Thesis for doctoral degree (Ph.D.)
2007

Hypnosis Monitoring during General Anaesthesia.

With focus on awareness

Andreas Ekman

Karolinska Institutet

Thesis for doctoral degree (Ph.D.) 2007

Hypnosis Monitoring during General Anaesthesia. Utility and limitations.

Andreas Ekman

From the Department of Physiology and Pharmacology
Section for Anesthesiology and Intensive Care Medicine
Karolinska Institutet, Stockholm, Sweden

HYPNOSIS MONITORING DURING GENERAL ANAESTHESIA

With focus on awareness

Andreas Ekman
M.D.

Stockholm 2007

To Mia, my great little sister.

Cover: Drawing by Rolf Ekman

All previously published papers were reproduced with permission from the publisher.

Printed by Larserics Digital Print AB

© Andreas Ekman, 2007

ISBN 978-91-7357-381-8

ABSTRACT

An objective measure of the hypnotic component of general anaesthesia has been sought for decades.

The electroencephalogram (EEG) was early recognized as a possible useful intraoperative monitor when the effects of anaesthetic drugs on human EEG recordings were noted. The last few years have brought forward a number of commercialized monitor devices that by an index claim to give the anaesthetist an objective measure of hypnosis.

Two diverse monitoring methods, differing in principle, have been developed: 1) passively processed EEG, and 2) stimulated and thereafter processed EEG. The Bispectral Index Scale™ (BIS) and the A-line ARX-Index™ (AAI) are two such monitors were BIS represents the first principle and AAI the second. In several studies the use of BIS and AAI has been shown to reduce the amount of anaesthetics given and expedite postoperative recovery as compared to standard practice. However a number of studies have also shown that the sensitivity and specificity for BIS and AAI are not perfect, and fears have been raised that the incidence of awareness even might increase if the anaesthetist aims at an upper threshold value. In this thesis, it is demonstrated that BIS monitoring during general anaesthesia in a non-cardiac, surgical population requiring endotracheal intubation and/or a neuromuscular blocking agent (NMBA) was associated with a significantly reduced incidence of awareness as compared to a historical control population. Our results suggest that BIS better displays drug related alterations in the level of hypnosis than AAI in an already anesthetized patient, and that there is no difference between BIS and AAI in the response time to a noxious stimulus. We have further seen that profound neuromuscular block attenuate BIS and AAI responses to a standardized noxious stimulation during sevoflurane anaesthesia as compared to a partial neuromuscular block or after neostigmine induced reversal, and that the monitor responses were not due to electromyogram (EMG) contamination of the EEG. It is demonstrated that EEG responses to noxious stimulation, in terms of power and coherence in the γ-band, are affected by profound neuromuscular block during light sevoflurane anaesthesia.

In conclusion we demonstrate that hypnosis monitoring can reduce the incidence of awareness, BIS is superior to AAI to display alterations in the level of hypnosis during aneasthesia and NMBAs affect the level of hypnosis during light general anaesthesia in stimulated patients.

Key words: hypnosis monitoring, electroencephalogram, BIS, AAI, neuromuscular block

”Never refuse a coffee break!”

Anders Erson, one of my very best clinical supervisors.

“Sometimes you have to think and sometimes you don’t! Sometimes you have to act and sometimes you don’t! But you always have to evaluate!

Karin Olofsson, one of my very best clinical supervisors.

“Maskiner tar över…
Är det nåt vi behöver?
Maskiner som söver…”

Alltid rött, Alltid rätt. Imperiet

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I. Ekman A, Lindholm ML, Lennmarken C, Sandin R.*
Reduction in the incidence of awareness using BIS monitoring.
Acta Anaesthesiol Scand 2004; 48: 20-6.

II. Ekman A, Brudin L, Sandin R.
A comparison of bispectral index and rapidly extracted auditory evoked potentials index responses to noxious stimulation during sevoflurane anesthesia.
Anesth Analg 2004; 99: 1141-6.

III. Ekman A, Stålberg E, Sundman E, Eriksson LI, Brudin L, Sandin R.
The effect of neuromuscular block and noxious stimulation on hypnosis monitoring during sevoflurane anesthesia.
Anesth Analg 2007; 105: 688-95

IV. Ekman A, Flink R, Sundman E, Eriksson LI, Brudin L, Sandin R**.**
Neuromuscular block and the electroencephalogram during sevoflurane anaesthesia.
Neuroreport 2007; 18: 1817-20

* *Position as first author shared with Maj-Lis Lindholm.*

CONTENTS

LIST OF ABBREVIATIONS

AAI	A-line ARX index (ARX = autoregressive model with exogenous input)
AEP	Auditory evoked potentials
BIS	Bispectral index scale
BMI	Body mass index
CNS	Central nervous system
EEG	Electroencephalogram
EMG	Electromyogram
EMG_{BIS}	Electromyogram from the BIS monitor
ET_{AA}	End tidal anaesthetic agent concentration
IFT	Isolated forearm technique
MAC	Minimum alveolar concentration
$MAC_{skin\ incision}$	Minimum alveolar concentration at skin incision when 50% of patients do not respond
MAC_{awake}	Minimum alveolar concentration when 50 % of patients are not awake
MLAEP	Middle latency auditory evoked potentials
NMB	Neuromuscular block
NMBA	Neuromuscular blocking agent
N_2O	Nitrous oxide
OR	Odds ratio
PRST	Blood pressure, heart rate, sweating, tear production
SNR	Signal to noise ratio
TIVA	Total intravenous anaesthesia
VAS	Visual analogue scale

INTRODUCTION

General anaesthesia

General anaesthesia is, by many, considered to have been born on October 16, 1846. That day, dentist William T. G. Morton demonstrated the use of ether inhalation for surgical anaesthesia on a patient at Massachusetts General Hospital, Boston, USA[53]. Ether anaesthesia was subsequently quickly adopted around the world. Before this day surgery was uncommon and often a horrific experience for the patient. Morbidity and mortality was very high. Even though our understanding and methods of administering general anaesthesia have evolved over time we still do not have a definition of general anaesthesia that is commonly agreed upon. Nonetheless, most anaesthetists would consider the following components as a prerequisite for general anaesthesia: unconsciousness or hypnosis, analgesia, autonomic reflex stability and muscle relaxation[38]. Anaesthesia can be defined as a reversible state of drug-induced unconsciousness that results in a patient that neither perceives nor recalls noxious stimulation. More broadly defined anaesthesia is unresponsiveness to the trauma of surgery[82].

What is "anaesthetic depth"?

One of the first descriptions of anaesthetic depth was John Snow's "five degrees of narcotism" for ether anaesthesia 1847[110]. In 1937 Guedel published his classic text describing the stages and planes of ether anaesthesia relating them to clinical signs and relevant reflexes. The signs involved somatic muscle tone, respiratory patterns and ocular signs[36]. Today, in general anaesthesia, different drugs are usually used to achieve various clinical responses to minimize each drug's side effects.
The goals of anaesthesia are reached using diverse drugs in combination or alone depending on the particular patient and the type of surgery that is performed[51]. Drugs are usually defined according to their major effect as e.g. hypnotics, analgesics, neuromuscular blocking agents (NMBAs) and cardiovascular acting drugs (most often used to counteract the side-effects from the other drugs and surgery itself). Commonly used drugs in clinical anaesthesia today include;
- Hypnotics: Inhalational agents (e.g. halothane, isoflurane, desflurane, sevoflurane, nitrous oxide), Intravenous agents (e.g. thiopental, propofol, ketamine, benzodiazepines).

- Analgesics (e.g. opoids, anti-inflammatory drugs, local anaesthetics, ketamine, nitrous oxide).
-NMBAs (e.g. rocuronium, vecoronium, atracurium, suxamethonium).
- Cardiovascular drugs (e.g. atropine, β-blockers, ephedrine, nitroglycerine).

Understanding anaesthesia as a spectrum of separate pharmacological actions that vary according to the goals of anaesthesia makes it almost impossible to determine depth of anaesthesia using only one measuring method[33,38,50]. Instead, both specifically defined stimuli and specific responses are needed to define depth of anaesthesia[112]. In the clinic, depth of anaesthesia depends of two antagonizing factors: the anaesthetic drug, or drugs, that induce the different components of anaesthesia and the variable surgical stimuli[38].

Awareness

Memory is a crucial and sustaining mental function that shapes our existence. All other cognitive functions would be meaningless or impossible without the ability to record and recall previous experiences[31]. Long term memory is currently classified into two types of memory; explicit or conscious memory, and implicit or unconscious memory. Explicit memory refers to the conscious recollection of previous experiences; it is equivalent to "remembering". Implicit memory refers to changes in behaviour or performance but without any conscious recollection of the previous experiences[30]. The term awareness is usually, and will be in this thesis, used to describe explicit memory, or rather, explicit recall of intraoperative events during general anaesthesia.
Since the first public demonstration of ether anesthesia by Morton, awareness has been a concern. Gilbert Abbott, the patient, experienced pain at the time and was aware that the operation was proceeding. "During the operation the patient muttered, as in a semi-conscious state, and afterwards stated that the pain was considerable, though mitigated; in his own words, as though the skin had been scratched with a hoe." surgeon Henry Bigelow wrote in his account of the event[6]. Today awareness is a rare but dreaded complication to general anaesthesia world-wide, which may result in severe immediate and long-lasting postoperative morbidity.

Incidence

In 1960 Ruth Hutchinson published the first study on the incidence of awareness during general anaesthesia. She found that 1.2% of 656 surgical patients remembered having been aware[41]. After that, several investigators have studied the incidence, and since 1991 six prospective studies including a reasonable number of patients subjected to different types of surgery have been published[58,75,76,88,99,104]. These studies from different continents (North America, Australia-New Zealand and Europe) suggest a world-wide incidence of awareness of 0.15% (0.1%-0.4%). The circumstances affecting the results in available studies are often lacking and there are several factors existing that probably influence the found incidence of awareness.

-Delayed memory

Delayed memory for explicit recall has been reported[1,62,94], and in one study[99] 11 785 patients were questioned at 3 different time points after anaesthesia. The last structured interview took place during the second week after surgery. In 50% of the ultimately identified awareness cases recall was delayed by several days. In the study by Sebel et al[104] a similar rate of awareness cases, not previously identified, were found at the second interview, at least one week after the anaesthesia.

-End Tidal Anaesthetic Agent Concentration (ET_{AA})

MAC-Minimum Alveolar Concentration, is a concept that was introduced in the 1970's and is used to describe the potency of inhalational agents. It is defined as the alveolar concentration of an inhalational anaesthetic at which 50% of the patients do not respond to a specified stimulus, the original stimulus being skin incision[67]. The concentration of inhalational anaesthetic agents can be measured at different time points during the respiratory cycle. The end expiratory (end tidal) concentration at steady state conditions is considered to reflect the alveolar and hence the cerebral concentration of the inhaled anaesthetic agent. However this system contains several weak points. The effectiveness of ET_{AA}-monitoring in order to prevent awareness has not yet been evaluated in a randomized study, albeit a poster addressing this question was displayed at the American Society of Anesthesiologists meeting in San Francisco this year. The number of awareness cases in the abstract[20], 4 patients, seems to low for firm conclusions. In a prospective cohort study where patients received neuromuscular block, a group of patients were subjected to ET_{AA}-monitoring and one group was not[99]. In that study the incidence of awareness was similar, 0.2%, in both groups. Intense noxious stimulation during laryngoscopy and intubation are important reasons for awareness, these events often occur before ET_{AA}-monitoring has been applied. In hemodynamically unstable cases when the inspired fraction of anaesthetic gas is rapidly and frequently altered, ET_{AA}-monitoring does not mirror the cerebral concentration of anaesthetic gases. Furthermore, the lowest concentration of an inhalational anaestetic that prevents awareness in all patients has not been established. Thus, one can not expect that the use of ET_{AA}-monitoring will eliminate awareness although it generally is very useful.

-Nitrous oxide (N_2O)

For more than 150 years nitrous oxide has been used during general anaesthesia. The use is now probably diminishing, mainly due to environmental issues, both occupational and global polluting aspects considered, but also because of recent findings indicating increasing incidence of complications after major surgery[72,115]. A meta-analysis raised the fear of increasing the risk of awareness if N_2O was omitted[120]. When scrutinizing the data of this meta-analysis one can see that seven of eight awareness cases came from the same study[18], 6 patients without, and one patient with N_2O. In this study the ET_{AA} of isoflurane was very low in the 6 patients receiving N_2O-free anaesthesia (on average 0.70±0.35% and in 4 of these patients the average was only 0.52±0.29% which is close to the concentration when 50% of patients are expected to be awake without any noxious stimulation (MAC_{awake})). The insufficient isoflurane anaesthesia is obviously the cause of the high incidence of awareness in the N_2O-free group and not the omission of N_2O *per se*. No other relevant information on awareness and N_2O is available.

-Neuromuscular block

The occurrence of awareness was not a problem until the introduction of curare into clinical practice in the mid 1940's. The clinical signs of impending awareness disappeared when curare was used and many clinicians were reluctant to use it[39]. Today there is no randomized clinical trial investigating if there is a difference in incidence of awareness in anaesthesia using an NMBA or not. Probably there is an increased incidence when using NMBAs compared to anaesthesia without NMBAs. The extremely low number of reported cases of awareness during anaesthesia without NMBAs, and the fact that all reported patients with severe suffering after anaesthesia have had anaesthesia including an NMBA indicate increased incidence when NMBAs are used[97].

-Total intravenous anaesthesia (TIVA)

No randomized clinical trial has compared the incidence of awareness in TIVA and other types of general anaesthesia. In one prospective case study using TIVA including an NMBA the incidence of awareness was 0.2%, i.e. the same as in other types of general anaesthesia[76].

-Type of surgery

Caesarean section, rigid bronchoscopy as well as cardiac- and trauma surgery have been considered as high-risk procedures for awareness.

Lyons and McDonald reported an incidence of only 0.4% in 1991 for 3000 patients subjected to Caesarean section[61]. Today, most Caesarean sections are performed during regional anaesthesia (spinal or epidural). However, when general anaesthesia is used, the risk of awareness has probably been reduced by more reasonable induction doses of thiopental or propofol and by more rational handling of the halogenated inhalational anaesthestics than before 1990.

Awareness during cardiac anaesthesia has for a long period been considered to occur in 1.1% to 23% of patients[34,39,80]. Ranta[86] showed that feedback to the anaesthetists about outcome led to a change of practice and a reduced incidence of awareness from 4% to 1.5%. A recent study, in 617 “fast-track” cardiac cases, showed an awareness incidence of 0.3%[16] and a the most recent study in standard coronary artery by pass patients found an incidence of 0.5%[87]. Thus it seems possible to reduce the incidence also in cardiac anaesthesia.

Trauma surgery has been associated with high incidences of awareness and explicit recall up to 43% has been reported[7]. Lubke et al.[59] found no case of explicit recall in a series of 96 trauma cases (although evidence of high incidence of implicit memory was found).

In a recent study by Pollard et al.[81] an incidence of awareness of approximately 1/15000 was found. This is the lowest incidence ever reported in a reasonably large study. The patients were questioned twice within 48 hours of surgery with a structured interview that deviated from the modified Brice interview[9,58], which has been the standard for years. On questioning, the two key questions in the modified Brice interview were left out (“Do you remember anything between going to sleep and waking up?” and “What was the worst thing about your operation?”). Furthermore, it is not known how many of the patients in the study that were given an NMBA or not (the 6 reported awareness cases all received an NMBA). Delayed memory and the way the patients were interviewed in this study probably underestimate the true incidence of awareness significantly[55,105].

Causes

The cause of awareness is inadequate anaesthesia in relation to the needs of the patient during the specific surgical procedure. There are mainly three situations associated with awareness[30]:

1. Intentionally light anaesthesia- e.g. due to circulatory compromise (hypovolaemia or minimal cardiac reserve) or for certain operations such as Caesarean section. Unintentionally light anaesthesia, misjudgment of depth of anaesthesia leads to “too little” anaesthetic drugs, especially when NMBAs are used for abolishing motor responses to pain, which probably is the best clinical sign of inadequate anaesthesia. Intense noxious stimulation during laryngoscopy and intubation are important reasons for awareness, and this probably applies also to other situations in which the degree of noxious stimulation is suddenly increased.
2. Equipment malfunction, e.g. vaporizer or intravenous pump failure, disconnected delivery tubing or central gas systems not working properly.
3. The patient with increased anaesthetic requirement e.g younger age, tobacco smoking and long-term use of certain drugs (alchohol, opiates or aphetamines).

Consequences

Many are the case reports describing the horror experiences of awareness. Immediate suffering in form of pain and sensation of paralysis are often mentioned. Other frequent complaints include hearing during surgery, sensations of weakness and feelings of helplessness, anxiety, panic and impending death[69,71,79]. However, not all patients suffer during wakefulness and therefore it is not possible to assess the average severity of suffering from case reports[98,99].

Awareness may cause temporary after-effects, including sleep disturbances, nightmares and daytime anxiety, which subsides eventually. In some patients, a post traumatic stress disorder develops, characterized by repetitive nightmares, anxiety and irritability, a preoccupation with death, and a concern with sanity that make the patients reluctant to discuss their symptoms[71,79].

Why some patients develop post traumatic stress disorder and some do not, is not known. Personality, predisposition to mental disease and the grounds for surgery could be some of the reasons[97].

Myles et al[75] investigated reasons for postoperative dissatisfaction among 10 811 anaesthetized patients. The incidence of awareness in the study was 0.11%. The adjusted odds ratio (OR) for patient dissatisfaction in case of awareness was 54.9, an

OR several times higher than that for moderate/severe postoperative pain (OR 6.95), severe postoperative nausea and vomiting (OR 4.09) or multiple complications (OR 6.25). This may not directly reflect the degree of suffering due to awareness but instead patient expectations of anaesthesia and surgery; patients may anticipate pain and nausea after surgery but they do not expect to attend their own surgery.
Today there are only six studies published concerning early and late sequelae after awareness[15,54,71,79,96,102]. Four of them are retrospective, and the cases have been enrolled in different ways; by advertisements, by referral from colleagues and by "closed-claims" analysis[15,71,79,102]. The way data are gathered may introduce selection bias, e.g. singling out patients with more severe symptoms, more dissatisfied patients and patients seeking economic compensation. Of the two prospective studies addressing the sequelae of awareness, one includes only 9 patients[54] and the other 46 patients[96]. The immediate suffering in terms of pain, panic and mental distress in both retrospective and prospective studies is around 50%. The incidence of late psychological symptoms in the most recent and larger study was 33%, which is less than in previous studies[96] (see *Table 1*).

Table 1.

Study	Late psychological symptoms, %
Moerman et al[71]	69
Schwender et al[102]	49
Osterman et al[79]	56
Domino et al[15]	84
Lennmarken et al[54]	39
Samuelsson et al[96]	33

Modified from reference 96

In USA over 20 million general anaesthetics are administered annually. Even though awareness is a rare complication, occurring in 1-2 cases per thousand, this will produce 20 000 to 40 000 cases of awareness each year[103]. Of these cases perhaps a third will have late psychological symptoms and some of these will develop a post traumatic stress disorder[96]. If one considers the actual number of general anesthesia's including an NMBA administered annually in Sweden the number of patients would be considerably less, but still 200-400 patients would experience awareness every year. Attempts to prevent this complication are therefore motivated.

Hypnosis monitoring

Depth of hypnosis has been and most often still is, assessed by the individual anaesthetist by direct observation of the patient and unsophisticated physiological parameters. Clinical scores/scales that have been constructed to generalize the subjective estimation, e.g. the PRST score (changes in blood Pressure, heart Rate, Sweating, and Tear production)[14]. Somatic reflexes (patient movements) are judged, the knowledge of pharmacokinetics and pharmacodynamics of the different drugs used as well as the ongoing surgery and the experience of the anaesthetist are all providing information that are used to the benefits of our patients. Ironically, the most common guide to overall anaesthetic effect is usually cardiovascular side effects. At present no definite clinical sign exists that can serve as a basis for rational administration of drugs to achieve unconsciousness[91].

In the awake patient, the function of the central nervous system (CNS) can be tested directly by physical examination. When general anaesthesia is used, direct testing of CNS function is not possible[63]. Monitoring the CNS effects of general anaesthesia in a quantitative, reliable way is an important issue to the specialty of anaesthesia and an objective measure of the hypnotic component of anesthesia has been sought for decades. Many are the attempts to bring forward a technique or a device to determine the depth of anaesthesia (see *Table 2*)[17]. One of those methods is the isolated forearm technique (IFT)[121]. Despite the fact that this method is generally regarded as a scientific “Gold-Standard” for detecting cognitive function during anaesthesia including a NMBA, it has failed to reach widespread clinical use. Some of the arguments for the reluctance to use the IFT have been reviewed and evaluated by Russell[92].Several of the techniques allow one to identify statistically significant differences in depth of anaesthesia during defined anaesthetic conditions in certain populations of patients, but none of the techniques have the sensitivity and specificity to allow the clinician to draw certain conclusions about the individual patient being treated.

Table 2. Techniques that have been used in the assessment of depth of anaesthesia

Isolated forearm technique (IFT)
Craniofacial electromyografi
Respiratory sinus arrhythmia
Heart rate variability
EEG derivatives
Spectral edge frequency
Median power frequency
Power band ratios
Evoked responses
P300
Middle latency evoked response
Auditory steady state response (ASSR)
Coherent frequency of the ASSR
Contingent negative variation
Lower oesophageal contractility

EEG = electroencephalogram From reference 17

Electroencephalogram (EEG)

The EEG was recognized early on as a possible useful intraoperative monitor when the effects of anesthetic drugs on human EEG recordings were noted[32].

In 1875, a physician in Liverpool, Richard Caton[12] reported his discovery of electric currents on the surface of rabbit and monkey brains. Caton even noted the change in epicortical currents with peripheral stimulation, thus providing the first description of evoked potentials. This seminal work was published 28 years before Einthoven's initial description of the electrocardiogram[83]. In 1929, Hans Berger[5], a psychiatrist in Jena, reported what is commonly accepted as the first systematic description of human EEG. EEG is classically classified as alpha (α), beta (β), delta (δ) and theta (θ) waves depending on their frequency after transformation to fundamental sinusoides. In 1937 Gibbs[32] reported the effects of ether, alcohol, barbiturates and other drugs on human EEG.

Advances in the field of neurophysiology, during the last 30 year, have increased understanding of the electrophysiology of the brain and the genesis of the EEG. Significant improvement in equipment that transduce, amplify and display EEG together with the introduction of microcomputer technology has made it possible to process and display data obtained from EEG in real-time[84].

The EEG is produced by summation of excitatory and inhibitory postsynaptic potentials produced in the cortical gray matter. The anatomy of the cerebral cortex provides a means of generating relatively robust signals. When large populations of neighbouring cells have similar and synchronous areas of altered membrane potentials, their current loops combine additively in the extra cellular fluid to much larger regional currents that can be detected by scalp electrodes[83]. The spontaneous EEG appears to be random tracings whose waves have no direct connection to known physiological or behavioural activity. In spite of this, more than one-half a century experiences of monitoring EEG has led to many known correlations of EEG patterns with normal and pathological states of cerebral cortex as well as different EEG patterns during general anaestheia[83]. The overall pattern of EEG changes is similar for many hypnotic agents, although individual agents can produce unique effects[112]. General anaesthesia is associated with a decrease in the average EEG frequency and an increase in the average EEG amplitude. This and added information from the complex raw EEG can be mathematically derived to create different indices that reflect anaesthetic effect on the EEG. The last few years have brought a number of commercialized hypnosis monitor devices that claim to give the anaesthetist an objective measure of hypnosis using an index[11].

Two principally different monitoring methods have been developed: passively processed EEG, and stimulated and thereafter processed EEG.

Bispectral Index Scale™ (BIS)

BIS is an example of passively processed EEG. The BIS monitor is the most used and studied hypnosis monitor up to now. The exact algorithm that is used to process the EEG is proprietary. Known is that it integrates various EEG descriptors (bispectral analysis, frequency- and power analysis, burst suppression and β-activation) into a single variable[84,107]. The mixture of sub-parameters of EEG activity was empirically derived from a prospectively collected database of volunteers and patients anesthetized using several different anesthetic regimens. The EEG was recorded and time-matched to clinically relevant endpoints and drug concentrations[45]. When the BIS is used in clinical practice, surface electrodes are placed on the forehead and the analogue EEG signal thus attained is processed in real time, resulting in an index value displayed on the monitor with a time lag of at least 15- 30 seconds depending on artefact handling and the settings chosen by the user. The BIS value is described using arbitrary units that ranges from 100 (awake) to 0 (isoelectric EEG) and the recommended value for surgical anesthesia is 40-60. As other hypnosis monitors, BIS measures the EEG effect and not the concentration of a particular drug. It can only assess the actual situation, not foresee what will happen in case of a change in the degree of noxious stimulation.

A-line ARX-Index™ (AAI)

AAI is an index that is derived from mid latency auditory evoked potentials (MLAEP), i.e. stimulated EEG[42,123].The auditory evoked potentials waveform is elicited by a repetitive clicking sound provided via earphones to the patient. The MLAEP represents the early cortical (primary auditory cortex) response to auditory stimuli, occurring 10 to 80 ms after the click stimulus. The MLAEP show similar changes to different hypnotics used within the clinical concentration range in general anaesthesia[118]. The EEG, from which the MLAEP are derived, is recorded from a surface electrode attached to the mastoid bone, referenced to a frontal electrode. The MLAEP are extracted in 2-6 seconds, and processed in real time resulting in a time lag at least 10 seconds long. The latest version of AAI is a composite index calculated from MLAEP and/or EEG changes depending on signal-to-noise ratio (SNR) of the extracted MLAEP. If SNR <1.45, the AAI is not calculated from MLAEP but is instead based on EEG β-ratio and burst suppression[127]. AAI ranges from 99 (awake) to 0 (deep hypnosis) and recommended range for surgical anesthesia is15-25.

Electromyogram (EMG)

EMG is generally considered to constitute an increasing part of the electrical power spectrum above the frequency of about 30 Hz (see *Figure 1*). Thus, EMG in the frontal muscle has a potential to distort the index calculating algorithms if higher frequencies are considered[13,43]. The BIS algorithm quantifies the spectral power between 70-110 Hz as an estimate of EMG activity, and the corresponding range for AAI is 65-85 Hz.

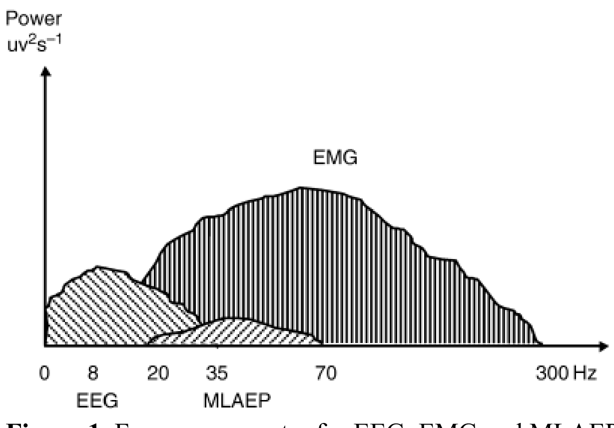

Figure 1. Frequency spectra for EEG, EMG and MLAEP. (From reference 43)
EEG = electroencephalogram, EMG = electromyogram, MLAEP = middle latency auditory evoked potentials

Neuromuscular block

A frequent observation is that a bolus of an NMBA reduces the displayed index value of a hypnosis monitor. This has been interpreted as decreasing EMG contamination and thereby distortion of the index calculating algorithms. There are conflicting data in the literature concerning the influence of NMBAs on the EMG signal and the resultant effect on BIS[10,35,68,108,124,128]. An unpublished observation by our group is that we have noted that fully awake, conscious, spontaneously breathing subjects given infusions of NMBA seem to be increasingly sedated in relation to depression of the first twitch in a train-of-four sequence. It has been suggested that NMBAs may affect the level of hypnosis by functional deafferentation, i.e. by suppressing muscle afferents to the spinal cord and thereby reducing arousing signalling to the brain[52].

In several studies BIS and AAI have been shown to reduce the amount of anesthetics given and expedite immediate postoperative recovery as compared to standard practice[28,57,89,111]. A number of studies have also demonstrated that the sensitivity and specificity for BIS and AAI are not perfect[26,27,33,56,100] and fears have been raised that the incidence of awareness might even increase if the anaesthetist aims at an upper threshold value[47,109,119].

AIMS

The overall aim of this thesis was to investigate the usefulness and limitations of hypnosis monitoring in a general surgical population, with focus on awareness. This was done using two commercialized hypnosis monitors whose indices are based on two principally different monitoring methods, BIS and AAI. The specific aims were:

- To investigate the effect of hypnosis monitoring on the incidence of awareness in clinical practice, using BIS monitoring as routine.
- To compare how BIS, AAI and commonly used hemodynamic variables display a sudden increase in sevoflurane concentration.
- To determine how BIS and AAI respond to a sudden noxious stimulation (laryngoscopy) during sevoflurane anaesthesia.
- To investigate the effect of rocuronium, an NMBA, with and without noxious stimuli, on BIS, AAI and the EMG during sevoflurane anaesthesia.
- To investigate the effect of rocuronium on the EEG with and without noxious stimulation during sevoflurane anaesthesia.

MATHERIAL AND METHODS

For detailed information see individual papers. All studies were performed after patients had given their informed consent and after approval by the local ethical committee at Linköping University.

Patients/Subjects

Paper I

A prospective cohort of 4945 consecutive surgical patients requiring an NMBA and/or intubation, aged 16 and older, was investigated. Exclusion criteria were inability to communicate in Swedish or English, surgery precluding the use of BIS sensors on the forehead, and failure to conduct any of the two last interviews for awareness. 7 826 patients from a previous study, without BIS monitoring, were used as a control group.

Paper II

21 patients scheduled for elective knee arthroscopy using general anaesthesia were enrolled. Exclusion criteria were body mass index (BMI) >30, neurological disorders, hearing disorders, and use of active psychotherapeutics.

Paper III

25 patients scheduled for elective surgery during general anaesthesia, expected to last more than 90 minutes, were included. Patients with BMI > 30, neurological or neuromuscular disorders, impaired hearing and patients with medications known to interfere with neuromuscular function or the CNS were excluded.

Paper IV

13 patients scheduled for elective surgery during general anaesthesia, expected to last more than 90 minutes were included. Exclusion criteria were the same as in papers 2 and 3 except for the hearing criteria since AAI was not studied.

Monitoring equipment

In all studies standard monitoring, including electrocardiogram, oxygen saturation by pulse oximetry, non-invasive blood pressure and end-tidal gas concentrations were obtained using the Datex Ohmeda ADU98/S5 monitor (GE Healthcare, Helsinki, Finland).

Paper I

Standard monitoring and hypnosis monitoring using the BIS A-2000™ monitor (BIS index version 3.4) (Aspect Medical Systems, Newton, MA, USA).

Paper II

Standard monitoring and hypnosis monitoring using the BIS A-2000™ XP monitor (BIS index version 4.0) (Aspect Medical Systems, Newton, MA, USA) and the A-line™ monitor (version 1.4) (Danmeter A/S, Odense, Denmark).

Paper III

Standard monitoring and hypnosis monitoring using the BIS A-2000™ XP monitor (BIS index version 4.0) (Aspect Medical Systems, Newton, MA, USA) and the AEP monitor/2™ (version 1.6, Danmeter A/S, Odense, Denmark). The Nervus® C16 amplifier (Cephalon A/S, Nörresundsby, Denmark) was used for recording EMG. Neuromuscular block was assessed by isometric mechanomyography of the adductor pollicis muscle using a Biometer Myograph 2000® neuromuscular transmission analyzer (Organon Teknika, Turnhout, Belgium). Tetanic electrical stimulation was delivered to the ulnar nerve via surface electrodes using a nerve stimulator (CEFAR Tempo®, CEFAR Medical AB, Lund, Sweden).

Paper IV

Standard monitoring and hypnosis monitoring using the BIS A-2000™ XP monitor (BIS index version 4.0) (Aspect Medical Systems, Newton, MA, USA).The Nervus® C16 amplifier (Cephalon A/S, Nörresundsby, Denmark) was used for recording the EEG. Biometer Myograph 2000® neuromuscular transmission analyzer (Organon Teknika, Turnhout, Belgium) was used for analysis of the neuromuscular block. The same nerve stimulator (CEFAR Tempo®, CEFAR Medical AB, Lund, Sweden) as in paper III was used.

Study protocols and data analysis

Paper I

All staff who routinely gave anaesthesia at two Swedish hospitals participated. BIS monitors were installed in every operating room. All anaesthesia providers received basic training on the use of the BIS monitor before the start of the study; education was repeated after 1 year. Staff members were instructed to maintain BIS values between 40 and 60, and definitely avoid values over 60. The standard anaesthesia regimens at the two hospitals were used, including inhalational, total intravenous and combined general and regional anaesthesia.

The recorded BIS trends were analyzed off line. The trends were divided in three parts before analysis: induction, maintenance and emergence. BIS data were analyzed for induction and maintenance phases only, as values were expected to be > 60 during emergence. The incidence of awareness observed in patients with BIS monitoring was compared with similar patients (n=7826) in a historical control group from a previous study[99] when no hypnosis monitoring was used.

Anaesthetists assessed to what extent BIS had been used to guide anaesthesia and to what extent they felt confident that the BIS monitor had worked properly on visual analogue scales (VAS).

Patients were interviewed for explicit recall on three occasions using the modified Brice interview[9,58].

Paper II

The patients were intubated after induction of anaesthesia with sevoflurane, rocuronium and remifentanil. After tracheal intubation, 15 min were allowed for obtaining a "steady state" BIS value of 50-55 by continuously adjusting the inspired fraction of sevoflurane. Within the following 15 min the patients were randomly assigned to noxious stimulation (laryngoscopy) at 1 of 7 predefined time points (0, 2, 4, 6, 9, 12 or 15 min) after a twofold increase in end tidal sevoflurane concentration (see *Figure 2*). BIS, AAI and hemodynamic responses were analyzed off line. The patients were interviewed for explicit recall twice postoperatively, using the modified Brice interview[9,58].

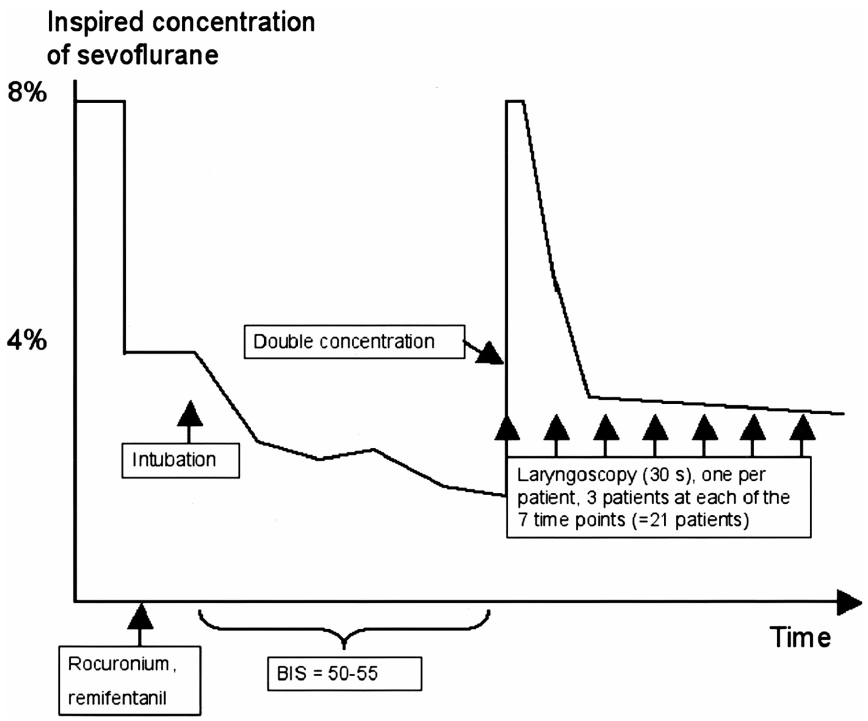

Figure 2. Schematic illustration of study protocol in paper II.

Paper III

Anaesthesia was induced with sevoflurane and remifentanil, the patients were intubated without NMBA. Sevoflurane was then titrated for 30 min to an end tidal concentration of 1.2%. Rocuronium was infused to 50% (partial) and 95% (profound) depression of the first twitch in a train-of-four response, the order being randomly chosen. Noxious tetanic electrical stimulation was applied at the arm not used for NMB monitoring at four occasions; 1) at baseline (control measurement), 2-3) at each degree of NMB, and 4) after neostigmine reversal. BIS, AAI and EMG from the frontal and temporal muscles were obtained 2 min before and 2 min after each noxious stimulation and analyzed off line. The patients were interviewed for explicit recall twice postoperatively, using the modified Brice interview[9,58].

Paper IV

Anaesthesia was induced and maintained with sevoflurane. Tracheal intubation was performed without NMBA. Noxious tetanic electrical stimulation was applied at two occasions; before and after profound neuromuscular block achieved with rocuronium. The resultant changes in BIS and an 8 lead EEG were recorded from 2 min before until 2 min after each noxious stimulation and were analyzed off line. The EEG spectral power and coherence in 9 different frequency bands (δ, θ, α, β and γ1- γ5) were analyzed. The patients were interviewed for explicit recall twice postoperatively, using the modified Brice interview[9,58].

Data acquisition

In paper I, the BIS trends were stored in the non-volatile memory of the A-2000 monitors and downloaded by the manufacturer representative in Sweden (Dansjö Medical AB, Stockholm, Sweden). In paper 2-4 all parameters including standard parameters were downloaded into lap top computers for subsequent analysis.

Statistics

Unless other ways stated, data are given as mean ± SD or median (interquartile range), when appropriate. A commercial statistical software was used (Statistica, StatSoft™, Tulsa, OK, USA) and p-values <0.05 were considered statistically significant. Detailed information about statistical analysis is found in the individual papers.

Paper I

Analysis of the outcome of awareness was performed using Fisher's exact test.
For demographic and procedural data the Student's *t*-test, double-sided, or the Chi-square test with Yate's correction were used as appropriate.

Paper II

A stepwise increase in delivery of sevoflurane leads to a rapid increase of blood concentration followed by a blood/multi-compartment equilibration. BIS and AAI responses to the stepwise increase differed markedly; therefore BIS responses were analyzed using the Hill equation[78,106] and an exponential function when analyzing non-normalized values, AAI responses were analyzed using linear regression. Correlations between different parameters' responses to noxious stimulation were tested by nonparametric tests.

Paper III and IV

Data were analyzed using non parametric tests and linear regression.

RESULTS

Paper I

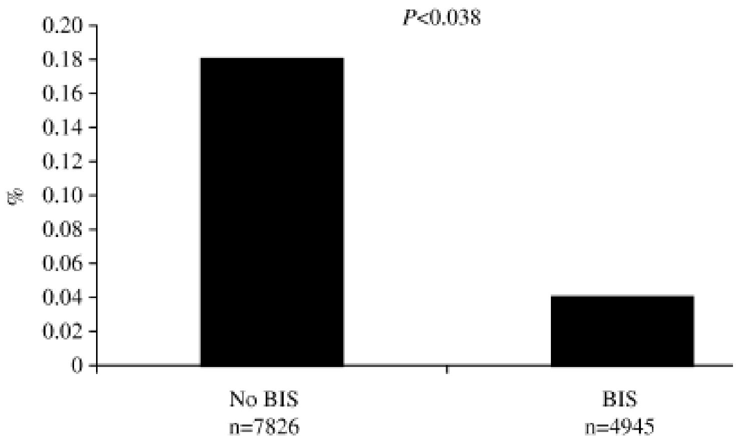

Figure 3. Comparison of incidence of awareness in patients with and without BISmonitoring.

Two patients in the BIS-monitored group, 0.04%, had explicit recall as compared to 0.18% in the control group (p<0.038) (see *Figure 3*). Both BIS-monitored patients with explicit recall were aware during intubation when they had high BIS values (>60) for 4 min, and more than 10 min, respectively (see *Figure 4*). However, periods with high BIS $\geq$ 4 min were also evident in other patients with no explicit recall. Episodes with high BIS, 4 min or more, were found in 19% of the monitored patients during induction and in 8% of cases during maintenance. The average BIS during maintenance was 38±8 (see *Figure 5*). VAS concerning to what extent BIS guided the conduction of anaesthesia was 41±32. The corresponding rating concerning reliability was 79±20.

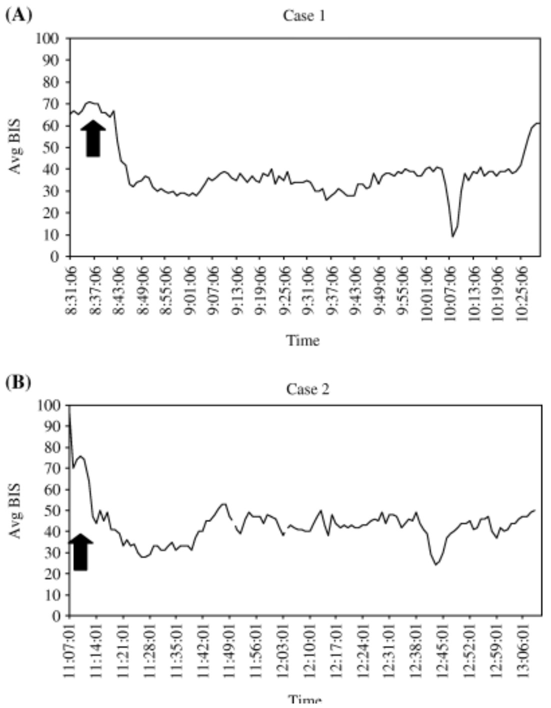

Figure 4. Average BIS trends for two patients who reported being awake at intubation. The times for awareness are indicated by arrows.

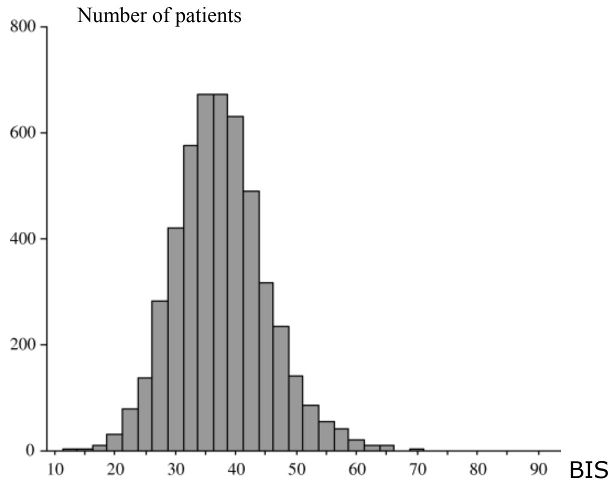

Figure 5
Average BIS during the maintenance phase.

Paper II

After the end-tidal concentration of sevoflurane was doubled, a substantial reduction in BIS-value from 50-55 to a new constant level, 25-30, was observed, whereas only a slight reduction in AAI was seen ($p<0.0001$) (see *Figure 6*). BIS/AAI responses to laryngoscopy were not attenuated with increasing wash-in of sevoflurane. Response times for BIS and AAI were 44.5±26 and 47±31s, respectively. After noxious stimulation, AAI exceeded the highest recommended value, 25, in 3 cases, whereas BIS did not exceed the recommended threshold, 60, in any of the patients. 20 of 21 patients responded with increased BIS and 19 of 21 patients responded with increased AAI after stimulation. No patient reported awareness.

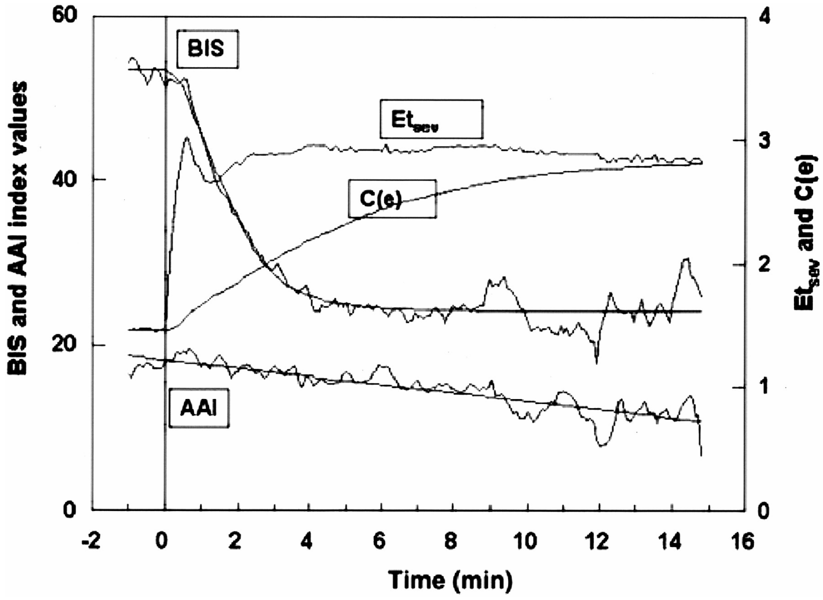

Figure 6. Normalized data (to time zero = time when vaporizer setting was doubled). Bispectral index (BIS), Alaris ARX index (AAI) values, end-tidal concentration of sevoflurane (Etsev) and estimated effective site concentration C(e) of sevoflurane. Values every 12th second are shown.

Paper III

Median BIS and AAI at baseline was 44 (39-50) and 15 (14-16), respectively. The two degrees of neuromuscular block did not affect BIS, AAI or EMG before noxious stimulation. In contrast, profound neuromuscular block altered the BIS and AAI responses to noxious stimulation as compared to partial neuromuscular block, (BIS p=0.01, AAI p<0.01), after neostigmine reversal (BIS p <0.01, AAI p=0.01) and compared to baseline (BIS p=0.08, AAI p=0.02) (see *Figure 7*). No significant increase in EMG was found. No patient reported awareness.

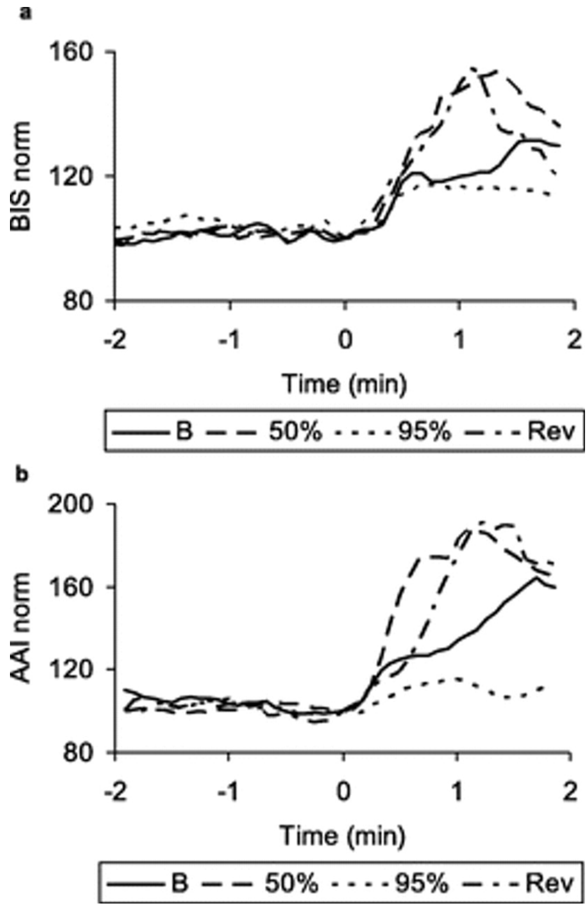

Figure 7.a) BIS and b) AAI recordings from two minutes before until two minutes after noxious tetanic stimulation at different degrees of neuromuscular blockade assigned by T1 twitch height depression in % as compared to baseline (B) and after neostigmine reversal (Rev). Values are normalized to 100 at the start of the tetanic stimulation. Values are mean for all patients.

PaperIV

During profound neuromuscular block the BIS response to noxious stimulation was attenuated significantly as compared to baseline (i.e. no neuromuscular block) ($p=0.019$). The responses in EMG_{BIS} after noxious stimulation were similar to changes in BIS ($p=0.041$). After noxious stimulation power was increased more at baseline than at profound neuromuscular block in all leads in the γ2 band (36-47 Hz) and in the γ5 band (70-110 Hz). The difference between the two study situations was significant in all leads except F4 in γ2 (p ranging from 0.002 to 0.028). After noxious stimulation at baseline the coherence in the γ2 band decreased numerically in all 28 pairs of leads. The decrease was significant in 9/28 pairs, especially between F3-T3, F3-F4 and F3-T4 (<0.01) (see *Figure 8*). In the γ5 band coherence decreased numerically in 26/28 pairs of leads and this was significant in 2/28 ($p\leq0.02$). In the γ2 band, during profound neuromuscular block, 26/28 pairs of leads showed a smaller decrease in coherence compared to no muscle block (significant in 5/28; p ranging from 0.010 to <0.041) (see *Figure 9*). No patient reported awareness.

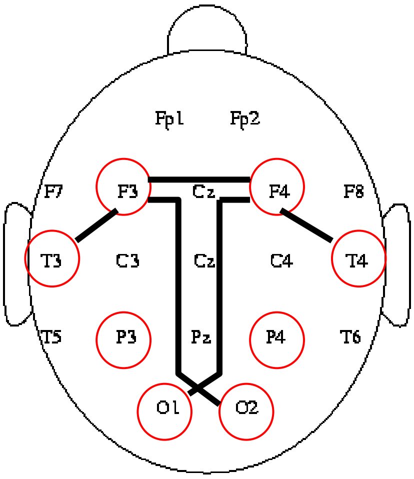

Figure 8. The encircled EEG-leads, placed and named according to the international 10-20 system were used in study IV. The decrease in coherence seen at noxious stimulation, were especially pronounced between the linked pairs of leads. EEG = electroencephalgram

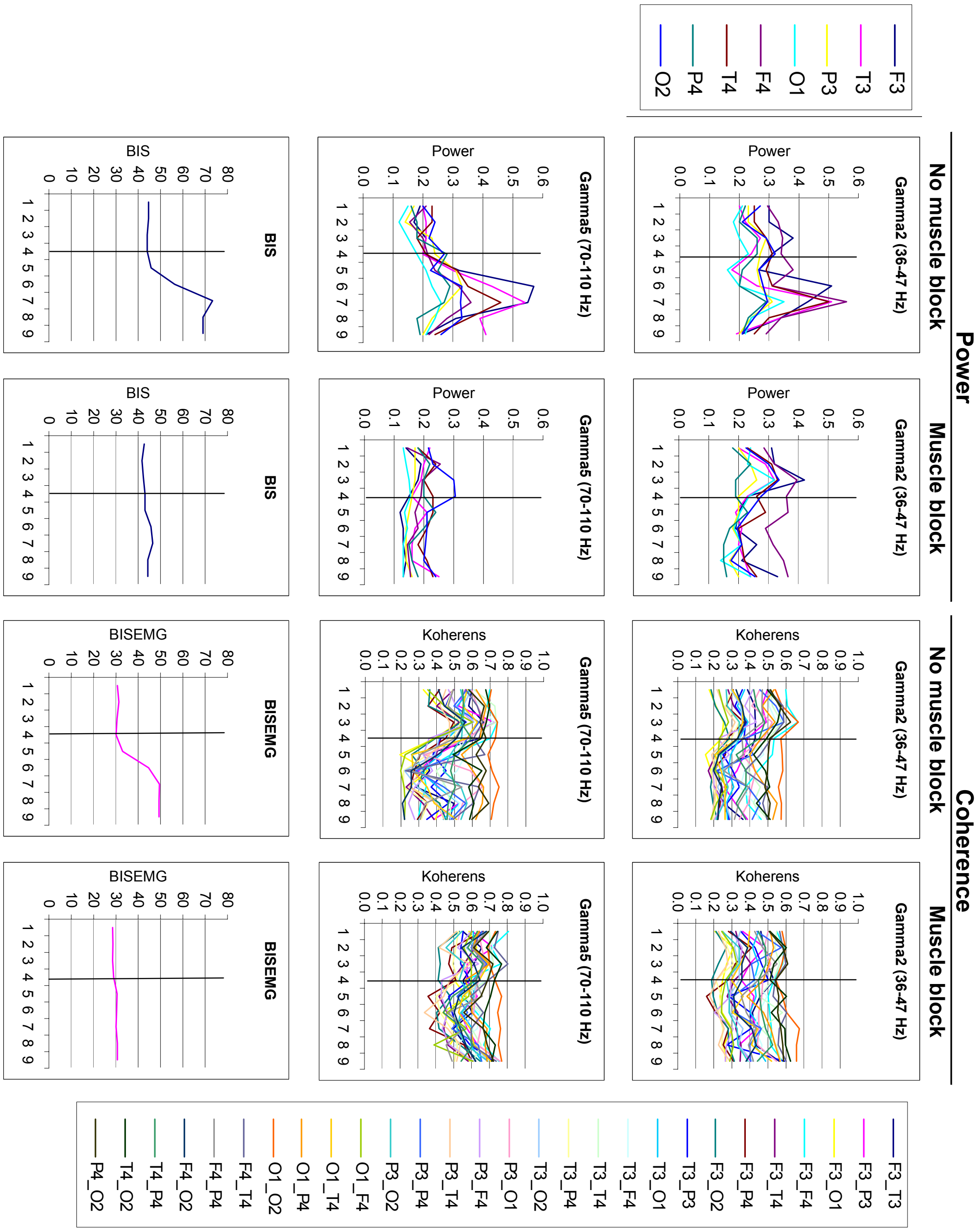

Figure 9. Changes of the spectral power and the coherence over the 2 min periods before and after noxious tetanic stimulation (vertical bar) in the γ2 and γ5 band. Power and coherence changes are shown as median for all 13 patients and between all electrodes (see colour code). Median values of bispectral index (BIS) and BIS_{EMG} changes are also shown. On the x-axis 1-9 represents the different sampling points during the experiment. On the y-axis power (μV^2), coherence (0-1), BIS and BIS_{EMG} values are shown, see Data analysis in paper IV

DISCUSSION

Even though the knowledge about the mechanisms of general anaesthesia has increased considerably since its introduction in clinical practice, it is still unknown how anaesthetics prevent consciousness[4]. This is largely because the mechanism by which brain physiology produces consciousness is unexplained[37]. The oscillations of EEG in the γ-band (i.e. frequencies > 30 Hz) and coherence between different regions of the brain are thought to be of great importance for human consciousness[37,64,90]. EEG is a phenomenon of the rostral structures, particularly the cerebral cortex. Higher cortical functions such as consciousness and cognition (i.e. explicit recall, memory and learning) are usually associated with EEG desynchronization as neurons act more independently. General anaesthesia and other mechanisms that depress consciousness are associated with increasing cortical synchronicity in the low frequency bands (< 30 Hz)[84]. Hence the rationale for using EEG derived indices to measure the pharmacodynamic effect of anaesthetics on the brain. Since their first commercial availability both BIS and AAI algorithms have undergone several revisions to improve handling of burst suppression-like EEG tracings and rejection of artefacts such as electrocautery, eye movements, and EMG activity[8]. The findings in this thesis may therefore be confined to the monitor versions used in individual papers. In paper I, the effect of introducing the BIS monitor on the incidence of awareness was investigated in clinical routine. In papers II and III, two different hypnosis monitors, BIS and AAI, were investigated and evaluated during general anaesthesia. BIS is a passive system analyzing spontaneous EEG while AAI is an active system providing active stimuli (auditory clicks) to assess the integrity of a defined neural pathway. Thus, the results in these papers are obtained by the use of two hypnosis monitor technologies based on different principles. In paper IV the effect of neuromuscular block during general anaesthesia on the raw EEG and BIS was studied.

Awareness and BIS monitoring

If the incidence of awareness is set to 0.1% in the general surgical population using standard monitoring, a sample size of more than 40 000 patients would be needed to do a randomized clinical trial to show a 50% reduction in the incidence of awareness using hypnosis monitoring in addition to standard monitoring (using 80% power)[77]. This study will probably never be done. Instead, in paper I, a prospective, non-randomized cohort study was conducted in a way so as to illustrate the result of incorporating BIS into a department-wide routine monitoring practice, a “real world” test. Our results demonstrated that BIS monitoring during general anaesthesia in a non-cardiac, surgical population requiring endotracheal intubation and/or NMBA was associated with a significantly reduced incidence of awareness as compared to a historical control population. In the BIS monitored group two patients with explicit recall were identified, corresponding to a 0.04% incidence rate compared with the incidence of 0.18% obtained in a well-matched group of patients in a previous study performed at the same two institutions 4 years earlier[99]. Both awareness cases in the BIS monitored group occurred during intubation and both presented high BIS values > 60, for 4 min, and at least 10 min, respectively. However, BIS values > 60 were evident in other patients with no explicit recall, both during induction and during maintenance. This may be due to amnesia[21], but also to inter-individual variability in the relation between cognitive capacity and BIS[48]. The time needed at high BIS or at a certain arousal state to evoke explicit recall is not known, but the likelihood for awareness increases with time at higher BIS values[60,93]. On average, anaesthesia was rather deep (BIS 38±8) during maintenance as related to the recommended BIS interval (40-60). The prevalence of both low (<40) and high (>60) BIS values in the study may indicate that prior experience and opinions on how to conduct anaesthesia had an impact on the drug administration. The anaesthesia providers also rated the extent to which BIS had guided anaesthesia to about 40% (41±32 on a 100-mm VAS). BIS was assessed to work properly in about 80% (79±20 on a 100-mm VAS) of cases, electrocautery being the most prevalent cause of interference. Our results indicate a satisfactory sensitivity for avoiding explicit recall while using an upper limit of BIS 60, but insufficient specificity of high BIS values for identifying awareness. Less than perfect sensitivity and specificity of available hypnosis monitoring is well known[26,27,100]. Better adherence to the BIS monitoring may have had given even more favourable results in terms of explicit recall. For anaesthetists, the acceptance of a hypnosis monitor not only rests on evidence of effectiveness, but also on their perception of the importance of awareness. Older anaesthetists seem to be more reluctant to use hypnosis monitoring since they rate awareness as a less important problem[74]. For patients, awareness is one of the most prominent sources of anxiety about, and dissatisfaction with anaesthetic care[75].

Due to the non-randomized study design, there is a possibility that other changes in clinical practice or knowledge of that the study of the BIS monitor was being conducted (the Hawthorne effect) may have influenced our findings[95]. Despite these theoretical limitations of our observational data, they are strengthened by a prospective, randomized, double-blind, multi-centre trial in patients considered at high risk for awareness (incidence about 1%) by Myles et al.[73]. Their finding of a reduction of the incidence of awareness with 82% in the BIS monitored group is in close agreement with our finding of a 77% reduction in awareness using BIS monitoring in addition to standard monitors. Taken together, our study and Myles study[73], suggest that BIS monitoring during general anaesthesia reduces the incidence of awareness.

BIS and AAI responses to increased sevoflurane delivery

In paper II, our data suggest that BIS better displays drug related alterations in the level of hypnosis than AAI in an already anesthetized patient. This is in agreement with Alpiger et al.[2] who did not find any graded response of AAI with stepwise transitions from end-tidal steady-state concentrations of sevoflurane in the 1-2% concentration range. These findings caused the manufacturer to create a new version of AAI (version 1.6) with the composite index consisting of both AEP and EEG signals. According to Kalkman and Drummond[47], MLAEP are almost completely suppressed soon after loss of consciousness. However, when smaller doses of anaesthetics affect the brain (BIS values between 50 and 95), the sedative effect evaluated by Observer’s Assessment of Alertness/Sedation Scale was better correlated to AAI than to BIS[29], and other studies have suggested that derivatives of MLAEP are better discriminators than BIS in tracing the transition from awake to the anaesthetized state[26,27,101] Hemodynamic variables are known to be poor indicators of the hypnotic state[70,116,125,130] and our data in paper II also supported this.

BIS and AAI responses to noxious stimulation

Laryngoscopy was used as noxious stimulation in paper II. It is an intense, clinically relevant stimulation that together with intubation is an important reason for awareness[97,99]. In paper III and IV we used tetanic electrical stimulation of the ulnar nerve. Although not as clinical relevant as laryngoscopy, it was chosen because it is easy to standardize and use repeatedly. Tetanic stimulation of the ulnar nerve has also been shown to be a noxious stimulation almost as potent as larygoscopy[129,130].
In paper II it was demonstrated that there is no difference between BIS and AAI in the response time to a noxious stimulus. The response time to earliest maximum value after stimulation for both monitors was approximately 45 s. This reflects the biological

response time and the index calculating time. Ideally the response times should be only a few seconds to allow the clinician to act immediately. The time it takes in an aroused state to evoke explicit recall is not known. However, from the results in paper I and the study by Flashion[21], it seems that the response times for both BIS and AAI may be sufficient to prevent awareness. Sevoflurane, as the only anaesthetic, did not attenuate the magnitude of BIS and AAI responses to laryngoscopy with increasing wash-in time. The hemodynamic variables relation to arousal was not found to be consistent as others also have shown[70,117,125,130].

Neuromuscular block and level of hypnosis

The effect of neuromuscular block on anaesthetic depth of hypnosis is an elusive question. During general anaesthesia including an NMBA the incidence of explicit recall is higher than during general anaesthesia without an NMBA, and in patients receiving an NMBA the posttraumatic consequences of explicit recall seem to be more pronounced[54,99]. Studies on the effect of neuromuscular block on the level of hypnosis have shown conflicting results[10,35,68,108,124,128]. One reason for this may be that EMG activity has contaminated the EEG signals to various degrees in different studies. EMG is generally considered to constitute an increasing part of the electrical power spectrum above the frequency of about 30 Hz[13,43]. Thus, EMG has a potential to distort index calculating algorithms if higher frequencies are considered. When surface electrodes are used to record the EEG and monitor the level of hypnosis, it cannot be determined whether the electrical activity picked up is generated in the brain or in the frontal muscle. It has been suggested that NMBAs may affect the level of hypnosis by functional deafferentation, i.e. by suppressing muscle afferents to the spinal cord and thereby reduce arousing signaling to the brain[52]. The afferentation theory is supported by reduced halothane requirement in man when pancuronium was administered[23] and by studies where central neuraxial blockades (i.e. epidural and spinal blockade), in the absence of noxious stimulation, have been shown to reduce the need for hypnotics[40,122]. However, the afferent theory was not confirmed by Fahey et al[19] looking at different NMBAs and their effect on $MAC_{skin\ incision}$ for halothane in man. Because non-depolarizing NMBAs do not cross the intact blood-brain barrier and, thus, have not been assigned any direct central effect[66,126] another possible mechanism for an NMBA effect on the central nervous system could be indirectly via a central effect by NMBA metabolites[8]. Atracurium and cisatracurim are metabolized into laudanosine which can cross the blood-brain barrier. It is detected after administration in the cerebrospinal fluid at clinically relevant concentrations[22]. This metabolite has analgesic properties in animals and could theoretically deepen the anti-nociceptive level and affect cortical activity by acting through both central nicotinic receptor subtypes and opioid receptors[22]. In this thesis rocuronium was used, which has no known central effect nor has its metabolites, when used in clinically relevant doses[25]. In paper III, it was demonstrated that profound neuromuscular block attenuated BIS and AAI responses to a standardized noxious stimulation during sevoflurane anaesthesia as compared to a partial neuromuscular block or after neostigmine induced reversal. This effect was probably not related to a depression of the EMG component of the BIS or AAI since directly measured EMG in frontal- and temporal muscles was absent or negligible. Neuromuscular block did not affect BIS or AAI during resting conditions. This finding is in accordance with studies in non-stimulated volunteers[35] as well as non-stimulated patients[124]. Results in paper IV confirm the finding of paper III, i.e. profound neuromuscular block attenuates the BIS response to a standardized noxious stimulation during sevoflurane anaesthesia as compared to no neuromuscular block. In the absence of neuromuscular blockade, noxious stimulation was associated with an increase in EEG power and a reduction in coherence. Both these reactions were attenuated by profound neuromuscular block. Interestingly, among the frequency bands studied, this decrease in coherence was most pronounced in the γ2-band (36-47 Hz), a frequency range that constitutes a major part of the two subparameters (beta ratio and bispectral component) operative in the BIS algorithm at light anaesthesia, as used in this experiment, and also during EEG activation[84]. There are several reasons our results most likely are due to a true EEG effect and not an EMG effect. Voluntary muscle movements increase the coherence of surface EMG instead of decreasing it[49]. In paper III, directly measured EMG in frontal- and temporal muscles was absent or negligible. The neuromuscular block dependent difference in coherence after noxious stimulation would have been expected to be more pronounced in the higher frequency bands if it was due to EMG. Decrease in the γ5-band coherence (70-110 Hz) is still clearly visible at profound neuromuscular block without any change in the EMG from the BIS monitor. The γ5-band (70-110 Hz) which is considered by the BIS algorithm as EMG may therefore also to a large part contain EEG. The decrease in coherence between multiple EEG leads when noxious stimulation is applied is in accordance with an arousal effect seen on visual inspection of the EEG as desynchronized and of low amplitude. John et al.[46] did a thorough study where they looked at reversible EEG changes during general anaesthesia and surgery. They saw decreased coherence at loss

of consciousness, which was increased again at emergence and regaining of consciousness in the γ-band (25-50 Hz). This is not in line with the findings in paper IV but may have been due to that our patients did not reach consciousness. The power in the γ-band was on the other hand affected in the same way as in our study.
In summary, the findings in papers III and IV demonstrate that EEG responses, as well as BIS and AAI responses, to noxious stimulation are affected by neuromuscular block during light sevoflurane anaesthesia. This effect is probably related to reduced afferent input from muscles and, thus, a true difference in arousal and hypnotic level. These findings support the afferentation theory proposed by Lanier[52]. However, in non-stimulated and/or deeply anaesthetized subjects[35,124] neuromuscular block does not seem to have any effect on level of hypnosis.

Future perspectives

Anaesthesia is still part art and part science and common sense will be needed to adequately apply new technology and be aware of its limitations[4]. One technology, hypnosis monitoring, has now been shown to reduce the incidence of awareness. It is a beginning to individualized anaesthetic delivery according to the patients needs. The consequences of inadequate anaesthetic dosage are not only confined to insufficient delivery, which is awareness. Recent findings indicate that general anaesthetics, dose dependently, influence neurodevelopment[24,44]. Inhalational agents, also dose dependently, offer neuroprotection in traumatic brain injury[113,114]. Balancing positive and negative effects from anaesthetics indicate the great importance of individualized delivery.
The hypnosis monitors have now diverted some of the anaesthetist's interest from spinal function (i.e. MAC) as a measure of anaesthetic effect to cerebral function, the primary target organ for general anaesthesia[3,85]. Even if current possibility to monitor the hypnotic state during anaesthesia is a valuable adjunct to previous methods for ensuring unconsciousness while under general anaesthesia, available monitors still lack the precision to discriminate between consciousness and unconsciousness in the individual patient in a satisfactory way. The findings in paper III and IV suggest that EEG γ-activity is altered when patients are aroused and that this high frequency activity is reduced by profound neuromuscular block. The possibility to improve the discrimination between consciousness and unconsciousness by incorporating information on γ-coherence in the hypnosis monitoring algorithms may ameliorate the performance of future hypnosis monitors. Such a new monitor would perhaps be found

sufficiently accurate, that the use of profound neuromuscular block in hemodynamically unstable cases instead of circulatory more compromising general anaesthetics could prove beneficial.

Finally, the significance of γ-activity for consciousness and general anaesthesia[37] has been illustrated in this thesis. Even if the perfect hypnosis monitor never will appear, our efforts will not be in vain. Integration of the science from anaesthesiology into the fields of psychology and neuroscience is a proposed way of increasing our understanding of the physiology of consciousness and the mechanisms of general anaesthesia[65].

CONCLUSIONS

- BIS monitoring, as clinical routine, during general anaesthesia including an NMBA reduced the incidence of awareness as compared to standard monitoring.
- BIS better displays drug related alterations in the level of hypnosis than AAI or hemodynamic parameters during sevoflurane anaesthesia.
- There is no difference between BIS and AAI in the response time to a noxious stimulus (laryngoscopy) during sevoflurane anaesthesia.
- Using rocuronium, BIS and AAI responses to noxious tetanic electrical stimulation are affected by the degree of neuromuscular block during sevoflurane anaesthesia, whereas there is no effect of neuromuscular block on BIS and AAI in the absence of noxious stimulation. Changes in directly measured EMG were absent or negligible.
- Using rocuronium, neuromuscular block significantly attenuated the effect of noxious stimulation on EEG power and synchrony in the γ-band during sevoflurane anaesthesia.

ACKNOWLEDGEMENTS

The most read pages of this book! There are many people involved in the creation of a thesis. In my case, almost all the work has been done at the Department of Anaesthesia and Intensive Care, Länssjukhuset, Kalmar, where all the staff in one way or another helped me out and I am truly grateful to all of them and to all the patients that volunteered to the studies. I also would like to thank all who supported and inspired me during the years, and especially:

Helena, my love, wife and best friend, for her clear sight, common sense and patience in letting me do what I do, interfering only when necessary…

Rolf Sandin, my tutor, a true scientific genius, a natural born investigator and a smooth operator without whom anaesthesia in Kalmar and the rest of the world would not be the same. For his skill and guidance in clinical research as well as in the wine lists, I owe him more than the money.
Lars Brudin, co-author, "Statistica® magica", a clinical physiologist with an energy like a nuclear power plant and enthusiasm that goes beyond that.
Lars I Eriksson, my co-supervisor, Professor and Academic Chairman, Department of Physiology and Pharmacology, Section of Anesthesiology and Intensive Care Medicine, KI, for immense encouragement and presence at the right times in spite of his heavy assignment book.
Roland Johansson, Chairman at the Department of Anaesthesia and Intensive Care, Kalmar, with abilities like nobody else and always with the "responsibility", for his reasonable way of handling my extensive research time this last year.
Eva Sundman, co-author, with a sharp pen and an open mind, **Maj-Lis Lindholm**, roommate and fellow PhD-student for sharing many of the ups and downs that you encounter as a freshman in the fields of research. **Erik Stålberg**, Professor emeritus and **Roland Flink**, Professor, both co-authors and both at the Department of Clinical Neurophysiology, Uppsala, for sharing their vast knowledge and introducing me to some of the secrets in the realm of neurophysiology.

Bodil Alexandersson, my own nurse, that whenever called, left whatever she was doing for sharing the fun of anaesthetizing patients with me. **Birgitta Törneke**, for stringent and impeccable work, when carrying out the patients in paper II.
Anette Williamsson, Chief Secretary at the Department in Kalmar, there is no problem she cannot handle, always before you ask and always with a smile.
Mats Johansson, **Natasa Zarki**, **Michelle Dobos** and **Ingvor Nilsson** at the Department of Clinical Physiology, Kalmar, for invaluable help with computers and EEGs.
Britt Ekelund, **Aune Rettrup** and **Birgitta Jonsson** for rescheduling patients and personal, often with short notice, in order to get me an operating theatre to play in.
Åke Nordlund, not only a gas passer, also an excellent syringe pump driver. **Ove Carlström**, who enticed our family to move to Kalmar. **Joanna Webb** for revising my English.
All my **colleagues**, past and present, at the Department in Kalmar, for relieving me of my clinical duties during the compilation of this thesis.

My **friends,** especially the disreputable "Lineroligan" and the **friends** from medical school with whom I learnt some about life and some about other things…

My **parents**, my **brother**, my late **sister** and my late **grand parents** for being the best considerable family to start with, my **mother-in law**, my **brothers-** and **sisters-in law** and their **children,** my **uncle** and **aunt,** my **cousins** and **Rita** for expanding and enriching the family.

Last and most **Helena** (once again) and our three wonderful children: **Elias**, **Ylva** and **Daniel** for your love.

The studies in this thesis were supported financially by Landstinget i Kalmar Län, the Research Council in South–East Sweden (FORSS), Swedish Research Council, Aspect Medical Systems, MA, USA, and Abbot Scandinavia AB, Sweden.

REFERENCES

1. Adam N: Disruption of memory functions associated with general anesthesia. *In* Kihlstrom JF, Evans FJ (eds): Functional disorders of memory. Hillsdale, New Jersey: Lawernce Erlbaum Associates, 1977, pp 219
2. Alpiger S, Helbo-Hansen HS, Jensen EW: Effect of sevoflurane on the mid-latency auditory evoked potentials measured by a new fast extracting monitor. Acta Anaesthesiol Scand 46:252, 2002
3. Antognini JF, Schwartz K: Exaggerated anesthetic requirements in the preferentially anesthetized brain. Anesthesiology 79:1244, 1993
4. Barker SJ: Too much technology? Anesth Analg 97:938, 2003
5. Berger H: Über das elektroenkephalogram des menschen. Arch Psychiatr Nervenkr 87:527, 1929
6. Bigelow HJ: Insensibility during surgical operations produced by inhalation. Boston Med Surg J 35:309, 1846
7. Bogetz MS, Katz JA: Recall of surgery for major trauma. Anesthesiology 61:6, 1984
8. Bonhomme V, Hans P: Muscle relaxation and depth of anaesthesia: where is the missing link? Br J Anaesth 99:456, 2007
9. Brice DD, Hetherington RR, Utting JE: A simple study of awareness and dreaming during anaesthesia. Br J Anaesth 42:535, 1970
10. Bruhn J, Bouillon TW, Shafer SL: Electromyographic activity falsely elevates the bispectral index. Anesthesiology 92:1485, 2000
11. Bruhn J, Myles PS, Sneyd R, et al: Depth of anaesthesia monitoring: what's available, what's validated and what's next? British Journal of Anaesthesia 97:85, 2006
12. Caton R: The electric currents of the brain. Br Med J 2:278, 1875
13. Dahaba AA: Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. Anesthesia & Analgesia 101:765, 2005
14. Daunderer M, Schwender D: [Depth of anesthesia, awareness and EEG]. Anaesthesist 50:231, 2001
15. Domino KB, Posner KL, Caplan RA, et al: Awareness during anesthesia: a closed claims analysis. Anesthesiology 90:1053, 1999
16. Dowd NP, Cheng DC, Karski JM, et al: Intraoperative awareness in fast-track cardiac anesthesia. Anesthesiology 89:1068, 1998
17. Drummond JC: Monitoring depth of anesthesia: with emphasis on the application of the bispectral index and the middle latency auditory evoked response to the prevention of recall. Anesthesiology 93:876, 2000
18. Eger EI, 2nd, Lampe GH, Wauk LZ, et al: Clinical pharmacology of nitrous oxide: an argument for its continued use. Anesth Analg 71:575, 1990
19. Fahey MR, Sessler DI, Cannon JE, et al: Atracurium, vecuronium, and pancuronium do not alter the minimum alveolar concentration of halothane in humans. Anesthesiology 71:53, 1989
20. Finkel KJ, Zhang L, Burnside BA, et al: Sensitivity of BIS and MAC in the B-Unaware trial. Anesthesiology:A728, 2007
21. Flaishon R, Windsor A, Sigl J, et al: Recovery of consciousness after thiopental or propofol. Bispectral index and isolated forearm technique. Anesthesiology 86:613, 1997
22. Fodale V, Santamaria LB: Laudanosine, an atracurium and cisatracurium metabolite. Eur J Anaesthesiol 19:466, 2002
23. Forbes AR, Cohen NH, Eger EI, 2nd: Pancuronium reduces halothane requirement in man. Anesth Analg 58:497, 1979
24. Fredriksson A, Ponten E, Gordh T, et al: Neonatal exposure to a combination of N-methyl-D-aspartate and gamma-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. Anesthesiology 107:427, 2007

25. Fuchs-Buder T, Strowitzki M, Rentsch K, et al: Concentration of rocuronium in cerebrospinal fluid of patients undergoing cerebral aneurysm clipping. Br J Anaesth 92:419, 2004
26. Gajraj RJ, Doi M, Mantzaridis H, et al: Analysis of the EEG bispectrum, auditory evoked potentials and the EEG power spectrum during repeated transitions from consciousness to unconsciousness. Br J Anaesth 80:46, 1998
27. Gajraj RJ, Doi M, Mantzaridis H, et al: Comparison of bispectral EEG analysis and auditory evoked potentials for monitoring depth of anaesthesia during propofol anaesthesia. Br J Anaesth 82:672, 1999
28. Gan TJ, Glass PS, Windsor A, et al: Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. Anesthesiology 87:808, 1997
29. Ge SJ, Zhuang XL, Wang YT, et al: Changes in the rapidly extracted auditory evoked potentials index and the bispectral index during sedation induced by propofol or midazolam under epidural block. Br J Anaesth 89:260, 2002
30. Ghoneim MM: Awareness during anesthesia. Anesthesiology 92:597, 2000
31. Ghoneim MM: Drugs and human memory (part 1): Clinical, theoretical, and methodologic issues. Anesthesiology 100:987, 2004
32. Gibbs FA, Gibbs EL, Lennox WG: Effecton the electroencephalogram of certain drugs which influence nervous activity. Arch Intern Med 60:154, 1937
33. Glass PS, Bloom M, Kearse L, et al: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology 86:836, 1997
34. Goldmann L, Shah MV, Hebden MW: Memory of cardiac anaesthesia. Psychological sequelae in cardiac patients of intra-operative suggestion and operating room conversation. Anaesthesia 42:596, 1987
35. Greif R, Greenwald S, Schweitzer E, et al: Muscle relaxation does not alter hypnotic level during propofol anesthesia. Anesth Analg 94:604, 2002
36. Guedel AE: Inhalational anesthesia: A fundamental guide. New York: Macmillan, 1937
37. Hameroff SR: The entwined mysteries of anesthesia and consciousness: is there a common underlying mechanism? Anesthesiology 105:400, 2006
38. Heier T, Steen PA: Assessment of anaesthesia depth. Acta Anaesthesiol Scand 40:1087, 1996
39. Heier T, Steen PA: Awareness in anaesthesia: incidence, consequences and prevention. Acta Anaesthesiol Scand 40:1073, 1996
40. Hodgson PS, Liu SS: Epidural lidocaine decreases sevoflurane requirement for adequate depth of anesthesia as measured by the Bispectral Index monitor. Anesthesiology 94:799, 2001
41. Hutchinson R: Awareness during anaesthesia. Br J Anaesth 34:348, 1962
42. Jensen EW, Lindholm P, Henneberg SW: Autoregressive modeling with exogenous input of middle-latency auditory-evoked potentials to measure rapid changes in depth of anesthesia. Methods Inf Med 35:256, 1996
43. Jensen EW, Litvan H, Struys M, et al: Pitfalls and challenges when assessing the depth of hypnosis during general anaesthesia by clinical signs and electronic indices. Acta Anaesthesiol Scand 48:1260, 2004
44. Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al: Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 23:876, 2003
45. Johansen JW, Sebel PS: Development and clinical application of electroencephalographic bispectrum monitoring. Anesthesiology 93:1336, 2000
46. John ER, Prichep LS, Kox W, et al: Invariant reversible QEEG effects of anesthetics. Conscious Cogn 10:165, 2001
47. Kalkman CJ, Drummond JC: Monitors of depth of anesthesia, quo vadis? Anesthesiology 96:784, 2002
48. Kerssens C, Lubke GH, Klein J, et al: Memory function during propofol and alfentanil anesthesia: predictive value of individual differences. Anesthesiology 97:382, 2002

49. Kilner JM, Baker SN, Salenius S, et al: Human cortical muscle coherence is directly related to specific motor parameters. J Neurosci 20:8838, 2000
50. Kissin I: Depth of anesthesia and bispectral index monitoring. Anesth Analg 90:1114, 2000
51. Kissin I: General anesthetic action: an obsolete notion? Anesth Analg 76:215, 1993
52. Lanier WL, Iaizzo PA, Milde JH, et al: The cerebral and systemic effects of movement in response to a noxious stimulus in lightly anesthetized dogs. Possible modulation of cerebral function by muscle afferents. Anesthesiology 80:392, 1994
53. Larson MD: History of anesthetic practice. *In* Miller RD (ed): Miller´s Anesthesia, ed 6. Philadelphia: Elsevier, Chuchill Livingstone, 2005, Vol 1, pp 12
54. Lennmarken C, Bildfors K, Enlund G, et al: Victims of awareness. Acta Anaesthesiol Scand 46:229, 2002
55. Leslie K: Awareness in a community-based anesthesia practice. Anesthesiology 107:671, 2007
56. Leslie K, Sessler DI, Schroeder M, et al: Propofol blood concentration and the Bispectral Index predict suppression of learning during propofol/epidural anesthesia in volunteers. Anesth Analg 81:1269, 1995
57. Liu SS: Effects of Bispectral Index monitoring on ambulatory anesthesia: a meta-analysis of randomized controlled trials and a cost analysis. Anesthesiology 101:311, 2004
58. Liu WH, Thorp TA, Graham SG, et al: Incidence of awareness with recall during general anaesthesia. Anaesthesia 46:435, 1991
59. Lubke GH, Kerssens C, Phaf H, et al: Dependence of explicit and implicit memory on hypnotic state in trauma patients. Anesthesiology 90:670, 1999
60. Luginbuhl M, Schnider TW: Detection of awareness with the bispectral index: two case reports. Anesthesiology 96:241, 2002
61. Lyons G, Macdonald R: Awareness during caesarean section. Anaesthesia 46:62, 1991
62. Macleod AD, Maycock E: Awareness during anaesthesia and post traumatic stress disorder. Anaesth Intensive Care 20:378, 1992
63. Mahla ME, Black S, Cucchiara RF: Neurologic monitoring. *In* Miller RD (ed): Miller's Anesthesia, ed 6. Philadelphia: Elsevier, Churchill Livingstone, 2005, Vol 1, pp 1511
64. Mashour GA: Consciousness unbound: toward a paradigm of general anesthesia. Anesthesiology 100:428, 2004
65. Mashour GA: Integrating the science of consciousness and anesthesia. Anesth Analg 103:975, 2006
66. Matteo RS, Pua EK, Khambatta HJ, et al: Cerebrospinal fluid levels of d-tubocurarine in man. Anesthesiology 46:396, 1977
67. Merkel G, Eger EI, 2nd: A comparative study of halothane and halopropane anesthesia including method for determining equipotency. Anesthesiology 24:346, 1963
68. Messner M, Beese U, Romstock J, et al: The bispectral index declines during neuromuscular block in fully awake persons.[see comment]. Anesthesia & Analgesia 97:488, 2003
69. Meyer BC, Blacher RS: A traumatic neurotic reaction induced by succinylcholine chloride. N Z Med J 61:1255, 1961
70. Mi WD, Sakai T, Takahashi S, et al: Haemodynamic and electroencephalograph responses to intubation during induction with propofol or propofol/fentanyl. Can J Anaesth 45:19, 1998
71. Moerman N, Bonke B, Oosting J: Awareness and recall during general anesthesia. Facts and feelings. Anesthesiology 79:454, 1993
72. Myles PS, Leslie K, Chan MT, et al: Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial.[see comment]. Anesthesiology 107:221, 2007

73. Myles PS, Leslie K, McNeil J, et al: Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial.[see comment]. Lancet 363:1757, 2004
74. Myles PS, Symons JA, Leslie K: Anaesthetists' attitudes towards awareness and depth-of-anaesthesia monitoring. Anaesthesia 58:11, 2003
75. Myles PS, Williams DL, Hendrata M, et al: Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients.[see comment]. British Journal of Anaesthesia 84:6, 2000
76. Nordstrom O, Engstrom AM, Persson S, et al: Incidence of awareness in total i.v. anaesthesia based on propofol, alfentanil and neuromuscular blockade. Acta Anaesthesiol Scand 41:978, 1997
77. O'Connor MF, Daves SM, Tung A, et al: BIS monitoring to prevent awareness during general anesthesia. Anesthesiology 94:520, 2001
78. Olofsen E, Dahan A: The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. Anesthesiology 90:1345, 1999
79. Osterman JE, Hopper J, Heran WJ, et al: Awareness under anesthesia and the development of posttraumatic stress disorder. Gen Hosp Psychiatry 23:198, 2001
80. Phillips AA, McLean RF, Devitt JH, et al: Recall of intraoperative events after general anaesthesia and cardiopulmonary bypass. Can J Anaesth 40:922, 1993
81. Pollard RJ, Coyle JP, Gilbert RL, et al: Intraoperative awareness in a regional medical system: a review of 3 years' data. Anesthesiology 106:269, 2007
82. Prys-Roberts C: Anaesthesia: a practical or impractical construct? Br J Anaesth 59:1341, 1987
83. Rampil I: Electroencephalogram. *In* Albin MS (ed): Textbook of neuroanesthesia with neurosurgical and neuroscience perspectives. New York: McGraw-Hill, 1997, pp 193
84. Rampil IJ: A primer for EEG signal processing in anesthesia.[see comment]. Anesthesiology 89:980, 1998
85. Rampil IJ, Mason P, Singh H: Anesthetic potency (MAC) is independent of forebrain structures in the rat. Anesthesiology 78:707, 1993
86. Ranta S, Jussila J, Hynynen M: Recall of awareness during cardiac anaesthesia: influence of feedback information to the anaesthesiologist. Acta Anaesthesiol Scand 40:554, 1996
87. Ranta SO, Herranen P, Hynynen M: Patients' conscious recollections from cardiac anesthesia. J Cardiothorac Vasc Anesth 16:426, 2002
88. Ranta SO, Laurila R, Saario J, et al: Awareness with recall during general anesthesia: incidence and risk factors. Anesth Analg 86:1084, 1998
89. Recart A, White PF, Wang A, et al: Effect of auditory evoked potential index monitoring on anesthetic drug requirements and recovery profile after laparoscopic surgery: a clinical utility study. Anesthesiology 99:813, 2003
90. Rodriguez E, George N, Lachaux JP, et al: Perception's shadow: long-distance synchronization of human brain activity. Nature 397:430, 1999
91. Rosow C, Manberg PJ: Bispectral index monitoring. Anesthesiol Clin North America 19:947, 2001
92. Russell IF: Memory when the state of consciousness is known: studies of anesthesia with the isolated forearm technique. *In* Ghoneim MM (ed): Awareness during anesthesia. Oxford: Butterworth-Heinemann, 2001, pp 129
93. Russell IF, Wang M: Absence of memory for intra-operative information during surgery with total intravenous anaesthesia. Br J Anaesth 86:196, 2001
94. Russell IF, Wang M: Absence of memory for intraoperative information during surgery under adequate general anaesthesia. Br J Anaesth 78:3, 1997
95. Sackett DL: Bias in analytic research. J Chronic Dis 32:51, 1979
96. Samuelsson P, Brudin L, Sandin RH: Late psychological symptoms after awareness among consecutively included surgical patients. Anesthesiology 106:26, 2007
97. Sandin R: Outcome after awareness with explicit recall. Acta Anaesthesiol Belg 57:429, 2006

98. Sandin R, Nordstrom O: Awareness during total i.v. anaesthesia. Br J Anaesth 71:782, 1993
99. Sandin RH, Enlund G, Samuelsson P, et al: Awareness during anaesthesia: a prospective case study. Lancet 355:707, 2000
100. Schneider G, Gelb AW, Schmeller B, et al: Detection of awareness in surgical patients with EEG-based indices--bispectral index and patient state index. Br J Anaesth 91:329, 2003
101. Schraag S, Bothner U, Gajraj R, et al: The performance of electroencephalogram bispectral index and auditory evoked potential index to predict loss of consciousness during propofol infusion. Anesth Analg 89:1311, 1999
102. Schwender D, Kunze-Kronawitter H, Dietrich P, et al: Conscious awareness during general anaesthesia: patients' perceptions, emotions, cognition and reactions. Br J Anaesth 80:133, 1998
103. Sebel PS: Comfortably numb? Acta Anaesthesiol Scand 48:1, 2004
104. Sebel PS, Bowdle TA, Ghoneim MM, et al: The incidence of awareness during anesthesia: a multicenter United States study.[see comment]. Anesthesia & Analgesia 99:833, 2004
105. Sebel PS, Bowdle TA, Rampil IJ, et al: Don't ask, don't tell. Anesthesiology 107:672; author reply 673, 2007
106. Sheiner LB, Stanski DR, Vozeh S, et al: Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. Clin Pharmacol Ther 25:358, 1979
107. Sigl JC, Chamoun NG: An introduction to bispectral analysis for the electroencephalogram. J Clin Monit 10:392, 1994
108. Sleigh JW, Steyn-Ross DA, Steyn-Ross ML, et al: Comparison of changes in electroencephalographic measures during induction of general anaesthesia: influence of the gamma frequency band and electromyogram signal. Br J Anaesth 86:50, 2001
109. Sneyd JR: How low can we go? Br J Anaesth 91:771, 2003
110. Snow J: On the inhalation on the vapors of ether in surgical operations: containing a description of the various stages of etherization, and a statement of the result of nearly eighty operations in which ether has been employed in St. George´s and University college hospitals. Reproduced by Lea & Febiger, Philadelphia, 1959, 1847
111. Song D, Joshi GP, White PF: Titration of volatile anesthetics using bispectral index facilitates recovery after ambulatory anesthesia. Anesthesiology 87:842, 1997
112. Stanski DR, Shafer SL: Measuring depth of anesthesia. *In* Miller RD (ed): Miller´s Anesthesia, ed 6. Philadelphia: Elsevier, Churchill Livingstone, 2005, Vol 1, pp 1227
113. Statler KD, Alexander H, Vagni V, et al: Comparison of seven anesthetic agents on outcome after experimental traumatic brain injury in adult, male rats. J Neurotrauma 23:97, 2006
114. Statler KD, Alexander H, Vagni V, et al: Isoflurane exerts neuroprotective actions at or near the time of severe traumatic brain injury. Brain Res 1076:216, 2006
115. Stenqvist O, Husum B, Dale O: Nitrous oxide: an ageing gentleman. Acta Anaesthesiol Scand 45:135, 2001
116. Struys MM, Jensen EW, Smith W, et al: Performance of the ARX-derived auditory evoked potential index as an indicator of anesthetic depth: a comparison with bispectral index and hemodynamic measures during propofol administration. Anesthesiology 96:803, 2002
117. Struys MM, Jensen EW, Smith W, et al: Performance of the ARX-derived auditory evoked potential index as an indicator of anesthetic depth: a comparison with bispectral index and hemodynamic measures during propofol administration.[see comment]. Anesthesiology 96:803, 2002
118. Thornton C, Sharpe RM: Evoked responses in anaesthesia. Br J Anaesth 81:771, 1998

119. Todd MM: EEGs, EEG processing, and the bispectral index. Anesthesiology 89:815, 1998
120. Tramer M, Moore A, McQuay H: Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials. Br J Anaesth 76:186, 1996
121. Tunstall ME: On being aware by request. A mother's unplanned request during the course of a Caesarean section under general anaesthesia. Br J Anaesth 52:1049, 1980
122. Tverskoy M, Shagal M, Finger J, et al: Subarachnoid bupivacaine blockade decreases midazolam and thiopental hypnotic requirements. J Clin Anesth 6:487, 1994
123. Urhonen E, Jensen EW, Lund J: Changes in rapidly extracted auditory evoked potentials during tracheal intubation. Acta Anaesthesiol Scand 44:743, 2000
124. Vasella FC, Frascarolo P, Spahn DR, et al: Antagonism of neuromuscular blockade but not muscle relaxation affects depth of anaesthesia. Br J Anaesth 94:742, 2005
125. Weber F, Seidl M, Bein T: Impact of the AEP-Monitor/2-derived composite auditory-evoked potential index on propofol consumption and emergence times during total intravenous anaesthesia with propofol and remifentanil in children. Acta Anaesthesiol Scand 49:277, 2005
126. Werba A, Gilly H, Weindlmayr-Goettel M, et al: Porcine model for studying the passage of non-depolarizing neuromuscular blockers through the blood-brain barrier. Br J Anaesth 69:382, 1992
127. Vereecke HE, Vasquez PM, Jensen EW, et al: New composite index based on midlatency auditory evoked potential and electroencephalographic parameters to optimize correlation with propofol effect site concentration: comparison with bispectral index and solitary used fast extracting auditory evoked potential index. Anesthesiology 103:500, 2005
128. Vivien B, Di Maria S, Ouattara A, et al: Overestimation of Bispectral Index in sedated intensive care unit patients revealed by administration of muscle relaxant.[see comment]. Anesthesiology 99:9, 2003
129. Zbinden AM, Maggiorini M, Petersen-Felix S, et al: Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. I. Motor reactions. Anesthesiology 80:253, 1994
130. Zbinden AM, Petersen-Felix S, Thomson DA: Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. II. Hemodynamic responses. Anesthesiology 80:261, 1994