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Measurements of adequacy of anesthesia and level of consciousness during surgery and intensive care

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Academic dissertation

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To my family

Contents

Abstract

The adequacy of anesthesia has been studied since the introduction of balanced general anesthesia. Commercial monitors based on electroencephalographic (EEG) signal analysis have been available for monitoring the hypnotic component of anesthesia from the beginning of the 1990s. Monitors measuring the depth of anesthesia assess the cortical function of the brain, and have gained acceptance during surgical anesthesia with most of the anesthetic agents used. However, due to frequent artifacts, they are considered unsuitable for monitoring consciousness in intensive care patients. The assessment of analgesia is one of the cornerstones of general anesthesia. Prolonged surgical stress may lead to increased morbidity and delayed postoperative recovery. However, no validated monitoring method is currently available for evaluating analgesia during general anesthesia.

Awareness during anesthesia is caused by an inadequate level of hypnosis. This rare but severe complication of general anesthesia may lead to marked emotional stress and possibly posttraumatic stress disorder. In the present series of studies, the incidence of awareness and recall during outpatient anesthesia was evaluated and compared with that of in inpatient anesthesia. A total of 1500 outpatients and 2343 inpatients underwent a structured interview. Clear intraoperative recollections were rare the incidence being 0.07% in outpatients and 0.13% in inpatients. No significant differences emerged between outpatients and inpatients. However, significantly smaller doses of sevoflurane were administered to outpatients with awareness than those without recollections ($p < 0.05$).

EEG artifacts in 16 brain-dead organ donors were evaluated during organ harvest surgery in a prospective, open, nonselective study. The source of the frontotemporal biosignals in brain-dead subjects was studied, and the resistance of bispectral index (BIS) and Entropy to the signal artifacts was compared. The hypothesis was that in brain-dead subjects, most of the biosignals recorded from the forehead would consist of artifacts. The original EEG was recorded and State Entropy (SE), Response Entropy (RE), and BIS were calculated and monitored during solid organ harvest. SE differed from zero (inactive EEG) in 28%, RE in 29%, and BIS in 68% of the total recording time ($p < 0.0001$ for all). The median values during the operation were SE 0.0, RE 0.0, and BIS 3.0. In four of the 16 organ donors, EEG was not inactive, and unphysiologically distributed, nonreactive rhythmic theta activity was present in the original EEG signal. After the results from subjects with persistent residual EEG activity were excluded, SE, RE, and BIS differed from zero in 17%, 18%, and 62% of the recorded time, respectively ($p < 0.0001$ for all). Due to various artifacts, the highest readings in all indices were recorded without neuromuscular blockade. The main sources of artifacts were electrocauterization, electromyography (EMG), 50-Hz artifact, handling of the donor, ballistocardiography, and electrocardiography.

In a prospective, randomized study of 26 patients, the ability of Surgical Stress Index (SSI) to differentiate patients with two clinically different analgesic levels during shoulder surgery was evaluated. SSI values were lower in patients with an interscalene brachial plexus block than in patients without an additional plexus block. In all patients,

anesthesia was maintained with desflurane, the concentration of which was targeted to maintain SE at 50. Increased blood pressure or heart rate (HR), movement, and coughing were considered signs of intraoperative nociception and treated with alfentanil. Photoplethysmographic waveforms were collected from the contralateral arm to the operated side, and SSI was calculated offline. Two minutes after skin incision, SSI was not increased in the brachial plexus block group and was lower (38 ± 13) than in the control group (58 ± 13, p<0.005). Among the controls, one minute prior to alfentanil administration, SSI value was higher than during periods of adequate antinociception, 59 ± 11 vs. 39 ± 12 (p<0.01). The total cumulative need for alfentanil was higher in controls (2.7 ± 1.2 mg) than in the brachial plexus block group (1.6 ± 0.5 mg, p=0.008). Tetanic stimulation to the ulnar region of the hand increased SSI significantly only among patients with a brachial plexus block not covering the site of stimulation.

Prognostic value of EEG-derived indices was evaluated and compared with Transcranial Doppler Ultrasonography (TCD), serum neuron-specific enolase (NSE) and S-100B after cardiac arrest. Thirty patients resuscitated from out-of-hospital arrest and treated with induced mild hypothermia for 24 h were included. Original EEG signal was recorded, and burst suppression ratio (BSR), RE, SE, and wavelet subband entropy (WSE) were calculated. Neurological outcome during the six-month period after arrest was assessed with the Glasgow-Pittsburgh Cerebral Performance Categories (CPC). Twenty patients had a CPC of 1-2, one patient had a CPC of 3, and nine patients died (CPC 5). BSR, RE, and SE differed between good (CPC 1-2) and poor (CPC 3-5) outcome groups (p=0.011, p=0.011, p=0.008, respectively) during the first 24 h after arrest. WSE was borderline higher in the good outcome group between 24 and 48 h after arrest (p=0.050). All patients with status epilepticus died, and their WSE values were lower (p=0.022). S-100B was lower in the good outcome group upon arrival at the intensive care unit (p=0.010). After hypothermia treatment, NSE and S-100B values were lower (p=0.002 for both) in the good outcome group. The pulsatile index was also lower in the good outcome group (p=0.004).

In conclusion, the incidence of awareness in outpatient anesthesia did not differ from that in inpatient anesthesia. Outpatients are not at increased risk for intraoperative awareness relative to inpatients undergoing general anesthesia. SE, RE, and BIS showed non-zero values that normally indicate cortical neuronal function, but were in these subjects mostly due to artifacts after clinical brain death diagnosis. Entropy was more resistant to artifacts than BIS. During general anesthesia and surgery, SSI values were lower in patients with interscalene brachial plexus block covering the sites of nociceptive stimuli. In detecting nociceptive stimuli, SSI performed better than HR, blood pressure, or RE. BSR, RE, and SE differed between the good and poor neurological outcome groups during the first 24 h after cardiac arrest, and they may be an aid in differentiating patients with good neurological outcomes from those with poor outcomes after out-of-hospital cardiac arrest.

List of original publications

I   Wennervirta J, Ranta S, Hynynen M. Awareness and recall in outpatient anesthesia. Anesth Analg 2002; 95: 72-77.

II   Wennervirta J, Salmi T, Hynynen M, Yli-Hankala A, Koivusalo A-M, Van Gils M, Pöyhiä R, Vakkuri A. Entropy is more resistant to artifacts than bispectral index in brain-dead organ donors. Intensive Care Med 2007; 33: 133-136.

III   Wennervirta J, Hynynen M, Koivusalo A-M, Uutela K, Huiku M, Vakkuri A. Surgical stress index as a measure of nociception/antinociception balance during general anesthesia. Acta Anaesthesiol Scand 2008; 52: 1038-1045.

IV   Wennervirta J, Ermes M, Tiainen M, Salmi T, Hynninen M, Särkelä M, Hynynen M, Stenman U-H, Viertiö–Oja H, Saastamoinen K-P, Pettilä V, Vakkuri A. Hypothermia-treated cardiac arrest patients with good neurological outcome differ early in quantitative variables of EEG suppression and epileptiform activity. Crit Care Med 2009; 37: 2427-2435.

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Abbreviations

AEP	auditory evoked potential
ASA	American Society of Anesthesiologists
BIS	Bispectral Index Scale
BPsys	systolic blood pressure
BSR	burst suppression ratio
cEEG	continuous electroencephalography
CI	confidence interval
CPC	Cerebral Performance Categories
CPP	cerebral perfusion pressure
CT	computed tomography
ECG	electrocardiography
EEG	electroencephalography
EMG	electromyography
EP	evoked potential
ESR	electroencephalogram silence ratio
fEMG	frontal electromyography
FFT	Fast Fourier Transformation
FPR	false-positive rate
$GABA_A$	gamma-aminobutyric acid subtype A
GCS	Glasgow Coma Scale
HACA	hypothermia after cardiac arrest
HBI	heart beat interval
HBI_{norm}	normalized heart beat interval
HR	heart rate
Hz	hertz
ICP	intracranial pressure
ICU	intensive care unit
kDa	kilodalton
kPa	kilopascal
μV	microvolt
mA	milliampere
MAC	minimal alveolar concentration
MCA	middle cerebral artery
MHz	megahertz
MLAEP	middle latency auditory evoked potential
N_2O	nitrous oxide
NIBP	non-invasive blood pressure
NICU	neurological intensive care unit
NIRS	near-infrared spectroscopy
NMBA	neuromuscular blocking agent
NPV	negative predictive value
NSE	neuron-specific enolase
OAA/S	Observer's Assessment of Alertness/Sedation scale
Pk	prediction probability

PPG   pulse plethysmography
PPGA   pulse photoplethysmographic amplitude
PPV   positive predictive value
PRST   pressure, rate, sweating, tears
qEEG   quantitative electroencephalography
RASS   Richmond Agitation-Sedation Scale
RE   Response Entropy
ROSC   return of spontaneous circulation
SAS   Sedation Agitation Scale
SD   standard deviation
SE   State Entropy
SEP   somatosensory-evoked potential
$SjVO_2$ jugular bulb venous oxygen saturation
SPI   Surgical Pleth Index
SpO_2 peripheral oxygen saturation
SQI   signal quality index
SSI   Surgical Stress Index
SVmR   skin vasomotor reflex
TCD   transcranial Doppler ultrasonography
VF   ventricular fibrillation
WHO   World Health Organization
WSE   wavelet subband entropy

1. Introduction

Intraoperative awareness with recall is a rare but potentially serious complication of general anesthesia. Its incidence has declined during the last decades. Currently, outpatient-surgery comprises more than 50% of the total number of surgeries, and the proportion is rising. In outpatient surgery, one of the main goals is to conduct operative procedures cost-effectively. This puts pressure on reducing operating theater change-over times and length of stay in the recovery room, thus necessitating the use of short-acting anesthetics. This might increase the risk of awareness during outpatient anesthesia.

Amnesia, analgesia, and immobility characterize modern balanced anesthesia. It has long been possible to measure the degree of muscle relaxation, and from the beginning of the 1990s, several EEG-based monitors have been used to evaluate the hypnotic component of anesthesia. The use of these depth-of-anesthesia monitors has been associated with a decreased incidence of awareness (Ekman *et al.* 2004, Myles *et al.* 2004), reduced administration of hypnotic drugs (Gan *et al.* 1997, Vakkuri *et al.* 2005), faster recovery from anesthesia (Gan *et al.* 1997, Johansen and Sebel 2000, Vakkuri *et al.* 2005), and a lower incidence of postoperative vomiting (Nelskylä *et al.* 2001). The depth-of-anesthesia monitors can not predict patient's movements or hemodynamic responses to surgical stimuli during general anesthesia (Johansen and Sebel 2000).

Although analgesia is one of the main components of balanced general anesthesia, a commercially available monitor for assessment of analgesia does not currently exist. During surgery the stress response is an unconscious systemic reaction to tissue injury that reflects autonomic, hormonal, and metabolic changes (Desborough 2000). Prolonged surgical stress may cause biochemical body reactions, which may lead to increased morbidity and delayed postoperative recovery (Kehlet 1997). The Surgical Stress Index (SSI, later Surgical Pleth Index, SPI) was developed in an effort to obtain balance between nociception (caused by surgical stimulation) and antinociception (opioid analgesia or neural blockade). SSI is based on the interval between successive heartbeats (HBI) and the pulse photoplethysmographic amplitude (PPGA), which are obtained from the photoplethysmographic waveform of the peripheral oxygen saturation measurement. The measures are normalized and combined to produce a single SSI value (Huiku *et al.* 2007). SSI has been clinically validated (Ahonen *et al.* 2007, Huiku *et al.* 2007, Struys *et al.* 2007), and will become commercially available in the near future.

Evaluation of consciousness, level of sedation, and neurological status are daily problems in intensive care units (ICUs). Most critically ill patients suffer from diseases that may influence brain function. Even if neurological status remains normal during the ICU stay, patients are usually sedated to allow adequate treatment. Over-sedation is associated with an adverse outcome, and strategies designed to avoid this have been demonstrated to have a positive effect on outcome (Kress *et al.* 2000). Due to unconsciousness, evaluation of neurological status and prediction of outcome are difficult. Status epilepticus has been related to poor neurological outcome in critically ill patients (Young and Doig 2005, Rundgren *et al.* 2006). Nonconvulsive status epilepticus (NCSE, status epilepticus without visible seizure) has an incidence of 8% in

comatose ICU patients (Towne *et al.* 2000). Longer seizure duration and delay to diagnosis are associated with increased mortality (Young *et al.* 1996). NCSE is detectable only with EEG monitoring, which supports the inclusion of continuous EEG in routine evaluation of comatose patients even when clinical seizure activity is not apparent; in addition, muscle relaxants will mask the clinical signs. Neuromonitoring is needed also among stroke and neurosurgical patients, with the aim of detecting treatable conditions and reducing secondary brain damage following acute brain injury. A noninvasive neuromonitoring method is required.

Automatic methods to measure the adequacy of the depth of anesthesia and analgesia in the operation theater and the level of consciousness in ICU, and possible artifacts related to these monitors were evaluated in this thesis. The incidence of awareness in outpatient anesthesia was also investigated. The monitors were evaluated in groups of patients for which they have not been previously tested or validated. Finally, the performance of the EEG-based indices was tested for the prediction of neurologic outcome in comatose ICU patients.

2. Review of the literature

2.1. Mechanisms of general anesthesia

According to current knowledge, most of the general anesthetics act via ligand-gated or voltage-gated channels on the main targets. Anesthetics interact with various molecular sites of neuronal action. They modulate the activity of ion channels and cause hyperpolarization of neurons in thalamocortical loops, thereby leading to disruption of effective connectivity in the cortex (Campagna *et al.* 2003, Århem *et al.* 2003). The effect of a certain drug depends on the connection and feedback in neural networks, and it may result in inhibition, excitation, or no effect on the central nervous system (Urban 2002). Whether the anesthesia-induced unconsciousness is a direct effect of anesthetics on the cerebral cortex (Velly *et al.* 2007), a direct (Alkire and Miller 2005) or indirect effect (Alkire 1998) on the thalamus, or arises from thalamocortical interactions remains unclear (John and Prichep 2005). Anesthetics seem to cause unconsciousness by targeting posterior lateral corticothalamic complex around the inferior parietal lobe and the medial cortical core. Unconsciousness is caused by preventing interactions among specialized brain regions or by reducing the number of activity patterns available to cortical networks (Alkire *et al.* 2008).

Most anesthetics act by either increasing the transmission of the primary inhibitory neurotransmitter gamma-aminobutyric acid (GABA) or decreasing the activation of the primary excitatory N-methyl-D-aspartate (NMDA) receptors (Århem *et al.* 2003). With increasing concentrations of anesthetics, the neurons begin to oscillate between a depolarized upstate and a hyperpolarized downstate. If the anesthetic dose rises beyond this, the upstate transforms to burst and the downstate becomes longer. These changes are seen in EEG when the low-voltage and high-frequency EEG pattern (typical of wakefulness) becomes a slow-wave and finally a burst-suppression pattern. (Alkire *et al.* 2008).

2.1.1. Gamma-amino butyric acid, GABA

GABA is the main inhibitory neurotransmitter in the mammalian central nervous system. Its fast inhibitory effects are mediated mainly through the inotropic $GABA_A$ receptors. Of the general anesthetics, barbiturates, propofol, etomidate, enflurane, isoflurane, sevoflurane, and desflurane are GABA agonistic agents (Alkire *et al.* 2008). At clinically effective concentrations, these anesthetics increase the sensitivity of receptors to GABA, prolong the inhibitory postsynaptic effect after a GABA release, and increase the inhibition of postsynaptic neuronal excitability (Campagna *et al.* 2003). However, the inhibitory effect of some GABAergic agents does not apply to all situations, as shown by the proconvulsive effect of enflurane (Rosen, I and Söderberg 1975) and deep sevoflurane anesthesia (Jääskeläinen *et al.* 2003). Deep anesthesia, combined with hyperventilation and hypocapnia, has been reported to elicit seizures

with both enflurane and sevoflurane (Rosen, I and Söderberg 1975, Yli-Hankala *et al.* 1999).

2.1.2. N-methyl-D-aspartate, NMDA

The major excitatory neurotransmitter in the central nervous system is glutamate, which produces neuronal excitation through glutamate receptors. The NMDA receptor is probably the most widely studied glutamate receptor subtype, and inhibition of NMDA receptors is important for the anesthetic effects of ketamine, xenon, and nitrous oxide (N_2O) (Franks and Lieb 1997, Campagna *et al.* 2003, Evers and Crowder 2009). EEG-based depth-of-anesthesia monitors perform well with GABA agonists, but are not reliable with those acting via NMDA receptors (Hans *et al.* 2005, Maksimow *et al.* 2006, Park *et al.* 2006).

2.1.3. α_2 –adrenoreceptor agonists

Although most anesthetics act via GABAergic or glutamatergic transmitter systems, there are also selective α_2-adrenoreceptor agonists, like dexmedetomidine, that induce hypnosis and analgesia, and these are used as sedative agents in ICU (Scheinin and Schwinn 1992).

2.2. Awareness and recall during general anesthesia

2.2.1. History

The invention of general anesthesia over 160 years ago was a turning point in the field of surgery. General anesthesia is defined as a state of drug-induced unconsciousness during which the patients neither consciously perceive nor recall noxious stimulation (Prys-Roberts 1987). Hypnosis, analgesia, and immobility with amnesia characterize modern balanced anesthesia.

During the early years of general anesthesia a major concern was excessively deep anesthesia and its fatal consequences. This situation arose because a single anesthetic agent had to attend to all of the components of general anesthesia. Since the first public demonstration of ether-anesthesia in 1846 by William Morton, there have also been reports about awareness and recall (hereafter merely "awareness") during general anesthesia (Ghoneim 2001). Awareness during anesthesia implies that patients are aroused by stimuli, leading to memory storage for future explicit recall (Ghoneim 2001). Traumatic awareness during general anesthesia became a problem after the introduction of curare as a muscle relaxant in 1942 (Griffith and Johnsson 1942). Winterbottom (1950) published the first case report of awareness related to use of

neuromuscular blocking agents (NMBAs) in 1950 and opened the gate for studies in this area.

2.2.2. Incidence and risk factors

Awareness is a rare adverse consequence of general anesthesia. Since the 1960s, when the first studies were published, the incidence of this complication has declined from 1.2% to 0.1% (Hutchinson 1960, Brice *et al.* 1970, Ranta *et al.* 1998, Sandin *et al.* 2000, Myles *et al.* 2004, Sebel *et al.* 2004, Ghoneim *et al.* 2009). Higher incidence of awareness (0.8-1.2%) among children than adults has been reported (Davidson *et al.* 2005a, Lopez *et al.* 2007). However, in certain adult patient groups, such as those undergoing anesthesia for cardiac, emergency trauma, or obstetric surgery, an increased risk for awareness has been described (Ghoneim and Block 1992, Ghoneim *et al.* 2009). Several factors increase the risk of awareness, including light anesthesia, a history of awareness, chronic use of central nervous system depressants, use of NMBAs during surgery, female sex, increased American Society of Anesthesiologists (ASA) physical status, younger age, smaller dose of primary anesthetic, inadequate or misused anesthesia delivery systems, and ignoring the use of EEG monitors when the risk is otherwise increased (Ghoneim and Block 1992, Ranta *et al.* 1998, Ekman *et al.* 2004, Myles *et al.* 2004, Sebel *et al.* 2004, Ghoneim *et al.* 2009).

In a meta-analysis, Ghoneim and colleagues (2009) compared the data of 271 cases of awareness published for the period 1950-2005 with the data of 19 504 patients without awareness. Overly light anesthesia was found to be the most common cause of awareness. Among the patients with awareness, no volatile anesthetic agents or propofol was used during the maintenance of anesthesia in 23% of cases. There was no difference in the use of N_2O between patients with and without awareness. Ranta and colleagues (1998) showed that patients with awareness received less propofol and isoflurane during surgery than patients without awareness.

Based on the existing literature, a complete muscle paralysis had been thought to be a significant risk factor for awareness during general anesthesia. There are no randomized controlled trials, but in the study of Sandin and colleagues (2000), the authors reported that the incidence of awareness was 0.1% without the use of muscle relaxants, doubling when they were used. Although Ghoneim and colleagues (2009) found no difference in the use of NMBAs between the patients with and without awareness, they recommended avoiding unnecessary use of NMBAs to avoid total paralysis.

Several studies have indicated that females are at increased risk of awareness (Ranta *et al.* 1997, Ghoneim *et al.* 2009). In the studies of Buchanan et al. (2006) and Gan et al. (1999) women recovered from anesthesia faster than men despite similar amounts of anesthetic drugs per kilogram weight administered. These findings suggest that females might be less sensitive to the central nervous system effects of anesthetics than males (Ghoneim *et al.* 2009).

In outpatient surgery, one of the main goals is to conduct operative procedures cost-effectively. This puts pressure on reducing operating theater change-over times and

length of stay in the recovery room, thus necessitating the use of short-acting anesthetics. This might increase the risk of awareness in outpatient anesthesia. However, upon interviewing 5216 ambulatory surgery patients, Enlund and Hassan (2002) detected no cases of awareness.

2.2.3. Classification of awareness

Awareness during general anesthesia contains consciousness and memories about intraoperative events (Jones 2000). Memory about intraoperative events can be divided into explicit (controlled, conscious) and implicit (automatic, unconscious) components (Hadzidiakos *et al.* 2009). Explicit memory means that a patient can recall intraoperative events or sensations also in a structured postoperative interview.

To establish the patients' reports of memories, it is a current norm that an independent group of referees judges all reported recollections and defines them as "definite", "probable / possible", or "no awareness" cases (Ghoneim 2007). Cases of awareness are described as definite or clear when patients have explicit recall of intraoperative events and as probable, possible, or doubtful when patients have unclear memories or dreams that might be related to intraoperative events (Ranta *et al.* 1998). The Michigan Awareness Classification Instrument was recently developed to decrease interobserver variability and facilitate the study of intraoperative awareness. It describes class 0: no awareness, class 1: isolated auditory perceptions, class 2: tactile perceptions, class 3: pain, class 4: paralysis, and class 5: paralysis and pain (Mashour *et al.* 2010).

In the study of Myles and colleagues (2004), the number of possible cases of awareness was double the number of confirmed cases. Dreaming is detected more often than awareness (Ghoneim and Block 1992). Myles et al. (2004) reported that 5% of bispectral index (BIS)-guided and 7% of routine care patients recalled dreaming during general anesthesia. Ranta and colleagues (1998) showed that women reported dreams significantly more often than men (14% vs. 9%).

2.2.4. Assessment of awareness

Assessment of awareness is always based on patients' subjective reports. Most of the incidence studies have been done with a structured interview, which was first described by Brice and colleagues in 1970 and later modified by Liu and colleagues (Liu, WH *et al.* 1991). The original questionnaire consists of four questions:

1. What was the last thing you remember before you went to sleep?
2. What was the first thing you remember when you woke up?
3. Can you remember anything in between these periods?
4. Did you dream during your operation?
(Brice *et al.* 1970).

It is accepted nowadays that more than one interview is needed. Several studies suggest that patients who might not remember awareness immediately after surgery may recall it later (Macleod and Maycock 1992, Sandin *et al.* 2000, Ghoneim *et al.* 2009). In a study of Sandin and colleagues (2000), recall of intraoperative events was delayed by several days in up to 50% of patients with awareness. Ghoneim and colleagues (2009) found that 37% of patients with awareness reported their memories for the first time more than one week after the surgery.

Hearing of voices seems to be the most commonly reported experience during awareness, reported in 30-89% of the awareness cases. Tactile perceptions have been described in 25-72%, and paralysis or sensation of weakness in 17-85% of cases (Moerman *et al.* 1993, Domino *et al.* 1999, Samuelsson *et al.* 2007, Ghoneim *et al.* 2009). In a closed claims analysis, pain was experienced by 21% of patients with awareness (Domino *et al.* 1999). In the studies of Samuelsson et al. (2007), and Ghoneim et al. (2009), 46% and 38% of patients with awareness, respectively, experienced pain.

2.2.6. After-effects of awareness

In a long-term follow-up, up to 50 % of patients experiencing awareness developed late severe psychiatric sequelae (Lennmarken *et al.* 2002, Samuelsson *et al.* 2007). The symptoms of these patients fulfill the diagnostic criteria of posttraumatic stress disorder. Typical symptoms after awareness are irritability, insomnia, nightmares, anxiety, depression, preoccupation with death, and fear of hospitals or future surgery (Blacher 1984, Ghoneim *et al.* 2009). Despite its infrequent occurrence, awareness under general anesthesia worries patients (Myles *et al.* 2000). In the study of McClean and Cooper (1990), over 50% of patients were afraid of the possibility of not being unconscious under general anesthesia when they were preoperatively interviewed. Even after having an uneventful and "nonawareness" surgery under general anesthesia, 25% of the same patients were still worried about not being asleep during future anesthesia (McCleane and Cooper 1990).

2.3. Methods for monitoring the depth of general anesthesia

2.3.1. Clinical signs

Traditionally, the judgment of inadequate general anesthesia has been based on clinical signs such as tachycardia, hypertension, sweating, pupillary dilatation, and lacrimation. However, signs of increased autonomic activity have not been associated with all cases of awareness, and they may also be absent due to use of opioids, cholinergic- and beta-adrenergic antagonists, vasodilators, and antihypertensive drugs (Ghoneim and Block 1992, Moerman *et al.* 1993, Domino *et al.* 1999), and are therefore inadequate to measure the depth of general anesthesia. Movements and breathing pattern may reflect the depth of anesthesia, but are not valid when NMBAs are used. The studies of Sandin

and colleagues (2000) and Sebel and colleagues (2004) have also shown that avoidance of muscle relaxants does not guarantee the avoidance of awareness.

2.3.2. Minimal alveolar concentration and isolated forearm technique

To prevent awareness, volatile-based anesthesia should be delivered at a concentration of at least 0.5 minimal alveolar concentration (MAC) (Chortkoff *et al.* 1995). The isolated forearm technique can be used to evaluate the depth of anesthesia even when NMBAs are used. In this technique, a tourniquet is applied to the forearm and inflated to above the level of arterial pressure before NMBA is administered. The forearm is thus not paralyzed, and the patient may move the arm if the anesthesia is insufficient (Tunstall 1977, Russell 2006). However, in the study of Bogod and colleagues (1990), the isolated forearm technique seemed to be an unhelpful indicator of awareness. Patients under general anesthesia can apparently even carry on conversations using hand signals and still have no postoperative recollections (Russell and Wang 1997).

2.3.3. EEG-based indices and monitors and auditory evoked potential

The interpretation of EEG requires special expertise and is therefore not suitable for routine monitoring during general anesthesia. Depth-of-anesthesia monitors, which are based on processed EEG signals and other biosignals (e.g. EMG), have been developed. These monitors include Bispectral Index Scale (BIS, Aspect Medical Systems, Norwood, MA, USA) (Rampil 1998), Narcotrend (MonitorTechnik, Bad Branstedt, Germany) (Kreuer *et al.* 2004), Patient State Index (Physiometrix Inc., North Billerica, MA,USA) (Prichep *et al.* 2004), Cerebral State Index (Danmeter, Odense, Denmark) (Cortinez *et al.* 2007), and Entropy (GE Healthcare, Helsinki, Finland) (Viertiö-Oja *et al.* 2004). Middle latency auditory evoked potential (MLAEP, A-line AEP monitor, Danmeter, Odense, Denmark), has also been widely studied and has proven to be a useful indicator of the depth of anesthesia, especially when light anesthesia is used (Thornton *et al.* 1989).

2.4. Measurements of analgesia during general anesthesia

Analgesia means "no pain" (Greek algos = pain; an = no). Pain is a subjective experience evoked by internal or external stimuli. Subjective perception of pain is not dependent on but may be caused by external stimuli. During general anesthesia the conscious experience of pain vanishes, although the reaction to painful surgical stimulus is reflected in a surgery-associated stress response. During surgery, the stress response is an unconscious systemic reaction to tissue injury that reflects autonomic, hormonal, and metabolic changes evoked by noxious stimulation (Desborough 2000). Prolonged surgical stress during anesthesia may cause biochemical bodily reactions, which may lead to increased morbidity and delayed postoperative recovery (Kehlet 1997). Intraoperative nociception due to improper surgical analgesia leads to measurable

reactions to noxious stimuli (Korhonen and Yli-Hankala 2009). Suppression of pain signaling pathways leads to antinociception and reduces stress responses. Here surgical stress refers to the balance between nociception and antinociception during surgery.

Several methods, including heart rate variability (Guignard 2006), suppression of photoplethysmographic pulse wave amplitude (Seitsonen *et al.* 2005, Rantanen *et al.* 2006), activation of facial muscles (Hynynen *et al.* 1985, Takamatsu *et al.* 2006), changes in skin conductivity (Storm *et al.* 2002), pupillometry (Larson *et al.* 1997), ocular microtremor (Kevin *et al.* 2002), and EEG-based monitoring (Takamatsu *et al.* 2006) have been proposed to assess the balance between nociception and antinociception.

2.4.1. Autonomic reactions

Clinically observed autonomic reactions, such as changes in breathing rate and volume, hypertension, tachycardia, sweating, lacrimation, and tearing, have been considered to indicate inadequate anesthesia (Guignard 2006). A method to standardize the measures of autonomic reactions has been proposed by Evans; this involves generating a PRST score (pressure, rate, sweating, tears) derived from measures of blood pressure, heart rate (HR), sweating, and tears to assess responsiveness (Evans *et al.* 1987, Guignard 2006). Of these signs, HR has been shown to be less consistent than blood pressure in its relation to nociception (Guignard 2006). The lack of motor response after painful stimuli does not predict the ability of an agent to affect blood pressure and HR (Zbinden *et al.* 1994).

2.4.2. Photoplethysmography (PPG)

Photoplethysmography (PPG), i.e. pulse oximetry, is primarily used to produce an estimation of the relative concentration of oxyhemoglobin in blood. PPG 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. A PPG waveform resembles that of arterial blood pressure. PPG is related to volume changes and contains information about the peripheral blood circulation, including skin vasomotion. Skin vasomotion is controlled by the sympathetic nervous system, which is activated during surgical stress. The amplitude of the PPG waveform correlates with perfusion and reflects the interplay of the left ventricular volume and the capacitance of the vasculature (Murray and Foster 1996, Korhonen and Yli-Hankala 2009). Changes in PPG amplitude (PPGA) reflect changes in the peripheral vascular bed, controlled by the sympathetic nervous system (Korhonen and Yli-Hankala 2009). Increased PPGA response (Luginbühl *et al.* 2002) and skin vasomotor response (Shimoda *et al.* 1998) have been associated with nociception during general anesthesia. In a review by Murray and Foster (1996), interpretation of the PPG in clinical monitoring is thoroughly discussed.

Several factors may cause artifacts in PPGA measurement. Movement of the probe (reflex or passive movement of the patient, coughing, tremor, train-of-four stimulus in

the measurement hand), physiological factors (hypothermia, hypovolemia, changing circulatory conditions), and pharmacological factors (anesthetics, analgesics, vasoactive drugs) may all have an effect on PPGA (Allen 2007, Korhonen and Yli-Hankala 2009).

Seitsonen and colleagues (2005) evaluated the relationship between motor reactions and physiological variables during skin incision. The normalized values of movers and nonmovers after incision were compared. The authors found that the best classification performance was achieved when Response Entropy (RE), RR interval (time between two successive beats in ECG), and PPG notch amplitude were combined. The classification performance of any single variable alone was considerably worse. Luginbühl et al. (2002) found that an absent skin vasomotor reflex (SVmR) does not predict a blunted arterial pressure or HR response to tracheal intubation and concluded that a decrease of pulse wave amplitude may be a better predictor of hemodynamic response.

2.4.3. Surgical Stress Index (SSI), Surgical Pleth Index (SPI)

Huiku and colleagues (2007) described the development of a Surgical Stress Index (SSI), later Surgical Pleth Index (SPI, GE Healthcare Finland Oy, Helsinki, Finland), based on the idea of creating a simple numerical measure of surgical stress level in anesthetized patients. SSI indicates the balance between intensity of surgical stimulation and the level of antinociception (opioid analgesia or neural blockade). SSI uses two continuous cardiovascular variables, both obtained from PPG waveforms of the peripheral oxygen saturation (SpO_2): the interval between successive hearts beats (HBI) and PPGA. When additional components were added to the algorithm, the reliability of the index was not increased further (Huiku *et al.* 2007).

To compensate for interindividual variability and intraindividual confounding factors (Allen 2007, Korhonen and Yli-Hankala 2009), a normalization with a histogram transformation was performed, decreasing the variability in HBI and PPGA not associated with surgical stress. If the distribution of a parameter is known, the transformation of the parameter results in the percentage of the measured values being smaller than or equal to the transformed value. The normalized indices range from 0 to 100 in all patients regardless of the distribution of the original parameter. A value of 50 represents an estimate of the average value of the particular parameter in an individual patient. SSI is calculated as follows: 100 - (0.7 x PPGAnorm + 0.3 x HBInorm). SSI values near 100 correspond to a high stress level, and values near zero to a low stress level. Huiku and colleagues (Huiku *et al.* 2007) have described the calculation of SSI in detail.

SSI correlated positively with the intensity of painful stimuli and negatively with the remifentanil concentration (Huiku *et al.* 2007). The study of Ahonen et al. (2007), was among the first concerning SSI as a measure of nociception/antinociception balance. The patients underwent general anesthesia maintained with a desflurane-N_2O-remifentanil or desflurane-N_2O-esmolol combination. RE and SE were targeted to 40 in both groups, and the infusions of remifentanil and esmolol were adjusted to maintain a stable hemodynamic state. During skin incision SSI increased in the esmolol group, but

not in the remifentanil group. SSI increased in both groups after the insertion of troacars, but stayed lower in the remifentanil group than in the esmolol group. Two patients in the esmolol group, but none in the remifentanil group, moved during the surgery.

Struys and colleagues (2007) found that during painful stimuli SSI correlated better with remifentanil concentration than SE, RE, PPGA, and HR, and was independent of propofol concentration, in contrast to Entropy indices.

2.5. EEG and quantitative EEG-derived indices

2.5.1. EEG during general anesthesia

German psychiatrist Hans Berger published the first systematic report of electrical signals recorded from the human scalp in 1929. He showed that electrical activity of the cortex differs between sleep and wakefulness compared with electrical activity in epilepsy (Berger 1929).

To monitor the effect of anesthetic agents, electrical signals from the cerebral cortex have been used. Routine clinical EEG measures voltage changes in the time domain with scalp electrodes. As the measured voltage differences are very small, amplifiers are needed to expand the voltage differences between surface electrodes attached to the scalp. During general anesthesia, EEG may also be used to monitor oxygen delivery to the brain and metabolic suppression of the cortex (Rampil 1998).

EEG signal has a wide frequency spectrum, ranging from 0 to 100 Hz (Martin 1991). The frequency bands used to classify EEG activity are delta (δ) < 3.5 Hz, theta (θ) 4-7.5 Hz, alpha (α) 8-13 Hz, and beta (β) >13 Hz (Niedermeyer 1998).

EEG during awareness is associated with desynchronized, low-voltage, and high-frequency patterns. In healthy adults, α-activity is a typical pattern in relaxed wakefulness with eyes closed. β-activity is associated with mental activity and attention. In healthy adults, δ-waves are seen only in sleep and also θ-activity increases in drowsiness and sleep. Fast gamma frequencies can be seen after administration of ketamine and N_2O (Freye and Levy 2005). Depression of consciousness with rising anesthetic doses eventually leads to slower EEG patterns with increased cortical synchrony (Rampil 1998).

Stockard and Bickford (1975) originally described the effect of a deepening level of anesthesia on EEG as follows:
> 1. Disorganized high-frequency activity (α- and β-activity)
> 2. Organized activity with an increase in rhythmicity and voltage (θ- and δ-activity)
> 3. Mixtures of slower (θ and δ) and faster frequencies (β) and at deeper levels increased delta activity

4. Burst suppression (with the duration of suppression becoming longer with deeper levels)
5. Suppression, inactive EEG

Several other biosignals are also present on the scalp. Electrocardiogram (ECG), EMG, and electroculogram may interfere with the EEG signal (Rampil 1998). Originally, the use of EEG as a measure of the depth of anesthesia was in the hopes of defining the anesthetic state with the reference to the EEG pattern regardless of the anesthetic agent used. However, different anesthetic agents and their combined use may cause variable changes to the EEG pattern (Clark and Rosner 1973). The anesthetics that produce both excitation and inhibition (e.g. diethyl ether, cyclopropane, sevoflurane) may cause an EEG pattern with generalized epileptiform activity (Vakkuri et al. 2000, Freye and Levy 2005). Ketamine induces an increase in fast γ-activity (40-60 Hz) of EEG, which may play a role in its CNS-stimulating effect (Hering et al. 1994, Maksimow et al. 2006).

2.5.2. Quantitative EEG-derived indices

Power spectral analysis is a standard method for quantification of the EEG. Power spectrum reflects the amount of activity in different frequency bands of the EEG signal. For power spectral analysis, EEG is digitized and Fast Fourier Transformation (FFT) is used to transform the time domain EEG to the frequency domain. Results of the FFT analysis display the EEG signal content as amplitude of power vs. frequency histogram without reducing the information within the EEG waveform. Several quantitative EEG (qEEG) variables have been calculated with FFT: absolute and relative power of each frequency band, total power of EEG, and median and spectral edge frequency (Rampil 1998).

Different methods to process the original EEG signal have been evaluated for the monitoring of the depth of anesthesia. These monitors utilize mathematically processed data from one or two EEG channels (including also other biosignals, such as EMG), measured from the forehead of the patient, and if simplified, use the loss of high frequencies and shift to low frequencies, as a measure of anesthetic drug action (Voss and Sleigh 2007). A single index most often ranging from zero to 100 is produced from several variables as a surrogate of the depth of anesthesia. Usually, a low index value indicates deep anesthesia and a high value alertness. As a measure of hypnosis during anesthesia, BIS (Glass et al. 1997), Entropy (Vakkuri et al. 2004), and AEP monitors (Struys et al. 2002) have gained acceptance. Despite their increasing popularity, the reliability and cost benefit of these monitors are still under debate (Bruhn et al. 2006).

2.5.3. Bispectral Index Scale (BIS)

Development and principles of BIS

In the 1960s, bispectral analysis was introduced in connection with ocean wave motion, atmospheric pressure changes, seismic activity, and sunspots by geophysists (Sigl and Chamoun 1994). Barnett et al. (1971) and Dumermuth et al. (1971) were the first to apply bispectral analysis to EEG signals in 1971 and described it in awake and sleeping subjects. Signal processing with bispectral analysis is capable of detecting and quantifying both linear and nonlinear signals, and is therefore suitable for quantifying subtle changes in brain electrical activity (Freye and Levy 2005). The BIS algorithm uses derivatives from conventional EEG and EMG power spectral analysis and elements of bispectral analysis, and measures the state of brain activity in relation to the depth of anesthesia (Sigl and Chamoun 1994). The BIS index is a result of a multivariate logistic regression analysis from a prospectively collected database of EEG recordings from anesthetized adult volunteers with behavioral assessments, clinically important endpoints, and hypnotic drug concentrations. The thorough review of Rampil (1998) outlines the principles of development and mode of action of BIS.

During general anesthesia BIS reflects the four following EEG components: the low-frequency feature during deep anesthesia, the high-frequency feature with beta-activation in a light anesthesia, the burst suppression ratio (BSR), and the degree of suppression. It is a weighted sum of EEG variables derived from the time domain, frequency domain, and bispectral domain. The degree of burst suppression is calculated from the time domain with two algorithms: BSR and "QUAZI". QUAZI improves burst suppression detection in the presence of a wandering baseline by incorporating information about low frequency power. A variable called BetaRatio is derived from the frequency bands of 30-47 Hz and 11-20 Hz, and a variable called SynchFastSlow is derived from the bispectral domain component of the epoch in the areas of the bifrequency plane defined by 40-47 and 0.5-47 Hz. BSR indicates the fraction of epoch length where the EEG voltage does not exceed 5 µV. (Rampil 1998).

Hypnotic titration and BIS

BIS creates a dimensionless number, scaled from 100 to zero, which reflects the depth of anesthesia; 100 represents an alert and orientated state, and zero complete electrical silence of the cerebral cortex (inactive EEG). FDA approved BIS for the monitoring of the anesthetic effect in 1996, and since 1997 BIS (Aspect Medical Systems Inc., Norwood, MA, USA) has been in clinical use. BIS was originally approved only for the monitoring of hypnosis, but has since then received an indication of reducing the incidence of intraoperative awareness during general anesthesia (FDA 2004) (Johansen 2006). BIS indices from 50 to 60 have been associated with low probability of response to verbal command, and indices between 45 and 60 indicate with a high probability unconsciousness of the patient.

Previous studies have documented that the use of BIS monitoring is connected to a reduction of the incidence of awareness (Ekman *et al.* 2004, Myles *et al.* 2004), a reduction of hypnotic drug administration (Gan *et al.* 1997), a faster recovery from anesthesia (Gan *et al.* 1997, Johansen and Sebel 2000), and a reduction of postoperative vomiting (Nelskylä *et al.* 2001). BIS cannot predict exactly when a patient's consciousness will return after general anesthesia. Neither does BIS predict a patient's movements or hemodynamic responses to surgical stimuli during general anesthesia (Johansen and Sebel 2000).

Awareness and BIS

Use of the BIS monitor has been shown to reduce the incidence of awareness during general anesthesia in both high-risk patients (Myles *et al.* 2004) and a mixed patient pool (Ekman *et al.* 2004). In a prospective cohort trial of 4945 patients (and 7826 historical controls), BIS monitoring reduced the incidence of awareness from 0.18% to 0.04%. The two patients with explicit recall in the BIS monitored group showed intraoperative BIS values above 60 (Ekman *et al.* 2004). In a prospective, randomized, multicenter study, Myles and colleagues (2004) studied 2463 patients at high risk of awareness (e.g. cardiac surgery, trauma surgery, Cesarean section). In their BIS guided group (targeted between 40 and 60), the incidences of awareness and recall were 82% lower than in randomized controls in the routine care group (2 patients vs. 11 patients). The number that needed to be treated in this population of high-risk patients was 138.

In some studies, no difference in the incidence of awareness between BIS guided and routine care patients exists (Sebel *et al.* 2004, Avidan *et al.* 2008). Avidan et al. (2008) randomized 967 patients into a BIS monitored group and 974 patients into an end-tidal anesthetic agent concentration monitored group. All patients were required to be at high risk for awareness. In addition to no statistical difference in the incidence of awareness between the groups, the use of BIS monitoring was not associated with reduced administration of volatile anesthetics (Avidan *et al.* 2008).

Other applications of BIS

A reduction of 9-43% in consumption of propofol, related to use of BIS, has been reported (Luginbühl *et al.* 2003, Gurses *et al.* 2004). Results on consumption of sevoflurane and desflurane are contradictory. A significant reduction of 20-30% in consumption of sevoflurane and desflurane has been described in some studies (Yli-Hankala *et al.* 1999, White *et al.* 2004) while others indicate no reduction (Luginbühl *et al.* 2003, Bruhn *et al.* 2005). A meta-analysis by Liu and colleagues (Liu, SS 2004) showed a decrease of 19% in all hypnotics if BIS was used during ambulatory anesthesia.

To date, BIS has also been applied to or at least evaluated for the uses other than those originally approved. It has been studied in pediatric anesthesia (Davidson *et al.* 2004, Klockars *et al.* 2006), detection of brain death (Vivien *et al.* 2002) and prediction of

neurological outcome after neurological trauma and cerebral ischemia (Fabregas *et al.* 2004). It has also been investigated as a monitor of sedation level in the ICU (Shapiro 1999). Renna and colleagues (Renna *et al.* 2003) reported that patients with dementia (caused by Alzheimer disease or multiple infarcts) had lower than normal "awake" BIS, and the index readings correlated with the Mini-Mental State Test.

In conclusion BIS seems to perform best as a reliable depth-of-anesthesia monitor during propofol anesthesia. It has some limitations during sevoflurane and enflurane anesthesia and does not perform at all with single agent hypnotic techniques with ketamine, dexmedetomidine, N_2O, and xenon (Johansen 2006).

2.5.4. Entropy

Background

Entropy was defined already in 1948 in the information theory by Shannon (1948a) and applied to a power spectrum of a signal in 1984 by Johnson and Shore (1984). When used in the context of information theory and signal analysis, entropy reflects irregularity, uncertainty, and complexity of a signal (Shannon 1948a, 1948b). As a physical idea, entropy is proportional to the logarithm of the number of microstates available in a thermodynamic system (Viertiö-Oja *et al.* 2004).

During deep anesthesia EEG includes only a few frequency components compared with the more variable mixture of high, medium, and low frequencies when awake or drowsy or with lighter anesthesia. This led to speculation that one method to gauge the depth of anesthesia might be to measure the degree of regularity of EEG with an entropy algorithm. Pincus (1991) suggested using approximate entropy for the analysis of physiological signals in 1991, and Bruhn (2001) applied it to the analysis of EEG. Approximate entropy measures the logarithmic likelihood that runs of patterns remain similar in the next consecutive period of comparison, and is applicable for short time series. However, consecutive EEG epochs are not statistically independent, which means that the requirements for approximate entropy calculation are not rigorously met (Schwilden 2006).

Spectral entropy originates from a measure of information called Shannon's entropy (Shannon 1948a, 1948b). To obtain spectral entropy, EEG signal is first subjected to Fast Fourier transformation to calculate the power spectrum. Shannon's entropy is then applied to the power spectrum to assign a specific value to each frequency present. The sum of these values is defined as spectral entropy (Viertiö-Oja *et al.* 2004). Spectral entropy is dependent on sampling frequency and windowing (Rezek 1998), but independent of the frequency components of the signal (Viertiö-Oja *et al.* 2004). During general anesthesia both the approximate and the spectral entropy decrease with increasing depth of anesthesia (Rezek 1998).

Time-frequency balanced spectral entropy

M-ENTROPY™ (hereafter Entropy) (GE Healthcare Finland, Helsinki, Finland) is an online depth-of-anesthesia monitor based on calculation of spectral entropy. The power spectrum is first calculated via Fourier transformation. To calculate the spectral entropy of an 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. Shannon's function (Shannon and Weaver 1949) is then applied to the normalized power spectrum of the specific frequency range. Finally, the resulting entropy value is adjusted between zero and one by dividing by logN, where N represents the number of frequency components. Zero corresponds to complete regularity and one to maximal irregularity. (Viertiö-Oja *et al.* 2004).

The original entropy value is subjected to a nonlinear transformation with a monotonous spline function to enhance resolution in a clinically interesting level of anesthesia. The steepness of the spline function is maximal at the levels of loss of consciousness, during a clinically adequate depth of anesthesia, and while a patient is wakening. As a result of the spline function, the original spectral entropy ranging from zero to one is changed to a scale from zero to 100. For automatic artifact analysis and rejection, each signal is sliced to epochs of 0.64 s. Each epoch is observed, and epochs containing artifacts are automatically omitted from the final analysis.

The random-appearing EEG signal consists of frequencies between zero and to over 100 Hz (Martin 1991). The same frequency band also contains artifacts caused by EMG, ECG, and electroculogram (Rampil 1998). Changing the time window used to assess each frequency component individually optimizes the response time of the Entropy algorithm. EEG sampling frequency of 400 Hz is used in the Entropy monitor. For frequencies of 32-47 Hz, a time window of 1.92 s is used, and for frequencies of 0-2 Hz 60.16 s. The time window for frequencies of 2-32 Hz lies between these two extremes. Viertiö-Oja et al. (2004) have described the calculation of Entropy index in detail.

State Entropy and Response Entropy

Entropy collects a 1-channel original biosignal from a patient's forehead with a self-adhesive three-electrode Entropy™ -sensor (GE Healthcare Finland, Helsinki, Finland). The collected biosignal contains both EMG and EEG signals from the frontotemporal region of the head. During anesthesia the total power of the EEG signal remains mainly within 0.5-30 Hz (Freye and Levy 2005). However, when an NMDA antagonist is used, high-frequency γ-waves of 40-80 Hz are also seen (Maksimow *et al.* 2006). The EMG signal has a distribution from zero to over 200 Hz (Goncharova *et al.* 2003).

The analysis of the original the EEG results in two numbers: State Entropy (SE) and Response Entropy (RE). SE is calculated from frequency bands of 0.8-32 Hz (Viertiö-Oja *et al.* 2004), which under general anesthesia consists mainly of EEG, although it also includes EMG (Freye and Levy 2005). The time window for calculation of SE is between 15 and 60 s. During anesthesia SE reflects primarily the function of cortical

neurons of the patient. RE is calculated from a frequency band of 0.8-47 Hz. The shortest time window for RE calculation is 1.92 s, which is used for entropy calculation between frequencies of 32 and 47 Hz, and the longest 15.36 s. Theoretically, SE measures EEG activity, and RE provides the combined information of EEG and frontal electromyography (fEMG). (Viertiö-Oja *et al.* 2004). However, it should be noted that during voluntary activation the typical frequency of motor units ranges between 5 and 20 Hz. This means that SE also contains EMG frequencies, although less than RE.

Entropy parameters range from zero (suppression of EEG) to 100 (alert) for RE and from zero to 91 for SE. The difference between RE and SE corresponds to the contribution from the fEMG-dominated high-frequency band (Viertiö-Oja *et al.* 2004). During general anesthesia fEMG activity may increase because of intensive noxious stimuli if analgesia is insufficient or at the end of surgery prior to awakening during light anesthesia (Paloheimo 1990). As an advantage for the short window length in the frequency band of 32-47 Hz, the algorithm allows fast detection of impending arousal related to increased fEMG activity. When no fEMG activity is present, SE and RE are equal. The facial muscles have been shown to be more resistant to neuromuscular blocking agents (NMBAs) than the muscles of the hand (Paloheimo 1990). In the presence of intense noxious stimuli, the facial muscles are activated, even if 80-90% of the postjunctional acetylcholine receptors are blocked (Tammisto *et al.* 1983).

During Entropy monitoring, burst suppression periods are detected with a method described in detail by Särkelä et al. (2002). BSR describes the relative amount of suppressed EEG within a one-min time window. During burst suppression a one-min time window is used for all frequency components of the SE and RE values. Entropy detects the suppressed EEG period and considers EEG to be a perfectly regular signal with zero entropy. (Viertiö-Oja *et al.* 2004)

Entropy and state of consciousness and unconsciousness

Entropy has been shown to be capable of differentiating between the states of consciousness and unconsciousness (Schmidt, GN *et al.* 2004, Vakkuri *et al.* 2004, Takamatsu *et al.* 2006, White *et al.* 2006). In the study of Vakkuri and colleagues (2004), 70 patients were anesthetized either with propofol, sevoflurane, or thiopental, and loss and regaining of consciousness were tested. Sensitivity, specificity, and prediction probability (Pk) for consciousness were high, and similar for SE, RE, and BIS. Increased RE indicated emergency from anesthesia 11-12 s earlier than SE and BIS.

Schmidt et al. compared (2004) Entropy and BIS in 20 patients anesthetized with a propofol-remifentanil combination. The authors found that during induction SE, RE, and BIS correlated with the OAAS values, but no significant difference in Pk values was found between these indices. Pk values of SE, RE, and BIS were high and similar also during emergence from anesthesia. White and colleagues (2006) reported similar results for SE, RE, and BIS in the detection of consciousness during propofol-desflurane anesthesia. During the maintenance of anesthesia, all indices responded similarly to changes in propofol and desflurane concentrations. The association between

SE and regional cerebral blood flow during propofol and sevoflurane anesthesia was evaluated in healthy volunteers. Both drugs induced a significant and similar reduction in SE and cortical and global cerebral blood flow measured with positron emission tomography. (Maksimow *et al.* 2005).

Dexmedetomidine, a highly selective α_2 –adrenoreceptor agonist, is indicated for short-term sedation of ICU patients. It produces a sleep-like state of sedation that mimics normal physiologic sleep. In healthy subjects, dexmedetomidine sedation produced EEG activity (sleep spindles) similar to that in normal sleep (Huupponen *et al.* 2008). Dexmedetomidine sedation has been associated with decreased BIS values, comparable with those achieved in sedation with propofol (Venn and Grounds 2001). Maksimow and colleagues (2007) showed that SE values decreased during dexmedetomidine sedation with an increasing dexmedetomidine dose in healthy volunteers. Pk and sensitivity values discriminated well between consciousness and unconsciousness.

Laitio and colleagues (2008) studied 17 healthy volunteers to evaluate the performance of BIS and Entropy monitors during xenon anesthesia. They found that BIS, SE, and RE showed a delay to detect loss of response. However, all indices differentiated between conscious and unconscious states with high prediction probability values. No difference between these two monitors was found.

Entropy and noxious stimuli

Vanluchenne and colleagues (2004) investigated the ability of SE, RE, and BIS to predict loss of response to verbal command and noxious stimuli. All indices detected loss of verbal command accurately, but at 100% sensitivity BIS performed better. Sensitivity and specificity for detection of loss of verbal commands decreased for all indices along with increased effect-site remifentanil-infusion. None of the indices predicted loss of response to noxious stimuli accurately.

Wheeler and colleagues (2005) evaluated the difference between RE and SE by subtracting SE values from RE values (RE-SE) caused by fEMG activation during a painful stimulation. An increase in the RE-SE as a response to noxious stimuli occurred more often in patients anesthetized with 0.8% isoflurane than in patients anesthetized with 1.4% isoflurane, and this difference was found with and without NMBAs. Increases in HR and mean arterial pressure were connected to an increased RE-SE difference. In a study by Takamatsu et al. (2006), 40 patients under sevoflurane anesthesia were evaluated. SE and RE were significantly lower in patients who did not move in response to electrical stimuli or skin incision. SE, RE, and BIS increased significantly with the increasing intensity of electrical stimulation. Tetanic stimuli caused an increase in the RE-SE difference, except at 2.5% sevoflurane. However, Valjus and colleagues (2006) noted that the RE-SE difference stayed small during surgery with both propofol-esmolol and propofol-remifentanil anesthesia. HR, blood pressure, and propofol requirement were all increased in the esmolol group relative to the remifentanil group. In the esmolol group, every patient moved in response to surgical stimuli, in contrast to none of the patients in the remifentanil group. Based on

these results, the RE-SE difference seems not to be a reliable measure of the level of analgesia.

Entropy and consumption of anesthetics

A reduced consumption of anesthetics during the general anesthesia related to Entropymonitoring has been reported (Vakkuri *et al.* 2005, Aimé *et al.* 2006). Vakkuri et al. (2005) investigated a total of 368 patients anesthetized with propofol-alfentanil-nitrous oxide. In the Entropy monitored group, a reduced consumption of propofol and hastened early recovery from anesthesia compared with the standard anesthesia group were reported. Aimé and colleagues (2006) studied 140 patients undergoing general anesthesia with propofol, sevoflurane, and sufentanil. Sevoflurane concentration was adjusted according to clinical variables in the control group, and in the BIS and Entropy guided groups (either BIS or Entropy, but not both in the same patient) an index value of 40-60 was targeted. Patients in the BIS and Entropy guided groups required 29% less sevoflurane (p<0.03) than patients in the control group. No difference was found between BIS and Entropy monitored groups. Recovery from anesthesia (eye opening, tracheal extubation) did not differ between the three groups.

Entropy and children

EEG changes in children as the brain matures. Since the frequency of the awake dominant background activity increases with age, this might have an influence on the performance of EEG-based monitors like BIS, which specifically include analysis of power–frequency relationships in their algorithm. As Entropy relies on a different derivative of the EEG, it is possible that the age-related limitations found with BIS may not be seen with entropy (Davidson *et al.* 2005b). Davidson et al. (2004) demonstrated that after awakening from isoflurane-nitrous oxide anesthesia, Entropy was higher than during anesthesia for all age groups. Pre-awakening Entropy was higher than Entropy during general anesthesia for children (1-12 years). This was not as apparent in infants (under 1 year of age). A strong correlation existed between BIS and Entropy for children. The correlation was less evident for infants. In two other studies (Davidson *et al.* 2005b, Klockars *et al.* 2006), children anesthetized with sevoflurane were evaluated. BIS and Entropy were inversely related to sevoflurane concentration for children aged 1-12 years. The changes in these indices were less definite for infants.

To date, only a few studies have dealt with the use of BIS and Entropy monitors in children. Previous studies considered BIS and Entropy monitors as suitable tools for the measurement of depth of anesthesia in children older than one year, but did not recommend them for infants (Davidson *et al.* 2005b, Klockars *et al.* 2006) However, these monitors have thus far been evaluated only during isoflurane and sevoflurane anesthesia. More studies with different anesthetic agents are needed.

2.5.5. Artifacts, EEG recording, and their effects on BIS and Entropy monitoring

EMG

The EMG signal has a wide, noise-like spectrum, which during general anesthesia typically dominates at frequencies higher than 30 Hz (Viertiö-Oja *et al.* 2004), but may also exist at frequencies from zero to over 100. Interference from EMG activity has been documented to elevate BIS in patients not receiving NMBAs. Vivien and colleagues (2003) evaluated 45 ICU patients who were continuously sedated with midazolam and sufentanil. BIS and EMG activity decreased significantly following administration of NMBAs. In another study, Vivien and colleagues (2002) showed that as EMG activity may be present even in brain-dead patients and high BIS values fell dramatically when NMBAs were administered, the artifactual increase in BIS can be falsely interpreted as cerebral electrical activity. Entropy monitoring and the possible artifacts related to this have not been investigated in brain dead patients before the present study.

Messner and colleagues (2003) evaluated the effect of EMG activity on BIS. When alcuronium and succinylcholine were administered to unanesthetized volunteers (no other drugs used), BIS decreased to a minimum of 9 (range 9-64). In a study by Liu et al. (Liu, N *et al.* 2005), patients received target-controlled infusions of propofol and remifentanil until loss of consciousness. After loss of consciousness, either a bolus dose of atracurium or placebo was administered. In lightly anesthetized patients, administration of NMBA decreased BIS and RE, but not SE.

Electrical device

Electrical appliances may interfere with EEG recording. These interferences may evolve from an infusion or motor-driven pump, a mechanical ventilator, a dialysis machine, a scan light, or a screen for patient monitoring (Freye and Levy 2005). Electrocautery, an atrial pacer, a warming blanket, and an endoscopic shaver have been shown to directly affect BIS monitoring (Dahaba 2005). During electrocautery no EEG recording can be done with any device because of large artifacts (Freye and Levy 2005). However, the hardware of Entropy is claimed to tolerate substantial electrocautery because of automatic artifact rejection. During Entropy monitoring a power of frequency range of 200-1000 kHz is continuously measured, and if electrocautery has affected the EEG signal, the epoch will be rejected from further analysis (Viertiö-Oja *et al.* 2004). White et al. (2006) reported that Entropy indices were significantly less influenced by electrocauterization during surgery than BIS indices (12% vs. 62%).

During Entropy monitoring the high sampling rate of the EEG signal ensures that sharp peaks associated with a pacer (and with electrocardiography, ECG) may be detected and removed from the underlying EEG signal (Viertiö-Oja *et al.* 2004). A power line electrical noise of 50-60 Hz may be identified on the original EEG and removed by switching off the causative electrical device (Freye and Levy 2005).

Biological artifacts

Eyelid movements, blinks, muscle activity during swallowing, movements of the body, muscle tremor, and sweating are possible causes of biological artifacts during EEG monitoring (Freye and Levy 2005). Different clinical conditions, such as hypoglycemia, hypovolemia, cerebral ischemia, cardiac arrest, and hypothermia, have an effect on the EEG and have been reported to affect BIS readings (Dahaba 2005). Postictal state, neurological disorders (Alzheimer, cerebral palsy), old age, and low-voltage EEG modify BIS values (Dahaba 2005).

2.5.6. Drug effects in EEG (interfering with the use of the derived indices)

Ketamine

Ketamine is an NMDA antagonist that produces dissociative anesthesia. It has been suggested that BIS (Hirota *et al.* 1999) and Entropy (Hans *et al.* 2005) cannot reliably assess the hypnotic component of anesthesia if racemic ketamine is used. Maksimow et al. (2006) evaluated the effects of S-ketamine on EEG in healthy volunteers. SE and RE decreased from baseline values during ketamine anesthesia. However, inter- and intraindividual variations in SE and RE were high, and their specificity in indicating unconsciousness was poor. Compared with propofol, S-ketamine produced more high-frequency EEG activity in the gamma band. During ketamine anesthesia the relative power of 20-70 Hz EEG activity was associated with high SE and RE indices, and fast gamma spindles were detected in visual analysis in all subjects. During propofol anesthesia no gamma spindles were detected. Compared with propofol, S-ketamine increased the amount of high-frequency EEG activity, while inducing less low-frequency activity. The authors suggested, that the differences in these low- and high-frequency bands may explain why Entropy is adequate in monitoring the depth of propofol anesthesia, but not of ketamine anesthesia (Maksimow *et al.* 2006).

Nitrous oxide

Nitrous oxide (N_2O) is an NMDA antagonist that produces a sympatholytic effect. A paradoxical decrease in the BIS index has been described after discontinuation of N_2O. This might be related to withdrawal-suppression, which has been described in connection with N_2O. After sudden discontinuation of N_2O, low-frequency δ- and θ-waves may occur diffusely in EEG (Henrie *et al.* 1961). This pattern is similar to the EEG seen in deep anesthesia. In the study of Rampil and colleagues (1998), different concentrations of N_2O were administered to healthy volunteers. A change from a higher to a lower concentration of N_2O produced transient slowing of the EEG signal. At the highest concentration of N_2O (50% atm), BIS did not differ significantly from baseline readings.

Sevoflurane

Sevoflurane is a short-acting volatile anesthetic that has gained acceptance especially for its suitability in mask induction. However, epileptiform activity related to sevoflurane anesthesia has been reported in EEG in both healthy adults and children (Yli-Hankala *et al.* 1999, Jääskeläinen *et al.* 2003) and also in patients with epilepsy (Iijima *et al.* 2000). The epileptiform activity has been related particularly to mask induction (Yli-Hankala *et al.* 1999, Vakkuri *et al.* 2001) and deep levels of anesthesia (1.5-2.0 MAC) (Jääskeläinen 2003). These findings indicate that epileptogenicity of sevoflurane might not be associated with changes in the level of anesthesia, instead being dependent on the dose of sevoflurane.

In a recent study, Sonkajärvi and colleagues (2009) showed that epileptiform patterns, spikes, polyspikes, and periodic epileptiform discharges were found in children anesthetized with 8% sevoflurane mask induction. These EEG findings were associated with an increase in HR, but no motor activity was noticed. An EEG was recorded with a 10- to 20-electrode system with a recording band of 0.016-70 Hz. The spikes and polyspikes had frontal multifocal maxima and might have been missed had only forehead electrodes of EEG-based depth-of-anesthesia monitors been used.

2.6. Neuromonitoring in the intensive care unit

2.6.1 Noninvasive methods

EEG

Different EEG characteristics have been related to ischemic brain damage. Suppression of EEG (Theilen *et al.* 2000), lack of EEG reactivity (Gutling *et al.* 1995), reduced alpha variability (Vespa *et al.* 2002), and generalized epileptiform activity (Young and Doig 2005) have been related to poor neurological recovery. However, the significance of individual EEG characteristics is partly unclear, as in many studies they have been considered only as combined groups of malign or benign phenomena (Wijdicks *et al.* 2006). EEG characteristics associated with a poor outcome after cardiopulmonary resuscitation seem to include EEG suppression and generalized epileptiform activity (Wijdicks *et al.* 2006), but at which stage of ICU treatment and how soon after resuscitation these characteristics indicate poor outcome are unknown.

The Observer's Assessment of Alertness/Sedation Scale (OAA/S) was used when the BIS algorithm was developed, and numerous studies have demonstrated the tight correlation between BIS, hypnotic drug concentration, and OAA/S for perioperative sedation. These studies suggest that BIS ranging between 65 and 80 is an acceptable level of loss of conscious information processing and recall during sedation (Iselin-Chaves *et al.* 1998, Kearse *et al.* 1998, Struys *et al.* 2003). Good correlations between BIS and Sedation Agitation Scale (SAS) (de Wit and Epstein 2003), BIS and Ramsay score (Mondello *et al.* 2002, Riess *et al.* 2002), BIS and Richmond Agitation-Sedation Scale (RASS) (Deogaonkar *et al.* 2004), and BIS and Glasgow Coma Scale (GCS) (Deogaonkar *et al.* 2004) have been reported during sedation.

Only a few studies have evaluated the ability of BIS to predict the outcome of ICU patients. These studies have mostly investigated traumatic head injury or cardiac arrest patients. Fabregas et al. (2004) investigated the relation between BIS and the probability of recovering consciousness in 25 acute brain-injured patients. Significantly lower BIS values were found in brain-injured patients who did not regain consciousness compared with those who recovered consciousness.

Myles et al. (2009) investigated the prognostic ability of BIS in unconscious patients with severe hypoxic-ischemic brain injury who needed emergency surgery because of their head trauma. Clinical examination was performed and BIS recorded before and during surgery. An abnormal BIS value (below ten) was indicative of poor neurological outcome. The false-positive rate (FPR) was lower for abnormal BIS and absent pupillary response than for clinical judgment. However, none of these methods was 100% specific. Evaluation of prognosis after serious hypoxic-ischemic injury should not be based solely on BIS monitoring.

In the recent study of Seder et al. (2009), BIS and suppression ratio (SR) were evaluated as predictors of neurological outcome during hypothermia treatment after cardiac arrest. BIS and SR of 97 patients were compared with the discharge Cerebral Performance Category (CPC). Forty percent were allocated to the good outcome group (CPC 1-2). BIS (measured after the first dose of NMBA) was higher in patients with good outcome, and BIS below 22 predicted poor outcome. An SR of 48 or more predicted poor outcome. BIS and SR predicted outcome better than return of spontaneous circulation (ROSC).

Entropy for monitoring and sedation

Only the two studies concerning Entropy as a sedation monitor in ICU patients have been published before the present studies. Walsh et al. (2008) first aimed to assess whether Entropy could be used as a measure of sedation level in critically ill patients. Thirty mechanically ventilated patients receiving continuous sedation (propofol or midazolam) were prospectively evaluated. Entropy monitoring continued up to 72 h. The level of consciousness was evaluated every 30 min using a modified Ramsay

scoring system. The scoring system was modified to standardize the stimuli by including a tetanic stimulus at deep sedation levels. The median SE and RE decreased when the Ramsay score increased, but wide variation occurred, especially in the Ramsay 4-6 categories. Discrimination between different sedation scores and between lighter (Ramsay 1-3) vs. deeper (Ramsay 4-6) sedation ranges was found to be inadequate, suggesting inadequate ability to distinguish lighter and deeper sedation from each other. A frequent "on-off" effect (entropy values changed rapidly from low to high and vice versa) was noticed. This effect was particularly present at deeper sedation levels. The on-off effect occurred for both RE and SE, and was associated with fEMG activity. High Entropy values during deeper sedation were strongly associated with simultaneous high relative fEMG powers. Based on that preliminary study of Entropy as a sedation monitor, the authors concluded that Entropy does not discriminate sedation state adequately for clinical use in ICU patients. As in most of the BIS-studies, frontal EMG activity was found to be a major confounder in clinical sedation ranges.

In the study of Haenggi and colleagues (2009), BIS and Entropy discriminated states with very deep, deep to moderate, and no sedation with similar Pk. However, inter- and intraindividual variability of Entropy and BIS indices was high. Hence, the authors concluded that determination of sedation levels by BIS and Entropy precludes defining a target range of values in critically ill patients.

Transcranial Doppler ultrasonography

Aaslid and colleagues (1982) introduced Transcranial Doppler ultrasonography (TCD) in 1982 as a noninvasive, continuous technique to monitor cerebral blood flow velocity in basal cerebral arteries through the intact cranium. TCD is based on a pulsed Doppler ultrasonic beam of a frequency of 2 MHz that crosses the skull at "window-points" and is then reflected back from the erythrocytes. Temporal, orbital, and foramen magnum "windows" can be used to insonate the cerebral arteries. The most commonly used artery is the middle cerebral artery (MCA), which is easy to find through the temporal window (Moppett and Mahajan 2004). An adequate window is absent in only 8% of patients (Itoh *et al.* 1993). Different analyses of blood flow velocity have been conducted. Of the available indices, the pulsatility index (Gosling and King 1974) is probably the most frequently used. The pulsatility index normally ranges from 0.6 to 1.1. It reflects resistance in the distal vessels and elasticity of the vessel wall. HR, arterial pressure, vascular compliance, and arterial oxygen and carbon dioxide tension may have an influence on the pulsatility index. (Czosnyka *et al.* 1996, Aggarwal *et al.* 2008).

TCD has been used to detect of high-velocity states such as vasospasm or hyperemia. Flow velocities more than 120 cm/s in MCA have been considered significantly high (Aaslid *et al.* 1984). High velocity after head trauma is an independent predictor of poor outcome (Zurynski *et al.* 1995). The estimation of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) from TCD waveform analysis has been reported to correlate with direct ICP and CPP measurements (Sidi and Mahla 1995, Schmidt, EA *et al.* 2001, Aggarwal *et al.* 2008). Hadani and coworkers (1999) found reduced or absent

diastolic flow, reverberant flow, and short systolic spikes in TCD to be related to brain death. These authors reported 100% specificity and 96% sensitivity.

Other noninvasive neuromonitoring methods

Somatosensory evoked potential (SEP) consists of the responses of subcortical and cortical neurons to stimulation of peripheral nerve trunks. Bilaterally absent short latency SEP (N20) waves to median/ulnar nerve stimulation predict permanent coma with a specificity of 100% in patients resuscitated from cardiac arrest, and this is not affected by hypothermia treatment (Tiainen *et al.* 2005). Adults in coma caused by hypoxic-ischemic encephalopathy showing absent SEPs have been reported to have less than a 1% chance of awakening (Robinson *et al.* 2003).

Mismatch negativity (MMN) is an automatic event-related brain response to a deviant stimulus, alternating with the standard tone. The response has been reported to correlate with recovery from the vegetative state after severe brain injury (Wijnen *et al.* 2007). In the prospective study of Fischer and colleagues (2004) with 346 comatose patients (caused by stroke, trauma, anoxia, neurosurgery, or encephalitis), the prognostic value of late auditory (N100) and cognitive evoked potentials (MMN) were analyzed. After a 12-month follow-up period, pupillary reflex and N100 proved to be the strongest predictive factors for awakening. If also MMN was present, comatose patients never moved to a permanent vegetative state. In the later study of Fischer et al. (2006), 62 comatose patients resuscitated from out-of-hospital cardiac arrest were evaluated. Patients with abolished SEP or MLAEP did not regain consciousness (100% specificity). All patients in whom MMN was present awakened with 100% specificity. Based on these studies, it may be concluded that when MMN is present it predicts awakening from coma with a high probability, and nonawakening when MMN and pupillary reflex are absent or cortical SEPs are abolished. Further studies comparing MMN, SEP, and EEG-derived indices are needed.

Near-infrared spectroscopy (NIRS) estimates the regional changes in cerebral oxygenation and is based on the ability of light waves of near-infrared wavelength (700-1000 nm) to pass through the scalp, skull, and brain to a depth of a few centimeters. (Owen-Reece *et al.* 1999). In head-injured patients, NIRS has been reported to be more specific and more sensitive than jugular bulb venous oxygen saturation ($SjVO_2$) (Kirkpatrick *et al.* 1995) and to correlate with cerebral perfusion (Dunham *et al.* 2002). However, the inability of NIRS to distinguish between intra- and extracranial changes in blood flow and oxygenation has limited its use in clinical practice (Bhatia and Gupta 2007a).

2.6.2. Invasive methods

Intracranial pressure (ICP)

ICP is the pressure within the cranial vault relative to atmospheric pressure (Bhatia and Gupta 2007b). ICP monitoring is recommended by the European Brain Injury Consortium for patients with severe brain injury (Maas *et al.* 2000). It can be measured intraventricularily, intraparenchymally, extradurally, or subdurally. Intraventricular catheters allow direct measurement by insertion of a catheter into one of the lateral ventricles, and they are considered the "golden standard" of brain monitoring in ICU for brain trauma patients (The Brain Trauma Foundation 2000). An average ICP above 25 mmHg over the whole period of monitoring doubles the risk of death after severe head injury (Czosnyka and Pickard 2004).

In neurosurgical units, where ICP is usually monitored, twofold lower mortality has been reported compared with general ICUs, where it is not monitored (Patel *et al.* 2003). On the other hand, Cremer et al. showed that among survivors beyond 24 h following severe brain injury, patients treated with ICP targeted intensive care did not have a better outcome than patients treated based on clinical observations and computed tomography (CT) findings (Cremer *et al.* 2005). Robertson et al. (1999) showed a decrease in ischemic insults in CPP-oriented therapy, but also an increase in respiratory complications compared with ICP-oriented therapy. No difference was found in overall neurological outcome between ICP- and CPP-guided groups.

Other invasive neuromonitoring methods

Venous oxygen saturation in the jugular bulb (SjVO$_2$) provides an estimate of global oxygen delivery. It also represents the relationship between cerebral blood flow and metabolism, enabling detection of hypo- and hyperperfusion (Dunn *et al.* 2006). However, SjVO$_2$ is a global measure of cerebral oxygenation, and regional ischemia may be missed (Gupta 2002). Both abnormally high and low SjVO$_2$ values after traumatic brain injury have been associated with poor outcome (Robertson *et al.* 1995, Macmillan *et al.* 2001).

Thermal diffusion flowmetry is based on the thermal conductivity of cortical tissue, which varies proportionally with cerebral blood flow. It has been reported to be more sensitive than TCD in detecting reversible vasospasm in patients with subarachnoid hemorrhage (Vajkoczy *et al.* 2001). Laser Doppler flowmetry measures the local circulatory blood flow. It has been used to assess autoregulation, carbon dioxide reactivity, and responses to therapeutic interventions (Kirkpatrick *et al.* 1996), and also to diagnose ischemia (Kirkpatrick *et al.* 1994).

Cerebral microdialysis measures the concentration of chemicals (molecules below 20 kDa) found in the extracellular space of the brain. Substances usually measured are energy-related metabolites (glucose, lactate, pyruvate, adenosine, xanthine),

neurotransmitters (glutamate, aspartate, γ-aminobutyric acid), markers of tissue damage or inflammation (glycerol, potassium, cytokines), and exogenous substances (drugs) (Gupta 2002). Cerebral microdialysis has been used mainly for research purposes. However, the consensus meeting on cerebral microdialysis recommended its use in brain injury patients, when ICP or CPP monitoring is needed (Hillered *et al.* 2005).

Measurement of brain tissue oxygenation involves insertion of microsensors into brain parenchyma. Commercially available microsensors measure directly brain tissue gases, either measuring brain tissue oxygen tension or partial pressures of oxygen, and carbon dioxide, or pH (Bhatia and Gupta 2007a). Brain tissue oxygen partial pressure less than 8-10 mmHg is related to ischemia (Kett-White *et al.* 2002), brain tissue carbon dioxide more than 60 mmHg to increased risk of vasospasm in patients with cerebrovascular disease (Charbel *et al.* 2002), and pH below 7 to increased risk of mortality in head injury patients (Gupta *et al.* 2004).

2.6.3 Laboratory parameters

Various blood markers have been evaluated for assessing neurological prognosis after cardiac arrest. Of these markers, neuron-specific enolase (NSE) and S-100B protein have gained acceptance. These markers are not secreted into extracellular fluid by intact cells, but are set free after destruction of cells with neuronal differentiation. The concentration of these markers in the blood has been assumed to be proportional to the extent of hypoxic brain injury after cardiac arrest. NSE is a gamma isomer of glycolytic enzyme enolase and is located in the cytoplasm of neurons and cells with endocrine differentiation (Schmechel *et al.* 1978). The high molecular weight of 78 kDa makes NSE unlikely to leave the cytoplasm unless brain injury occurs. It is composed of two γ-subunits and has a biological half-life of 24 h. Increased serum NSE levels have been reported after cardiac arrest (Rosen, H *et al.* 2001, Tiainen *et al.* 2003), stroke (Cunningham *et al.* 1991), and brain injury (Skogseid *et al.* 1992).

S-100B protein is a calcium-binding protein with two subtypes. The αβ-subtype is found in astroglial cells, and the ββ-subtype mainly in astroglial and Schwann cells, but has also been demonstrated in some neoplasms and in melanocytes, adipocytes, and chondrocytes (Zimmer *et al.* 1995). The molecular weight of the S-100B protein is 21 kDa, and its biological half-life of 0.5 h (Jonsson *et al.* 2000). Increased levels of serum protein S-100B have been reported in patients after traumatic brain injury (Elting *et al.* 2000), stroke (Missler *et al.* 1997, Elting *et al.* 2000), cardiac arrest (Rosen, H *et al.* 1998, Tiainen *et al.* 2003), and cardiac surgery (Jonsson *et al.* 2001).

Although several studies exists of NSE and S-100B in comatose patients, only a few controlled, randomized studies have been done on patients surviving from cardiac arrest and treated with mild therapeutic hypothermia. In a substudy of the European hypothermia after cardiac arrest (HACA) trial, Tiainen and coworkers (2003) analyzed NSE and S-100B values in 34 hypothermia-treated cardiac arrest patients and in 32 normothermic cardiac arrest patients. They found that the levels of NSE, but not the levels of S-100B, were lower in hypothermia-treated patients than in normothermia-treated patients. In 88% of the hypothermia-treated patients, NSE decreased between 24

and 48 h; the corresponding proportion in normothermia-treated patients was 50%. The decrease in NSE values was associated with survival, recovery of consciousness, and good neurological outcome. In the study of Tiainen et al., no significant difference was present in S-100B values between 24 and 48 h. On the other hand, Hachimi-Idrissi and coworkers (2005) found that S-100B decreased significantly between the time of admission and at 24 h after cardiac arrest in patients treated with hypothermia.

In the study of Rosen and coworkers (Rosen, H *et al.* 2001), S-100B peaked already within 24 h of cardiac arrest, and levels elevated above 0.217 µg/l on day 2 after ROSC indicated severe neurological injury and predicted poor outcome with a 100% positive predictive value (PPV). In the same study, a serum level of NSE above 23.3 µg/l had a 100% PPV for coma, permanent vegetative state, or death. Zandbergen et al. (2006) showed that 60% of patients resuscitated after cardiac arrest had NSE more than 33 µg/l on day 1 to day 3. All of these patients had a poor neurological outcome. The cut-off point for an FPR of zero has been difficult to define, and variation between 20 and 65 µg/l has been reported (Wijdicks *et al.* 2006). Attempts have also been made to define cut-off values for S-100B in the same patient material. Zandberger and coworkers (2006) reported the median FPR of zero to be 5%, but in other studies this has ranged between zero and 54% (Martens *et al.* 1998, Rosen, H *et al.* 1998, Tiainen *et al.* 2003).

Little research has been performed on survivors of cardiac arrest treated with mild therapeutic hypothermia. In addition, the results of the previous studies are partly contradictory concerning the cut-off values of blood markers. The present study was conducted to evaluate whether blood markers correlate with the EEG-derived indices as early prognostic markers after cardiac arrest.

2.7. Cardiac arrest and therapeutic hypothermia

Cardiac arrest is associated with the loss of cerebral perfusion, which leads to anoxic brain injury or post-resuscitation encephalopathy (Maramattom and Wijdicks 2005). Most of these patients have a poor prognosis for recovery (Booth *et al.* 2004). Neurological recovery is primarily determined by the extent of hypoxic-ischemic encephalopathy that develops during and after circulatory arrest. After ROSC, the following reoxygenation may lead to additional inflammatory reactions that can continue for several days, leading to the concept of global ischemia-reperfusion injury. Techniques directed to minimize the inflammatory response and cell death during the reperfusion period may improve the neurological outcome after cardiac arrest (Castren *et al.* 2009).

Based on clinical, randomized trials, therapeutic hypothermia after cardiac arrest has been shown to be beneficial with regard to neurological prognosis (Bernard *et al.* 2002, Hypothermia after Cardiac Arrest Study Group 2002). Several studies have shown mild (body temperature 32-34°C) therapeutic hypothermia to be a safe therapy, with only a few complications, and it is recommended by the American Heart Association and the International Liaison Committee on Resuscitation for comatose survivors of cardiac arrest (Nolan *et al.* 2003, Froehler and Geocadin 2007, Castren *et al.* 2009).

Already in 1944, hypothermia has been reported to decreases cerebral oxygen utilization (Field *et al.* 1944). A linear relationship between temperature decrement, cerebral blood flow, and oxygen consumption has been observed down to 25ºC (Ehrlich *et al.* 2002). The beneficial effects of hypothermia also include reductions in the following phenomena: apoptotic neuronal cell death (Zhu *et al.* 2004), intracellular acidosis (Chopp *et al.* 1989), lipid peroxidation (Lei *et al.* 1994), accumulation of glutamate (Takata *et al.* 2005), release of glycine (Baker *et al.* 1991), inflammation (Kimura *et al.* 2002), and production of nitric oxide and free radicals (Castren *et al.* 2009). Hypothermia treatment has been shown to reduce immediate postischemic hyperperfusion, delayed postischemic hypoperfusion, blood-brain barrier disruption, brain edema and neuronal damage after cerebral ischemia (Karibe *et al.* 1994). The International Liaison Committee has recommended that all comatose cardiac arrest patients with initial ventricular fibrillation (VF) should receive hypothermia treatment for 12-24 h (Nolan *et al.* 2003).

2.8. Nonconvulsive status epilepticus in ICU

Status epilepticus is defined as continuous seizure activity lasting at least 30 min, or intermittent seizures occurring over a 30-min period without recovery of consciousness between each convulsion (Gastaut 1983). It is a life-threatening condition with a one-month mortality rate of 22% (DeLorenzo *et al.* 1995). The incidence of status epilepticus is approximately 18 to 41 episodes per population of 100 000 per annum in the United States (DeLorenzo *et al.* 1996). This incidence refers to clinically detectable episodes of status epilepticus, not incorporating the incidence of nonconvulsive status epilepticus (NCSE). NSCE might be the second most common acute neurological emergency after vascular accidents (Costello and Cole 2007). NCSE may occur independently or visible status may continue subclinically and be evident only in EEG recording.

NCSE is a form of the status with no visible seizures and is an often unrecognized cause of coma. The definition of NCSE is evolving. Classifications based on clinical presentation and underlying pathophysiology have been suggested (Fountain and Lothman 1995, Kaplan 1999). NCSE is characterized by behavioral or cognitive change from baseline for at least 30 min with EEG evidence of seizures. Diagnosis of NCSE cannot be reliably done without multichannel EEG recording. The cognitive changes during NCSE may incorrectly be associated with a postictal state, intoxication, psychogenic or psychotic states, or even mental retardation (Kaplan 1999).

Towne and colleagues (2000) evaluated the presence of NCSE in 236 comatose patients with no clinical signs of seizure activity. EEG monitoring demonstrated that 8% of these patients met the criteria for the diagnosis of NCSE. The authors concluded that NCSE is an under-recognized cause of coma, and EEG should be included in the routine evaluation of comatose patients even if clinical seizure activity is not apparent. In the study of Claassen and colleagues (2004), 570 patients with continuous EEG monitoring (cEEG) (because of detection of subclinical seizures, evaluation of decreased level of consciousness, or titration of antiepileptic drugs) were retrospectively evaluated. Seizures were detected in 19% of these patients. Of the seizures, 88% were detected

within the first 24 h of monitoring, but in 7% of patients the first seizure was detected only after 48 h of monitoring. Young and colleagues (1996) monitored 49 patients with cEEG. The overall mortality was 33% (16 of 49). Of the 23 patients with NCSE, 13 died (mortality 57%). Age, presence of NCSE, seizure duration, hospital and NICU length of stay, and delay to diagnosis were variables significantly associated with mortality. However, when data were analyzed with multivariate logistic regression, only seizure duration and delay to diagnosis were associated with increased mortality.

Oddo and colleagues (2009) studied retrospectively the risk factors and predictive value of electroencephalographic seizures and periodic epileptiform discharges in a population of 201 medical ICU patients without known acute neurological injury. Patients were cEEG-monitored for investigation of possible seizures or changes in mental status. Of the patients, 60% had sepsis as the primary admission diagnosis and 48% were comatose at the time of cEEG. Of these patients, 10% had EEG-detected seizures, 17% periodic epileptiform discharges, and 5% both. Seizures were noticeable only in cEEG in 67% of patients. Sepsis patients showed higher rates of both seizures and periodic epileptiform discharges than patients without sepsis (32% vs. 9%). Electroencephalographic seizures or periodic epileptiform discharges were associated with poor neurological outcome (death or severe disability) at hospital discharge (89% with electroencephalographic seizures or periodic epileptiform discharges vs. 39% without).

2.9. Monitoring epileptiform EEG and seizures

The automatic detection of epileptiform seizures has been studied since the 1970s (Ives *et al.* 1974, Gotman and Gloor 1976). The algorithms to detect the seizures are mainly based on identification of epileptiform spikes and special rhythmic EEG patterns associated with epileptiform seizures. Gloor (1975) described a spike as a triangular transient distinguishable from the rest of the background EEG activity, and in many algorithms the estimation of the relation between the amplitude of the epileptiform spike and the amplitude of background activity plays a fundamental role (Gotman 1982). The methods based on half-wave decomposition (Gotman and Gloor 1976) and wavelet transforms (Goeltz *et al.* 2000, Saab 2005) have been described.

Wavelet entropy has been proposed for the analysis of short-duration EEG signals (Rosso *et al.* 2001). A novel quantitative variable, wavelet subband entropy (WSE), was described for characterizing the evolution of the epileptiform EEG waveforms (Särkelä *et al.* 2007). WSE is based on a dyadic multiresolution decomposition of the signal performed with a discrete wavelet transform using the Mallat algorithm (Mallat 1989). A detailed description of WSE is published in the article of Särkelä and colleagues (2007). In this study, EEG data of 60 patients under sevoflurane mask induction were investigated. WSE variables were calculated from different frequency bands. The ability of the WSE in detecting and quantifying epileptiform EEG activity and also in recognizing misleading BIS readings caused by epileptiform activity was evaluated. WSE from the frequency bands of 4-16 and 16-32 Hz was found to be sufficient for quantifying epileptiform activity. For monophasic pattern monitoring, the lower frequency band was used, and for spike activity monitoring, the higher frequency band

was used. WSE values of the lower and higher bands followed the time evolution of epileptiform activity with prediction probabilities of 0.809 and 0.804. In deep anesthesia with epileptiform activity, WSE detected EEG- patterns causing BIS greater than 60, with an event sensitivity of 97% (Särkelä 2007).

Although several methods have been evaluated, none of these automatic monitors can reliably differentiate all of the spikes caused by artifacts from actual epileptiform activity. The original EEG signal always contains artifacts that must be visually recognized and excluded before further processing of the EEG signal. However, many of the critically ill patients suffer from neurological disturbances, and epileptiform activity may go undiagnosed because of inadequate monitoring or a lack of expertise with the interpretation of the original EEG signal. In addition, NCSE and the use of NMBAs may complicate the diagnosis of epileptiform activity in the ICU. A noninvasive, easy-to-interpret method for neuromonitoring is needed. More studies should therefore be conducted to validate WSE in ICU circumstances.

2.10. Brain death

The Ad Hoc Committee of the Harvard Medical School first defined the concept of brain death in 1968 (Ad Hoc Committee of the Harvard Medical School 1968). It enabled the function of organs other than the brain to be maintained after death, and modern organ transplantation programs were launched. The diagnosis of brain death is based on clinical examination showing an absence of both cranial nerve reflexes and spontaneous breathing. Various confirmatory tests, demonstrating circulatory arrest or loss of electrical activity in the brain, have been used. These include transcranial Doppler sonography (TCD), scintigraphy, four-vessel angiography, dynamic computed tomography, magnetic resonance imaging, positron emission tomography, EEG, or evoked potential testing (Randell 2004). In some European countries, one or all of these tests are mandatory, but only conventional angiography is recognized as a reliable confirmatory test by all European countries (Haupt and Rudolf 1999). In Finland, brain death diagnosis is based on clinical examination, and confirmatory tests are used only when the neurological examination and apnea testing are not reliable because of facial or thoracic injury or pulmonary disease (Randell 2004).

In the absence of sedatives, the presence of electrocerebral silence in EEG (combined with clinical findings) is highly reliable in the diagnosis of brain death. Electrocerebral silence is defined to be present when electrical activity is absent at levels higher than 2 µV with the instrument set at a sensitivity of 1 µV per millimeter for at least 30 min (American Electroencephalographic Society 1994). Using high sensitivity of an EEG machine increases the visible amount of physiological and nonphysiological artifacts. EMG artifacts reflecting remaining motor activity may contaminate EEG recordings, and a definite diagnosis for electrocortical silence cannot be made in such situations without using NMBAs. Fifteen percent contraction of the frontalis or temporalis muscles may produce detectable EMG activity over the entire scalp (Goncharova *et al.* 2003).

BIS has been tested for its capacity to detect brain death. Escudero et al. (2005) found a BIS value of zero and BSR 100 to correlate with physiological and confirmatory examinations in confirming brain death. Vivien et al. (2002) showed that all the patients with GCS below 5, BIS value zero, and burst suppression 100 were brain-dead, as confirmed by physiological status, traditional EEG, and angiography. The authors concluded that BIS might be used to detect the onset of brain death in severely comatose patients. Misis et al. (2008) retrospectively observed patients, meeting the clinical criteria of brain death and organ donation protocol criteria during their ICU stay. A gradual decrease in BIS values and an increase in BSR were observed when the patient evolved toward brain death. At the time brain death was diagnosed, all patients showed BIS zero and BSR 100. The authors concluded that although BIS has not been validated for the brain death diagnosis it is a continuous bedside monitoring method that can be used to detect the moment of brain death.

EEG and indices derived from it are vulnerable to several artifacts. Entropy has not been previously studied in connection with brain death.

3. Aims of the study

The aim of the study was threefold. First, to evaluate the usefulness and possible sources of artifacts of noninvasive depth-of-anesthesia and analgesia monitoring methods in the operating theater and in the intensive care unit (ICU) in patient groups in which these monitors were not previously studied or validated. Second, to examine the incidence of intraoperative awareness and necessity of the depth-of-anesthesia monitors in outpatient anesthesia. Third, to evaluate the feasibility of these automatic-monitoring methods in the prediction of neurologic recovery in comatose intensive care patients.

Specific objectives were as follows:

1. To evaluate whether the incidence of intraoperative awareness and explicit recall during general anesthesia is different in outpatients relative to inpatients (I).

2. To compare the feasibility of BIS and Entropy monitoring in brain-dead organ donors during organ retrieval and to determine the sources of the EEG signal artifacts that may disturb monitoring with these automatic indices of brain function (II).

3. To evaluate whether the SSI (SPI) levels differ in patients undergoing the same type of surgery with clinically different analgesic levels. In addition, the ability of SSI to detect nociceptive reflexes was compared with conventional clinical indicators of surgical stress (III).

4. To evaluate the feasibility and the optimal time window for the use of quantitative EEG-derived monitoring indices to separate patients with good and poor neurological outcome after cardiac arrest. Wavelet subband entropy (WSE), burst suppression ratio (BSR), State Entropy (SE), and Response Entropy (RE) were evaluated against visual EEG signal analysis, Transcranial Doppler ultrasound, and biomarkers of neuronal apoptosis (IV).

4. Patients and methods

Patients

The original studies were conducted in Jorvi Hospital of Helsinki University Central Hospital (I), Meilahti Hospital of Helsinki University Central Hospital (II, IV), and the Surgical Hospital of Helsinki University Hospital (II, III) between April 1998 and February 2007. The local Ethics Committee of Helsinki University Hospital approved all study protocols. In Studies I, III, and IV, patients or their next of kin gave their written consent for participation after receiving written and personal information. In Study II, the Ethics Committee of Helsinki University Hospital did not consider consent by next of kin to be necessary.

The total number of patients was 3913. In Study I 2360 patients were of ASA physical status 1, 1152 of ASA 2, 313 of ASA 3, and 16 of ASA 4. In Study II, all patients were brain-dead organ donors. In Study III, patients were of ASA 1-2, and in Study IV, patients were comatose after resuscitation from cardiac arrest. Designs and demographics of the original studies are shown in Table 1. In Study II, three cases were discarded due to missing data (collected original EEG data were insufficient). In Study III, two patients were excluded from the final analyses because of unsuccessful plexus blocks, and two because of lacking data (collected plethysmographic wave data were insufficient). In Study IV, 82 h of low-quality EEG recordings were rejected (4.7% of all recordings) from the analyses after visual analysis by an expert.

Table 1. Study designs and patient demographics. N=number of patients, BMI=body mass index. Demographic data are median (range).

Study	I	II	III	IV
Design	prospective open cross-sectional	prospective open observational	prospective randomized single-blind	prospective open observational
N	3841	16	26	30
Age (years)	38 (15-91)	56 (16-67)	51 (25-67)	58 (24-77)
Height (cm)	166 (147-202)	173 (162-183)	173 (157-188)	175 (158-190)
Weight (kg)	66 (38-146)	78 (52-110)	82 (59-114)	80 (55-140)
BMI (kg/m^2)	24 (14-48)	26 (20-33)	26 (20-33)	25 (19-39)
Male/Female	891/2950	8/8	16/10	24/6

Designs and protocols of the original studies

Study I. The incidence of intraoperative awareness and explicit recall in outpatient anesthesia was studied with a standardized interview. All outpatients 15 years or older undergoing surgery with general anesthesia during the study period were included. Inpatients (patients who came through a surgical ward and stayed at the hospital overnight) served as controls. Patients who did not speak Finnish or Swedish or who were unable to respond or refused to be interviewed were excluded from the study. The attending nurse performed the first interview in the recovery room. The interview was structured and based on the questions originally described by Brice et al. (Brice *et al.* 1970). Those patients who had recollections were reinterviewed during the same or following day. To evaluate whether patients with recollection had prolonged after-effects (sleep disturbances, anxiety, depression, preoccupation of death), they were reinterviewed by phone 12-24 months after the operation. Awareness and recall were graded into two types: type 1 as doubtful; patients had unclear memories or dreams that might have been related to intraoperative events, and type 2 as certain; patients had clear, explicit recall about intraoperative events. Patients with possible residual relaxation were graded as type 2. Patients were also questioned about dreaming during anesthesia. Dreams were described as neutral, pleasant, or nightmares. The anesthesia staff was aware of the study, but no specific instructions were given to them to standardize their anesthesia methods.

Study II. The hypothesis that Entropy would be more accurate than BIS in differentiating true EEG from EMG activity was tested in brain-dead organ donors. In addition, the sources of artifacts affecting EEG signal were evaluated. According to Finnish law, the diagnosis of brain death is based on clinical examination showing absence of both cranial nerve reflexes and spontaneous breathing. The diagnosis of brain death had been completed before the study began, independently of the researchers. Computed tomography of the brain was performed on all patients and cerebral angiography on six patients before brain death was diagnosed. The cause of brain death was intracerebral and/or subarachnoidal hemorrhage in ten, subdural hematoma in three, and cerebral ischemia after hemorrhage in three cases. The mean interval between the clinical diagnosis of brain death and the beginning of the organ harvest operation was 420 ± 167 min.

Study III. The ability of the Surgical Stress Index (SSI, later Surgical Pleth Index, SPI) to differentiate patients undergoing shoulder surgery with two clinically different analgesic levels was tested. The hypothesis was that during surgery SSI values would be lower in patients who had received an interscalene plexus block preoperatively than in patients who did not receive such a block. Patients were randomized (by computer-generated random numbers sealed in envelopes) either to the plexus group (general anesthesia + plexus block) or to the control group (general anesthesia only). In the plexus group, a neurostimulator guided interscalene plexus block with mepivacaine (35-40 ml 2% mepivacaine with 5 μg/ml epinephrine) and/or bupivacaine (15-20 ml 2% mepivacaine with 5 μg/ml epinephrine and 15-20 ml bupivacaine with 5 μg/ml epinephrine) was applied preoperatively. The first four patients received a plexus block with mepivacaine only. To prolong analgesia, the remaining patients were locally

anesthetized with a mixture of mepivacaine and bupivacaine. The block was tested (cold sensation, ability to adduct the shoulder and flex the forearm and hand against gravity) before the induction of general anesthesia, and considered sufficient if it covered dermatomes C3-C6 and T2. General anesthesia was induced with propofol (2 mg/kg), alfentanil (15 µg/kg), and rocuronium (0.4 mg/kg), and maintained with desflurane with 50% oxygen in air. The targeted level of hypnosis was SE 50, which was achieved by adjusting the concentration of desflurane. Patients were intubated and mechanically normoventilated ($EtCO_2$ 5.0). Noninvasively measured mean blood pressure above 65 mmHg was maintained. Increase in HR (>30 beats/min) or in blood pressure (>30 mmHg), movement, coughing, or RE-SE difference > 5 during a 20-s period were considered signs of nociception and led to a bolus dose of alfentanil (0.25 mg intravenously).

Study IV. The hypothesis that EEG-derived indices (BSR, SE, RE, WSE) would predict neurological outcome was tested. The time window in which these variables could differentiate patients with good neurological outcome from those with poor outcome, was also evaluated. Thirty consecutive comatose adult patients (≥ 18 years) with GCS of eight or below resuscitated from a witnessed ventricular fibrillation within an interval of < 35 min from collapse to ROSC and admitted to ICU for mild therapeutic hypothermia treatment were included. Patients with terminal illness, psychoactive or anticonvulsive medication, history of neurologic disease, or alcohol or drug abuse were excluded. Hypothermia of 33°C was induced immediately after arrival to ICU with an intravascular cooling device (CoolGard 3000, Alcius, Irvine, CA, USA). After 24 h of hypothermia treatment, patients were slowly (0.5°C/hour) rewarmed to normothermia. Pancuronium was used for muscle relaxation and to prevent shivering. Patients were treated according to departmental guidelines; they were kept in a 30° semirecumbent position and normoventilated, mean arterial blood pressure was kept above 65 mmHg, and blood glucose level was maintained between 4.4 and 8.0 mmol/l. Continuous 4-channel EEG monitoring began on arrival to the ICU, and the first blood samples were taken. Patients regaining consciousness were extubated as soon as possible. Patients who remained unconscious were treated in the ICU for at least 3 days after cardiac arrest. Conventional multichannel EEG, CT, or SEP recording was performed if needed.

Methods

Interview to screen awareness

In Study I, all patients were structurally interviewed during their stay in the recovery room by the attending nurse. The questions were those originally described by Brice et al. (1970): 1. What was the last thing you remember before going to sleep for your operation? 2. What is the first thing you remember on waking after your operation? 3. Do you remember anything in between? 4. Did you have any dreams? 5. What was the most unpleasant thing you remember from your operation and anesthesia? Additional questions asked of patients who reported awareness were as follows: 1. What did you notice: sounds, tactile sensations, visual perception, pain, or paralysis? 2. Did you feel

something in your mouth or throat? 3. What went through your mind? 4. Did you believe you were dreaming? 5. How long did it last? 6. Did you try to alert anyone? 7. How was your preoperative mental state? 8. Have there been any consequences of awareness? 9. Did you inform hospital staff? 10. Have you changed your opinion about anesthesia?

Any patient suspected of having experienced awareness was reinterviewed on the operation day or the next day by the author. Patients with awareness were also reinterviewed by phone 12-24 months after the operation. Patients with explicit recollections were graded into two types: type 1 was doubtful (unclear memories that might have been related to intraoperative events), and type 2 was certain (clear explicit recall of intraoperative events). Patients with possible residual relaxation were included in the type 2 group. Patients were also asked about dreaming during general anesthesia. If dreams were related to possible intraoperative events, these patients were classified into the type doubtful awareness group.

Premedication and sedation

Only in Study III, was premedication standardized and routinely used. One hour before entering the operation theatre, 5 mg of oral diazepam was given to patients. In Study I, most of the inpatients and some of the outpatients were premedicated with diazepam, but this was not standardized. In Study II, patients were brain-dead organ donors, and hence, no premedication was used. In Study IV, patients were resuscitated from cardiac arrest and were comatose when entering ICU. During the hypothermia treatment they were medicated with continuous infusions of midazolam (0.125 mg/kg/h) and fentanyl (2 µg/kg/h), until their body temperature reached 36°C during the rewarming period. In Study I, the total dose of inhaled anesthetics was calculated as follows: the inspired concentration was multiplied by the time the concentration was used. Concentration and time totals were added to form a grand total. The result was then divided by the total duration of anesthesia (Ranta *et al*. 1998). To estimate the MAC values, the total dose of sevoflurane was divided by 2.05 and the total dose of isoflurane by 1.15 (Koblin 2000).

Monitoring

Electrocardiography (ECG), SpO_2, and inspiratory and expiratory concentrations of oxygen and carbon dioxide were measured (Studies I-IV). Expiratory concentrations of isoflurane (Study I), sevoflurane (Study I), and desflurane (Study III) were measured. Blood pressure was monitored noninvasively every 5 min in Studies I and III. In Studies II and IV, arterial blood pressure was measured. Data were recorded with the S/5 Collect 4.0 program (GE Healthcare Finland Oy) in the Studies II-IV, and manually in Study I.

EEG, BIS, and Entropy monitoring and data collection

In all studies, skin was prepared with alcohol before electrodes were placed on the patient's forehead according to manufacturers' recommendations (Studies II and III). In Study II, BIS and Entropy sensors were placed in the immediate vicinity of each other (Entropy sensor below BIS sensor). In Study IV, electrodes were applied below the hairline, as shown in Figure 1. In Study IV, EEG was recorded from channels Fp1-At1, Fp2-At2, At1-A1, and At2-A2, and an Entropy sensor was positioned interhemispherically above the Fp1 and Fp2 electrodes.

BIS was collected with a BIS module (version 4.0, Aspect Medical Systems, Norwood, MA, USA) of S/5 Compact Monitor (GE Healthcare Finland, Helsinki, Finland), and BIS-XP Sensor Quatro electrodes were used (Aspect Medical Systems, Norwood, MA, USA) in Study II. Entropy was collected with an Entropy module (GE Healthcare Finland, Helsinki, Finland) of S/5 Compact Monitor (GE Healthcare Finland, Helsinki, Finland), and Entropy Sensor electrodes were used (GE Healthcare Finland, Helsinki, Finland) in Studies II and III. Zipprep electrodes (Aspect Medical Systems, Norwood, MA, USA) were used in Study IV. The EEG sampling frequency for BIS calculation (Study II) was 256 Hz, and for Entropy (Studies II and III) 400 Hz. In Study IV, EEG was recorded with a sampling frequency of 500 Hz. Impedance values below 7.5 Ω (for Entropy) and 10 Ω (for BIS) were considered acceptable according to the manufacturers' recommendations.
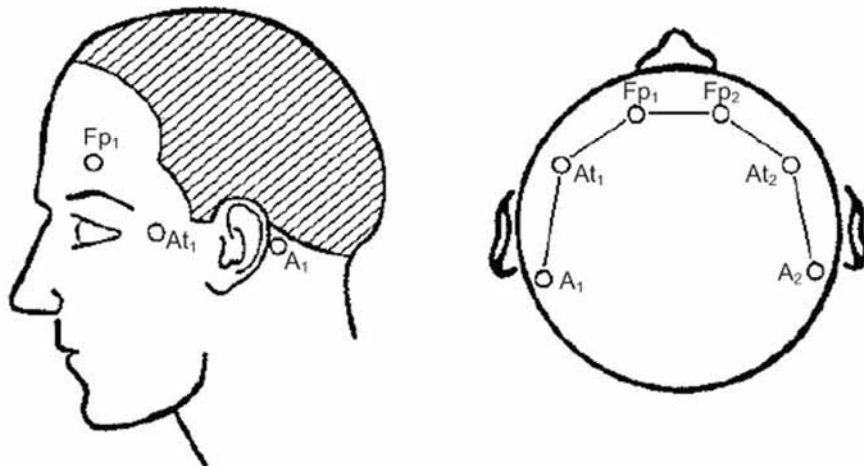

Figure 1. Placement of EEG electrodes used in Study IV. In addition, an Entropy sensor was located above the Fp1 and Fp2 electrodes. At1/At2 = electrode placement on both temporal bones laterally to the eyes. The picture is modified from Bridgers SL, Ebersole JS. EEG outside the hairline: Detection of epileptiform abnormalities. Neurology 1988; 38:146-149 and reproduced with permission from Neurology.

In Studies II and IV, the EEG data were converted to EDF format, which is readable with the Nervus EEG 3.4 viewer (Taugagreining, Reykjavik, Iceland). A senior clinical neurophysiologist retrospectively analyzed this converted original EEG signal offline. In Study II, nonprocessed EEG activity was analyzed to evaluate artifacts and possible residual EEG activity in brain-dead organ donors. In Study IV, the neurophysiologist was blinded to the clinical outcome, other electrophysiological tests, results of laboratory measurements, and radiological findings. Continuity, suppression, burst suppression, epileptiform discharges, spindles, and status epilepticus were evaluated from EEG (Study IV). Periods of low-quality EEG recordings were manually removed from the final analysis (Studies II and IV).

WSE was calculated offline with Matlab (version 7.5, Mathworks, Natick, MA, USA) and Matlab Wavelet Toolbox (version 2.2) (Study IV). WSE was calculated with mother wavelet Daubenchies 3 from a scale corresponding to an EEG frequency range between 16 and 32 Hz.

Surgical Stress Index (Surgical Pleth Index)

In Study III, Surgical Stress Index (SSI, later Surgical Pleth Index, SPI) was calculated offline from the formula SSI = 100- (0.7 x PPGAnorm + 0.3 x HBInorm). During the study SSI was still under development and was therefore calculated offline. SSI was calculated at the following phases during general anesthesia: before incision, after incision, and during the rest of the operation. "Before incision" referred to the mean SSI during a 10-min period immediately before incision. "After incision" referred to mean SSI during the first 2-min period after the incision. "Rest of the operation" referred to the mean SSI during the period from 2 min after incision to extubation.

The reactivity of SSI was tested before surgery with standard tetanic stimuli 5 min after intubation. A 30-s tetanic stimulus (80mA, 100 Hz, Innervator 252®, Fischer & Paykel, Auckland, New Zealand) was given above the nervus ulnaris on the wrist on the side of the shoulder surgery and the possible plexus block. The measurements of PPGA and HBI were performed on the contralateral hand (the hand not operated on).

Trancranial Doppler Ultrasonography

The Pulsatile Index of Transcranial Doppler Ultrasonography (TCD, Pioneer TC 4040, Nicolet-EME, Überlingen, Germany) was measured for each patient in Study IV. The middle cerebral artery was insonated at a depth of 49-55 mm. The measurement was taken when patients were normothermic after hypothermia treatment, but within 48 h after cardiac arrest. The same investigator performed all the measurements.

Laboratory measurements

NSE, S-100B, creatine kinase MB, Troponin T, hemoglobin, glucose, lactate, and pH were measured for all patients in Study IV. Blood was sampled from an arterial catheter. Blood tests were sampled at the same time when EEG monitoring started on arrival to ICU (NSE, S-100B), 24 h after cardiac arrest (NSE), upon rewarming to 35.5°C (NSE, S-100B), 48 h after cardiac arrest (NSE), and when EEG monitoring ended (NSE, S-100B). Markers of myocardial damage (creatine kinase MB and troponin T) were evaluated according to the ICU´s protocol daily, and arterial blood gas analysis (including hemoglobin, natrium, potassium, calcium, glucose, lactate, pH) was done at least every 4 h. The reference range for NSE was 0.05-16 µg/l, and for S-100B 0.005-0.11µg/l (Elecsys, Roche, Basel, Switzerland). Additional NSE values were measured at 24 and 48 h after cardiac arrest as per the ICU´s protocol. S-100B values do not belong to these routinely measured values and were measured only on arrival to ICU, upon rewarming and when EEG monitoring ended.

Functional outcome

In Study IV, neurologic status was examined daily during the ICU stay and also at discharge from the hospital. A neurologist evaluated patients six months after cardiac arrest, and assessed neurologic outcome with the Glasgow-Pittsburgh Cerebral Performance Categories (CPC). CPC classifies outcome into five categories:
CPC of 1 refers to normal cerebral function, 2 to moderate cerebral disability, 3 to severe neurologic disability, 4 to comatose or vegetative state, and 5 to death (Cummins *et al.* 1991). The overall neurologic outcome was defined as "good" if the best-achieved CPC score was 1 or 2 at any point within the six-month follow-up period after cardiac arrest. CPC scores of 3-5 indicate "poor" neurologic outcome.

Statistical analysis

In Study I, Chi-squared test with Yates continuity correction was used to compare frequencies of awareness, and Students *t*-test was applied for independent samples. Power analysis was performed to estimate the number of patients needed to be interviewed. The incidence of awareness in the group of inpatients was expected to be 0.7% (based on a previous study by the same group of researchers (Ranta *et al.* 1998)), and twice as high (i.e. 1.4%) in the group of outpatients. For a significance level of 5% and power of 90%, 1500 patients per group were required.

In Study II, recorded BIS and Entropy data were not normally distributed and were expressed as median and range. The demographic data were reported as mean ± standard deviation (SD). Wilcoxon´s test was used to compare paired samples of SE, RE, and BIS.

In Study III, the differences between plexus and control groups were evaluated with two-tailed Mann-Whitney tests for numeric variables and two-tailed Fisher's exact tests for categorical differences. SPSS (SPSS Inc, Chicago, IL, USA) was used for all calculations. The consecutive measurements within one subject are correlated; therefore, a single mean value was calculated for the specified period. Statistical comparisons were performed by using these single values for different subjects. Significant differences were reported without correction for multiple comparisons. Pk statistics was used to evaluate how consistently SSI, HR, systolic blood pressure, and RE-SE difference could separate the low-stress situation from the high-stress situation. Pk was calculated with Matlab (MathWorks Inc., Natick, MA, USA). The jackknife method of Matlab was used to compute the standard error of the estimate (Study III).

In Study III, the SSI values before patient responses requiring an alfentanil-bolus were compared with values during the period of no clinical nociceptive responses. The response SSI value of a patient was calculated as the mean of the peak SSI values that preceded each response that led to alfentanil administration. A one-min time window was used to calculate the response SSI value. If repeated alfentanil boluses were needed without a 5-min period between them, the latter period was not included to the calculation. The no-response SSI value was calculated as the mean of the peak SSI values from one minute in the middle of a period of no responses, and no alfentanil administration within 11 min (i.e. 5 min before and 5 min after the included one-minute period when there were no responses and no alfentanil doses were given). The response and nonresponse SSI values were calculated separately for plexus and control groups and compared between groups with the unpaired Mann-Whitney test.

Power analysis was performed to estimate the required sample size also in Study III. Clinically significant reduction in the mean required dose of alfentanil (after the induction dose) was estimated to be 25%. Based on the Hospital's clinical database, a minimum of 2 mg alfentanil per surgery was estimated to be the mean consumption during acromioplasty without preoperative plexus block but with N_2O used during general anesthesia. To provide 80% power to detect a 25% change (two-sided) in alfentanil need with an alpha of 0.05, 24 patients per group were needed. N_2O is routinely used in the study hospital, and it has an antinociceptive effect. N_2O was not included in the study protocol in order to minimize its confounding analgesic effects in the control group. Hence, the power calculation was only an approximation, as patient data from shoulder surgery under general anesthesia without N_2O did not exist. The results were analyzed after 30 patients, and significant differences in alfentanil consumption and SSI values were found. Thus, the sample size was considered adequate, and patient recruitment was stopped.

In Study IV, patients were divided into good and poor neurologic outcome groups based on the CPC evaluation. All data have a non-Gaussian distribution and were given as medians and ranges. Mann-Whitney U-test was used to evaluate the difference between the medians of good and poor outcome groups for scalar parameters. Chi-squared test was used to test the associations between nominal scale parameters and outcome or EEG groups. SPSS (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Preliminary prediction analysis was carried out with a General Diagnostic Optimizer program, which uses a stepwise heuristic Bayesian process.
A p-value of 0.05 or below was considered statistically significant (Studies I-IV).

5. Results

Incidence of awareness and recall in outpatient anesthesia (Aim 1)

In Study I, 1500 outpatients and 2343 inpatients were interviewed. During the study period 89% of the outpatients and 67% of the inpatients operated on under general anesthesia were interviewed.

One of the outpatients reported a short-lasting, but clear episode of awareness. Four other outpatients reported doubtful awareness. Long-lasting episodes were not detected among the outpatients. Three inpatients described clear episodes of awareness and three additional patients described doubtful awareness. The incidence of clear awareness was 0.07% among outpatients and 0.13% among inpatients when they were interviewed in the recovery room. No statistical difference was present in the incidence of awareness between the groups.

Patients with clear or doubtful awareness were interviewed a second time 12-24 months after the surgery. Five outpatients and three inpatients with awareness had the same recollections as in the first interview. Three inpatients (who had recollections in the first interview) did not have persisting recollections in the second interview.

All of the patients with awareness were females (in both study group), but the difference in sex distribution was not significant (p=0.08). Nor was there a difference in ASA physical status, body mass index (BMI), or age between the patients with and without awareness. Only one patient experienced pain. Altogether 22% of outpatients and 14% of inpatients reported neutral or pleasant dreams. Dreaming was more common in women. Of the patients with awareness, one outpatient reported nightmares and sleep disturbances, and one inpatient depression as after-effects from awareness.

Benzodiazepine premedication was administered to 88% of inpatients and 15% of outpatients. No difference in the incidence of awareness was found between patients with and without premedication. The proportions receiving NMBAs were 97% of inpatients and 19% of outpatients. No difference emerged in the incidence of awareness between patients who had received muscle relaxants and those who had not. Outpatients with awareness received less sevoflurane than outpatients without this complication (p<0.05) (Study I).

BIS and Entropy monitoring in brain-dead organ donors (Aim 2)

In Study II, Entropy and BIS data from 16 brain-dead organ donors were recorded during organ harvest surgery. SE differed from zero in 28% (range 3-99%), RE in 29% (4-99%), and BIS in 68% (16-100%) of the recorded time. SE, RE, and BIS values over 40 were recorded in 1%, 1%, and 4% of the total recorded time, respectively. The

median SE during the organ harvest operation was 0.0 (range 0-91), the median RE was 0.0 (0-100), and the median BIS was 3.0 (0-98). SE, RE, and BIS were all significantly different from 0 (p<0.0001), and RE > SE, BIS > SE, and BIS > RE (p<0.0001 in all cases). The median BSR recorded with the Entropy Module was 100.0 (range 0-100).

Offline analysis of the time-domain EEG revealed some persistent unphysiologically distributed, nonreactive, rhythmic θ-activity with an amplitude between 10 and 40 µV during the initial or entire monitoring in four of 16 cases (Figure 2). After excluding cases with residual EEG, the median SE was 0.0 (range 0-90), median RE was 0.0 (0-98), and median BIS was 2.0 (0-96). The indices differed from zero as follows: SE 17%, RE 18%, and BIS 62% of the recorded time (Figure 3).
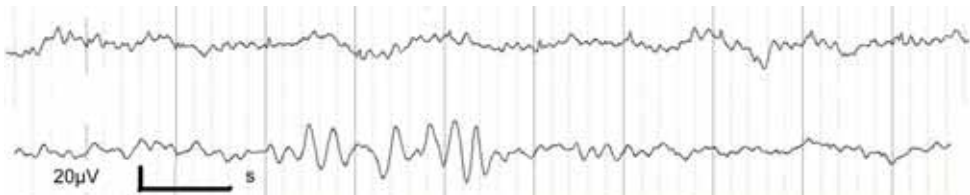

Figure 2. Persistent, nonreactive, rhythmic, low-amplitude EEG activity in clinically brain-dead organ donor.
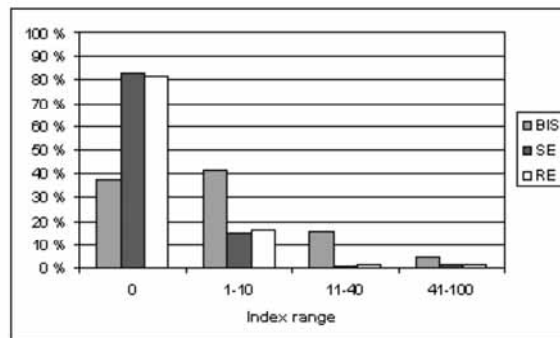

Figure 3. Proportions of operating time when SE, RE, and BIS were zero, 1-10, 11-40, and 41-100, after excluding recordings containing residual EEG.

Sources of EEG signal artifacts (Aim 2)

Electrocauterization, handling of the patient, ballistocardiography (caused by small rhythmic movements of the head induced by cardiac contraction and ejection of blood through the vessels), EMG, 50-Hz artifact, ECG, and external warmer all caused artifacts to the EEG signal and falsely increased the values of EEG-based indices (Study II). Figure 4 demonstrates different artifacts and the related original EEG recordings.
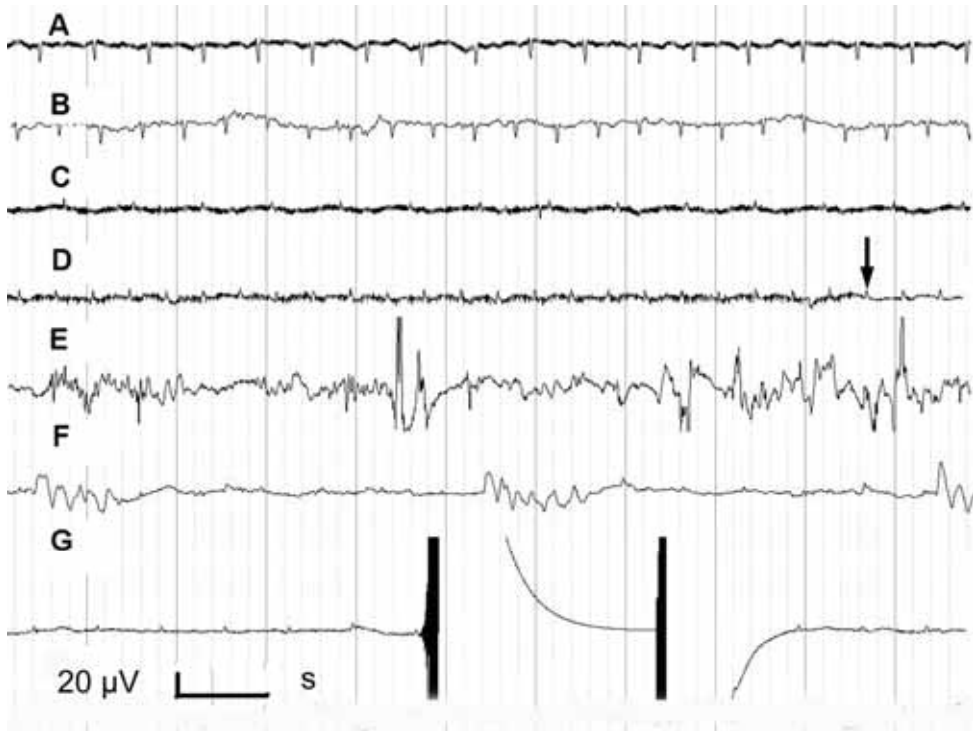
Figure 4. Different artifacts in the EEG recordings. (A) ECG with 50-Hz interference. (B) Tachycardic ECG signal. (C) Rhythmic slow oscillation due to ballistocardiography. (D) EMG artifact eliminated by neuromuscular blockade (arrow). Note that ECG artifact persists after administration of NMBA. (E) Movement artifacts. (F) External warmer. (G) Electrocauterization, large artifact blocks the amplifier for 2 s.

The highest BIS and Entropy values were recorded without muscle relaxation. Initially high BIS indices decreased after administration of NMBAs. The median decline in BIS index after administration of NMBA was 1.0 (0-61) ($p < 0.05$). Entropy indices did not decrease as markedly; the median ΔSE was 0.0 (0-1), and the median ΔRE was 0.0 (0-2). SE and RE decreases were not statistically significant (Figure 5).

Extended use of electrocauterization or handling of the donor increased indices in 81% of organ donors. In 44% of recordings, the source of recorded electrical potential was a ballistocardiography, in 38% of cases EMG, and in 25% of cases a 50-Hz artifact. In 19% of the recordings, an ECG artifact was noted. The ECG artifact was usually related to tachycardia (HR over 100 beats/minute), and well visible in the time-domain EEG.
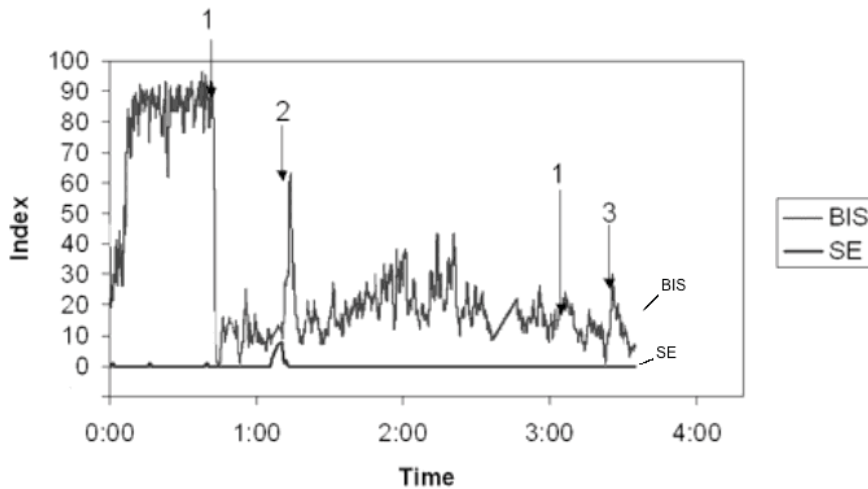
Figure 5. Typical course of BIS and SE trend recordings during organ harvest. 1 = administration of the neuromuscular blocking agent, 2 = sternotomy, 3 = organ perfusion with preservation fluid.

SSI (SPI) levels during shoulder surgery with clinically different analgesic levels (Aim 3)

SSI (SPI) in 26 patients undergoing shoulder surgery under general anesthesia with or without interscalene plexus block (plexus group and control group, respectively) was recorded continuously from the unoperated side. Preoperatively, after tetanic stimulus, the increase in SSI was 26 ± 21 in the plexus group and 23 ± 17 in the control group. The difference between the groups was not significant. However, in four patients, plexus block covered also the ulnar side of the hand. Among these four patients, SSI did not increase (ΔSSI 0.5 ± 3) during tetanic stimulation, indicating efficacy of the plexus block (Figure 6).
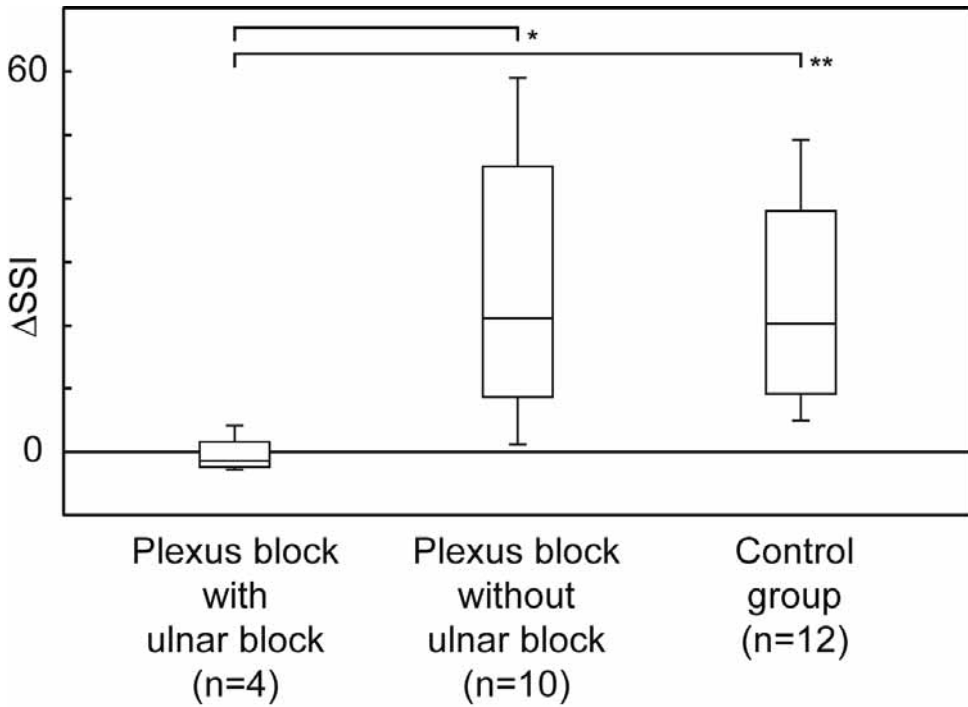
Figure 6. Change of SSI (ΔSSI) in response to tetanic stimulus at the ulnar side of the wrist (* p<0.05 compared with patients with no ulnar block in the plexus group and ** p<0.01 compared with control group patients).

Before the skin incision, SSI values were similar in the plexus and control groups (38 ± 11 vs. 39 ± 10). During the first two minutes after skin incision SSI showed lower values in the plexus group than in the control group (38 ± 13 vs. 58 ± 13, p<0.005). The mean SSI during the rest of the anesthesia did not differ between plexus and control groups (46 ± 9 vs. 48 ± 10). Figure 7 demonstrates typical SSI and Entropy trends during anesthesia and surgery in patients with and without plexus block (Figure 7).
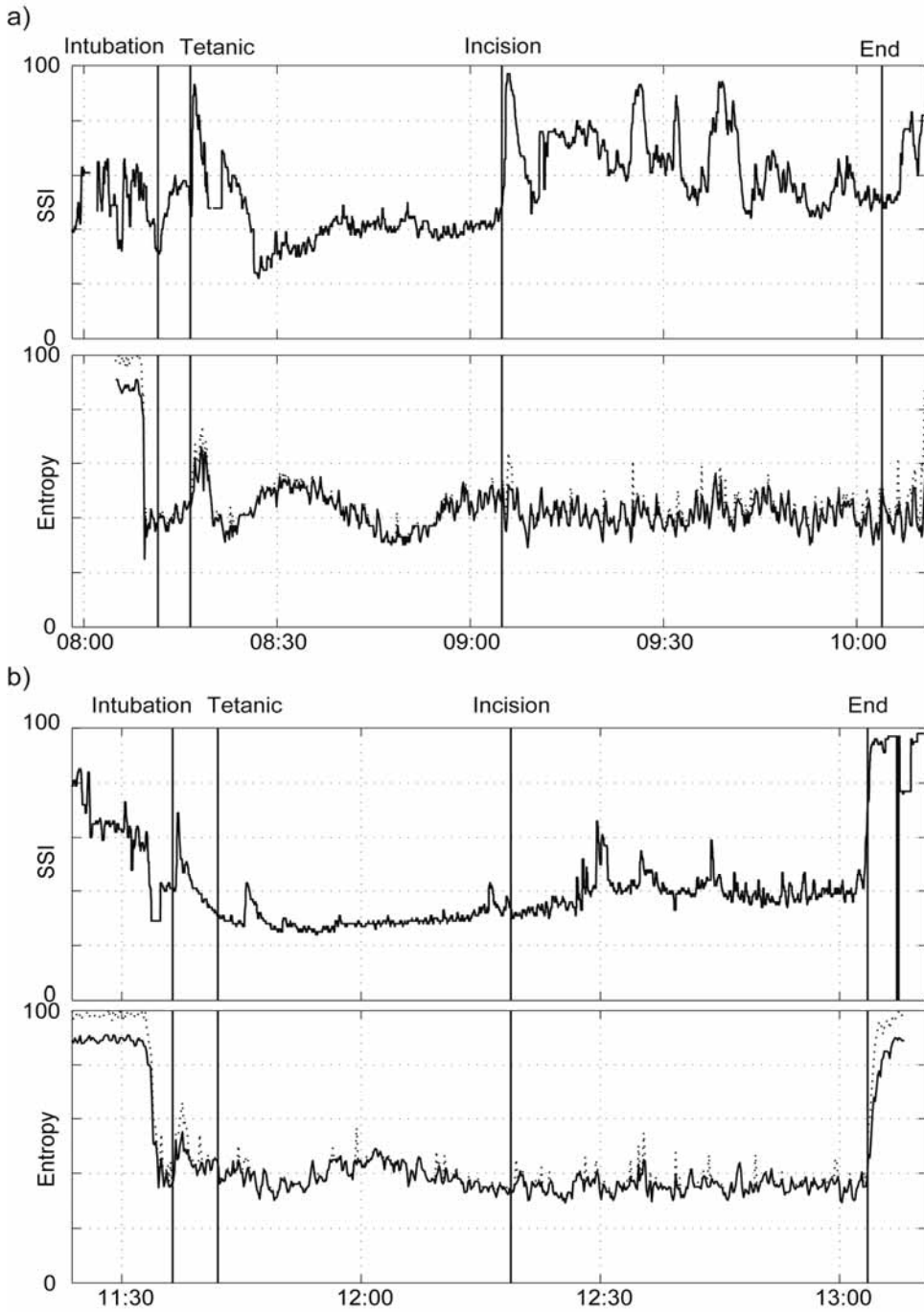
Figure 7. SSI and Entropy trends (SE, solid line and RE, dotted line) a) in a patient without a plexus block and b) with an effective plexus block covering also the ulnar nerve distribution.

Pk value ± SD was used to compare the ability of SSI and traditional hemodynamic parameters to detect the higher stress level (=increased parameter values after the nociceptive stimulus). Pk values before vs. after skin incision in the control group: SSI 0.88 ± 0.07, Systolic Blood pressure (BPsys) 0.65 ± 0.12, HR 0.69 ± 0.12, RE-SE difference (RE-SE) 0.63 ± 0.13, after skin incision in the plexus vs. control groups: SSI 0.86 ± 0.08, BPsys 0.79 ± 0.10, HR 0.79 ± 0.10, RE-SE 0.60 ± 0.13, before vs. after tetanic stimulation in the control group: SSI 0.88 ± 0.09, BPsys 0.65 ± 0.14, HR 0.66 ± 0.13, RE-SE 0.66 ± 0.14, and before vs. after tetanic stimulation in patients with plexus block that had not spread to the ulnar side: SSI 0.88 ± 0.10, BPsys 0.49 ± 0.16, HR 0.66 ± 0.16, RE-SE 0.69 ± 0.17. HR, BPsys and SSI values at various time-points during the anesthesia and surgery are given in Table 2.

Time	SSI Plexus	SSI Control		HR Plexus	HR Control		NIBP plexus	NIBP control	
Before intubation	45 ± 10	48 ± 11	N.S.	67 ± 10	69 ± 12	N.S.	158 ± 31	138 ± 37	N.S.
After intubation	53 ± 8	51 ± 10	N.S.	71 ± 10	75 ± 18	N.S.	147 ± 27	137 ± 40	N.S.
Before incision	38 ± 11	39 ± 10	N.S.	66 ± 12	67 ± 17	N.S.	116 ± 14	128 ± 23	N.S.
After incision	38 ± 13	58 ± 13	P=0.001	64 ± 11	78 ± 14	P=0.01	115 ± 14	139 ± 25	P= 0.01
After 5 min	40 ± 11	44 ± 9	N.S.	64 ± 10	74 ± 18	N.S.	116 ± 15	150 ± 26	P= 0.001
After 10 min	43 ± 9	44 ± 17	N.S.	64 ± 11	72 ± 19	N.S.	117 ± 14	144 ± 30	P= 0.013
After 15 min	41 ± 9	44 ± 14	N.S.	63 ± 10	74 ± 22	N.S.	115 ± 18	152 ± 22	P= 0.000

Table 2. Surgical Stress Index (SSI), heart rate (HR), and noninvasive systolic blood pressure (NIBP) at various time-points.

A diminished need for additional alfentanil analgesia in the plexus group was detected. In the plexus group, alfentanil was administered 25 times, and in the control group 86 times. In the plexus group, the reason for alfentanil administration was increased HR and/or BPsys four times, RE-SE > 5 over 20 s 15 times, and a combination of these indicators six times. In the control group, the reason for alfentanil administration was increased HR and/or BPsys 70 times, RE-SE > 5 over 20 s once, and a combination of these indicators 15 times. The mean number of alfentanil boluses given per patient after the induction of anesthesia was 1.8 ± 1.8 and 7.2 ± 4.2 in the plexus and control groups, respectively (p<0.001). The total cumulative dose of alfentanil during anesthesia (including induction dose) was 1.6 ± 0.5 mg and 2.7 ± 1.2 mg in the plexus and control groups, respectively (p=0.008). SSI and HR values, cumulative alfentanil dose, RE, SE, and desflurane concentrations at different time-points during general anesthesia are presented in Figure 8.

In the plexus group, the response SSI was 47 ± 14 (n=9), and the no-response SSI value was 45 ± 12 (ns). In the control group, the response SSI value was 59 ± 11 (n=12), and the no response SSI value was 39 ± 12 (p<0.01). The response SSI value was calculated as the mean of the peak SSI values preceding each response leading to additional alfentanil administration (one-minute window). The no-response SSI value was

calculated as the mean of the peak SSI values from one minute in the middle of a period of no-responses and no additional administration of alfentanil within 11 min. For more details, see the statistical analysis in the Methods section.
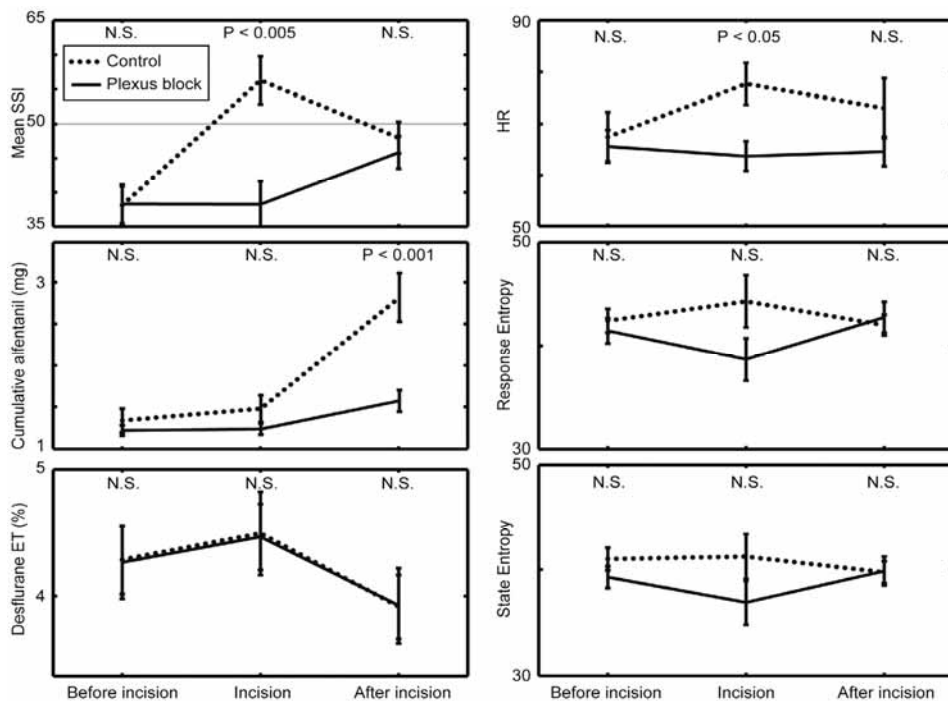

Figure 8. Mean ± SEM SSI and HR values, cumulative alfentanil dose, Response and State Entropy, and desflurane concentrations at different time-points during general anesthesia. Before incision= mean value during a 10-min period before incision, incision= mean value up to two minutes after incision, and after incision= mean value from two minutes after incision to extubation. Cumulative alfentanil doses are given as total doses given before the end of these specific time-points, respectively. Statistical comparisons were done between the groups.

Ability and time schedule of the quantitative EEG variables (WSE, BSR, SE, and RE) to differentiate patients with good and poor neurological recovery (Aim 4)

In Study IV, EEG monitoring was started 3-13 h after cardiac arrest. A total of 1754 h of EEG was recorded. After manual rejection of low-quality EEG signal and artifacts, 667 h of EEG (22/patient) registered in the first 24 h after cardiac arrest, and 541 h (18 h/patient) in the period between 24 and 48 h after cardiac arrest were further analyzed.

Twenty-one patients had a best CPC of 1 or 2 (CPC 1: 13 patients, CPC 2: 8 patients), four patients had a CPC of 3, and five patients had a CPC of 4 during the six-month follow-up period. At six months after cardiac arrest, nine patients had died, and 21 were alive. No patient remained in a persistent vegetative state. Five patients remained comatose until the treatment was withdrawn. All patients with CPC 1 or 2 (described as good neurological outcome) returned home. Baseline demographics and clinical characteristics were similar in both outcome groups (Table 3).

	Good outcome (n=21)	Poor outcome (n=9)	p
Age	55 (24-74)	60 (26-77)	0.176
Sex (male/female)	16 / 5	8 / 1	0.426
BMI (kg/m^2)	25 (19-35)	28 (21-39)	0.209
GCS	3 (3-8)	3 (3-5)	0.278
SOFA 24 h	8 (3-12)	9 (5-13)	0.304
ROSC (min)	16 (9-33)	22 (15-31)	0.104
CPR (yes/no)	14 / 7	6 / 3	0.500
BCLS (min)	7 (3-13)	7 (5-11)	0.406
ACLS (min)	14 (3-35)	16 (12-25)	0.263
Time to target temperature (h)	3 (1-5)	2 (0-13)	0.449
Time to normothermia (h)	32 (30-36)	31 (30-39)	0.304
LOS ICU (days)	3 (1-14)	4 (2-13)	0.244
LOS Hospital (days)	18 (5-36)	13 (5-31)	0.226

Table 3. Demographics and baseline clinical characteristics in Study IV.
BMI = body mass index, GCS = Glasgow Coma Scale on admission, SOFA = Sequential Organ Failure Assessment, ROSC = return of spontaneous circulation, CPR = bystander cardiopulmonary resuscitation, BCLS = response interval to basic cardiac life support, ACLS = response interval to advanced cardiac life support, Time to target temperature since arrival to ICU, Time to normothermia since initiating hypothermia treatment, LOS ICU = length of stay at intensive care unit, LOS Hospital = length of stay at Helsinki University Hospital.

When EEG monitoring started, all patients demonstrated a slow burst suppression pattern in EEG, which gradually subsided and a low-amplitude rhythmic activity appeared. There were no differences in the occurrence of continuous EEG between the outcome groups during hypothermia, but during normothermia, the good outcome group more often showed continuous EEG than the poor outcome group (p<0.001). Status epilepticus during normothermia was related to poor neurological outcome (p=0.001). Other EEG patterns were not associated with outcome. Findings in visually analyzed EEG during hypo-and normothermia according to outcome are presented in Table 4.

	Good outcome, n = 21 (%)	Poor outcome, n = 9 (%)
Hypothermia		
Continuous EEG	14 (67)	4 (44)
Discharges	1 (5)	3 (33)
Suppression/ B-S	5 (24)	1 (11)
Status epilepticus	0 (0)	0 (0)
Spindles	1 (5)	0 (0)
Myoclonia	0 (0)	1 (11)
Normothermia		
Continuous EEG	20 (95)*	3 (33)ᵘ *
Discharges	1 (5)	1 (11)
Suppression/ B-S	0 (0)	1 (11)
Status epilepticus	0 (0)**	4 (44)**
Spindles	0 (0)	0 (0)
Myoclonia	0 (0)	0 (0)

B-S = Burst suppression. ᵘ Theta coma . * p < 0.001, ** p = 0.001

Table 4. EEG findings during hypo- and normothermia according to outcome. Values are numbers and percentages.

Patients with good outcome had significantly lower BSR (shorter suppression episodes) during the first 48 h after cardiac arrest than patients with poor outcome. This difference in BSR was more pronounced during hypothermia. SE and RE were significantly higher in the good outcome group during the first 24 h, but not during the period between 24 and 48 h. WSE was at borderline higher in the good outcome group during the period from 24 to 48 h (Table 5).

	Good outcome (n = 21)	Poor outcome (n= 9)	p
0-24h			
WSE	0.84 (0.75 - 0.85)	0.83 (0.69 - 0.85)	0.137
BSR (%)	18 (0 - 81)	65 (4 - 74)	0.011
RE	20 (3 – 51)	10 (4 - 22)	0.011
SE	19 (3 - 50)	9 (4 - 22)	0.008
24-48h			
WSE	0.84 (0.80 - 0.86)	0.82 (0.65 - 0.85)	0.050
BSR (%)	0 (0 – 17)	2 (0 - 26)	0.045
RE	67 (26 - 83)	55 (29 - 78)	0.150
SE	58 (24 - 76)	46 (28 - 68)	0.193

Table 5. *Median and range of quantitative parameters associated with good and poor neurological outcome during the first and second day after cardiac arrest.*
WSE = wavelet subband entropy, BSR = burst-suppression ratio, RE = Response Entropy, SE = State Entropy

Status epilepticus patients had lower WSE between 24 and 48 h than other patients (p= 0.022). The evolution of WSE in status epilepticus patients is presented in Figure 9. A neurophysiologist defined the onset of status epilepticus in each patient as the time-point when discharges over 50% of the time were detected. In Figure 9, the onset of status epilepticus was set to 0 h, and the hourly distribution of WSE from 12 h before to 24 h after the beginning of status epilepticus are given.
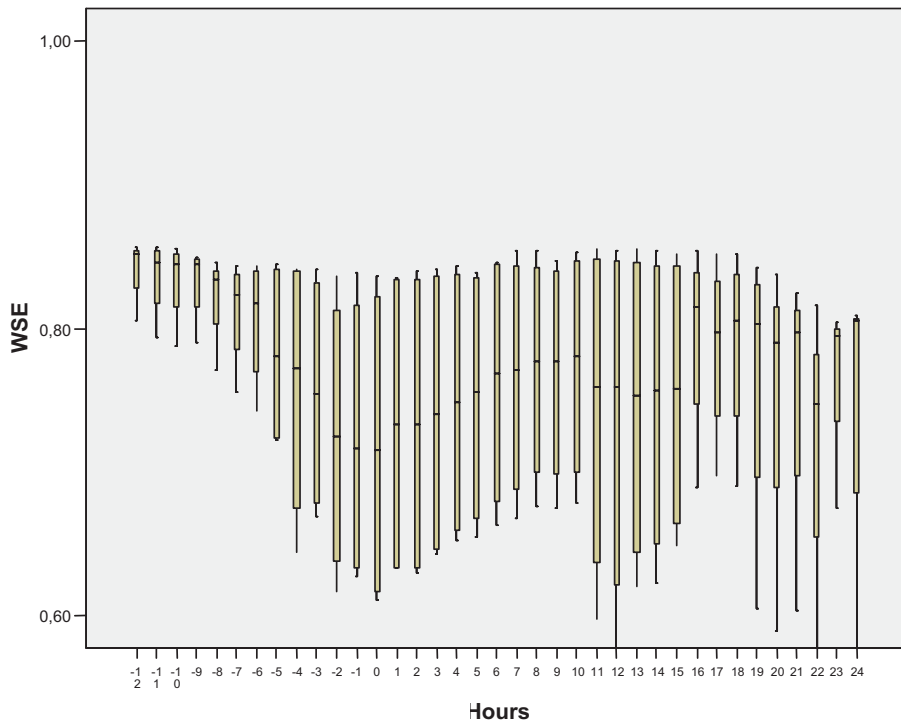

Figure 9. Evolution of WSE in status epilepticus patients. The beginning of status epilepticus is denoted by 0 h. The distribution of hourly WSE values between 12 h before and 24 h after onset of status epilepticus is shown. The box displays the distribution from the 25th to 75th percentile. The horizontal line within the box represents the median value. The whiskers cover the distribution up to 1.5 times the box length from the edges of the boxes. The boxes depict the distribution of hourly average values within the group.

Sensitivity, specificity, positive prediction value (PPV), and negative prediction value (NPV) for the prediction of poor neurological outcome after cardiac arrest were calculated. In Table 6, thresholds of WSE, BSR, SE, RE, NSE, and S-100B are adjusted to maximize the number of correctly predicted outcomes. In Table 7, the thresholds of these variables are adjusted for 100% specificity.

Variable	Threshold	Sens	Spec	PPV	NPV
WSE 24h	≤ 0.84	0.89	0.52	0.44	0.92
WSE 48h	≤ 0.83	0.67	0.71	0.50	0.83
BSR 24h	≥ 21	0.89	0.62	0.50	0.93
BSR 48h	≥ 0	0.89	0.57	0.47	0.92
RE 24h	≤ 13	0.78	0.81	0.64	0.89
RE 48h	≤ 64	0.89	0.62	0.50	0.93
SE 24h	≤ 12	0.78	0.81	0.64	0.89
SE 48h	≤ 56	0.89	0.57	0.47	0.92
NSE 0h	≥ 19	0.44	0.48	0.27	0.67
NSE 24h	≥ 21	0.56	0.62	0.38	0.76
NSE 35.5°C	≥ 20	0.78	0.71	0.54	0.88
NSE 48h	≥ 20	0.78	0.80	0.63	0.89
NSE end	≥ 16	0.63	0.78	0.55	0.83
S100B 0h	≥ 0.36	0.78	0.81	0.64	0.89
S100B 35.5°C	≥ 0.10	0.89	0.76	0.62	0.94
S100B end	≥ 0.09	0.88	0.44	0.40	0.89

Table 6. Sensitivity, specificity, positive prediction value, and negative prediction value for the prediction of poor neurological outcome.
Sens= sensitivity, Spec= specificity, PPV= positive prediction value, NPV= negative prediction value, WSE= wavelet subband entropy, BSR= burst suppression ratio, RE= Response Entropy, SE= State Entropy, NSE= neuron-specific enolase, S100B= protein 100B

Variable	Threshold	Sens	Spec	PPV	NPV
WSE 24h	≤ 0.74	0.22	1.00	1.00	0.75
WSE 48h	≤ 0.77	0.33	1.00	1.00	0.78
BSR 24h	≥ 82	0.00	1.00	-	0.70
BSR 48h	≥ 22	0.11	1.00	1.00	0.72
RE 24h	≤ 2	0.00	1.00	-	0.70
RE 48h	≤ 25	0.00	1.00	-	0.70
SE 24h	≤ 2	0.00	1.00	-	0.70
SE 48h	≤ 23	0.00	1.00	-	0.70
NSE 0h	≥ 33	0.00	1.00	-	0.70
NSE 24h	≥ 52	0.11	1.00	1.00	0.72
NSE 35.5°C	≥ 40	0.11	1.00	1.00	0.72
NSE 48h	≥ 59	0.11	1.00	1.00	0.72
NSE end	≥ 66	0.13	1.00	1.00	0.73
S100B 0h	≥ 0.82	0.33	1.00	1.00	0.78
S100B 35.5°C	≥ 0.20	0.33	1.00	1.00	0.78
S100B end	≥ 1.00	0.00	1.00	-	0.70

Table 7. Sensitivities, specificities, positive prediction values and negative prediction values for the prediction of poor outcome. The thresholds of the variables are adjusted for 100% specificity.
Sens= sensitivity, Spec= specificity, PPV= positive prediction value, NPV= negative prediction value, WSE= wavelet subband entropy, BSR= burst suppression ratio, RE= Response Entropy, SE= State Entropy, NSE= neuron-specific enolase, S100B= protein 100B

The combination of WSE (from the first 24 h after cardiac arrest) and S-100B (after normothermia was reached) predicted correctly the outcomes of 26 of 30 patients. The Bayesian approach for this combination resulted in sensitivity of 89%, specificity of 86%, positive prediction value of 73%, and negative prediction value of 95%. Other combinations were also tested. Among the combinations of two variables (S-100B at 35.5°C, WSE 24 h after cardiac arrest, BSR 24 h after cardiac arrest, and NSE 24 h after cardiac arrest), the combination of WSE and S-100B predicted outcome most accurately.

6. Discussion

Methodology

Design

In certain patient groups, such as those undergoing anesthesia for cardiac, emergency trauma, or obstetric surgery, an increased risk for intraoperative awareness has been reported (Ghoneim and Block 1992, Ghoneim et al. 2009). In Jorvi Hospital, where Study I was conducted, no cardiac surgery was performed. Therefore, any conclusions from the results should be considered by taking into account the patients included. Patients unable to respond because of their condition (too sick) were also excluded and this may have had an influence on the results. Furthermore, in Study I patients were interviewed only once during their stay in hospital. Several studies have subsequently shown that repeated interviews during the first postoperative weeks may be needed to improve detection of cases with awareness and recall (Macleod and Maycock 1992, Sandin *et al.* 2000, Ghoneim *et al.* 2009).

In Study I, cases of awareness were classified as doubtful or certain. Incidence percentages are based on the patients with clear explicit recall of intraoperative events. In clear cases of intraoperative recollections, there are no problems in deciding whether or not the patient has been aware during the anesthesia. The decision is much more difficult with a patient with vague memories or dreams possibly related to intraoperative events. Because of the difficulty in definition of awareness, also patients with vague memories or dreams were reported in the results.

A relatively small and homogeneous population of ASA 1-2 patients participated in the Study III. Elderly or overweight patients and patients with a known history of untreated hypertension, medication affecting the central nervous system, history of neurological or connective tissue diseases, diabetes, or a history of alcohol or drug abuse were not included. Studies with larger populations, including also the above-mentioned patient groups, are needed in the future to test the feasibility of SSI.

Analgesics, local anesthetics, epinephrine

According to the protocol in the Study III, the induction dose of alfentanil was 15 µg/kg, which followed the clinical practice of the participating hospital (Surgical Hospital). The rescue dose of alfentanil was set at 0.25 mg. Outside the study, the commonly used bolus dose of alfentanil would be 0.5-1.0 mg for high BP, HR, sweating or movements. A low rescue dose was chosen to enable differentiation between ongoing nociception and unspecific reasons for these autonomic reactions. Uncovered

nociception needed several 0.25-mg doses of alfentanil, and it was not confused with spontaneous variation in baseline HR level.

The first four patients in Study III received only mepivacaine for their brachial plexus block. For the purpose of prolonged postoperative analgesia the remaining patients received a mixture of mepivacaine and bupivacaine. The quality of all blocks was tested before the induction of general anesthesia, and the duration between anesthesia induction and start of surgery was short. Therefore, it may be relatively safe to conclude that in the patients with recorded successful block, the analgesic effect of mepivacaine and of the mixture of mepivacaine and bupivacaine covered the total duration of surgery, and the local anesthetic probably did not cause any bias in the results.

Interscalene plexus block was performed with 5 µg/ml of epinephrine. Epinephrine was used in both groups to minimize bleeding. Local anesthetics or epinephrine may have had an influence on peripheral circulation and PPGA and HBI values through absorption into the circulation and systemic distribution, inducing changes in skin microcirculation. However, there was a similar increase in SSI after tetanic stimulus in the plexus group patients in whom the plexus block did not cover the ulnar side of the wrist, but who had received a small dose of epinephrine with the local anesthetic solution, and in those patients with no plexus block at all. This implies that the increase was because of nociception, rather than because of the epinephrine of the local anesthetic solution. Likewise, the SSI level prior to skin incision was similar between groups. The effect of the small amount of epinephrine seemed not to be a major confounding factor in Study III. However, in future studies, the blood concentration of epinephrine should be measured.

EEG

BIS (Study II) and Entropy (Studies II-IV) sensors were placed on the patient's forehead according to manufacturers´ instructions. In Study II, both BIS and Entropy sensors were used, and they were placed next to each other on the patient's forehead. Using Entropy or BIS with an S/5 monitor, it is possible to choose the original time-domain EEG signal on the monitor display, not only the index trends. Derivations used in Entropy and BIS monitoring are not compatible with the classical 10-20 electrode system, only being compatible with the one recommended by the manufacturers. The closest one resembling a 10-20 system derivation would be Fpz – F7 (or Fpz - F8). In Study IV, EEG electrodes were placed below the hairline to record channels Fp1-At1, Fp2-At2, At1-A1, and At2-A2. Because EEG was recorded with a very limited number of channels, it did not exclude residual EEG (Study II) or epileptiform activity (Study IV) that might have been recorded from 10-20 system locations. Rather high electrode impedances are acceptable according to the manufacturers (Entropy below 7.5 kΩ, BIS below 10 kΩ), which may give rise to more artifacts than in conventional EEG recordings (below 2 kΩ). The difference in the highest accepted electrode impedance may also be one of the reasons why Entropy was more resistant to artifacts during organ harvest (Study II).

Hemodynamic monitoring

Blood pressure was measured noninvasively (NIBP) and intermittently in Study III. Had blood pressure been measured continuously with an arterial line, the measurement would have reacted faster to changes in nociception. However, intermittently measured blood pressure and SSI are noninvasive and monitored with sensors routinely used in the operation theater. Thus, comparing the performance of SSI and NIBP is for most anesthesiologists more relevant than comparing the performance of SSI and invasive BP.

Outcome parameters

In Study IV, neurologic outcome after cardiac arrest was assessed with the Glasgow-Pittsburgh Cerebral Performance Categories (CPC) (Cummins et al. 1991). The overall neurologic outcome was defined as "good" if the best-achieved CPC score was 1 or 2 at any point within the six-month follow-up period after cardiac arrest. CPC scores from 3 to 5 referred "poor" neurologic outcome. Best-achieved CPC was chosen rather than final CPC at six months after cardiac arrest because some patients initially recover good neurological function, but die later of non-neurological causes.

Sample size and statistical analysis

At the time when sample size of the Study I was determined, no figure for incidence of awareness in outpatients was available in the literature. The hypothesis was that outpatients would be at higher risk for awareness. This was based on the assumption that the pressure for fast tracking and rapid recovery would predispose outpatients to receive less anesthetics, leading to increased risk for awareness. Power analysis was used to estimate the number of patients needed to be interviewed. For this purpose, it was estimated that the incidence of awareness would be 0.7% in the group of inpatients, and 1500 patients per group would be needed to detect a significant difference if the incidence of awareness were two times higher in the group of outpatients. The incidence of 0.7% in inpatients was based on a previous study by the same group of researchers (Ranta *et al.* 1998). If Study I were repeated today, the incidence of awareness would be anticipated to be lower than 0.7%. However, because contrary to the primary hypothesis, the incidence of awareness appeared to be even smaller (although not significantly) in outpatients than in inpatients, it may be relatively safe to conclude that outpatient surgery does not predispose patients to an increased risk of awareness. Altogether 89% of the consecutive outpatients and 67% of the inpatients were interviewed. The proportion of interviewed patients and the absolute number of patients (n=3843) were considered large and sufficiently representative of the hospital patient population not to cause any major sample bias.

Doses of anesthetics were compared between patients with awareness and those without it (Study I). A sample of 600 anesthetic records was considered representative to

describe the average doses of anesthetics. Case matching would have been another option for the statistical analysis. The benefit of case match would be less of data collection. On the other hand, there might have been a problem in finding suitable matches, especially as it is likely that more than one matching character would be needed. Thus, there would have been a danger of over-matching.

Power analysis was performed to estimate the required sample size also in Study III. Clinically significant reduction in the mean required dose of alfentanil (after the induction dose) was estimated to be 25%. Based on the Hospital's clinical database, a minimum of 2 mg alfentanil per surgery was estimated to be the mean consumption during acromioplasty without preoperative plexus block but with N_2O used during general anesthesia. To provide 80% power to detect a 25% change (two-sided) in alfentanil need with an alpha of 0.05, 24 patients per group were needed. N_2O is routinely used in the study hospital and it has an antinociceptive effect. N_2O was not included in the study protocol to minimize its confounding analgesic effects in the control group. Hence, the power calculation was only an approximation, as patient data from shoulder surgery under general anesthesia without N_2O were unavailable. The results were analyzed after the first 30 patients, and significant differences in alfentanil consumption and SSI values emerged. Thus, the sample size was considered adequate, and patient recruitment was stopped.

In Study III, the performance evaluation was used to compare how consistently SSI, HR, BPsys, and RE-SE could separate the low stress situation (before incision or effective plexus block at the site of nociception) from the high stress situation (after tetanic stimulus without effective block at the site of stimulation or skin incision in control group). When separating two reference values, as in this study, the Pk value of two categories is equal to the area under the curve of a ROC plot, which is a commonly used measure of the performance of a parameter predicting a known difference.

The limited number of patients in Study IV did not allow statistically reliable testing of the prediction properties of the measured indicators. Reporting a prediction model based on a combination of EEG-based indices and blood markers would have been clinically interesting. Preliminary results of the prediction powers of selected indicators are presented. A stepwise Bayesian classifier, which does not assume normal distribution of the variables, was used to examine the prediction power of a combination of EEG parameters and biochemical markers. The model correctly predicted the outcomes of 26 of the 30 patients, resulting in a sensitivity of 89%, a specificity of 86%, a positive prediction value of 73%, and a negative prediction value of 95%. The results are, however, preliminary, and the model should be tested with a separate independent group of patients. Other combinations than WSE + S100B were also tested, but among the combinations of two variables (one blood marker and one EEG-derived index), WSE and S-100B predicted outcome more reliably than others. Following the advise of an outside statistician, a p-value of 0.05 (WSE, Study IV) was reported as significant; the exact value was under 0.050 before rounding off to three decimals.

Incidence of explicit awareness and recall in outpatient anesthesia (Aim 1)

Results of Study I indicate that outpatients are not at increased risk for awareness during general anesthesia compared with inpatients. The results are in line with Enlund and Hassan (2002), who prospectively evaluated 5216 day-case or short-stay patients with a Brice interview and found that none of the patients interviewed indicated awareness. The incidence of awareness among inpatients in Study I was smaller than earlier incidence figures (Liu, WH *et al.* 1991, Ranta *et al.* 1998). The true incidence of awareness might have been underestimated because patients unable to respond due to their condition or those refusing to be interviewed were excluded. The incidence of awareness and recall might have been higher had patients with at increased risk for complications been included.

Premedication was administered to 15% of outpatients and 88% of inpatients. No difference in the incidence of awareness was found with respect to premedication, which agrees with the suggestion of a minor role of premedication in protection from awareness (Sandin et al. 2000). However, the timing of premedication in relation to the operation was not standardized, and the duration of surgery varied considerably. Therefore any conclusions about the effect of premedication on the incidence of awareness should be drawn cautiously.

Only 19% of outpatients received NMBAs, in contrast to 97% of inpatients. One outpatient with clear awareness, and four outpatients with doubtful awareness, all without muscle relaxants, emerged (Study I). No difference was seen in the incidence of awareness with respect to the administration of NMBAs. However, Study I was not designed to detect significant differences in the incidence of awareness in relation to the administration of NMBAs.

Contrary to the primary hypothesis, dosing of anesthetics was similar during in- and outpatient surgery. When isoflurane and sevoflurane were converted to MAC-equivalents, no significant difference in the dosing of inhaled anesthetics between outpatients and inpatients was found. Outpatients with awareness received smaller doses of sevoflurane during the maintenance of their general anesthesia than outpatients without awareness. However, the statistical difference in the dosing of anesthetics between the patients with and without awareness should be considered cautiously because of the small overall incidence of awareness. Further, no difference in the dose of isoflurane, the main volatile anesthetic in inpatients, was observed between patients with and without awareness and recall. Nevertheless, the finding with sevoflurane may indicate that smaller dosing of anesthetics is a major factor in predisposing patients to awareness (Ghoneim *et al.* 2009).

Effect of EEG artifacts on BIS and Entropy monitoring in brain-dead organ donors (Aim 2)

In Study II, BIS and Entropy monitoring in brain-dead organ donors during organ harvest was evaluated in order to determine the robustness of these methods in artifact rejection. Brain death was diagnosed according to Finnish law and legislations. Clinical examination, apnea challenge test and CT were performed on all patients. If angiography was performed (in eight patients), it was done on arrival to hospital for diagnostics, not as a confirmatory test for the diagnosis of brain death. Multichannel EEG measurement as a confirmatory test was not performed. This special group of patients was chosen with the assumption that at least most of the biosignals measured from forehead should consist of signals other than EEG (i.e. artifacts).

BIS and Entropy indices differed from zero in brain-dead organ donors for noticeably long periods during the organ harvest (SE in 28%, RE 29%, and BIS 68% of total recorded time). The result may indicate better detection and rejection of EEG epochs containing artifacts with Entropy monitoring than with BIS. Residual EEG activity was detected in four of 16 clinically brain-dead organ donors. CT of these patients showed herniation in two cases and severe brainstem injury in the other two cases.

At onset of brain death, patients are usually treated in the ICU with mechanical ventilation and numerous other electronic devices, possibly disturbing the EEG recording. In Finland, the diagnosis is based on clinical examination only, but as a confirmatory test EEG (which must demonstrate electrocortical silence over 30 min) is utilized in many countries (Haupt and Rudolf 1999, Randell 2004). Several biological and technical artifacts are related to the use of EEG in the diagnosis of brain death, but they are readily recognized in the visual analysis of the time-domain signal. EEG-based indices have also been suggested for the use of detection of brain death onset (Vivien *et al.* 2002). SE, RE, and BIS are equal to zero when their suppression detection algorithms assume suppressed EEG for a sufficiently long time. Index calculation from the original EEG adds more potential sources of error because artifacts cannot always be traced. In Study II, the sources of errors increasing the indices were evaluated, and several situations with erroneous increase of indices were detected. Whether special circumstances, such as metabolic disorders or mild hypothermia, could induce false-zero index values were not evaluated.

BIS and Entropy are recorded from a single derivation from the forehead (approximating Fpz – F7 or Fpz -F8) that does not represent the whole brain area. Index values equal to zero in the frontal region could be recorded in brain-dead patients if no artifacts were present in the EEG. However, this cannot guarantee that there is no EEG activity outside the frontal region. Therefore, using an inactive EEG to define brain death is totally different than that using index values equal to zero, both theoretically and in practice. To obtain an inactive EEG, several measurement locations with a long interelectrode distance outside the frontal region must be used. Amplification and filtering have to be changed during the recording. The inactive EEG should be permanent, not only periodic, as in burst suppression. Residual EEG has been reported in clinically brain-dead patients. Grigg et al. (Grigg *et al.* 1987) reported that 20% of brain-dead patients had some residual EEG activity that lasted up to 168 h. This is in

line with the results of Study II, demonstrating preserved EEG activity in 25% of organ donors. The short delay between brain death diagnosis and the beginning of organ retrieval (420 min) may explain the relatively high incidence of preserved EEG activity.

It has been stated, that no single test could confirm the disappearance of function of all cortical neurons (Guerit 2007). Clinical examination does not cover the whole brain, and even in optimal recordings, the persistence of a few hundred cortical neurons would be sufficient to produce identifiable EEG activity. Multimodality evoked potentials test only a part of the central nervous system. Even the techniques that demonstrate the arrest of cerebral blood flow may be inadequate to confirm whole-brain destruction. Persistent EEG activity has been found in some clinically brain-dead patients in whom four-vessel angiography demonstrated cerebral blood flow arrest (Grigg *et al.* 1987, Guerit 2007). The diagnosis of brain death has to be approached as a pathophysiological situation to make modern organ transplantation from brain dead-organ donors possible. It means verifying a pathophysiological process sufficient to cause irreversible and widespread neuronal destruction that prevents any persistence or eventual functional recovery of the neural networks required for human consciousness. However, even according to the pathophysiological approach, EEG may not be reliable in the context of brain death diagnosis, because it is sensitive to artifacts and metabolic disturbances (Guerit 2007).

BIS and Entropy values decreased after administration of NMBAs, BIS significantly more than Entropy. EMG artifact may be more pronounced in cases with low-amplitude EEG signals. Despite the use of BIS-XP electrodes (the modern version of BIS electrodes that has been claimed to be more resistant to artifacts), EMG induced high BIS readings more often than high Entropy readings. However, administration of NMBAs was not controlled in the study protocol (Study II). Hence, the exact time of sustaining a 100% block was not recorded, and with longer operations, the block has faded the course of time after the bolus dose of NMBAs. Therefore, we were unable to calculate whether the percentages of recorded time with an index value differing from zero remained significantly different between BIS, SE, and RE after NMBAs. As already discussed, the higher acceptable electrode impedance in BIS may increase the risk of artifacts compared with Entropy.

An ECG artifact was reported to lead to apparently "normal" BIS values in a severely brain-injured patient with complete burst suppression in EEG (Myles and Cairo 2004). Among organ donors with absent or weak residual EEG signals, the role of the ECG as a potential source of artifacts should be emphasized. Falsely elevated Entropy and BIS values during complete suppression of the EEG signal were detected in Study II. Visual inspection of EEG recording revealed easily detectable QRS complexes of the ECG. Potential sources of error might be also in the algorithm of BIS and Entropy. Low-amplitude EEG has been described in elderly people during anesthesia. Whether such low-amplitude EEG could become erroneously interpreted as suppression by the index calculation algorithm has not been investigated. If dedicated studies were conducted, other potential sources of error might appear, disturbing index calculation at the low end of the scale.

BIS and Entropy were developed to quantify hypnotic depth of GABA-ergic, drug-induced general anesthesia. For this purpose they perform well. When applying them

outside this originally described function, the potential sources of error should be known. Although Entropy may be more resistant to artifacts than BIS in brain-dead subjects, these indices are not diagnostic tools and should not be used to aid in the diagnosis of brain death. Diagnosis of brain death is based on clinical examination, and due to numerous artifacts, EEG-derived indices are not suitable for making this diagnosis.

Performance of Surgical Stress Index (Surgical Pleth Index) in patients with clinically different analgesic levels (Aim 3)

Surgical Stress Index (SSI, later Surgical Pleth Index, SPI) values recorded during the first two minutes after skin incision were significantly lower in patients undergoing shoulder surgery with an interscalene plexus block than in patients without the block. Tetanic stimulation to the ulnar region of the hand resulted in an increase of SSI values only in the patients with plexus block not covering the site of electrical stimulation. Consistent with effective analgesia at the site of surgery, the need for opioids during surgery was significantly lower in the plexus group. These findings support the usefulness of SSI for monitoring adequate analgesia during surgery. To date, no studies demonstrating the feasibility of SSI in ICU patients are available; thus, studies are needed before SSI or other analgesia monitories may be used in critically ill patients.

SSI predicted a noxious stimulus (skin incision, tetanic stimulus) better than HR, blood pressure, or RE-SE difference, which have traditionally been considered signs of inadequate anesthesia. Pk for SSI to detect noxious stimuli was higher than for those traditional variables in all of the studied nociceptive incidents: after skin incision in the plexus vs. control groups, before vs. after tetanic stimulation in the control group, and before vs. after skin incision in the control group. BP was measured intermittently (Study III). Therefore, Pk value of BP is not strictly comparable with other variables after the tetanic stimulation because it was measured only every five minutes. This might be too long an interval to detect a noxious stimulus lasting only 30 s. The results of Study III are in line with the previous studies of Ahonen et al. (2007) and Stryus et al. (2007), in which SSI has also been found to correlate better with noxious stimuli than HR and BP. In all of these previous studies, SSI has been calculated offline, and compared retrospectively and separately with HR and BP. Study III was followed by an editorial (Hoymork 2008), in which further studies with SSI as a tool for titrating analgesics during surgery were demanded.

When considering the results of Study III, it must be taken into account that exact Pk values are comparable only between identical study conditions. During this study, alfentanil was administered according to predefined clinical criteria without knowledge of SSI values. When SSI values were evaluated retrospectively, they were equal whether alfentanil was administered or not in the plexus group. In contrast to this, SSI values were higher if alfentanil was administered compared with the periods of no clinical signs of inadequate antinociception and no alfentanil administration in the control group. Thus, in the control group, traditional signs of inadequate antinociception and SSI values coincided. In the plexus group, the pain was adequately controlled, but changes in clinical parameters traditionally interpreted as indicating nociception

triggered alfentanil administration. SSI did not differ between the groups before skin incision. After the initial increase in SSI after the incision in the control group, frequent bolus doses of alfentanil decreased SSI values efficiently, and during the rest of the operation there were no significant differences in SSI values between the groups.

The population of Study III was heterogeneous with respect to the extent of the sensor and motor blockade. The block was tested before general anesthesia and considered efficiently analgesic for the shoulder surgery if it covered dermatomes C3-C6 and T2. In four patients, also the ulnar side of the hand was affected. Ulnar spread of the block did not affect nociception level during surgery (which was exclusively in the shoulder area), and thus, had an effect only on the results of tetanic stimulation. A delayed onset of ulnar block cannot be ruled out. However, most of the patients reacted to the tetanic stimulation, which would have been a surprising finding if they had had an effective ulnar block. Furthermore, even if second testing had been performed after recovery from general anesthesia, we still would not know whether the possible delayed block had started to take effect before or after the tetanic stimulation.

Modern balanced general anesthesia aims at individually optimized dosing of anesthetics. The need for anesthetics varies between patients and also within the same patient following surgical events. Despite the overlapping effects of anesthetics, each of the components should be able to be modulated individually. With complementary information about patients' hypnotic and analgesic balances available, the choice of medication might be more accurate in terms of expected effects and side-effects. SSI has been shown to be capable of differentiating decreases in HR achieved with opioid from those accomplished with a beta blocker (Ahonen et al. 2007). SSI provides continuous information about the nociception/ antinociception balance derived from circulation parameters that are routinely monitored in all patients under general anesthesia. An optimal range for SSI during anesthesia has not yet been recommended. A definition of acceptable activation of the sympathetic-adrenergic system with noxious stimulation during surgery is lacking. Systolic blood pressure values were significantly higher during surgery in the control group than in the plexus group. In addition, BPsys remained constant in the plexus group during surgery, but tended to increase in the control group. Based on this study alone, the highest acceptable level of sympathetic-adrenergic activation for the general well being of the patients cannot be determined. However, the study did show that SSI reacted consistently to sudden expected changes in sympathetic activation and its inhibition.

SSI was calculated from PPGA recordings of the contralateral hand to the surgery in both groups. A blockade of the sympathetic nervous system may change circulation also on the contralateral side (Landsverk et al. 2006), which might have had an influence on PPGA readings in the plexus group. Hypothermia, hypovolemia, arrhythmias, and medication affecting the autonomic nervous system may also impact SSI values, but they were not analyzed in this study. Monitoring of central venous pressure and body temperature may clarify other potential factors that have an independent effect on SSI. Further studies are needed to evaluate the effect of these possibly confounding factors on SSI.

Ability and time schedule of the quantitative EEG-derived indices in differentiating patients with good and poor neurological recovery after cardiac arrest (Aim 4)

The quantitative EEG variables BSR, RE, SE, and WSE were associated with neurological outcome after cardiac arrest in mild hypothermia-treated patients during the first 24 h (BSR, RE, and SE), and between 24 and 48 h (BSR and WSE). Status epilepticus after cardiac arrest was associated with significantly lower WSE and with death. WSE detected three of four patients with status epilepticus.

Prediction of neurological recovery after successful resuscitation from cardiac arrest is generally thought to require several days (Edgren *et al.* 1994, Zandbergen *et al.* 1998). In the present study, associations of RE and SE with discrimination between good and poor outcomes during the first 24 h were demonstrated. However, it should be noted that while Entropy algorithm detects burst suppression in the EEG, SE and RE are also calculated using burst-suppression information, and therefore, they have a strong correlation with BSR. BSR maintained its association with poor outcome during 24–48 h after cardiac arrest, but SE and RE did not. The result suggests that continuity of the EEG signal is the relevant feature associated with outcomes. This is in line with a recent study demonstrating that BIS and suppression ratio predicted outcome even better than ROSC (Seder et al. 2009). Deep hypothermia may result in high BSR without an association with poor outcome, but EEG is not significantly affected at a body temperature of 33°C, which is commonly used in hypothermia treatment (Michenfelder and Milde 1991, Stecker *et al.* 2001). In the present study, the depressive effects of hypnotics and analgesics on EEG readings during hypothermia are obvious, but are equal in both outcome groups. The use of midazolam and fentanyl has not been related to increased suppression in healthy volunteers. Barbiturates, propofol, etomidate, and γ-hydroxybuturate increased BSR in a dose-dependent manner. The critical range of 20-25% of BSR measured 24-96 h after admission to the ICU correlated with poor outcome. (Theilen *et al.* 2000). Similarly, in the present study, a decision boundary at 20% mean BSR at 24 h after cardiac arrest would have resulted in 89% sensitivity and 57% specificity for detection of poor outcome.

In previous studies, status epilepticus in original EEG monitoring has been associated with poor outcome (Young and Doig 2005, Rundgren *et al.* 2006). All of our patients with status epilepticus died. Because these patients were paralyzed, their status was nonconvulsive, thus visible only in the EEG, and was detected when data were analyzed offline for study purposes. Hence, no specific treatment to abolish status could be undertaken. Only sub-hairline EEG channels were used, and therefore, possible localized epileptiform activity elsewhere was not detected. Duration of seizures and delay to diagnosis are associated with increased mortality (Young *et al.* 1996). Based on these and previous results, continuous EEG monitoring in all comatose patients should be adopted.

WSE has previously been used to quantify epileptiform activity during sevoflurane anesthesia (Särkelä *et al.* 2007). In the present study, a gradual decrease in median WSE values was demonstrated from 12 h before onset of status epilepticus in three of four

status epilepticus patients. Decreasing WSE value might alert ICU care providers unfamiliar with EEG of threatening status epilepticus. However, the WSE method has thus far been studied only during sevoflurane anesthesia and now among cardiac arrest patients. It has been shown to react to epileptiform activity, but not to typical EEG patterns of anesthesia, except for burst suppression. Before WSE could be considered a clinically reliable tool in intensive care, further studies with larger patient material are required. Low WSE values caused by eye movements and burst suppression without epileptiform activity should be identified (Särkelä *et al.* 2007). WSE should also be studied in connection with different kinds of encephalopathy caused by critical illness. For a definite diagnosis of status epilepticus, the traditional multichannel EEG is still irreplaceable.

The limited number of patients did not allow statistically reliable testing of the prediction properties of the measured indicators. However, preliminary results of the prediction powers of selected indicators are presented. An outcome prediction analysis with a stepwise Bayesian approach was performed to examine the prediction power of a combination of EEG parameters and biochemical markers. Compared with other tested parameters (NSE 24 h and BSR 24 h), WSE (from the first 24 h) and S-100B (when rewarmed to 35.5°C) predicted outcome most accurately. The model predicted correctly the outcomes of 26 of the 30 patients, resulting in a sensitivity of 89%, specificity of 86%, PPV of 73%, and NPV of 95%. To validate these promising preliminary results, the classification model should be tested with a separate independent group of patients.

S-100B was lower in patients with good outcome than in patients with poor outcome already on arrival to ICU. After mild hypothermia treatment, both S-100B and NSE values were lower in the good outcome group. Both S-100B and NSE values had a decreasing trend in the good outcome group and an increasing trend in the poor outcome group. This study is in line with that of Tiainen et al. (2003) when considering NSE values, but not S-100B values, as prognostic markers in hypothermia-treated cardiac arrest patients. Although having similarities in study populations, treatment protocol, and design, these studies also have major differences. Tiainen et al. focused on the time course of serum NSE and S-100B in hypothermia- compared with normothermia-treated ICU patients. They did not find an association between the trends of S-100B measured 24 and 48 h after cardiac arrest and outcome, nor did they find a difference in the levels of serum S-100B between good and poor outcome in hypothermia-treated patients at 24 h. Tiainen et al. considered the clinical prognostic value of S-100B to be poor because of the remarkably low sensitivity (20-30%) when specificity was at least 95%. In the present study, the sensitivity of S-100B was slightly better, 38% with specificity of 100%, when S-100B was measured either on arrival to ICU or when patients had been rewarmed to 35.5°C (31-32 h after cardiac arrest). S-100B was measured earlier than in the study of Tiainen et al., namely on arrival to ICU and 31-32 h after cardiac arrest. The different time-points make it more difficult to compare the results from these two studies. The discrepancy may be also related to the relatively small number of patients in both studies. The biologic half-life of S-100B is very different from that of serum NSE, only 0.5-2 h, and thus, earlier measurements of S-100B may better reflect the initial degree of hypoxic-ischemic damage. Hachimi-Idrissi et al. (Hachimi-Idrissi *et al.* 2002) have previously reported that S-100B measured upon arrival at hospital differed significantly between patients who recovered

consciousness and those who did not, but their patients were not treated with hypothermia.

The pulsatile index of TCD was significantly lower in patients with good outcome than in patients with poor outcome. The result of the present study is comparable with that of Soehle et al. (Soehle *et al.* 2007), indicating that a pulsatile index higher than 0.8 was predictive of unfavorable outcome after subarachnoid hemorrhage. A pulsatile index higher than 2.0 has been associated with increased intracranial pressure among comatose patients with liver failure (Aggarwal et al. 1993).

7. Conclusions

The following conclusions can be drawn from these studies:

1. The incidence of intraoperative awareness and explicit recall during general anesthesia was not increased in outpatients relative to inpatients, in fact being even lower in outpatients than inpatients.

2. In brain-dead organ donors, values of Spectral Entropy, Response Entropy, and BIS differed significantly from zero during organ retrieval. The value of RE was greater than that of SE, and the value of BIS was greater than that of SE or RE. Sources of artifacts were as follows: electrode artifacts (electrocauterization and handling of patient, in 81% of recordings), ballistocardiography (44%), electromyography (38%), 50-Hz artifact (25%), and electrocardiography (19%). The highest index values were recorded without muscle relaxation. Entropy was more resistant to artifacts than BIS.

3. Surgical Stress Index (SSI, later Surgical Pleth Index, SPI) was significantly lower in patients with effective antinociception (brachial plexus block) in response to tetanic stimulation and skin incision. Pk for detecting nociceptive reactions was higher for SSI than for HR, noninvasive blood pressure, or RE-SE difference. SSI may offer a useful tool for determining adequate analgesia during surgery.

4. The EEG-derived indices (burst suppression ratio, Response Entropy, State Entropy, and wavelet subband Entropy) differed in hypothermia-treated patients with good and poor neurological outcome after cardiac arrest during the first 24 h (BSR, RE, and SE) and between 24–48 h (BSR and WSE). Prolonged high BSR, discontinued EEG, and status epilepticus indicated poor prognosis. Lower WSE was associated with status epilepticus and death.

8. Clinical considerations

1. Outpatients undergoing general anesthesia are not at increased risk for intraoperative awareness and explicit recall relative to inpatients.

2. In clinically brain-dead patients, BIS and Entropy values may differ considerably from zero due to artifacts. Persistent, unphysiologically distributed, nonreactive EEG activity is found in a considerable proportion of clinically diagnosed brain-dead patients. Several artifacts disturb the adequacy of BIS and Entropy monitoring during an organ harvest operation. Entropy seemed to be more resistant to these artifacts than BIS. However, these indices should not be considered an indicator of brain death.

3. Surgical Stress Index detected nociception better than HR, blood pressure, and RE-SE difference. Before commercially available depth-of-analgesia monitors became available for clinical use, further studies are needed to evaluate the clinical feasibility of SSI to titrate analgesia during general anesthesia.

4. In addition to conventional EEG and long-term monitoring, the EEG-derived indices may be used for early prognostication of neurological recovery after cardiac arrest. The number and length of suppressed EEG periods (BSR) seem to be the most relevant features associated with neurological outcome. Continuous EEG monitoring of all comatose patients should be recommended to detect nonconvulsive, fatal status epilepticus. Decreasing WSE value might alert medical personnel to the existence of status epilepticus, but normal WSE is not reliable in excluding status epilepticus.

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Johanna Wennervirta

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