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UTILITY OF BISPECTRAL INDEX (BIS) MONITORING DURING GENERAL ANESTHESIA

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Stockholm 2009

Published by Karolinska Institutet. Printed by Larserics Digital Print AB

ISBN 978-91-7409-697-2

"man får ta de data man får"
- comforting words from Mats Wolgast to my tutor, who in turn passed them on to me….

ABSTRACT

The possibility to objectively measure effects from anesthetics on the level of consciousness has since long been desired. General anesthetics cause changes in brain electrical activity, seen as changes in the electroencephalogram (EEG). Devices utilizing processed EEG for pseudo-quantification of "anesthetic depth" have been available for more than ten years. These monitors display the anesthetic, or rather, hypnotic depth as an index number. In this thesis, some aspects of the use and utility of one such device, the Bispectral index scale (BIS) has been evaluated.

The effects from experience and education on the use and utility of BIS monitoring were analyzed within a group of nurse anesthetists. Available BIS monitoring was found to have minimal effect on anesthetic gas delivery and BIS levels, and this did not change with growing experience and repeated education. However, the user approval, expressed as subjectively rated utility of the monitoring, increased markedly with mounting experience.

The BIS has been thoroughly investigated concerning potential short term benefits, achieved by titrating of anesthesia by the use of the monitor. Marginal reduction in wake up time, shortening of time spent in the postoperative ward, and a reduced incidence of postoperative nausea and vomiting have been shown, but only when BIS values were close to the upper limit of the recommended range.

Regarding long term effects from deep anesthesia, time spent at deep hypnotic level as displayed by BIS < 45, has been associated with increased postoperative mortality. It has been speculated that deep anesthesia could cause or worsen malignant disease, possibly by negatively affecting the immune system. In this thesis, no such relation was found between postoperative mortality within two years after surgery and time spent with BIS< 45. Neither was any relation found between the development of new malignant disease within five years after surgery and time spent at deep hypnotic level.

Underdosing of anesthetics may result in unintended wakefulness, awareness, which besides being a very unpleasant experience, can have long term psychological consequences for the individual. We compared the incidence of awareness in a BIS monitored cohort of patients to that in a historical control group with no such monitoring. Compared to standard praxis, we found a reduction in the incidence of awareness by 77% when BIS monitoring was used.

In summary, the possibility to avoid unnecessarily deep anesthesia by the use of BIS was not adhered to despite mounting experience and educational efforts. Increasing experience was, however, associated with increased subjectively rated utility of the BIS technology. Since anesthesia exposure in terms of time with low BIS was not found to affect long term mortality or the occurrence of malignant disease, the main benefit of BIS monitoring thus far seems to be the possibility to reduce the risk of underdosing of anesthetics, that is, awareness.

LIST OF PUBLICATIONS

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

II. Lindholm ML, Brudin L, Sandin R
Bispectral index monitoring: appreciated but does not affect drug dosing and hypnotic levels
Acta Anesthesiol Scand 2008; 52: 88-94

III. Lindholm ML, Träff S, Granath F, Greenwald SD, Ekbom A, Lennmarken C, Sandin R
Mortality within 2 years after surgery in relation to low intraoperative Bispectral index values and preexisting malignant disease
Anesth Analg 2009; 108: 508-12

IV. Lindholm ML, Granath F, Eriksson LI, Sandin R
Exposure to anesthesia and new malignant disease within five years after surgery
Manuscript

** Position as first author shared with Andreas Ekman.*

CONTENTS

LIST OF ABBREVIATIONS

AEP	Auditory evoked potential
AMPA	α-amino-3-hydroxy-5-metyl-4 isoxalazole proponic acid
BIS	Bispectral index scale
BLA	Basolateral amygdala
CRNA	Certified registrered nurse anesthetist
EEG	Electroencephalogram
ET_{AGC}	End tidal anesthetic gas concentration
GABA	γ-amino-butyric acid
LC	Locus coeruleus
LOC	Loss of consciousness
LTM	Long term memory
LTP	Long term potentiation
NA	Noradrenalin
NMDA	N-metyl D-aspartate
N_2O	Nitrous oxide
PACU	Postoperative care unit
POCD	Postoperative cognitive dysfunction
PONV	Postoperative nausea and vomiting
PTSD	Posttraumatic stress disorder
RNA	Ribonucleic acid
SIR	Standard incidence ratio
TCI	Target controlled infusion
VAS	Visual analogue scale

INTRODUCTION

GENERAL INTRODUCTION

General anesthesia has, since it was first used more than 160 years ago, revolutionized surgery. Progress in anesthetic pharmacology and technology during the last decades has allowed for the conductance of complex surgical procedures that were unthinkable before.

"Sleep" is often used as a metaphor for the anesthetized state. There are similarities between natural sleep and general anesthesia, but there are also important dissimilarities. One important difference between the two states is that while natural sleep is endogenously regulated, the anesthetized state is due to exogenous administration of drugs. This can lead to side effects, not only caused by the delivery of unnecessarily much or, conversely, an insufficient dose of anesthetics resulting in unintended wakefulness, that is, awareness. The anesthetic drugs may also have inherent effects other than those causing reversible anesthesia and may have long term consequences for the individual.

Estimation of whether a patient has been given an adequate amount of anesthetics or not has for a long time relied on the ability of the anesthetized individual to move in response to noxious stimulation, and to exhibits adverse effects from the cardio-vascular- and sympathetic nervous systems. Taken together, these so called "clinical signs" have limited accuracy, especially in the patient undergoing anesthesia which includes neuromuscular blocking drugs.

A key feature of general anesthesia is that the patient is unaware of otherwise surgically induced discomfort, that is, "unconscious". The ability to objectively determine whether the patient is unconscious or not, and preferably also to define an optimal anesthetic drug effect on the brain has for a long time been desired. Even if anesthetics have actions on the spinal cord that contribute to unconsciousness, the brain is clearly the major target. General anesthetics cause changes in brain electrical activity seen in the registration of brainwaves, the electroencephalogram (EEG). Devices utilizing anesthesia induced changes in the EEG for pseudo-quantification of "anesthetic depth" have become commercially available and have been used for more than ten years. In the studies included in this thesis I have evaluated one of these devices, the Bispectral index (BIS®) monitor.

My studies evaluate whether information from the BIS is actually used for the identification of optimal delivery of anesthetics during daily clinical work or not, and also, when actually used, if the BIS can be expected to alter the risk for insufficient anesthesia in terms of awareness or, conversely, if long term morbidity and mortality is affected by avoiding unnecessarily deep anesthesia.

Before going into study details I will briefly review a number of concepts of relevance to my studies including current thinking about the physiology behind memory and the, still not definitely defined, state called "unconsciousness".

GENERAL ANESTHESIA

There is no unanimous definition of general anesthesia, but four modalities are needed to be reversibly attenuated to a sufficient degree, namely mental distress, activation of nociceptive pathways, somatic responses and autonomic responses. To achieve desired effects and minimize side effects, general anesthesia is usually composed of a combination of hypnotics and analgesics, and when needed, muscle relaxants and/or cardiovascular drugs to regulate somatic and autonomic responses.

There is a good understanding how the most used class of analgesics, opioids, exert their action, and also about how the effects of muscle relaxants are achieved. The effects of the general anesthetics, or rather, hypnotics used, both inhaled and intravenous agents, are less well understood. These agents are very diverse but they all, by definition, cause unresponsiveness and unconsciousness. Notably, the loss of consciousness (LOC) occurs abruptly over a small change in concentration (1).

Previously it has been thought that the effects from both inhaled anesthetic agents such as sevoflurane, and intravenous agents, such as propofol and barbiturates, were achieved by disruption of lipid bilayers or nonspecific action. These theories have been abandoned, and it is now thought that most hypnotics exert their effect by binding directly to specific protein targets (1). Among the known proteins, $GABA_A$ receptors are regarded as an important target for intravenous agents, and to some extent also for inhaled hypnotics. Other receptors found to be of importance are two-pore-domain K^+ channels, NMDA receptors and glycine receptors.

Anesthetics bind preferentially to preformed cavities on the proteins. The binding affects receptor function and neuronal activity and is correlated to a dose dependant alteration of consciousness (2). At higher doses the patient becomes unresponsive and is regarded to be unconscious.

CONSCIOUSNESS AND ANESTHESIA

It is not known how consciousness arises in the brain, and hence, it is not known how anesthetics interfere with this state. The thalamus, which is essential in the regulation of sleep, becomes deactivated during anesthesia. General anesthetics somehow disrupt thalamocortical connectivity and ”isolate the cortex from the environment” (1). If anesthetic drugs primarily act on the cortex or on the thalamus, or if an effect on arousal or sleep pathways causes this disruption is not clear. In any case, this loss of thalamocortical interaction might be an essential common feature of anesthetic action (1).

A number of theories on how anesthetics work have been put forward in which cortical connectivity is highlighted (1-6). According to one theory, which has some support from empirical data, consciousness is thought to require “an integrated system with a large repertoire of discriminable states” (2). It has been shown, both during natural

sleep in humans and during desflurane anesthesia in rats, that the initial local response pattern following stimulation of the cortex, does not propagate to other brain regions, which is the case in the awake brain (3,7). The disruption of connectivity is thought to abolish the possibility to make sense of the information that reaches the primary cortical area of the brain (3), and this might be an important functional mechanism behind general anesthetic action, irrespective of where the anatomical site for the drug effect is located (2).

The patient is considered unconscious when failing to respond to command or other stimulation. Absence of response is, however, no guarantee for unconsciousness. General anesthetics can make the patient unwilling to respond, but also block working memory so the patient immediately forgets what to do in response (2). Neither is lack of explicit recall a guarantee for unconsciousness. This has been shown in studies using the isolated forearm technique where a tourniquet is applied to the arm before paralysis is induced which allows the hand to move while the rest of the body is paralyzed. Thus, patients have responded to verbal command during general anesthesia, without any postoperative memory of the event (8).

MEMORY

Memory can be categorized into three different subtypes, immediate (lasts seconds), short-term (seconds to about 60-90 min), and long-term memory (LTM) (>90 min). The hippocampus has since long been recognized as being necessary for the encoding of new memories. After the encoding of a new memory, this memory first exists in a labile state before consolidation and storage in LTM. The memory storage is thought to be located initially in the hippocampus, but long term memories can over time be relocated to different parts of the cortex (9).

The consolidation of LTM is associated with physical changes in synapses due to long-term potentiation (LTP) mediated by the activation of NMDA receptors and a subsequent increase in the number of AMPA receptors (10). These changes, referred to as synaptic plasticity, require synthesis of new messenger-RNA (mRNA) and protein synthesis, resulting in strengthening of synapses and facilitated communication.

Some structures of importance to memory and consciousness are illustrated in Figure 1. Evidence strongly indicates that emotionally charged memories are better remembered than neutral ones. Influences from the basolateral amygdala (BLA), which is associated with in particular negative emotions, have been proposed as an explanation for these findings (11,12). The amygdala can modulate hippocampal responses directly, possibly by regulating the expression of plasticity-related products (13). The amygdala can affect, and can also in turn be affected by central arousal through bidirectional connections to locus coeruleus (LC), the sole source of noradrenalin (NA) in the brain. NA is known to sharpen perception and allocate attention to select and store, for the situation relevant information.

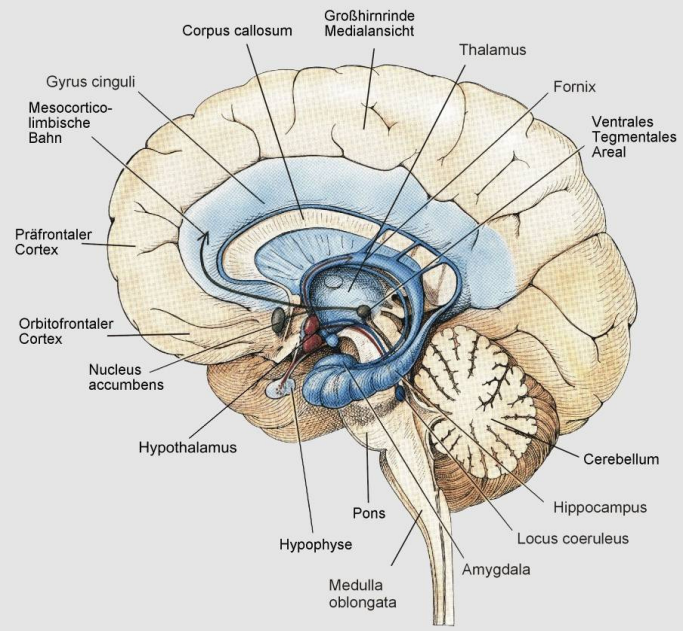

Figure 1. *Some brain structures relevant to memory and consciousness.*

General anesthesthetics, as sevoflurane and propofol are known to produce amnesia. Anesthesia induced amnesia is, at least in part, thought to be mediated through enhancing effects on $GABA_A$ receptors in the BLA. These effects have been shown to result in a reduction in the expression of a cytoskeletal protein in the hippocampus, known to play an important role in synaptic plasticity, albeit no reduction in synthesis of new mRNA coding for the protein was shown (14). Thus, $GABA_A$ dependent amnesia may be due to a block in the translation of cytosceletal protein from mRNA in the hippocampus. The amnesic effects from sevoflurane may also be due to effects exerted on the BLA (15). Long-term memories exist in an active or inactive, consolidated, state. For a memory to be activated, it needs to be retrieved from long-term memory storage. An activated memory is susceptible to modification, which gives place for incorporation of new information, and it has been suggested, that the instability of a retrieved memory is due to synaptic protein degradation (16). To maintain a memory after activation, it has to be reconsolidated, a process requiring formation of new mRNA and new protein synthesis, just as the initial memory consolidation (17). At least for emotional memories, the noradrenergic system is thought to be involved in the retrieval, but also in the reconsolidation process (18,19). The knowledge about the influence from the noradregenic system on retrieving and reconsolidation of emotional memories, and about the instability of retrieved, activated memories, has been used in treatment of patients suffering from posttraumatic stress

disorder (PTSD). Propranolol given after memory activation of the past traumatic event, was found to reduce the psychological response during subsequent mental imagery of this event (20).
Memories can also be categorized as being explicit, consciously retrievable, or implicit, memories not possible to consciously activate. Implicit memories, which are thought to be formed unconsciously, including during adequate anesthesia, can affect behaviour and feelings without our understanding or knowledge. In most studies showing implicit memory formation during anesthesia, this has been found to take place during surgical stimulation, and especially during light anesthesia (21,22). It is not known how common implicit memories are, and to establish the occurrence, time consuming tests are needed which are hardly possible to use in larger scale investigations. It is difficult to separate implicit memories from explicit ones, and to evaluate the influence from implicit memories seems to be even harder, although there appears to be growing evidence of their importance (21).

EFFECTS FROM INADEQUATE ANESTHESIA

Insufficient anesthesia - Awareness

In this thesis, awareness is defined as an explicit memory from the anesthesia period during which the patient should have been, and in most cases was regarded to be, unconscious. Awareness is an experience that patients, when questioned, have regarded as the most dissatisfactory event during the perioperative period (23).

Incidence of awareness

During the last ten years, the incidence of awareness has been reported to be about 0.1-0.2% in three large studies conducted in different parts of the world (23-25), but in two recent studies somewhat higher incidences (0.4%, and 0.6%, respectively) were found (26,27). In a report using data from a questionnaire intended for quality assurance in the postoperative period, the incidence of awareness was found to be as low as 0.0068%. This study was, however, not designed to detect awareness and the interview was leaving out the two most important questions for this purpose (questions 3 and 5; see box in page 14) (28).
The risk of experiencing awareness is regarded to be increased in patients undergoing heart surgery, Caesarean section and in trauma patients, but also in patients with a history of long-term use of drugs like opioids and benzodiazepines, and daily alcohol consumption (29). However, it has been shown that it is possible to reduce the incidence of awareness even in “high risk surgery cases”, which means that the increase could be related to the anesthetic technique rather than to the type of surgery (30-32).

Even if it seems possible to reduce the incidence in this population as well, an increased risk of awareness during open heart surgery is still evident (33,34).

Detection of awareness

It has become a well known fact that patients who have experienced awareness are reluctant to talk about it, if not directly asked (29). Interview methods has been developed, first by Brice (35) and later modified by Liu (36). This modified Brice interview has been widely adopted and is nowadays used in most studies for detecting awareness.

The questions asked are:

1. What is the last thing you remember before you went to sleep for your operation?
2. What is the first thing you remember after your operation?
3. Can you remember anything in between?
4. Did you dream during your operation?
5. What was the worst thing about your operation?

Since it has been shown that memories of awareness can be delayed, the interview will have to take place within the first couple of days, but also be repeated after about one week, to be able to detect explicit recall (25,37).

Consequences of awareness

The consequences of experiencing awareness vary within a wide range from denial of any late symptoms that could be related to this experience, to persisting mental problems requiring psychiatric care. The most frequently reported symptoms have been nightmares, anxiety and flashbacks (38,39). The duration of the symptoms varies. In some patients the symptoms have faded away within a couple of months while others have problems lasting for years. Experience of acute negative emotions during the awareness episode has been found to be related to the risk of late psychological symptoms (38-40).

The reported degree of the psychological problems is not consistent between investigations. This is possibly due to different ways of recruiting patients. In a recent study, in which patients were prospectively included, fewer and milder problems were found than in earlier, predominantly retrospective studies (39).

EFFECTS FROM EXCESSIVE ANESTHESIA

In addition to negative effects from excessive anesthesia in the immediate perioperative setting, possible long term consequences are currently debated and being investigated.

Short term effects from excessive anesthesia

General anesthetics affect the circulation and cause hypotension by concentration-dependent myocardial depression and effects on blood vessel tone. This adverse effect, since long a cornerstone for assessing "anesthetic depth", can be detrimental, especially to patients with heart disease, and also to patients who are already circulatory compromised due to an acute condition such as hypovolemia or sepsis. In addition, there are indications that unnecessarily generous administration of anesthetics may affect the risk for postoperative nausea and vomiting (PONV) (41-43), delay recovery, and result in longer stay in the postoperative care unit (PACU) (43-46).

Long term morbidity and excessive anesthesia

There is a currently ongoing controversy, among professionals as well as in the lay press, as to whether anesthetics may have adverse long term effects on cognitive function, in the very young as well as in the elderly (47-49). There is also some data indicating that anesthetics may affect long term survival (50), and also alter the risk for recurrent malignant disease (51-53).

ASSESSMENT OF HYPNOTIC DEPTH

For a long time, observation of somatic and autonomic response to stimulation has been the common way by which the administration of anesthetic agent is adjusted to the anticipated need of the patient. During anesthesia including neuromuscular blockade, i.e. when the patient is deprived of the possibility to move, the assessment of anesthetic, or rather, hypnotic depth, is further restricted to gross changes in blood pressure, heart rate and the occurrence of sweating and tearing of the eyes. In the circulatory unstable patient, the drug dosage during anesthesia is further complicated by the necessity to give priority to adequate blood circulation.

End-tidal anesthetic gas concentration

The endtidal anesthetic gas concentration (ET_{AGC}), which today is routinely monitored when inhaled anesthetics are used, gives reasonably adequate information about the effect site (brain) concentration under steady state conditions. However, since stimulation varies and circulation sometimes is unstable during surgery, a steady state is not always achieved. The pharmacodynamic effect of inhaled anesthetics also depend on age in addition to individual variation (54,55), and furthermore, the ET_{AGC} is of no value during intubation, an event constituating a very strong noxious stimulus.

Target controlled infusion

In intravenous anesthesia, no surrogate measurement of anesthetic concentration in the brain is currently available. The use of target controlled infusion (TCI) has probably simplified dosing of intravenous anesthetics, but the targeted values have been shown to deviate from serum concentrations, and, just as for inhaled anesthetics, the pharmacodynamic effect from the concentration achieved differs between individuals (56).

EEG based monitoring

Finding an objective way of measuring the hypnotic depth, that is, to be able to monitor the pharmacodynamic effect from drugs rather than the concentration or dose given, has since long been desired. The EEG was early considered as a possible alternative, and the first studies of the effects from different anesthetics on the EEG were conducted around 1950 (55).

It was found that the EEG pattern changed with the level of consciousness, but the changes were not consistent between drugs. It also turned out to be impractical to use a whole set of EEG electrodes for monitoring during anesthesia. However, the interest in EEG changes in relation to drug administration persisted and has eventually resulted in commercial monitors for measurement of hypnotic depth, typically displaying the EEG information transferred to a single index value.

The available hypnosis monitors either use a passively recorded EEG, like the BIS monitor, or EEG recorded after stimulation like the auditory evoked potentials (AEP) monitor (AEP monitor/2®).

The BIS monitor is the EEG based device used in the studies included in this thesis, and other available monitors will therefore not be further discussed.

Bispectral index monitoring

The BIS monitor uses frontal EEG passively recorded via a strip containing 4 electrodes applied to the patients´ forehead according to Figure 2.

Figure 2. *Montage of the four EEG sensors.*

The EEG, which is an analogue signal, is digitized, artefact filtered and split into epochs. The epochs, which are small periods of time, in this case 2 s, are then transformed to a power spectrum by the use of a fast Fourier analysis as illustrated in Figure 3. The EEG, which looks chaotic, is composed of a number of sine waves of different frequencies put together. The fast Fourier analysis splits the EEG epochs into the different frequencies, and estimates the power in each frequency. This information is then used to analyze two of the four parameters which sums up to give the BIS index, the beta ratio and the sync fast slow. The beta ratio compares the energy in the 11-20 Hz band to the energy in the 30-47 Hz band, and the sync fast slow, the ratio of bispectrum peaks in the 0.5-47 Hz band relative to the 40-47 Hz band. The EEG is also analysed to detect periods of burst suppression shown as suppression ratio (SR; the time of isoelectric EEG). A fourth analysis, QUASI, is used to detect background noise to be able to correctly define the burst suppression periods.

These four parameters are combined, by a proprietary algorithm, to give a dimensionless number between 0-100 called the BIS index where 0 represents the isoelectric EEG and 95-100 the fully awake patient. The different parameters are weighted differently at different clinical states. The impact of the different parameters has been determined by the use of a body of data gathered from patients who received various anesthetics while EEG and behavioural data were collected. The recommended level during surgical anesthesia is 40-60 (55,57).

The BIS monitor uses cortical activity as a proxy measure for consciousness which leads to a number of shortcomings. The state of the cortex at a given moment will not accurately predict the response to a noxious stimulus. The monitor does not differentiate well between different levels of arousability, and can not accurately discriminate between the awake and unresponsive state (58). The changes in the index number do not represent the same level of consciousness for all anesthetics, and the

monitor can be fooled by, for example, the genetically-determined low amplitude EEG found in 5-10% of the population (59,60).
However, despite the fact that the BIS monitor, as other currently available EEG devices for assessing hypnotic depth, has a number of shortcomings, it should be remembered that the older measures such as heart rate and blood pressure have repeatedly been shown to discriminate even more poorly between consciousness and unconsciousness.

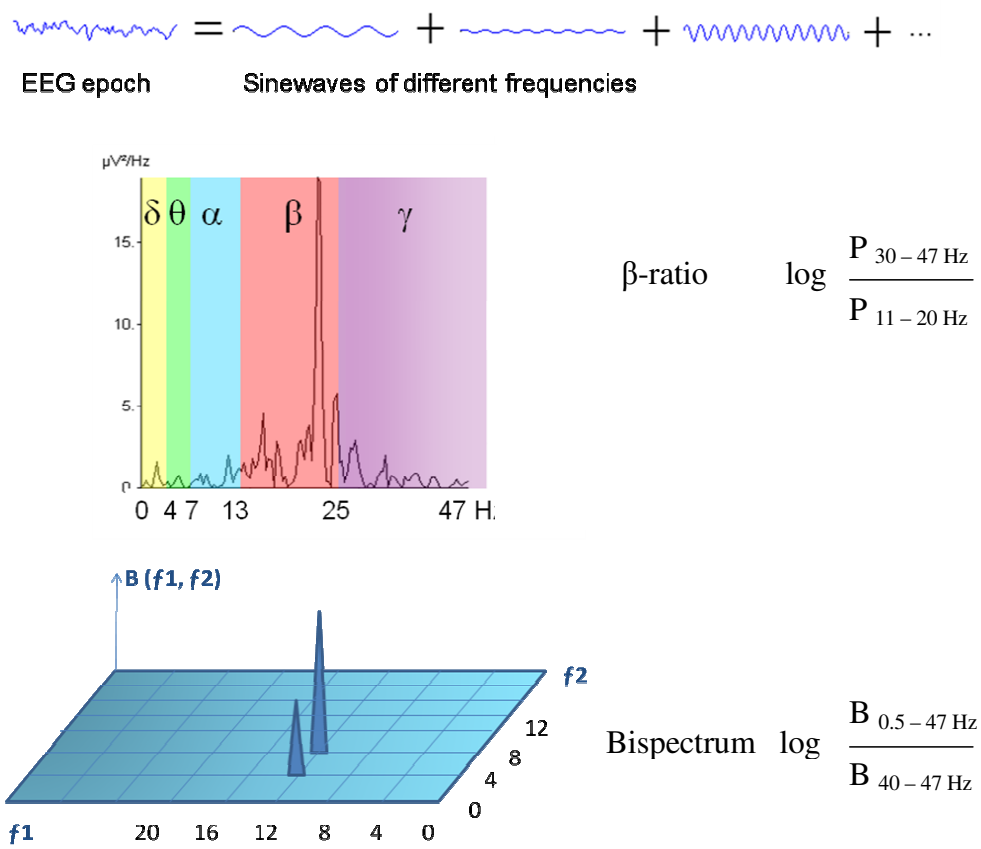

Figure 3. *Principal signal handling by the BIS technology starting with fast Fourier analysis (upper panel) and subsequent derivation of β-ratio from the power spectrum (middle panel). Bispectral analysis (lower panel) quantifies the phase correlation between different frequencies in the EEG. The third subparameter (not shown) is burst suppression, that is, electrical activity < 5mV for >0.5 s. The fourth subparameter, QUASI (not shown) is a correction for deviation of the electrical baseline.*

AIMS

The overall aim of this thesis was to investigate the use and utility of an EEG-based monitor of hypnotic depth, the BIS, with focus on potential consequences from too light and unnecessarily deep anesthesia. That is, my studies evaluate whether information from the BIS is actually used for the identification of optimal delivery of anesthetics during daily clinical work or not, and also, when actually used, if the BIS can be expected to alter the risk for insufficient anesthesia in terms of awareness or, conversely, if long term morbidity and mortality is affected by avoiding unnecessarily deep anesthesia.

Paper I
The aim was to investigate if the use of BIS monitoring during general anesthesia could reduce the incidence of awareness as compared to standard practice.

Paper II
The aim was to investigate the impact of BIS monitoring on anesthesia handling. A second goal was to evaluate the effects of education and experience from such monitoring on anesthetic depth, drug consumption, and subjective attitudes to the utility of this monitoring.

Paper III
The aim was to investigate if previous findings of a relation between deep anesthesia in terms of time spent with low intraoperative BIS values and mortality within one year, could be confirmed or refuted.

Paper IV
The aim was to investigate a possible relation between deep anesthesia in terms of time spent with low intraoperative BIS values, and the development of new malignant disease within five years after surgery.

MATERIAL AND METHODS

All studies were approved by the local ethical committee at Linköping University and for study III and IV, also by the National Board for Health and Welfare in Sweden. Informed consent was obtained from patients in paper I, from certified registrered nurse anesthetists (CRNA) in paper II, and from the Heads of departments for the included patients in papers III and IV.

STUDY PROTOCOLS AND DATA ANALYSIS

Paper I

During 17 months, 4945 patients undergoing surgery requiring general anesthesia with endotracheal intubation and/or muscle relaxation were prospectively included at two hospitals and investigated concerning the incidence of awareness. The patients were monitored with BIS (BIS A-2000^{TM} monitor, version 3.4, Aspect Medical Systems, Newton, MA, USA). Before the study start, all anesthesia providers were introduced to the monitoring equipment, and received basic training. They were instructed to keep BIS values between 40 and 60 during induction and maintenance of anesthesia. The patients were interviewed using the modified Brice interview on three occasions, that is, in the postoperative ward, between 24-72 hours postoperatively, and between 7-14 days postoperatively. Exclusion criteria were; patients under 16 years of age, unable to communicate in Swedish or English, unavailable for monitoring due to the surgery field, and failing to conduct any of the two last interviews. The result was compared to that in a historical control group of 7826 patients at the same two hospitals, receiving the same kind of anesthesia during a period when no hypnosis monitoring was used. BIS trends were downloaded and analysed off line. Data from induction and maintenance was used.

Paper II

This study is based on a retrospective material illustrating the first experience from BIS monitoring in our department, and a subesequent, prospective part in which effects from experience and additional educational efforts were evaluated. The two parts were separated by a 1 year period during which BIS monitoring was unavailable. For study design see Figure 4.

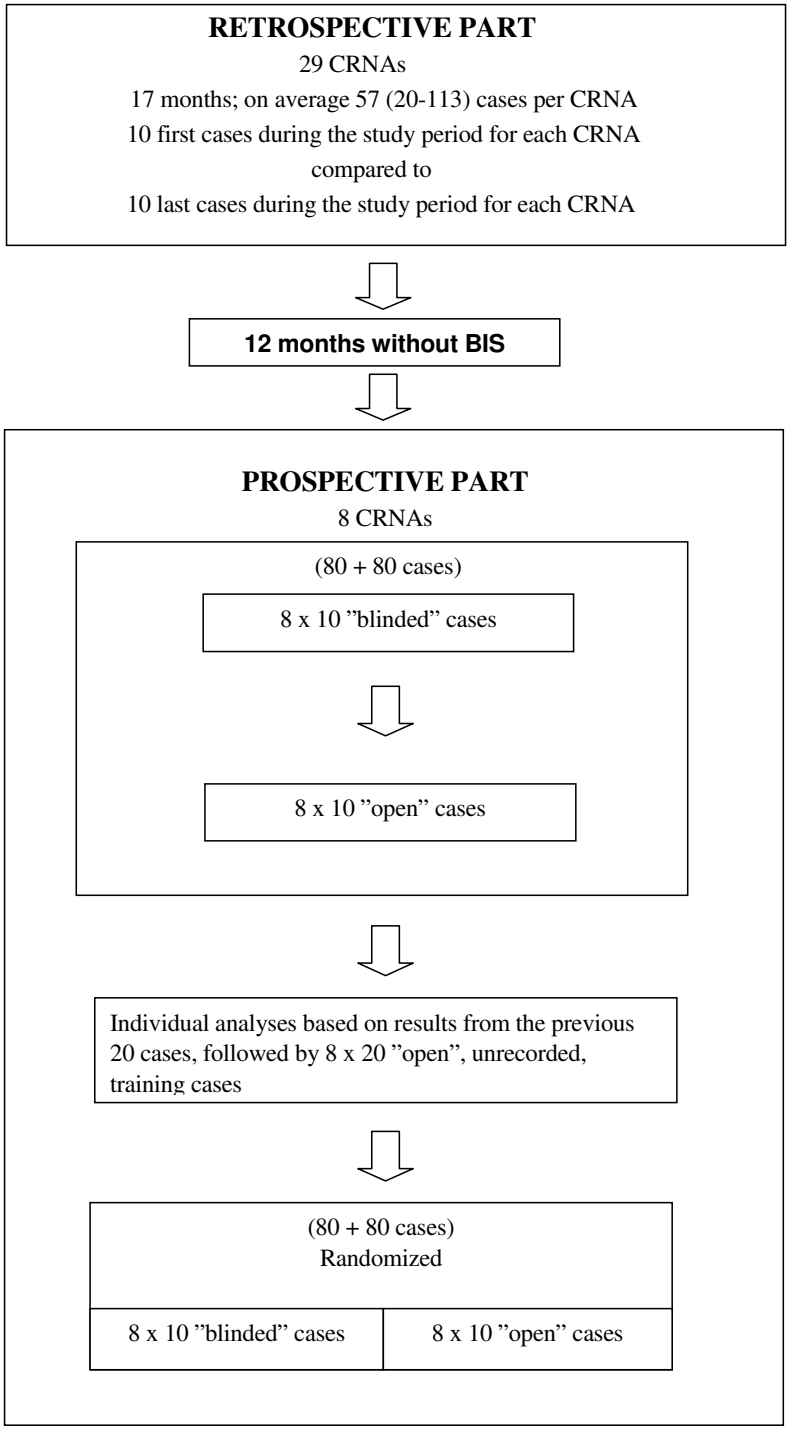

Figure 4. *Study protocol in Paper II.*

Data from Paper I was used as retrospective background. During a 17 month period, data from the first 10 cases was compared to the last 10 cases for each of 29 CRNAs. Fraction of time with BIS spent within or out of the recommended range, mean BIS during maintenance, and mean BIS during induction were calculated (Figure 5).

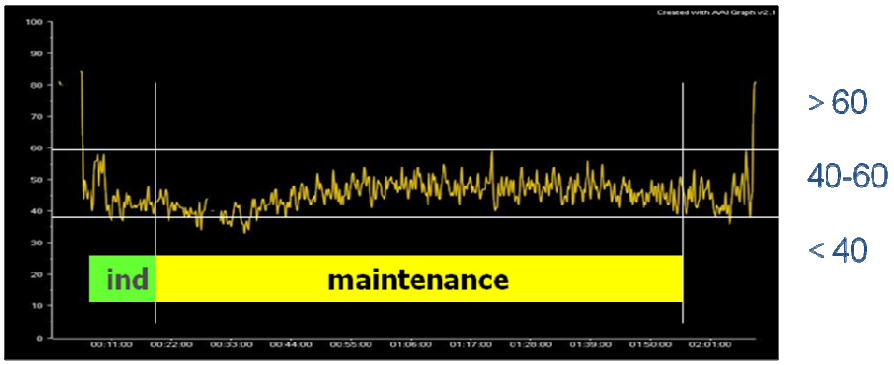

Figure 5. *BIS trend illustrating the recommended range, and the induction and maintenance periods.*

In addition, subjective rating of utility and function of the BIS monitoring technology was assessed. Only sevoflurane-N_2O based anesthesia including muscle relaxants was included since this was the anesthetic regimen used in the second, prospective part of the study. Before starting this part of the study, the BIS monitors were not used for about one year.

After that year, eight of the CRNAs were reintroduced to BIS monitoring (BIS A-2000™ monitor, version 3.4, Aspect Medical Systems, Newton, MA, USA).

In the prospective part of the study, each of the eight CRNAs first conducted 10 cases with hidden BIS monitoring followed by 10 cases with available BIS. They were instructed to keep BIS values between 40-60 when BIS was available. Assessment of BIS data and opinions on utility and function was as in the retrospective material. In addition, data on anesthetic gas delivery was collected. Thereafter, a teaching event took place including feedback on the results in the first part, followed by at least 20 training cases with the BIS aimed to increase confidence to adhere to the 40-60 interval.

After conducting the training cases, another 10 blinded and 10 open cases were conducted in a randomized manner by each of the eight CRNAs. Data on BIS levels, anesthetic gas delivery and subjective opinions on the monitoring device was gathered as previously. All data from BIS monitoring as well as physiological parameters and gas delivery were recorded on a lap top computer every 5 s.

Paper III

The relationship between death within one and two years after surgery and deep anesthesia in terms of time spent at BIS < 45 was analyzed in 4087 patients. Official data from The National Board of Health and Welfare in Sweden was used to identify patients who died within one and two years after surgery. Cause of death was obtained from the patient records, and data concerning preexisting malignancy was retrieved from The National Cancer Registry in Sweden. As malignancy was found to be the predominant cause of death in our study as well as in the previous report, data was first analyzed without, and then repeated with, preexisting malignant disease at the time of surgery as a co-variate.

Paper IV

The relation between contracting a new malignant diagnosis within five years after surgery and time with deep anesthesia in terms of time spent at BIS < 45, was analysed in 4083 patients. Secondary analyses for specific cancer forms were performed for all subtypes with more than 15 events. Malignancy status at the time of surgery and data on new malignant diagnoses within five years after surgery was obtained from The National Cancer Registry in Sweden. Standard data on the expected incidence of malignant disease were used for comparison with our cohort in a model including age and gender.

STATISTICS

Paper I
Comparison of awareness incidence 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
Non-parametic statistics were used due to nonnormally distributed parameters. When comparing three or more groups, Kruskal-Wallis ANOVA by ranks was used followed by Mann-Whitney`s *U*-test in case of significance. The latter was also used when two groups were primarily compared.

Paper III
The risk of dying within one and two years after surgery was analysed by the means of Cox´s proportional hazard models.

Paper IV
The risk of contracting a diagnosis of malignant disease within five years after surgery was analysed by means of Cox´ proportional hazard models. Secondary analyses for specific cancer forms were corrected for multiple end-points by means of the Bonferroni-Holm method.

RESULTS

Paper I

Two cases of awareness were found in the BIS monitored cohort compared to 14 cases in the historical control group, which represents a risk reduction in the incidence of awareness by 77%. The two patients expierencing awareness both had BIS values > 60 during four and ten minutes, respectively, correlating to the awareness episodes. Both incidents occurred during intubation. In the whole cohort 19% of the patients had episodes of BIS values > 60 for four minutes or more during induction, and 8% of the patients had at least one such episode during maintenance. The mean BIS during maintenance was 37.

Paper II

No differences concerning BIS values or subjective opinions were found between the beginning and the end of the observational period in the retrospective material. Nor were there any differences found between the four different experimental situations of the prospective part, which means no differences between “open” and “blinded” cases, and no differences before and after repeated education and training. Comparing the BIS levels between the first retrospective and subsequent prospective parts of the study, the fraction of time spent between 40-60 had increased, but was still < 50%. However, the opinion on utility reflecting user approval had increased by 60 % to 74 mm on the 100 mm visual analogue scale (VAS).

Paper III

An association was found between deep anesthesia, in terms of time spent with BIS < 45, and death within one and two years after surgery. The main cause of death was malignant disease (71%). When the occurrence of preexisting malignant disease at the time for surgery was included as a covariate in the analysis, the relation between time spent at low intraoperative BIS values and postoperative death within one and two years was no longer significant.

Paper IV

No association between deep anesthesia, in terms of time spent with BIS < 45, and identification of new malignant disease within five years after surgery was found in the cohort. Standard incidence ratio (SIR) for development of malignancy was 1.47, that is 47% more than expected.

DISCUSSION

The BIS monitor is by far the most used device for measuring hypnotic depth, and also the most thoroughly investigated one. The intension of this work was to analyse some aspects of BIS monitoring that previously had been insufficiently investigated or not studied at all.

THE ATTITUDE TO-, AND USE OF BIS MONITORING IN CLINICAL ANESTHESIA

The initial experience with BIS monitoring in our department, on average 57 (20–113) cases, had not led to any change in BIS levels or attitudes to the utility of this monitoring. After that initial experience, BIS was unavailable for one year. After that year, concealed BIS monitoring revealed that performance was almost unchanged in terms of the fraction of time spent within the recommended BIS interval. Subsequent availability to BIS monitoring at this level of experience was not associated with any difference in BIS levels or anesthetic gas consumption as compared with concealed monitoring, not even after repeated education and encouragement to adhere to the 40–60 interval. Our result is in line with Pavlin et al. who found no more than a statistical, albeit clinically insignificant reduction in anesthetic gas delivery when BIS was used in common practice (61). The limited individual experience from BIS in the study by Pavlin may not have been the reason for their result. An average individual experience from as much as 108 cases of BIS monitoring during anesthesia including muscle relaxants in our study was associated with only modest changes in BIS levels and no differences in anesthetic gas consumption. Notably, despite limited impact on BIS levels or anesthetic gas consumption, we found that BIS monitoring was associated with markedly increased user rated utility.

Thus, results from ordinary anesthesia practice seem to be at odds with several studies aiming at reducing the delivery of anesthetics by BIS guided administration (43-46,62-68). There may be several explanations for this discrepancy. In our, as well as in Pavlin's study, anesthesia was conducted by anesthesiologists doing their ordinary job. In the Pavlin study, anesthesia was handled by residents and CRNAs, and in our study by CRNAs, in both cases collaborating with senior physician anesthesiologists. Anesthesiologists directly involved in studies showing a reduced consumption of anesthetics when BIS was used may have been more confident and prepared to accept index values closer to the upper recommended level as compared with the average anesthesiologist or CRNA. It seems that the anesthesiologist must be motivated for "light" anesthesia if BIS monitoring is going to make a difference (63), whereas the reason for "light" anesthesia, economical or patient related, may not always be obvious

to the anesthesia provider in the ordinary clinical setting. In addition, titrating anesthesia to the upper part of the recommended BIS interval requires continuous adjustment of the anesthetic delivery if values above 60 are to be avoided. Potential economical advantages from less deep anesthesia include shorter waking-up time (43-46,63,66-69), shorter stay in the PACU (43-46), criteria fulfilled for possibility to by-pass the PACU (45,69), and reduced drug consumption and, hence, reduced drug cost (43-46,62-68). However, economical advantages may be of greater immediate interest to persons with budget responsibilities than to staff anesthesiologists. Furthermore, it may not always be possible to substantiate theoretical savings, and any savings must also be balanced against the cost for monitoring (43,64). In addition to limiting hypotension in circulatory compromised patients, suggested patient-related advantages from "light" anesthesia include less post-operative nausea and vomiting (41-43), but this effect seems to be of limited magnitude (43).
Thus, the potential advantages from "light" anesthesia may not be obvious to, or rewarding for the ordinary anesthesia provider, whereas a case of awareness may put personal qualification into question in addition to the risk of a law suit.

BIS AND AWARENESS

We found a risk reduction in the incidence of awareness by 77% when BIS monitoring was used compared to an historical control with no such monitoring. It could be argued that a randomized trial should have been conducted, but to be able to detect a difference in a mixed surgical population, as in our study, about 50,000 patients would have to be included for detection of a 50% risk reduction. The reason why we still did a study in a restricted number of patients was due to the fact that the actual potential for risk reduction was not known, and the assumption that a randomized study in 50,000 patients would not be possible. Another way to overcome this statistical problem was used in a study by Myles et al. (70). They did a study in a high risk population, expected to have a tenfold higher incidence of awareness, thus, reducing the required number of included patients to approximately 2500. They found a risk reduction in the incidence of awareness by 82% when BIS monitoring was used, that is, very similar to our result, and, thus, lending support to our finding.
The two patients in our study who experienced awareness were both found to have had BIS values above the recommended upper limit of 60 for a considerable time. This means that these two cases probably could have been avoided if the monitoring had been used according to its purpose. However, a significant number of other patients had periods with BIS over 60 without any recall, indicating that the threshold of 60 is arbitrary. Indeed, there are also a few reports indicating that patients have been aware at BIS below 60 (71,72). An even more striking deviation from the recommended BIS interval in our study is indicated by the fact that the mean BIS during maintenance was 37, that is, several patients have spent considerable time below the lower recommended limit of 40. This means that even though all anesthesia providers were instructed to

keep BIS between 40 and 60, this was not the case, and it is possible that the markedly increased user approval during the course of our study indicate that BIS monitoring predominantly was used for avoiding awareness, not reducing the amount of anesthetics.

BIS AND POTENTIAL LONG TERM EFFECTS FROM ANESTHESIA

In 2005, a relationship between deep anesthesia, in terms of time spent at BIS <45, and death within one year after surgery, was suggested in a study by Monk and colleagues (50). Since the predominant cause of death was malignancy, it was speculated that this relation could be due to impairment of the immune system caused by effects from deep anesthesia, leading to development of malignant disease. In study III, we found a similar relationship, which was valid also when the observational period was extended to two years. In our study, as well as in the previous publication by Monk, malignancy was found to be the main cause of death. Including pre-existing malignancy as a covariate in the analyses, erased the significance for the previously found relation between time with BIS < 45 and postoperative mortality within two years. Our result thus suggests a non causal relationship between time spent with BIS < 45 and mortality.

However, since contracting a malignant diagnosis is not necessarily lethal, a possible relation between development of malignant disease and low intraoperative BIS values had not definitely been ruled out. Therefore, this was investigated in study IV.

The main findings in this study were that there was no impact by exposure to anesthesia on the development of malignancy during a 5 year follow-up period, albeit the risk for being assigned new malignancy was 47% higher in the study cohort compared with what would have been expected in an age and gender matched non-surgical cohort. Some argue that drugs used for general anesthesia may impair the immune response in a time-concentration dependent manner. For instance, non-randomized human data have indicated that regional anesthesia in addition to general anesthesia could be associated with less recurrence of malignant disease, possibly by reducing the need for general anesthetics (52,53). The hypothesis put to test was that malignant diagnoses would be more common during a 5 year follow-up period in patients with more profound exposure to anesthetics, i.e. longer time spent at BIS-values below 45, as compared to those with less time spent below this threshold. No such relation was found, irrespective of whether the patient had a malignant disease or not at the time for surgery. A BIS value of 45 was chosen since it has been used in earlier work on adverse effects from anesthesia (50), and the finding was confirmed when the analyses were repeated with a threshold for BIS of 40 (the lower limit for surgical anesthesia recommended by the manufacturer).
Despite this lack of statistical relation to anesthetic exposure, the incidence of new malignant disease within 5 years after surgery was 47% higher than expected in a non-

surgical population. A possible explanation for this finding could be that the investigated cohort, basically identified by a requirement for surgery, may have differed from an age and gender matched non-surgical population in the propensity for malignant disease. It could also be that time spent at BIS < 45 may not adequately mirror exposure to anesthetic drugs. Finally, other, non-anesthetic cancer promoting effects in the perioperative setting may have been instrumental in affecting the immune system (51).

FUTURE PERSPECTIVES

The main benefit of BIS monitoring thus far seems to be the possibility to reduce the risk of underdosing of anesthetics, that is, awareness. When it comes to avoiding unnecessarily deep anesthesia by the use of BIS, my studies do not support the assumption that doing so will affect long term mortality or the occurrence of malignant disease. My findings do not, however, rule out that specific patient groups may benefit also in the long perspective from avoiding more intense exposure to anesthetic drugs than what is needed for unconsciousness.

Randomized studies on postoperative recurrence of specific malignant diseases in relation to exposure to general anesthetics are currently being planned or conducted by others.

Animal studies and cell studies, showing toxic effects caused by anesthesia on the immature brain and neuronal cells (73-75), have led to suggestions that anesthesia in the very young individual may contribute to later learning disabilities (47). It has not yet been proven that the animal and cell data actually applies to humans. If this should turn out to be the case, the next logical step would be to investigate if this holds true for anesthetic drugs used in clinical practice, and if there is a concentration dependent toxic effect that could be attenuated by the use of neuromonitoring such as BIS.

Another potentially vulnerable and growing category of patients is the elderly. A possible effect from deep anesthesia in terms of low intraoperative BIS values on the level of POCD has been investigated, but so far, results have been inconsistent (48,49). The incidence of circulatory events within one year after surgery, are correlated to even moderately elevated postoperative levels of troponin in the elderly (76). Whether cognitive and circulatory compromise, and the need for postoperative hospitalization in this subpopulation is affected by “depth of anesthesia” is currently being investigated by us.

An additional future perspective relates to whether the currently available cerebral monitoring algorithms actually display the most relevant information when it comes to identifying an anesthetic effect on the brain that quenches consciousness, but just barely so. Ongoing research will increase our understanding about the biologic foundations for consciousness and how this state is affected by the anesthetic drugs, and this may allow for improved monitoring technologies.

CONCLUSIONS

Based on the studies in this thesis, it is concluded that,

- the use of BIS monitoring during general anesthesia reduced the incidence of awareness compared to standard practice,

- BIS monitoring did not significantly affect anesthesia practice in terms of drug consumption and hypnotic levels despite education and increasing experience. Despite this, the users' ratings of the utility of BIS increased with growing experience from this monitoring,

- there was no relation between deep anesthesia in terms of time spent with BIS < 45 and mortality within one year after surgery. This result was valid also when the observational period was extended to two years,

- there was no relation between deep anesthesia in terms of time spent with BIS < 45 and the development of new malignant disease within five years after surgery.

ACKNOWLEDGEMENTS

Many people have contributed in different ways to this thesis, and I want to express my gratitude to all members of staff at the Anesthesia and Intensive care unit at Kalmar County Hospital and also to all participating patients, without whom the studies would never have been conducted.
I want to thank all my friends and workmates in the ICU, PACU and operation theatres for taking interest and being supportive.

There are, however, a few people who deserve a more personal appreciation:
First my supervisor, **Rolf Sandin**, who gave an insight in the world of science, who believed in me, encouraged me and supported me through the years.
Lars I Eriksson, who, even after resigning as my co supervisor, remained supportive and helpful.
Lars Brudin, a great resource to all researchers in our hospital, always willing to help and guide in the complicated statistical world.
Mats Johansson, technician at the Clinical Physiological Department, for invaluable help saving the data I thought I had lost.
Former and present Chairman of the Department, **Roland Johansson** and **Olle Engdahl**, for their positive attitude towards me and my research projects.
Ann-Marie Engström, **Monika Ebenhart**, **Eva Svanholm**, **Kerstin Näsman**, **Bodil Alexandersson**, **Christina Johansson**, **Birgitta Törneke** and **Liselotte Fritz**, for dedicated work in study II, and **Aune Rettrup** for scheduling the staff to make the study run smoothly.
Fredrik Granath and **Anders Ekbom** for statistical help and shared wisdom and knowledge during the work on study III an IV.
Peter Möller for providing his expert judgement in study IV.
Joanna Webb for proofreading and revising my English.
Andreas Ekman and **Peter Samuelsson**, who both beat me to the PhD, for sharing my study problems and supporting me.
Anette Williamsson, always willing to help
Kim Gommesen and **Brian Andersen** for help with data analysis programming.
Stefan Träff for his dedicated work on the Norrköping part in study III.
Scott Greenwald at Aspect Medical Systems, for kindly providing me with the data I needed.
Nicki, my oldest and best friend for being just the person she is.
My brother **Sigvard** and **IngMarie** for being my family.
And last, again, **Rolf**, for sharing my life, making every single day in his company precious.

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PAPERS I-IV