorating impedance values (Reilly 1999).

The amplification or sensitivity of the system can be varied according to the amplitude of the recorded signal. Sensitivity is the magnitude of input voltage required to produce an output of standard amplitude. Gain is defined as the ratio of output voltage to input voltage. The relationship between the output and input is linear over the dynamic range of the amplifier (Edmonds *et al* 2004a).

The frequency response of the amplifier is adjusted by the high and low pass filters. The cut-off frequencies correspond to the frequencies at which the signal amplitude is attenuated to 70.7 % of the original (–3 decibels, dB). The high- and low-pass filters represent a compromise between the reduction of noise and the preservation of fidelity in reproducing the signal. Low-pass filters may round off spikes and prevent their clear identification. The frequency response of the high-pass filter is related to its time constant, determined by the resistance

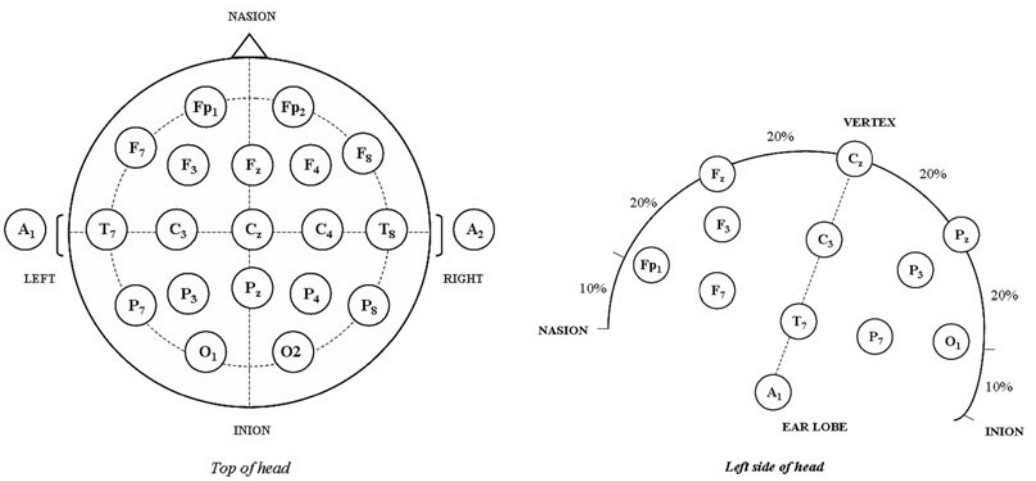

Figure 2. Schematic diagram of the modified international 10–20 electrode placement system. Modified from Guideline thirteen: guidelines for standard electrode position nomenclature 1994 and Edmonds *et al* 2004a.

and capacitance of the filter. The time constant and the cut-off frequency are inversely related. A time constant of one second results in the suppression of slow oscillations of less than 0.16 Hz (Kamp and Lopes da Silva 1999, Reilly 1999).

In digital EEG recordings, broad-band filters (commonly 0.1–70 Hz for scalp recordings) are used in the analog amplification stage. Subsequently, digital filters can be applied according to specific measurement purposes and situations. The high-pass filter, ranging from 0.01 to 5 Hz, stabilizes baseline drift. The low-pass filter, usually ranging from 30 to 100 Hz, is used to remove noise that occurs above the frequencies of interest and to prevent aliasing during signal digitization. In addition, a sharply attenuating notch filter at 50 Hz (power mains frequency) can be used (Krauss and Webber 1999).

The analog to digital converter measures the continuous analog signal at discrete time intervals. The amplitude resolution of digital EEG equipment can be expressed in bits (usually 8–16 bits). Recording with 12 bits means that the full-scale voltage deflection is represented in 2^{12} (=4096) increments. Approximately 5–10 samples per cycle are needed to accurately represent a waveform. An insufficient sampling rate results in loss of information of high frequency events and the distortion of lower frequency signals. In extracranial EEG recordings sampling rates of 200–400 Hz are commonly used (Krauss and Webber 1999).

The EEG artifact caused by QRS complexes is often intermittent, which complicates its detection. The ECG should always be monitored in parallel with EEG, and changes in heart rate compared with the frequency of a suspected transient. The ECG artifact is most pronounced in channels oriented transversely to the primary ECG vector. Cardiac pacemakers can produce brief, regular spikes in all EEG channels. Pulsating vessels can induce localized artifacts expressed either as smooth rhythmic slow waves or triangular waves of higher frequency. The beating of the heart may produce an actual movement artifact. The electro-oculographic artifact, caused by the rotating eyeball, can be recognized by the characteristic pattern of transient slow wave activity in awake or lightly sedated subjects or by formal eye movement monitoring. The frequency bands of ocular potentials overlap those of the EEG. A residual powerline or high-frequency signal, picked up by the body from the surrounding electromagnetic field, and fEMG, may be attenuated to some extent by filtering. Significant overlap, however, exists between frequencies of EEG and fEMG activity. Also, the fEMG in itself may provide valuable information. Mouth and tongue movements may produce relatively large amplitude signals in the frontal channels. In addition, the movement of fluids in plastic tubing produces electric potentials. A roller pump may cause a sinusoidal artifact mainly in the frontal channels (Rampil 1998, Reilly 1999, Edmonds *et al* 2004a).

The difficulties arising from different artifacts are illustrated in the study by Wennervirta and colleagues, in which EEG was monitored during solid organ harvest from brain dead donors. For a significant portion of the total recording time both BIS and time-frequency balanced spectral entropy differed from zero, even when the donors with non-isoelectric EEG (4/16) were excluded from analysis (Wennervirta *et al* 2007).

Electroencephalogram rhythms and synchronization

EEG rhythms consist of regularly recurring waveforms of similar shape and duration (Steriade 1999). The α rhythm has a frequency range of 8–13 Hz. It is associated with the waking state, and is pronounced over the occipital cortex in the eyes closed state. The α rhythm mainly spreads through cortico-cortical pathways, but thalamocortical interaction is also involved (Steriade *et al* 1990). δ waves (1–4 Hz) appear normally during deep sleep. They are probably generated by pyramidal cells during partial cortical deafferentation, and reflect sequencies of excitatory and inhibitory processes. Cholinergic stimulation from the basal forebrain during arousal suppresses the δ waves. Limbic θ waves (4–8 Hz) are more pronounced in lower mammals than in humans.

The septal area is a pacemaker for this rhythm. EEG waves in the θ frequency range may occur during reduced cerebral metabolism and blood flow, representing a slowing down of α waves or precursors of δ waves (Steriade *et al* 1990). According to John and Prichep, strong activation of the limbic areas with cortical projections can generate widespread θ rhythms (John and Prichep 2005). Fast waves (γ or fast β) occur during states of increased alertness. The term β rhythm is commonly used of 13–30 Hz activity, and the term γ rhythm of activity faster than 30 Hz. Fast rhythms expressed on the EEG are generated by synchronized activity in cortical neuronal networks. Subcortical structures, particularly the thalamus, also participate in the generation of fast rhythms (Steriade 1999). On the other hand, fast oscillations seem to characterize the spontaneous or background activity of cortical and thalamic cells during depolarization (Steriade *et al* 1996b). Patterns of γ band synchrony and desynchrony have been linked to active cognitive integration during perception (Desmedt and Tomberg 1994, Rodriguez *et al* 1999).

The reticular thalamic nucleus, a key structure in the generation of spindle oscillations, is an important pacemaker in the brain. The GABA-ergic thalamic reticular neurons produce inhibition of the thalamocortical neurons, which in turn provide feedback excitation to the reticular cells during rebound activity. The thalamocortical cells project to the cortical neurons, which in turn project back to the thalamus, completing a second oscillatory loop. Spindle waves appear during unconsciousness and are associated with interruption of synaptic transmission through the thalamus. They are characterized by waxing and waning 1.5–2 s sequencies of 7–14 Hz activity recurring at a 0.1–0.2 Hz rhythm. In deeper sleep stages, the incidence of spindles diminishes, and slower EEG rhythms progressively emerge. In addition to cortically generated δ waves, thalamic cells also display an intrinsic δ rhythm associated with membrane hyperpolarization. Spindles and δ waves are grouped by a very slow (< 1 Hz) cortical oscillation. During waking and rapid eye movement sleep or arousal, spindles and slow waves are blocked and they are replaced by low-amplitude fast waves in the thalamocortical circuit, associated with diffusely increased synaptic excitability. Brain activation is associated with focally synchronized fast activity (Steriade *et al* 1990, Steriade *et al* 1996a, Steriade *et al* 1996b, Steriade 1999). The blockage of spindling and slow waves is effected by mainly cholinergic projections from the brainstem (reticular formation of the tegmentum) and basal forebrain to the thalamus and cortex. The thalamocortical projection neurons are stimulated and the inhibitory thalamic reticular cells are hyperpolarized, resulting in a switch from burst firing mode to tonic firing mode of thalamic and cortical neurons. Tonic firing is associated with enhanced information processing. The brainstem monoaminergic neurons are also involved in regulating behavioral states (Steriade *et al* 1990).

Hyper- or hyposynchronous brain states are associated with impaired consciousness. Perceptual or cognitive processing may either increase or decrease the level of synchronization in the brain (Stam 2005).

Frequency domain analysis

The Fourier transform is used to represent a time-varying signal as a sum of sinusoids, each having a characteristic frequency, amplitude, and phase. The Fourier transform gives the complex amplitudes, containing information of both the magnitude and phase angle, as a function of frequency. The inverse Fourier transform returns the original signal. The power spectrum can be estimated by the squared magnitudes of the complex amplitudes of the frequency components, and can be calculated by multiplying the Fourier transform of a signal by its complex conjugate. The power spectrum does not contain phase information (Rampil 1998, Viertiö-Oja *et al* 2004).

The Fourier transform assumes that the signal is stationary, *i.e.* its statistical properties do not vary with time. In reality, physiological signals are nonstationary. They are divided into quasi-stationary segments or epochs before processing, either overlapping or continuous. In the case of digitized data, the discrete

Fourier transform (DFT) can be applied. Fast Fourier transform (FFT) algorithms allow efficient computation of the DFT. In order for the digitized signal to be fully representative of the original signal, the sampling rate must be greater than twice the highest frequency contained in the original signal (Shannon 1949, Krauss and Webber 1999). The power spectral density function (PSD) can be estimated by using the squared magnitude values of the results of the DFT, also called the periodogram. In the Welch periodogram method, the periodograms of short partly overlapping epochs are averaged to generate a smoother PSD.

Power spectral variables

Variables used to characterize the PSD include the median frequency (MF), which divides the power spectrum into two equal halves, the spectral edge frequency (SEF), below which lies a certain percentage (most often 95 %; SEF95) of the total power, and either the absolute or relative power in different frequency bands. The frequency bands most often used in EEG analysis are called δ (1–4 Hz), θ (4–8 Hz), α (8–13 Hz) and β (13–30 Hz). Occasionally, a high frequency band γ (or β_2) (30–55 Hz) is recognized. The δ waves are characterized by a high amplitude. The β (γ) waves consist of low amplitude irregular activity. It may be that the dominant frequency of EEG activity is determined by the level of sensory processing, which is controlled separately from the level of vigilance (Edmonds *et al* 2004a).

The interindividual variability in the distribution of EEG power among the different frequency bands is large. Different drugs have different effects on the EEG (Billard *et al* 1997). The power spectral variables are highly dependent on the filter settings of the amplifier. Major shifts in the lower frequency bands can occur without a change in SEF95 (Tonner and Bein 2006). The spectral content of awake EEG varies with age. The total EEG power decreases with age. During deep propofol anesthesia the amplitude of δ waves is smaller in elderly patients than in younger individuals (Schultz *et al* 2004).

The power spectral variables do not change in a monotonic fashion during changing anesthetic depth. They also depend on the specific anesthetic agent used. Thus they do not convey explicit information of the anesthetic depth (Todd 1998). During anesthetic induction, the power in the α and β bands first increases and then decreases with increasing sedation. The change in δ activity is also biphasic, but the decrease in δ power occurs at deeper levels of anesthesia. The values of different EEG variables at the moment of loss of consciousness vary widely between individuals (Kuizenga *et al* 2001). Correspondingly, the response of SEF95 and MF to increasing anesthetic concentrations is biphasic: with deepening sedation these variables first increase compared to awake values and then decrease (Katoh *et al* 1998, Kuizenga *et al* 2001). Thus, for example, a certain value of SEF may be associated with different anesthetic depths within a patient, or represent different anesthetic depths with different drugs. When burst suppression occurs, many spectral calculation methods fail, or SEF may paradoxically increase, reflecting the high frequency bursts. The univariate EEG descriptors may be useful as trend monitors regarding changes in hypnotic depth, especially during surgical anesthesia as opposed to light sedation. Power spectral variables can be used to assess the pharmacodynamic effect of some single-agent infusions, especially opioids (Todd 1998, Tonner and Bein 2006).

Katoh and colleagues found the SEF95 and MF to predict the level of sedation better than chance alone, but significantly worse than BIS or end-tidal sevoflurane concentration (Katoh *et al* 1998). Although better than the MF or power in different EEG frequency bands, the SEF95 was found to be a less accurate measure of midazolam-induced sedation than BIS (Liu *et al* 1996). In a study by Sleigh and Donovan the sensitivity, specificity and negative and positive predictive values of SEF95 for discriminating between awake and anesthetized conditions during propofol induction were around 70 %. They reported that the overlap in SEF values between different stages of anesthesia was greater than that in BIS values (Sleigh and Donovan 1999).

When interpreting processed EEG variables, it is important to refer to the raw signal. The waveform of the raw EEG and transient phenomena are lost with transformation to frequency domain (Yli-Hankala *et al* 1993b). Also, the basic requirements of correct signal acquisition must be met, for example, the impedance of the electrodes must be acceptable (van Gils *et al* 1997).

Dynamics of the electroencephalogram signal

In a linear dynamical system, changes in the state of the system can be modeled by linear equations. In a nonlinear system nonlinear equations are required. In a linear system, the output is proportional to the input, whereas in a nonlinear system, small changes in the input may have a large effect, which is not directly proportional to the change in input (Stam 2005). A dynamical system is deterministic if its state changes can be described by linear or nonlinear equations, otherwise it is stochastic.

In healthy, waking subjects most EEG epochs cannot be distinguished from a linear stochastic process, but occasionally significant nonlinearity can be detected (Stam *et al* 1999, Stepien 2002). In contrast to the normal EEG signal, epileptic seizures often display strongly nonlinear dynamics (Pijn *et al* 1997, Ferri *et al* 2001, Burioka *et al* 2005). Watt and Hamerof were the first to suggest that EEG analysis based on nonlinear dynamics could be used to assess the depth of anesthesia (Watt and Hameroff 1988).

Higher order spectra

In the time domain, the first moment or expected value of a time series is the mean. The second moment of a discrete, zero-mean signal is the autocorrelation function, the expected value of the signal multiplied by the same signal with a certain time lag. If the time lag is zero, this is the variance of the signal. A Gaussian signal can be fully characterized by its mean and variance (McLaughlin *et al* 1995, Schwilden 2006).

Higher order moments are the expected values of functions with progressively more lag terms, *e.g.* the third moment depends on two independent lags. Higher than second-order moments are needed to describe the probability distribution of non-gaussian signals. If the time series is generated by a Gaussian process, the higher-order moments are either zero (*e.g.* the third-order moment) or contain redundant information. Also, if the phases of the signal are random, the higher moments are zero (McLaughlin *et al* 1995, Schwilden 2006).

In the frequency domain, the power spectrum (second-order spectrum) can be calculated by performing a DFT of the autocorrelation function or by multiplying the Fourier transform of the signal by its complex conjugate. Similarly, the Fourier transform of the higher moments of a time series define higher-order spectra. The bispectrum (third-order spectrum) can be calculated by taking a two-dimensional DFT of the third-order cumulant (a function of the first to third moments) or by forming the product of the Fourier transforms at two different frequencies and the complex conjugate at their sum (McLaughlin *et al* 1995, Schwilden 2006).

The bispectra of the original signals and surrogate signals with identical power spectra, but random phases, can be compared to investigate whether the original signal contains information in the phase spectrum. Schwilden and colleagues found that in over 90 % of stationary EEG segments the normalized bispectrum, the bicoherence, was zero or a constant (Schwilden 2006).

Whereas the power spectrum is related to the variance, the bispectrum is related to the skewness of the probability distribution function of the signal. When the distribution of the signal is skewed, the bispectrum differs from zero. For stochastic wide-band signals, the bicoherence is a measure of the signal skewness. For deterministic signals, a peak in bicoherence may indicate the presence of quadratic phase coupling, a type of nonlinearity (McLaughlin *et al* 1995, Schwilden 2006). Nonlinear systems typically display phase coupling. That is, the

phases of certain frequency components are dependent on the phases of other frequency components in the signal (Sigl and Chamoun 1994). Quadratic phase coupling between the frequency components f_1 and f_2 implies that the phase of $f_1 + f_2$ equals the phase of f_1 + the phase of f_2 (Bullock *et al* 1997).

The magnitude of the bispectrum is given by the magnitude of the product of the complex amplitudes of f_1 and f_2 and the complex conjugate of $f_1 + f_2$, averaged over several epochs. If one of the three frequency components is small or absent, or if the phase angles are not aligned, this average product will be small and the bispectral energy will be low. Thus in the absence of phase coupling the bispectrum will tend toward zero. The real triple product is calculated as the product of the squared magnitudes of the complex amplitudes of the three frequency components, averaged over the epochs. Its square root is an analog of the bispectrum with maximal phase coupling. Both the bispectrum and the real triple product depend on the signal power. The ratio of the magnitude of the bispectrum and the square root of the real triple product gives the bicoherence, which is independent of the amplitude or power of the signal. The bicoherence varies from zero to one according to the degree of phase coupling among the three frequency components (Sigl and Chamoun 1994, Rampil 1998).

Electroencephalography during anesthesia

In the practise of anesthesia, EEG may be used to evaluate the adequacy of oxygen delivery to the brain, to monitor therapeutic metabolic suppression in the cortex, or to assess the level of functional CNS suppression induced by anesthetic agents (Rampil 1998). One to four channels are commonly registered for these purposes. Gibbs and colleagues were the first to suggest that EEG patterns could be used as a measure of anesthetic depth. They reported that EEG changes during sedation resembled those during natural sleep and EEG patterns of very deep anesthesia were similar to those observed during a coma from whatever cause (Gibbs *et al* 1937).

Awareness is associated with desynchronized, low voltage, high frequency EEG patterns. Depression of consciousness leads to slower EEG patterns with increased cortical synchrony (Rampil 1998). General anesthesia interferes with synaptic function (el-Beheiry and Puil 1989). Interestingly, by modifying the probability of activation of adjacent units in a cellular automaton model, and using the number of active units as a surrogate of EEG amplitude, Sleigh and Galletly were able to simulate the amplitude and frequency changes that occur in the EEG during changing anesthetic depth. Above a critical connection probability the activity of the network tended to be self-sustaining, whereas below the critical threshold almost all induced signals rapidly died out (Sleigh and Galletly 1997).

Alkire demonstrated that during increasing anesthetic effect and decreasing CMR, the EEG total power and relative δ power tend to increase, whereas relative β, α and θ powers, SEF95, and MF tend to decrease. In that study, BIS was the strongest predictor of CMR reduction during propofol and isoflurane anesthesia. The study was performed on volunteers, and the CMR reductions mostly varied from 40 % to 60 % (Alkire 1998).

John and colleagues investigated quantitative EEG during various different anesthetic techniques (induction with propofol, thiopental, or etomidate, maintenance with isoflurane, sevoflurane, desflurane, propofol with or without N_2O, and opioids). They observed that a general increase in EEG power occurred at loss of consciousness (LOC), together with a shift toward anterior predominance. The increase in power was most marked in the δ and θ bands. In contrast, power in the γ band decreased sharply at LOC (after increasing during sedation) and decreased further during the maintenance of anesthesia, most markedly around 40 Hz. With induction, the coupling between left and right prefrontal cortices and between the prefrontal and frontal cortices within each hemisphere increased, consistent with the occurrence of large amplitude slow waves. On the other hand, the coherence between the frontal and occipital cortices within each hemisphere and between left and right frontal and oc-

cipital cortices decreased. During emergence the decreased coherence in the δ and θ bands failed to reverse. In contrast, recoupling was observed in the γ band during emergence and at return of consciousness (ROC) the γ power and coherence was increased in all areas. The power in the δ and θ bands decreased at ROC (John *et al* 2001). Recoupling in δ and α bands occurred only several minutes after responsiveness was restored (John and Prichep 2005). The inferred anatomical regions displaying the most marked slow wave changes included the prefrontal cortex, the superior frontal gyrus, the limbic system, the basal ganglia, and the thalamus. The authors concluded that the observed electrophysiological changes are associated with blockade of perception at induction (John *et al* 2001).

Ketamine produces a frontally dominant rhythmic θ EEG activity. With increasing dose, polymorphic large amplitude δ activity and interspersed low amplitude β activity increase (Hirota 2006). In addition to prominent increases in θ activity, ketamine anesthesia is associated with the appearance of γ spindles. Increasing the ketamine dose also increases α and β power (Maksimow *et al* 2006). N_2O increases fast β activity, associated with analgesia and depressed consciousness. The EEG effects of xenon resemble those of the potent volatile agents, with an increased β activity at low doses and then gradual increases in rhythmic θ and δ activity with loss of consciousness (Hirota 2006).

The main EEG effect of opioids is a shift of the frequency spectrum to the δ band (Billard *et al* 1997). Olofsen and colleagues found that in the unstimulated state, the overall effect of remifentanil on the pharmacodynamic relationship between end-tidal sevoflurane concentrations and EEG effect, as estimated by BIS, a canonical univariate parameter, and SEF, was minor. Of these variables, BIS seemed to most closely reflect the effect-site concentration of sevoflurane. During surgery, the prediction of EEG effect based on end-tidal sevoflurane concentrations was poor when the pharmacodynamic parameters derived in the unstimulated state were used (Olofsen *et al* 2002).

Bouillon and colleagues found that the interaction of propofol and remifentanil on BIS and approximate entropy (ApEn) was additive, but with concentrations less than 8 ng / ml the effect of remifentanil on either EEG measure was modest. Due to a strong synergistic interaction between propofol and remifentanil for suppression of responsiveness to noxious and non-noxious stimulation, the EEG state (as measured by *e.g.* BIS or ApEn) at loss of responsiveness depends on the particular combination of hypnotic and analgetic concentrations. ApEn may be more sensitive to opioid effects than BIS (Bouillon *et al* 2004).

The total EEG power was the first processed EEG variable used in assessing and controlling the depth of anesthesia (Bickford 1950). It is insensitive to significant changes in the frequency distribution, however, and it is affected by electrode location (Rampil 1998).

Burst suppression

Burst suppression is an EEG pattern characterized by alternating periods of high and variable amplitude, mixed frequency activity, and periods of partial or complete attenuation of cortical electrical activity. In the context of anesthesia, this is a fully reversible phenomenon indicative of excessively deep anesthesia, whereas in the context of brain damage it is a sign of irreversible damage associated with a very poor prognosis (van Gils *et al* 1997). During deepening anesthesia, the suppression periods become progressively longer, until continuous suppression occurs. The exact morphology of bursts varies with different anesthetic agents (Yli-Hankala and Jäntti 1990, Jäntti *et al* 1993, Särkelä *et al* 2002). The burst onset and offset are associated with DC shifts (Jäntti *et al* 1993). These shifts are abrupt during isoflurane and sevoflurane induced bursts, whereas during propofol anesthesia the onset and offset of bursts are smooth (Huotari *et al* 2004). Occasionally, bursts may turn into epileptic discharges (Jäntti and Yli-Hankala 1990). The bursts share several features of epileptic discharges: sharp spikes, a negative DC shift during the burst, and an increase in heart rate at burst onset.

Before the onset of burst suppression, the cortical neurons are hyperpolarized, and the slow rhythm of intracellular depolarizations (< 1 Hz) associated with anesthesia is progressively disorganized. The cortical cells begin to display transient, shorter depolarizations separated by periods of complete electrical silence. The electrocorticography closely follows the intracellular events, as does the mass electrical activity of the brainstem. The synaptic excitability of cortical neurons is reduced, but some stimuli may induce sustained recovery from burst suppression. Some thalamic neurons may retain rhythmic electrical activity during periods of electrocorticography suppression, reflecting their intrinsic pacemaker properties. With very deep burst suppression, however, the thalamic cells become silent. It was observed that the frequency of thalamic intracellular depolarizations during a burst closely corresponded to the frequency of spiky waves in the EEG. Increased K^+ conductance may be important for the initial hyperpolarization (Steriade *et al* 1994).

During isoflurane anesthesia, deep enough to induce EEG suppression, bursts can be evoked by non-noxious and noxious stimuli. The spontaneous bursts may represent responses to some internal stimuli, or they may reflect properties of a burst pacemaker (Ylı-Hankala *et al* 1993a, Hartikainen *et al* 1995b, Hartikainen *et al* 1995a). Different stimulation modalities induce different burst waveforms, the morphology of which is stable within the same individual at a constant anesthetic level. Noxious stimulation is the most effective in activating the EEG, and may restore the continuous EEG pattern. During deepening anesthesia, the probability of stimulus-evoked bursts decreases. Also, stimulus-offset evoked bursts may predominate over stimulus-onset evoked bursts during deeper anesthetic levels. Deepening anesthesia is probably associated with both increasing inhibition and increasing neuronal excitability (Hartikainen *et al* 1995b). During propofol anesthesia, deep enough to induce EEG suppression, bursts can be evoked by noxious electrical stimulation. The sharp evoked negative wave and the burst wave, which during isoflurane or sevoflurane anesthesia seem to be merged, are temporally separate during propofol anesthesia and may occur independently. Deep propofol anesthesia is characterized by the occurrence of spindles both during bursts and during suppressions (Huotari *et al* 2004).

Time-domain analysis techniques can be used in burst suppression detection. Suppression can be defined as a period of EEG longer than 0.5 s, during which the EEG amplitude is less than ±5 μV. A frequently used quantitative measure of burst suppression is the burst suppression ratio (BSR), that is the fraction of the epoch length where suppression is present. Because burst suppression is a very variable phenomenon, the BSR should be averaged over at least 60 s (Rampil 1998). Several different approaches to burst suppression detection and quantification have been reported. Särkelä and colleagues suggested that the average energy present in the bursts should also be quantified. They compared an amplitude-based burst suppression detection method with a method based on the Nonlinear Energy Operator (NLEO). They found that after high-pass (> 47 Hz) and low-pass (< 8 Hz) filtering and applying agent-specific decision threshold values for classification, the NLEO method resulted in more sensitive artifact detection and in the case of propofol more sensitive suppression detection compared to the amplitude-based method (Särkelä *et al* 2002). The NLEO method is used for burst suppression detection in time-frequency balanced spectral entropy (M-Entropy®) monitoring.

Arousal reactions

Event-related desynchronization corresponds to a decrease of power in certain EEG frequency bands during cortical sensory or cognitive information processing, or motor behavior. It reflects increased cellular excitability in the thalamocortical circuits. Event-related synchronization refers to an increase of power in certain EEG frequency bands. γ band synchronization reflects active information processing, perhaps related to sensorimotor integration (Pfurtscheller 1999).

Kuramoto and colleagues demonstrated in anesthetized dogs that during noxious stimulation the CMR and EEG desynchronization responses were closely coupled (Kuramoto *et al* 1979).

Röpcke and colleagues showed that compared to the unstimulated state, in the presence of surgical stimulation considerably higher desflurane concentrations were required to maintain a certain level of EEG activity, as measured by BIS (v. 2.5), SEF95, and MF. Surgery was thus associated with an EEG arousal response (Röpcke *et al* 2001).

A noxious mechanical stimulus caused decreases in the total EEG power and the δ, θ and α band power in goats under 0.6 or 0.9 MAC isoflurane anesthesia, whereas no significant change in EEG activity was observed after the stimulus at 1.1 or 1.4 MAC. The β power was unchanged at all anesthetic concentrations. At the lower isoflurane concentrations, desynchronization was observed in thalamic and MRF areas as well (Antognini and Carstens 1999).

In a rodent study, Orth and colleagues found that propofol infused at a rate around that needed to prevent a movement responses to tail clamping blunted the EEG arousal reaction to repetitive and supramaximal noxious stimuli, whereas halothane at a concentration around one MAC did not. EEG desynchronization and increases in SEF95 and MF were observed at 1.2 MAC halothane with electrical stimulation and tail clamping. With 1.2 ED_{50} propofol a decrease in SEF95 was seen after the supramaximal stimuli (Orth *et al* 2005).

Electrical stimulation of the midbrain reticular formation induced EEG activation in rats during 1.2 MAC halothane anesthesia, but not during 1.2 ED_{50} propofol anesthesia. At some stimulation intensities, a decrease of SEF95 / MF at 1.2 ED_{50} propofol anesthesia occurred. Noxious mechanical or electrical stimulation of the tail caused some EEG activation at 0.8 ED_{50} propofol, but little at 1.2 ED_{50} propofol. The EEG activation induced by tail stimulation was considerably greater during 0.8–1.2 MAC halothane anesthesia. Thus, propofol and halothane have different electrophysiological effects on cortical activity and generation of movement (Antognini *et al* 2006).

Bimar and Belleville described the occurrence of both EEG desynchronization responses and sudden shifts of the power spectrum to lower frequencies with increased amplitude during relatively light levels of halothane–N_2O or opioid–N_2O anesthesia (Bimar and Bellville 1977). Kochs and colleagues also reported increases in δ and decreases in α and β band activity after surgical stimulation during isoflurane–N_2O anesthesia, especially in frontal leads. The changes were pronounced during 0.6 % isoflurane and attenuated during 1.2 % isoflurane. The authors concluded that different doses of anesthetics and different states of the reticular activating system may lead to varying EEG arousal responses (Kochs *et al* 1994).

Kiyama and Takeda showed an EEG arousal response to abdominal skin incision during isoflurane–N_2O anesthesia in patients without an epidural blockade, whereas no EEG changes were noted in patients who had received an epidural blockade before incision. In the former group, SEF95, MF, and relative θ, α, and β band powers decreased after the skin incision, and relative δ power increased, accompanied by an increase in blood pressure. The authors emphasized the importance of considering the adequacy of analgesia when interpreting intraoperative EEG changes (Kiyama and Takeda 1997).

Isoflurane effect in the spinal cord influences the probability of EEG desynchronization caused by peripheral noxious stimulation or electrical MRF stimulation, in the presence of constant brain isoflurane concentrations. The increase in MRF single unit activity in response to peripheral noxious stimulation is also inhibited by increasing isoflurane concentrations in the spinal cord. Isoflurane action in the spinal cord thus affects the arousal state of the brain, presumably by dose-dependent blocking of ascending somatosensory neuronal transmission (Antognini *et al* 2000b, Antognini *et al* 2003). The direct brain effect and the indirect spinal cord effect of isoflurane on the EEG desynchronization and thalamic single unit response to noxious stimulation seem to be approximately equally important (Antognini *et al* 2000a).

Menigaux and colleagues showed that esmolol attenuated the somatic, hemodynamic and BIS arousal reactions to laryngoscopy and tracheal intubation. Esmolol did not affect BIS values before noxious stimulation. The authors speculated that esmolol might inhibit an EEG arousal response by blocking the β-adrenoreceptors in the reticular activating system (Menigaux *et al* 2002). In a relatively small, placebo-controlled study Johansen observed that during propofol–alfentanil anesthesia an infusion of esmolol was associated with a decrease in BIS values and an increase in the suppression ratio. Surgical stimuli were not controlled (Johansen 2001).

Wilder-Smith and colleagues reported an EEG arousal reaction with laryngoscopy and intubation after propofol–N_2O or thiopentone–N_2O induction. The relative EEG θ, α and β band powers increased, and the relative δ power decreased, together with an increase in blood pressure. The EEG changes were more pronounced after thiopentone induction, despite similar pre-stimulus EEG profiles. The authors concluded that even though prediction of the response to nociception based on pre-stimulus EEG patterns may not be possible, the arousal reactions themselves could be used to study intraoperative nociception (Wilder-Smith *et al* 1995).

Epileptiform activity and seizures

Epileptiform discharges may be reflected in the surface EEG as monophasic negative, monophasic positive, or polyphasic waves. A negative DC shift occurs during the seizure (Speckmann and Elger 1999).

Spikes and sharp waves are closely related paroxysmal discharges, suggestive of epileptic activity. A spike is a pointed, multiphasic EEG transient with a variable amplitude and a duration of 20–70 ms, which is clearly distinguishable from the background activity. They may represent hypersynchronous neural discharges. Spikes may be followed by a slow negative component. A sharp wave is a pointed, multiphasic EEG transient with a duration of 70–200 ms. They usually appear as random focal discharges. Multiple spike complexes or polyspikes are bursts of closely associated diphasic spikes occurring more or less rhythmically. On the scalp, they usually occur as bilateral or generalized synchronous discharges. Discharges consisting of spike and slow wave complexes may represent the alternation of excitation and inhibition. Periodic discharges usually occur in severe CNS disease such as encephalitis, infarction, acute anoxia, metabolic disorders, or neoplasia, associated with paroxysmal or epileptogenic properties. They may also occur during complex partial status epilepticus. The periodic discharges may present as sharp waves or complex patterns with mixed spiky and slower components (Brenner and Schaul 1990, Niedermeyer 1999). The mechanism of periodicity is not clear. Periodic lateralized discharges may represent an unstable ictal-interictal neurophysiological state (Niedermeyer 1999). Focal periodic epileptiform discharges indicate structural damage. When generalized, they are associated with severely impaired consciousness (Edmonds *et al* 2004b).

Seizure activity is generally associated with a marked elevation of HR and blood pressure (Prudic *et al* 1987). Other sympathetic responses such as a decrease in skin resistance (sweating) and vasoconstriction may also occur (Johnson and Davidoff 1964). The magnitude of HR change may depend on the extent of seizure spread and the presence or absence of spikes and clinical manifestations. Occasionally, transient HR slowing or rhythm abnormalities may occur during seizures (Johnson and Davidoff 1964, Epstein *et al* 1992). A hyperdynamic cardiovascular reaction associated with epileptiform EEG activity has also been shown during sevoflurane anesthesia (Yli-Hankala *et al* 1999b, Vakkuri *et al* 2000, Vakkuri *et al* 2001).

Spike-wave (SW) or spike-wave / polyspike-wave (SW / PSW) seizures, the latter often associated with fast paroxysmal runs (Lennox-Gastaut seizures), are likely generated within the neocortex. They distribute synaptically to other cortical areas and eventually to the thalamus. The paroxysmal depolarization shifts in cortical neurons during SW / PSW seizures are followed by rhythmic spike bursts in the

inhibitory thalamic reticular neurons. During cortical fast runs, thalamic reticular neurons fire spike doublets or triplets, followed by an after-depolarization. Reticular neurons in turn project to the thalamocortical neurons. The majority of the thalamocortical cells display sustained hyperpolarization and phasic IPSPs during SW / PSW seizures and do not project back to the cortex, but instead are "disconnected" from the outside world. The phasic IPSPs show the same frequency as the cortical spikes and the reticular cell spike bursts. The remaining minority of thalamocortical cells may have a role in enhancing the coherence of activity betwen different cortical areas during seizures. At the end of cortical seizures thalamocortical cells fire at high rates (Timofeev and Steriade 2004).

The properties of cortical and thalamic neurons are modulated by synaptic activity in corticothalamic networks and during different behavioral states. During sleep, spindles are generated by thalamic reticular cells, regular δ activity by thalamocortical cells, and slower rhythmic oscillations (< 1 Hz) by cortical cells. The highly synchronized activity in thalamocortical circuits during slow wave sleep promotes seizure paroxysms. Both local increases in excitation and decreases in synaptic activity may trigger seizures, as partial deafferentation increases synaptic excitability. Ultra-fast oscillations generated by fast rhythmic bursting cortical cells have been implicated in the initiation of seizures. If these field potential "ripples" reach a critical amplitude, neuronal excitability is increased, resulting in recruitment of inactive neurons into synchronous firing. This feedback amplification may be responsible for the initiation and the spread of paroxysmal activity. The amplitudes of EPSPs, leading to action potentials, progressively increase prior to the onset of seizures (Timofeev and Steriade 2004).

Isolated paroxysmal depolarization shifts may evolve into full-blown seizures. The paroxysmal depolarization shifts during SW complexes, manifested as EEG spikes, contain an important inhibitory component. The wave component is associated with hyperpolarization, probably due to K^+ currents and decreased excitatory input. Hyperpolarization leads to increased excitability and rebound depolarization, inducing the next paroxysmal cycle. The neuronal synchrony is increased during interictal spikes, and is even higher during seizures. During the seizure a progressive depolarization, which reaches its maximum during fast runs, occurs and the end of the seizure is followed by a prolonged hyperpolarization. The termination of seizures may be due to overwhelming K^+ currents and decreased synaptic responsiveness (partly due to decreased extracellular Ca^{2+} concentration), which prevents further recurrent excitation (Timofeev and Steriade 2004).

Bispectral index scale monitoring

The development and technique of bispectral index scale monitoring

Dumermuth and colleagues and Barnett and colleagues were among the first to describe the EEG bispectrum in waking and sleeping subjects (Barnett *et al* 1971, Dumermuth *et al* 1971). Bullock and colleagues reported in a series of depth EEG recordings in epileptic patients during wakefulness, sleep, and seizures that pairs of frequency components with prominent bicoherence can appear episodically between long periods of virtually no significant bicoherence. When present, the pattern of quadratic phase coupling is very variable and changes rapidly along both time and distance. EEG bicoherence generally increases during sleep and seizure activity. Some seizures display a "hair-brush" bicoherence pattern, with narrow peaks occurring at regular intervals in the bifrequency plane. Also, bicoherence is generally relatively high in deep temporal structures. The authors noted that changes in bicoherence may result not only from changes in the absolute amount of quadratic phase coupling, but also from changes in the amount of non-quadratically coupled power at the corresponding frequencies. They also noted that transient sharp events appear to be a common cause of quadratic phase coupling (Bullock *et al* 1997).

The development of bispectral index scale monitoring was begun by collecting a database of artifact-free EEGs from 195 subjects with different anesthetic regimens. Of these subjects, 59 were volunteers for whom the clinical end-point was the maximal EEG effect of the drug (propofol or alfentanil). For the other subjects, data was collected during surgical procedures, and movement or hemodynamic responses to noxious stimulation were used as the clinical end-points. From a large set of variables derived from the EEG bispectrum, a subset that best predicted the associated clinical end-point was selected. Discriminant analysis was used to compute coefficients that maximized the separation between responders and non-responders, for these variables. The possible values of the linear combination of variables were limited to 0–100 with sigmoidal scaling (Kearse *et al* 1994a). Subsequently, additional EEG records (up to roughly 1500 patients) with time-matched clinical end-points and drug concentrations were collected and used for updating the BIS algorithm. Different time domain, frequency domain, and bispectral EEG descriptors were extracted from the artifact-free EEGs and statistically ranked by their ability to predict the corresponding clinical condition. The best descriptors were fitted to a multivariate logistic regression analysis and the derived index was prospectively tested (Rampil 1998, Johansen and Sebel 2000).

Bispectral index monitoring was approved by the FDA for monitoring of anesthetic effect in 1996. BIS is a dimensionless number scaled from 100 to 0, 100 representing the awake state and 0 representing complete cortical electrical silence. Versions 2.0 and higher have been optimized to correlate with the level of sedation and hypnosis. The latest revisions, 4.0 and 4.1, have been designed for use with a four-lead proprietary sensor. They apply enhanced artifact recognition and rejection algorithms (fEMG, eye movements, electrocautery) (Johansen and Sebel 2000, Johansen 2006).

The bispectral index is calculated from digitized and band-pass filtered EEG in 2 s epochs. Several algorithms are used to reject artifacts. The degree of burst suppression is estimated with two different algorithms, BSR, and "QUAZI". The latter improves burst suppression detection in the presence of a wandering baseline by incorporating information of low frequency (< 1 Hz) power. A Blackman window is applied to the artifact-free epoch, and then FFT and the bispectrum are calculated. The spectral and bispectral values are smoothed by using a moving average. BetaRatio is a variable defined by the logarithm of the ratio of power in the frequency bands 30–47 Hz and 11–20 Hz. SynchFastSlow is calculated as the logarithm of the ratio of summed bispectrum values in the areas of the bifrequency plane defined by 40–47 Hz and 0.5–47 Hz. Due to symmetry and the limit imposed by the sampling frequency, only a subset of the associated frequency combinations need to be considered. The bispectral index is computed by a nonlinear function combining the variables BetaRatio, SynchFastSlow, BSR and QUAZI. The different subparameters are weighted according to the depth of anesthesia. In contrast to power spectral variables, BIS decreases monotonously with increasing depth of anesthesia (Rampil 1998).

The association of bispectral index values with the sedation level and the loss and return of consciousness

BIS correlates well with the observer's assessment of alertness / sedation (OAA / S) scale with various anesthetic agents (Glass *et al* 1997, Katoh *et al* 1998, Iselin-Chaves *et al* 2000, Mourisse *et al* 2004). Katoh and colleagues found that the prediction probability (P_K) value of BIS (v. 3.2) for predicting OAA / S was 0.93 during sevoflurane sedation (Katoh *et al* 2000). Mourisse and colleagues reported a similar P_K value of 0.88 (v. 3.4) during propofol sedation (Mourisse *et al* 2004). Stryus and colleagues reported that BIS (v. 3.4), the A-line Autoregressive Index based on MLAEP, and the estimated propofol effect-site concentration had similarly high P_K values (0.87–0.95) for predicting the OAA / S level and the loss of the lash reflex, and the addition of remifentanil 2–4 ng / ml did not affect their performance (Struys *et al* 2003).

Struys and colleagues reported that the BIS (v. 3.4) values associated with 50 % and 95 % probabilities of LOC during propofol anesthesia were 61 and 55 (Struys *et al* 2003). Katoh and colleagues found the BIS (v. 3.2) values associated with 50 % and 95 % probabilities of loss of response to a loud verbal command to be 73 and 65 during sevoflurane anesthesia. As the intensity of non-noxious stimulation increases, the BIS-response curve is shifted to lower BIS values (Katoh *et al* 1998). LOC occurred at similar BIS values across different adult age groups (from 18 to 85 years) (Katoh *et al* 2000). Glass and colleagues reported 50 % and 95 % probabilities of LOC at BIS (v. 3.0) values 65 and 51 from combined data of volunteers receiving propofol, isoflurane, or midazolam (Glass *et al* 1997). Overall, loss of consciousness in 50 % and 95 % of patients occurs roughly at BIS values 65–70 and 50–60 (Glass *et al* 1997, Iselin-Chaves *et al* 1998, Vanluchene *et al* 2004a). Return of consciousness tends to occur at BIS values approximately 75–85 (Doi *et al* 1997, Liu *et al* 1997).

In volunteer studies conducted by Iselin-Chaves and colleagues, the P_K of BIS (v. 2.0 and 3.0) for LOC was better than those of target effect-site or measured plasma concentration of propofol. The P_K of BIS for LOC was similar (0.94 or more) during propofol monoanesthesia and during propofol–alfentanil (100 ng / ml) anesthesia (Iselin-Chaves *et al* 1998, Iselin-Chaves *et al* 2000). A similarly high P_K (0.89–0.98) of BIS (v. 3.0) for LOC was observed by Glass and colleagues (Glass *et al* 1997). In contrast, Schneider and colleagues found P_K values of BIS (v. 3.3) just under 0.70 for detection of consciousness during sevoflurane–remifentanil or propofol–remifentanil anesthesia. A wide variation in BIS values at LOC and ROC was observed, although the mean values at LOC were lower than at ROC (Schneider *et al* 2003).

The large interindividual variability in BIS values (v. 4.0, XP) and overlap between responders and non-responders to verbal command during LOC and ROC with rapid wash-in and wash-out of sevoflurane was emphasized by Anderson and colleagues (Anderson *et al* 2003). A similar large overlap between BIS values (v. 3.0) associated with consciousness and unconsciousness was reported by Gajraj and colleagues during propofol sedation (Gajraj *et al* 1998).

The association of bispectral index values with intraoperative recall

Glass and colleagues reported that BIS (v. 3.0) values of 64 and 86 during propofol, isoflurane, or midazolam anesthesia or sedation were associated with a 95 % and 50 % probability of loss of free or cued recall (Glass *et al* 1997). In volunteers, during propofol or propofol–alfentanil sedation, Iselin-Chaves and colleagues obtained similar results. In that study, the presence of alfentanil did not affect the BIS (v. 3.0) values associated with loss of recall (Iselin-Chaves *et al* 1998). Liu and colleagues reported that with BIS values less than 80, only 8 % of pictures presented intraoperatively were recalled in patients with regional anesthesia and propofol sedation. A considerable interindividual variability in recall at different BIS values and OAA / S scores was found (Liu *et al* 1997).

In a study on trauma patients subjected to isoflurane–fentanyl anesthesia, Lubke and colleagues found that the intraoperative BIS level was a weak but significant predictor of postoperative memory performance, as measured by a word stem completion test with intraoperatively presented words and distractor words. Memory performance increased with increasing BIS values, and was higher than that caused by chance in the BIS range 40–60, but not at BIS values less than 40. The data suggested that the observed memory performance consisted of implicit memory. The authors concluded that at anesthetic levels considered adequate by BIS monitoring, some patients process auditory information without conscious access to this data after recovery (Lubke *et al* 1999). On the other hand, Kerssens and colleagues found no explicit or implicit memory formation in elective surgical patients during adequately controlled propofol hypnosis, with BIS (v. 3.2) values between 40 and 60 (Kerssens *et al* 2001).

Bispectral index, the adequacy of the level of hypnosis, and outcome

BIS values correlate well with the concentrations of hypnotic agents (Doi *et al* 1997, Katoh *et al* 1998, Lysakowski *et al* 2001).

In coronary artery bypass surgery patients, adjustment of propofol administration to achieve BIS (v. XP) 40–50, combined with a constant remifentanil infusion, resulted in a roughly 30 % decrease of propofol consumption compared to the control group, without affecting the neurohumoral or cytokine stress response and with no intraoperative recall. An unnecessarily deep anesthetic level was observed in 50 % of the control group patients, with a fixed propofol infusion rate (Bauer *et al* 2004). In a study by Luginbühl and colleagues titrating BIS (v. 3.3) between 45–55 (up to 65 during the last 15 min of the procedure) was associated with a reduced hypnotic drug use and a faster extubation in propofol patients, whereas desflurane patients experienced fewer episodes of inadequate hypnosis (BIS value above 60), less nausea, and greater subjective satisfaction with the anesthetic compared to controls (Luginbühl *et al* 2003).

In a prospective observational study, Monk and colleagues found the cumulative deep hypnotic time, defined as BIS values less than 45, to be an independent predictor of 1-year mortality after major noncardiac surgery, in addition to patient co-morbidity and the cumulative systolic hypotension time. The relative risks associated with these variables were 1.24 (per h), 16.12 (the Charlson co-morbidity score ≥ 3 *vs.* 0–2), and 1.04 (per min). The authors speculated that a relative overdose of anesthetic agents may adversely alter the inflammatory response after surgery (Monk *et al* 2005). The study protocol excluded patients with known neurological diseases and patients scheduled for procedures conferring a high risk of neurological deficits. Even so, it is not certain that there exists a causal relationship between the observed anesthetic depth and outcome. The total anesthetic dose was not assessed. An unknown risk factor may predispose patients to both low BIS values and poor outcome.

Bispectral index and intraoperative awareness

Myles and colleagues showed that BIS monitoring reduced the incidence of intraoperative awareness in adult patients at high risk for this complication during general anesthesia with neuromuscular blockade. In this population with an approximately 1 % baseline risk of intraoperative awareness the number needed to treat (NNT) was 138, corresponding to an absolute risk reduction of 0.74 % (Myles *et al* 2004). Similarly, Ekman and colleagues found that compared to a historical control group, the implementation of BIS monitoring reduced the incidence of awareness in an unselected surgical population. Based on the results of that study, the NNT in the general population would be 714, corresponding to an absolute risk reduction of 0.14 %. The authors concluded that the sensitivity of a BIS cut-off value of 60 seems to be adequate for prevention of awareness, although the specificity is less than 100 % (Ekman *et al* 2004). Reducing the incidence of awareness during general anesthesia was approved by the FDA as an indication of BIS monitoring in 2004 (Johansen 2006).

Regarding the risk of awareness, not only the absolute BIS value but also the duration of BIS elevation seems to be important (Luginbühl and Schnider 2002). Awareness has been observed at BIS values at the upper end of the recommended 40–60 range (Bevacqua and Kazdan 2003). In the study by Myles and colleagues, one patient had confirmed awareness during an intraoperative episode with registered BIS values between 55 and 59 (Myles *et al* 2004). This case demonstrates the inherent individual variation in biosignals and the probabilistic interpretation of BIS values.

The electromyogram and other issues in interpreting bispectral index values

Sleigh and Donovan demonstrated a hysteresis effect both during induction and emergence from anesthesia such that the BIS (v. 3.12) values at syringe drop were not different from awake values, and at recovery a period of clini-

cal awareness occurred with low BIS values. BIS, however, usually increased to more than 95 within 20–30 s. The authors discussed the possibility that in addition to the lag in updating the BIS values, an intrinsic lag between the transition between consciousness and unconsciousness and EEG changes could be involved. The sensitivity, specificity, and negative and positive predictive values of BIS for discriminating between awake and anesthetized conditions during propofol induction were around 95 % or better (Sleigh and Donovan 1999). Similarly, Doi and colleagues showed that during emergence from propofol–N_2O anesthesia, BIS (v. 3.0) values, SEF95, or MF immediately before and after ROC did not differ, whereas AEP index values effectively discriminated between the awake and anesthetized states. BIS values at ROC were lower than before induction. The transition to consciousness occurred at BIS values of 64–80 (Doi *et al* 1997). Gajraj and colleagues have suggested that BIS reflects the level of global suppression of cortical activity, as opposed to the sudden transition from unconsciousness to consciousness, which may be a threshold event determined by deeper brain structures (Gajraj *et al* 1999).

Katoh and colleagues observed a plateau of BIS (v. 3.2) decrease at sevoflurane concentrations of around 1.8 % (Katoh *et al* 1998). A similar BIS (v. 3.22) plateau with sevoflurane and isoflurane concentrations above 2 % and 1 % was found by Olofsen and colleagues (Olofsen and Dahan 1999). Ellerkman and colleagues found that in patients anesthetized with sevoflurane, with a BSR over 40 % a linear relationship between BIS (v. XP) and BSR existed, with little or no interindividual differences (Ellerkmann *et al* 2004). Using various anesthetic techniques, Vakkuri and colleagues demonstrated a similar linear relationship between BIS (v. 3.12) and BSR with a BSR over 50 %. A plateau was observed in BIS values below 40 during desflurane–N_2O and propofol–N_2O anesthesia, but not during sevoflurane–N_2O anesthesia, where no burst suppression was present. A short plateau was also found in BIS values over 60. The authors ascribed these plateau phases to transitions between the three different algorithms used in computing BIS (Vakkuri *et al* 2004). Similar results were reported by Bruhn and colleagues during propofol anesthesia. With suppression ratios of 5 %–40 % the average BIS value was constant (30–40). Suppression ratios over 40 % were linearly correlated with BIS (v. 3.22) values from 30 to 0 (Bruhn *et al* 2000a).

The frequency ranges of EEG and EMG overlap. EMG activity, interpreted by the BIS algorithm as high frequency, low amplitude waves, may occasionally falsely elevate BIS values. Efforts have been made to reduce the EMG contamination in later BIS versions (Johansen 2006). The A-2000 EEG monitor discards data contaminated by monopolar electrocautery. Bipolar electrocautery generates a low-amplitude, high frequency signal, which may interfere with EEG processing. Other electrical devices and even forced air-flow warming blankets used in the operating room may also cause subtle signal contamination and result in misleadingly high BIS values (Hemmerling and Fortier 2002, Dahaba 2005). Falsely elevated BIS values may also occur with high electrode impedances (Johansen 2006).

Neuromuscular blockade (NMB) does not affect BIS (v. 3.3–3.4) values in deeply sedated, unstimulated subjects (Greif *et al* 2002, Vasella *et al* 2005). In patients with increased EMG activity, the administration of NMB drugs can decrease the BIS values (Dahaba 2005, Liu *et al* 2005). Vasella and colleagues found that during steady propofol anesthesia in unstimulated patients, neuromuscular blockade was associated with a decrease in frontal EMG power but no change in BIS (v. 3.4) values or AAI. The administration of neostigmine–glycopyrrolate was associated with an increase in both BIS and AAI values exceeding those induced by glycopyrrolate alone. The authors concluded that this effect of neostigmine probably did not represent a frontal EMG artifact, but rather a genuine arousal resulting from increased afferent signals from muscle stretch receptors (Vasella *et al* 2005). Dahaba and colleagues reported that the onset of mivacurium effect induced a transient BIS deviation, which had opposite directions in the BIS 3.4 and 4.0 algorithms. It was suggested that version 4.0 may indicate systematically lower BIS values than

previous algorithms (v. 3.4), especially during recovery from anesthesia and during periods of artifacts (Dahaba *et al* 2004).

Various cerebral disorders which affect the EEG characteristics or brain metabolism are reflected in BIS values (Dahaba 2005). A genetically determined low EEG voltage variant can result in abnormally low awake BIS values (Schnider *et al* 1998). The very low voltage EEG during a phase of emergence from sevoflurane, isoflurane, or remifentanil anesthesia can be misinterpreted by the BIS algorithm as burst suppression, resulting in inappropriately low BIS values (Muncaster *et al* 2003, Hagihira *et al* 2004a). Gunawardane and colleagues have shown that a pathological increase in low frequency EEG activity, such as that occurring in the post-ictal state, may produce low BIS values that are not associated with the level of consciousness (Gunawardane *et al* 2002).

It has been observed that BIS (v. 4.0) values tend to be higher during halothane anesthesia than during anesthesia with other potent volatile agents at similar anesthetic levels (as assessed by MAC multiples). This may be due to differences in EEG profiles induced by the different agents and differences in relative effects on the brain and subcortical structures (Edwards *et al* 2003, Davidson and Czarnecki 2004).

Bispectral index and hemodynamic responses

In an early study with thiopental–N_2O–opioid anesthesia, the pre-laryngoscopy BIS values distinguished patients with a significant blood pressure response to intubation from non-responders, whereas none of the investigated power spectral variables did. Overlap, however, occurred in BIS values between responders and non-responders (Kearse *et al* 1994b). With a later BIS version (v. 3.12), Driessen and colleagues reported that pre-stimulus BIS values did not correlate with the blood pressure response to intubation and sternotomy during fentanyl–midazolam anesthesia (Driessen *et al* 1999). The correlation between the hemodynamic and BIS responses to noxious stimulation is not good (Mi *et al* 1998, Driessen *et al* 1999). No correlation between the concentrations of various stress hormones and BIS during anesthesia has been found (Bauer *et al* 2004, Ledowski *et al* 2005).

Bispectral index, nitrous oxide, xenon, ketamine, and dexmedetomidine

Rampil and colleagues described the changes in the spectral content of the EEG during N_2O sedation (10 %–50 %). In general, higher N_2O concentrations increased the high-frequency EEG activity and EMG activity. Steady-state N_2O alone did not influence BIS (v. 3.22) values. A prominent transient EEG slowing, also reflected in decreased BIS values, was noted upon withdrawal of N_2O. The subjects remained awake and alert throughout the study. The authors concluded that N_2O exerts both excitatory and inhibitory actions on the CNS (Rampil *et al* 1998).

N_2O does not seem to affect BIS values in the absence of noxious stimulation (Barr *et al* 1999, Coste *et al* 2000). Analgesia induced by N_2O attenuates the central nervous system arousal response to noxious stimulation. Therefore, N_2O may indirectly affect BIS values during noxious stimulation (Hans *et al* 2001). This effect has not been found in all studies (Barr *et al* 1999, Coste *et al* 2000). In some patients, N_2O may increase BIS values, even when combined with a potent volatile anesthetic, presumably by altering the relative β ratio. In such instances, withdrawal of N_2O may result in a decrease in BIS values (Puri 2001).

Due to increased fast activity in the EEG caused by ketamine (Hering *et al* 1994, Maksimow *et al* 2006), BIS monitoring does not track the hypnotic effect of ketamine (Hans *et al* 2005b). In the presence of moderate doses of ketamine the loss of responsiveness to verbal and noxious stimulation (mechanical stimulation of nasal mucosa) occurs at higher BIS values compared to propofol anesthesia alone (Sakai *et al* 1999). In a study by Hirota and colleagues, the addition of N_2O (20 %–70 %) to stable propofol–fentanyl anesthesia had no effect on BIS values. The addition of ketamine

(bolus 0.4 mg/kg and infusion 1 mg/kg/h) increased both BIS and SEF significantly (Hirota *et al* 1999).

Dexmedetomidine sedation seems to be associated with decreased BIS values, comparable to those achieved by propofol sedation (Venn and Grounds 2001).

Even though xenon decreases BIS values similarly to isoflurane, during emergence from xenon anesthesia the EEG pattern and the BIS values (v. 3.22) may display greater variability than during emergence from isoflurane anesthesia, such that some patients regain consciousness with slow EEG patterns and low BIS values (Goto *et al* 2000).

Bispectral index and opioid analgesics

Clinically relevant doses of opioid analgesics have relatively little influence on the electroencephalogram (Scott *et al* 1985, Shafer and Varvel 1991, Barvais *et al* 2003, Hagihira *et al* 2004b), even though the sedative effect of opioids may be clinically evident (Lysakowski *et al* 2001). Glass and colleagues showed that alfentanil concentrations up to 200 ng/ml alone did not induce unconsciousness and produced minimal decreases in BIS (v. 3.0) values in volunteers (Glass *et al* 1997).

In a placebo-controlled study, Lysakowski and colleagues demonstrated that in the presence of clinically relevant doses of opioid analgesics LOC occurs at higher BIS (v. 3.12) values and lower propofol effect-site concentrations than with propofol alone. The correlation between BIS and effect-site propofol concentration was preserved in the presence of opioids (Lysakowski *et al* 2001). Mi and colleagues found that LOC and the loss of response to mechanical stimulation of the nasal mucous membrane occurred with lower propofol doses and at higher BIS (v. 3.2) values in the presence of than in the absence of an analgetic dose of fentanyl (2 μg/kg). The reduction of propofol requirements was greater for noxious than for non-noxious stimuli. In that study, the correlation between BIS values and plasma propofol concentrations was weaker in the presence of than in the absence of fentanyl (Mi *et al* 1999). Mustola and colleagues reported that the loss of response to tetanic electrical stimulation occurred at higher BIS (v. 3.3) values and with lower doses of propofol during combined propofol and remifentanil infusions than during a propofol infusion combined with placebo (Mustola *et al* 2005).

Large doses of opioids, in relation to the amount of stimulation, may increase sedation and lower BIS values (Billard *et al* 1997, Strachan and Edwards 2000, Koitabashi *et al* 2002). In a study by Guignard and colleagues, during propofol anesthesia, no significant changes in BIS (v. 3.12) were noted with remifentanil administration before noxious stimulation, even with the highest remifentanil target effect-site concentration of 16 ng/ml (Guignard *et al* 2000). The arousal reaction of the cortex, and thus also the BIS response to noxious stimulation is modulated by the level of opioid analgesia (Hans *et al* 1999, Guignard *et al* 2000) and perhaps also by β-adrenergic blockade (Menigaux *et al* 2002). Guignard and colleagues found that during propofol anesthesia, the increase in BIS (v. 3.12) at laryngoscopy and intubation was inversely correlated with the target effect-site concentration of remifentanil (Guignard *et al* 2000). Iselin-Chaves and colleagues found that the BIS (v. 3.0) response to a noxious mechanical stimulus was reduced by both an increase in propofol concentration and the presence of alfentanil (Iselin-Chaves *et al* 1998).

Bispectral index, noxious stimulation and movement responses

A substantial increase in noxious stimulation during surgery can cause an arousal response with clinical signs and an increased BIS value even when the pre-stimulus hypnotic effect is profound and the corresponding BIS value is low. In such instances the BIS lags behind the clinical change by 5–10 s (Rosow and Manberg 2001). Mi and colleagues reported that BIS was more sensitive than SEF or MF in detecting arousal caused by noxious stimulation during propofol or propofol–fentanyl anesthesia (Mi *et al* 1998).

In the beginning phase of bispectral index development, Kearse and colleagues reported that the bispectral index was a significant predictor of movement responses to skin incision during propofol–N_2O anesthesia (Kearse *et al* 1994a). In another early study, pre-incision BIS values were different in movers and non-movers to incision during isoflurane–alfentanil and during propofol–alfentanil anesthesia. BIS was a significant predictor of movement responses (Vernon *et al* 1995). In a study conducted with BIS version 1.1, overall the pre-incision BIS values were lower in non-movers than in movers to skin incision. The correlation between BIS values and the probability of movement was much less significant when opioids were used as anesthetic adjuvants than with hypnotic-based anesthesia. Thus, opioid analgesia suppressed movement responses at effect-site concentrations, which had little effect on the EEG. Both BIS and the estimated effect-site opioid concentration were independent predictors of movement responses in the combined data set from patients anesthetized with isoflurane or propofol, N_2O, and opioids (Sebel *et al* 1997).

The P_K values reported for the pre-stimulus values of later BIS versions (v. 3.12–3.22) for movement responses to noxious stimulation have been low or modest (0.54–0.68) (Katoh *et al* 1998, Doi *et al* 1999, Kurita *et al* 2001, Bruhn *et al* 2003, Doi *et al* 2005). The same applies to SEF95 (reported pre-stimulus P_K values 0.55–0.63) (Katoh *et al* 1998, Doi *et al* 1999, Bruhn *et al* 2003, Doi *et al* 2005). Some authors, however, have found a statistically significant association between BIS (v. 3.0–3.3) (Leslie *et al* 1996, Singh *et al* 1999) or SEF95 (Dutton *et al* 1996, Leslie *et al* 1996) and movement responses to noxious stimulation.

Bispectral index and recovery from anesthesia

Gan and colleagues showed that titrating the administration of propofol–alfentanil–N_2O anesthesia to achieve BIS (v. 3.0) values between 45 and 60 (60–75 during the final 15 min of surgery) was associated with a reduced consumption of propofol and a faster recovery compared to a standard practice group, without an increase in adverse intraoperative responses (Gan *et al* 1997). Song and colleagues found that titrating desflurane–fentanyl–N_2O or sevoflurane–fentanyl–N_2O anesthesia to a target BIS (v. 3.12) value of 60 reduced the consumption of the volatile agents and hastened the emergence from anesthesia compared to the control groups, where the average BIS value was in the range of 40–45. In that study, more mivacurium was used in the BIS-titrated groups than in the control groups, but the consumption of fentanyl was similar among both groups. The times to home-readiness did not differ between the groups (Song *et al* 1997).

In elderly patients undergoing orthopedic surgery with isoflurane–fentanyl–N_2O anesthesia, titration of the isoflurane dose to achieve BIS 50–60 during maintenance was associated with reduced isoflurane consumption and faster post-operative orientation compared to standard clinical practice, despite similar BIS values at the end of anesthesia (Wong *et al* 2002).

Nelskylä and colleagues showed that titrating sevoflurane–alfentanil–N_2O anesthesia to maintain BIS (v. 3.21) values at 50–60 was associated with a decreased incidence of emetic symptoms and improvement in some of the early recovery parameters, compared to guiding anesthesia with hemodynamic signs. The times to achieving home-readiness were similar in the BIS and the control groups after gynecologic laparoscopy (Nelskylä *et al* 2001). Similarly, the incidence of nausea and the antiemetic drug requirement 24 h after desflurane anesthesia were reduced in BIS (v. 3.3) monitored (target BIS 45–55) patients compared to a control group (Luginbühl *et al* 2003).

White and colleagues found that compared to a control group, both early and intermediate recovery, including the times to home-readiness and actual discharge, were significantly faster in both BIS-guided (target 50–60) and AAI-guided groups after desflurane–N_2O anesthesia for gynecological laparoscopic surgery. Desflurane consumption was reduced and the subjective quality of recovery was improved in the EEG monitored groups. The mean BIS and AAI values during anesthetic maintenance

were significantly lower in the control group than in the EEG monitored groups (White *et al* 2004).

Ahmad and colleagues reported very high PACU bypass rates after gynecological laparoscopic surgery, regardless of whether sevoflurane anesthesia was guided by BIS values (50–60) or hemodynamic signs. In that study, the mean sevoflurane concentrations in the two groups were remarkably similar and in the suturing phase only N_2O was used as needed. No significant differences emerged in any other recovery parameters, either (Ahmad *et al* 2003). Song and colleagues reported that the BIS (v. 3.12) value at the end of laparoscopy did correlate with the time to achieving fast-track eligibility after both desflurane–fentanyl–N_2O and propofol–fentanyl–N_2O anesthesia. No correlation between the BIS values at the end of the procedure and the times to home-readiness or actual discharge was found (Song *et al* 1998).

In a multicenter study using desflurane–remifentanil anesthesia, Bruhn and colleagues did not find significant reductions in recovery times with either BIS-guided (target 50, and 60 during the last 15 min of surgery) or AAI-guided anesthesia, compared to the standard practice. The standard practice group had BIS values similar to those of the BIS group (Bruhn *et al* 2005).

In an open, observational study including a large number of heterogenous patients, Johansen and colleagues found that titration of anesthetic administration to achieve a BIS (v. 3.0) range of 50–65 during maintenance was associated with shortened times to extubation, OR exit, and PACU discharge, compared to unmonitored controls. The frequency of PACU extubations was also reduced, as were the average total doses of desflurane and isoflurane. The recovery times of patients maintained mostly at BIS values less than 50 were similar to those of unmonitored controls (Johansen *et al* 2000).

Pavlin and colleagues investigated a large, heterogenous group of surgical inpatients in a randomized cross-over design. BIS monitoring with a suggested target range of 50–60 resulted in a mean BIS 47 during anesthetic maintenance. BIS values were not available in the control group. No significant differences in the recovery parameters between the BIS monitored group and the control group were observed. The authors speculated that there may have been a reluctance to use lighter levels of anesthesia in inpatients. They concluded that since multiple medical and non-medical factors influence the time to discharge, it may be impossible to hasten recovery by small adjustments in the delivered anesthetic dose, especially when using anesthetic agents with fast kinetics (Pavlin *et al* 2005).

Cost issues in bispectral index monitoring

Yli-Hankala and colleagues found that the cost of BIS monitoring exceeded the savings from the decreased consumption of propofol and sevoflurane in patients whose anesthesia was guided by BIS values. The increase in direct costs with BIS monitoring was mainly due to expensive designated EEG electrodes. The price of drugs has only a marginal role in the total costs of operative treatment. The authors concluded that potential financial benefit may be gained indirectly from an improved recovery profile with BIS-monitoring (Yli-Hankala *et al* 1999a). O'Connor and colleagues argued that if only the potential prevention of intraoperative awareness is regarded, it may be difficult to justify routine BIS monitoring. The cost of preventing a rare event is high and increases with less than perfect performance of the monitoring technique. In populations at high risk for awareness, however, BIS-monitoring could be cost-effective (O'Connor *et al* 2001). A meta-analysis by Liu concluded that the use of BIS monitoring for ambulatory anesthesia was economically inefficient. Even though BIS monitoring modestly reduced anesthetic use and the risk of post-operative nausea and vomiting, the time spent in the PACU was only marginally reduced, and the ability to bypass PACU or the time spent in the ambulatory surgery unit were not changed. Even without the capital costs of the monitoring system, the cost of the BIS electrodes exceeded the savings by approximately 5 US dollars per patient (Liu 2004).

Critique on bispectral index monitoring

Miller and colleagues have questioned the benefit of bispectral analysis over power spectral analysis of the EEG for differentiating the awake and anesthetized states. They found that during the induction of anesthesia, an analog of the BIS SyncFastSlow parameter based on the amplitude-independent bicoherence did not change at all, whereas SyncFastSlow was closely tracked by its analog based on the power spectrum (instead of the bispectrum). Thus, changes in SyncFastSlow during induction mostly reflected changes in high frequency spectral power. Both SyncFastSlow and its power spectrum analog equally discriminated the awake and the anesthetized states. The authors concluded that because the EEG is a stochastic signal, the bispectral power in fact measures the degree of deviation from gaussianity, namely the skewness of the signal, and does not necessarily imply the presence of quadratic phase coupling. The magnitude of the bispectrum depends on the signal power (amplitude). Also, short data lengths bias the bispectrum and bicoherence away from zero, falsely indicating quadratic phase coupling (Miller *et al* 2004). In another study, Sleigh and colleagues demonstrated that during the induction of anesthesia, the BetaRatio performed as well as BIS (v. 3.12) in distinguishing the awake and anesthetized states. They emphasized the importance of the high frequency (γ) band in detecting LOC (induced by GABA-ergic agents) (Sleigh *et al* 2001).

Schwilden and Jeleazcov examined the statistical properties of EEG during isoflurane–alfentanil anesthesia, and concluded that over 90 % of the EEG epochs had to be considered as representing a linear random signal, whereby the bicoherence is constant and most of the information content of the signal is given by the power spectrum (Schwilden and Jeleazcov 2002). Similar results were obtained during propofol–alfentanil anesthesia. The proportion of EEG epochs with nontrivial bispectra was approximately 10 % (Jeleazcov *et al* 2005). The authors concluded that although the underlying neuronal processes may be nonlinear to some extent, the transmission of the electrical signal to the scalp may introduce some kind of phase randomization. Similarly to Sleigh and colleagues, these authors pointed out that a non-trivial bispectrum is to be expected whenever the amplitude distribution of the EEG is skewed (Schwilden and Jeleazcov 2002, Jeleazcov *et al* 2005).

Entropy

The concept of entropy

Entropy is related to the randomness or regularity of a process, but the precise definition depends on the setting in which it is applied (Pincus 1991). The concept of entropy has been used in thermodynamics, statistical mechanics, and information theory. As a physical concept, entropy is proportional to the logarithm of the number of microstates available to a thermodynamical system (Viertiö-Oja *et al* 2004). The Kolmogorov-Sinai entropy is a generalization of the probabilistic definition of entropy (Shannon entropy) (Pincus *et al* 1991).

In 1991 Pincus suggested using entropy for the analysis of physiological signals. Approximate entropy (ApEn), a modification of the Kolmogorov-Sinai entropy, measures the logarithmic likelihood that runs of patterns that are similar remain similar in the next incremental comparisons. It can be applied to reasonably short time series, and an appropriately selected filtering parameter decreases its sensitivity to noise. ApEn is a relative measure, the absolute value of which depends on the choice of the input parameters (Pincus *et al* 1991). Pincus used the ApEn algorithm for the analysis of HRV and Bruhn applied it to EEG analysis. Adjacent EEG epochs are not statistically independent, however, so the requirements for calculating the approximate entropy are not rigorously met (Schwilden 2006).

The Shannon entropy is a measure of uncertainty, originally applied to information theory. It is related to the probabilities of system states (Shannon 1948a, Shannon 1948b). Shannon defined the entropy of a set of probabilities $p_1,...p_N$ as

$$H = -\Sigma\, p_i \log p_i$$

The range of measured values of a signal can be divided into bins, each with a certain probability of occurrence. From these probabilities the Shannon entropy can be calculated. It is independent of the order of occurrence of values of different magnitudes (Schwilden 2006). The Shannon entropy is insensitive to infrequently occurring values (Bruhn *et al* 2001b). It is largest (equal to logN) when all values have the same probability of occurrence, *i.e.* 1 / N (the probability density function is uniform) (Shannon 1948a, Shannon 1948b).

If the area under the power spectral density function is normalized to one, it can be considered as the probability density function of the frequency components, and the spectral entropy can be calculated (Rezek and Roberts 1998, Schwilden 2006). The spectral entropy, a modification of Shannon's entropy, estimates the degree of irregularity or complexity in the frequency distribution. It is affected by the sampling frequency and windowing (Rezek and Roberts 1998). It is independent of the absolute magnitudes of the frequency components of the signal (Viertiö-Oja *et al* 2004).

Entropy and anesthesia

Rezek and colleagues demonstrated that both ApEn and spectral entropy decrease with increasing anesthetic depth (Rezek and Roberts 1998). Bruhn and colleagues found that ApEn predicted desflurane effect-site concentrations as well as or better than spectral parameters and BIS. ApEn decreased as the desflurane concentration increased (Bruhn *et al* 2000b). They reported that after the onset of burst suppression, ApEn indicates the increasing pharmacodynamic effect more accurately than spectral parameters or BIS (v. 3.22) (Bruhn *et al* 2000c, Bruhn *et al* 2001a).

In a study by Sleigh and Donovan the sensitivity, specificity and negative and positive predictive values of approximate entropy for discriminating between the awake and the anesthetized conditions during propofol induction were slightly over 70 %, compared to over 90 % for BIS (v. 3.12) (Sleigh and Donovan 1999). Bruhn and colleagues found that the overall P_K values of ApEn, BIS (v. 3.22), and SEF95 for predicting a modified OAA / S score during propofol–remifentanil anesthesia were 0.89, 0.85, and 0.83, respectively. The P_K values for predicting unconsciousness were 0.95, 0.94, and 0.92. The P_K values for predicting the response to noxious stimulation (laryngeal manipulation) were much lower, namely 0.70, 0.62 and 0.63 (Bruhn *et al* 2003).

Bruhn and colleagues found that the Shannon entropy of the EEG amplitude values, ApEn, SEF95 and BIS (v. 3.12) correlated equally well with the desflurane effect-site concentration. As the probability distribution of EEG amplitude values becomes broader and more uniform during deepening anesthesia, the Shannon entropy of amplitude values increases with increasing desflurane concentrations. The absolute values of the calculated Shannon entropy may vary considerably between individuals despite a similar anesthetic state, and thus it is not suitable for anesthetic depth monitoring (Bruhn *et al* 2001b).

Time-frequency balanced spectral entropy

Datex-Ohmeda, now part of GE Healthcare, recently developed a concept called time-frequency balanced spectral entropy (M-Entropy®), intended for on-line monitoring of anesthetic effect. The algorithm is based on spectral entropy. To calculate the spectral entropy of a particular epoch and frequency range, the power spectrum of the epoch is normalized, so that the sum of the normalized power spectrum over the selected frequency range equals one. Then Shannon's function is applied to the normalized power spectrum over the specific frequency range. The resulting entropy value is adjusted to range between one (corresponding to maximum irregularity) and zero (corresponding to complete regularity) by dividing with logN, where N is the number of frequency components (Viertiö-Oja *et al* 2004).

By individually changing the time window used to assess each frequency component, the response time of the algorithm is optimized. An epoch of 1.92 s is used for frequencies between 32 and 47 Hz, whereas for frequencies of

less than 2 Hz an epoch of 60.16 s is used. The time windows used for frequencies between 2 and 32 Hz are intermediate between these two extremes. The sampling frequency is 400 Hz (Viertiö-Oja *et al* 2004).

The activity of facial muscles produces a broad-band, noise-like EMG signal that is dominant above roughly 30 Hz, whereas the EEG signal dominates at lower frequencies and its power decreases exponentially above 30 Hz. The increase in the fEMG power is a key arousal phenomenon, induced by *e.g.* noxious stimuli in the absence of sufficient analgesia. Because of the short window length used in updating the frequency band 32–47 Hz, the algorithm of time-frequency balanced spectral entropy allows rapid detection of impending arousal. The M-Entropy® module displays two separate entropy values, RE and SE. The former is calculated over the frequencies 0.8–47 Hz, including frequencies associated with EMG activity, whereas the latter is calculated over 0.8–32 Hz and reflects mainly cortical EEG activity. The calculation of SE is adjusted so that when the power in the range 32–47 Hz is zero, RE and SE are equal. This is achieved by multiplying the normalized entropy value in the 0.8–32 Hz range by the factor logN[0.8–32 Hz] / logN[0.8–47 Hz]. When RE > SE, EMG activity is present (Viertiö-Oja *et al* 2004). Vakkuri and colleagues recommended that the train-of-four (TOF) stimulation count be kept at a minimum of one or two in order to benefit from the RE-SE difference as an indicator of EMG activation (Vakkuri *et al* 2005). Vanluchene and colleagues demonstrated that the RE-SE difference decreased nonlinearly toward zero with increasing effect-site concentrations of propofol (Vanluchene *et al* 2004b).

EEG burst suppression is detected by applying a method described by Särkelä and colleagues (Särkelä *et al* 2002). A one-minute time window is used for all frequencies, if suppression periods have been detected during the preceding 60 s. A suppressed EEG is considered to be a perfectly regular signal with zero entropy, and entropy associated with bursts is computed in the same way as during lighter levels of anesthesia. To enhance resolution in the clinically interesting range, the original entropy value is subjected to a non-linear transformation with a monotonous spline function. The slope of the spline function is highest in the range of clinically relevant anesthesia and emergence. The output is presented as two-digit integer values ranging between 0–100 (RE) or 0–91 (SE) (Viertiö-Oja *et al* 2004).

Time-frequency balanced spectral entropy and anesthesia

Maksimow and colleagues have shown that calculated entropy values, corresponding to SE, correlate with CBF, and thus presumably with neuronal function, during sevoflurane and propofol anesthesia. The correlation extended to deep (1.5–2 MAC / EC_{50}) levels of anesthesia (Maksimow *et al* 2005). McKay and colleagues demonstrated a consistent relationship between RE / SE and effect-site sevoflurane concentrations. The steepness of the relationship was much larger during deepening than during lightening anesthesia. The authors proposed that this might be due to the rapid phase transition which occurs at LOC. They found that above the sevoflurane concentration of 3 % the changes in RE / SE were minimal. A large interindividual variability in the RE / SE values at LOC was observed (McKay *et al* 2006).

Ellerkman and colleagues found similar P_K values for discriminating different effect-site sevoflurane concentrations with RE / SE and BIS (v. XP) (0.82–0.84 and 0.80). The PK and PD parameters obtained by modeling were nearly identical for RE / SE and BIS (Ellerkmann *et al* 2004). For discriminating different effect-site propofol concentrations, the P_K value of BIS (v. XP) was better than those of RE / SE (0.84 *vs.* 0.76–0.77) (Ellerkmann *et al* 2006). The P_K values of BIS (v. 4.0), SE and RE for predicting effect-site propofol concentrations reported by Vanluchene and colleagues were 0.91. 0.86, and 0.89. The PD model describing the relationship of effect-site propofol and the EEG parameters was steeper for RE / SE than for BIS. The authors demonstrated a monotonic nonlinear decrease in RE / SE during burst suppression and concluded that RE / SE was superior to BIS

in detecting burst suppression (Vanluchene *et al* 2004b).

During propofol induction, Schmidt and colleagues showed a very good correlation between the sedation level and RE/SE (P_K values for modified OAA/S 0.88–0.89). P_K values for LOC were 1.00 and 0.97 for SE and RE. The start of a remifentanil infusion of 0.4 µg/kg/min in the unstimulated state resulted in slight decreases in RE/SE and BIS. The P_K values of BIS (v. 4.0), SE, and RE for discriminating the anesthetized state and the first somatic response during emergence were 0.91, 0.82, and 0.85 (Schmidt *et al* 2004). Vakkuri and colleagues found that the P_K values of both RE/SE and BIS (v. 3.12) for discriminating between the conscious and unconscious states were 1.0 with a variety of anesthetic techniques. The sensitivities and specificities for classifying consciousness and unconsciousness were also uniformly over 90 %. For both RE/SE and BIS, higher indicator values associated with unconsciousness than with consciousness were only observed at the transition between consciousness and unconsciousness. During emergence, RE/SE were found to recover closer to their baseline values than BIS. RE increase preceded the increase in SE or BIS by 11–12 s during emergence from anesthesia. The authors suggested that in addition to the shorter response time of RE compared to SE and BIS, this may reflect faster resolution of anesthetic effect at the brainstem level than at the cortex (Vakkuri *et al* 2004).

Iannuzzi and colleagues reported that during propofol induction, the P_K value of SE for detecting LOC was even better than that of BIS (v. XP), although the difference was not statistically significant (0.94 *vs.* 0.82). The SE values associated with a 50 % and 95 % probability of LOC were 50 and 42 (Iannuzzi *et al* 2005). During sevoflurane induction, the P_K values of BIS (v. 3.4), SE and RE for detecting LOC were 0.84, 0.83 and 0.84 (Takamatsu *et al* 2006). White and colleagues reported ROC areas for detecting unconsciousness during propofol–desflurane anesthesia for BIS (v. XP), SE, and RE to be 0.97, 0.93 and 0.98. The degree of interindividual variability was similar for all indices. All indices responded consistently to bolus doses of propofol and changes in the inspired desflurane concentration. The entropy module was significantly less susceptible to interference from electrocautery than the BIS monitor (White *et al* 2006).

In a study by Takamatsu and colleagues, a significant difference in the pre-stimulus RE/SE values and the end-tidal sevoflurane concentration between movers and non-movers to skin incision emerged, whereas no significant difference in the pre-stimulus BIS values was observed. The RE/SE value at which 50 % of patients were non-responsive to skin incision was 26. The logistic regression model gave very low (near zero) estimates for RE/SE values associated with a 95 % probability of non-responsiveness to skin incision. Progressively more intense tetanic electrical stimuli induced progressively larger increases in BIS and RE/SE, which were attenuated by increasing sevoflurane concentrations. Tetanic electrical stimuli caused increases in the RE-SE difference, except at 2.5 % sevoflurane. The authors encouraged caution in interpreting the RE-SE difference during anesthesia. They discussed the possibility that the fEMG response might be part of the overall motor response to nociception and be suppressed earlier than the adrenergic response. They noted that fEMG activation occurs not only during nociception but also during other arousal reactions (Takamatsu *et al* 2006).

Wheeler and colleagues showed that clear increases in the RE-SE difference in response to noxious stimulation, followed by increases in SE, occurred more often in patients under 0.8 % isoflurane anesthesia than in patients under 1.4 % isoflurane anesthesia. This was observed both with and without neuromuscular blockade. RE-SE and SE increases were accompanied by increases in the mean arterial pressure (MAP) and HR (Wheeler *et al* 2005). Valjus and colleagues observed that during gynecological laparoscopic procedures, the RE-SE difference was small with both propofol–N_2O–esmolol and propofol–N_2O–remifentanil anesthesia, even during the most stressful periods. The HR, blood pressure and propofol requirement were greater in the esmolol group. Also, all of the patients in the esmolol group

moved in response to surgical stimulation at some point, whereas none of the patients in the remifentanil group did. A minority of the movements were associated with simultaneous increases in SE, RE, and BIS values (Valjus *et al* 2006).

Dierckens and colleagues found a very good agreement between RE / SE and BIS during laparotomy under isoflurane–N_2O anesthesia. The RE-SE difference was small throughout the procedure. No significant variation in RE / SE or BIS was observed at incision, placement of retractors, peritoneal lavage, or skin closure, despite the occurrence of hemodynamic reactions. The areas under the ROC curve for predicting the need for sufentanil bolus, based on a significant hemodynamic response during an adequate hypnotic level (BIS 40–60), were 0.71 and 0.69 for RE and SE. Both areas were statistically significantly different from 0.5. The maximal sensitivities and specificities were 86 %–88 % and 55 %–57 %. The authors used a continuous *i.v.* infusion of atracurium and the level of neuromuscular blockade was not reported. They concluded that the results do not preclude the possibility that RE might be an indicator of nociception in unparalyzed patients (Dierckens *et al* 2007).

Vakkuri and colleagues showed that titration of propofol–alfentanil–N_2O anesthesia by using RE / SE monitoring (SE target 45–65, RE-SE target < 10) decreased propofol use and hastened early recovery without increasing adverse intra- or post-operative reactions. The average SE value during anesthesia was 50 in the experimental group and 44 in the control group in which anesthesia was guided by hemodynamic variables (Vakkuri *et al* 2005).

Caveats in interpreting time-frequency balanced spectral entropy and other entropy measures

Anderson and Jakobsson induced unresponsivess to verbal stimulation with N_2O and found that RE / SE values were unchanged compared to the awake state (Anderson and Jakobsson 2004). Hans and colleagues found that the addition of N_2O to sevoflurane anesthesia during surgery was associated with significant decreases in SE and RE (Hans *et al* 2005a). During stable sevoflurane anesthesia, a ketamine bolus was found to induce an increase in both BIS (v. 4.0) and RE / SE. The RE-SE difference remained unchanged (Hans *et al* 2005b). Maksimow and colleagues found that the inter- and intraindividual variability in RE / SE was much higher during S-ketamine than during propofol anesthesia. Whereas propofol markedly increases δ activity, increases in θ and γ activity were characteristic of ketamine anesthesia. More spectral peaks are observed during ketamine than during propofol anesthesia. Although very good P_K values and sensitivites for discriminating the conscious and unconscious states during ketamine anesthesia were found with RE / SE, the specificities were modest. High relative powers within the high β and γ EEG bands were associated with high RE / SE values. The amount of high frequency EEG activity increased towards the end of ketamine anesthesia, with corresponding increases in RE / SE values (Maksimow *et al* 2006).

During remifentanil–propofol induction RE, EMG power, and BIS (v. XP) were lower after a bolus of atracurium than after a saline bolus. SE and SEF did not differ between the atracurium and placebo groups. The authors concluded that the light anesthetic level with a relatively high baseline EMG activity explained these findings (Liu *et al* 2005). Wennervirta and colleagues investigated the usefulness of processed EEG in brain-dead donors during solid organ harvest. They found that both BIS (v. 4.0) and RE / SE differed from zero at times during the procedure, but entropy was less vulnerable to artifacts than BIS (Wennervirta *et al* 2007).

In a study on stress responses to noxious stimulation, Gjerstad and colleagues reported that two out of twenty patients displayed high RE / SE values during surgical propofol–remifentanil anesthesia, with no other signs of stress. Increasing the propofol concentration did not result in reduction of RE / SE in these cases (Gjerstad *et al* 2007).

ApEn decreases during epileptic seizures (Burioka *et al* 2005). The spectral entropy of electrocorticography in sheep was reported

to be falsely elevated during spikes induced by deep enflurane and sevoflurane anesthesia (Voss *et al* 2006). Gunawardane and colleagues studied patients undergoing electroconvulsive therapy, and found that similarly to BIS, the broad-band spectral entropy did not increase with return of consciousness in post-ictal patients. High frequency (20–40 Hz) spectral entropy was more sensitive to ROC. They concluded that in patients with abnormal low-frequency EEG activity, the spectral entropy or BIS values may not correlate with the level of consciousness (Gunawardane *et al* 2002).

Electromyography

The motor nucleus of the seventh cranial nerve receives input from the cortex, the extrapyramidal system, several brainstem nuclei, and the spinal cord. The mimic muscles also receive direct sympathetic innervation. The voluntary contractions of mimic muscles are under cortical control, whereas emotional expressions are generated by the extrapyramidal system. Startle reflexes can be elicited by touch, light, or sound. The electrical activity of the upper facial mimic muscles (*m. corrugator supercilii, m. frontalis, m. orbicularis oculi, m. pyramidalis nasi*) is a signal source for the biopotentials registered from the forehead. Other facial and neck muscles may also contribute to the signal. Induction of anesthesia reduces the spontaneous facial EMG activity due to reduced efferent motor output (Paloheimo 1990).

The motor unit actiopotential is produced by the summated action potentials of nearly simultaneously firing individual muscle fibers in a motor unit (Kamen and Caldwell 1996). These spikes produced by single motor units can be recorded during weak muscle activity. With an increasing firing rate and recruitment of additional motor units a complex interference pattern is produced (Hopkins and Ellis 1996). Surface electrodes usually record the activity of several motor units simultaneously. After amplification and low-pass filtering the signal can be integrated and divided by the length of the corresponding time window to yield a measure of time-dependent changes in the signal (time-domain analysis). The power spectrum of the EMG signal can be obtained by the Fourier transform (frequency domain analysis) (Paloheimo 1990).

The morphology, amplitude, and frequency content of the recorded potentials depend on the number and characteristics of the active muscle fibers or motor units, the firing rate, the surrounding tissue, the recording distance, the placement of the electrodes, and the properties of the recording apparatus. The action potential conduction velocity along the muscle fiber membrane is an important determinant of the surface EMG. For example, the power spectrum of the more rapidly conducting fast-twitch fibers is characterized by higher frequencies than that of slow-twitch fibers. The general increase in high-frequency content with increasing muscle force is probably related to the progressive recruitment of motor units with faster conducting properties (Kamen and Caldwell 1996). During intensive facial muscle contractions, the EMG power distributes over frequencies up to 300 Hz (Paloheimo 1990).

In 1960, Fink used abdominal EMG to assess the level of muscle relaxation during anesthesia. He observed increases in EMG activity with skin incision, dissection of abdominal muscles or the peritoneum, and traction of mesenterial structures (Fink 1960). The use of the frontal EMG signal as an indicator of arousal reactions to noxious stimuli during anesthesia was suggested at the end of 1970's (Harmel *et al* 1978, Hollmén *et al* 1982).

The Anesthesia and Brain Monitor® (ABM2, Datex/Instrumentarium Corp., Helsinki, Finland) was one of the first applications of online EEG and EMG monitoring in the field of anesthesia. Besides displaying the end-tidal carbon-dioxide, non-invasive blood pressure, and the TOF stimulation response the device provided a graphical (series of ten-second averages) and numerical (updated every second) display of the mean integrated amplitude of one-channel EEG (1.5–25 Hz) and frontal EMG (65–300 Hz) signals. The monitor used non-linear scaling of the ouput to emphasize low-amplitude changes. The frequency content of the EEG signal was estimated by the mean

zero-crossing frequency (ZXF) (Edmonds and Paloheimo 1985).

Edmonds and Paloheimo demonstrated that fEMG responded readily to acoustic stimulation even during deep isoflurane anesthesia or coma (Edmonds *et al* 1986). They also showed that neuromuscular blocking agents depressed the neuromuscular transmission in the frontal muscle to a lesser degree than in the hypothenar muscle (Edmonds *et al* 1986, Paloheimo *et al* 1988). In a study by Greif and colleagues on deeply sedated unstimulated subjects, the frontal-temporal EMG intensity (power in the 70–100 Hz range relative to 0.0001 μV^2) was stable during varying neuromuscular blockade (T1 twitch intensity 0%–80% of the level before mivacurium infusion) as measured by supramaximal electrical stimulation of the ulnar nerve at the wrist (Greif *et al* 2002). The data of Tammisto and Toikka suggest that monitoring the EMG activity of neck muscles might provide an even more sensitive method to detect arousal during anesthesia than the fEMG, at least with neuromuscular block levels less than 90% (Tammisto and Toikka 1991). Without EMG monitoring, subtle movements may go undetected during anesthesia. EMG channels including the mastoid process may reveal EMG activation at deeper levels of anesthesia than facial channels, but may be more affected by neuromuscular blockade than facial channels (Dutton *et al* 1998).

In a study by Edmonds and colleagues the administration of opiate analgesics decreased the fEMG amplitude, although this was not uniformly associated with subjective analgesia in conscious, post-operative patients (Edmonds *et al* 1986, Edmonds *et al* 1988). A low fEMG amplitude often occurred in the absence of moderate or severe pain, however, whereas a high fEMG activity was consistently associated with moderate or severe pain. A significant correlation between the log pain score and the log fEMG amplitude existed (Edmonds *et al* 1986). The same authors showed a dose-response relationship between fEMG amplitude and the intensity of an electrical stimulus to the infraorbital nerve (Edmonds *et al* 1988).

Mathews and colleagues reported that the fEMG power displayed by the BIS monitor was useful in titrating fentanyl administration to an opiate-exposed, unparalyzed patient during desflurane anesthesia, resulting in a rapid and smooth emergence after surgery (Mathews *et al* 2003).

Heart rate variability

Origin and analysis of heart rate variability

Heart rate variability (HRV) refers to oscillation in the interval between consecutive cardiac cycles or between consecutive instantaneous heart rates. This oscillation represents the complex interplay of the central and autonomic nervous system regulation, the humoral and electrophysiological environment, and the cardiovascular and thermal status, which modulate the intrinsic rhythmicity of the sinus node. Mechanical factors (changes in the lung volume) can also influence the HRV (Fleisher 1996, Heart rate variability: standards of measurement, physiological interpretation and clinical use 1996). The first clinical application of HRV was the evaluation of fetal well-being (Hon and Lee 1963). Since then, important fields of HRV research have been risk assessment in patients with myocardial infarction or heart failure and the evaluation of diabetic neuropathy (Fleisher 1996, Heart rate variability: standards of measurement, physiological interpretation and clinical use 1996).

HRV can be analyzed in the time domain or in the frequency domain. Alternatively, methods based on the detection of rhythm patterns or on nonlinear dynamics can be used. The latter address the correlation properties and the complexity of the signal (Heart rate variability: standards of measurement, physiological interpretation and clinical use 1996, Lombardi 2002). Dynamic beat-to-beat measures may be more sensitive than traditional methods of HRV analysis during unstable HR dynamics such as may occur during accentuated sympathovagal interaction (Tulppo *et al* 1998).

The time domain methods describe the statistical properties of either the cycle length (R-to-R or normal-to-normal (N-to-N) interval) or the instantaneous heart rate, or the

differences between successive cycle lengths or heart rates. Examples include SDNN (the standard deviation of N-to-N intervals), an estimate of the overall HRV, and RMSSD (the root of mean squared successive differences in N-to-N intervals), an estimate of the short-term components of HRV. The overall HRV can also be described by the geometrical properties of the probability density distribution of cycle lengths or their differences. The time domain methods are ideal for analysis of long-term recordings. Frequency domain measures are based on estimation of the power spectral density (PSD) of the signal by either parametric or nonparametric methods. The nonparametric fast Fourier transform (FFT) is commonly used for this purpose. In short-term recordings, two major power peaks can be observed in clinical data, the low-frequency (LF) and high-frequency (HF) components. These correspond to the bands 0.04–0.15 Hz and 0.15–0.4 Hz. Frequency domain methods are well suited for short-term recordings (Heart rate variability: standards of measurement, physiological interpretation and clinical use 1996). Similar oscillations can be found in arterial pressure and in peripheral flow. The RRI oscillations may be most sensitive to altered physiological states, however. The spectral variables show a great interindividual spread of values (Mainardi *et al* 1997).

The HF component of HRV is predominantly under vagal, or parasympathetic control, whereas sympathetic activity is a major contributor to LF (Pagani *et al* 1986, Heart rate variability: standards of measurement, physiological interpretation and clinical use 1996). It is thought that the slower response time of the adrenergic system compared to the parasympathetic cholinergic system is responsible for the characteristic LF frequency modulation (van Ravenswaaij-Arts *et al* 1993, Fleisher 1996). Parasympathetic activity may also influence LF, especially in the resting supine position (Akselrod *et al* 1981, Pomeranz *et al* 1985). LF and HF frequency modulation can be found in both sympathetic and vagal efferent nerve discharge, with LF being predominant in the sympathetic outflow and HF in the vagal outflow (Malliani *et al* 1991). The ratio of LF to HF has been used as an index of the sympatho-vagal interaction (Fleisher 1996, Heart rate variability: standards of measurement, physiological interpretation and clinical use 1996). The origin of slower HRV rhythms (very low frequency and ultra-low frequency), which account for the majority of the total power in a 24-h recording, is unclear. Thermoregulatory and peripheral vasomotor mechanisms, the renin-angiotensin system and circadian rhythms may be involved, in addition to sympathetic and parasympathetic influences (Akselrod *et al* 1981, Fleisher 1996).

At normal breathing frequencies, parasympathetic outflow is decreased during inspiration and increased during expiration (Gilbey *et al* 1984). Usually the respiration related rhythmic activity in vagal and sympathetic nerves is almost completely reciprocal. Co-activation of both the vagal and sympathetic systems is involved in some adaptive responses (Koizumi *et al* 1983).

Both diminished autonomic input and a very high level of sympathetic activity lead to decreased variance of R-to-R intervals (RRI) and thus to decreased HRV, although in the latter case the fraction of total HRV in the LF band may increase (Fleisher 1996, Heart rate variability: standards of measurement, physiological interpretation and clinical use 1996). Similarly, during very high vagal activity fixed heart rate dynamics may occur (Tulppo *et al* 1998). HRV does not reflect the mean level of neural input, but rather how variable the neural input is (Malik and Camm 1993, Hedman *et al* 1995). It is important to consider the changes in HR (RRI) when interpreting changes in HRV (Korhonen *et al* 2001). Bradycardia can amplify the effects of any source of variability affecting the sinus node. In general, the effect of (other than sedative) drugs on HRV seems to be small and mostly attributable to changes in heart rate (Lombardi 2002). Aging and several cardiovascular and neurological diseases are associated with reduced HRV (van Ravenswaaij-Arts *et al* 1993, Fleisher 1996).

Normal heart rate dynamics have a fractal or scale-free character, *i.e.* both short-term and long-term correlations exist between RR intervals. This represents a balance or compro-

mise between randomness and order. With aging and disease the fractal dynamics typically degrade into either excessive regularity (loss of complexity) or uncorrelated randomness. It is thought that this is associated with a reduction in adaptive capacity (Laitio *et al* 2000, Goldberger *et al* 2002).

The Poincaré plot displays the current value of a variable against the previous value. Normal and abnormal heart rate dynamics can be discriminated by the shape of the resulting Poincaré plot. The normal pattern resembles a comet: an increasing RRI is associated with increasing beat-to-beat dispersion (Tulppo *et al* 1998). The form of the plot can be quantitatively described by the SD of the residuals against the lines $y = x$ (SD1) and $y' = (-x)+2m$ (SD2), where m is the mean of the variable during the epoch of interest (Korhonen *et al* 2001). SD1, a measure of the instantaneous beat-to-beat variability, quantifies vagal modulation of heart rate. SD2 is a measure of the longer-term RRI variability (Tulppo *et al* 1996). SD1 is strongly correlated with RMSSD and HF. SD2 is strongly correlated with RRI SD, and slightly less with LF (Korhonen *et al* 2001).

Heart rate variability and anesthesia

Induction of anesthesia causes a marked reduction in HRV (Kato *et al* 1992, Latson and O'Flaherty 1993, Galletly *et al* 1994b). As early as in 1985, the degree of respiratory sinus arrhythmia (RSA) was suggested to be a potential on-line indicator of the level of general anesthesia in humans (Donchin *et al* 1985). Pomfrett and colleagues used circular statistical analysis to estimate the degree of RSA during propofol anesthesia. They found that changes in RSA followed changes in anesthetic depth and preceded corresponding changes in EEG MF. In two lightly anesthetized patients RSA also increased at skin incision (Pomfrett *et al* 1993). Similar results were obtained during isoflurane–N_2O anesthesia. RSA increased during skin incision, whereas EEG MF or SEF95 did not. The authors concluded that as an indicator of brainstem activity RSA is ideal for the early detection of arousal (Pomfrett *et al* 1994).

N_2O (67 %) does not affect the HRV power spectra (Tanaka and Nishikawa 2004). The effect of opioids may be more readily detected by nonlinear measures than time-domain measures of HRV (Storella *et al* 1995). Morphine has been reported to decrease LF more markedly than HF, consistent with a vagotonic effect (Michaloudis *et al* 1998).

Constant and colleagues demonstrated in isoflurane-anesthetized children that the residual HRV during anesthesia was mainly composed of HF fluctuations (Constant *et al* 2000). Similarly, during isoflurane–N_2O or desflurane–N_2O anesthesia in spontaneously breathing patients, normalized LF decreased and normalized HF increased (Widmark *et al* 1998). Korhonen and colleagues demonstrated that during deep propofol sedation in cardiac surgery patients, the regular peaked RSA related to mechanical ventilation was practically the only modulation of HR (Korhonen *et al* 2001). VLF power was found to be relatively preserved during propofol anesthesia, possibly due to the direct vasodilator effect of propofol (Galletly *et al* 1994a). This may also be an indication of loss of stability of cardiovascular control during propofol anesthesia (Keyl *et al* 2000).

The onset of burst suppression during isoflurane anesthesia was associated with a transient increase in the total HRV power (Kato *et al* 1992). Yli-Hankala and colleagues demonstrated that the onset of a burst episode is associated with a decrease in the RRI, and the onset of a suppression episode is associated with an increase in RRI in most patients. The magnitude of the RRI changes varies between individuals. The authors suggested that the onset of suppression is associated with an increase of vagal inhibitory influence on HR, which is abruptly released at burst onset (Jäntti and Yli-Hankala 1990, Yli-Hankala and Jäntti 1990, Yli-Hankala *et al* 1990). In a later study the authors showed that the EEG related changes in RRI were abolished by atropine. Atropine did not affect the amplitude of RSA during anesthesia with mechanical ventilation. Thus RSA does not seem to be exclusively under parasympathetic control during positive pressure ventilation (Yli-Hankala *et al* 1993c).

RSA depends on both central respiratory drive and sensory input from lung inflation (Gilbey *et al* 1984). Pagani and colleagues found that in awake healthy volunteers the transition from spontaneous breathing (15/min) to metronome controlled breathing (20/min) was associated with an increase in HF, producing a single narrow spectral peak corresponding to the respiratory frequency (Pagani *et al* 1986).

Nakatsuka and colleagues reported that during 2% sevoflurane–N_2O anesthesia, apnea caused a reduction in HF. The authors ascribed this effect to reduced blood pressure variation in the absence of thoracic movement. During deeper anesthesia with an isoelectric EEG, HF was very low and no change in HF with apnea compared to mechanical ventilation was observed. The respiratory pattern had no significant effect on LF (Nakatsuka *et al* 2002).

Pöyhönen and colleagues investigated the effects of the CO_2 level, tidal volume and respiratory rate on HRV in awake volunteers and anesthetized patients. During a controlled CO_2 level and respiratory rate, an increase or decrease in tidal volume increased or decreased, respectively, the absolute and normalized HF power in spontaneously breathing volunteers. During mechanical ventilation, either awake or anesthetized (0.4 MAC isoflurane), the changes in HF power were not statistically significant. The authors suggested that the activity of the respiratory center is important in modulating HRV and not tidal volume *per se*. A decrease in the respiratory rate from 12/min to 8/min was associated with a decrease of normalized HF power and an increase of normalized LF power in both spontaneously breathing and mechanically ventilated volunteers, as well as in anesthetized patients. Thus the effect of the respiratory rate on HRV is presumably mediated via afferent input from receptors inside the thorax. The authors concluded that in anesthetized patients, small changes in the CO_2 level or tidal volume do not modulate HRV significantly, if the respiratory rate is controlled (Pöyhönen *et al* 2004).

Sleigh and Donovan found that the ability of HRV variables to detect the transition to unconsciousness during propofol induction was worse than that of EEG variables. The sensitivity, specificity, and negative and positive predictive values of HRV were less than 70% (Sleigh and Donovan 1999).

Pichot and colleagues observed that arousal from isoflurane anesthesia was associated with abrupt, simultaneous increases in HR, total HRV power, LF, and normalized LF (Pichot *et al* 2001). Similarly, Constant and colleagues reported that the increase in LF and LF/HF ratio at emergence from anesthesia was especially pronounced, indicating sympathetic activation (Constant *et al* 2000).

Heart rate variability and noxious stimulation

Schubert and colleagues reported that maximal intra-abdominal surgical stimulation during isoflurane–N_2O or enflurane–N_2O anesthesia was associated with an increase in LF power and the LF/HF ratio. In that study, tracheal intubation and skin incision did not cause sympathetic activation. The authors concluded that HRV may be useful in the evaluation of the anesthetic effect relative to the magnitude of the stressor event. The intraindividual variation in HRV variables was large (Schubert *et al* 1997).

Latson and colleagues found that total HRV and normalized LF increased at skin incision during propofol–fentanyl anesthesia, but not during isoflurane–N_2O–fentanyl anesthesia. It is possible that the overall level of anesthesia was deeper in the isoflurane group in this study, as evidenced by lower total HRV and lower MAP compared to the propofol group. Isoflurane-anesthetized patients often displayed transient heart rate decelerations at skin incision. The authors concluded that isoflurane may have a particularly pronounced effect on sympathetic activity (Latson and O'Flaherty 1993). Huang and colleagues demonstrated a transient increase in LF/HF power and HR with tracheal intubation after thiopentone–fentanyl induction (Huang *et al* 1997).

Wodey and colleagues found that HF power decreased after skin incision in children during sevoflurane anesthesia, consistent with sympathetic activation (Wodey *et al* 2003).

Toweill and colleagues found transient increases in total HRV, LF, LF / HF and a measure of long-range correlations in the RRI signal at noxious stimulation during propofol anesthesia in children. ApEn displayed a transient decrease. The authors concluded that HF could be used as an indicator of depth of anesthesia and LF as an indicator of sympathetic reactions (Toweill *et al* 2003). In a study by Rantanen and colleagues RRI decreased and RRI SD1, SD2, and RRI SD increased at skin incision during propofol–remifentanil anesthesia. With an increasing remifentanil dose, the RRI response was attenuated and the SD1 response was enhanced (Rantanen *et al* 2006a).

The Anemon Index (AI; MCSA, Geneva, Switzerland) was developed for online monitoring of the activity of the autonomic nervous system by analyzing HRV. The proprietary index ranged from 0 to 200, with increasing values indicating progressively more sympathetic activity. Carrasco-Jiménez and colleagues showed in sevoflurane-anesthetized dogs that the AI uniformly increased at tracheal intubation, whereas no significant changes where observed in BIS or hemodynamic variables. Surgical stimuli did not induce significant changes in AI, BIS, or hemodynamic variables. The interindividual variability in both BIS and AI were considerable during anesthesia with a constant sevoflurane concentration (Carrasco-Jiménez *et al* 2004). A trend toward increased AI at intubation was also reported in sevoflurane–anesthetized pigs. No changes in AI during mechanical test stimuli or two different fentanyl doses were observed. No surgical stimulation was reported, however, and some of the test stimuli were of limited intensity (Martín *et al* 2003).

Pulse plethysmography

The pulse plethysmography waveform

According to the Beer-Lambert law, the absorption of light increases (*i.e.*, the intensity of transmitted light decreases) exponentially as a function of distance and the concentration of dissolved substances (Szocik *et al* 2005). This is the basic principle of photoplethysmography (PPG), which measures the intensity of transmitted (or reflected) light of a specific wavelength in order to monitor changes in the volume of the light-absorbing structure. During anesthesia, pulse oximeters whose primary function is to produce an estimate of the relative concentration of oxyhemoglobin, also provide a photoplethysmographic waveform, related to the arterial pulsations of the vascular bed.

The total amount of light transmitted to the photodiode detector depends on the optical density of the solid tissues and the amount of blood in the vascular bed. The small variations in the intensity of transmitted light with arterial pulsations are amplified and converted to a voltage signal. The amplitude of the PPG waveform correlates with perfusion, usually of the fingertip or earlobe, although it does not provide quantitative information of the magnitude of arterial pulse waves (Dorlas and Nijboer 1985, Murray and Foster 1996). The blood volume changes depend on the pulse pressure and the distensibility of the vascular wall, as do the PPG amplitude changes. The distensibility is modulated by autonomic nervous system input to the smooth muscle of the vessel walls (Dorlas and Nijboer 1985). The PPG waveform reflects the interplay of the left ventricular ejection and the capacitance of the vasculature (Murray and Foster 1996).

Both pressure and flow waves in the arterial system consist of a forward wave and a composite backward wave, generated by reflection at different parts of the system where the impedance changes. During increased resistance, the reflection (backward wave) is increased, and during decreased resistance it is decreased (Westerhof *et al* 1972). The steepness of the slope of the ascending limb of the PPG waveform is related to the force of left ventricular contraction. Changes in the stroke volume may produce beat-to-beat variations in the PPG amplitude and the area under the curve. If the vasculature is very elastic and the fluid filling is adequate, the waveform is broad and rounded, and the amplitude and the area under the curve of the PPG waveform are large. During hypovolemia and vasoconstriction the PPG waveform becomes more narrow and

peaked, and the amplitude decreases. A steep descending limb of the PPG waveform with a relatively prolonged baseline may indicate an inadequate stroke volume relative to the vascular compliance (Murray and Foster 1996).

The dicrotic notch on the descending limb of the waveform may be related to the closure of the aortic valve, but also to the pressure wave reflection. The dicrotic notch is usually situated approximately in the middle of the PPG waveform (figure 3). During vasoconstriction the dicrotic notch occurs relatively earlier and is situated closer to the peak of the waveform. With vasodilation the dicrotic notch is delayed and occurs relatively lower on the descending limb of the pulse waveform. It also becomes more prominent (Burch 1986, Murray and Foster 1996). The PPG amplitude increases during vasodilation, *e.g.* during deep anesthesia (Dorlas and Nijboer 1985). During extreme vasodilation and an increased cardiac output the dicrotic notch may even be found on the ascending limb of the next PPG waveform. The origin of occasionally observed double dicrotic notches is not clear (Murray and Foster 1996).

Thermoregulation is an important determinant of skin blood flow. During cooling, the PPG amplitude decreases exponentially in relation to the frequency of sympathetic vasoconstrictor bursts. The vasomotor and sudomotor sympathetic fibers have a tendency to synchronous firing. Arousing stimuli evoke bursts of vasoconstrictor impulses, and usually sudomotor impulses also (Hagbarth *et al* 1972, Wallin and König 1976, Bini *et al* 1980). Both spinal and supraspinal reflex arcs may be involved in the generation of these reflex bursts (Hagbarth *et al* 1972). They are attenuated by general and regional anesthesia (Wallin and König 1976, Lundin *et al* 1990). Preganglionic sympathetic fibers innervating the upper extremities arise from the Th2–Th7 spinal segments. The α_1-adrenergic receptors are involved in both maintenance of skin vasoconstrictor tone at rest and phasic vasoconstriction (Khan *et al* 1988).

In addition to respiratory frequency modulation, a coherent 0.1 Hz rhythm has been demonstrated in both the PPG wave, RRI, and blood pressure. The respiratory frequency variability of PPG and blood pressure are interpreted as having a mainly mechanical origin, whereas the 0.1 Hz rhythm reflects the effect of the sympathetic nervous system. During sympathetic activation, both the power in the 0.1 Hz range and the synchronization between the 0.1 Hz variability of these different cardiovascular signals increase. Very low frequency fluctuations in the PPG wave are probably due to local control mechanisms (Bernardi *et al* 1996). An increased amplitude of the respiratory fluctuations in the PPG waveform may be associated with hypovolemia (Dorlas and Nijboer 1985, Murray and Foster 1996).

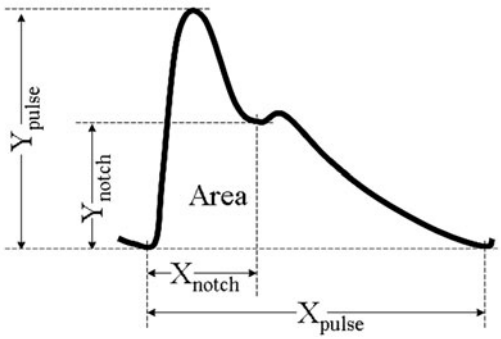

Figure 3. A typical PPG waveform. Y_{pulse} = PPG amplitude, Y_{notch} = dicrotic notch amplitude, X_{pulse} = pulse duration, X_{notch} = latency of the dicrotic notch minimum from the start of the pulse upstroke. PPG area is defined as area under the curve. Notch relative amplitude = Y_{notch}/Y_{pulse}. Notch relative latency = X_{notch}/X_{pulse}. Reprinted from Seitsonen et al 2005; Acta Anaesthesiol Scand 49: 284–92, with the permission of the copyright holder.

Pulse plethysmography and anesthesia

Induction of anesthesia causes an increase in the PPG amplitude, related to vasodilation caused by sympatholysis (Dorlas and Nijboer 1985, Nijboer and Dorlas 1985, Luginbühl *et al* 2002). A noxious stimulus, such as tetanic electrical stimulation, elicits a transient vasoconstriction in the extremities, which can be measured with PPG (Dorlas and Nijboer 1985, Nijboer and Dorlas 1985, Luginbühl *et*

al 2006). Neuromuscular blockade slightly attenuates the PPG amplitude response to electrical stimulation of the ulnar nerve or muscle (Luginbühl *et al* 2002). The regulation of blood flow in the earlobes is different from that of the digits. The vasoconstrictor responses are much less pronounced in the ear than in the fingers (Nijboer and Dorlas 1985, Awad *et al* 2001). Separate vasoactive reflex mechanisms, including a vasodilator mechanism, may exist for different orofacial regions. The magnitude of the blood flow reduction in the skin of the finger (and the MAP response) depends on the intensity of the stimulus (Kemppainen *et al* 2001).

In 1985, Nijboer and Dorlas suggested that the finger PPG could be used to monitor blockade by "stress-free" anesthesia of autonomic responses to surgical stimulation (Nijboer and Dorlas 1985). Murray and Foster noted that a decreased PPG amplitude, usually combined with an elevation of the dicrotic notch is a signal of sympathetic activity during lightening anesthesia (Murray and Foster 1996).

Shimoda and colleagues used laser Doppler flowmetry to measure the skin vasomotor reflex (SVmR) to tetanic electrical stimulation of the ulnar nerve during sevoflurane–N_2O anesthesia. They reported that in patients with normal autonomic function, the SVmR amplitude, in response to a tetanic electrical stimulus immediately before laryngoscopy, correlated with the magnitude of the systolic blood pressure response to intubation, but not with the HR response (Shimoda *et al* 1998b). The magnitude of the SVmR correlated with the strength of the tetanic electrical stimulus, the duration of stimulation, and the depth of anesthesia. Sevoflurane attenuated the SVmR to noxious stimulation in a dose-dependent manner. Neuromuscular blockade did not influence the SVmR. The authors concluded that the SVmR may be helpful in the assessment of nociception and antinociception during general anesthesia (Shimoda *et al* 1998a).

The absence of a significant decrease in the PPG amplitude in response to a tetanic electrical test stimulus to the ulnar nerve may predict attenuation of significant hemodynamic responses to tracheal intubation better than the absence of the SVmR. The SVmR measures superficial perfusion to the depth of a few millimeters. During volatile anesthesia and active heating of the patient the PPG, which measures blood volume changes in deeper vessels, may detect vasoconstriction responses more sensitively than the SVmR. The PPG response and the SVmR are not directly correlated with skin temperature, however (Luginbühl *et al* 2002).

An increasing opioid concentration exponentially decreases the reflex vasoconstriction elicited by tetanic electrical stimulation. The PPG amplitude response to tracheal intubation correlates with the opioid analgesic concentration (Luginbühl *et al* 2002). Nakahara and colleagues reported that the sevoflurane concentration required to block the skin vasomotor reflex to skin incision was 3.07 % or 1.75 MAC in oxygen. The amplitude of the SVmR did not correlate with either blood pressure or heart rate changes at skin incision (Nakahara *et al* 2002).

Singham and colleagues investigated changes in the pulse transit time (PTT, defined as the time from the R-wave of the ECG to the maximum upslope of the corresponding PPG waveform) during isoflurane–N_2O anesthesia after propofol–opioid induction. The PTT increased at the induction of anesthesia. A large decrease in PTT was observed at laryngoscopy and tracheal intubation. No significant changes in PTT were observed at the start of surgical stimulation. No consistent association between PTT and movement responses ($N = 5$) was found. The authors noted that the withdrawal reflexes and the autonomic responses to nociceptive stimuli may be differentially affected by anesthesia and analgesia (Singham *et al* 2003). Dahan and colleagues reported that the PTT was shorter during light than during deep hypnotic levels, and correlated with BIS (v. 3.3) and HR. Noxious stimuli, movement responses, and arousal were associated with decreases in the PTT. They noted that the PTT reflects changes in the arterial compliance, which is under autonomic control and influences the arterial shock wave velocity (Greenwald *et al* 2002). In a study by Rantanen and colleagues the PPG amplitude and PTT decreased, and the PPG amplitude SD2 increased at skin incision

during propofol–remifentanil anesthesia. The changes in the PPG variables were similar in both movers (N = 5) and non-movers (N = 50) to skin incision (Rantanen *et al* 2006a).

Luginbühl and colleagues investigated the effect of a tetanic electrical test stimulus on PPG variability during propofol–remifentanil anesthesia. They found that the change in PPG amplitude SD2 differed between hemodynamic responders and non-responders to tracheal intubation, and the change in PPG amplitude SD was a statistically significant predictor of hemodynamic response to intubation in a logistic regression model. The PPG variability response to the test stimulus, however, conferred no benefit over using the predicted remifentanil effect-site concentration and BIS (v. XP) as predictors of the hemodynamic response to tracheal intubation in a logistic regression model. No significant differences in PPG variability responses to the test stimulus were observed between groups with different remifentanil and propofol concentrations. The authors noted that inter-individual variability may have concealed any drug-induced differences in PPG variability (Luginbühl *et al* 2006).

Drug interactions, pharmacokinetics and pharmacodynamics

The equilibration of the plasma concentration of a drug with the effect-site concentration can be described with a first-order differential function (van Meurs *et al* 1998):

$$dC_e(t) / dt = k_{eo} [C_p(t) - C_e(t)]$$

where C_e is the effect-site concentration, C_p is the plasma concentration, t is time, and k_{eo} is the first-order rate constant, which characterizes the temporal aspects of equilibration between plasma and effect-site. A pharmacodynamic (PD) model describes the physiological effect of a drug as a function of its concentration at the effect-site, the compartment where the drug interacts with receptors or other targets. Due to the time lag of plasma and effect-site equilibration, the display of plasma concentration *vs.* effect produces two curves, one for increasing and one for decreasing concentrations (a hysteresis loop), whereas the relationship between effect-site concentration *vs.* effect can be displayed in a single curve (collapsed loop). The hysteresis between the plasma concentration and effect is influenced by perfusion, diffusion, nonspecific binding and receptor events (Scott *et al* 1985, Egan *et al* 1996). The half-time of equilibration ($T_{½}\ k_{eo}$) between the plasma and effect-site concentrations is given by $\ln 2 / k_{eo}$ (Lötsch 2005).

The hysteresis between plasma concentrations and EEG effect is considerably smaller with alfentanil than with fentanyl. The $T_{½}\ k_{eo}$ is 0.9–1.1 min (k_{eo} 0.63–0.77 / min) for alfentanil *vs.* 4.7–6.4 min (k_{eo} 0.11–0.15 / min) for fentanyl (Scott *et al* 1985, Scott and Stanski 1987, Egan *et al* 1996). After a bolus dose, the peak alfentanil effect-site concentration is reached at approximately 1.4 min *vs.* 3.6 min for fentanyl (Shafer and Varvel 1991).The rapid initial redistribution from the effect-site is an important factor determining the resolution of alfentanil effect. With fentanyl, this rapid redistribution is not apparent at the effect-site. Instead, fentanyl has an extended effect profile (Ebling *et al* 1990).

Depending on the PK parameters and the EEG measure of effect used, the $T_{½}\ k_{eo}$ reported for propofol is 1.5–3.5 min (k_{eo} 0.20–0.46 / min) (Billard *et al* 1997, Kazama *et al* 1999, Schnider *et al* 1999). The time to peak effect after a bolus dose of propofol is 1.6–2.0 min (Schnider *et al* 1999, Struys *et al* 2000).

A commonly used pharmacodynamic model is the sigmoid E_{max} model (van Meurs *et al* 1998, Minto *et al* 2000):

$$E = E_o + (E_{max} - E_o) [C_e^{\gamma} / (C_e^{\gamma} + EC_{50}^{\gamma})]$$

where E is the value of the measured variable at the drug effect-site concentration C_e, E_o is the value of the measured variable in the absence of the drug, E_{max} is the value of the variable when the drug effect is maximal, EC_{50} is the effect-site concentration that produces half of the maximal effect, and γ is a parameter describing the slope of the concentration-response relationship. In models estimating the probability of a certain response, E_o is 0 and E_{max} is the

maximal probability, usually assumed to be 1.

Bouillon and colleagues used a hierachical PD model to describe the interaction between an opioid, remifentanil, and a hypnotic agent, propofol. They found that the hierarchical model resulted in a considerably better fit to the data compared with a model introduced by Minto and colleagues, where each fixed combination (ratio) of two or more drugs is regarded as a "new drug" with its own response curve (Minto *et al* 2000). Also, in contrast to the Minto model, the hierarchical model did not predict that remifentanil alone can ablate the response to non-noxious or noxious stimulation. The hierarchical model estimates the potency of remifentanil with respect to the attenuation of noxious stimuli, not with respect to an end-point where a hypnotic effect is required. Thus the EC_{50} of remifentanil was much lower in the hierarchical model than in the Minto model (approximately 1 ng/ml *vs.* 19 ng/ml) (Bouillon *et al* 2004).

The authors demonstrated that remifentanil alone could not suppress responsiveness to non-noxious or noxious stimulation in clinically relevant concentrations. Modest concentrations of remifentanil profoundly decreased the propofol concentration required to suppress responsiveness to noxious stimulation, whereas high propofol concentrations were required in the absence of remifentanil. A ceiling effect for remifentanil was also observed. The interaction between propofol and remifentanil was synergistic for suppression of the clinical responses to stimulation, and additive for the EEG effects. At remifentanil concentrations less than 8 ng/ml, however, the EEG effect was minor. Approximate entropy was found to be more sensitive to opioid effect than BIS (v. 3.22). The combination of propofol and remifentanil selected to suppress responsiveness had a major effect on the associated EEG state (Bouillon *et al* 2004).

Kazama and colleagues showed a synergistic action between propofol and fentanyl for the suppression of somatic and hemodynamic responses to abdominal surgical stimuli. A 50 % reduction in the propofol EC_{50} to suppress somatic responses to skin incision, peritoneum incision, and abdominal wall retraction was produced by fentanyl plasma concentrations of 1.2, 1.8, and 2.8 ng/ml. The blood pressure responses to surgical stimuli correlated negatively with the fentanyl concentration. The authors concluded that less than 3 ng/ml of fentanyl is not adequate to control the hemodynamic response to peritoneum incision or abdominal wall retraction, even when the concentration of propofol is sufficient to suppress somatic responses (Kazama *et al* 1998). Similarly, Katoh and colleagues showed that fentanyl attenuates the hemodynamic responses to tracheal intubation in a dose-dependent manner. A ceiling effect of fentanyl for suppressing movement responses to tracheal intubation is achieved at lower doses than for suppressing hemodynamic responses during sevoflurane anesthesia (Katoh *et al* 1999).

Westmoreland and colleagues reported that isoflurane MAC was reduced by 50 % with fentanyl at 0.5 ng/ml or alfentanil at 29 ng/ml. An apparent ceiling effect for the reduction of isoflurane requirements was achieved with fentanyl above 3 ng/ml or alfentanil above 500 ng/ml (Westmoreland *et al* 1994). A similar ceiling effect for fentanyl was also observed by Smith and colleagues. A 50 % reduction in propofol C_{p50} for preventing movement due to skin incision was achieved with fentanyl at 0.6 ng/ml. Increasing the fentanyl concentration to 3 ng/ml decreased the propofol C_{p50} for skin incision by 89 %. Fentanyl at 3 ng/ml decreased the propofol C_{p50} for LOC by 40 %. Thus the interaction between propofol and fentanyl was much weaker for a non-noxious stimulus than a noxious stimulus (Smith *et al* 1994).

In a study by Bruhn and colleagues, propofol and remifentanil were found to interact synergistically with respect to somatic and hemodynamic responses to a series of test stimuli, including laryngeal manipulation. Their PD model applied to the measured blood concentrations and predicted effect-site concentrations resulted in P_K values of 0.86, for both, for predicting the overall modified OAA/S score, 0.93 and 0.92, for predicting unconsciousness, and 0.60 and 0.71, for predicting the response to laryngeal stimulation (Bruhn *et al* 2003).

Sevoflurane, desflurane and hemodynamic responses

Ebert and Muzi reported that both the initiation of desflurane anesthesia and the transition from 1.0 to 1.5 MAC desflurane concentration resulted in hypertension, tachycardia, and a significant increase in the muscle sympathetic nerve activity. They did not observe these changes during isoflurane anesthesia (Ebert and Muzi 1993). A rapid increase in the end-tidal concentration of desflurane from 0.55 MAC to 1.66 MAC resulted in larger transient increases in heart rate and blood pressure than a corresponding increase in the end-tidal isoflurane concentration. Desflurane also induced greater increases in plasma catecholamine and vasopressin concentrations than did isoflurane. The onset of the sympathoadrenal response was within 30 s after the first breath of increased desflurane concentration and within 60 s after the first breath of increased isoflurane concentration. The authors suggested that the increased anesthetic concentration stimulates medullary centers either via respiratory irritant receptors or directly, resulting in a transient increase in sympathetic outflow and pituitary stimulation. The transient increases in heart rate and blood pressure are caused by the release of adrenalin and vasopressin together with an increased sympathetic outflow. The rapid attenuation of these responses would be caused by either adaptation to the stimulus or direct central nervous system depressant effects of the anesthetics (Weiskopf *et al* 1994b).

Yli-Hankala and colleagues observed that a rapid increase in the end-tidal isoflurane concentration caused an increase in heart rate, blood pressure, and the mixed venous blood noradrenalin concentration. The authors concluded that the sympathoadrenal activation may be due to the irritating effect of isoflurane on the airways, but an unknown autonomic control mechanism may also be involved (Yli-Hankala *et al* 1993d).

In a volunteer study by Muzi and colleagues, a linear increase in the end-tidal concentration of desflurane from 3.6 % to 11 % resulted in a rate-dependent increase in sympathetic nerve activity, whereas linearly increasing end-tidal isoflurane from 0.6 % to 1.8 % was not associated with a significant increase in sympathetic nerve activity. The rate of desflurane increase did not significantly affect the heart rate response, possibly due to the dependence of the heart rate on multiple control mechanisms. The effect of the rate of desflurane increase on the MAP response was less consistent than that on the sympathetic nerve activity response. The peak increase in MAP was greater with desflurane than with isoflurane, whereas peak increases in heart rate were similar. The threshold for sympathetic nerve activation seemed to be slightly lower than that for the heart rate or MAP increase, although no single threshold for triggering a sympathetic or hemodynamic response was found (Muzi *et al* 1996b). Topical airway or systemic lidocaine administration does not block the neurocirculatory response to desflurane (Muzi *et al* 1996a).

In a rabbit model, a similar biphasic sympathetic response as with desflurane was observed with other respiratory irritant vapours, isoflurane, and enflurane. N_2O (10 %–70 %) also increased renal sympathetic nerve activity (Pac-Soo *et al* 2000a). In an experiment on dogs, the increase in heart rate during deepening inhalation anesthesia was greatest for desflurane and least for halothane, and intermediate for sevoflurane, isoflurane, and enflurane. The authors suggested that the vagolytic activity of the volatile agents may be involved in the generation of tachycardia. Even though the increase in heart rate was larger with desflurane than with sevoflurane, however, the decrease in HRV indices of vagal activity was similar for the two agents (Picker *et al* 2001).

Wajima and colleagues observed that in the absence of sympathetic stimulation by N_2O, a rapid increase in the inspired sevoflurane concentration to 2.9 MAC was not associated with tachycardia or an increase in the plasma adrenalin concentration, in contrast to isoflurane. The plasma noradrenalin concentration increased with rapid increases in both sevoflurane and isoflurane concentrations (Wajima *et al* 2000).

Weiskopf and colleagues concluded that the sympathetic stimulation following a rapid

increase in desflurane concentration is likely mediated by both pulmonary and richly perfused systemic receptors (Weiskopf *et al* 1995). Rodig and colleagues rapidly increased the concentration of desflurane or sevoflurane in the membrane oxygenator's gas supply line during mildly hypothermic cardiopulmonary bypass, so that concentrations corresponding to 1.5 MAC were measured from the exhaust gas within two minutes. In the desflurane group the systemic vascular resistance index initially remained unchanged, and decreased only after five minutes, whereas in the sevoflurane group there was an immediate decrease in the systemic vascular resistance index. The endogenic plasma catecholamine concentrations did not change with time in the desflurane group, but decreased in the sevoflurane group. The authors concluded that these findings suggest an extrapulmonary site mediating the sympathetic effects of desflurane (Rodig *et al* 1997).

Stimulation of the lower airways by desflurane is associated with greater increases in heart rate, MAP and muscle sympathetic nerve activity than stimulation of the upper airways. The muscle sympathetic nerve response may be linked to a systemic effector site, whereas the heart rate and MAP responses can be elicited by local lung exposure without increasing the systemic desflurane concentration. Alternatively, the muscle sympathetic activity may be less sensitive to desflurane than the regulation of the heart rate. The response of both lungs to desflurane may be a summation of the responses of the right and left lungs (Muzi *et al* 1996a).

Movement responses

Nociceptive reflexes

The motor response to a noxious stimulus may be a simple withdrawal reflex, or a more complex escape or defense pattern. Peripheral nociceptors synapse with second-order neurons in the spinal cord dorsal horn, and these in turn synapse with motoneurons either directly or indirectly via interneurons or central pattern generators (Antognini and Carstens 2002). Large-diameter sensory afferent fibers excite motoneurons directly (the monosynaptic reflex). Small-diameter sensory afferents (Aδ- and C-fibers) excite motoneurons via interneurons, generating the slow ventral root potential associated with nociception. The spinal motoneurons receive tonic inhibitory input as well as both feed-forward and feedback inhibition (Kendig 2002).

Withdrawal responses are generally produced by reflex circuits organized within the spinal cord or the trigeminal nucleus, although they can be modified by higher brain centers. Spinal motoneurons receive excitatory or inhibitory input via the reflex arc so that the net result is removal of the affected body part from the noxious stimulus. Previous injury to the site exciting the withdrawal reflex can induce facilitation of the reflex due to central sensitization. Noxious stimulation at other areas can cause descending supraspinal inhibition of the withdrawal reflex. In some instances, anesthesia may attenuate this descending inhibition (Clarke and Harris 2004).

The development of both the pain sensation and the nociceptive flexor reflex seem to share a common spinal relay. Both the nociceptive reflex magnitude and the associated pain sensation are attenuated by morphine in a dose-dependent manner, most likely mainly through a direct spinal mechanism. In the absence of supraspinal influences, when their spontaneous activity is increased, spinal neurons may be even more sensitive to the effects of morphine (Willer 1985).

The generation of movement responses involves temporal summation. Dutton and colleagues showed in a rat model that increasing the isoflurane concentration above 0.6 MAC increases the latency between the onset of noxious stimulation and the onset of movement, and movement responses are abolished at concentrations greater than one MAC. At a given isoflurane concentration, increasing frequency of stimulation produces shorter latencies to EMG activation and movement. With increasing frequency of stimulation, greater isoflurane concentrations are required to increase the latency of movement and to abolish movement responses. Short interstimulus interval pulses

produce a buildup of EMG activity, resulting in a burst of sustained EMG activity and movement. Movement responses are slightly more sensitive to isoflurane than the buildup of muscle tone and EMG activation. During NMDA blockade, which interferes with temporal summation, the concentration of isoflurane required to suppress movement is not increased with shortening interstimulus intervals, and the MAC (to tail-clamping) is reduced. Above a threshold intensity, the difference between isoflurane concentrations required to suppress movement at two different interstimulus intervals is independent of stimulus intensity. The authors suggested that isoflurane may diminish the stimulus available for temporal summation, or the downstream effect of temporal summation (Dutton *et al* 2003).

Minimum alveolar concentration

The term MAC, defined as "the minimal alveolar anesthetic concentration required to keep a dog from responding by gross purposeful movement to a painful stimulus", was coined in 1963 by Merkel and Eger (Merkel and Eger 1963). The next year MAC was defined as the concentration at one atmosphere at which 50 % of patients moved in response to surgical incision. MAC is determined during inhaled monoanesthesia at equilibrium, using skin incision or tail clamping as the supramaximal stimulus. "Gross purposeful movement", usually of the head or extremities, is considered a positive response. Coughing, swallowing, or chewing are not considered positive responses in the original MAC concept. The interindividual variation is usually 10 %–20 %. MAC decreases with age. Sex does not affect MAC values. Changes in CNS metabolism, such as may occur *e.g.* with changes in body temperature or CNS catecholamine release, are associated with alterations in MAC values. In clinical practice MAC multiples or fractions are used to describe different levels of CNS depression, assuming that the dose-response curves of different inhaled agents are roughly parallel. On the other hand, the relative toxicity of different agents, *e.g.* regarding cardiovascular depression, can be compared by using MAC multiples (Quasha *et al* 1980).

Zbinden and colleagues demonstrated how the end-tidal (arterial) concentration of isoflurane required to prevent movement responses depends on the intensity of the stimulus. Intubation was the strongest stimulus, and evoked hemodynamic responses even when gross purposeful movement was inhibited (Zbinden *et al* 1994a).

In a classic study, Rampil and colleagues observed that the isoflurane MAC for tail clamping was similar in precollicular decerebrate and sham-operated rats. The authors concluded that the mechanism by which isoflurane produces unresponsiveness to noxious stimulation is independent of the forebrain structures, and may include actions on the midbrain or spinal cord (Rampil *et al* 1993). In a subsequent study, Rampil demonstrated in rats that hypothermic transection of the spinal cord at C7 did not change isoflurane MAC for tail clamping in the absence of spinal shock. This result suggested that the site of anesthetic inhibition of motor response to noxious stimulation resides in the spinal cord (Rampil 1994). Antognini and Schwartz showed in a goat model that isoflurane MAC for dew-claw clamping was considerably higher when isoflurane was delivered only to the isolated brain circulation as compared with delivery to the whole body (2.9 % *vs.* 1.2 %). The authors concluded that unconsciousness and suppression movement responses during anesthesia may be associated with different sites of anesthetic action (Antognini and Schwartz 1993). Using a similar experimental arrangement, the authors found that when the isoflurane concentration in the cranial circulation was decreased to 0.2 %–0.3 %, the torso MAC was decreased to 0.8 % compared to 1.4 % during whole-body isoflurane administration. They suggested that changes in the balance of excitatory and inhibitory input to the spinal cord neurons might explain the results (Borges and Antognini 1994).

Consciousness (and voluntary action) is lost at much lower anesthetic concentrations than those needed to suppress movement responses to noxious stimulation (Kazama *et al* 1997, Eger 2001). Rampil and Laster found

in rodents that during isoflurane anesthesia, movement responses to noxious stimulation occurred in some animals simultaneously with substantial periods of EEG suppression. None of the investigated EEG variables correlated with movement responses (Rampil and Laster 1992). Similar results were found in goats during halothane anesthesia (Antognini *et al* 2002). Sub-MAC concentrations of isoflurane (0.7 %) diminish the cortical blood flow responses to tactile stimulation and ablate the cortical blood flow responses to noxious electrical stimulation. At supramaximal stimulation, during 0.7 % isoflurane anesthesia, only subcortical blood flow responses are observed. At 1.3 % (1 MAC) isoflurane the subcortical blood flow response is also suppressed, even though some subjects would be expected to move in response to supramaximal stimulation at this isoflurane concentration in the absence of neuromuscular blockade (Antognini *et al* 1997).

Mechanisms behind anesthetic-induced immobility

In rats, several inhaled anesthetics are hyperalgesic at low concentrations of 0.1 MAC, as measured by the hind paw withdrawal latency to thermal stimulation. At 0.4–0.8 MAC, they significantly increase hind paw withdrawal latency. Isoflurane already produces an analgesic effect at 0.2 MAC. With the exception of N_2O and diethyl ether, the analgesic concentration of inhaled agents overlaps that producing unconsciousness (Zhang *et al* 2000). In rats, sub-MAC concentrations of isoflurane seem to primarily diminish the number of movement responses to noxious stimulation. At supra-MAC concentrations the force of movements is also decreased (Antognini *et al* 1999b).

Although clinically relevant concentrations of inhaled anesthetics may increase the discharge activity of C-fiber nociceptors (MacIver and Tanelian 1990), peripheral actions of volatile agents are probably not important with respect to immobility (Antognini and Kien 1995). Axonal transmission and the excitability of postganglionic sympathetic neurons to direct intracellular stimulation have been shown to be far less sensitive to halothane than synaptic transmission induced by stimulation of preganglionic sympathetic nerves (Bosnjak *et al* 1982). Thin unmyelinated fibers may be more sensitive to isoflurane than myelinated fibers (Berg-Johnsen and Langmoen 1986).

Sevoflurane, propofol, and thiopental decrease the number and amplitude of indirect corticospinal potentials (I-waves) evoked by transcranial electrical stimulation. The later I-waves are more sensitive to anesthetics than the early ones, possibly reflecting longer synaptic chains generating the later I-waves. The complex direct corticospinal potential (D-wave) is relatively resistant to anesthetics (Woodforth *et al* 1999). Clinical concentrations (3.7 %–7.4 %) of desflurane, with or without N_2O, do not affect either peripheral or central nerve conduction velocities or neuromuscular transmission. Desflurane profoundly depresses motor potentials evoked by epidural spinal cord electrical stimulation, and dose-dependently decreases the amplitudes of segmental spinally relayed motor responses evoked by peripheral stimulation. Thus it seems to act preferentially on central synapses (Péréon *et al* 1999).

Subanaesthetic concentrations of propofol and sevoflurane depress the transsynaptic and centrally mediated motor responses to both transcranial magnetic stimulation and peripheral stimulation. Spinal integration seems to be even more sensitive to anesthetic action than cortical excitability, as measured by BIS (v. 3.22) and MLAEP changes. Since both the spinal components of somatosensory evoked potentials and the brainstem auditory evoked potentials are relatively resistant to anesthetics, it seems that in both spinal and brainstem motor reflex responses the efferent part of neural transmission is preferentially suppressed by anesthetic agents (Kammer *et al* 2002).

Antognini and colleagues demonstrated in goats that isoflurane effect in the spinal cord depresses the spontaneous activity of nociceptive dorsal horn neurons. The magnitude of noxious stimulus evoked activity in dorsal horn neurons is greater when the torso isoflurane concentration is 0.3 % compared to 1.3 %. Very high isoflurane concentrations (around

9 %) in the brain attenuate the noxious stimulus evoked activity in dorsal horn neurons, even when the torso isoflurane concentration is low. A brain isoflurane concentration of 3 % did not change dorsal horn neuronal responses compared to 1.3 %, during either moderate (1.3 %) or low (0.3 %) torso isoflurane concentrations. The authors concluded that very high brain isoflurane concentrations may influence descending modulatory pathways, affecting both sensory and motor neurons (Antognini *et al* 1998). Anesthetic doses of propofol were also shown to directly depress spinal dorsal horn neuronal responses to noxious mechanical stimulation. Propofol delivered only to the cranial circulation was ineffective (Antognini *et al* 2000c). Isoflurane was shown to attenuate noxious stimulation evoked EEG and thalamic responses by both cranial and spinal actions (Antognini *et al* 2000a).

The same group investigated the effect of 0.75–1.4 MAC isoflurane and halothane on dorsal horn neuronal responses to noxious thermal stimulation in rats. Both agents dose-dependently decreased the spontaneous activity of dorsal horn nociceptive neurons, although the mean spontaneous activity in this concentration range was larger under halothane than under isoflurane. Evoked dorsal horn activity was similar or greater with isoflurane than with halothane. Halothane dose-dependently decreased evoked dorsal horn neuronal responses, with simultaneous reductions in withdrawal force. In contrast, the dorsal horn neuronal responses at 1.4 MAC isoflurane were similar to those at 0.75–0.9 MAC isoflurane, with a slight increase at 1.1 MAC. The withdrawal force was dramatically reduced, however, at the transition from 0.9 to 1.1 MAC isoflurane anesthesia. With both anesthetics, withdrawal responses were either markedly reduced or absent at 1.1 MAC. The authors concluded that depression of nociceptive transmission in the dorsal horn seems to contribute to the immobilizing effect of halothane, whereas more ventral components of the reflex arc are important to the immobilizing effect of isoflurane (Jinks *et al* 2003).

Antognini and colleagues showed in a goat model that when halothane is delivered only to the cranial circulation and the torso halothane concentration is low (0.1 %–0.2 %), the cranial halothane concentration required to prevent movement to noxious mechanical stimulation is 3.4 % compared to 0.9 % during whole-body administration. In two of five animals movement responses could not be prevented even with a 4 % cranial halothane concentration (Antognini *et al* 2002). The corresponding values during cranial and systemic isoflurane delivery were 2.9 % and 1.2 % (Antognini and Schwartz 1993). The high cranial halothane or isoflurane concentrations resulted in pronounced EEG depression with periods of burst suppression or isoelectricity, but movement responses still occurred. In contrast, the cranial thiopental concentration required to prevent movement to noxious mechanical stimulation was only twice that observed during systemic thiopental delivery, and the EEG remained active despite the suppression of movements. The authors concluded that whereas halothane (and isoflurane) suppress movement predominantly via a spinal action, thiopental may have an important supraspinal (subcortical) target with respect to immobility, perhaps mediated by descending inhibition (Antognini *et al* 2002).

Jinks and colleagues studied the effect of isoflurane and noxious thermal stimulation on the RVM ON- (cells which increase their activity with reflex movement) and OFF-cells (cells which are inhibited during movement) in rats. Isoflurane dose-dependently depressed the spontaneous activity of ON-cells and enhanced the activity of OFF-cells. It also significantly decreased the responses of the ON-cells to noxious thermal stimulation at 1.15 MAC. The large changes in the spontaneous activity of both the ON- and OFF-cells (and in the evoked activity of ON-cells) at 1.15 MAC were associated with a nearly complete absence of withdrawal responses to noxious thermal stimulation (Jinks *et al* 2004).

Injection of a μ opioid agonist into the RVM suppressed both the spontaneous and the evoked activity of ON-cells in anesthetized rats. In cases where the μ agonist effectively inhibited the tail-flick reflex, the activity of OFF-cells increased and changed from perodic to

continuous. The pause in the activity of OFF-cells, which followed noxious stimulation and preceded the tail-flick reflex, was abolished (Heinricher *et al* 1994). Similar changes in OFF-cell activity were observed after intravenous administration of morphine, which abolished the tail-flick reflex to noxious heat (Fields *et al* 1983). The disinhibition of OFF-cells seems to be crucial to the antinociceptive effect of a μ agonist within the RVM (Heinricher *et al* 1994). Application of morphine to the PAG or to the spinal cord also results in activation of RVM OFF-cells and antinociception (Cheng *et al* 1986, Heinricher and Drasner 1991).

It has been suggested that the anesthetic-induced decrease in the excitability of spinal motoneurons, as measured by peripherally evoked and spinally relayed motor responses, may be involved in suppressing movement responses to noxious stimulation (King and Rampil 1994, Rampil and King 1996, Zhou *et al* 1998). The spinally relayed motor responses are depressed, however, at lower anesthetic concentrations than those required for the suppression of movement responses, or those causing EEG depression. The effect of anesthetics on spinally relayed motor responses occurs more slowly (longer $T_{½}$ k_{eo}) than the EEG effect (Antognini *et al* 1999a, Rehberg *et al* 2004a, Baars *et al* 2006a, Baars *et al* 2006b). The arousal caused by noxious stimulation transiently increases the spinally relayed motor responses during anesthesia (Rehberg *et al* 2004b, Baars *et al* 2005, Baars *et al* 2006b).

Both pre- and postsynaptic mechanisms are probably involved in anesthetic action on spinal motoneurons. Spinal motoneurons receive tonic inhibition via $GABA_A$ and glycine receptors. Blockade of $GABA_A$ and glycine receptors increases volatile anesthetic requirements by a maximum of about 40 %. They may be more important for propofol and barbiturates. Volatile agents can inhibit both AMPA and NMDA receptor mediated excitatory currents in spinal motoneurons, independent of actions on GABA or glycine gated inhibitory chloride channels. Thus anesthetic actions on the motoneuron glutamate receptors are probably important. No specific site on the glutamate receptors for the volatile agents has, however, been identified. Anesthetic agents may also modulate the intrinsic excitability of motoneurons via various ion channels. Volatile anesthetic agents depress the monosynaptic reflex at concentrations equivalent to one MAC or lower, whereas it is little affected by *i.v.* anesthetic agents or opioids, at least in *in vitro* preparations. The monosynaptic reflex is mediated primarily via glutamate AMPA receptors, with a contribution from NMDA receptors. The slow ventral root potential, which is presumed to be associated with nociception, is more sensitive to anesthetic agents than the monosynaptic reflex. Hypnotic agents display some selectivity for the early component, mediated by the NMDA receptor. The late component, mediated by various metabotropic (G-protein-coupled) receptors, is sensitive to opioids and α_2-agonists (Kendig 2002).

In a mouse spinal cord preparation, enflurane depressed motoneuron EPSCs evoked both by electrical stimulation (synaptic transmission) and by glutamate application, when presynaptic mechanisms were excluded by the administration of tetrodotoxin. The enflurane effect on synaptic transmission was slightly larger than the direct postsynaptic effect, indicating a possible contribution from presynaptic effects. The blockade of $GABA_A$ and glycine receptors did not significantly diminish the effect of enflurane on glutamate-evoked EPSCs. The $GABA_A$ antagonist bicuculline, however, attenuates enflurane effects in intact mouse spinal cords. The currents mediated by both AMPA and NMDA receptors were equally affected by enflurane. The authors concluded that with respect to suppression of nocifensive movement, receptors other than $GABA_A$ or glycine are important targets of volatile anesthetics (Cheng and Kendig 2000).

At or close to the concentration required for general anesthesia, propofol and barbiturates depress the slow ventral root potential and enhance the dorsal root potential (involved in presynaptic inhibition) via their action on the $GABA_A$ receptor (Jewett *et al* 1992).

Sevoflurane and propofol dose-dependently decreased the spontaneous firing rate of rat spinal cord ventral interneurons *in vitro*. Whereas high sevoflurane concentrations completely

suppressed the spontaneous activity, propofol displayed a ceiling effect near 60 % reduction. Based on testing in the presence of bicuculline and strychnine, the authors estimated that 38 % and 45 % of the sevoflurane effect is mediated by $GABA_A$ and glycine receptors, and 17 % by other receptors, probably including glutamate receptors. The effect of propofol at clinically relevant concentrations is mediated almost exclusively by $GABA_A$ receptors (Grasshoff and Antkowiak 2004).

In a rodent spinal cord preparation, sevoflurane markedly depressed both the motoneuron action potential wind-up evoked by repetitive stimulation of nociceptive (C-fiber) afferents and the underlying cumulative depolarization (the summation of successive slow ventral root potentials) already at subanesthetic concentrations. The effect of sevoflurane was dose-dependent and reached its maximum at anesthetic concentrations. The effect of propofol was smaller and occurred at relatively higher concentrations (the cumulative depolarization was significantly reduced only at supraclinical concentrations). The monosynaptic reflex was depressed by sevoflurane, but not by propofol. Thus the effect of sevoflurane on both nociceptive and non-nociceptive spinal transmission is considerably stronger than that of propofol (Matute *et al* 2004).

The correlation of hemodynamic variables and movement responses

Generally, the correlation between pre- or post-stimulus hemodynamic variables and movement responses is poor (Vernon *et al* 1995, Kazama *et al* 1997, Sebel *et al* 1997, Kochs *et al* 1999). Johansen and colleagues reported that in a logistic regression analysis, the pre- and post-incision heart rates emerged as significant predictors of movement responses to skin incision during propofol–N_2O anesthesia, but the effect was too small to be included in the final model (Johansen *et al* 1997). Hemodynamic variables are also not reliable indicators of unconsciousness (Struys *et al* 2002). Subcortically mediated physiological variables, such as MLAEP and fEMG, may reflect the arousal preceding movement responses better than hemodynamics or surface EEG (Yli-Hankala *et al* 1994).

The relationship between electroencephalogram derived variables and movement responses

Sebel and colleagues investigated patients during isoflurane–N_2O, isoflurane–opiod, or propofol–opioid anesthesia in a multicenter study. They found that BIS (v. 1.1), the estimated opioid effect-site concentration, and MAP were the best independent predictors of movement response to skin incision according to logistic regression analysis. Combining information from the BIS values and the opioid effect-site concentrations significantly improved the prediction performance. When isoflurane–opioid anesthesia was used, however, the incidence of movement responses was low, and no association between BIS values and movement responses appeared. With increasing opioid concentrations, the probability of movement in the presence of low isoflurane concentrations and high BIS values decreased. The modeled relationship between BIS values and the probability of movement responses was much closer with isoflurane or propofol than with opioids. Overall, the movement response rate to noxious stimulation was lower in patients whose BIS values were titrated to less than 60, compared to the control group. The average BIS values in the control and BIS-guided groups were 66 and 51 (Sebel *et al* 1997).

Leslie and colleagues found that the pre-stimulus BIS (v. 3.0), SEF95, MF, and relative β power all had P_K values exceeding 0.80 for the movement response to tetanic electrical stimulation during propofol–N_2O anesthesia in healthy volunteers, as did the pupillary constriction velocity. The P_K values of the pre-stimulus relative δ power and systolic blood pressure were 0.79 and 0.78. The pre-stimulus blood and effect-site propofol concentrations and the pupillary reflex amplitude had P_K values of 0.74–0.76. Heart rate did not predict movement responses. Thus, hemodynamic and pupillary indicators were not superior to surface EEG variables. The observations

used in calculating the prediction probabilities, however, were not strictly independent. Individually computed P_K values were even higher. The most pronounced change in the recorded variables in response to noxious stimulation was the rapid pupillary dilation, which was sustained longer in movers than in non-movers (Leslie *et al* 1996).

Singh and colleagues found that pre-incision BIS (v. 3.3) values were lower in non-movers than in movers reacting to skin incision during propofol–fentanyl anesthesia, whereas pre-incision SEF95 values did not differ between movers and non-movers. Increasing doses of fentanyl resulted in fewer movement responses (Singh *et al* 1999).

Dutton and colleagues found that the SEF95 was a statistically significant predictor of movement responses to surgical stimulation during isoflurane–N_2O–fentanyl anesthesia. The response curves shifted to higher frequencies with increasing doses of fentanyl or the use of N_2O (Dutton *et al* 1996). Similarly, Schraag and colleagues reported that although the overlap in SEF95 values between responders and non-responders was considerable, SEF95 was a statistically significant predictor of both LOC and movement responses to skin incision in a logistic regression model during propofol–N_2O–sufentanil anesthesia. No significant association between MF and LOC or movement responses to skin incision was observed. The authors noted that theoretically, very low SEF95 values (<7 Hz) would be required in order to achieve a 95 % probability of no movement response to skin incision (Schraag *et al* 1998).

Doi and colleagues reported that both BIS (v. 3.12) and SEF95 were unable to predict movement responses to laryngeal mask insertion during propofol–alfentanil anesthesia (P_K value 0.55 for both indices). The pre-stimulus hemodynamic variables and predicted blood propofol concentrations were also similar between movers and non-movers. In that study, the auditory evoked potential index did predict movement responses (P_K 0.87) (Doi *et al* 1999). Similarly, Kurita and colleagues reported that the P_K values of the auditory evoked potential index, end-tidal sevoflurane concentration, and BIS (v. 3.2) for movement responses to skin incision during sevoflurane anesthesia were 0.91, 0.86 and 0.54. It was not possible to relate BIS and movement responses with logistic regression. The presence of the endotracheal tube seemed to elevate the auditory evoked potential index values compared to the values preceding intubation. The authors concluded that the auditory evoked potential index, which partly reflects the activity of subcortical neuronal pathways may be an indicator of arousal during anesthesia and noxious stimulation (Kurita *et al* 2001). Katoh and colleagues found that the P_K values of the end-tidal sevoflurane concentration, BIS (v. 3.2), SEF95, and MF for movement responses to skin incision during sevoflurane anesthesia were 0.90, 0.66, 0.57, and 0.52. None of the EEG variables predicted movement better than chance alone (Katoh *et al* 1998).

In a study by Kochs and colleagues a five-second tetanic electrical test stimulus applied before skin incision during isoflurane–N_2O anesthesia did not induce any significant changes in the EEG, MLAEP or hemodynamic variables, and did not predict reactions to skin incision. The pre-incision values of any of the variables were not different between movers and non-movers to skin incision. The increases in MLAEP amplitudes and EMG power and the decreases in α and θ EEG power after skin incision were larger in movers than in non-movers. The authors noted that in order to establish whether the level of anesthesia is sufficient to prevent movement responses to noxious stimulation in unparalyzed patients, either the level of analgesia and / or the level of motoneuron depression would have to be assessed (Kochs *et al* 1999).

Antinociception

Hypnosis, antinociception and the adequacy of anesthesia

Loss of consciousness cannot be achieved reliably by administering opioids alone (Jhaveri *et al* 1997). Similarly, opioids alone are insufficient to suppress motor and hemodynamic

responses to surgical stimulation (Hug *et al* 1988, Lang *et al* 1996). Opioid analgesia reduces both hemodynamic and movement responses to noxious stimulation (Sebel *et al* 1997, Katoh *et al* 1999, Guignard *et al* 2000, Valjus *et al* 2006).

In a study by Guignard and colleagues, during propofol anesthesia, the increases in HR and MAP at laryngoscopy and intubation were inversely correlated with the target effect-site concentration of remifentanil. The number of movers to laryngoscopy and intubation decreased progressively as the remifentanil concentration increased (Guignard *et al* 2000). Supplemental doses of both propofol and alfentanil were found to be effective in controlling the blood pressure and catecholamine responses to retropubic dissection during propofol–alfentanil anesthesia (Monk *et al* 1992).

The analgesic, or rather the antinociceptive component of anesthesia, influences the hypnotic component and the state of the autonomic nervous system (Kochs and Schneider 2001). After induction of anesthesia with propofol, fentanyl, isoflurane, and N_2O individual patients may respond to laryngoscopy by increases in fEMG and HR and decreases in PPG amplitude even in the presence of 30 % BSR, whereas others show no response at lighter levels of anesthesia (Paloheimo M, unpublished observations).

Electroencephalogram arousal responses

Wilder-Smith and colleagues suggested that although it is difficult to predict the responses to noxious stimuli based on the level of cortical depression before the stimulus, the elicited EEG arousal reactions themselves could be used for the assessment of nociception during anesthesia (Wilder-Smith *et al* 1995). Guignard and colleagues suggested that increases in BIS (v. 3.12) in association with noxious stimulation could be used as indicators of insufficient analgesia during anesthesia (Guignard *et al* 2000).

In a volunteer study by Iselin-Chaves and colleagues both an increase in the concentration of propofol and the presence of alfentanil (50–100 ng / ml) were associated with an attenuated BIS response to a noxious mechanical stimulus (Iselin-Chaves *et al* 1998). Valjus and colleagues reported that during propofol–N_2O–remifentanil or propofol–N_2O–esmolol anesthesia, some spontaneous intraoperative movements (occurring mostly shortly after intubation or at the start of surgical stimulation) were associated with simultaneous and similar increases in RE / SE and BIS. The majority of movements did not elicit any changes in the level of hypnosis or RE values, and overall SE, RE, and BIS values were very similar in both groups. Thus in that study, RE was not more sensitive to arousal reactions or the level of intraoperative opioid analgesia than SE or BIS (Valjus *et al* 2006).

Hagihira and colleagues have introduced a method of employing the bispectral analysis of the EEG in assessing the adequacy of anesthesia (Hagihira *et al* 2001, Hagihira *et al* 2002). In their recent work they found that skin incision during isoflurane or sevoflurane anesthesia was associated with a significant reduction in the two peak heights (at approximately 10 Hz and 4 Hz) of the EEG bicoherence, and that this reduction was counteracted by fentanyl analgesia. In that study, both BIS (v. 3.4) and SEF95 increased, decreased or remained stable, depending on whether desynchronization, δ wave arousal patterns, or mixed fast and slow EEG activity was elicited by the surgical stimulus. Because of the individual variability, no overall change in BIS or SEF95 values was observed after the skin incision. The administration of fentanyl restored the EEG waveforms to patterns similar to those observed before skin incision. Fentanyl administration alone, without surgical stimulation, did not induce significant changes in the EEG derivatives. The authors speculated that the decrease in the two bicoherence peaks reflects the disruption of the EEG synchronization, associated with anesthesia, by sensory input to the thalamus. This sensory input can be blocked by sufficient antinociception, either by regional anesthesia or opioid analgesics. In their practice, the authors consider reduced peak bicoherence values as an indication of inadequate antinociception, when the concentration of hypnotic agents is stable. Thus the bicoherence values are used

as a guide to the administration of analgesic agents (Hagihira *et al* 2004b).

The A-line ARX (autoregressive modeling with exogenous input) Index (A-AEP™, Alaris Medical Systems, Hampshire, UK) was reported to respond more sensitively than BIS (v. 3.1) to noxious stimulation during sevoflurane–N_2O or propofol–N_2O–fentanyl anesthesia, perhaps partly due to the faster response time of the AAI compared to BIS (Nishiyama and Hanaoka 2004, Nishiyama *et al* 2004). Bonhomme and colleagues observed that the A-Line Autoregressive Index (AAI™, Danmeter A/S, Odense, Denmark) increased in response to skin incision during sevoflurane anesthesia, when BIS (v. 3.4) was maintained between 40 and 60 by adjusting the sevoflurane concentration. The increase in AAI due to nociceptive stimulation was attenuated by epidural analgesia. Based on a logistic regression model, the authors suggested a threshold value of the AAI (20) for adjusting the antinociceptive component of anesthesia during a constant hypnotic level. The authors hypothesized that an intermittent facilitation of MLAEP by ascending spinoreticular or spinothalamic nociceptive input might explain the increases in AAI despite a stable cortical level of anesthesia (Bonhomme *et al* 2006).

Pulse plethysmography and heart rate variability responses

Luginbühl and colleagues found that both the decrease in the PPG waveform amplitude (pulse wave reflex, PWR) and the decrease in the superficial skin perfusion as measured by laser-Doppler flowmetry (SVmR), after a tetanic electrical stimulus to the forearm, were exponentially suppressed by increasing concentrations of alfentanil during sevoflurane–N_2O anesthesia. Neuromuscular blockade diminished the PWR to both muscle and nerve stimulation, and the SVmR to muscle stimulation. The PWR after a tetanic stimulus was a more reliable predictor of the hemodynamic response to tracheal intubation than the SVmR (Luginbühl *et al* 2002).

Later the authors found that the variability in the amplitude of the PPG waveform induced by tetanic electrical stimulation was similar between patients who mounted a significant hemodynamic response to tracheal intubation and those who did not, except for SD2 derived from Poincaré analysis of the PPG amplitudes, which was larger in responders than in non-responders. Different remifentanil concentrations or different BIS (v. 3.3) levels did not influence the stimulation-induced PPG variability, but were significant predictors of the hemodynamic response to intubation in a logistic regression model. The ratio of the post- and pre-stimulus PPG amplitude SD also predicted the response to intubation, but did not significantly improve the overall accuracy of the logistic model compared to the model including the remifentanil concentration and BIS alone (Luginbühl *et al* 2006).

Analysis of HRV variables from the same patients revealed that generally intubation induced larger HRV responses than the tetanic stimulus (except in RRI RMSSD and Poincaré SD1), but different remifentanil concentrations or different BIS (v. 3.3) levels did not influence the stimulation-induced HRV responses. A significant interaction between the anesthetic group and the stimulus type was found, however, for the mean RRI, RRI SD, RRI Poincaré SD2, and the RRI spectral entropy (0.04–0.4 Hz). The tetanus-induced increases in the RRI SD and the Poincaré SD2 and the intubation-induced RRI decrease were smallest in the group with the highest remifentanil concentration (4.7 ng/ml). Both the HRV responses to tetanic electrical stimulation and the HRV variables preceding intubation were similar between patients who mounted a significant hemodynamic response to tracheal intubation and those who did not. The RRI decrease following intubation was larger in responders than in non-responders. Again, only the calculated remifentanil effect-site concentration and the BIS level were significant predictors of the hemodynamic response to intubation in a logistic regression model. The authors concluded that generally the hemodynamic responses differ between different levels of opioid analgesia only when very strong noxious stimuli are applied, and that at present the hemodynamic

responsiveness of an anesthetized patient is best evaluated by the estimated opioid concentration and information from an indicator of the hypnotic level, such as BIS. The HRV variables are similar over a wide range of surgical anesthesia, and thus their value in assessing the hemodynamic responsiveness is limited (Luginbühl *et al* 2007).

The RRI and PPG notch amplitude responses to a very strong tetanic electrical stimulus (30 s) during propofol–remifentanil anesthesia were dependent on the remifentanil concentration (Rantanen *et al* 2004).

Response index of Nociception and the Surgical Stress Index

Rantanen and colleagues investigated changes in physiological variables at skin incision during propofol–remifentanil anesthesia. They found that the RRI and PPG amplitude decreased, and HRV (RRI SD, Poincaré SD1 and SD2), PPG variability (Poincaré SD2), and RE increased. The relative position of the PPG notch changed, and PTT decreased. RE-SE increased in movers, but not in non-movers. Higher remifentanil concentrations (3 or 5 ng/ml *vs.* 1 ng/ml) were associated with smaller decreases in the RRI, larger increases in the RRI SD1, smaller increases in RE, and larger decreases in PTT. The responses of individual variables were similar in patients with a large *vs.* a small skin incision. The authors developed an empirical clinical reference score (Clinical Signs – Stimulus – Antinociception score, CSSA) for estimating the nociception–antinociception balance during general anesthesia. The score includes evaluation of the intensity of surgical stimulation (incision), the level of the analgesic drug concentration, and the presence or absence of somatic signs of inadequate anesthesia (Rantanen *et al* 2006a).

With the CSSA score as reference, they developed a potential online scaled index (Response index of Nociception, RN) of the nociception–antinociception balance, based on variables derived from the time-frequency balanced spectral entropy, RRI and PPG. This index successfully discriminated patients receiving different remifentanil concentrations during propofol anesthesia, movers *vs.* non-movers, and patients subjected to a large *vs.* a small skin incision. RRI, and RE or RE-SE correlated best with the remifentanil concentration and somatic responses at skin incision, respectively. The magnitude of the skin incision correlated best with PPG amplitude SD1, SD2, and SD1/SD2. No single variable was associated with all three components of the CSSA score, but the combination of information from different signals provided an adequate prediction of CSSA. The P_K values of RN for the CSSA score were 0.78 and 0.73 in the development and test data sets. The authors observed that the magnitude of skin incision seemed to be less important in determining the nociception–antinociception balance than the remifentanil concentration (Rantanen *et al* 2006a).

Huiku and colleagues recently described the development of an index designed to measure the level of surgical stress, which is dependent on both the intensity of surgical stimulation and the level of antinociception provided by opioid analgesia (or neural blockade). The authors investigated the correlation of a large number of physiological variables with the estimated strength of surgical stimulation and with the concentration of remifentanil during propofol–remifentanil anesthesia. Different time- and frequency-domain measures of PPG amplitude and RRI variability, as well as measures obtained by Poincaré analysis, were explored. Non-invasive blood pressure, PTT, RE, and EEG variables were also investigated (Huiku *et al* 2007).

In order to reduce interindividual variability in the physiological variables, a histogram transformation was performed. The raw values of the variables were mapped to a cumulative distribution function, which was formed by combining the population distribution from the entire development data set (54 patients) and the individual distribution collected during anesthesia. When five minutes or more of data had been collected, the weights used for the population and individual distributions were 0.3 and 0.7. The distributions were modelled as normal distributions. The mean of the

individual distribution was defined as that observed during anesthesia for that patient, but the SD was fixed to the average value observed in the entire development population. The output of the histogram transformation was a normalized value of the variable in question, ranging from zero to 100, where the output value of 50 roughly corresponds to the individual median value, and the values of 25 and 75 correspond to the individual first and third quartile (Huiku *et al* 2007).

The noxious intensity of different anesthetic and surgical events was estimated based on existing data on the pharmacodynamic interaction between propofol and remifentanil for suppressing clinical responses, and the hierarchical PD model of Bouillon and colleagues (Bouillon *et al* 2004). The total surgical stress (nociceptive–antinociceptive balance) was estimated as TSS = (intensity of stimulation) – (effect-site remifentanil concentration / 3 ng / ml). The three variables which best correlated with the intensity of stimulation were the normalized PPG amplitude ($PPGamplitude_{norm}$), the PTT and the systolic blood pressure. The three variables which best correlated with the concentration of remifentanil were $PPGamplitude_{norm}$, the systolic blood pressure and the normalized heart beat interval (HBI_{norm}), derived from the PPG signal. The $PPGamplitude_{norm}$ explained a larger amount of variability in the TSS than any other single variable. The addition of HBI_{norm} in a linear combination reduced the amount of unexplained variability. The performance of the model was slightly improved by the systolic blood pressure, but it was discarded due to the discontinuous nature of the noninvasive blood pressure measurement. RE or variables derived from the EEG did not improve the model performance. The optimization of the linear combination of $PPGamplitude_{norm}$ and HBI_{norm} resulted in the Surgical Stress Index (SSI):

$$SSI = 100 - (0.7\ PPGamplitude_{norm} + 0.3\ HBI_{norm})$$

The SSI correlated positively with the estimated intensity of stimulation and negatively with the remifentanil concentration. During surgery, SSI increased less in the presence of remifentanil at 5 ng / ml than with remifentanil at 1 or 3 ng / ml, both in the development (N = 54) and the validation (N = 12) data sets (Huiku *et al* 2007).

Ahonen and colleagues investigated SSI during desflurane–N_2O–remifentanil or desflurane–N_2O–esmolol anesthesia. RE / SE was around 40 in both groups, and the infusions of remifentanil or esmolol were adjusted to maintain a stable hemodynamic condition. At skin incision, SSI increased in the esmolol group, but not in the remifentanil group. After the insertion of troacars SSI increased in both groups, but remained significantly lower in the remifentanil group compared to the esmolol group. The required desflurane concentration was larger in the esmolol group than in the remifentanil group. Two patients in the esmolol group moved during the procedure, whereas none in the remifentanil group did. The intraoperative movements were associated with high SSI values, whereas RE remained low. The authors observed that the autonomic changes related to emergence from anesthesia resulted in high SSI values, which were unrelated to the subjective sensation of pain at ROC. They concluded that the SSI seems to reflect the level of surgical stress, and may be useful in the assessment of the effect of opioid analgesics and intraoperative nociception (Ahonen *et al* 2007).

In another study, high SSI values were associated with an increased risk of intraoperative movement responses during propofol–remifentanil anesthesia, although there was considerable overlap in SSI values between movers and non-movers (Uutela *et al* 2006). During laparotomy in patients anesthetized with propofol, SSI was higher when the effect-site remifentanil concentration was 1 ng / ml compared to 5 ng / ml. This difference was observed despite the gradual development of moderate hypothermia, which potentially could interfere with PPG monitoring. The SSI had a significant negative correlation with the remifentanil concentration (Aho *et al* 2006).

Vanpeteghem and colleagues investigated SSI responses to a standardized tetanic electrical stimulus during propofol–remifentanil anesthesia. SSI was independent of the propofol effect-site concentration. Both the baseline and the maximum post-stimulus SSI values were

significantly higher at remifentanil effect-site concentrations of 0–2 ng/ml than at higher remifentanil concentrations. At remifentanil concentrations above 2 ng/ml the SSI response to tetanic stimulation was small (Vanpeteghem *et al* 2006). Similarly, Ojala and colleagues found that varying propofol concentrations during surgery did not significantly influence SSI values, but were associated with different SE values. The SSI was higher during laparotomy than before surgery, whereas SE was not (Ojala *et al* 2006).

Wennervirta and colleagues found that during desflurane–alfentanil anesthesia, SSI was significantly higher at skin incision in patients who had not received regional anesthesia pre-operatively, than in those with established regional anesthesia of the surgical site. The alfentanil requirement was significantly larger in the former group (Wennervirta *et al* 2006). Similar results were obtained during sevoflurane–N_2O–sufentanil anesthesia. The difference observed at skin incision in the SSI values between patients with and without regional anesthesia decreased over time (Yli-Hankala *et al* 2006).

A visual approach toward online monitoring of the nociceptive–antinociceptive balance during anesthesia was described by Paloheimo and Penttinen. They generated a two-dimensional, beat-to-beat display of the PPG amplitude plotted against the RRI, with a number of recent beats displayed in white, and the five most recent beats displayed in red. Rapid deflections of the red spot occur in response to noxious stimuli exceeding the antinociceptive effect of balanced anesthesia. A sustained deviation toward short RRIs and low PPG amplitudes may reflect the humoral response to nociception (Paloheimo and Penttinen 2004).

Other approaches to the assessment of antinociception

Storm and colleagues investigated the changes in palmar skin conductance, associated with sympathetically mediated sweating, during propofol–remifentanil anesthesia. Compared to a clinical stress score including hypertensive responses, coughing, tearing, movements, and fEMG activation, the number of fluctuations in skin conductance was found to detect discomfort during anesthesia with a sensitivity and specificity of 86%. Generally, the number of fluctuations in skin conductance seemed to be more sensitive than the clinical stress score during surgical stimulation. Interestingly, one patient displayed a vigorous movement and fEMG response during intubation despite systolic hypotension, a BIS value of 40, and no indication of stress by the skin conductance. The authors suggested that arousal with impending wakefulness may be differentiated from a mere nociceptive response by the associated skin conductance patterns. During arousal, the increase in the number of skin conductance fluctuations was accompanied by an increase in the mean skin conductance level and BIS (over 50). During noxious stimulation, without arousal, the number of skin conductance fluctuations increased, whereas the mean level of skin conductance was stable and BIS remained low (less than 50). The amplitude of skin conductance fluctuations was larger during arousal than in the absence of arousal (Storm *et al* 2005).

During intubation under propofol–remifentanil anesthesia, the number of skin conductance fluctuations was a more sensitive indicator of stress than either a clinical stress score (including muscle activity, sweating, tearing, and hypertensive responses) or RE-SE. The correlation with the clinical stress score was stronger for the number of skin conductance fluctuations than for RE-SE. The number of skin conductance fluctuations also indicated the stress associated with tetanic electrical stimulation, whereas the clinical stress score or RE-SE did not. In addition, the increase in the number of skin conductance fluctuations at tetanic stimulation was smaller in the presence than in the absence of remifentanil analgesia, whereas RE-SE was not sensitive to remifentanil. The authors suggested that the number of skin conductance fluctuations may be a sensitive indicator of subclinical stress during anesthesia, and could be used to monitor the opioid analgesic effect (Gjerstad *et al* 2007).

Alfentanil dose-dependently decreased the maximum amplitude of pupillary dilation in

response to tetanic electrical stimulation during isoflurane anesthesia (Larson *et al* 1997). During propofol–remifentanil anesthesia, the pupil size decreased with an increasing remifentanil concentration, reaching a plateau at slightly less than 2 mm (at 3 ng / ml remifentanil) in the unstimulated state. A linear inverse correlation between the pupillary dilation to tetanic electrical stimulation and the target remifentanil effect-site concentration was found. The pupillary dilation response to noxious stimulation was abolished at 4–5 ng / ml of remifentanil (EC_{50} 2.3 ng / ml). The authors concluded that the pupil dilation response reflected the remifentanil effect more sensitively than did hemodynamic variables or BIS (Barvais *et al* 2003). Similarly, in children over two years old, reflex pupillary dilation was shown to be a very sensitive indicator of nociception during 1.5 MAC sevoflurane–N_2O anesthesia. A significant pupillary dilation was observed in all patients, whereas none of them moved in response to skin incision. A small bolus of alfentanil restored the pupillary diameter to baseline within two minutes, in parallel with hemodynamic variables (Constant *et al* 2006). Thus it has been suggested that the pupillary dilation in response to noxious stimulation could be used to evaluate the level of the analgesic component of anesthesia (Larson *et al* 1997).

The benefit of analgesia

Regional anesthetic techniques represent the most effective means of attenuating the endocrine-metabolic responses to surgical injury, especially with lower body procedures (Kehlet and Wilmore 2002, Moraca *et al* 2003). Pain relief and the prevention of the stress response are not directly coupled. The pathways mediating the neuroendocrine stress response may be inadequately blocked despite effective pain control (Liu *et al* 1995, Carr and Goudas 1999).

The sympathetic stress response can be deleterious to patients with coronary artery disease. Good intra- and post-operative analgesia is an important factor in maintaining optimal hemodynamics and coronary perfusion. Volatile anesthetic agents and delta opioid receptor agonists may have direct cardioprotective effects (Warltier *et al* 2000). Epidural blockade was found to reduce intraoperative and early post-operative myocardial ischemia, compared with general anesthesia alone, in patients with coronary artery disease undergoing upper abdominal surgery (Limberi *et al* 2003).

Although propofol–sufentanil–N_2O anesthesia was associated with lower intraoperative cortisol and catecholamine concentrations than enflurane–N_2O anesthesia, it did not prevent the post-operative metabolic stress response (Schricker *et al* 2000). An extensive epidural block attenuated the catecholamine response in radical esophagectomy patients, but did not prevent the cortisol or cytokine response or the changes in immune function (Yokoyama *et al* 2005).

A meta-analysis by Rodgers and colleagues concluded that compared with general anesthesia alone, intraoperative neuraxial blockade was associated with a reduced overall 30-day mortality and reduced risks of thromboembolism, bleeding, respiratory depression and pneumonia. The data also suggested reduced risks of myocardial infarction and renal failure. A trend towards fewer infective complications other than pneumonia in the neuraxial blockade group appeared (Rodgers *et al* 2000). In contrast, Rigg and colleagues found no difference in mortality at 30 days between high-risk patients assigned to intra- and post-operative epidural analgesia *vs.* general anesthesia alone. They did find a reduced risk of respiratory failure and improved analgesia in the epidural group compared to general anesthesia alone. No differences in the frequency of cardiovascular events, renal failure, or infectious complications were found between the groups. The study by Rigg and colleagues included abdominal and thoracic surgery and had fewer observed fatalities than the study by Rodgers and colleagues, in which the effect on mortality was most pronounced in orthopedic cases (Rigg *et al* 2002).

High dose opioid anesthesia may attenuate the hormonal stress response to surgery (Kono *et al* 1981, Blunnie *et al* 1983). Anand and col-

leagues compared deep sufentanil-based anesthesia and post-operative sufentanil or fentanyl infusion with lighter general anesthesia (halothane–ketamine–morphine) and post-operative intermittent morphine and diazepam boluses in 45 critically ill neonates undergoing cardiac surgery. The neuroendocrine and metabolic stress response was significantly decreased in the high dose sufentanil group compared with the light general anesthesia group. The incidences of sepsis, disseminated intravascular coagulation, persistent metabolic acidosis, and mortality were smaller in the high dose sufentanil group (Anand and Hickey 1992). High dose intrathecal sufentanil attenuated the intraoperative adrenocorticotropic hormone and cortisol secretion during major abdominal surgery more effectively than *i.v.* sufentanil (Borgdorff *et al* 2004). In another study, the incidence of major post-operative complications after abdominal aortic surgery did not differ between patients receiving intrathecal versus *i.v.* opioid analgesia during surgery, although the post-operative pain relief was better and the consumption of morphine was less in the former group (Fleron *et al* 2003).

Ledowski and colleagues found no correlation between stress hormone levels and BIS values, hemodynamic variables, or HRV variables during minor ear-nose-throat procedures with sevoflurane–remifentanil or propofol–remifentanil anesthesia, except for a weak correlation between HRV LF / HF and the noradrenalin level. In the sevoflurane group, BIS values and total HRV power were lower and noradrenalin concentrations higher than in the propofol group during skin incision and maximal surgical stimulation. The overall consumption of remifentanil, adjusted according to hemodynamic variables, was similar in the two groups (2.8 mg and 3.0 mg in the sevoflurane and propofol groups) (Ledowski *et al* 2005).

On the cellular level, a cascade of reactive changes is initiated in the spinal cord dorsal horn within one hour after tissue injury (Carr and Goudas 1999). As a result of plastic changes in the structure, function or electrochemical properties of peripheral and central nerve cells the response of the nociceptive transmission system to repeated stimuli is progressively increased (Woolf and Salter 2000). The level of pre-operatively existing pain may also influence central sensitization (Aida *et al* 2000). Opioids inhibit the initial responses of the dorsal horn nociceptive neurons but not wind-up. Combined to NMDA antagonists, however, which directly inhibit wind-up but not the initial responses to incoming nociceptive information, they produce profound antinociception (Chapman and Dickenson 1992).

In a study of elective abdominal hysterectomy patients, the patients who had received fentanyl intraoperatively displayed a greater sensory inhibition (higher pain detection and tolerance thresholds) at five days post-operatively than those who had received ketamine or magnesium intraoperatively. Just after surgery the fentanyl group had less generalized (central) sensory inhibition than the other groups, but displayed significant multisegmental (spinal) inhibition not present in the other groups. With post-operative morphine patient-controlled analgesia, the pain verbal rating scale scores and total morphine consumption were similar in all groups (Wilder-Smith *et al* 1998). In an earlier study, the same authors demonstrated that compared with placebo, intraoperative fentanyl prevented segmental somatosensory sensitization and was associated with greater general sensory inhibition after isoflurane–N_2O anesthesia for elective intervertebral disc surgery. In that study, the post-operative pain verbal rating scale scores and total morphine consumption were also similar in both groups (Wilder-Smith *et al* 1996). Severe post-operative pain, along with long-term pre-operative pain, intraoperative and post-operative nerve damage, and psychological factors, is a predisposing factor to the development of chronic pain (Perkins and Kehlet 2000).

Isoflurane alone was far less effective than intrathecal morphine in attenuating central sensitization after subcutaneous formalin injection in rats (Abram and Yaksh 1993). In addition to local anesthetics and opioids, central sensitization, and thus post-operative pain, may be reduced by other compounds such as gabapentidoids (Dirks *et al* 2002) or spinal clonidine (De Kock *et al* 2005).

Gottschalk and colleagues compared epidu-

ral fentanyl or bupivacaine treatment, initiated before surgery, with aggressive post-operative epidural analgesia alone, initiated before emergence from isoflurane anesthesia for radical prostatectomy (control group). They found that the pre-emptive groups had lower pain ratings than the control group during hospitalization and at nine and a half weeks after discharge. At three and a half weeks post-operatively, the pre-emptive groups were more physically active than the control group. At nine and a half weeks, 86 % of patients in the pre-emptive groups were pain-free *vs.* 47 % of patients in the control group. Although a trend existed toward epidural pre-emptive bupivacaine being more effective than fentanyl, the difference was not statistically significant (Gottschalk *et al* 1998). This study is an example of "protective analgesia", aimed at preventing hypersensitivity to pain. As central sensitization can develop not only during surgery but in the post-operative period as well, a short "pre-emptive" analgesic treatment without adequate post-operative pain relief may not be effective (Dahl and Moiniche 2004).

Taken together, the above-mentioned studies indicate that the correlation between the hormonal stress response to surgery and indicators of the adequacy of anesthesia is not always good. High-dose opioid administration may attenuate the endocrine-metabolic response to some degree, but regional anesthesia is more effective in this respect, and may be associated with a reduction in some post-operative complications compared to general anesthesia alone. Neither regional anesthesia or opioid analgesia is able to abolish the neuroendocrine stress response completely. Perhaps the greatest significance of intraoperative antinociception lies in the potential prevention of central sensitization induced by tissue injury during surgery, and of cardiac complications in patients with heart disease.

Aims of the study

The aim of this thesis was threefold. First, to study aspects of EEG bispectral index monitoring during anesthesia. Second, to compare EEG features and heart rate responses during desflurane and sevoflurane anesthesia. Third, to explore the interaction of hypnosis and antinociception, and possibilities to monitor the nociceptive–antinociceptive balance during general anesthesia. The specific objectives were:

1. To determine whether inexpensive ECG electrodes are equally acceptable as the designated EEG electrodes in BIS monitoring with the A-1000 EEG monitor, in terms of skin-electrode impedance and measured BIS values (I).

2. To determine whether the tachycardia caused by a rapid increase in the administered desflurane concentration is associated with epileptiform EEG (II).

3. To compare the recovery of gynecological ambulatory surgery patients after isoflurane and sevoflurane anesthesia, when the administration of the volatile agent was adjusted according to BIS values in both groups (III).

4. To compare the effectiveness of a propofol bolus of 0.7 mg / kg i.v. and an alfentanil bolus of 0.5 mg i.v. in preventing the recurrence of movement during uterine dilatation and curettage (IV).

5. To explore which variables derived from a variety of biosignals are associated with the degree of intraoperative nociception, defined as the presence or absence of movement responses to noxious stimulation (IV, V).

Patients and methods

Patients

The original studies (table 1) were conducted in the Women's Hospital of the Helsinki University Central Hospital between September 1998 and June 2002. The patients were adult females classified pre-operatively as ASA physical status I–II (Dripps *et al* 1961) and scheduled for elective surgery under general anesthesia. The total number of patients analyzed was 344 (table 2).

All studies were approved by the local ethics committee. All patients gave their written consent for participation after receiving both written and personal information of the purpose and protocol of the studies.

In the second part of study I, data from one patient was excluded due to the short duration of anesthesia, with a minimal maintenance phase. In study II, the first ten randomized patients were considered pilot cases and were not included in the analysis. In study III, the surgical procedure was cancelled in two randomized patients, and converted from laparoscopy to laparotomy in two other patients, whereby the patients were no longer eligible for discharge on the same day. Two patients experienced a surgically complicated post-operative course.

Table 1. Designs of the original studies and demographics of the patients. N = number of patients. Demographic data are median [25 % percentile; 75 % percentile]. BMI = body mass index (body mass divided by squared height in meters).

	I	*II*	*III*	*IV*	*V*
Design	Prospective, controlled, observational	Prospective, randomized, controlled, double-blind regarding EEG effects	Prospective, randomized, controlled, single-blind	Prospective, randomized, controlled, single-blind	Prospective, controlled, observational
N	85	31	120	82	26
Age (years)	41 [33; 52]	36 [29; 41]	35 [31; 40]	33 [29; 37]	47 [38; 54]
Height (cm)	164 [161; 170]	165 [162; 169]	166 [163; 170]	166 [162; 172]	168 [162; 173]
Body mass (kg)	62 [58; 72]	63 [52; 68]	63 [57; 70]	64 [57; 72]	66 [57; 72]
BMI (kg/m^2)	23 [21; 25]	23 [20; 24]	23 [21; 25]	23 [21; 25]	23 [21; 26]

Table 2. The number of patients in the original studies.

Study	Randomized patients	Patients excluded from analysis	Analyzed patients
I	–	1	85
II	41	10	31
III	126	6	120
IV	129	47	82
V	–	10	26
Total	296	74	344

These six patients were excluded from the analysis. In study IV, 26 patients who moved in response to a non-noxious stimulus were given rescue medication and excluded form the analysis. Three patients were excluded because of protocol failure and nine patients due to missing data. The study was cancelled in eight cases due to logistic problems. One patient was excluded because removal of an intrauterine device, instead of uterine dilatation and curettage, was performed. In study V, five of the originally randomized patients were excluded due to missing or poor quality data, and three patients because of spontaneous movement less than five minutes before skin incision, necessitating rescue medication. The study was cancelled in two cases because hysteroscopy, instead of laparotomy, was performed. The total number of patients recruited but excluded from analysis in studies I–V was 74 (table 2).

Designs and protocols of the original studies

The randomization in studies II–IV was performed in blocks of four using the random numbers generator of the Excel® 97 spreadsheet program. The group assignment codes were contained in sealed envelopes until recruitment was complete.

Study I. In the first study, the skin-electrode impedance values of different electrode – skin pretreatment combinations, and the BIS values measured with different electrodes were compared. The study consisted of three parts. In the first part, the skin-electrode impedance values of Zipprep® EEG electrodes, with alcohol swab pretreatment of the skin, and Nikomed® ECG electrodes, with either alcohol swab pretreatment alone or both electrode paste abrasion and alcohol swab pretreatment of the skin were compared in 51 patients. The impedances were measured before induction and after the completion of the surgical procedure with the impedance check algorithm of the Aspect A-1000 EEG monitor. In the second part, the BIS values measured simultaneously with a set of four Zipprep® EEG electrodes and a set of four Nikomed® ECG electrodes, placed just cephalad of the respective Zipprep® electrodes on the frontotemporal area, were compared in 26 patients. The principal outcome parameter was the average BIS value difference between the ECG and EEG electrodes. In the third part, BIS values measured with two sets of four Zipprep® EEG electrodes were compared in eight patients. The skin was prepared and the electrodes were placed in the same way as in the second part of the study to evaluate the effect of the location of the electrodes on the BIS values. The principal outcome parameter was the average BIS value difference between the two sets of EEG electrodes.

Study II. The hypothesis that tachycardia induced by a rapid increase in the administered desflurane concentration is associated with epileptiform EEG activity, similarly as has been observed with sevoflurane, was tested. The principal outcome parameter was the incidence of epileptiform EEG activity. A total of 31 patients were randomized to receive either desflurane or sevoflurane anesthesia. After induction of anesthesia with propofol and remifentanil, and a ten-minute equilibration period at approximately 0.7 MAC desflurane–N_2O or sevoflurane–N_2O anesthesia, the inspired concentration of the volatile agent was adjusted to the highest possible setting on the vaporizer (18 % and 7 %) for five minutes. A Bain's circuit placed between the tracheal tube connector and the Y-piece of the ventilator was used to achieve a rapid rise in the alveolar anesthetic concentration. Normocapnia, as defined by the end-tidal carbon dioxide concentration, was maintained by adjusting fresh gas flow. Heart rate and non-invasive blood pressure were manually recorded at one-minute intervals. After the five-minute study period the Bain's circuit was removed and the inhaled concentration of the volatile agent was decreased to a clinically appropriate level. Three EEG channels and ECG lead II were recorded with an A-1000 EEG monitor. The EEG tracings from the five-minute study period were classified according to the presence or absence of epileptiform activity by an experienced neu-

rophysiologist who was unaware of the group assignment.

Study III. The hypothesis that the recovery of gynecological ambulatory surgery patients is equally fast after isoflurane–N_2O anesthesia as after sevoflurane–N_2O anesthesia, when the administration of the volatile agent is adjusted according to BIS values, was tested. In all 120 patients were randomized to receive either isoflurane–N_2O anesthesia or sevoflurane–N_2O anesthesia. After induction of anesthesia with propofol and fentanyl, the inhaled concentration of the volatile agent was adjusted so that the BIS remained between 50 and 60. If the heart rate or blood pressure increased during anesthesia by 25 % or more compared to the pre-induction baseline, and the level of hypnosis was adequate as defined by the BIS value, one to two doses of fentanyl 50 µg *i.v.* were given. If the hyperdynamic response persisted, one to two doses of labetalol five mg *i.v.* were administered. If no hyperdynamic responses were present, fentanyl 50 µg *i.v.* was administered every 45 minutes. All patients received either ketoprofen 100 mg or propacetamol 2000 mg *i.v.* at the end of anesthesia. The anesthetic gases were abruptly discontinued when the procedure was complete. The main outcome parameter was the time to home-readiness after anesthesia. Several other early and intermediate recovery parameters were registered. Psychomotor performance (DSST test) (Hindmarch 1980), pain, and nausea (VAS) were evaluated at 30, 60, 90, and 120 minutes after anesthesia in the PACU. VAS has been validated as a measure of pain (Jensen *et al* 2003), and has been found useful in the assessment of nausea (Boogaerts *et al* 2000).

Study IV. The effectiveness of an alfentanil bolus and a propofol bolus in preventing the recurrence of movement responses during uterine dilatation and curettage was compared. In addition, the association of a measure of HRV (Anemon-I®), heart rate, BIS, SEF95 and fEMG power with movement responses to noxious stimulation was evaluated. A total of 82 patients were randomized to receive either an alfentanil bolus of 0.5 mg *i.v.* or a propofol bolus of 0.7 mg / kg *i.v.* in case of movement in response to cervical dilatation and uterine curettage after a propofol–alfentanil induction. The procedure was resumed 90 seconds after the group drug administration. The main outcome parameter was the incidence of recurring movement after the group drug administration. If movement recurred, patients in the alfentanil group received a propofol bolus of 0.7 mg / kg *i.v.*, and patients in the propofol group received an alfentanil bolus of 0.5 mg *i.v*. After the second movement response, all patients were given a propofol bolus of 0.7 mg / kg *i.v.* in the event of recurring movement. Heart rate and the Anemon-I index were registered with a proprietary monitor. EEG and fEMG were registered with the Aspect A-2000 EEG monitor. The relationship between movement responses induced by cervical dilatation and subsequent surgical stimulation and HR, the Anemon-I index, EEG-derived variables, and fEMG power was explored. Standardized variables (relative to pre-stimulus values) were used to classify movers and non-movers.

Study V. The relationship between movement responses induced by skin incision and various noninvasive cardiocirculatory variables, EEG-derived variables, and fEMG power was explored in 26 patients. After a combined intravenous (propofol and fentanyl) and sevoflurane inhalation induction, a 14-minute wash-in period was allowed to achieve a stable sevoflurane anesthesia of 0.9 MAC before skin incision. After skin incision, the patients were observed closely for two minutes to detect any visible somatic reactions. The ECG, PPG, EEG and fEMG were registered with the Datex-Ohmeda AS / 3 Anesthesia Monitor and the Aspect A-2000 EEG monitor. The pre- and post-stimulus values of several variables calculated from the aforementioned signals were compared. Standardized variables (relative to pre-stimulus values) were used to classify movers and non-movers.

Methods

Premedication

Oral diazepam (5 mg) roughly one hour before anesthesia was used as premedication in studies I–II and studies IV–V. In study III, no sedative premedication was given routinely, but 8 patients received oral diazepam (2.5–10 mg) pre-operatively due to subjective anxiety.

Monitoring and signal acquisition

General. Routine monitoring consisted of ECG (lead II), heart rate, peripheral pulse oximetry, noninvasive automated blood pressure measurement, inspired concentration of oxygen, expired concentrations of carbon dioxide and N_2O, and peak airway pressure. The expired concentrations of sevoflurane, desflurane and isoflurane were also monitored (studies I–III and V). The ventilatory and gas measurements were performed from the ventilatory circuit at the connection piece close to the endotracheal tube (studies I–III and V) or face mask (study IV). Datex-Ohmeda AS / 3 Anesthesia monitor was used in studies I–III and V. In study IV, the Capnomac Ultima® monitor with a Dinamap® device was used.

Study I. The electrode positions in the first part of the study were just caudal to Fp_z (according to the international 10–20 electrode system; reference), Fp_1 (ground), and left and right temporal (next to the lateral canthus of the eyes; active electrodes). These were also the electrode positions of the more caudal electrodes in the second and third parts of the study. Another set of electrodes (Nikomed® ECG electrodes and Zipprep® EEG electrodes in parts two and three, respectively) was attached just cephalad of the aforementioned positions. Two A-1000 EEG monitors (Aspect Medical Systems, Natick, MA, USA) and two lap-top computers were used in the second and third parts of the study. The EEG was band-pass filtered (0.5–30 Hz), amplified and digitized with a sampling rate of 128 Hz. Datalogger® software was used to collect the EEG signal. In the first part of the study, alcohol swab skin pretreatment was used for the reference and ground (Zipprep® EEG electrodes), and also for the left temporal electrode (Nikomed® ECG electrode). For the right temporal electrode (Nikomed® ECG electrode) the skin was first abraded with electrode paste (Elektrodipasta comp.®, Christian Nissen Div., Berner Corp.), and then degreased with an alcohol swab. Alcohol swab skin pretreatment was used for all electrodes in the second and third parts of the study. All electrodes were pressed firmly for at least 6 s after placement. Skin-electrode impedances below 10 kΩ were considered acceptable.

Study II. The EEG montage used in study II was F7: left mastoid, F8: right mastoid, Fpz: left temporal, with the ground electrode on the upper right forehead. The three EEG channels and ECG lead II were recorded with the Aspect A-1000 EEG monitor, and collected on a lap-top computer with Datalogger® software. The EEG was band-pass filtered (1–50 Hz), amplified and digitized with a sampling rate of 128 Hz. Alcohol swab skin pretreatment was used for the pregelled silver / silver chloride (Ag / AgCl) Zipprep® EEG electrodes. Skin-electrode impedances below 5 kΩ were considered acceptable.

Study III. The electrode positions were just caudal to Fp_z (according to the international 10–20 electrode system; reference), Fp_1 (ground), and left and right temporal (next to the lateral canthus of the eyes; active electrodes). The EEG was recorded with the Aspect A-1000 EEG monitor, and collected on a lap-top computer with Datalogger® software. The EEG was band-pass filtered (0.5–30 Hz), amplified and digitized with a sampling rate of 128 Hz. Alcohol swab skin pretreatment was used for the pregelled Ag / AgCl Zipprep® EEG electrodes. Skin-electrode impedances below 5 kΩ were considered acceptable.

Study IV. Heart rate and Anemon-I index were obtained from lead II with a proprietary monitor via pregelled Ag / AgCl Nikomed® ECG electrodes. The EEG and fEMG were registered with the Aspect A-2000 EEG monitor®

via a BIS Standard Sensor®. Alcohol swab skin pretreatment and firm pressure after electrode placement were used. The electrode positions corresponded to Fp_z, Fp_2, and right temporal (next to the lateral canthus of the right eye). The EEG was band-pass filtered (0.5–30 Hz), amplified and digitized with a sampling rate of 128 Hz. fEMG power (in the 70–110 Hz range) was obtained directly from the A-2000 monitor. The Anemon-I index, heart rate, and the A-2000 monitor data were collected with custom-made software on a lap-top computer at five-second intervals. Skin-electrode impedances below 5 kΩ were considered acceptable.

Study V. The EEG and fEMG were registered with the Aspect A-2000 EEG monitor® via a BIS Standard Sensor®, and with a research prototype of the Datex-Ohmeda AS / 3 Anesthesia Monitor. Alcohol swab skin pretreatment and firm pressure after electrode placement were used. The electrode positions corresponded to Fp_z, Fp_2, and right temporal (next to the lateral canthus of the right eye). The EEG was band-pass filtered (0.5–47 Hz), amplified and digitized with a sampling rate of 400 Hz. fEMG was defined as the power above 60 Hz. The signal from ECG lead II was sampled at 300 Hz. The pulse plethysmography signal was sampled at 100 Hz. Central® and Wincollect® software were used to collect the data on a laptop computer.

Anesthesia

A fentanyl bolus of 1–2 µg / kg *i.v.* (studies I, III and V), remifentanil bolus of 1 µg / kg *i.v.* (study II), or alfentanil bolus of 0.5 mg *i.v.* (study IV) was administered before the induction of anesthesia. Anesthesia was induced with a propofol bolus of 1.5–2.5 mg / kg *i.v.* in studies I–IV. In study V, hypnotic induction with a propofol bolus of 1 mg / kg *i.v.* was supplemented with inhalation of sevoflurane 8 %. A rocuronium bolus of 30–40 mg *i.v.* was used to facilitate endotracheal intubation in studies I–III. A glycopyrrolate bolus of 0.2 mg *i.v.* was given at anesthetic induction in studies I and III, unless the pulse rate exceeded 90 / min in the absence of hypovolemia. It was not given routinely in studies II and IV–V. In study I, anesthesia was maintained according to clinical needs. In studies II and V, desflurane or sevoflurane were administered according to a specific protocol during the study period, and according to clinical needs thereafter. In study III, the inhaled concentration of isoflurane or sevoflurane was adjusted so that the BIS remained between 50 and 60 throughout the procedure. In study IV, anesthesia was maintained with N_2O (67 %) and supplemented with propofol or alfentanil boluses. N_2O (50 %–67 %) was also used as an adjunct in studies I–III. If the level of hypnosis was adequate as defined by the BIS value, hyperdynamic responses were treated with either fentanyl boluses of 50 µg *i.v.* or labetalol boluses of five mg *i.v.* If no hyperdynamic responses were present, a fentanyl bolus of 50 µg *i.v.* was administered every 30–60 minutes. Ketoprofen (maximum daily dose 300 mg), ibuprofen (maximum daily dose 2400 mg) or paracetamol (maximum daily dose 3000 mg) were used perioperatively as analgesic adjuncts.

Post-operative surveillance

The patients were observed in the PACU until they were alert with stable vital signs, and pain and nausea were controlled. If discharge on the operating day was considered, pain was treated with fentanyl bolus doses of 25–50 µg *i.v.* up to a total dose of 250–300 µg, along with non-steroidal anti-inflammatory agents. If the patient stayed in the hospital for the night, oxycodone boluses of 2–4 mg *i.v.* or 0.1 mg / kg *i.m.* were used as needed. Nausea and vomiting were treated with a droperidol bolus of 0.5–0.75 mg *i.v.*, an ondansetron bolus of 4 mg i.v., or a metoclopramide bolus of 10 mg *i.v.* The patients were considered home-ready when they had stable vital signs, were oriented and co-operative, were able to retain orally consumed fluids, to walk unsupported, to dress and void, and had no more than mild nausea or pain, controllable with oral analgesics. For discharge, an adult escort who accompanied the patient overnight was also required. All patients received instructions for care at

home and a telephone number to call in case of problems. In studies III–V, the patients were interviewed in the PACU regarding memories of the intraoperative period. The patients in study III were also interviewed at 24 hours after the anesthesia.

Electroencephalogram processing

Study I. The electrode impedances were measured with the impedance check algorithm of the Aspect A-1000 EEG monitor. Aspect Medical Systems software v. 3.12 was used for calculation of the BIS values, obtained at five-second intervals.

Study II. The raw EEG tracings from the five-minute study period were classified according to the presence or absence of epileptiform activity by an experienced neurophysiologist. The main criteria for epileptiform activity were the occurrence of spikes (pointed waveforms standing out from the background, with a duration of 20–70 ms), polyspikes (spikes with more than two negative and positive deflections), rhythmic polyspikes (polyspikes occurring at nearly regular intervals) or periodic epileptiform discharges (repetitive sharp waves, spikes or sharply contoured waves occurring at regular intervals and without clear evolution in frequency or location). The criteria for epileptiform EEG corresponded to those employed by Yli-Hankala, Vakkuri and colleagues (Yli-Hankala *et al* 1999b, Vakkuri *et al* 2000). Spectral analysis of ten-second EEG epochs from immediately before the rapid increase in the inhaled volatile concentration, at two minutes after the rapid increase in the inhaled volatile concentration and at the end of the five-minute study period was performed with MATLAB 7® software (MathWorks Inc., Natick, MA, USA).

Study III. Aspect Medical Systems software v. 3.3 was used for calculation of the BIS values, obtained at five-second intervals.

Study IV. Aspect Medical Systems software v. 3.4 was used for calculation of the processed EEG variables (BIS, SEF95) and fEMG, obtained at five-second intervals.

Study V. The EEG was analyzed in five-second epochs, with 50 % overlapping. Epochs with excess amplitudes were excluded. The threshold for rejection was defined individually by visual inspection. The PSD was estimated for each epoch with the Welch averaged periodogram method (Kay 1988). SEF95 and fEMG were computed from the PSD. EEG RE and SE were calculated off-line according to a published algorithm (Viertiö-Oja *et al* 2004).

Electrocardiogram processing

In study IV, an Anemon-I index value, along with a smoothed trend value, was obtained every five seconds. The algorithm applied by the proprietary monitor has not been published. It is based on heart rate variability. The heart rate recording was also updated every five seconds. In study V, the R-waves of the ECG were automatically detected. They were verified by visual inspection and corrected if necessary. A beat-to-beat RRI signal was constructed as a series of time differences between successive heart beats. RRI SD and RMSSD were used as time domain measures of HRV. For frequency domain analysis, the RRI signal was linearly interpolated and resampled at two Hz. The resulting signal was detrended, and the PSD was estimated with the Welch averaged periodogram method (Kay 1988). LF (0.04–0.15 Hz) and HF (0.15–0.4 Hz) spectral powers, and their ratio (LF / HF) were computed from the PSD. Poincaré plots were constructed by plotting the RRI interval of the current beat as a function of the RRI interval of the previous beat. The SD against the axes $y = x$ ($SD1$) and $y = (-x) + 2m$ ($SD2$), where m is the mean RRI during the epoch of interest, as well as their ratio ($SD1 / SD2$) were calculated (Tulppo *et al* 1996).

Pulse plethysmography processing

The amplitude of the PPG waveform and the

location of the dicrotic notch were automatically detected in study V. They were verified by visual inspection and corrected if necessary. The absolute (vertical) dicrotic notch amplitude was defined as the distance from pulse baseline to the notch minimum. The absolute (horizontal) dicrotic notch position was defined as the distance from the beginning of the pulse rise to the crossing of a vertical line drawn through the notch minimum with the pulse baseline. The relative (vertical) dicrotic notch amplitude was defined as the ratio of the absolute (vertical) notch amplitude and the total pulse amplitude. The dicrotic notch latency was defined as the ratio of the absolute (horizontal) notch position and the total pulse duration. Heart beats with PPG artifacts were excluded from the analysis. Beat-to-beat time series were constructed for the PPG amplitude, the area under the PPG waveform, the absolute and relative vertical and horizontal dicrotic notch positions and the PPG maximum derivative, *i.e.* the maximum slope at the rising edge of the waveform. For PPG amplitude, Poincaré analysis was carried out similarly to the RRI data.

Statistical analysis

General. Statistical analysis was performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA), versions 9.0, 10.0, 11.0.1 and 12.0.1, except in study I, where NCSS 97 (NCSS, Kaysville, Utah, USA) and the statistical functions of Excel 97® software were used. MATLAB® (MathWorks, Natick, MA, USA) was used in data processing in studies II, IV and V.

Study I. BIS data from the maintenance phase of anesthesia was used in the statistical analyses. In the first part of the study, the overall variation in impedance values between the three different electrode-skin preparation combinations was evaluated with Friedman's two-way analysis of variance by ranks. Pairwise comparisons of impedance values between the different electrode-skin preparation combinations and between the beginning and the end of surgery were made with Wilcoxon's signed ranks test. In the second and third parts of the study, the difference between the simultaneous BIS values measured with the two sets of four electrodes was calculated at 30-second intervals. Further, a grand average of individual mean BIS value differences was calculated. The hypothesis that the grand average BIS difference obtained in the second part of the study equals zero was tested by the one-sample t-test. The 95 % confidence interval for the grand average BIS value difference was calculated in the second and third parts of the study. The grand average BIS differences obtained in the second and third parts of the study were compared with the independent samples t-test, and the 95 % confidence interval for their difference was calculated. In the second part of the study, the variation of BIS value differences over time was evaluated by applying Friedman's two-way analysis of variance by ranks to 50 consecutive BIS differences from each patient. Overall interindividual variation in BIS differences was assessed by Kruskal-Wallis nonparametric analysis of variance. In addition, the incidences of BIS value differences exceeding 10 % in at least 50 % of the measurement points (at 30-second intervals) in the second and third parts of the study were compared with Fisher's exact test.

Study II. The incidence of epileptiform EEG activity in the two groups was compared using the χ^2-test and Fisher's exact test. The heart rate during the five-minute study period was analyzed in a six by two ANOVA for repeated measures, with time as a within-subjects factor and group assignment as the between-subjects factor. The paired samples and independent samples t-test, as appropriate, and the estimated marginal means provided in the SPSS syntax were used for pairwise comparisons.

Study III. The means of the normally distributed variables, as defined by the Kolmogorov-Smirnov test, were compared between the groups using the independent samples t-test. The medians of non-normally distributed variables were compared between the groups using the Mann-Whitney U-test. The overall change

with time in the VAS scores for pain and nausea was analyzed by the Friedman's two-way analysis of variance by ranks, and pairwise comparisons were made using the Wilcoxon's signed ranks test within groups, and the Mann-Whitney U-test between groups. The DSST scores were analyzed in a four by two ANOVA for repeated measures, with time as a within-subjects factor and group assignment as a between-subjects factor.

Study IV. Anemon-I values, heart rate, BIS, SEF95, and EMG power were averaged over the periods 60 s before and 60 s after CD, RP and movement events using MATLAB® software. The means of the normally distributed variables, as defined by the Kolmogorov-Smirnov test, were compared using the independent samples or paired samples t-test. The medians of the non-normally distributed variables were compared using the Mann-Whitney U-test or the Wilcoxon's signed ranks test.

Prediction probability (P_K) values associated with the response (movement or no movement) to noxious stimulation were calculated with the spread-sheet program PKMACRO®. The prediction probability P_K is a nonparametric measure of association, introduced by Smith and colleagues in 1996 for assessing the performance of anesthetic level indicators (Smith *et al* 1996b). It is a rescaled variant of Kim's $d_{y \cdot x}$. The P_K can be described as the probability that given two randomly selected data points with distinct anesthetic levels, the associated indicator values correctly predict the rank order of the anesthetic levels. A P_K value of 1 reflects perfect prediction, and a P_K value of 0.5 means that the indicator performs no better than chance alone. P_K values between 0 and 0.5 mean that discordances (indicator and anesthetic level change in opposite directions) are more likely than concordances (indicator and anesthetic level change in the same direction). The P_K is independent of distribution assumptions, units of measurement, and the choice of a particular threshold value, and its value is asymptotically independent of sample size. A valid comparison of different indicators with P_K necessitates collection of data under similar experimental conditions and over the same distribution of anesthetic levels (Smith *et al* 1996b). The P_K is equal to the nonparametric area under the ROC curve for a dichotomous outcome (Smith *et al* 1996a).

Logistic regression models with the response (movement or no movement) to noxious stimulation as the dependent variable were formed for combinations of variables which had a statistically significant P_K value, unless the variables had a significant linear correlation. The models were evaluated by the model χ^2-value, the overall correct classification rate and the area under the ROC curve associated with the model. The ROC curve is sensitivity plotted against 1-specificity. The area under the ROC curve represents the probability of correctly classifying a randomly selected positive-negative pair (in this case, a mover – non-mover pair). The curve itself shows all possible combinations of sensitivity and specificity associated with different cut-off values. The models were compared by the χ^2-value asssociated with the difference in –2 log likelihood (–2LL) values between the models. Logistic regression was also used to analyze the effect of group assignment and the remaining procedure time on the recurrence of movement. Proportions were analysed with the Fisher's exact test.

Study V. The RRI, EEG and PPG variables were averaged over the periods 120 s before and 120 s after skin incision with the MATLAB® software. Pre- and post-incision values were compared using Wilcoxon's signed ranks test. The post-incision values were normalized with respect to the corresponding pre-incision values by either dividing the post-incision value by the pre-incision value or by subtracting the pre-incision value from the post-incision value (for those variables with values close to zero). The normalized values of movers and non-movers were compared using the Mann-Whitney U-test. Those normalized variables, which yielded statistically significant differences between movers and non-movers, were used in different combinations to construct logistic regression equations to classify the patients into movers and non-movers. The models were compared by the overall correct classification performance, as defined by leave-one-out cross validation.

Sample size and power analysis. As there was no previous knowledge of the end-points in studies I–II and V, the sample sizes were not based on power analysis. In study III, power analysis was based on data from a previous study at the same institution on similar patients. In that study, the range of home-readiness times was 500 and 600 minutes for isoflurane- and sevoflurane-anesthesized patients. A sample size of 120 (60 per group) would give a 90 % power (with a 5 % α error rate) to detect a standardized difference (difference in group means divided by the standard deviation of the variable in question) of 0.6 (Altman 1999). Assuming similar variability in home-readiness times as in the previous study, and that the standard deviation is roughly one quarter of the range, this would correspond to a 75–90 minute difference in the group means. Based on previous experience, the general incidence of recurring movement in study IV was estimated to be 50 %. The sample size needed to detect a difference of 25 % in the incidence of recurring movement with an 80 % power (and a 5 % α error rate) was 110 (55 per group) (Pocock 1983).

Results

Electrocardiography electrodes versus designated electroencephalography electrodes in bispectral index monitoring (Aim 1)

The skin-electrode impedance values before anesthetic induction and after surgery with different electrode types and positions are shown in table 3. The ECG electrodes with both abrasion paste and alcohol swab skin pretreatment were superior to EEG electrodes with only alcohol swab skin pretreatment, in terms of the skin-electrode impedance ($p \leq 0.001$, Wilcoxon's test). If only alcohol swab skin pretreatment was used, ECG electrodes were inferior to EEG electrodes ($p < 0.001$, Wilcoxon's test). Impedance values decreased during anesthesia with all electrode-skin preparation combinations ($p \leq 0.002$, Wilcoxon's test).

The BIS values registered with a set of ECG electrodes were higher than the BIS values simultaneously registered with a set of EEG electrodes (grand average BIS value difference 5.2, 95 % CI [3.5; 7.0], $p < 0.001$ *vs.* 0, one-sample t-test). The difference was stable during the maintenance phase of anesthesia ($p = 0.22$, Friedman's test). The BIS values simultaneously registered with two sets of EEG electrodes were similar (grand average BIS value difference 1.7, 95 % CI [−0.1; 3.4]; $p = 0.061$ *vs.* 0, one-sample t-test). The interindividual variation in BIS

Table 3. Impedance values at the beginning and at the end of anesthesia in the three parts of study I with different electrode types and positions. Data are given in ohm. Both the median (interquartile range, IQR) and minimum and maximum values are presented. EEG = Zipprep® electrode with alcohol swab skin pretreatment. ECG = Nikomed® electrode with alcohol swab skin pretreatment. ECGpaste = Nikomed® electrode with abrasion paste and alcohol swab skin pretreatment. Ref = reference electrode above nasion (Nz). A1 = active electrode at left temple. A2 = active electrode at right temple. For part III, pooled impedance data for the two sets of Zipprep® electrodes are presented.

			Beginning		*End*	
Part	Electrode	Position	Median (IQR)	[Minimum, Maximum]	Median (IQR)	[Minimum, Maximum]
I	EEG	Ref (Nz)	700 (500)	[200, 5500]	500 (300)	[200, 4900]
	ECG	A1	2600 (2500)	[500, 16 300]	1600 (1700)	[400, 6300]
	ECGpaste	A2	400 (300)	[200, 1200]	400 (300)	[100, 1100]
II	EEG	Ref (Nz)	1000 (700)	[400, 2200]	800 (500)	[400, 2200]
	EEG	A1	1600 (900)	[500, 2400]	1300 (1200)	[400, 2300]
	EEG	A2	1300 (600)	[400, 3400]	1100 (700)	[400, 4400]
	ECG	Ref (Nz)	3300 (4400)	[900, 17 800]	2000 (2800)	[400, 9800]
	ECG	A1	9500 (13 300)	[1400, 50 000]	4800 (4800)	[1200, 15 500]
	ECG	A2	9600 (11 100)	[900, 41 900]	5500 (8900)	[1100, 23 800]
III	EEG	Ref (Nz)	800 (800)	[200, 2000]	800 (600)	[600, 1700]
	EEG	A1	900 (400)	[500, 1600]	1000 (600)	[500, 1500]
	EEG	A2	1000 (500)	[500, 2000]	900 (600)	[500, 2200]

value differences was considerable in both the second and third parts of study I ($p < 0.001$, Kruskal-Wallis test) (figures 4–5). The difference between the grand average BIS value differences from the second and third parts of the study was statistically significant (5.2 *vs.* 1.7, $p = 0.033$, independent samples t-test; difference in grand average BIS value differences 3.6, 95 % CI [0.3; 6.9]).

Electroencephalogram features and tachycardia during a rapid increase in the administered desflurane concentration (Aim 2)

Epileptiform EEG activity was detected in eight of the 15 sevoflurane patients during the rapid increase in the inspired volatile concentration, and in none of the 16 desflurane patients (incidences 0.53 *vs.* 0, $p < 0.001$, Fisher's exact test; difference in incidences 0.53, 95 % CI [0.23; 0.75]). The epileptiform phenomena were rhythmic polyspikes, rhythmic spiky bursts, or periodic epileptiform discharges. The epileptiform activity disappeared when the end-tidal sevoflurane concentration decreased after the study period. Nearly all subjects developed EEG burst suppression patterns or at least a few short suppression segments toward the end of the five-minute study period in study II.

RE / SE values calculated off-line for three time periods are given in table 4. The time periods are immediately before the rapid increase in inhaled volatile concentration (1), at two minutes after the increase (2), and at the end of the study period, *i.e.* at five minutes after the increase (3).

RE / SE values calculated off-line for the three time periods, separately for subjects with normal and epileptiform EEG in the sevoflurane group, are given in table 5.

Five patients in the sevoflurane group received a bolus of efedrin (5–10 mg *i.v.*), for the treatment of hypotension at three to four min-

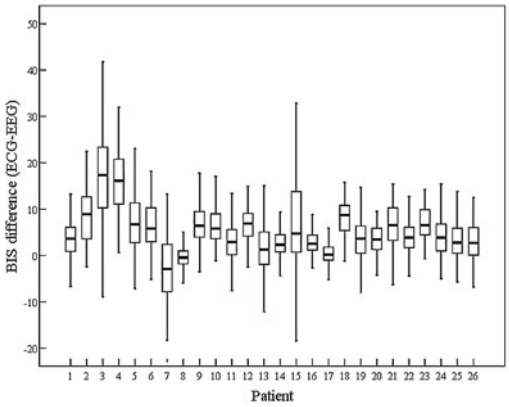

Figure 4. Differences between BIS values simultaneously registered (at 30 s intervals) with a set of ECG electrodes and a set of EEG electrodes in individual patients during maintenance phase anesthesia in the second part of study I. The two sets of electrodes were placed adjacent to each other in a cranial (ECG electrodes)-caudal (EEG electrodes) orientation. Boxes represent the median (bold horizontal line) and quartiles. Whiskers denote the minimum and maximum values (outliers > 1.5 times the IQR excluded). The few outliers have been omitted for the sake of clarity.

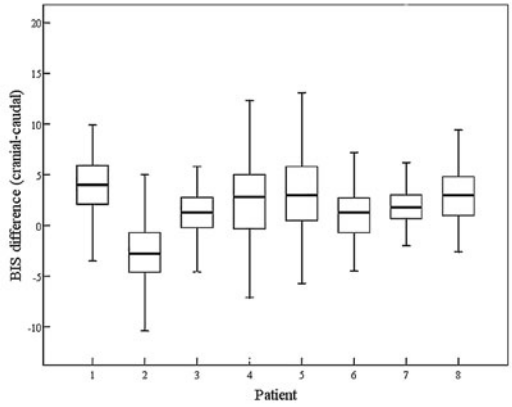

Figure 5. Differences between BIS values simultaneously registered (at 30 s intervals) with two sets of EEG electrodes in individual patients during maintenance phase anesthesia in the third part of study I. The two sets of electrodes were placed adjacent to each other in a cranial-caudal orientation. Boxes represent the median (bold horizontal line) and quartiles. Whiskers denote the minimum and maximum values (outliers > 1.5 times the IQR excluded). The few outliers have been omitted for the sake of clarity.

utes after the start of the study period. The hemodynamic data of these patients was excluded from analysis. In addition, two other patients in the sevoflurane group and one patient in the desflurane group received a bolus of efedrin (5–10 mg *i.v.*), for the treatment of hypotension after the study period (at five minutes). The heart rate increased at the initial rapid increase in the inhaled anesthetic concentration. In the desflurane group, the increase was pronounced [$F(5,18) = 16.39$, $p < 0.001$] and transient. In the sevoflurane group, the increase was slower and more subtle [$F(5,18) = 3.05$, $p = 0.037$]. The repeated measures ANOVA yielded a significant interaction effect for the within-subjects factor (time) and the between-subjects factor (group) [$F(5,18) = 3.29$, $p = 0.028$]. In pairwise comparisons, heart rate was significantly lower in the desflurane group than in the sevoflurane group at zero and at five minutes from the increase in inhaled anesthetic concentration ($p < 0.05$), although the group main effect was not significant due to the interaction (figure 6). In the desflurane group, heart rate increased significantly from zero to two minutes ($p < 0.01$) during the study period, and then decreased significantly from three to five minutes ($p < 0.01$). In the sevoflurane group, the heart rate at two minutes from the start of the study period was higher than at the start of

Table 4. Values comparable to RE and SE, calculated off-line for time periods immediately before the increase in the inhaled anesthetic concentration (1), at two minutes after the increase (2) and at the end of the five-minute study period (3) in study II. Data at period 3 are given separately for patients with high (> 15 %) and low (< 15 %) burst suppression ratios (BSR). Data are the medians (IQR) of values averaged over 10 s. ** $p < 0.01$ *vs.* desflurane, Mann-Whitney U-test.

Desflurane

	Period 1 (N = 13)	Period 2 (N = 13)	Period 3 low BSR (N = 6)	Period 3 high BSR (N = 7)
RE	61 (19)	12 (11)	17 (7)	6 (7)
SE	59 (17)	12 (11)	16 (7)	5 (7)

Sevoflurane

	Period 1 (N = 14)	Period 2 (N = 14)	Period 3 low BSR (N = 9)	Period 3 high BSR (N = 5)
RE	57 (26)	26 (14) **	20 (7)	1 (19)
SE	56 (24)	26 (15) **	19 (7)	1 (18)

Table 5. Values comparable to RE and SE, calculated off-line for time periods immediately before the increase in the inhaled anesthetic concentration (1), at two minutes after the increase (2) and at the end of the five-minute study period (3) in study II. Data are the medians (IQR) of values averaged over 10 s. * $p < 0.05$ *vs.* normal EEG, Mann-Whitney U-test.

Normal EEG (sevoflurane group, N = 6)

	Period 1	Period 2	Period 3
RE	58 (27)	27 (17)	10 (19)
SE	57 (28)	26 (17)	10 (18)

Epileptiform EEG (sevoflurane group, N = 8)

	Period 1	Period 2	Period 3
RE	57 (25)	26 (16)	22 (7) *
SE	56 (21)	26 (15)	20 (7) *

the study period (p = 0.047) (figure 6).

There was no statistically significant difference in heart rate between patients with epileptiform EEG and those with normal EEG during the study period (figure 7).

Comparison of recovery of gynecological ambulatory surgery patients after isoflurane or sevoflurane maintenance with bispectral index monitoring (Aim 3)

No significant differences in the demographics, types of procedures, duration of anesthesia, doses of intraoperative medications, or the frequencies or doses of post-operative analgesic and antiemetic medications between the isoflurane and sevoflurane groups occurred. The post-operative DSST scores and VAS scores for pain and nausea were similar in both groups.

The grand median BIS values during the maintenance phase were 52.1 (IQR 6.7) and 51.3 (IQR 6.3) in the isoflurane and sevoflurane groups (difference –0.2; 95 % CI [–2.0; 1.7], p = 0.84, Mann-Whitney U-test). The median BIS values at the end of the procedure were 57.0 (IQR 11.5) and 56.1 (IQR 9.2) in the isoflurane and sevoflurane groups (difference –0.1, 95 % CI [–2.9; 2.6], p = 0.95, Mann-Whitney U-test). The percentages of maintenance time when BIS was outside the targeted range were similar between the groups.

The median end-tidal anaesthesic concentrations during maintenance were 0.40 % (95 % CI [0.40 %; 0.50 %]) and 0.80 % (95 % CI [0.70 %; 0.90 %]) in the isoflurane and sevoflurane groups. Assuming that in 35 year old patients the MAC values of isoflurane and sevoflurane in 67 % N_2O are 0.45 % and 0.75 % (Nickalls and Mapleson 2003, Lerou 2004), the median MAC values during maintenance were 0.89 MAC and 1.07 MAC in the isoflurane and sevoflurane groups (difference –0.13, 95 % CI [–0.22; 0.0], p = 0.035, Mann-Whitney U-test).

None of the patients had recall of the intraoperative events, based on interviews both on the operating day and the first post-operative day.

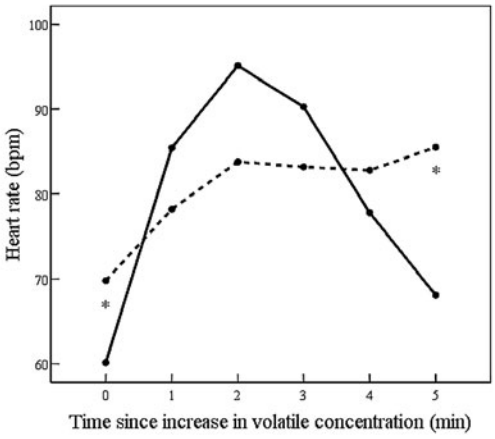

Figure 6. Mean heart rate in beats per minute (bpm) during the rapid increase in inhaled desflurane (solid line; N = 14) or sevoflurane (dashed line; N = 10) concentration in study II. Start of the increase marked with 0. * p < 0.05 desflurane *vs.* sevoflurane, significance test based on estimated marginal means.

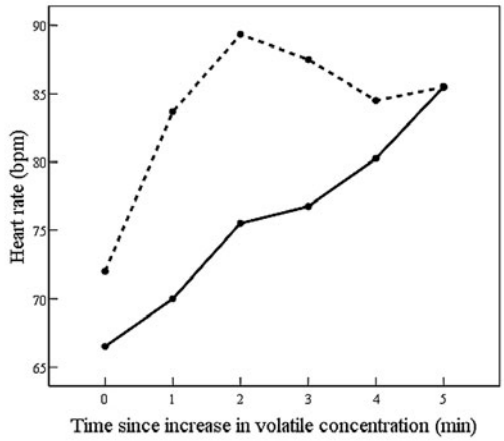

Figure 7. Mean heart rate in beats per minute (bpm) during the rapid increase in inhaled sevoflurane concentration in study II. Start of the increase marked with 0. No statistically significant differences in heart rate between patients displaying epileptiform EEG phenomena (dashed line; N = 6) and those with a normal EEG (solid line; N = 4) at any of the time points.

No statistically or clinically significant difference in the time to home-readiness between the isoflurane and sevoflurane groups emerged, when BIS was titrated between 50 and 60 during the maintenance of anesthesia. All other early and intermediate recovery parameters were also similar (table 6). The recovery times were also similar between the two groups among both the outpatients and the admitted patients. The incidence of slow recovery was similar in the two groups (home-readiness achieved in more than 8 hours in 22 % and 33 % of patients in the isoflurane and sevoflurane groups; difference –12 %, 95 % CI [–27 %; 4 %], p = 0.22, Fisher's exact test).

In study III, home-readiness was defined as being achieved one hour after the last dose of parenteral medication, when the other criteria were fulfilled. Applying alternative home-readiness criteria did not change the result of no difference between the two groups. If home-readiness was defined as being able to walk, drink and void, it was achieved in 300 (IQR 252) min and 294 (IQR 167) min in the isoflurane and sevoflurane groups (difference –22 min, 95 % CI [–84; 31]). If the time of the last dose of parenteral medication was taken into account, home-readiness was achieved in 307 (IQR 232) min and 327 (IQR 245) min in the isoflurane and sevoflurane groups (difference –33 min, 95 % CI [–104; 28]).

The incidence of dreaming during anesthesia was high in both groups, based on interviews in the PACU shortly after emergence (table 7). The grand median BIS values during maintenance in non-dreaming and dreaming patients were 52.1 (IQR 5.1) and 51.9 (IQR 9.8) (difference 0.8; 95 % CI [–1.6; 3.1], p = 0.53, Mann-Whitney U-test). The corresponding grand median MAC values were 1.07 (IQR 0.53) and 1.00 (IQR 0.30), (difference 0.00; 95 % CI [–0.07; 0.18], p = 0.57, Mann-Whitney U-test). No significant differences in the grand median BIS (p = 0.89, Kruskal-Wallis test) or MAC values (p = 0.33, Kruskal-Wallis test) between different categories of dreaming oc-

Table 6. Early and intermediate recovery parameters in all patients in study III. Data are the medians (IQR). * p = 0.049 isoflurane *vs.* sevoflurane, Mann-Whitney U-test.

	Isoflurane (N = 60)	Sevoflurane (N = 60)	Difference [95 % CI]
Opening of eyes (min)	5.0 (2.8)	5.3 (4.0)	–0.5 [–1.4; 0.3]
Obeying commands (min)	5.8 (2.7)	6.0 (3.3)	–0.6 [–1.5; 0.2]
Orientation to current date (min)	6.9 (3.2)	8.0 (3.6)	–0.9 [–1.8; 0.0] *
Fluid per os (min)	32 (30)	32 (23)	0 [–4; 4]
Sitting unsupported (min)	83 (50)	80 (57)	0 [–13; 9]
Walking unsupported (min)	113 (230)	123 (253)	–6 [–35; 19]
Voiding (min)	300 (239)	294 (161)	–22 [–83; 31]
Home-readiness (min)	331 (254)	347 (249)	–38 [–106; 29]

Table 7. The incidence of dreaming during anesthesia in study III, based on interviews in the PACU. No significant difference between the groups.

	Isoflurane (N = 52)	Sevoflurane (N = 50)	Difference [95 % CI]
No dreaming	56 %	56 %	0 % [–19 %; 18 %]
Pleasant dreams	23 %	20 %	3 % [–13 %; 19 %]
Neutral dreams	19 %	22 %	–3 % [–19 %; 13 %]
Unpleasant dreams	2 %	2 %	0 % [–9 %; 8 %]

curred. One patient from each group had unpleasant dreams during anesthesia. The grand median BIS, end-tidal anesthetic, and MAC values in these patients were 58.6, 0.50 %, and 1.11 MAC (isoflurane) and 43.9, 0.90 %, and 1.20 MAC (sevoflurane).

Effectiveness of a propofol bolus versus an alfentanil bolus in preventing the recurrence of movement during uterine dilatation and curettage (Aim 4)

The demographic variables and the pre-operative pain VAS values, nausea VAS values, and DSST scores for both groups were similar, with the exception of mean weight, which was larger in the propofol group than in the alfentanil group (67.7 kg *vs.* 61.5 kg, $p < 0.01$, independent samples t-test). The times from anesthetic induction to the start of the procedure and from the administration of the group drug to the end of the procedure, as well as the duration of the procedure were comparable in the two groups. The median total propofol doses were 170 (70) and 200 (60) mg in the alfentanil and propofol groups (difference –25, 95 % CI [–40; –5], $p = 0.013$, Mann-Whitney U-test). The median total alfentanil doses were 1000 (500) and 500 (250) µg in the alfentanil and propofol groups (difference 500, 95 % CI [0; 500], $p < 0.001$, Mann-Whitney U-test). The distribution of the number of movement responses during the procedure is presented in table 8.

In the alfentanil group, the median VAS value for pain at 20 min after anaesthesia was higher than the baseline value or the values at 40–60 min after anaesthesia (2.9 *vs.* 0.0, $p < 0.01$, Wilcoxon's signed ranks test). In the propofol group, the VAS values for pain were higher at baseline and at 20 min after anaesthesia compared to the values at 40–60 min (0.3 and 1.0 *vs.* 0.0, $p < 0.01$, Wilcoxon's signed ranks test). No statistically significant difference between the two groups in the VAS values for pain existed at any of the time points. The median VAS value for nausea was zero in both groups at all time points.

Repeated measures ANOVA for DSST scores yielded a significant time main effect [$F(3,72) = 143.9$, $p < 0.001$] but no treatment group or interaction effect. That is, no significant differences in the DSST scores between the two groups occurred at any of the evaluated time points. The DSST values reached the pre-operative level by 40 min after the anaesthesia, and increased even further by 60 min after anaesthesia (figure 8).

After the first movement response during uterine dilatation and curettage, a propofol bolus of 0.7 mg / kg *i.v.* was more effective than an alfentanil bolus of 0.5 mg *i.v.* in preventing further movement responses during the procedure. The incidences of recurring movement were 73 % and 38 % in the alfentanil and propofol groups (difference 35 %, 95 % CI [9 %; 56 %], $p = 0.014$, Fisher's exact test).

According to logistic regression analysis, both the group assignment and the time from the administration of the group drug to the end of the procedure were significantly associated with the probability of recurring movement (model χ^2 7.16, $p = 0.007$ and 12.90, $p < 0.001$,

Table 8. Distribution of movement responses during the procedure in the two groups in study IV. Data are the number of patients (N) and the percentage of all patients within the group. $p = 0.016$ alfentanil *vs.* propofol group, Fisher's exact test.

Number of movement responses	Alfentanil group (N = 45)	Propofol group (N = 37)	Difference [95 % CI]
0	12 (27 %)	13 (35 %)	–8 % [–28 %; 11 %]
1	9 (20 %)	15 (41 %)	–21 % [–39 %; –1 %]
2	18 (40 %)	4 (11 %)	29 % [10 %; 45 %]
3	6 (13 %)	5 (14 %)	0 % [–16 %; 15 %]

for group assignment and the remaining procedure time). Inclusion of both variables in the model (model χ^2 19.23, $p < 0.001$) resulted in a significantly better fit than either variable alone, as judged by the −2 log likelihood criterion ($p < 0.001$ *vs.* group assignment alone, $p < 0.02$ *vs.* remaining time alone). According to this model, the times associated with a 50 % (95 %) probability of recurring movement were 2.4 (7.4) min and 5.1 (10.1) min after the first movement in the alfentanil and propofol groups (figure 9). The confidence intervals around the probability curves of this model were wide, suggesting that a large amount of variance remained unexplained.

For the alfentanil group, the curve depicts the equation:

$$p = \frac{1}{1 + e^{0{,}589\ (\text{time since first movement in min}) - 1.418}}$$

For the propofol group, the curve depicts the equation:

$$p = \frac{1}{1 + e^{0{,}589\ (\text{time since first movement in min}) - 2.993}}$$

where p equals the probability of no recurring movement.

The association of physiological variables with movement responses during anesthesia (Aim 5)

The pre- and post-stimulus values of the investigated physiological variables in non-movers and movers, respectively, in studies IV and V, are given in tables 9–11.

In study V, the heart rate increased (RRI decreased) in both non-movers and movers at skin incision. In study IV, the changes in heart rate at CD and at RP were subtle. At RP, heart

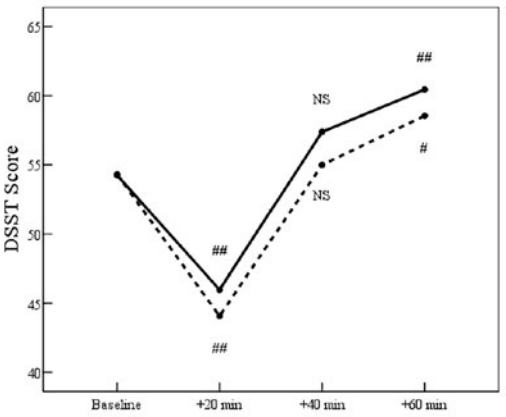

Figure 8. The mean DSST scores at baseline and at 20 min, 40 min, and 60 min after the end of anesthesia in study IV, in the alfentanil group (dashed line) and propofol group (solid line). ## $p < 0.001$ *vs.* baseline, # $p < 0.01$ *vs.* baseline in the respective groups. NS indicates not significantly different from baseline. No significant differences between the groups at any of the time points. The significance tests are based on the estimated marginal means provided in the SPSS syntax.

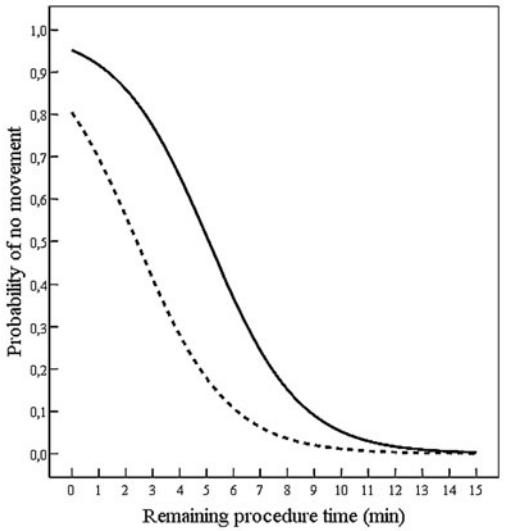

Figure 9. Logistic regression curves describing the relationship between the remaining procedure time (0–15 min) after the administration of the group drug at the first movement (time 0), group assignment, and the probability of no recurring movement in study IV. Dashed line = alfentanil group, solid line = propofol group. The wide 95 % confidence intervals have been omitted for clarity.

rate increased in movers. In study V, RRI SD, RRI SD2, and RRI LF/HF increased in both non-movers and movers at skin incision. RRI HF power decreased overall and in movers, but not in non-movers. RRI SD1/SD2 decreased in both non-movers and movers at skin incision. In study IV, the Anemon Index increased overall at CD. Interestingly, a statistically significant increase was seen in non-movers, but not in movers. At RP, the Anemon Index did not change significantly in either non-movers or movers. These results may be partly due to the very large variability in Anemon-I values (tables 9–10). The observed HR and HRV changes are consistent with an increase in sympathetic activity and a decrease in parasympathetic activity.

In study V, the PPG amplitude, PPG area, and PPG maximum derivative decreased in both non-movers and movers as a sign of sympathetic stimulation. The PPG amplitude SD2 increased, and the PPG amplitude SD1/SD2 decreased in both non-movers and movers. The PPG notch amplitude decreased overall and in movers, but not in non-movers. The relative notch amplitude did not change overall, but a slight increase was seen in non-movers. The notch latency increased overall and in movers, but not in non-movers. The slightly different heart rate and vasoconstriction responses in non-movers and movers may explain the different changes in the configuration of the PPG waveform.

In study V, fEMG power and RE did not change overall at skin incision, but they increased in movers. RE-SE increased overall

Table 9. The averaged values of the variables at the beginning of cervical dilation (CD) for non-movers and movers in study IV. Pre refers to values averaged over 60 s before CD. Post refers to values averaged over 60 s after CD. Data are the medians (IQR). For non-movers, N = 44 for HRV variables, N = 43 for EEG variables. For movers, N = 38. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. Pre. # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ *vs.* non-movers. For the abbreviations, see page 11.

	Non-movers		*Movers*	
	Pre	Post	Pre	Post
Anemon Index	57.4 (43.3)	74.5 (39.3) *	61.4 (29.1)	69.0 (21.2)
Heart rate (beats/min)	66.9 (17.0)	67.2 (17.0)	68.4 (14.2)	67.9 (13.7)
fEMG power (μV^2)	0.078 (0.037)	0.072 (0.032) **	0.101 (0.054) #	0.111 (0.270) ** ###
BIS	32.8 (10.1)	35.0 (12.1) ***	38.4 (15.7) ##	47.0 (20.7) *** ###
SEF95 (Hz)	13.3 (5.2)	14.3 (2.9) ***	14.7 (4.8)	16.6 (3.5) *** #

Table 10. The averaged values of the variables at the resumption of the procedure after the administration of the study drug (RP) for non-movers and movers in study IV. Pre refers to values averaged over 60 s before RP. Post refers to values averaged over 60 s after RP. Data are the medians (IQR). For non-movers, N = 37. For movers, N = 18 for HRV variables, N = 17 for EEG variables. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. Pre. # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ *vs.* non-movers. For the abbreviations, see page 11.

	Non-movers		*Movers*	
	Pre	Post	Pre	Post
Anemon Index	67.3 (29.7)	70.2 (19.8)	60.4 (38.4)	80.3 (18.7) #
Heart rate (beats/min)	61.8 (14.8)	61.6 (14.9)	58.9 (10.6)	61.6 (11.8) *
fEMG power (μV^2)	0.126 (0.355)	0.089 (0.095) ***	0.110 (0.267)	0.135 (0.593) #
BIS	54.5 (13.8)	47.9 (24.1) **	61.8 (13.2)	67.1 (25.9) ##
SEF95 (Hz)	19.3 (4.1)	16.6 (3.9) ***	20.9 (4.9)	20.3 (7.4) #

and in movers, but not in non-movers. In study IV, fEMG power did not change overall at CD, but increased in movers and decreased in non-movers. At RP, fEMG power decreased in non-movers, and remained stable in movers. These changes are consistent with a greater frontal motor activity in movers. Similarly, the absolute and relative β2 power increased overall and in movers, but not in non-movers at skin incision in study V.

In study V, SE and SEF95 did not change significantly at skin incision either in movers or in non-movers. In study IV, BIS and SEF95 increased at CD in both non-movers and movers. At RP, BIS and SEF95 decreased in non-movers, and remained stable in movers. Thus the EEG arousal response was greater in movers both at CD and at RP in study IV.

In study IV, the pre-stimulus fEMG power and BIS values were higher in movers than in

Table 11. The averaged values of the variables at skin incision for non-movers and movers in study V. Pre refers to values averaged over 120 s before skin incision. Post refers to values averaged over 120 s after skin incision. Data are the medians (IQR). For non-movers, N = 14 for HRV variables, N = 12 for EEG variables, N = 14 for PPG variables. For movers, N = 12 for HRV variables, N = 10 for EEG variables, N = 12 for PPG variables. The β2 band is defined as 20–47 Hz. AU = arbitrary units. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs.* Pre. # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ *vs.* non-movers. For the abbreviations, see page 11.

	Non-movers		*Movers*	
	Pre	Post	Pre	Post
RRI (ms)	888 (160)	761 (116) **	911 (263)	658 (191) **
RRI SD (ms)	18.3 (9.3)	53.0 (18.9) **	17.4 (9.5)	94.8 (75.7) ** #
RRI RMSSD (ms)	10.3 (7.1)	9.6 (6.9)	9.1 (8.2)	9.0 (7.3)
RRI LF power (ms^2)	20.2 (75.0)	10.9 (52.5)	13.8 (17.9)	5.0 (34.3)
RRI HF power (ms^2)	13.3 (11.7)	2.8 (8.1)	9.3 (22.1)	1.8 (5.4) **
RRI LF/HF ratio	1.22 (5.21)	5.25 (7.77) *	1.38 (2.36)	5.58 (7.74) *
RRI SD1 (ms)	7.27 (5.02)	6.78 (4.95)	6.49 (5.85)	6.26 (5.00)
RRI SD2 (ms)	23.9 (13.5)	73.7 (26.4) **	21.6 (12.4)	131.7 (106.9) ** #
RRI SD1/SD2	0.287 (0.250)	0.092 (0.050) **	0.248 (0.290)	0.046 (0.020) ** ###
RE	45 (16)	46 (11)	41 (9)	47 (20) *
SE	43 (18)	43 (10)	39 (10)	40 (19)
RE-SE	2.6 (5.7)	3.8 (4.1)	1.9 (1.4)	7.9 (5.3) **
SEF95 (Hz)	14.1 (4.4)	13.6 (2.4)	13.0 (2.6)	13.8 (4.4)
β2 power (μV^2)	25.6 (20.6)	28.5 (25.2)	24.1 (19.6)	35.0 (24.4) **
Relative β2 power (μV^2)	1.59 (2.15)	1.47 (0.89)	1.08 (0.89)	1.48 (0.80) **
fEMG power (μV^2)	2.4 (14.9)	4.0 (14.0)	2.0 (2.8)	23.5 (135) * #
PPG amplitude (AU)	7.91 (4.38)	6.29 (3.19) **	9.24 (3.25)	6.60 (2.56) **
PPG area (AU)	271 (109)	186 (85.9) **	311 (166)	183 (87.3) **
dPPG (AU)	1.49 (0.84)	1.22 (0.60) **	1.78 (0.55)	1.31 (0.44) **
Notch amplitude (AU)	2.37 (1.02)	2.06 (1.09)	2.82 (2.02)	1.51 (0.92) **
Notch relative amplitude (%)	27.7 (17.1)	31.2 (24.2) *	31.7 (14.2)	28.5 (10.4)
Notch latency (%)	30.9 (5.0)	33.1 (7.0)	32.1 (8.9)	37.2 (6.1) **
PPG amplitude SD1 (AU)	0.198 (0.068)	0.213 (0.115)	0.242 (0.179)	0.247 (0.169)
PPG amplitude SD2 (AU)	0.419 (0.197)	1.45 (0.845) **	0.477 (0.217)	1.54 (0.966) **
PPG amplitude SD1/SD2	0.451 (0.181)	0.137 (0.058) **	0.486 (0.154)	0.141 (0.057) **

non-movers at CD, but not at RP. The post-stimulus fEMG power, BIS and SEF95 were higher in movers than in non-movers at CD and RP. The post-stimulus Anemon-I index was higher in movers than in non-movers at RP. In study V, the pre-stimulus values of the investigated variables were similar in movers and non-movers. The post-stimulus fEMG power was higher in movers than in non-movers. The post-stimulus RRI SD and RRI SD2 were higher, and RRI SD1 / SD2 ratio was lower in movers than in non-movers.

Significant associations between movement responses and RRI-, EEG-, fEMG- and PPG-derived variables were found. In general, the statistically significant associations were reactive, *i.e.* the post-stimulus value either as such or normalized with respect to the pre-stimulus value discriminated movers from non-movers. The variables with statistically significant P_K values for movement to noxious stimulation in studies IV (at the beginning of cervical dilatation and at the resumption of the procedure after the administration of the study drug) and V (at skin incision) are shown in table 12.

The combination of two or three variables with logistic regression models resulted in better discrimination of movement responses compared with models using only one variable (table 13).

Table 12. The P_K values of variables that discriminated movers from non-movers in studies IV (at the beginning of cervical dilatation, CD, and at resumption of procedure, RP, after the administration of the study drug) and V (at skin incision). Data are P_K (SE). P_K values less than 0.5 indicate that the value of the variable decreases with increasing likelihood of movement. Pre refers to averaged values of the variable over 60 s (study IV) or 120 s (study V) before the stimulus. Post refers to averaged values of the variable over 60 s (study IV) or 120 s (study V) after the stimulus. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ *vs.* 0.5. For the abbreviations, see page 11.

	Study IV (CD)		*Study IV (RP)*		*Study V*	
	Variable	P_K	Variable	P_K	Variable	P_K
HR / RRI			HR Post / Pre	0.72 (0.08) **	RRI Post / Pre	0.18 (0.09) ***
HRV			Anemon Index Post	0.71 (0.08) **	RRI SD Post	0.76 (0.11) *
					RRI SD Post / Pre	0.82 (0.09) **
					RRI SD2 Post	0.74 (0.11) *
					RRI SD2 Post / Pre	0.79 (0.10) **
					RRI SD1 / SD2 Post	0.07 (0.05) ***
					RRI SD1 / SD2 Post / Pre	0.25 (0.10) *
EEG	BIS Pre	0.68 (0.06) **	BIS Post	0.73 (0.09) *	β2 power Post / Pre	0.81 (0.10) **
	BIS Post	0.77 (0.06) ***	BIS Post / Pre	0.69 (0.07) *	Relative β2 power Post / Pre	0.88 (0.09) ***
	BIS Post / Pre	0.66 (0.06) *	SEF Post	0.71 (0.09) *	RE Post-Pre	0.83 (0.09) **
	SEF Post	0.68 (0.06) **	SEF Post / Pre	0.70 (0.08) **	RE-SE Post-Pre	0.89 (0.08) ***
fEMG	fEMG Pre	0.64 (0.06) *	fEMG Post	0.70 (0.08) **	fEMG Post	0.77 (0.11) *
	fEMG Post	0.78 (0.05) ***	fEMG Post / Pre	0.82 (0.07) ***	fEMG Post / Pre	0.90 (0.08) ***
	fEMG Post / Pre	0.72 (0.06) ***				
PPG					PPG area Post-Pre	0.23 (0.10) **
					PPG notch amplitude Post-Pre	0.23 (0.10) **
					PPG amplitude LF Post-Pre	0.74 (0.11) *

Table 13. Performance of the logistic regression classifiers using different sets of normalized (with respect to values preceding the resumption of the procedure after the administration of the study drug in study IV, and values preceding skin incision in study V) variables in studies IV and V. The performance was evaluated by leave-one-out cross-validation. The variables marked with * are normalized by subtracting the pre-stimulus value from the post-stimulus value. All other variables are normalized by dividing the post-stimulus value by the pre-stimulus value. The model $\chi 2$ value and its statistical significance are indicated. Sensitivity is defined as the ratio of the number of movers correctly classified as movers to the actual number of movers. Specificity is defined as the ratio of the number of non-movers correctly classified as non-movers to the actual number of non-movers. A 50 % probability of movement is used as the cut-off value in the calculation of overall performance, sensitivity, and specificity. The number of patients are indicated in parentheses (number of correctly classified cases / total number of cases). The ROC area describes the probability that the classifier will correctly discriminate a mover from a non-mover, taking into account all possible cut-off values.

Study IV

Variables	$\chi 2$	p value	ROC area	Overall performance	Sensitivity	Specificity
EMG	15.2	< 0.001	0.82	78 % (42 / 54)	41 % (7 / 17)	95 % (35 / 37)
HR	5.8	0.016	0.72	71 % (39 / 55)	22 % (4 / 18)	95 % (35 / 37)
SEF95	6.1	0.013	0.70	67 % (36 / 54)	18 % (3 / 17)	89 % (33 / 37)
fEMG & HR	18.9	< 0.001	0.87	81 % (44 / 54)	53 % (9 / 17)	95 % (35 / 37)
EMG & SEF95	17.4	< 0.001	0.83	74 % (40 / 54)	41 % (7 / 17)	89 % (33 / 37)
HR & SEF95	11.4	0.003	0.81	72 % (39 / 54)	41 % (7 / 17)	86 % (32 / 37)
EMG & HR & SEF95	20.7	< 0.001	0.87	74 % (40 / 54)	47 % (8 / 17)	86 % (32 / 37)

Study V

Variables	$\chi 2$	p value	ROC area	Overall performance	Sensitivity	Specificity
RE*	8.5	0.004	0.83	77 % (17 / 22)	70 % (7 / 10)	83 % (10 / 12)
RRI	9.3	0.002	0.82	73 % (19 / 26)	58 % (7 / 12)	86 % (12 / 14)
PPG notch amplitude*	6.6	0.010	0.77	65 % (17 / 26)	50 % (6 / 12)	79 % (11 / 14)
RE* & RRI	14.6	0.001	0.91	91 % (20 / 22)	90 % (9 / 10)	92 % (11 / 12)
RE* & PPG notch amplitude*	18.4	< 0.001	0.96	91 % (20 / 22)	90 % (9 / 10)	92 % (11 / 12)
RRI & PPG notch amplitude*	11.2	0.004	0.84	73 % (19 / 26)	58 % (7 / 12)	86 % (12 / 14)
RE* & RRI & PPG notch amplitude*	21.2	< 0.001	0.97	96 % (21 / 22)	90 % (9 / 10)	100 % (12 / 12)

Discussion

Methodology

Design

In study II, the EEG effects were evaluated in a double-blind fashion and the assessment of the hemodynamic effects was open (single-blinded). If a blinded observer had been used in studies III–IV (and in study II regarding hemodynamic effects) the risk of investigator bias would have been decreased. The studies were conducted in a single hospital on a homogenous group of relatively healthy, middle-aged females, who had no evidence of autonomic dysfunction. The results may not be directly applicable to other, dissimilar patient groups. The use of placebo was not applicable in the study protocols. In study IV, it would have been unethical to give an ineffective treatment to patients exhibiting movement responses during the procedure. In addition, the aim of the study was to directly compare the effects of a hypnotic and an analgesic agent.

The level of hypnosis

The MAC-awake value is roughly 0.35 MAC for sevoflurane and desflurane, and 0.6 MAC for N_2O (Eger 2001). Study II was conducted in the unstimulated state, before the start of surgery. During the first ten minutes, 0.7 MAC sevoflurane–N_2O or desflurane–N_2O anesthesia was used. During the following five minutes, supraclinical concentrations of both anesthetic agents were used. Thus the probability of awareness during the study was low. The transient epileptiform EEG activity in some patients in the sevoflurane group was not associated with any adverse post-operative reactions.

In study IV, the incidence of movement responses either before or after the start of cervical dilatation among the recruited patients was 65.1 % (84 / 129). The incidence of a wakeful response, defined by eye opening or voicing during the procedure was 8.5 % (11 / 129). The duration of a wakeful response during anesthesia influences the probability of memory formation (Dutton *et al* 1995). The wakeful responses which occurred in study IV lasted only a few seconds.

The BIS value associated with a 95 % probability of loss of consciousness is of the order 50–60 (Glass *et al* 1997, Katoh *et al* 1998, Struys *et al* 2003). In studies I and III–V, rescue medication was given if BIS unexpectedly exceeded 70. In order to exclude intraoperative awareness, repeated interviews during the post-operative period are recommended (Sandin *et al* 2000). The patients were interviewed regarding possible intraoperative awareness on arrival to the PACU in studies III–V, and in study III again at 24 h post-operatively. None of the patients reported memories of the intraoperative period.

Measurements and outcome parameters

In study III, the primary outcome parameter was the time to achieving home-readiness, defined by the criteria presented by Korttila (Korttila 1995) and modified by the inclusion of the need for parenteral medication. These clinical criteria are more stringent than the Postanesthetic Discharge Scoring System introduced by Chung (Chung 1995) and may explain the relatively prolonged home-readiness times observed in study III. Due to the nature of the surgical procedures performed, however, the patients in study III were at a high risk for post-operative urinary retention, and thus the inclusion of voiding in the home-readiness criteria was appropriate (Awad and Chung 2006).

Traditionally, movement responses during anesthesia have been defined as "gross and purposeful", usually affecting the head or the extremities. Coughing, chewing, swallowing and grimacing have been ignored (Quasha *et al* 1980, Antognini and Schwartz 1993, Leslie *et al* 1996, Katoh *et al* 1998). In studies IV–V movement was defined as any visible somatic response, as has been done by other authors (Kearse *et al* 1994a, Doi *et al* 1999, Kurita *et al* 2001, Bruhn *et al* 2003). The movement response was also used as an indicator of significant nociception in studies IV–V. It was assumed that the level of nociception was higher in patients exhibiting movement responses compared to those who did not move. Spontaneous movement during anesthesia may not be entirely specific for nociception. Increases in the level of consciousness can also be associated with movement responses, although nociception and arousal are closely related phenomena.

Sample size and statistical power

Formal power analysis to estimate a sufficient sample size was not attempted in studies I–II and V. Statistically significant differences, however, were found in all three studies. In study I, the wide 95 % confidence interval of the difference in the grand average BIS values between the second and third parts of the study suggests that a more accurate result would have been obtained had the sample size been larger, especially in the third part of the study. In study II, a difference in the main outcome measure (incidence of epileptiform EEG activity) was shown. The logistic regression equation obtained in study V yielded a very good classification performance (96 %) and due to leave-one-out cross validation this estimate of classification performance was unbiased, despite the restricted sample size.

In study IV, the power analysis was based on a presumed incidence of recurring movement of 50 %. With a sample size of 55 patients in each group, the study would have had 80 % power (with a 5 % α error rate) to detect an absolute difference of 25 % in the incidence of recurring movement. Although patients were recruited in excess of the estimated sample size, we had to exclude more patients from the analysis than anticipated, leaving only 82 patients to be analyzed. Thus the study had less than 80 % power to detect the originally planned difference, but had 80 % power to detect a 28.5 % difference (Pocock 1983). Since a statistically significant difference in the incidence of recurring movement did emerge, statistical power is not crucial to study IV.

The question of statistical power is relevant to study III, in which no difference in the main outcome measure between the two groups was found. With a sample size of 60 patients in each group, the study had a 90 % power (with a 5 % α error rate) to detect a standardized difference (difference in means divided by the standard deviation of the variable in question) of 0.6 in the recovery times (Altman 1999). The variability in the recovery times, however, was large. Thus the study had less than 90 % power to detect differences smaller than 145 min (or less than 80 % power to detect differences smaller than 123 min, standardized difference 0.5) in the main outcome measure of home-readiness. This difference was larger than estimated in the original power analysis (90 min based on a previous study conducted at the same institution). Thus, based on power analysis it was not possible to reliably exclude a difference smaller than 123–145 min in home-readiness times. The 95 % confidence interval of the difference in all of the recovery times included zero, however, and the confidence interval was generally skewed in favor of isoflurane.

The effect of the type and location of electrodes on bispectral index monitoring (Aim 1)

According to Manberg, artifact processing, suppression detection, and EEG feature extraction in BIS monitoring are sensitive to electrode placement (Manberg 2003). In a study by Hall and Lockwood, BIS values (v. 2.51) registered with a bifrontal montage using ECG electrodes were on average 68 % (95 % confidence interval 65 %–71 %) of the BIS values registered with

a more cranial fronto-central montage, with silver dome electrodes in the central locations. In a few cases, however, the agreement between BIS values obtained from the fronto-central and the bifrontal montage was excellent. The impedances of both electrode types were similar and clinically acceptable (median 2425Ω and 2700Ω, for ECG and silver dome electrodes). Skin pretreatment was performed using alcohol and abrasion paste for the ECG electrodes and abrasion and adhesive paste for the silver dome electrodes (Hall and Lockwood 1998).

Horiuchi and colleagues compared the BIS values obtained with two BIS Standard Sensors (A-2000 EEG monitor), one in the recommended position and the other inverted and dislocated slightly caudally. They found that during stable propofol–fentanyl anesthesia, the bias (mean difference) between the two BIS values was only -1.2, with limits of agreement [−9.7; 7.4] (Horiuchi *et al* 2007). Shiraishi and colleagues found a good correlation between BIS (v. 3.3) values recorded from frontal and occipital positions in neurosurgical patients. Limits of agreement were not reported (Shiraishi *et al* 2004).

Thøgersen and Ørding found good agreement between BIS values (v. 3.12) registered simultaneously with a set of Zipprep electrodes and a set of ordinary ECG electrodes using the A-1000 EEG monitor during both light and deep sevoflurane or propofol anesthesia (limits of agreement [−11.1; 10.1] and [−10.6; 11.6] in the sevoflurane group). The bias was close to zero in all measurements. The precise location of the two sets of electrodes relative to each other was not reported. The impedances achieved with the ECG electrodes after alcohol skin pretreatment were higher than those measured with Zipprep electrodes and they decreased with time (Thøgersen and Ørding 2000).

Hemmerling and Harvey constructed a custom-made connector, including a small proximal part of the original BIS Sensor®, in order to use ordinary ECG electrodes in BIS monitoring with the A-2000 EEG monitor. Crocodile connectors were used to attach the ECG electrodes to the custom-made connector. The self-test of the A-2000 monitor recognized this system. In that study, the ECG electrodes were placed caudal to the original BIS Sensor®. Again, the impedance values of the ECG electrodes were significantly higher than those of the BIS Sensor. In most patients, the BIS values recorded with the ECG electrodes were higher than those recorded with the BIS Sensor, but generally a good agreement was achieved (bias −1.3, limits of agreement [−7.1; 4.4] for the difference between BIS values obtained with the BIS Sensor and ECG electrodes). The authors concluded that BIS values obtained with either Zipprep electrodes or ECG electrodes can be used interchangeably (Hemmerling and Harvey 2002).

The impedances observed in the first part of study I for ECG electrodes after combined abrasion paste and alcohol skin pretreatment were lower than those reported by Hall and Lockwood. The reason for this is unclear, but may be related to the smaller number of patients in the study by Hall and Lockwood, or to differences in skin abrasion technique. The impedances of ECG electrodes after alcohol skin pretreatment alone were similar to those reported by Thøgersen and Ørding and lower than those reported by Hemmerling and Harvey, both at the temporal position in the first part and at the reference position in the second part of study I. In contrast, the impedances measured at the temporal positions in the second part of study I were higher than those reported by Thøgersen and Ørding or Hemmerling and Harvey. The discrepancy in impedance values of ECG electrodes at the temporal position between the first and second parts of study I may be related to the use of a mixture of different electrodes in the first part of the study.

Although the montage used may affect the BIS values obtained, the positions of the sets of EEG and ECG electrodes in the second part of study I were quite near each other. Also, in the study by Hemmerling and Harvey the craniocaudal arrangement of the electrode sets was opposite to that used in study I, but the direction of the difference in BIS values between the two sets was similar to that observed in study I. In study I, the bias and limits of agreement

(mean ± 2sd) (Bland and Altman 1986) were +5.5 and [−10.1; 21.1] in part 2 *vs.* +1.6 and [−7.0; 10.2] in part 3, based on 50 consecutive BIS differences per patient. If only one observation per patient (average BIS difference) was considered, the bias and limits of agreement were +5.2 and [−3.6; 14] in part 2 *vs.* +1.7 and [−2.5; 5.9] in part 3. Clearly, a larger positive bias emerged in part 2 than in part 3, contrary to the findings of Hemmerling and Harvey or Thøgersen and Ørding. It is possible that the specific type of ECG electrodes used in study I may have resulted in a larger BIS difference than observed by the above-mentioned authors.

In the second part of study I, the scatter in BIS differences (shown in the Bland-Altman plot) between the values measured with ECG electrodes *vs.* EEG electrodes was largest at the high end of the clinically important BIS range and diminished with low BIS values. This may be related to the general decrease of impedance values during anesthesia with all electrodes, possibly related to increased skin hydration (sweat secretion under the electrodes). Unfortunately, an experiment comparing the parallel BIS values measured with a set of ECG electrodes after abrasion paste pretreatment and a set of EEG electrodes after alcohol swab pretreatment was not performed in study I.

The electroencephalogram and hemodynamic effects of desflurane and sevoflurane (Aim 2)

The tendency of sevoflurane to induce epileptiform EEG patterns during anesthesia in epileptic patients is greater than that of isoflurane (Iijima *et al* 2000). Rampil and colleagues did not find any evidence of epileptiform EEG activity during 6%–15% desflurane anesthesia, with or without N_2O, in healthy volunteers, even during hypocapnia and auditory stimulation (Rampil *et al* 1991). Even though N_2O activates the EEG (Yli-Hankala *et al* 1993b), its epileptogenic potential seems to be low. High doses of opioid analgesics have been observed to produce seizure activity in animals, but the origin of abnormal movements sometimes observed after opioid administration in humans is unclear (Modica *et al* 1990).

Periodic epileptiform discharges and other interictal epileptiform phenomena have been demonstrated during sevoflurane anesthesia in adults and in children, especially with controlled ventilation and respiratory alkalosis (Kaisti *et al* 1999, Yli-Hankala *et al* 1999b, Vakkuri *et al* 2000, Vakkuri *et al* 2001, Jääskeläinen *et al* 2003). These may occasionally evolve into seizures (Woodforth *et al* 1997). The occurrence and severity of epileptiform EEG activity depends on the sevoflurane dose (Jääskeläinen *et al* 2003). Periodic epileptiform discharges during sevoflurane anesthesia may reflect widespread neuronal hypersynchronization preceding generalized seizure activity. They are associated with hemodynamic acceleration (Vakkuri *et al* 2000).

Voss and colleagues recorded electrocorticography in sheep during anesthesia with increasing concentrations of different volatile agents. They found that the propensity to produce electrocorticography spikes was greatest for enflurane, followed by sevoflurane. Isoflurane and desflurane were associated with a very low spike rate. In an inhibitory sigmoid E_{max} model, the maximal spike rates during burst suppression level anesthesia were 17.2, 5.3, 0.7, and 0.5 spikes/min for enflurane, sevoflurane, isoflurane, and desflurane (Voss *et al* 2006). Desflurane has been used in the treatment of refractory status epilepticus (Sharpe *et al* 2002).

In accordance with these results, epileptiform EEG activity was observed in 8/15 patients in the sevoflurane group during the rapid increase in the inspired volatile concentration, and in none of the 16 patients in the desflurane group in study II.

The calculated MAC multiples (Nickalls and Mapleson 2003, Lerou 2004) corresponding to the measured end-tidal volatile concentrations at periods 1, 2, and 3 (immediately before the increase in the inhaled anesthetic concentration, at two minutes after the increase, and at the end of the five-minute study period) were 0.7–0.8 MAC, 2.3–2.4 MAC, and 2.5–2.7 MAC for desflurane and 0.8 MAC, 3.1–3.3 MAC, and 3.4–3.6 MAC for sevoflurane. RE/SE

values at period 2, however, were higher in the sevoflurane group than in the desflurane group. The observed differences in the calculated entropy values between the two groups in study II probably represent the combined result of agent-specific EEG effects and epileptiform phenomena. Patients with epileptiform activity had higher RE / SE values at period 3 compared to patients with a normal EEG in the sevoflurane group. The data highlight the fact that numerical indices derived from the EEG are a simplified representation of EEG phenomena, with many confounding factors. Unfortunately, BIS values were not retrieved during study II.

Rapid increases in the desflurane concentration have been shown to induce hypertension, tachycardia, a release of catecholamines and vasopressin, and a rate-dependent increase in sympathetic outflow (Ebert and Muzi 1993, Weiskopf *et al* 1994b, Muzi *et al* 1996b). In healthy volunteers, increasing the inspired sevoflurane concentration from 1 % to 3 % during anesthetic induction was not associated with significant changes in muscle sympathetic nerve activity or HR, whereas both were significantly increased when the inspired desflurane concentration increased from 3 % to 9 %. MAP displayed a biphasic response after a step change in the desflurane concentration from 6 % to 9 % (Ebert *et al* 1995).

Pac-Soo and colleagues suggested that the concentration-dependent sympathoexcitation induced by desflurane is mediated primarily via pulmonary vagal afferents, with a small alternative extravagal afferent pathway. The sympathetic depression associated with high desflurane concentrations is likely centrally mediated. The authors concluded that there is no hard evidence for extrapulmonary receptors mediating the desflurane-induced sympathoexcitation (Pac-Soo *et al* 2000b), although such receptors have been suggested by other authors (Weiskopf *et al* 1995, Rodig *et al* 1997). Weiskopf and colleagues observed that the hemodynamic and adrenalin responses were attenuated with repeated increases in end-tidal desflurane concentration, consistent with the hypothesis that rapidly adapting airway receptors might produce the initial sympathoadrenal response (Weiskopf *et al* 1994a).

Tanaka and colleagues found no significant changes in heart rate when the inhaled concentration of sevoflurane was increased from 0.9 MAC to 2.7 MAC (Tanaka *et al* 1996). In contrast, a significant increase in heart rate during sevoflurane induction has been reported by other authors (Sloan *et al* 1996, Constant *et al* 1999, Hall *et al* 2000). The cardiac, vascular and autonomic nervous system effects of sevoflurane interact. Possible mechanisms for the increase in heart rate during increasing sevoflurane concentration, even without epileptiform EEG activity, include the residual activity of the baroreceptor reflex (Ma *et al* 1998, Hall *et al* 2000) and the vagolytic effect of sevoflurane (Constant *et al* 1999, Picker *et al* 2001), although at concentrations exceeding 3 MAC the baroreceptor reflex is likely profoundly depressed (Ma *et al* 1998).

In study II, the rapid increase in the inspired desflurane concentration was associated with a pronounced and transient increase in heart rate, peaking at two minutes. A similar biphasic response was observed in systolic blood pressure, in accordance with the results of Ebert and colleagues (Ebert *et al* 1995). In the sevoflurane group, the heart rate increased gradually. The systolic blood pressure decreased with increasing concentrations of sevoflurane, reaching a plateau at three to four minutes into the study period. These hemodynamic results are in agreement with the observations of other authors (Constant *et al* 1999, Hall *et al* 2000). The difference in heart rates between the patients with and without epileptiform EEG in the sevoflurane group did not reach statistical significance, possibly due to the small number of patients.

The effect of bispectral index monitoring on the recovery of gynecological ambulatory surgery patients after isoflurane or sevoflurane maintenance (Aim 3)

Many studies have indicated faster early recovery after sevoflurane anesthesia compared

to isoflurane anesthesia, whereas the times to the recovery room or hospital discharge generally do not differ. In most of these studies the administraton of the volatile agents was guided by hemodynamic signs (Frink *et al* 1992, Eriksson *et al* 1995, Campbell *et al* 1996, Philip *et al* 1996). In these studies, a slightly higher isoflurane exposure, as expressed in MAC-hours, compared to sevoflurane exposure, or a slightly higher isoflurane MAC fraction at the end of anesthesia, compared to sevoflurane MAC fraction, may have influenced the results. In some studies, the difference in early recovery has been less clear or absent (Sloan *et al* 1996, Karlsen *et al* 2000, Godet *et al* 2001). In the study by Sloan and colleagues, both anesthetics were administered at about 0.8 MAC concentration, a relatively light anesthetic level. In the study by Godet and colleagues the isoflurane exposure may have been slightly lower than the sevoflurane exposure, although these were not precisely reported. Eriksson and colleagues found that intermediate recovery was similar after sevoflurane–N_2O or isoflurane–N_2O anesthesia (Eriksson *et al* 1995).

A systematic review by Gupta and colleagues concluded that the times to eye opening, obeying commands, transfer from phase I recovery to phase II recovery, home-readiness and discharge were statistically significantly shorter after sevoflurane anesthesia than after isoflurane anesthesia. The weighted mean differences were small, however, less than five minutes for the early recovery parameters and less than ten minutes for the intermediate recovery parameters. The result on home discharge (weighted mean difference 25 min) was based on only two studies, with a wide confidence interval and a marginal statistical significance. Drowsiness was more frequent after isoflurane than after sevoflurane anesthesia (Gupta *et al* 2004).

A meta-analysis by Robinson and colleagues concluded that sevoflurane anesthesia is associated with a faster early recovery than isoflurane anesthesia, but no difference in the times to the recovery room discharge were found (Robinson *et al* 1999). Similar results were reported earlier by the same authors. The difference in early recovery was not observed in cases where the duration of anesthesia was less than one hour. After isoflurane anesthesia, early recovery was progressively delayed with increasing case duration (Ebert *et al* 1998).

In study III, no difference between the sevoflurane and isoflurane groups in either the early or intermediate recovery times was found. This may be partly due to the use of BIS monitoring, which avoided relative overdosing of anesthetic agents. The target BIS range in study III was 50–60. Several studies have found faster early recovery in patients with target BIS values over 45–50 compared to patients in whom anesthesia was adjusted based on clinical (hemodynamic) signs (Gan *et al* 1997, Song *et al* 1997, Johansen *et al* 2000, Nelskylä *et al* 2001, Luginbühl *et al* 2003, Recart *et al* 2003, White *et al* 2004). In some studies, the intermediate recovery has also been hastened (Gan *et al* 1997, Johansen *et al* 2000, Recart *et al* 2003, White *et al* 2004). In addition, N_2O was used in all patients in study III. The elimination of N_2O, which diminished the total exposure to isoflurane or sevoflurane, is very fast. Another factor contributing to the similarity in recovery between the two groups was the relatively short case duration (median less than 60 minutes).

The blood / gas partition coefficient of isoflurane (1.4) is higher than that of sevoflurane (0.65), whereas the tissue-blood partition coefficients of isoflurane are similar or slightly lower than those of sevoflurane (Eger 2005). The increase in the recovery time with either an increase in the delivered concentration or the duration of administration is steepest for the most soluble volatile agents. The deeper the anesthetic level, the more the time to recovery is affected by the solubility characteristics of the volatile agent. After light or short-term anesthesia the differences in recovery times between volatile agents with different solubilities are small (Eger and Johnson 1987). When the duration of anesthesia is short, only the richly perfused tissues are equilibrated with the partial pressure of the volatile anesthetic in blood. Thus, after the discontinuation of anesthetic delivery, the more slowly equilibrating compartments contribute to recovery by continuing to take up anesthetic (Eger 2005).

Generally, the quality of recovery after isoflurane and sevoflurane anesthesia is similar, with no significant differences in the frequency of adverse events (Frink *et al* 1992, Eriksson *et al* 1995, Campbell *et al* 1996, Ebert *et al* 1998, Karlsen *et al* 2000). In some studies, the post-operative sedation or confusion has been more pronounced after isoflurane than after sevoflurane anesthesia (Philip *et al* 1996, Sloan *et al* 1996). One study reported a higher incidence of PONV after isoflurane anesthesia compared to sevoflurane anesthesia (Philip *et al* 1996). On the other hand, another study found that both PONV, headache, and perioperative respiratory and cardiovascular complications were more frequent in association with sevoflurane anesthesia than with isoflurane anesthesia (Elcock and Sweeney 2002). Some studies have suggested that the quality of recovery may be improved by adjusting the anesthetic administration according to BIS monitoring, as compared to clinical signs alone (Gan *et al* 1997, Nelskylä *et al* 2001, Luginbühl *et al* 2003, Recart *et al* 2003).

In study III, no significant differences in the post-operative DSST scores, or the degree of pain or nausea were found. Both the frequencies and doses of post-operative analgesic and antiemetic medications, and the incidence of PONV at 24 h post-operatively was similar in both groups. This is probably due to both the modest overall exposure to the volatile agents and the use of BIS monitoring, which allowed individual titration of the anesthetic agents, and avoided unnecessary overdosing.

The reported incidence of dreaming during anesthesia varies between 5 %–14 % (Ranta *et al* 1998, Myles *et al* 2004, Sebel *et al* 2004, Huang *et al* 2005). It has been suspected that a light level of anesthesia predisposes patients to both dreaming and intraoperative awareness (Ranta *et al* 1998, Huang *et al* 2005). On the other hand, Hellwagner and colleagues found no difference in EEG MF between dreaming and non-dreaming patients (Hellwagner *et al* 2003). Leslie and colleagues reported that the frequency of signs of light anesthesia in non-dreaming patients was similar to that in dreaming patients (7 % and 4 %) (Leslie *et al* 2005). At present it is unclear whether dreaming represents a light level of anesthesia, corresponding to near-awareness (Myles *et al* 2004, Sebel *et al* 2004). An increased incidence of dreaming has been reported for young and healthy individuals, for female patients (Ranta *et al* 1998, Sebel *et al* 2004, Leslie *et al* 2005), and for those undergoing elective or ambulatory surgery (Sebel *et al* 2004). In accordance with these studies, the overall incidence of dreaming was high (43 % and 38 % in the isoflurane and sevoflurane groups; difference 5 %, 95 % CI [–14 %; 23 %]) in the patients of study III, who had all of the above-mentioned characteristics. None of the patients had recall of the intraoperative events. It would be interesting to compare these results with the incidence of dreaming during a deeper level of anesthesia (for example, BIS 40–50) in a similar population.

Hypnotic versus analgesic supplementation during uterine dilatation and curettage (Aim 4)

Opioids alone are not able to suppress responses to noxious or non-noxious stimulation, in clinically relevant concentrations (Jhaveri *et al* 1997, Mertens *et al* 2003, Bouillon *et al* 2004).

Alfentanil reduces the concentration of propofol required for loss of consciousness by a synergistic interaction (Vuyk *et al* 1996). Similarly, alfentanil and propofol suppress responses to laryngoscopy, intubation, and stimuli from abdominal surgery, displaying a synergistic interaction (Vuyk *et al* 1995). The interaction between alfentanil and propofol is weaker for loss of consciousness than for noxious stimuli (Vuyk *et al* 1996). Pavlin and colleagues found a synergistic interaction between propofol and alfentanil for the prevention of movement responses to tetanic electrical stimulation in the presence of N_2O (60 %). In their study, the EC_{50} of propofol alone (with N_2O) was 6.1 µg / ml, and the EC_{50} of propofol in the presence of alfentanil at 50, 100, and 150 ng / ml was 3.3, 2.3 and 2.2 µg / ml. A ceiling effect for the reduction of propofol requirements was observed with alfentanil concentrations above approximately 100 ng / ml (Pavlin *et al* 1999).

At least around 1 μg/ml propofol is required for loss of consciousness or suppression of noxious stimuli, even in the presence of high alfentanil concentrations (Vuyk *et al* 1995, Vuyk *et al* 1996). With blood propofol concentrations above 4 μg/ml, small amounts of alfentanil are very effective in obtunding responses to noxious stimuli, whereas with low propofol concentrations (*e.g.* 2 μg/ml) considerably larger amounts of alfentanil are required, and the overlap between response and no response is more pronounced (Vuyk *et al* 1995).

Propofol and alfentanil also display a pharmacokinetic interaction such that propofol concentrations are higher in the presence than in the absence of alfentanil, and alfentanil concentrations are higher in the presence than in the absence of propofol. The hemodynamic changes induced by the drugs may also influence the pharmacokinetics (Pavlin *et al* 1996, Mertens *et al* 2001, Mertens *et al* 2004).

Many different combinations of propofol and an opioid can produce unresponsiveness, and the specific proportions of the drugs determine the associated EEG state (Bouillon *et al* 2004). The work of Vanluchene and colleagues illustrates the hypnotic-opioid interaction. During propofol anesthesia alone, BIS or RE/SE values around 30 (20) are required to suppress the response to tetanic electrical stimulation in 50% (95%) of the patients. Combined to 2 ng/ml of remifentanil the corresponding BIS or RE/SE values are around 50 (40) (Vanluchene *et al* 2004a).

In study IV, the median estimated propofol effect-site concentration at the start of cervical dilatation (CD) was around 4.5 μg/ml (Gepts *et al* 1987), and the median estimated alfentanil effect-site concentration was around 75 ng/ml (Scott and Stanski 1987). The frequency of movement responses was 46.3%. Comparison of these data with those of Pavlin and colleagues (Pavlin *et al* 1999) suggests that cervical dilatation is a more intense noxious stimulus than tetanic electrical stimulation of the ulnar nerve.

In study IV, a propofol bolus of 0.7 mg/kg was more effective than an alfentanil bolus of 0.5 mg in preventing recurring movement responses. The probability of recurring movement also depended on the time elapsed from the administration of the study drug, consistent with the rapid resolution of drug effects. Propofol and alfentanil were administered as bolus doses, and the patients were young and healthy. Under these conditions, the level of hypnosis was the more critical factor determining the probability of movement responses, as compared to the level of analgesia. This is illustrated by the median estimated effect-site concentrations of propofol and alfentanil at the resumption of the procedure after the administration of the study drug (RP) in the alfentanil group (roughly 4.5 μg/ml and 130–140 ng/ml, respectively; frequency of movement 37.5%) *vs.* in the propofol group (roughly 5.3 μg/ml and 40–45 ng/ml, respectively; frequency of movement 26.1%). Both the bolus administration and the pharmacokinetic interaction between propofol and alfentanil may have affected the accuracy of these estimations, however.

In the data of Vuyk and colleagues, the requirement for alfentanil to suppress responses to intra-abdominal surgical stimulation increased steeply at propofol concentrations less than 4 μg/ml, consistent with the results of study IV. In a dose-response study on young, healthy adults, Yu and colleagues found that the incidence of somatic responses to laryngeal mask insertion progressively decreased with an increasing alfentanil bolus dose, in conjunction with a propofol bolus of 2.5 mg/kg. Based on probit analysis they estimated that all somatic responses, including laryngospasm, would be abolished by 17.6 μg/kg of alfentanil in 95% of patients. The ED_{95} of alfentanil for head or limb movements was predicted to be 10.7 μg/kg (Yu *et al* 2006). The dose of alfentanil used in study IV was not adjusted according to the weight of the patient, and was rather modest (7–10 μg/kg). The outcome might have been different, had a larger dose of alfentanil been used.

The possible role of physiological variables as indices of nociception during anesthesia (Aim 5)

Heart rate and heart rate variability responses

Similarly to studies IV and V, most studies have found no significant differences in the pre-stimulus hemodynamic variables between movers and non-movers or hemodynamic responders and non-responders to a noxious stimulus during anesthesia (Vernon *et al* 1995, Doi *et al* 1999, Kochs *et al* 1999, Luginbühl *et al* 2007). In a study by Leslie and colleagues, however, the pre-stimulus blood pressure was predictive of a movement response to tetanic electrical stimulation during propofol–N_2O anesthesia, whereas the pre-stimulus heart rate was not (Leslie *et al* 1996). Sebel and colleagues found that during isoflurane or propofol anesthesia, the pre-stimulus MAP was predictive of movement responses to skin incision in a logistic regression model (Sebel *et al* 1997). Johansen and colleagues reported that the pre-stimulus heart rate was predictive of a movement response to skin incision during propofol–N_2O–esmolol anesthesia in a logistic regression model (Johansen *et al* 1997). Thus in some particular circumstances the pre-stimulus hemodynamic variables may be indicative of the overall arousal level of the patients.

Kochs and colleagues found no significant differences in the post-stimulus hemodynamic variables between movers and non-movers to tetanic stimulation or skin incision during isoflurane–N_2O anesthesia. The systolic blood pressure response was greater in movers than in non-movers to skin incision, but did not reach statistical significance (Kochs *et al* 1999). Johansen and colleagues reported that the post-stimulus heart rate discriminated movers and non-movers to skin incision during propofol–N_2O–esmolol anesthesia in a logistic regression model (Johansen *et al* 1997). Luginbühl and colleagues found a significant difference in the post-stimulus RRI between hemodynamic responders and non-responders to tracheal intubation during propofol–remifentanil anesthesia (Luginbühl *et al* 2007). In accordance with these studies, the HR and HRV responses were associated with movement responses in studies IV and V. In study IV, none of the HR or HRV variables discriminated movers from non-movers at CD, but the normalized heart rate and the post-stimulus Anemon Index did so at RP. In study V, the normalized RRI, RRI SD, RRI SD2, and RRI SD1 / SD2 had P_K values significantly different from 0.5 with respect to movement responses at skin incision, as did the post-stimulus values of RRI SD, RRI SD2, and RRI SD1 / SD2. Of these, the normalized HR and the normalized RRI were included in the logistic regression models with the best discrimination performance in studies IV and V.

Pulse plethysmogram responses

The HRV and PPG changes observed at skin incision in study V were similar to those reported by Luginbühl and colleagues at tetanic electrical stimulation and at tracheal intubation (Luginbühl *et al* 2006, Luginbühl *et al* 2007) and by Rantanen and colleagues at skin incision during propofol–remifentanil anesthesia (Rantanen *et al* 2006a).

The large interindividual differences in physiological variables complicate the determination of threshold values associated with significant nociception. In studies IV and V, the investigated variables were normalized with respect to the pre-stimulus values before entering them into logistic regression analysis. Luginbühl and colleagues observed that even normalized HRV and PPG responses to tetanic stimulation were unable to discriminate patients displaying a significant hemodynamic response to intubation from non-responsive patients, however, with the exception of the normalized PPG amplitude SD, which showed some classification ability. The normalized PPG amplitude SD2 at tetanic electrical stimulation was also significantly different between responders and non-responders, but did not improve the prediction of the response to tracheal intubation in a multivariate logistic regression model (Luginbühl *et al* 2006, Luginbühl *et al* 2007).

In study V, the normalized PPG area and the normalized PPG notch amplitude, and also the normalized PPG amplitude LF had P_K values significantly different from 0.5 with respect to movement responses at skin incision. Of these, the normalized PPG notch amplitude was included in the logistic regression model with the best discrimination performance.

Electroencephalogram and electromyogram responses

Yli-Hankala and colleagues observed that during emergence from isoflurane–N_2O anesthesia, fEMG power and the MLAEP amplitude increased before spontaneous movements, whereas the heart rate and the EEG zero-crossing frequency were stable during the five minutes preceding movement (Yli-Hankala *et al* 1994). Rampil and Laster found no significant differences in the pre-stimulus values of EEG variables between rats which displayed a movement response to tail clamping and those which did not during isoflurane anesthesia (Rampil and Laster 1992). Similarly, Kochs and colleagues found no significant differences in the pre-stimulus values of EEG-derived variables between movers and non-movers to tetanic electrical stimulation or skin incision during isoflurane–N_2O anesthesia (except β power, 12.5–30 Hz, before tetanic electrical stimulation) (Kochs *et al* 1999).

Some studies have found a significant difference in the pre-stimulus BIS values between movers and non-movers to noxious stimulation during anesthesia (Vernon *et al* 1995, Sebel *et al* 1997, Singh *et al* 1999, Vanluchene *et al* 2004a), whereas others have not (Doi *et al* 1999, Kurita *et al* 2001). Thus some studies have found BIS to be predictive of movement responses to noxious stimulation during anesthesia (Vernon *et al* 1995, Leslie *et al* 1996, Sebel *et al* 1997). Vanluchene and colleagues found a significant difference in the pre-stimulus RE/SE values between movers and non-movers to tetanic electrical stimulation during propofol–remifentanil anesthesia (Vanluchene *et al* 2004a).

Some studies found a significant difference in the pre-stimulus values of SEF95 between movers and non-movers to noxious stimulation during anesthesia, and reported that SEF95 was predictive of movement responses (Vernon *et al* 1995, Dutton *et al* 1996, Leslie *et al* 1996, Schraag *et al* 1998), whereas others did not (Kearse *et al* 1994a, Doi *et al* 1999, Singh *et al* 1999). Generally, no significant differences in the pre-stimulus values of MF between movers and non-movers to noxious stimulation during anesthesia have been found (Kearse *et al* 1994a, Vernon *et al* 1995, Schraag *et al* 1998, Doi *et al* 1999). Sebel and colleagues reported a significant difference in the pre-stimulus values of relative δ power between movers and non-movers to noxious stimulation during anesthesia (Sebel *et al* 1995), whereas others did not (Kearse *et al* 1994a, Vernon *et al* 1995).

Leslie and colleagues found that BIS, SEF95, MF, relative β power, and relative δ power predicted movement responses to tetanic electrical stimulation during propofol–N_2O anesthesia. They suggested that a multivariate approach might improve the predictive performance. In their study, the differences between the pre- and post-stimulus values of BIS or SEF95 were not statistically significant (Leslie *et al* 1996). Doi and colleagues and Kurita and colleagues reported that the auditory evoked potential index was predictive of movement responses to noxious stimulation, but BIS was not (Doi *et al* 1999, Kurita *et al* 2001).

Thus, the relationship between the pre-stimulus values of EEG-derived variables and movement responses is not consistent. A significant difference in the pre-stimulus BIS values between movers and non-movers to noxious stimulation has generally been more likely to occur during propofol-based anesthesia than during inhalation anesthesia. The level of opioid analgesia may also influence the results. For example, in the data of Sebel and colleagues, a significant difference in the pre-stimulus BIS values between movers and non-movers to skin incision was observed during isoflurane or isoflurane–N_2O anesthesia, but not during isoflurane–N_2O–opioid anesthesia (Sebel *et al* 1997).

Bruhn and colleagues observed that the P_K values of BIS (v. 3.22), EEG ApEn and SEF95

for unconsciousness (response to non-noxious stimulation) exceeded 0.90, but were only 0.62–0.70 for the responses to noxious airway stimulation in healthy volunteers with varying concentrations of propofol and remifentanil (Bruhn *et al* 2003). Analogous results were reported by Katoh and colleagues. The P_K values of the end-tidal sevoflurane concentration, BIS (v. 3.2), SEF95, and MF for the OAA/S score were 0.97, 0.95, 0.81, and 0.62. For the movement response to skin incision, however, the corresponding P_K values were 0.90, 0.66, 0.57 and 0.52. Only the sevoflurane concentration was able to predict movement responses to skin incision better than chance alone (Katoh *et al* 1998).

Similarly, in a study by Struys and colleagues the P_K values of BIS (v. 3.4), AAI, and the effect-site propofol concentration for predicting the loss of response to tetanic electrical stimulation were lower than those for predicting the level of sedation or the loss of consciousness, and deteriorated when the level of opioid analgesia varied during propofol anesthesia. The P_K values were 0.93–0.95 for the loss of consciousness and 0.72–0.75 for the loss of response to noxious stimulation in the pooled data with varying remifentanil concentrations (0–4 ng/ml) (Struys *et al* 2003).

During propofol monoanesthesia, the P_K values of BIS (v. 3.4), AAI, and the effect-site propofol concentration for predicting the loss of response to tetanic electrical stimulation were 0.87, 0.88 and 0.82. The P_K values of hemodynamic variables were much worse, 0.59–0.72 (Struys *et al* 2002). During propofol–remifentanil anesthesia, the P_K values of SE for LOC and for the loss of response to tetanic electrical stimulation were 0.81–0.86 and 0.65–0.80. The corresponding P_K values of RE were 0.83–0.89 and 0.67–0.85. In that study, the P_K values of BIS (v. 4.0) for LOC and for the loss of response to tetanic electrical stimulation were 0.89–0.91 and 0.69–0.77. A wide range of overlap was observed between the response and no-response values, especially with the noxious stimulus (Vanluchene *et al* 2004a).

With BIS, RE/SE, or AAI, sensitivities and specificities around 80%–90% can be obtained for LOC, *vs.* only 70%–80% for the loss of response to noxious stimulation (Struys *et al* 2002, Struys *et al* 2003, Vanluchene *et al* 2004a). At 100% sensitivity to detect the loss of response to tetanic stimulation the specificity of BIS, RE/SE and AAI are very low. The cut-off values at the highest overall performance and at 100% sensitivity are influenced by remifentanil in a dose-dependent manner for both LOC and the loss of response to noxious stimulation. Generally, the difference in the best cut-off values is larger between remifentanil at 0 and 2 ng/ml than between remifentanil at 2 and 4 ng/ml (Struys *et al* 2003, Vanluchene *et al* 2004a).

During propofol monoanesthesia, no cases of consciousness occur at BIS values less than 53–58, SE values less than 37, RE values less than 50, or propofol effect-site concentrations more than 4.0 μg/ml. When remifentanil at 2 ng/ml is combined with propofol, no cases of consciousness occur at BIS values less than 65–68, SE values less than 50, RE values less than 62, or propofol effect-site concentrations more than 3.0 μg/ml. During propofol monoanesthesia, no cases of a response to tetanic electrical stimulation occur at BIS values less than 12–29, SE values less than 7, RE values less than 7, or propofol effect-site concentrations more than 7.0 μg/ml. When remifentanil at 2 ng/ml is combined with propofol, no cases of a response to tetanic electrical stimulation occur at BIS values less than 43–57, SE values less than 40, RE values less than 45, or propofol effect-site concentrations more than 3.5 μg/ml (Struys *et al* 2002, Struys *et al* 2003, Vanluchene *et al* 2004a).

EEG-derived variables clearly correlate best with the level of sedation or hypnosis, and less with the responsiveness to noxious stimulation. This is natural, since nociceptive reflexes during anesthesia are subcortically mediated. Table 14 illustrates the interaction between the level of hypnosis, EEG-derived variables, opioid analgesia, and noxious stimulation.

Kochs and colleagues reported that there was a significant difference in the changes in fEMG power, MLAEP amplitudes, and EEG θ and α power between movers and non-movers to skin incision during isoflurane–N_2O anesthesia (Kochs *et al* 1999). Rantanen and col-

leagues observed that RE increased at skin incision during propofol–remifentanil anesthesia, and the increase was dose-dependently attenuated by remifentanil. No difference in the RE increase between movers and non-movers was observed. The RE-SE difference increased in movers, but not in non-movers (Rantanen *et al* 2006a). Valjus and colleagues reported that although some intraoperative movement responses were associated with increases in RE / SE and BIS, most of them were not (Valjus *et al* 2006). Struys and colleagues found that tetanic electrical stimulation caused transient increases in BIS and AAI with mean delays to maximum effect of 39 s and 20 s, respectively (Struys *et al* 2002). Experimental data concerning the responses of different physiological variables to noxious stimulation during anesthesia are scarce.

Edmonds and Paloheimo found that changes in the fEMG, EEG amplitude, and ZXF were not consistently related to changes in hemodynamic or motor responsiveness. In some cases, increases in fEMG were observed during decreasing anesthesia, but most frequently fEMG increases were practically coincident with limb movements. Also, large interindividual variability in fEMG was observed (Edmonds and Paloheimo 1985).

After barbiturate induction, fEMG and abdominal EMG activity increased in response to endotracheal intubation, despite complete neuromuscular blockade in the hypothenar muscle, in 28 / 30 and 29 / 30 patients. After administration of enflurane, some patients (8 / 30) still reacted to skin incision with an increase in fEMG and abdominal EMG amplitude. During decreasing anesthesia, the fEMG increase preceded the clinical signs of arousal in 16 / 30 patients (Paloheimo *et al* 1989).

During isoflurane washout, while maintaining N_2O inhalation, noxious and non-noxious stimulation resulted in an initial persistent (over 30 s) increased craniofacial EMG response in 47 % (14 / 30) and an initial combined EMG and movement response in 40 % (13 / 30) of the patients. Thus, the EMG response does not always herald movement before it occurs. Compared to isolated EMG responses, combined EMG and movement responses were associated with more abrupt increases in EMG power, longer durations of increased voltage, and shorter latencies from the onset of stimulation. Isolated EMG responses occurred on average at 0.11 % higher isoflurane effect-site concentrations than combined EMG and movement responses (Dutton *et al* 1998).

Chang and colleagues reported larger fEMG responses in patients who moved in response to surgical stimulation during metohexital–N_2O anesthesia compared to those who did not move. The fEMG responses often occurred almost simultaneously with movement. Large fEMG increases occurred more often in inadequately anesthetized (as defined by somatic or hemodynamic responses) patients than in adequately anesthetized patients. The interindividual variability in fEMG values was con-

Table 14. The values of BIS (v. 3.4–4.0), SE and RE associated with 50 % and 95 % probability of unresponsiveness (ED_{50} and ED_{95} values) to non-noxious (loss of consciousness) and noxious (tetanic electrical) stimulation, during propofol monoanesthesia and propofol combined with remifentanil 2 ng / ml. The data are observations of Struys and colleagues and Vanluchene and colleagues (Struys *et al* 2002, Struys *et al* 2003, Vanluchene *et al* 2004a).

	Propofol alone				*Propofol + remifentanil 2 ng / ml*			
	Loss of consciousness		Loss of response to tetanic electrical stimulation		Loss of consciousness		Loss of response to tetanic electrical stimulation	
	ED_{50}	ED_{95}	ED_{50}	ED_{95}	ED_{50}	ED_{95}	ED_{50}	ED_{95}
BIS	61–71	52–55	32–41	17–29	68–80	65–66	53–72	45–56
SE	64	53	37	22	68	60	50	39
RE	70	57	39	22	74	69	53	41

siderable. Notably, the authors were unable to correlate changes in the mean integrated frontal EEG amplitude or ZCF with clinical signs of inadequate anesthesia (Chang *et al* 1988).

In agreement with the above-mentioned studies, in studies IV and V the fEMG arousal response, but generally not the pre-stimulus fEMG power discriminated movers to noxious stimulation from non-movers.

In study IV, the pre- and post-stimulus values and the normalized values of BIS and fEMG power discriminated movers from non-movers at CD, as did the post-stimulus value of SEF95. At RP, neither pre-stimulus EEG variables or fEMG had P_K values significantly different from 0.5. The post-stimulus values and the normalized values of BIS, SEF95, and fEMG power discriminated movers from non-movers at RP. The more variable balance between hypnosis and analgesia at RP compared to CD may have lead to the lack of predictive performance of EEG variables and fEMG at RP. Movement was associated with an EEG and fEMG arousal response at both CD and RP. fEMG power was included in the logistic regression model with the best discrimination performance at RP in study IV.

In study V, the normalized values of the absolute and relative β power, RE and RE-SE discriminated movers from non-movers at skin incision, as did the post-stimulus value and the normalized value of fEMG power. Of these variables, the normalized value of RE was included in the logistic regression model with the best discrimination performance.

Movement responses as an indicator of nociception

In studies IV and V, movement responses were used to investigate the relative importance of different physiological variables in the evaluation of nociception. Autonomic responses were generally more pronounced in movers than in non-movers, consistent with greater nociception in movers. Even when movement responses are blocked, hemodynamic responses may still occur (Zbinden *et al* 1994b, Kazama *et al* 1997). Kazama and colleagues observed that the C_{p50} values of propofol with respect to movement responses to tetanic electrical stimulation and skin incision were similar, whereas skin incision induced a larger hemodynamic response than did tetanic stimulation (Kazama *et al* 1997). Thus movement responses may be less sensitive indicators of nociception than hemodynamic responses.

In a study by Sebel and colleagues, the pre-stimulus opioid concentration predicted both the movement and the hemodynamic responses to skin incision during isoflurane or propofol anesthesia (Sebel *et al* 1997). The remifentanil concentration predicted significant hemodynamic responses to tracheal intubation during propofol–remifentanil anesthesia in a logistic regression model (Luginbühl *et al* 2006, Luginbühl *et al* 2007). The strength of the correlation between the opioid concentration and the heart rate or blood pressure responses to noxious stimulation during anesthesia is strongest for the most noxious stimuli. Movement and blood pressure responses show a modest correlation with only the most noxious stimuli (Kazama *et al* 1997).

Some studies show that the pre-stimulus propofol concentration predicts movement responses to noxious stimulation (Leslie *et al* 1996, Johansen *et al* 1997, Struys *et al* 2002, Struys *et al* 2003), whereas others do not (Vernon *et al* 1995, Sebel *et al* 1997, Doi *et al* 1999). Generally, the pre-stimulus concentrations of potent volatile anesthetic agents are predictive of movement responses to noxious stimulation (Vernon *et al* 1995, Sebel *et al* 1997, Katoh *et al* 1998, Kurita *et al* 2001).

Different anesthetic agents act preferentially on different parts of the central nervous system to suppress movement responses (Antognini *et al* 2002, Jinks *et al* 2003, Baars *et al* 2006a, Baars *et al* 2006b). For example, the effect of sevoflurane on both nociceptive and non-nociceptive spinal neural transmission is considerably stronger than that of propofol (Matute *et al* 2004). Thus the extent to which EEG variables or measures of spinal excitability correlate with movement responses varies with different drugs. In study IV, the pre- and post-stimulus BIS and SEF95 values showed some association with movement responses to noxious stimula-

tion, consistent with a predominant supraspinal action of propofol. In contrast, in study V, where sevoflurane was used, no significant associations between EEG measures of hypnosis and movement responses emerged.

The probability of a response to noxious stimulation depends fundamentally on the prevailing combination of hypnotic and opioid concentrations. Because opioids have little effect on the EEG at clinically used concentrations, the EEG state alone cannot predict the probability of response (Bouillon *et al* 2004). Cortical depression *per se* does not contribute significantly to the suppression of movement responses (Rampil and Laster 1992, Antognini *et al* 2002). Accordingly, the association of subcortically mediated autonomic and fEMG responses with movement was stronger than that of EEG-derived variables in studies IV and V.

Models for discriminating movers and non-movers

In study IV, the performance of the normalized fEMG power in classifying movers and non-movers at RP could not be improved, according to the –2LL criterion, by adding other variables to the logistic regression model. For example, the comparison of the models including the combination of fEMG power and HR *vs.* fEMG power alone did not quite reach statistical significance. The combination of fEMG power and HR, however, did yield slightly better sensitivity, overall performance, and ROC area than fEMG power alone. The performance of weaker variables was improved by adding another variable to the logistic model. Overall the sensitivity of the acquired models was poor. This is probably due to the rapidly changing balance between drug-induced suppression and surgical stimulation during the non-steady state conditions of uterine dilatation and curettage.

In study V, two-variable combinations yielded significantly better logistic regression models than did single variables (with the exception that the performance of RRI alone could not be improved by adding PPG notch amplitude). According to the –2LL criterion, the logistic model including the normalized RE, RRI and PPG notch amplitude was no better than the combination of RE and PPG notch amplitude, but the former did yield a better overall performance and specificity. The sensitivity of the acquired models was much better in study V than in study IV, perhaps because the surgical stimulus was less variable, and anesthesia at the time of stimulation approached steady-state conditions during continuous administration of sevoflurane. In both studies the fEMG power and HR showed potential as indicators of significant nociception. Unfortunately, PPG was not investigated in study IV.

The assessment of the adequacy of anesthesia

When the antinociception provided by anesthesia is insufficient, surgical stimuli may induce motor, autonomic, and humoral reactions, as well as changes in EEG activity. Monitoring of the humoral responses is impractical, and usually motor responses are blocked during anesthesia by hypnotic, analgesic, and neuromuscular blocking agents. Frontal EMG activation is probably more sensitive to nociception than visible somatic responses. Some evidence suggests that the MLAEP may be more sensitive to nociception than other processed EEG variables during anesthesia. Different autonomic responses may provide a continuous measure of the nociceptive–antinociceptive balance during anesthesia, but it is unclear which of them is the most sensitive and robust indicator of nociceptive responses. The changes in blood pressure and heart rate provide a crude measure of the autonomic state of the anesthetized patient. In addition to PPG, the changes in palmar skin conductance or pupillary reflex dilation may detect more subtle nociception-related reactions. Not only nociception, but also increases in the level of consciousness, and, for example, hemodynamic crises or seizures can influence the autonomic responses. In addition, aging and illness, as well as drugs affecting the cardiovascular system, may change the autonomic responses to nociception. Thus the problem of the on-line assessment of the

nociceptive–antinociceptive balance during anesthesia is very complex.

Both consciousness and the nociceptive responses are simultaneously depressed by anesthetic agents. In 2000, Viertiö-Oja and colleagues concluded that the independent measurement of the hypnotic and analgesic components of general anesthesia is challenging due to their strong interactions (Viertiö-Oja *et al* 2000). Wilder-Smith and colleagues suggested that while the EEG is of limited use in predicting responses to noxious stimuli, the EEG arousal reactions may be useful in the evaluation of nociception during anesthesia (Wilder-Smith *et al* 1995). *Arousal*, which integrates both increases in consciousness and autonomic nociceptive responses, could be a sensible end-point for the assessment of the adequacy of anesthesia. If EEG monitoring is combined with monitoring of the sympathetic reactions, EMG, and perhaps MLAEP, a more complete picture of the arousal responses may be obtained. In addition to new monitoring possibilities, the advent of new short-acting anesthetic agents, especially remifentanil, has increased the flexibility of adjusting general anesthesia to meet the dynamically changing surgical needs.

Future studies will reveal whether a reliable on-line estimation of the nociceptive–antinociceptive balance can be achieved with a mathematical index based on a specific weighted combination of different physiological variables, or whether the information derived from different sources is best integrated by the anesthesiologist, or perhaps a neural network. In any case, the description and quantification of different sympathetic and other arousal responses will be useful in advancing the insight into the physiology of nociception and anesthesia, and in providing new monitoring possibilities.

Conclusions

The following conclusions can be drawn from the studies:

1. When only alcohol swab skin pretreatment is used, the skin-electrode impedance values of Nikomed® ECG electrodes are higher than those of Zipprep® EEG electrodes. With careful skin preparation, low skin-electrode impedance values can be achieved with Nikomed® ECG electrodes. The BIS values (v. 3.22) registered with an Aspect A-1000 EEG monitor with a set of Nikomed® ECG electrodes are higher than those registered with a set of Zipprep® EEG electrodes, when alcohol swab is used as skin pretreatment. The influence of a cranial displacement of the electrodes by two to three centimeters on the resulting BIS values is minor.

2. The probability of epileptiform EEG activity is very low during desflurane anesthesia, even at high concentrations. It was confirmed that a rapid increase in the inspired concentration of sevoflurane is associated with epileptiform EEG activity in a significant portion of healthy patients. The tachycardia induced by a rapid increase in the inspired desflurane concentration is more pronounced than that induced by sevoflurane. It reaches its maximum in roughly two minutes.

3. When the dose of the inhaled agent is individually titrated to maintain BIS values between 50–60, the recovery profile is similar after isoflurane–N_2O or sevoflurane–N_2O anesthesia in healthy gynecological ambulatory surgery patients.

4. When anesthesia is maintained by the inhalation of 67 % N_2O and bolus doses of propofol or alfentanil after a propofol–alfentanil induction, in young healthy unparalyzed patients, a bolus of propofol (0.7 mg / kg) is more effective in preventing recurring movement responses than a bolus of alfentanil (0.5 mg).

5. Several variables derived from the surface EEG, fEMG, ECG (HR / RRI or HRV), and PPG display mainly reactive associations with movement responses to noxious stimulation during propofol–N_2O–alfentanil or sevoflurane anesthesia. The fEMG or RE, RRI (HR), and PPG notch amplitude, normalized to their prestimulus values, may be useful as indicators of nociception during anesthesia, but their performance needs to be validated in future studies. Combining more than one variable by logistic regression analysis may improve the discrimination of the level of nociception, as defined by the presence or absence of movement responses to noxious stimulation.

Clinical considerations

1. The use of designated EEG electrodes instead of ECG electrodes in BIS monitoring is recommended. The position of the electrodes should follow the instructions of the manufacturer.

2. It may be prudent to avoid using sevoflurane, at least in high concentrations, in epileptic patients. Desflurane may be a safer volatile agent in this patient group. A rapid increase in the inspired desflurane concentration may be risky in patients with cardiac disease, due to transient sympathoexcitation.

3. If the administration of the potent volatile agent is adjusted to maintain BIS at 50–60, isoflurane–N_2O anesthesia is equally acceptable as sevoflurane–N_2O anesthesia in healthy ambulatory surgery patients, in terms of the speed and quality of recovery.

4. When anesthesia for a minor procedure is maintained by the inhalation of 67 % N_2O and administration of modest bolus doses of propofol or alfentanil after a propofol–alfentanil induction, in young healthy unparalyzed patients, movement responses are best avoided by ensuring a relatively deep hypnotic level (a relatively high propofol concentration).

5. Currently, all anesthesiologists can detect signs of nociception during anesthesia by observing changes in heart rate, blood pressure, and the PPG waveform. Many also have access to EEG monitoring. Other possibilities for monitoring the autonomic and evoked potential responses to noxious stimulation during anesthesia (e.g. measurement of the palmar skin electrical conductance, pupillometry, MLAEP) may become routinely available. In the future, quantification of the nociception-related changes in physiological variables and mathematical data compression may help the clinician in decision-making regarding the administration of hypnotic and analgesic agents. The combination of information from different sources may improve the assessment of the nociceptive–antinociceptive balance.

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