The use of fast extracted mid-latency auditory evoked potentials monitoring to improve the measurement of the hypnotic component of anesthesia

Het gebruik van het monitoren van snel-geëxtraheerde mid-latente akoestisch uitgelokte hersenpotentialen om meting van de hypnotische component van anesthesie te verbeteren

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“The secret of all success
is to finish what you started”

Preface and acknowledgements

After completing my training as an anesthesiologist, I was ready for a new challenge. The department of anesthesiology at the Ghent university hospital offered me the perfect opportunity, when they started a consortium to develop a strategy for validating new technology for measuring the cerebral hypnotic drug effect. For five years, I combined research work and writing this thesis with a full time clinical activity. During that time I learned that such a challenge has some repercussions. Combining both duties has at times made heavy demands on the nervous system. On the one hand, I experienced a lot of personal satisfaction when through persistence and motivation I reached new deadlines. But on the other hand it also turned out to be a confrontation with the limits of what a person can take. Therefore, I guess that's exactly what made this work my 'personal' challenge. I have learned a lot about myself in the process.

Writing this thesis was a demanding task, not only for me but also for my family. That's why I want to dedicate this thesis to my loved ones. I also thank my dearest friends and family for their unrelenting confidence and patience. I hope they will find the result worthwhile.

I want to pay my respects to Prof. Dr. M. Struys, the promotor and Prof. Dr. E. Mortier, the co-promotor of this thesis for their constant support and trust. It is a privilege to be a part of the team.

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Chapter 1
Introduction and aims of the thesis

Chapter 1 Introduction and aims of the thesis

Before any methods for measuring “anesthetic drug effects” can be suggested, one needs to define the exact clinical phenomenon to be measured. Therefore, we have to define “anesthesia”.

Until today, scientists do not fully understand the neurophysiologic and neuro-anatomical mechanisms of the clinical condition called “anesthesia”. However, throughout the history of medicine, many methods to deliberately interfere with consciousness have been discovered and optimized, on a mainly empirical basis. Even now, performing anesthesia remains an individual pharmacological experiment, during which unexpected individual responses can occur. This clinical reality is the result of a large biological variability that characterizes the human species.

Currently, the “anesthetic state” is considered to be a combination of three important clinical endpoints. The “hypnotic component of anesthesia”, the “analgesic component of anesthesia” and “immobility”.(1) To have a better understanding of the complex endpoints that we attempt to monitor in this thesis, a more detailed description of these three components will be given in chapter 2.

The endpoint of interest for this thesis is **“the hypnotic component of anesthesia”**. This can be obtained by “hypnotic anesthetic drugs”, such as propofol and inhaled anesthetics. By means of these hypnotic drugs, the anesthesiologist aims to obtain “unconsciousness”. “Unconsciousness” implies that the patient becomes unaware of his surroundings during the surgical procedure. However, the intensity of hypnotic drug effect that is aimed for can be variable.

It is often sufficient, in minor procedures, to avoid “memory formation”. The patient remains responsive to verbal command, but will not remember anything afterwards. This goal can be obtained by using low doses of a hypnotic drug. This anesthetic technique is called “sedation” or “conscious sedation”.(2-8)

For major surgery, more profound levels of hypnotic drug effect are necessary, in order to avoid any response to verbal command, and to decrease the incidence of “awareness”. Awareness is an accidental return of consciousness during surgery, a very traumatic experience, resulting in long term morbidity.(9-18) In many publications and in this thesis, we will refer to this level of hypnotic drug effect as the “surgical level of hypnotic drug effect”.(19,20)

If excessive doses of a hypnotic drug are administered, the patient will be unresponsive as required, but the incidence of side effects will increase. Until now, it is not clear whether excessive hypnotic drug effects result in a worse long-term outcome, but a recent study by Monk et al, has evoked a fierce debate on this potential risk.(21) Determining the risks of excessive hypnotic drug effect is one of the research areas of interest in anesthesia. Excessive hypnotic drug dosages will also increase the probability of a delayed recovery due to accumulation of anesthetic drugs in the fatty tissues of the patient.(22,23)

In order to **avoid insufficient, as well as excessive hypnotic drug effect**, it is mandatory to **implement, validate and optimize monitoring devices** based on **physiological parameters, that are a reflection of the "hypnotic" component of anesthesia.**(1,24)

This thesis will focus on one neurophysiologic measure, called **the "auditory evoked potential" (AEP),** as a tool for monitoring the **hypnotic component of anesthesia.**(25-28)

The auditory evoked potential (AEP) is an electrical wave, extracted from the electroencephalogram (EEG), that is evoked by repeated acoustic stimuli (clicks or tone bursts) to a normally hearing person.(29,30) The AEP, measured by means of electrodes on the scalp, consists of several positive and negative deflections, which are a **reflection of the intact acoustic neuro-anatomical pathway.**(31) A standardized click stimulus will evoke a very constant and homogenous shape of the AEP. (Figure 1)

As the AEP has a tenfold smaller micro voltage compared to the superimposed spontaneous EEG, an **averaging technique** is mandatory for extracting AEP out of the EEG.(27,32,33) A commonly used technique is the **moving time average (MTA).** The MTA is based on the **averaging of a number of sweeps** of the raw EEG. "Sweeps" or "**epochs"** are small periods of EEG registration, ranging between 80 to 125 milliseconds. Due to the repetition of the standardized acoustic clicks, epochs containing an AEP wave will have more homogenous features, compared to epochs containing EEG without AEP. The averaging of a number of epochs, will enhance the homogenous characteristics (amplitude and latency) of the AEP. The "random" features of the spontaneous EEG will not be enhanced. This technique enables visualization and further analysis of the AEP components. A major drawback of this MTA technique is the need for large amounts of epochs, which causes a **considerable delay** in extracting AEP derived information.(27,33,34)

Once AEP is extracted from the raw EEG by means of the MTA, the sub-components are analyzed further. AEP has three major components, depending on the latency (= delay of appearance) after the auditory click stimulus (Figure 1). The three components are: the brainstem auditory evoked potentials (BAEP), **the mid-latency auditory evoked potentials (MLAEP)** and the long latency auditory evoked potentials (LLAEP).(30,35) BAEP are rather insensitive for anesthesia drugs. LLAEP disappear even at very low doses of hypnotic drugs.(28,36,37) Consequently, **MLAEP are best suited for anesthesia purposes**.

Thornton et al, and Schwender et al, found that the amplitude of the Pa and Nb curves of MLAEP decreases, while the latency increases, in a consistent way with increasing doses of hypnotic drugs.(25,26,35,36,38-40) They suggested that by quantifying these changes in the main components of the MLAEP wave, a numerical endpoint could be defined that would act as a measure for cerebral hypnotic drug effect.(41,42)

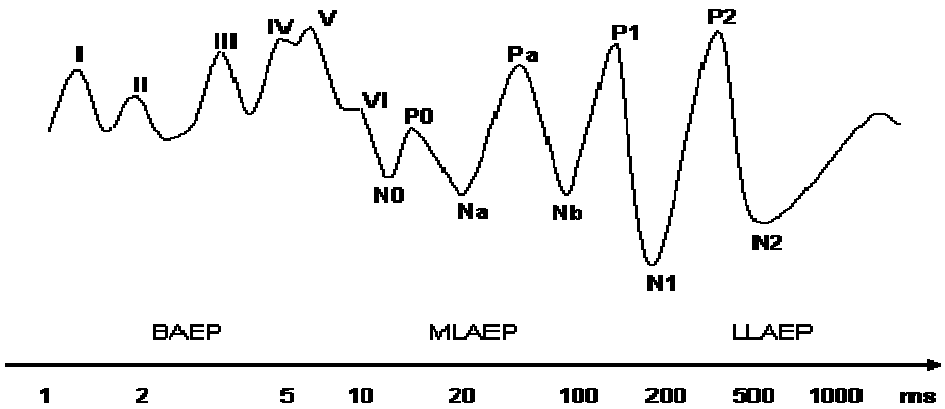

Figure 1. Schematic presentation of the Auditory Evoked Potential. The graph is semi-logarithmic, meaning that the x-axis is logarithmic and the y-axis is linear. If the acoustic stimulus is given on time 0, than the respective waves will be measured on the scalp with a latency (=delay after the click) shown on the timescale. BAEP = brainstem auditory evoked potentials (Waves I through VI); MLAEP = Mid-Latency auditory evoked potentials (Waves N_0 through N_b); LLAEP = Long Latency auditory evoked potentials (Waves P1 through N2)

Major drawbacks had to be overcome. The detection and interpretation of the raw MLAEP demands special expertise of the observer, as he or she must decide which curves are relevant and which are not. The quantification of amplitudes and latencies is subjective, making the first application of MLAEP in anesthesia prone for observer's bias.(43,44) In a constantly changing setting of clinical anesthesia, the time delay needed for extracting information from the raw MLAEP, was excessively long.(33) Several technological solutions have been suggested and tested for bypassing these difficulties.

In a first commercialized device for anesthesia purposes (Audiomedix, Glasgow, Scotland), a numerical index, called the AEPex, was implemented and tested for clinical use.(45) With this device, the AEP components are extracted by means of the classic moving time average technique, using 256 epochs of 144 milliseconds each. This resulted in a 36.9 seconds time delay for index calculation during optimal measurement conditions. The AEPex algorithm reduced the amplitudes and latencies into one single number, ranging between 100 to 0.(45,46) In this way, the observer's bias for MLAEP interpretation is eliminated. AEPex has been clinically validated by Kenny et al, but the number of trials remain limited.(47-51) Additionally, the commercial success of AEPex was minimal, as more competitive AEP derived monitors became available on the market.

More recently, Erik Weber Jensen applied a new mathematical approach for MLAEP extraction, called the **autoregressive modeling with exogenous input (ARX).**[19] The ARX technology uses a limited amount of epochs for a primary MLAEP extraction, while running a classic MTA technique in the background, as a quality control. This technology allows data extraction from MLAEP within six seconds.(19,33,34,52-55) The limited delay time was a

major advantage in comparison with the older MTA technology, as demonstrated by Urhonen et al.(34) The ARX technology was incorporated in a commercialized MLAEP monitor for anesthesia purposes, called **the A-Line® auditory evoked potential monitor (Danmeter, Odense, Denmark).** It produces a numerical unitless index, called the **A-Line® Auditory Evoked Potential Index (AAI)**. This index is calculated using the "area under the curve"(AUC) implemented on the fast extracted MLAEP measured between 20 and 79.9 milliseconds after every click stimulus. By means of this algorithm, AAI reflects the changes in raw MLAEP evoked by hypnotic drugs with minimal delay. The scale of AAI ranges between 100 and 0. The target for obtaining a surgical level of anesthesia ranges between 25 and 15.

This thesis is the result of a close cooperation between three participants of a consortium. The first participant is Erik Weber Jensen, inventor of the AAI technology and driving force for innovating and improving the algorithms. The second participant is Danmeter (Odense, Denmark). This medical company provides hardware technology for monitoring AAI in human subjects, conform European regulations, and has a commercial interest in AAI technology. The third participant is the promoter and the author of this thesis, as representatives of the University of Ghent and the department of anesthesia, University Hospital Ghent.

The aim of this consortium (and this thesis) is to develop a strategy for validating and optimizing the new MLAEP technology, during clinical anesthesia practice and as a tool for pharmacological research. Within this consortium, the independent position of the researcher must be guaranteed. Therefore, all costs for the studies were covered by departmental funding only. Danmeter provided all necessary hardware for performing the measurements. The engineering department of Danmeter and Erik Weber Jensen provided technical and mathematical support, if requested by the researcher. The methodology of all studies, the ownership of the obtained data and the rights for publishing the results are completely in the hands of the independent researcher. In return, Danmeter was informed on the results before the date of publication in order to allow commercial strategy adaptations, if deemed necessary.

Until now, no real standardized methodology is available in the scientific literature for "validating" a new monitor of hypnotic drug effect. Consequently, this thesis includes **a search for an acceptable and reproducible method to compare different measures of the "hypnotic component of anesthesia"**. As these neurophysiologically derived indices use diverse principles and mathematics, our search sometimes resembles a comparison between "apple and pear". Consequently, not much statistical tests are available for describing such a dataset. However, by combining pharmacokinetic-pharmacodynamic models with neurophysiologic technology, we feel to have succeeded in creating an objective and reproducible methodology for evaluating index performances.

In a **first publication,**(56) we investigated the ability of the AAI to discriminate several clinical endpoints of hypnotic drug effect: the "loss of response to name calling" as described by the Observers Assessment of Alertness and Sedation scale (OAAS/S), the "loss of eyelash reflex" and the "loss of response to a painful stimulus". This was done both during a mono-administration of propofol, as well as during the combined administration of an increment dose of opioids (remifentanil) and propofol.(56) We compared the performance of AAI with bispectral index (BIS) (Aspect Medical, Newton, MA, USA), which is an index of hypnotic drug effect derived from the raw EEG, and the predicted effect-site concentration of

propofol (Ce_{PROP}), which is a pharmacological endpoint of hypnotic drug effect. Ce_{PROP} is a prediction of the propofol concentration at the (theoretical) site of drug action, based on validated pharmacokinetic-pharmacodynamic models.(57,58)

We found that AAI, BIS and Ce_{PROP} were equally effective in discriminating the "absence" or "presence" of a clinical sign of hypnotic drug effect. AAI, BIS and Ce_{PROP} were not able to accurately predict a response to a painful stimulus. This confirms that AAI, BIS and Ce_{PROP} reflect the "hypnotic component of anesthesia", rather than the analgesic component of anesthesia. The addition of remifentanil to propofol did affect the threshold levels of AAI, BIS and Ce_{PROP} for detection of the respective clinical endpoints, but the specificity and sensitivity remained unaltered.

Although these results can be considered as a clinical validation of AAI, the methodology chosen has some intrinsic drawbacks. We attempt to validate a continuous parameter (AAI, BIS and Ce_{PROP}) in its ability to discriminate between dichotomous or categorical clinical endpoints. "Dichotomous" means that the clinical endpoint can only be "absent" or "present". There is no gradual transition from one condition to the other. Consequently, it can be a very challenging task for the observer to determine the exact moment of transition from one condition to the other. This drawback introduces a potential observer's bias in the methodology.(59) Moreover, by using dichotomous endpoints only a very limited range of anesthetic drug effects is tested.(59) More advanced statistical methods are mandatory to better appreciate the subtle differences between hypnotic drug effect monitors.

In a **second publication,**(60) we introduced a continuously available pharmacological endpoint of hypnotic drug effect as a reference for comparing monitoring systems. We already used Ce_{PROP} as a measure (or prediction) for hypnotic drug effect (dependent variable). In contrast, this study introduces Ce_{PROP} as an independent variable. Ce_{PROP} is a prediction of the propofol concentration at the (theoretical) site of drug action. For a hypnotic drug, this site of action should be somewhere in the brain. As Ce_{PROP} is calculated from a pharmacokinetic-pharmacodynamic model, developed in a standardized population by Schnider et al,(57,58) and clinically validated by Struys et al,(61) we know that Ce_{PROP} has a close relationship with the clinical anesthetic drug effect in the patient. Moreover, the technology for Ce_{PROP} prediction is available to any anesthesiologist, as it is incorporated in several commercialized target controlled infusion (TCI) systems.

In this protocol, we performed a standardized propofol induction, while simultaneously calculating the corresponding Ce_{PROP}, using target controlled infusion technology. Meanwhile, measurements of AAI, BIS and Spectral Entropy[1] (GE Healthcare, Helsinki, Finland) were performed. Propofol was continued in such a way that the patient gradually evolved from a "fully awake" condition towards very deep anesthesia (detected by burst-suppression patterns on the EEG).

With this data set, we are able to compare the performance of continuously available neurophysiologically derived indices concerning their ability to detect another (pharmacologically derived) continuous parameter. We used advanced statistical methods for this goal. (Prediction Probability (Pk) analysis, the Individualized Spearmann Rank

[1] Spectral entropy by GE Healthcare (Helsinki, Finland), is a recently commercialized hypnotic drug effect monitor, extracted from the spontaneous electroencephalogram. Two indices are calculated by this monitor: the state entropy (SE) and the response entropy (RE)

Correlation, Non Linear Mixed Effect Modeling, …) This methodology revealed some major weaknesses for AAI in comparison to BIS and Spectral entropy. The baseline variability (= the difference in AAI values of the awake patient) was unacceptably high. The discriminating power of AAI for deep levels of anesthesia was considered to be inadequate.(60)

Based on the results from the first validation, the consortium reflected on potential improvements in the AAI algorithm. Erik Weber Jensen developed a new algorithm and software package (version 1.6) for calculating an index with higher performance. The new index was called $AAI_{1.6}$ and is implemented in a commercialized monitor, called the AEP monitor/2 (Danmeter, Odense, Denmark). This monitor incorporates important adaptations, both on the technological level, as on the neurophysiologic measures used for extracting information. The $AAI_{1.6}$ is a "composite index", combining information from MLAEP, the spontaneous EEG and the percentage of burst suppression patterns. Whenever MLAEP quality is low, information on the cerebral hypnotic drug effect is extracted from spontaneous electroencephalogram rather than MLAEP. Whenever burst suppression patterns appear, indicating very profound hypnotic drug effects, the percentage of burst suppression versus normal EEG is the only factor for AAI calculation. This composite index could theoretically solve the lack of discriminating power at deep levels of anesthesia, and could improve the robustness of information acquisition on cerebral hypnotic drug effect.

For decreasing the baseline variability, the upper scale limit of AAI was decreased from 100 to 60. Additionally, the AEP monitor/2 is equipped with an acoustic stimulus volume controller, using fuzzy logic technology. This volume controller adapts the click stimulus intensity according to the measured signal-to-noise ratio, to avoid the potentially interfering "startle response". The "startle response" is an acoustically evoked post auricular muscle response, causing a very homogenous electrical interference on the electroencephalogram. The startle response has been mentioned as a cause for false high AAI calculations due to erroneous signal detection, and could be a cofactor for the high baseline variability found in our second study.

In a **third publication**,(62) we re-evaluated the $AAI_{1.6}$ by comparing it with the old AAI (version 1.5) and BIS, in a comparable protocol as used for the second trial. We applied the same advanced statistical methodology, and found that the new $AAI_{1.6}$ had considerable improved baseline variability, although BIS still performed better. The discriminating power at deep levels of anesthesia was improved due to the inclusion of electroencephalographically derived information next to the MLAEP. The decrease of the upper scale limit improved the baseline variability even more. However, our study could not exclude a potentially decreased sensitivity during sedation levels of anesthesia.

As an **additional clinical validation** we investigated the effects of **"difficult hypnotic molecules"** on AAI. Ketamine is a dissociative anesthetic drug, that disrupts the transfer of sensory input to the association areas of the brain. The patient still receives sensory input, but the brain is not able to organize this data in a comprehensive way. Consequently, the patient is "unconscious" to his sensory experiences. Administration of ketamine evokes changes on the EEG, often compared with epileptic insults. All monitors based on raw EEG, can be distorted by this electroencephalographic effect of ketamine.

In a **fourth study**,(63) we tested the effects of ketamine during a steady state propofol anesthesia, on the first version of AAI, and compared it with BIS.(63) We found that AAI was not altered by ketamine. In contrast BIS increased after ketamine. As an additional finding,

an increase in variability of AAI was observed. In some patients, this was accompanied by an increased electromyographic activity[2]. We hypothesized that the increased variability in AAI could be (partially) caused by this change in EMG. Additionally, we found in literature, that the basic locomotor rythmicity in cats is dependent on the N-Methyl-D-Aspartaat (NMDA) receptor. Ketamine is an inhibitor of the NMDA receptor.

In a **fifth study**,(64) we studied whether a neuro-muscular blocking agent (NMBA) could alter the effects of ketamine on the new version of AAI, BIS and spectral entropy. A NMBA (rocuronium), given in sufficiently high dosage, is able to block all electromyographic activity. By comparing patients in steady-state propofol anesthesia (control group), with three study groups, receiving respectively rocuronium, ketamine or both, we explored the effects of electromyographic interferences on the distortion of EEG, evoked by ketamine. We concluded that rocuronium did not significantly alter the effects of ketamine in any of the tested devices. Consequently, our hypothesis on the interference of ketamine with the electromyogram, as stated after the former study, was rejected.

This thesis demonstrates that the **use of MLAEP**, as a measure of the hypnotic component of anesthesia, has **improved considerably** over the last five years. However, technologic improvement is still possible. The use of **headphones** for eliciting the acoustic stimuli, limits the communication capacity between anesthesiologist and patient at the start of the induction. A potential solution could be the use of bone conduction. However, this should be explored further.

Other **practical issues** remain. The **risk of a very long application** of acoustic stimuli is insufficiently investigated, which could limit the use of MLAEP on the intensive care. The currently commercialized AEP monitor/2 is not available in “module” version, which might result in **ergonomic problems** for the OR. Moreover, the **costs** for monitoring MLAEP in clinical practice remain rather high. Due to such practical considerations, the commercial success for the AEP monitor/2 could be hampered compared to spontaneous EEG derived indices. Therefore, a new spontaneous electroencephalographic derived index, called the **Cerebral State Index (CSI)**, was developed using raw binary files registered with the AEPmonitor/2 in our studied population. The CSI algorithm combines “neural networking“ and an “ANFIS” mathematical model for index calculation. This new index has abandoned the raw MLAEP as a source of information, but aims to have an equal clinical performance for measuring the cerebral hypnotic drug effect.

In a sixth trial,(65) we validated CSI**,** by investigating its performance using a retrospective control group of raw data files, extracted from our own studied populations. Moreover, in this study we compared the performance of the new CSI algorithm with the composite index AAI as a validated pharmacodynamic endpoint. This study is an example of how AAI can be used in clinical pharmacological studies as a reflection of cerebral hypnotic drug effect.

Additionally, the new CSI index opens possibilities for simultaneous extraction of MLAEP and EEG derived information using identical electrode positions. After further clinical validation, this index will allow location specific measurements of simultaneously derived cortical (EEG) and subcortical (MLAEP) neurophysiologic processes. This CSI validation study has won the

[2] A fraction of the electrical activity measured during electroencephalographic registrations, is considered to be evoked by muscle activity rather than by cortical brain activity. This fraction in the measured spectrum is called “electromyogram”(EMG).

“best clinical trial” award 2006 of the Belgian Society of Anesthesia and Resuscitation (BSAR).

The technologic evolution described in this thesis, suggests that additional drastic improvements for MLAEP monitoring in anesthesia are not expected by the industry. In contrast, new indications for using MLAEP in anesthesia are currently under investigation in the academic world, preserving future perspectives for MLAEP in anesthesia.

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Chapter 2
Basic principles and technical background

Chapter 2 Basic principles and technical background

This chapter contains several topics that are relevant for a better comprehension of the methodology used in the six trials presented in this thesis:

1 The definition and components of anesthesia
2 Methods for monitoring the hypnotic component of anesthesia
3 The physiological and anatomical background of AEP measurement
4 The pharmacological background of commonly used anesthetic drugs, with an emphasis on drugs used in our trials
5 The principles and practice of target controlled infusion (TCI) systems
6 Specific statistical analyzing methods as used in several trials

2.1 The definition and components of anesthesia

Throughout history, the clinical state of anesthesia has been defined in many ways. First, it was defined as a continuum of clinical symptoms resulting from the progressively increasing dose of a single drug. This concept appeared valid as long as general practice was restricted to the use of one single drug (e.g. ether) for evoking adequate anesthesia. Several sequences of clinical signs, related to anesthesia, have been described using this concept of a single continuum e.g. by Plombey, Guedel and Artusio.(1-3)

Kissin contributed to the definition of anesthesia, by stating that a general anesthesia condition could be obtained through a wide spectrum of pharmacological actions, activated by different drugs.(4,5) This conclusion was based on the experience that many combinations of drugs could result in an "adequate anesthesia". The introduction of new drugs allowed the development of a "balanced anesthesia" method. In a "balanced anesthesia", all clinical goals of anesthesia are managed by separate groups of medication: hypnotic drugs for obtaining sedation or "unconsciousness", analgesic techniques for relieving pain, and neuromuscular blocking agents for immobility. These groups of medication interact with each other, resulting in a need for lower dosages and avoidance of side-effects, without compromising the quality of anesthesia. This theory is reflected in graphical presentations such as "the triangle of anesthesia", which visualizes the interaction between all clinical goals of anesthesia. (Figure 2) However, this triangle appears to be a major simplification of a much more complex reality.

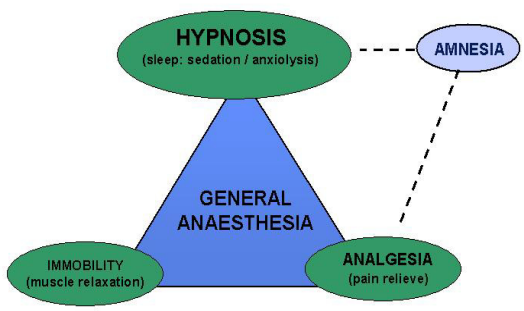


Figure 2: The triangle of anesthesia

Recent improvements in neuro-imaging techniques, drug titration methods and online neurophysiologic monitoring, have participated in the creation of a more detailed picture of the complex mechanisms of anesthesia. Currently, it has been proven that anesthetics have various sites of action, both located at the spinal cord as well as at the level of supraspinal cerebral structures.(6,7) Simultaneously, important progress has been made on a molecular level, as several receptors have been identified as mediators for anesthesia effects.(6,8,9) With these findings in mind, Peter Glass suggested a new concept for describing the interaction of hypnotics and opioids, in their ability to obtain "loss of consciousness" and "loss of response to a painful stimulus". He states that both endpoints are the result of separate neurophysiologic phenomena, that have to be targeted independently by the anesthetic drugs.(10)

General anesthesia is a process requiring a state of unconsciousness (produced primarily by the volatile anesthetics and propofol). Simultaneously, these hypnotic drugs have an independent effect on the memory formation function, resulting in amnesia.(11) Both the effects on consciousness and memory formation are considered to be mediated at the

supraspinal level (hippocampus, amygdala, frontal cortex etc…) and are defined as the "*hypnotic component of anesthesia"*. (7,12-17)

This primary obtained hypnotic drug effect can be affected by all sensory input, such as a noxious stimulus, that reaches the higher cerebral centers through the spinal cord.(17,18) A noxious stimulus must be inhibited from reaching this supraspinal level, as it will interfere with the ongoing hypnotic processes, resulting in a tendency to return to consciousness. This effect is called the *"arousal response"*.(19) One could hypothesize that this arousal response reflects some kind of survival mechanism. Although a patient is unconscious for the perception of "pain", his system will detect "harm" and attempts to wake up the patient in order to protect the integrity of the body. All mechanisms that aim to inhibit the effects of a noxious stimulus, are combined in the *"analgesic component of anesthesia*".(10) In general, this is achieved by the administration of opioids, or by the application of a locoregional analgesic technique.

A problem for this definition of anesthesia is the inadequate description of "response to a painful stimulus".(10) A painful stimulus can result in various clinical responses, ranging from "an activation of the autonomous nervous system without movement", over "an inadequate movement", or "an adequate redrawal reflex". All these potential "responses" use different neurophysiologic pathways, and should be explainable within an "ideal" definition of anesthesia. As "immobility" remains an important necessity for performing surgery in an adequate way, the definition of anesthesia should preferentially include "immobility" as an endpoint. Therefore, Ted Eger has suggested an alternative approach for defining anesthesia.(20) He states that the clinically relevant goals of anesthesia are limited to "amnesia" and "immobility". In this view, all other cerebral drug effects, such as "the inhibition of the autonomic stress response", "unconsciousness" and "relaxation" are side effects and not essential for "general anesthetic drugs". This definition relies on the historical reality that "immobility" operationally has been used as an endpoint for anesthetic potency, as described by the "minimal alveolar concentration" (MAC) (21) One MAC is the minimal concentration of an inhaled anesthetic in the lung alveolus, that is required in a group of study subjects, to prevent movement in 50% of this population, after receiving a standard noxious stimulus. Therefore, the anesthetic potency is commonly described as a function of movement. The approach of Ted Eger is also based on the finding that all "general anesthetics" are able to target "amnesia" and "immobility" in a reversible way, in contrast to the "side effects", that are not consistently present for all commonly used anesthetics. (20)

Although substantial differences can be found between the approach of Peter Glass versus Ted Eger, they both describe a differential effect of anesthetics at two separate levels, the spinal cord (response to painful stimulus versus movement) and the supraspinal areas of the brain (unconsciousness and amnesia). Both views discriminate between "analgesic" versus "hypnotic" components of anesthesia. The measurements studied in this thesis aim to quantify the hypnotic components of anesthesia.

2.1.1 The hypnotic component of anesthesia

The endpoint of interest for this thesis is “the hypnotic component of anesthesia”. It can be obtained by the administration of a “hypnotic anesthetic drug”, such as propofol, sevoflurane, etc…. By means of these hypnotic drugs, the anesthesiologist aims to obtain a predefined level of “unconsciousness” (sedation) and “amnesia” (loss of explicit memory formation). Both endpoints are separate phenomena, based on different neurophysiologic pathways.(11,22) Hypnotic drugs have a distinct effect on both, although the intensity and dose-effect relationship can be variable between molecules.(23,24)

Several studies have shown that during sedation, other forms of memory formation can remain present on a subconscious level.(25) This unconscious process of data management is often referred to as “implicit memory formation”. It can be detected by means of specific postoperative questionnaires. These tests explore the potential changes in behavior after an exposure to a stimulus that was not recalled by the patient. This stimulus can be either a “list of words” or a “story” that was told during “apparently” adequate anesthesia conditions. Although “implicit memory formation” might be considered as a fraction of the “hypnotic component of anesthesia”, it is currently not established if implicit memory formation has any importance for the outcome of anesthesia.(26,27)

The fundamental cerebral mechanisms of both “consciousness” and “memory formation” are insufficiently understood.(28) In the setting of anesthesia, “unconsciousness” implies that the patient loses all cognition, in such a way that he becomes *unaware* of his surroundings during a surgical procedure. Although one might argue that “consciousness” versus “unconsciousness” is a phenomenon that is either “present” or “absent”, more gradual changes have been described, ranging between “fully awake and responsive” to “unresponsive to any (verbal or sensory) stimulus”.(29,30) These gradations of levels of consciousness have been described for both pharmacological induced conditions, such as anesthesia, as well as for pathological conditions (Coma).(31,32)

In clinical practice, the anesthesiologist targets a predefined level of hypnotic drug effect, depending on the intensity of the surgical procedure. In minor procedures, it is sufficient to avoid “memory formation”. Although the patient will have amnesia for what happened, he remains responsive to verbal command (reflecting a maintained consciousness at the time of the command). Generally, the subjective experience of the patient is one of having been asleep throughout the duration of the procedure. This anesthetic technique is called *“sedation”* or *“conscious sedation”*.(33-39)

For major surgery, more profound levels of hypnotic drug effect are needed, in order to avoid any response of the patient to verbal command and to decrease the incidence of *“awareness”*. Awareness is an accidental return of consciousness during surgery, a very traumatic experience, resulting in long term morbidity for some patients.(40-43) Most cases of “awareness” are linked to a human or technical error resulting in insufficient administration of hypnotic drugs.(44) Some anesthetic techniques or specific surgical procedures are characterized by an increased risk for awareness.(45) However, the incidence of awareness (0.1% to 0.2%) appears to be comparable in every region of the world, independent of the local differences in applied anesthesia techniques.(27,43,45) The problem of “awareness” has become more important due to the introduction of neuro-

muscular blocking agents (NMBA) in anesthesia practice. The NMBA abolish the ability of a patient to make a voluntary movement, thereby masking an important endpoint for inadequate anesthesia. Consequently, an accidental return of consciousness might get unnoticed by the anesthesiologist, unless an alternative method for quantifying the level of hypnotic drug effect is available. The level of hypnotic drug effect needed for major surgery, is referred to as the *"surgical level of hypnotic drug effect"*.(46,47)

If excessive doses of a hypnotic drug are administered, the patient will remain unresponsive as required, but the incidence of side effects will increase. Establishing the risks of excessive hypnotic drug effect is one of the research areas of interest in anesthesia. The side effects can result in hemodynamic or respiratory instability, but additionally, studies are performed to evaluate the effects of anesthetic drugs on the progression of dementia or the incidence of subtle neuropsychological changes due to anesthesia effects.(48-52) Until now, it is not indisputably proven that excessive hypnotic drug effect results in a worse long-term outcome, although a study by Monk et al, has evoked a fierce debate on this potential risk.(53) From a pharmacological point of view, excessive hypnotic drug dosages will increase the probability for a delayed recovery due to accumulation of anesthetic drugs in the fatty tissues of the patient.(54,55) The application of a monitor for hypnotic drug effect would allow optimal hypnotic drug titration, adapted to the individual response of the patient.(56)

2.1.2 The analgesic component of anesthesia

The "analgesic component of anesthesia" aims to protect the patient against the deleterious effects of pain. A patient that receives a sufficiently large dose of hypnotic drugs, will not experience pain in a conscious way. However, the human body reacts on any painful stimulus with either a reflex movement, an inflammatory or humoral stress response or both.(57-61) The reflex movement can interfere with ongoing surgical procedures, whereas the stress response is correlated with a higher incidence of postoperative morbidity.(57,60,61) These deleterious effects of a noxious stimulus can be avoided by the intravenous administration of strong analgesic drugs, such as remifentanil, sufentanil or fentanyl, or by a locoregional anesthesia technique. Locoregional techniques use local anesthetics, such as lidocaine or bupivacaine, to block sensory input to the brain at the level of the spinal cord or at the site of the surgical procedure. The site of action of intravenously administered analgesic drugs is located at receptors of the spinal cord, the brain and almost every tissue of the human body.

It has been questioned if one can use the word "pain" when a patient is unconscious. "Pain" implies the presence of some kind of subjective interpretation of the sensory input. By definition one needs to be conscious to allow a subjective interpretation. Therefore, more recently, the "analgesic component of anesthesia has also been described as a balance between *"nociception versus antinociception"*. Nociception describes the ability of the spinal system to process sensory (noxious) information to the supraspinal areas. Antinociception describes the level of inhibition on this process, which correlates strongly to the level of analgesic drug effect.(62)

2.1.3 Interaction between the hypnotic and analgesic component

When a hypnotic drug is given to a patient, he will lose consciousness once an individually determined drug concentration has been reached at the site of drug action. Although the exact mechanism of action for hypnotic drugs is generally unknown, the site of action certainly is located within the higher brain structures. In anesthesia practice, it is well known that the administration of an opioid, given before the hypnotic drug, will result in a need for a lower dose of hypnotics to obtain the same clinical finding of "loss of consciousness". This macroscopic fenotypical expression of an interaction between opioids and hypnotics is used on a daily basis by anesthesiologists to obtain "balanced" anesthesia.

Consequently, if we aim to obtain a predefined anesthetic effect, such as "loss of response to intubation", several drug choices will be effective. A high dose of opioids combined with a small dose of hypnotics, is equally effective for obtaining unresponsiveness, compared to a high dose of hypnotics and a low dose of opioids.(63) The appropriate choice in clinical practice will be determined by the experience of the anesthesiologist, the condition of the patient and the expected side-effects of, opioids and hypnotics respectively.

Although opioids are not considered to have "real" hypnotic effects, the administration of a massive dose of opioids can provoke a state of unresponsiveness, which is clinically indistinguishable from anesthesia evoked by hypnotic drugs. Apparently, the shift in balance between "nociception and antinociception", evoked by large quantities of opioids on a subcortical level, inhibits all sensory input to the higher brain structures. Consequently, a natural tendency towards "decreased concentration capacity" and "sleepiness" sets in.(64) Moreover, in this condition the patient will not respond to moderate or even severe painful stimuli either. However, once a sensory stimulus is sufficiently powerful to exceed the blocking capacity of the analgesic action, the patient might return to consciousness immediately. This phenomenon confirms the limited direct hypnotic effects of opioids and it has been suggested as a cause for the higher incidence of awareness in anesthesia for cardiac surgery, where high doses of opioids were commonly combined with low doses of hypnotics.(65)

Whether this clinical interaction is evoked by pharmacokinetic or rather by pharmacodynamic mechanisms is subject of specifically designed interaction studies. (63) However, a thorough discussion of the currently available interaction models between opioids and hypnotics is considered not relevant for this thesis as our studies mainly focus on the macroscopic clinical expression of a limited amount of combinations of respectively analgesic and hypnotic drug concentrations.

2.1.4 Immobility

The third endpoint for obtaining an adequate surgical level of anesthesia is "immobility". As mentioned before, involuntary reflex movements can occur as a response to pain, but also voluntary movements might occur during periods of insufficient hypnotic drug effect. These movements can be potentially harmful during delicate surgery. Other reasons to advocate "immobility" are: the need for a smooth intubation of the patients' trachea, avoiding excessive muscle tone during abdominal surgery, avoiding hiccups or coughs during delicate neurosurgical or liver procedures etc…

When we consider “immobility” as an endpoint of adequate anesthesia, it should be evaluated as the result of a spinal process. Therefore, it can only be evaluated in a valid way when neuro-muscular blocking agents (NMBA) are not in use. NMBA block the muscarine receptors at the neuromuscular junction, resulting in an inability of acetylcholine to bind to the receptor. Acetylcholine is a neurotransmitter that is released by the motor-neurons, whenever an action potential reaches the neuromuscular endplate. Therefore, if NMBA are administered, the neuronal stimulus is not transmitted towards the muscles, rendering the patient immobile, even if the brain voluntarily commands the muscles to move. The introduction of NMBA, has enabled the anesthesiologist to decrease the amount of hypnotic and analgesic drugs, while guaranteeing immobility, in a “balanced anesthesia”.(4,5) But on the other hand the elimination of a voluntary movement implies that an important clinical sign of insufficient hypnotic drug effect becomes undetectable. This condition renders the patient more susceptible for “awareness” during surgery.(40) The introduction of NMBA in anesthesia practice increases the need for an objective quantification of the hypnotic component of anesthesia, as all clinical signs of insufficient hypnotic drug effect are abolished by NMBA.

2.2 Methods for monitoring the hypnotic component of anesthesia

Why do anesthesiologists want to measure consciousness and the level of cerebral hypnotic drug effect? The most obvious reason is to avoid awareness. Additionally, better individualized drug titration might decrease the incidence of movement, prevent hemodynamic, respiratory or adrenergic disturbances during surgery, minimize drug dosing for obtaining a rapid recovery from anesthesia, shorten post anesthesia care unit stay and eventually, minimize costs.

What are the characteristics of a “perfect” measure of hypnotic drug effect? It should deliver information on the changes in the patient’s state in a continuous way. The measure of hypnotic drug effect should have a gradual (monotonic) correlation with the clinical transition from awake to deeply anesthetized. It should have a strong correlation with the respective effect-site concentrations of hypnotic drugs. It should have a comparable response when equipotent doses of different hypnotic drugs are given. The measurement should only minimally suffer from interfering external factors, such as the electromyogram, the electro-cardiogram, electrocoagulation, mechanical interferences (e.g. hot air blankets) or drugs without hypnotic effect such as neuro-muscular blocking agents (NMBA). Ultimately, monitors should be able to detect the hypnotic effect of “atypical” hypnotic drugs such as ketamine, Xenon or Nitrous Oxide.

Various measures are used to detect the level of hypnotic drug effect on a clinical basis. They are based on the description of a response to a verbal or tactile stimulus. The clinical endpoints are used in daily practice, due to their simplicity. But one might criticize the objectivity and reproducibility. They only reflect a limited fraction of the sequences found during the transition from fully awake to completely unresponsive. Moreover, the sequence of “appearance” or “disappearance” can differ between individuals and depends on the choice of anesthetic drugs. Consequently, the correlation between many clinical signs and the actual mechanism of “loss of consciousness” can be questioned. Additionally, as the measurements depend on the stimulus given by the observer, the timing and frequency of measurement is critical.

Clinical scales of hypnotic drug effect have been developed, such as the *Observer’s Assessment of Alertness and Sedation Scale (OAA/S)*. These are sequences of progressively more intense stimuli, allowing a categorical description of the level of hypnotic drug effect. Much of the previously mentioned drawbacks of solitary clinical measures remain, but the suggested clinical scales are the best available alternative for clinical description of the hypnotic component of anesthesia.

The neurophysiological and anatomical mechanisms of “consciousness” are insufficiently understood. As it is currently not possible to measure “consciousness” in a direct way, several “surrogate” measures of consciousness, based on changes in the spontaneous or evoked electroencephalogram (EEG), are increasingly available in clinical practice for quantifying the cerebral hypnotic drug effects. Currently, validations of these neurophysiologic indices are often limited to vague descriptions of the correlation between one clinical endpoint and the studied index. We demonstrate in this thesis that this approach is inadequate for detecting subtle differences between monitors. We propose to implement more standardized study procedures to validate monitors of cerebral hypnotic drug effect.

2.2.1 Clinical measures

2.2.1.1 Loss of memory formation or Amnesia

Memory formation can be inhibited at very low levels of hypnotic drug effect. Several levels of memory formation have been described during anesthesia: “explicit memory formation”, “implicit memory formation” and “implicit learning”. Currently, it is impossible to test memory formation in a direct way during anesthesia. It can only be tested in a post hoc setting.

“Awareness” is mainly used for defining “unintentional” return of consciousness during anesthesia, which is independent of the memory formation function. In contrast, “explicit memory formation” implies both return of consciousness and a sustained memory formation of the event. Explicit memory formation also applies to sedation conditions at intensive care, where the occurrence of memory formation is not always “undesired”. Explicit memory formation always indicates that awareness was present, but lack of explicit memory gives no clear indication about whether or not awareness occurred.

Awareness can be tested by standardized questionnaires, to test if the patient has remembered anything during anesthesia. But there have been reports of explicit memory formation, the onset of which can be delayed by days, or even weeks. Therefore, any “awareness” testing should be repeated at several time intervals after anesthesia to increase sensitivity.

During anesthesia, some sensory (mainly auditory) processing can occur at an unconscious level. “Implicit memory formation” can be detected using specific postoperative psychoanalytical tests. A certain level of unconscious learning has also been reported during anesthesia.(25) At this time it is not established if implicit memory formation is harmful when it occurs during anesthesia.(66-68)

2.2.1.2 Loss of response to name calling

The anesthetist repeats the patients name at a constant time interval until the patient does not respond anymore. The response should be discussed with the patient in advance, before any hypnotic drug is given. The response of the patient should be simple and logic (e.g. answer “yes”). Calling the patient’s name has the advantage that people tend to instinctively focus attention.

Several drawbacks can provoke “false negative” registrations. “Loss of response to name calling” is not feasible in patients with an important hearing deficiency. A patient might hear his name, but due to the hypnotic effect, does not care to answer anymore. Response can be delayed due to the speech being sluggish and slow. “Amnesia” may occur before “loss of consciousness”. Consequently, the patient might have forgotten the adequate response, although the name is adequately heard. These problems can be minimized (but not excluded) by agreeing on a logic and spontaneous answer (such as “yes”). The test is only possible in conditions without any NMBA effect. At the end of a procedure, residual NMBA effects must be excluded first. Many publications using this measure do not provide sufficient details on the exact procedure of data registration,thus decreasing the reproducibility of study results.

2.2.1.3 Loss of response to verbal command

This measure is very similar to “loss of response to name calling”. In this case the stimulus is a request to do a simple task (“Squeeze my hand twice?”) or to answer a question (“What is your date of birth?”). It tests not merely the return of consciousness, but also the ability to deliver adequate responses. Generally, this is considered to be a higher cortical function. Consequently, this measure tests a lower level of hypnotic drug effect, compared to “the response to name calling” method. The response should be adequate and readily given, to be considered “positive”. Comparable problems can occur as with “the response to name calling”. The task must be carefully defined or agreed, to avoid including phenomena appearing by coincidence. For instance, when one asks to squeeze the hand only once, it is difficult to categorize a slight movement of the fingers.

“Asking a question” includes some degree of memory formation testing. It can only be performed in non intubated patients. Moreover, the question must be comprehensible for the patient, and the answer must be well known by the patient.

2.2.1.4 Loss of response to eyelash reflex

The eyelash reflex is an involuntary blinking reflex of the eyelid whenever the eyelashes are touched. In contrast to the former clinical measures, this measure needs a tactile stimulation. As the sensory input of tactile stimulations can be inhibited by opioids, the loss of eyelash reflex can disappear either before or after the loss of response to name calling, depending on the balance between hypnotics and opioids. The correlation between this test and the “loss or return of consciousness” is not established at all. However, this test is used by many clinicians to evaluate hypnotic drug effect in daily practice.

Recently, automatic electromyographic registrations of the eyelash reflex have been tested in order to obtain a more objective approach for measuring the hypnotic component of anesthesia.(69,70)

2.2.1.5 Loss of response to a painful stimulus

The use of a painful stimulus enables a further categorizing of the level of consciousness, after detection of unresponsiveness to a normally spoken voice. A general drawback of these methods is the diverse neurophysiologic pathways used for the sensory input of tactile stimuli versus the auditory pathway of the spoken voice. Therefore, the use of opioids must be considered whenever interpreting these clinical signs of hypnotic drug effect.

2.2.1.5.1 Trapezius and index finger squeeze

A variety of painful stimuli have been used as a measure of anesthetic drug effect. This ranges from a mild shaking of the shoulder, to squeezing the index finger or squeezing the trapezius muscle. The latter is included in the “Observers assessment of alertness and sedation” (OAA/S) scale, which will be discussed in more detail. One might question the reproducibility of such painful stimuli, as the pain intensity might differ between observers. Additionally, the clinical value of a painfull stimulus is limited as no objective measure of

pain intensity is available. Consequently, no clear correlation is known between the “low intensity” stimulations and the response on laryngoscopy, intubation or incision. In some studies, it is not clearly defined what response can be considered a positive response. When a “response to a painful stimulus” is used as a measurement of hypnotic effect, one could argue that reflex movement is not a very accurate response. It rather indicates insufficient analgesic effect. However, as the differentiation between voluntary and reflex movements is difficult to determine, any response is mostly considered as “positive response”.

2.2.1.5.2 Standard incision on forearm

One of the oldest population based measures of anesthetic potency, the “minimal alveolar concentration” (MAC) has been determined using a standardized incision on the forearm.(71) One MAC is the percentage of an inhalational anesthetic in the alveolar gas mixture that is able to inhibit movement in 50% of the population after a standardized incision of the forearm. MAC allows comparison between several inhalational anesthetics in equipotent conditions.

From a modern neurophysiologic point of view this measure is rather arbitrary as it combines both hypnotic and analgesic endpoints of anesthesia. No distinction is made between responses performed as a voluntary act or rather as a reflex movement, although these findings represent entirely different neurophysiologic pathways. Most inhalational anesthetics have both hypnotic and analgesic capacity, which can additionally obscure comparisons between intravenous and inhalational anesthetics. Due to all these drawbacks, MAC may be considered a less appropriate method for quantifying the hypnotic component of anesthesia when using the most recent definition of anesthesia. MAC does not enable an adequate differentiation between the “hypnotic” versus “analgesic” components of anesthesia.

The MAC principle is used in daily practice and is very well validated for all kind of endpoints. Therefore, it will remain necessary to compare new proposals for quantifying the level of hypnotic drug effect with this “traditional” approach.

2.2.1.5.3 Tetanic stimulation

It is not convenient to use a standardized incision at the forearm of patients, just for clinical research goals, when this is not intended for the planned surgery. Therefore, other approaches are being suggested to enable “harmless” painful stimulation in a standardized way. By means of a neurostimulator, validated for measuring the intensity of the NMBA activity, we can deliver a standardized electrical current with predefined characteristics and fixed time duration. A tetanic stimulation, given at the level of the nervus medianus, provokes a painful sustained contraction of the flexor muscles of the hand. The advantages of this method are: it is harmless to the patient, the intensity of the stimulation is comparable between patients and multiple researchers will deliver a comparable stimulation. A disadvantage is that it has not yet been validated in comparison with the classic “incision of the forearm” or other painfull stimuli.

2.2.1.5.4 Laryngoscopy, intubation, laryngeal mask placement

Painful stimuli are able to categorize the level of hypnotic drug effect in many different endpoints. However, the clinical importance of these stimuli is debatable. In practice, it is much more interesting to evaluate the chance of response to laryngoscopy, the intubation of the trachea or the placement of a laryngeal mask. Such endpoints have much more direct implications for daily practice, as they are often the first noxious stimulation during the procedure. Therefore, the response to these stimuli may indicate if anesthesia is sufficient to allow further surgery. For instance, the response on laryngoscopy (as measured by bispectral index) has been suggested as a good predictor for response to intubation, during propofol and remifentanil anesthesia.(72) Laryngoscopy has also been used as a painful stimulus for developing the interaction model between propofol and remifentanil by Bouillon et al.(63)

A disadvantage of this method is the high intensity of pain provoked by these stimuli. Therefore, this method evaluates rather deep ranges of anesthetic depth. Less painfull methods will remain mandatory for quantifying lower levels of hypnotic drug effect.

2.2.1.6 The Observer's Assessment of Alertness and Sedation Scale (OAA/S)

To standardize the clinical signs of hypnotic drug onset and offset, the *Observer's Assessment of Alertness and Sedation Scale* has been developed.(73) (table 1) The original scale, as described by Chesnik et al, included measures of responsiveness, facial expression, the quality of speech and some features of the pupil. The responsiveness score ranged from category 5 to 1, as it mainly aimed to describe the hypnotic clinical effects of benzodiazepines.(73) In order to adapt this scale to anesthesia conditions, a Modified OAA/S scale has been suggested.(74) (table 2) It includes category 0, which is the "disappearance of response to a painful stimulus", as this is an important endpoint for general anesthesia goals. The modified OAA/S scale does focus more on the hypnotic responsiveness during the induction and recovery of anesthesia. It is easily determined and can be tested repeatedly with short intervals.

However, the accuracy of the OAA/S scale is still dependent on the frequency and intervals of measurement. Also, the tactile stimuli of the OAA/S score are rather related to the spinal action of hypnotics than to cerebral actions. Due to the interaction between opioids and hypnotics the sequence of responses to the OAA/S scale may be distorted. In some patients it is found that several steps in the scale are skipped without gradual transition.

Table 1: The Observer's Assessment of Alertness/Sedation Scale*

Category†	Observation	Score
Responsiveness	Responds readily to name spoken in normal tone	5
	Lethargic response to name spoken in normal tone	4
	Responds only after name is called loudly and/or repeatedly	3
	Responds only after mild prodding or shaking	2
	Does not respond to mild prodding or shaking	1
Speech	Normal	5
	Mild slowing or thickening	4
	Slurring or prominent slowing	3
	Few recognizable words	2
Facial expression	Normal	5
	Mild relaxation	4
	Marked relaxation (slack jaw)	3
Eyes	Clear, no ptosis	5
	Glazed or mild ptosis (less than half of the eye)	4
	Glazed and marked ptosis (half of the eye or more)	3

*From Chernik et al[4] and Liu et al.[7]

†Responsiveness indicates responsiveness to calling the patient's name and/or using physical stimuli; speech, while asking the patient to repeat a standard sentence such as "The quick brown fox jumps over the lazy dog."; facial expression, degree of facial relaxation; and eyes, ability of subject to focus eyes ptosis.

Table 2 **Responsiveness Scores of the Modified Observer's Assessment of Alertness/Sedation Scale[24]**

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

2.2.1.7 The Ramsay score

This score was developed for evaluating the sedation level of intensive care patients.(75-77) It is a categorical scale ranging from 1 (excitation) over 2 (quiet and oriented) to 6 (no response to any verbal stimuli). In contrast to the OAA/S scale, the RAMSAY score describes the consciousness state in more subjective terms, with a less clear description of the stimuli that should be given in order to get a positive response. The disappearance of response to a painful stimulus is also not included as an endpoint. Generally it aims to quantify less profound levels of anesthetic drug effect compared to the OAA/S scale.

Table 3: The Ramsay Score

Score	Assessment
1	Patient is anxious and agitated or restless or both
2	Patient is cooperative, oriented, and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response

2.2.2 Electrophysiological measures

Due to the limitations of the clinical findings of anesthetic drug effect, a search for more continuously available measures of the hypnotic component of anesthesia is needed. Measures obtained from the spontaneous and the evoked EEG have been explored as a "surrogate measure of the hypnotic component of anesthesia".

2.2.2.1 Spontaneous electroencephalogram

The spontaneous electrical activity of the brain cortex can be measured using non invasive electrodes attached to several locations of the patients' head. An internationally accepted grid system is available to aid consistent electrode placement.(78) This measurement has been developed for many diagnostic applications in neurology.(79-81) The first experiments of the use of EEG to monitor the anesthetized patient were performed some 55 years ago.(82-86) Meanwhile, great advances have been made on signal processing techniques, improving the clinical robustness of electroencephalographic measurements.

Particularly, in the operation room, there are many electrical interfering devices. Most of the external interference radiates a 50 Hz line frequency to the patient, a common voltage mode that has much higher intensity compared to the measured EEG. Differential amplifiers are able to minimize this line frequency noise, but additionally, a bandpassfilter is necessary to remove unwanted frequency components that do not contain relevant information. For intraoperative monitoring, a bandpassfilter between 0.5 and 30 Hz is often used.(19)

2.2.2.1.1 Classic electroencephalogram analysis

The traditional representation of the EEG is a strip chart containing 8 to 32 channels displayed as voltage versus time. Conventional chart speed is 30 mm/s and a typical vertical scale is 100µV/cm. As the EEG is a complex registration, standardized analyzing methods are needed for describing the alterations in EEG, evoked by drugs or pathological conditions.

Interpretation of the EEG is classically performed by extensive cross-channel comparisons, combining pattern recognition technology and semiquantitative measures of height and frequency of the wave components. The electroencephalographic frequency ranges have been arbitrary divided into four subranges or frequency bands: alpha (8-12 Hz), beta (13-30 Hz), theta (4-7 Hz) and delta (0.5-3 Hz).

Three classes of intravenously administered anesthetic drugs can be defined according to different effects on the spontaneous EEG: hypnotics (thiopental and propofol), opioids (fentanyl, sufentanil, alfentanil, remifentanil) and benzodiazepines (midazolam, diazepam). For instance, propofol changes the EEG from a low-voltage, high-frequency awake signal, over an initial activation (excitation) signal, with increased frequency and voltage features, to a progressive high-amplitude low-frequency signal. Eventually, at very deep levels of propofol effect, "burst suppression" patterns occur. "Burst suppression" is a registration of complete electrical silence, interrupted by short periods of high frequency waves.(87-89) In contrast, increasing opioids concentrations cause a progressive increase in high-amplitude

low frequency patterns in the delta band (0.5-3Hz). These changes only become apparent once “unconsciousness” is achieved. This implies that rather high doses of opioids are needed for evoking clear changes on the EEG. Benzodiazepines cause increases in the EEG voltage with specific activation in the beta range (13-30 Hz).

The application of computer processing of the spontaneous EEG aims at compressing the massive amount of information, into a more compact parameter, that can be interpreted by an anesthetist, without specific expertise on EEG. Special care must be taken that this compact “parameter” provides all relevant information from the changes in the raw EEG. As the most apparent changes in EEG during anesthesia are located into the frontal leads, the montage of electrodes in anesthesia related monitors are generally limited to the frontal region.(19)

2.2.2.1.2 The power spectrum analysis

The transition from raw EEG detection into a single numerical trend needs several steps:(90)

1. Amplification and filtering of the electrical biosignal
2. Digitization of the amplified signal into a discrete numerical time series of a predefined interval
3. Dividing the time series into segments by grouping, according to the algorithm of the monitor. The algorithm can be based on two major principles: time domain analysis versus frequency domain analysis.

The *“time domain analysis”* evaluates the alterations of one variable in the EEG over time. An example of clinical importance is the quantification of the “burst suppression” patterns in most currently available monitors. Burst suppression is quantified as a ratio based on the percentage of “electrical silence” versus “high frequency bursts” detected during a predefined time period, ranging between 20 to 60 seconds. Other measures, based on “time domain analysis” have been described in literature for quantifying the electroencephalographic changes, but none of these are currently applied in clinical practice.(91)

“Frequency domain analysis” or “spectral analysis” is based on the theorem stating that any function in time can be described as a superposition of sinus waves of different frequencies.(90) Hence, additional information can be extracted compared to time domain analysis. Analyzing the frequency domain depicts the separate frequency bands versus their respective amplitudes (expressed in voltage) or versus their power (voltage^2). The “power” part is the most interesting, as it represents how strong a specific frequency band contributes to the total EEG. This transformation from the “time domain” registration to a “power spectrum analysis” is called the “Fourier transformation”. This is a basic step in the majority of modern algorithms used for EEG quantification.

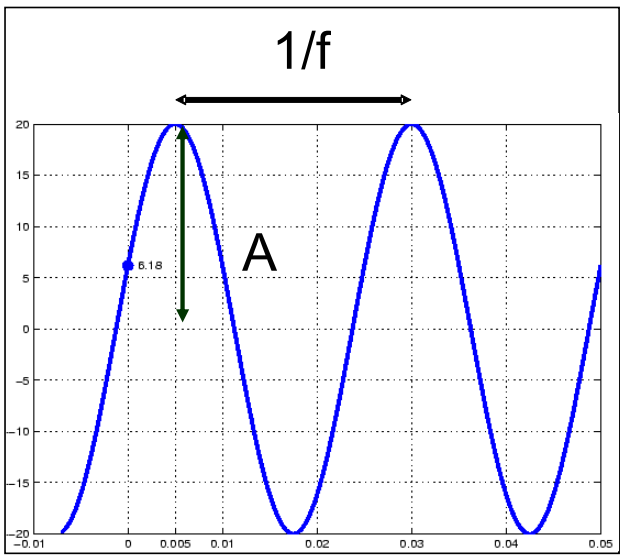


Figure 3: Basic characteristics of a sine wave, characterized by frequency f, amplitude A and phase θ

The Fourier transformation transforms the raw EEG, characterized by a summation of sinus waves, into a mathematical description of every available frequency, by its corresponding amplitude A and phase θ. Some authors claim that the "phase" contains no additional information on electroencephalographic behavior.(92) Hence, "phase" data are discarded in classic EEG analysis.

The theoretical concept used for "power spectrum analysis" is based on ideally obtained samples with infinite duration. In reality, we have to determine the power spectrum from a finite segment of a few seconds. This implies the occurrence of a measurement error. Hence, one has to apply an extrapolating technique on the finite sample for making a prediction of the "probable" spectrum, when the sample would have lasted for an "infinite" time. The two most common techniques for doing so are: *"the fast Fourier transformation (FFT)"* and the *"maximum entropy"*. The FFT repeats the measured sample identically to infinity, whereas the maximum entropy uses a way of extrapolation, that maximizes the entropy of the total signal.(90)

2.2.2.1.3 Single descriptors of the power spectrum

To parameterize the changes in power spectrum associated with anesthesia and hypnotic drug administration, many single descriptors of the power spectrum have been suggested and tested in clinical practice:

1. The total power: the area under the power spectrum curve (Figure 4)
2. Absolute power: the area under the power spectrum curve for one specific frequency band
3. Relative power: the ratio between the area under the power spectrum curve for one specific frequency band versus the total power
4. The spectral edge frequency 95% (SEF95%): the upper frequency correspondent to 95% of the total power (Figure 4)
5. Median frequency (MF): the upper frequency correspondent to the median value of the total power (Figure 4)
6. Delta Power or Peak power: the frequency correspondent to the highest power. (Figure 4)

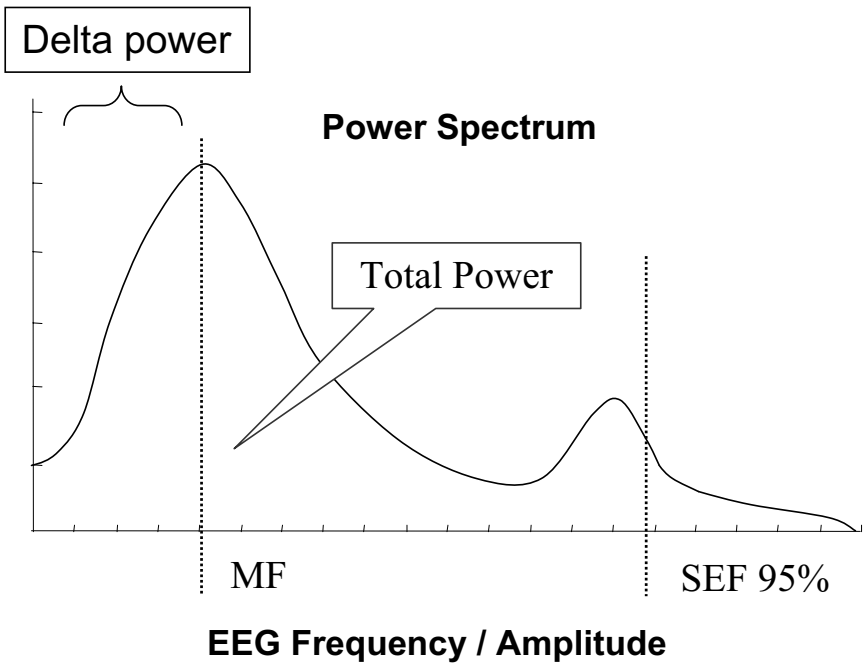


Figure 4: Presentation of a theoretical power spectrum analysis of the spontaneous electroencephalogram. MF = Median Frequency, SEF 95% = spectral edge frequency 95%, EEG = electroencephalogram

Various studies have been performed using these single descriptors in anesthesia as a measure of the hypnotic component of anesthesia.(88,93-97) As not all parameters appear equally sensitive for monitoring several hypnotic drugs the SEF95% and MF are probably best suited for anesthetic purposes. As we do not further explore these classic parameters in this thesis, we refer to the specialized literature, for additional information on threshold values and general performance of SEF95% and MF.(87,95-101)

2.2.2.1.4 Bispectral index

The power spectrum analysis assumes that the distribution of the analyzed data is Gaussian, that the frequency distribution behaves according to a first order linear model within the EEG and that data are stationary, which means that they will remain within certain predefined limits over time. In reality, biologic systems exhibit significant non-linear complexities that do not meet these assumptions.(53) Moreover, the elimination of phase information, has been questioned. Therefore, new signal processing algorithms have been developed, capable of tracking non-linear as well as linear changes in spontaneous EEG.

The “bispectral index” (BIS) (Aspect Medical System, Newton, MA, USA) combines the widely used Fast Fourier Transformation with an additional, second order (quadratic) analyzing model for the EEG, called bispectral analysis. This implies the quantification of the phase coupling (= bicoherence) between two frequencies and the corresponding harmonic. The extent of coupling can vary between 0% (if no harmonic is present) to 100% (if a harmonic is generated during the entire epoch).

As demonstrated in figure 5, two very different complex waveforms, reflecting two different clinical conditions can result in identical power spectra. The additional bispectral analysis is able to differentiate between both conditions.

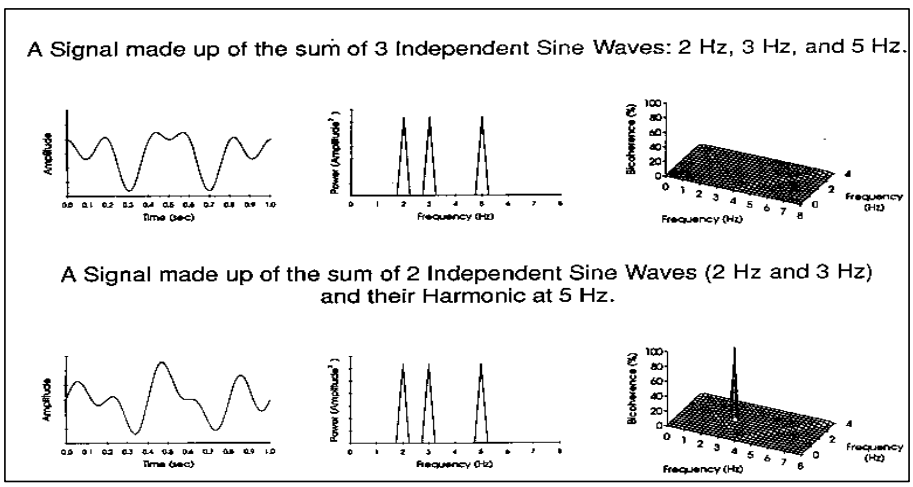


Figure 5: Two different complex waves (left panel) can result in identical power spectrum analysis (middle panel). The bispectral analysis (right panel) is able to differenciate between both conditions due to the inclusion of phase.
(from: Sebel PS, et al: EEG bispectrum predicts movement during thiopental/ isoflurane anesthesia. J Clin Monit 1995, 11, 83-91.)

The BIS, as incorporated in a commercialized device called BIS XP® (Aspect medical, Newton, MA, USA), is developed by identifying the key features of the EEG, measured in a large database of patients, receiving one or more of the most commonly used hypnotic drugs. The key features are defined by combining bispectral analysis and classic power spectrum analysis. Several electroencephalographic features were identified as strongly correlated to a specific level of clinical hypnotic drug effect. By means of multivariate statistical models, an optimal combination of features was defined in order to describe the full spectrum of cerebral hypnotic drug effect. The database of empirically derived electroencephalographic registrations was eventually transformed to a linear dimensionless scale, ranging between 0 and 100. (Figure 6)

The awake patient will have a BIS between 100 and 95. BIS values between 80 and 60 are compatible with “sedation”. Between 60 and 40, the ideal “surgical level of anesthesia” is obtained, whereas values under 40 indicate excessive drug effect. BIS has a burst suppression detection algorithm, shown on screen as a percentage called the “suppression ratio” (SR). Every SR higher than zero reflects intensive inhibition of all cortical electrical activity, which is not necessary for adequate anesthesia.

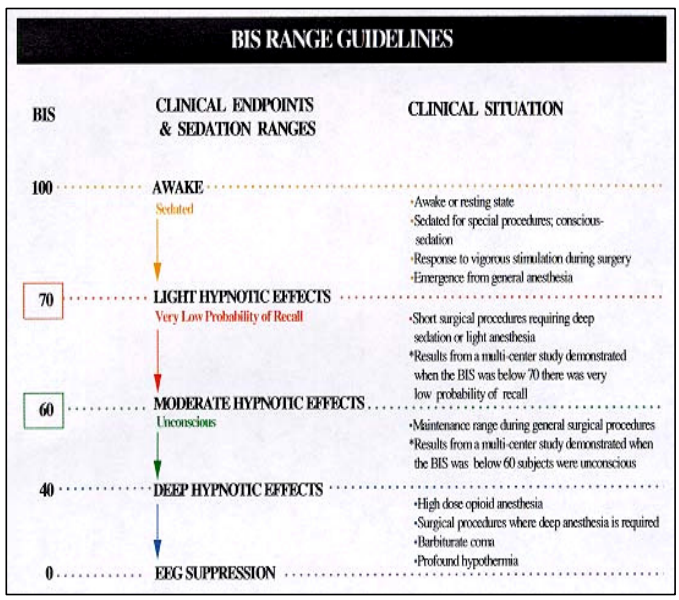


Figure 6: Guidelines of BIS ranges as included in the user guide of BIS XP® (Aspect Medical, MA, USA), toestemming Paul Manberg (cfr. Prof. Struys)

The result of this technology is an index that reflects alterations in the cortical electrical activity, closely correlated to the typical changes found in an anaesthetized population. However, other states of the brain, accompanied with an increased amplitude and

decreased frequency pattern of the EEG, will be reflected by BIS. Therefore, BIS can be reduced during natural sleep or during ischemic conditions of the brain.

Bispectral Index has been studied in more than 1000 publications, both for clinical applications as for pharmacological research.(27) Moreover, Bispectral Index is the only neurophysiologic measure that has gathered some evidence, as a monitor for reducing awareness in a high risk population for awareness.(43,45) Bispectral index was introduced as an anesthesia device for monitoring anesthetic drug effect, but currently, BIS has also been investigated as a monitor for brain ischemia,(27) for titration of sedation on intensive care,(102) for pediatric purposes,(38,103-105) and for differential diagnosis in coma patients.(106)

2.2.2.1.5 Spectral Entropy

Entropy is a concept first introduced in thermodynamics to indicate the amount of irregularity in molecular movements at a certain temperature. This concept has been adapted for applications in signal processing technology, as it allows quantification of the amount of irregularity within the signal. The EEG can be considered as a complex signal that evolves from a very irregular pattern towards a more regular slow frequency wave as hypnotic drug effect sets in. (Figure 7)

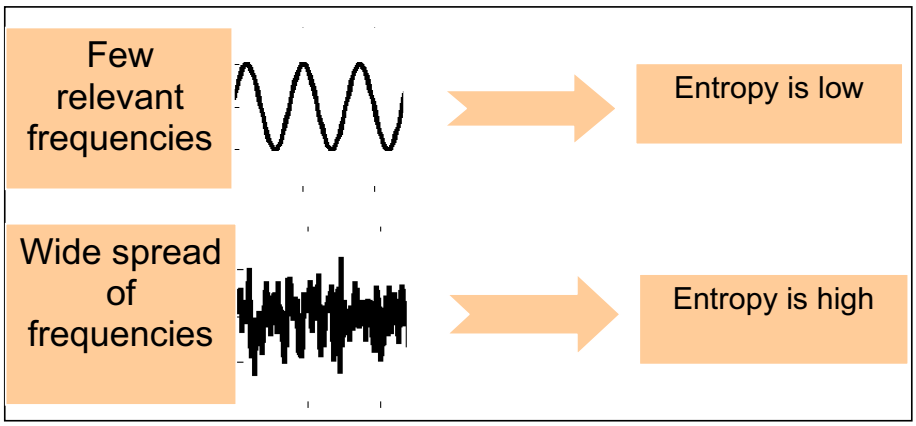
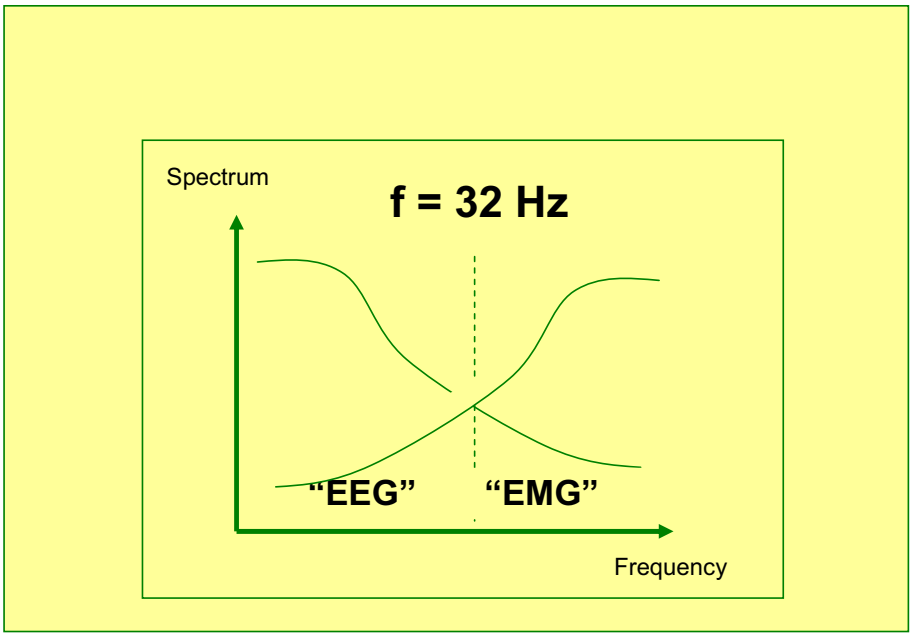


Figure 7: Concept of entropy as adapted to the irregularity of the EEG. When the raw EEG consists out of a wide spread of sinus waves with different frequencies, the entropy will be high. During anesthesia, the raw signal contains a smaller range of frequencies, resulting in low entropy.

Recently, different entropy concepts have been applied to describe the “amount of order” in the EEG.(107-109) One of these, Shannon entropy, has been shown to be a useful measure of anesthetic drug effect.(108) Shannon entropy measures the predictability of future amplitude values of the EEG based on the probability distribution of amplitude values already observed in the signal. Unfortunately, Shannon entropy as described is not normalized to the total power of the EEG. Therefore, its absolute value may vary between individuals because of interindividual differences in signal strength, precluding routine clinical use.

To overcome these shortcomings, spectral entropy has been developed. The spectral entropy is obtained by applying the Shannon entropy concept to the power distribution of the Fourier-transformed electroencephalographic signal, which has been normalized to unit power. Spectral entropy permits separation of the contributions from different frequency ranges. For example, using spectral entropy, one can separate the high-frequency contribution above 32 Hz, (which is likely electromyographic) or from the low-frequency contribution below 32 Hz (which is likely encephalographic). (Figure 8) The detailed spectral entropy algorithm is published elsewhere.(110)



Spectral Entropy has become commercially availably (M-ENTROPY module; GE Healthcare, Helsinki, Finland). In this device, two spectral entropy indicators are considered, state entropy (SE), calculated over the frequency range (0.8–32 Hz) that is likely dominated by the EEG, and response entropy (RE), calculated over the frequency range (0.8–47 Hz) that includes both the EEG and electromyogram (EMG). Sudden appearance of the electromyographic signal data often indicates that the patient is responding to some external stimulus, such as a painful stimulus, *i.e.*, nociception, due to some surgical event.(111,112) Such a response may result in arousal if the level of analgesia is insufficient. In theory, in the nonparalyzed patient's EMG can provide a rapid indication of impending arousal.

The M-Entropy module has a scale ranging between 100 and 0. When no neuromuscular blocking agents are used, the RE is always a little higher than the SE. The awake patient will have SE and RE values between 100 and 90. For sedation, SE and RE values between 80 and 60 are targeted. A surgical level of anesthesia is obtained between values of 60 to 40. Below 40, the level of hypnotic drug effect is excessive. These thresholds are equal to the BIS thresholds. This is probably a commercially inspired intention rather than a coincidence.

2.2.2.1.6 Other indices based on electroencephalogram

Increasing numbers of new algorithms are explored in literature. The most important are: the narcotrend,(113-117) the patient state index,(118,119) SNAP(120-125) and the cerebral state index.(126,127) Some of these are incorporated in commercialized devices, others are only developed for academic purposes. Although some interesting alternatives

for BIS and Spectral Entropy are available, it appears that most of these indices encounter comparable limitations compared to BIS and Spectral Entropy. One could question if these indices add anything but complexity to the already complicated interpretation of monitoring cerebral hypnotic drug effect. On the other hand, a vivid competition on the market avoids monopolization and decreases costs. Therefore, it remains mandatory to explore new algorithms and hardware solutions for improving the performance of electroencephalographic measures of the hypnotic component of anesthesia.

2.2.2.2 Evoked electroencephalogram

As the level of consciousness can be determined clinically, by evaluating the response to verbal stimuli, it appears logic that measuring the neurophysiologic response to auditory stimuli could reveal additional information on the cerebral hypnotic drug effect. Moreover, the neuroanatomical description of the auditory pathway is restricted to a well known number of neuronal synapses. In contrast, the interpretation from the spontaneous activity of many millions of cortical neurons, representing many disparate subpopulations, is much more complex. Therefore, it might eventually be feasible to link the behavior of an evoked response during anesthesia, with a direct receptor activity located on the specific pathway. Whether this potential advantage has any validity, remains to be seen.

Chronologically speaking, most of the effects of hypnotic drugs found on evoked responses were discovered empirically, and only then it was taken in consideration to use them as measures of cerebral drug effect. As this thesis mainly focuses on the quantification of the hypnotic component of anesthesia, we will restrict this discussion to auditory evoked potentials monitoring. Other evoked potentials, such as somatosensory evoked potentials (SSEP) or visual evoked potentials (VEP) are out of the scope of this thesis.

2.2.2.2.1 The Auditory Evoked potentials (AEP)[1]

2.2.2.2.1.1 Definition, components, anesthetic effects

The AEP is defined as the passage of electrical activity from the cochlea to the cortex, which produces a waveform consisting of 11 waves in the EEG. These can be divided into three parts: brainstem auditory-evoked potential (BAEP), middle-latency auditory-evoked potential (MLAEP), and long-latency auditory-evoked potential (LLAEP). These parts indicate the sites in the brain from which the various waves are believed to originate. (Figure 1)

The BAEP is represented by the Roman numerals I–VI and extends from 0 to 10 ms after the stimulus. These waves represent the process of stimulus transduction in the brainstem: acoustic nerve (I), cochlear nucleus (II), superior olivary complex (III), ventral nucleus of the lateral lemniscus and preolivary region (IV), inferior colliculus (V), and medial geniculate body (VI).(9,128,129) The early cortical or middle-latency auditory-evoked potentials, marked by the waves N0, P0, Na, Pa, and Nb, are thought to originate from the medial geniculate body and the primary auditory cortex.(130) These waves occur from 10 to

[1] Modified from "*Jensen EW, Martinez P, Litvan H, Vereecke HE, Rodriguez B, Struys MM:* **Chapter 33: Recent Advances In Composite AEP/EEG Indices For Estimating Hypnotic Depth During General Anesthesia,** Akay/Handbook Of Neural Engineering, 2007 Edited by Akay M, Wiley-IEEE Press, 2007, pp 535-553

100 ms after the stimulus. The third part, more than 100 ms after the stimulus, called LLAEP, reflects the neural activity of the frontal cortex and association areas.

Factors known to affect the BAEP are the age and sex of the subject; the rate, amplitude, and polarity of the stimulus; the filter settings used; and the dose of certain administered anesthetic agents and other drugs. Original studies have shown that the BAEP peaks change during anesthesia with volatile agents(131-135) but not during anesthesia maintained with intravenous agents.(136-140) The LLAEP show great intra- and interindividual variations because these signals, are heavily influenced by the hypnotic drug effect and the subject's individual emotional state and alertness.(141,142) The MLAEP, on the other hand, show graded changes in their latencies and amplitudes for a variety of anesthetic agents and less intra- and interindividual variations than LLAEP. (138-140) Therefore, MLAEP have been widely examined as a measure of depth of anesthesia.

Apart from anesthetic applications, the AEP is clinically useful in detecting and localizing lesions in the auditory pathway and in the investigation of hearing loss in infants and in other non-communicative subjects. The AEP is present in the first days of life. In the infant, the latencies of the peaks are prolonged and the amplitudes diminished. With advancing age, the peaks will evolve toward latencies and amplitudes found in a normal adult. There is good evidence that the AEP is useful in the evaluation of the state of maturation in newborn infants.(143)

The first evoked potential measurement systems were based on the superposition of ink-written or photographic traces, and electronic or digital averagers were applied to AEP-averaging processes. The signal-to-noise ratio (SNR) of AEP is often very poor. Hence they are more difficult to extract than, for example, visual-evoked potentials. This is a problem, especially in the operating theatre, due to the use of other electric equipment producing vast amounts of noise. Modern instrumentation amplifiers with a high common-mode rejection ratio (CMRR) can overcome the problems of a moderate level of electrical noise; however, the noise arising from electrical surgery (diathermy), which produces a strong electrical field, renders AEP monitoring impossible.

Research applying MLAEP for monitoring depth of anesthesia was initiated in the beginning of the 1980s.(131,132) Since then a vast number of papers have been published in this field of interest.(131-140) Generally, with increasing doses of a hypnotic drug, the amplitude (latency) of the main MLAEP components (Na, Pa and Nb) decrease (increase) in a dose dependent way. (Figure 9)

The absolute changes in MLAEP are not very reproducible as there are big interindividual differences of response to anesthetics. Combining results of several studies, one can conclude that thiopental, propofol, etomidate, enflurane, and isoflurane all show a dose–response suppression of the MLAEP, whereas receptor-specific agents such as midazolam, diazepam, and flunitrazepam have very little effect on the MLAEP.(131,137,144-146) The additive interaction between isoflurane and nitrous oxide (N_2O) was also not detected by MLAEP.(147)

Schwender et al. also correlated end-tidal concentrations of desflurane with changes in various peaks of the MLAEP. A tendency towards increased latency of Pa, P1, and Nb waves and decreased Na/Pa amplitude was noticed when the end-tidal concentration of desflurane was increased; however, it was not statistically significant.(148) The study also

showed that the latency of peak V of the BAEP changed very little through the entire period of anesthesia. It was concluded that only end-expiratory concentration greater than 4.5% significantly suppress the different MLAEP components.

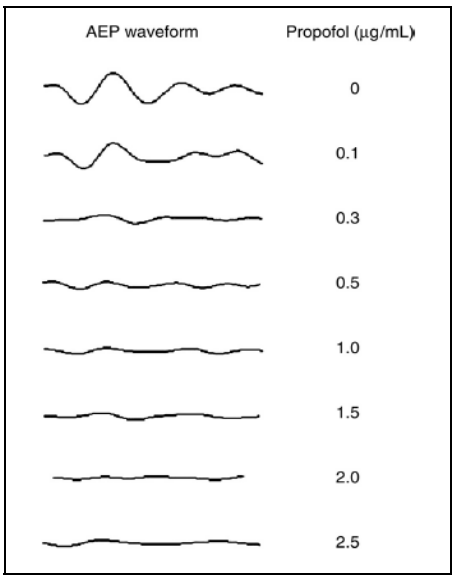


Figure 9: Gradual changes in amplitude and latency of the major components of mid-latency auditory evoked potentials. The doses are just an example, as large interindividual differences in MLAEP response exist.
(Extracted from ref 1 footnote p. 40)

A variant of MLAEP monitoring is the 40-Hz auditory steady-state response (ASSR) described by Plourde.(149,150) The ASSR is elicited with a stimulus frequency of approximately 40 Hz. This high stimulus frequency causes overlapping of the responses to the successive stimuli. Both inhalational agents and intravenously administered drugs cause a profound attenuation of the amplitude of the 40-Hz ASSR. The author concludes that the 40-Hz ASSR depends on the level of consciousness; however, further validation is needed.(149,150)

2.2.2.2.1.2 Extraction methods of AEP

As the AEP has a tenfold smaller microvoltage compared to the superimposed spontaneous EEG, an averaging technique is mandatory for extracting AEP out of the EEG.(151-153) The most common averaging technique, called *Moving Time Average (MTA)*, is based on the averaging of a number of sweeps of the raw EEG. “Sweeps” are small periods of electroencephalographic registration, ranging between 80 to 125 milliseconds, also called epochs. Due to the repetition of the standardized acoustic clicks, epochs containing an AEP wave will have more homogenous features, compared to epochs containing EEG without AEP. The averaging of a number of epochs, will enhance the homogenous characteristics (amplitude and latency) of the AEP. The variable features of the spontaneous EEG will not be enhanced. This technique enables visualization and further analysis of the MLAEP components. A major drawback for MTA is the need for large amounts of epochs, which causes a considerable delay for extracting MLAEP derived information.(152-154)

The interpretation of the raw MLAEP wave demands special expertise of the observer, as he must decide which curves are relevant and which are not. Moreover, the quantification of amplitudes and latencies is subjective, making this technique prone for observers bias.(155,156) In a constantly changing setting of clinical anesthesia, the time delay caused by the classic MTA extraction technique, was excessively long.(153)

Throughout the last two decades a number of methods have been explored in order to facilitate a single-sweep or a few-sweeps extraction of the MLAEP. The main focus of this technical section is to review some of these methods with particular emphasis on the *autoregressive model with exogenous input (ARX model)*, as this technique is the main topic of this thesis. The performance of the ARX approach is examined extensively in clinical applications, whereas other methods for single-sweep analysis are only briefly described. This section is important as it demonstrates that, in future, the delay for receiving information of MLAEP can be reduced below 6 seconds, if this would appear necessary.

2.2.2.2.1.2.1 Wavelets

Wavelets have found use in a number of signal processing applications in biomedical engineering. The *wavelet transformation (WT)* is a signal decomposition into a set of basic mathematical functions, called wavelets. Bartnik et al.(157) applied the WT to the AEP and concluded that an AEP from a single sweep could be extracted even though the AEP and the EEG are in the same frequency range.

However, the signal-to noise ratio of the AEP could be improved by allowing some preaveraging (which increases the delay again). WT has been successfully applied to visual-evoked potentials (VEP) by Geva et al.(158) Recently Kochs et al.(159) have applied WT in clinical studies for AEP extraction. WT is a promising tool for single-sweep analysis of evoked potentials that should be explored further.

2.2.2.2.1.2.2 Optimal Vector Quantization

Haig et al.(160) suggest the use of global optimal vector quantization to classify single-trial event-related responses (such as AEP). It was concluded that this method facilitates a more detailed analysis as compared with MTA. This method has not yet been applied in clinical applications.

2.2.2.2.1.2.3 Maximum Length Sequences

In 1982 Eysholdt and Schreiner reported on the use of m-pulse sequences (also called maximum length sequences) to extract the BAEP from the ongoing electroencephalographic activity.(161) In theory, this is also applicable on MLAEP. The method allows a faster stimulus rate compared with that allowed by moving time averaging and therefore decreases the processing time necessary to extract the AEP. The method was further refined by Shi and Hecox.(162) Drawback is a potential change in the AEP morphology due to the increased stimulus rates. An examination of the effects of increased stimulus rate has been performed by Don et al.(163)

2.2.2.2.1.2.4 Autoregressive model with exogenous Input (ARX)

The autoregressive model is a mathematical model enabling fast extraction of information on signal morphology, without decreasing the output quality. It differentiates the AEP morphology within a much shorter time, compared to the classic MTA, as it only uses 15 to 18 sweeps containing both EEG and MLAEP (Figure 10). Additionally, an “exogenous input” is applied to the model. The exogenous input is a -high quality, long delay- AEP extraction, produced by averaging the latest 256 sweeps, used as a feedback controller for the fast extracted calculations. This quality control has a delay comparable to the classic MTA.

ARX has already been applied in neurophysiological monitoring. The application of ARX models to visual evoked potentials (VEP) was originally described by Cerutti(164,165) and later by Liberati and Cerutti(166) and applied by Magni.(167) As the signal-to-noise ratio (SNR) of the VEP is considerably larger than that of the auditory evoked potential (AEP), single-sweep analysis was possible. In contrast, for AEP extraction, a preaverage of 15–50 sweeps improves the SNR before applying the ARX model.(168)

The ARX model has been implemented in a commercialized fast extracting AEP monitor, called A-Line® (Danmeter, Odense, Denmark). The output of the device is called the *A-Line® Auditory Evoked Potential Index* or *A-Line® ARX Index* (AAI). AAI is calculated using an “area under the curve” algorithm, implemented on the fast extracted MLAEP wave, measured within the latency range between 20 and 79.9 milliseconds after click stimulus. Figure 10 describes the signal processing from the raw registration until the actual output of the AAI.(168,169)

The AAI is projected on a unitless scale, ranging between 100 and 0. All values above 60 are considered to be compatible with the awake patient. Values between 40 and 25 are compatible with the sedation range. The surgical level of anesthesia correlates with AAI values between 25 and 15. Below 15, the hypnotic drug effect is considered excessive.

In this algorithm, an estimation of the signal-to-noise ratio (SNR) is critical to guarantee adequate detection of the AEP signal, due to the decreased number of sweeps.(153) The SNR algorithm quantifies the amount of “desired” signal versus the amount of “undesired” background noise. Currently, the decision to define “signal” versus “noise” for AEP measurement, is based on the assessment of a number of sweeps, or epochs, obtained in two different ways. For defining “signal”, the epochs are obtained synchronously with every click stimulus. These epochs do contain AEP at a constant latency. Subtracting or averaging of these synchronous epochs will enhance the peak amplitudes of the AEP. This is called the *synchronous average*. For defining “noise”, the epochs are obtained in a random, asynchronous way with the click stimulus. These sweeps lack the homogenous features of the synchronous epochs. Subtracting or averaging of the asynchronous epochs will not enhance peak amplitudes. This is called the *asynchronous average*. The SNR is the ratio between the maximum amplitude of the synchronous average, versus the maximum amplitude of the asynchronous average.(153)

A closed-loop control system, using a proportional–integral–differential (PID) controller, is applied to control the SNR of the averaging processes. A desired SNR is defined between 1.4 and 4, and reflects the adequate AEP extraction range. The controller acts on the averaging process in the following manner: If the estimated SNR of the extracted AEP is low (less than the desired SNR of 1.4), the number of averages is increased in order to improve the SNR. This has the disadvantage of reducing the system’s ability to track fast changes on the AEP. In contrast, if the estimated SNR is higher than desired, the number of averages of the averaging process is reduced to improve the detection of fast changes of the AEP. This control system balances the quality of the extraction with the speed of the averages.

The “take away” message of this section is, that the A-Line® guarantees optimal information extracted from MLAEP, at all times. However, during conditions with low signal-to-noise ratio, the guarantee in quality decreases the speed for detecting sudden changes in the MLAEP.

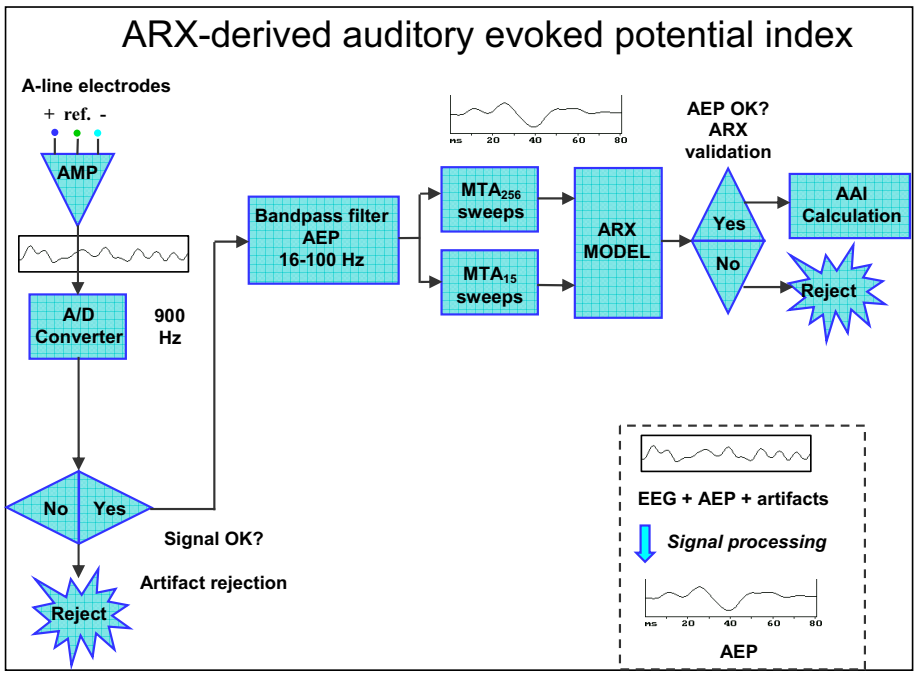


Figure 10: Schematic presentation of the signal processing algorithm in the A-Line® monitor. After amplification of the raw signals and digitalization by an A/D converter, a first artifact rejection is performed using a bandpassfilter with upper limit of 900 Hz. All segments, not defined as artifact, are further analyzed within a frequency range of 16 to 100Hz. This window is averaged using a moving time average of 15 sweeps (MTA_{15}), resulting in a fast extracting output. Simultaneously, the "exogenous input" is calculated using moving time average over 256 sweeps (MTA_{256}). These are the input values for the autoregressive model with exogenous input (ARX). If the output applies to the model, AAI is shown on screen, if not it is rejected. If necessary, the MTA_{15} will increase the number of sweeps according to the signal-to-noise controller.

2.3 Anesthetic drugs used in our study protocols

2.3.1 Hypnotics

2.3.1.1 Propofol (Diprivan®, AstraZeneca)

Propofol (di-isopropyl-phenol) is one of the commonly used hypnotic drugs for anesthesia applications, producing a dose dependent inhibition of consciousness. It is used for intravenous induction and maintenance of anesthesia, both in adults and children. As it has no analgesic activity, propofol is generally combined with a strong intravenous analgesic or a locoregional analgesic technique. The main reason for its widespread use is the interesting pharmacokinetic and pharmacodynamic characteristics. It is a rapidly redistributed and eliminated hypnotic drug, allowing to decrease recovery time after long times of drug administration, compared to barbiturates or benzodiazepines.(170-175) Therefore, it is also applied as a sedative drug for intensive care patients, who often need hypnotics over several days.

The present formulation is a 1% oil in water emulsion containing 10% soybean oil, 1.2% egg phosphatide and 2.25% glycerol. Propofol has a pKa of 10.76 and an octanol/water partition coefficient of 5000. Due to the lipids, propofol has a typical white color. A disadvantage of the emulsion is that a large proportion of patients experience a pain at the site of injection, probably due to a direct venous irritation, that is difficult to treat. Other important side effects are hypotension due to vasodilatation of the arteries, temporary respiratory depression after bolus injection, postoperative nausea and vomiting, and tonic-clonic convulsions at induction.

Pharmacokinetics-pharmacodynamics:

Propofol is 97-98% bound to the plasma proteins and is highly lipid soluble. Consequently, after a single bolus injection, propofol is quickly redistributed in the body with a primary half life, ranging between 1.8 to 8.3 minutes. The liver is the primary metabolizer, by conjugating propofol at a metabolism rate of 1.5 to 2 L/min. The beta elimination half time ranges between 34 and 64 minutes. Inactive metabolites are cleared by the kidneys.

Several pharmacokinetic-pharmacodynamic models have been described for propofol in order to develop adequate target controlled infusion (TCI) systems, and allow better drug titration compared to a single bolus, repeated boli, or a bolus followed by a continuous infusion. This TCI technology, and the available models will be discussed in more detail in a later section.(176-179)

Clinical anesthesia is obtained with plasma concentrations between 4 and 6 µg/ml, when nitrous oxide or an analgesic drug is associated. However, a large population variability is seen both on pharmacokinetic and pharmacodynamic levels. Concentrations between 1.64-6.38 µg/ml have been found in volunteers at the point of loss of consciousness, and concentrations of 1.0-2.19 µg/ml when consciousness returned.(180)

2.3.1.2 Ketamine (Ketalar®, Pfizer)

Ketamine (2-(O-Chlorophenyl)-2-(methylamino) cyclohexanon chloorhydrate)) is a fast acting, non barbiturate hypnotic anesthetic, with a unique “dissociative” effect on the cerebral function. Mediated by a strong N-methyl D-Aspartate (NMDA) receptor inhibition, the transfer of sensory input to the corresponding association areas is disrupted, causing a clinical effect of unconsciousness, catalepsy, amnesia, and strong analgesic effects.

An important advantage of ketamine is that it preserves cardiovascular and respiratory stability. Blood pressure and heart frequency are increased due to an adrenergic activation, and spontaneous ventilation is maintained. This is why not medically trained soldiers could use this drug in the Vietnam war, as an intramuscular anesthetic, for painless evacuation of injured colleagues. Ketamine is often called the “battle field drug”. In anesthesia practice, ketamine is used as an adjuvans to potentiate other hypnotic drugs or as a low dose infusion for decreasing the postoperative need of opioids.(181-184)

Disadvantages are the frequent hallucinations, of a very frightening nature (near death experiences, nightmares, delirium). Therefore, the use of ketamine should be avoided without combining a benzodiazepine or other hypnotic drug for evoking amnesia of the bad experience. Bronchospasme and apnoe have been reported after intravenous bolus doses, nausea and vomiting, increased muscle tone with tonic clonic convulsions and increased intracranial and intraocular pressure. This latter excludes the use of ketamine for ophthalmic and neurosurgical procedures.

Pharmacokinetics-pharmacodynamics:

After a single bolus of ketamine of 2.5 mg/kg, peak plasma concentrations are 2 µg/ml. The distribution phase ranges between 7 and 17 minutes and elimination takes 130 to 186 minutes. Elimination is performed primarily by the liver, where N-demethylation results in cyclohexanon. After hydroxylation, the metabolites become water soluble and are excreted in urine. Metabolite 1 (norketamine) has a tenfold decreased activity than ketamine but it has a very long elimination halftime of 4 hours. Metabolite 2 (dehydronorketamine) has no hypnotic effect. The elimination halftime is 7 hours. Ketamine is minimally bound to proteins.

The unique effect on cerebral function is reflected in the EEG.(44) The dissociation between cortex and subcortical structures results in a disruption of the coordinated cortical subunits activity. The resulting electrical activity has been compared to “epileptiform” changes in EEG. Most derived indices of hypnotic drug effect, based on EEG, lose sensitivity when ketamine is associated, as the cortical alterations often result in a false increase of index calculation.(185)

Ketamine has no effect on the raw MLAEP as shown by Schwender et al.(186,187) The effects of ketamine on the recently developed MLAEP derived indices are a subject of this thesis, and are discussed in more detail.

2.3.2 Analgesics

2.3.2.1 Remifentanil (Ultiva®, GSK)

Remifentanil (figure 11) is a strong analgesic opioid, from the group of phenylpiperidines, used for analgesia during general anesthesia, and for sedation of mechanically ventilated patients on intensive care.

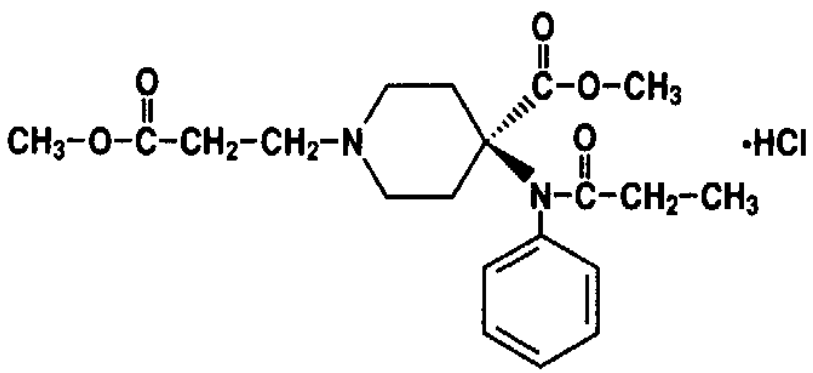


Figure 11: The molecular structure of remifentanil.

As a μ-opioid receptor agonist, all known effects and side effects of other opioids are present. The desired effect is the strong analgesia. Side effects are: cardiovascular inhibition with hypotension and bradycardia, respiratory inhibition and apnoe, muscular rigidity, nausea and vomiting, constipation and pruritus.(188,189) The risk for addiction is debatable, due to the unique pharmacokinetic characteristics. A more complex problem is the suggested phenomenon of the acute tolerance against the effects of remifentanil, that has been suspected after long administration times and at high doses.(190-196) However, it has not been fully untangled if this problem has major clinical implications.

Pharmacokinetics-pharmacodynamics:

Remifentanil has a unique pharmacokinetic profile within the group of opioids.(189) As the structure is an ester, the elimination is based on a constant metabolization by non-specific esterases. These are available in large quantities in blood and almost all tissues. Therefore, the elimination is independent of liver- or kidney function. Moreover, the elimination is ultra rapid, as the elimination half time ranges between 3 and 10 minutes. Due to the lack of any accumulating effect, the half time remains constant, independent of the duration of drug administration.

This ultra rapid offset time, implies that remifentanil can only be given in a continuous infusion or by TCI. Whenever the infusion is stopped, all effects of the opioid disappear within a very short time. This allows very predictable recovery conditions, but it also demands a change in anesthesia practice for postoperative pain relief. With intermediate or long acting opioids, much of the immediate post operative pain is avoided by residual opioid effect. For remifentanil, no residual analgesia can be expected. Therefore, the postoperative pain therapy must be commenced before and during the anesthetic procedure, to avoid the "valley of no analgesia" at the end of surgery.

2.3.3 Neuro-muscular blocking agents (NMBA)

2.3.3.1 Rocuronium (Esmeron®, Organon)

Rocuronium is a non depolarizing neuromuscular blocking agent (NMBA) of the group of aminosteroids. All NMBA's provoke a complete paralysis of the patient, due to a competitive binding with the cholinergic nicotine receptors at the level of the neuromuscular endplate. Rocuronium is used as adjuvans in anesthesia for improving the intubation of the patients' trachea during routine and emergency procedures and for maintaining immobility throughout the surgical procedure.

Pharmacokinetics-pharmacodynamics:

The most impressive feature of rocuronium is a rapid onset time. At a dose of 0.6 and 0.9 mg/kg, rocuronium is able to completely block the nicotine receptors within 1 min and 45 seconds respectively.(197,198) The clinical duration of rocuronium is dependent of the dose given. For 0.45 mg/kg to 1.2 mg/kg, the duration of action is respectively, 22 and 73 minutes. Following intravenous administration of rocuronium, plasma levels follow a three compartment open model. The rapid distribution half-life is 1 to 2 minutes and the slower distribution half-life is 14 to 18 minutes. Rocuronium is approximately 30% bound to human plasma proteins.

Studies of distribution, metabolism, and excretion in cats and dogs indicate that rocuronium is eliminated primarily by the liver. But an important fraction (between 20 to 40%) is excreted by the kidneys. In general, patients undergoing cadaver kidney transplant have a small reduction in clearance which is offset by a corresponding increase in distribution volume, such that the net effect is an unchanged plasma half-life. Patients suffering from liver cirrhosis have a marked increase in their volume of distribution resulting in a plasma half-life approximately twice that of patients with normal hepatic function.

A NMBA has no hypnotic effects. Consequently, NMBA should not evoke any alteration in the EEG that resembles hypnotic drug effect. However, the frontal muscles located between the cerebral cortex and the electrodes that measure the EEG can produce interfering electrical activity. This is defined as the electromyogram (EMG). The frequency ranges of EMG exceed those of spontaneous EEG. Therefore, noise filters have been developed to avoid excessive interference of EMG on the EEG registration. Although the noise filter technology of electroencephalographers has improved considerably, it appears that an important fraction of the measured electrical activity remains EMG dependent. This EMG signal can be inhibited by NMBA. Consequently, NMBA has an influence on the

power spectrum calculations of EEG and can provoke a change in the output of both bispectral index, spectral entropy and the first version of the A-Line® ARX Index.(199-201)

2.4 The principles and practice of target controlled infusion (TCI) systems

2.4.1 Theoretical concept

Target Controlled Infusion (TCI) is a computer generated administration of intravenous agents, whereby the user does not set an infusion rate in ml/h or µg/kg/min, but rather sets a desired (target) plasma (or effect-site) concentration for the drug.(202) The user enters some demographic data of the patient into the computer that compares the variables of the patient with those of a previously studied patient population. By combining the individual demographic data with the pharmacological data obtained from the studied (modeled) population, the computer will make a prediction of the ideal infusion speed, in order to reach and maintain the requested plasma (or effect-site) concentration with as little error and delay as possible.

2.4.2 Plasma and effect-site concentration

Pharmacology describes the relation between drug dose and drug effect. This relationship is depicted in two separate phases.

Pharmacokinetics (PK) describe the time course of a *drug concentration* in the body after administration of a drug dose. Depending on the route of administration and the physicochemical properties of the drug, we can distinguish an absorption phase, followed by (re)distribution and elimination (by metabolization or excretion).

Pharmacodynamics (PD) describes the relationship between the *drug concentration* (as described by PK) and the actual *drug effect*. PD represents a sequence of molecular processes eventually resulting in the clinical effect of the drug. The first step is the interaction between the drug and a receptor in the biophase. The biophase is the direct environment of the receptor at the site of drug action. The interaction at the biophase results in a process called “effectuation”. This could be, for instance, the formation of a second messenger, the inhibition of an enzyme or the physicochemical change in an ion channel. These cellular processes ultimately result in a clinical response, called the “drug effect”.

In a human population, large variability can be found in the clinical response to administration of a drug. At the level of PK, common reasons for this large variability are: differences in body composition, organ function and state of disease. At the level of PD, different responses between individuals can result from variations in receptor density and sensitivity, structural receptor disorders within organs or neurotransmitter pathways.

TCI systems aim to optimize drug administration by using a pharmacokinetic-pharmacodynamic (PKPD) population model, extracted from studies that investigate the behavior of drug-concentrations and drug-effects in a standardized population of patients. These PKPD models are mathematical simplifications of the complexity of the human body, enabling to calculate (or predict) the probable concentrations and drug effects in an individual patient, after drug administration.

For intravenously administered hypnotic and analgesic drugs, PK are generally described by a three compartmental model (Figure 12). The main determinants of this model are: the

three volumes of distribution (central compartment (V_1), rapidly equilibrating (V_2) and slowly equilibrating (V_3) compartments) and the clearances (systemic clearance (k_{10}) versus rapid (k_{12}) and slow (k_{13}) inter- compartmental clearances). When a dose of drug is administered intravenously, it immediately disperses into the central compartment, resulting in a "central compartment concentration". This central compartment concentration is also called **"the plasma concentration"**, although the theoretically defined central compartment has little to do with the real "plasma volume". Rather, it is a reflection of the "mean" drug concentration behavior in the population. Initially, a fast distribution to the rapid and slowly equilibrating compartments sets in, resulting in a steep decrease of central drug concentrations. Once the rapid equilibrating compartment is in equilibrium with the central compartment, the central drug concentrations will decrease with a more moderate rate. Finally, when all three compartments are in equilibrium, the drop in central compartment concentrations has a log linear shape. This terminal phase is also called the "elimination phase", as the main mechanism for the final descent is based on the excretion of drug from the body.

The volumes and equilibration constants of the three-compartmental PK model can be estimated, by administering a bolus dose of drugs in a standardized population. Thereafter, blood samples are drawn at different points in time, and the change in drug concentration over time is plotted. By means of advanced population modeling statistics (e.g. NONMEM), the optimal values of the PK model variables can be estimated. The estimate that fits the measured data samples best, without allowing excessive complexity in the models, is considered for further validation. Ideally, the final PK model should be validated prospectively, before conclusions on clinical applicability can be drawn.

For hypnotics and opioids, the site of action is not the plasma. As such, a theoretical effect-site compartment has been added to the PK model, which represents the site of drug action. (Figure 12) The effect-site volume is considered to be negligible. Consequently, it has no impact on the PK behavior of the drug. However, the effect-site compartment does have a drug concentration, called **the effect-site concentration**. The behavior of the effect-site concentration over time is determined by the equilibration constant "ke0", which describes the rate of definitive drug elimination out of the effect-site. The total amount of drug eliminated from the effect-site is negligible, and is not considered to return to the central compartment.

As the effect-site is a theoretical concept, the effect-site concentration can not be measured directly. However, this theoretical drug concentration is closely related to the actual clinical drug effect. Therefore, continuous surrogate measures of hypnotic drug effect, such as EEG and MLAEP derived indices, are excellent tools for making assumptions on the behavior of the effect-site concentration in the population. Consequently, neurophysiologic monitoring has become closely entangled with TCI technology. A continuous search for convenient neurophysiologic endpoints of hypnotic drug effect remains mandatory to optimize future TCI models.

TCI technology currently allows us to target both plasma- and effect-site concentrations with acceptable accuracy.(203) Moreover, once a desired effect is obtained, TCI enables to maintain this effect over an unlimited amount of time (in "pseudo" steady-state anesthetic conditions). The condition is called "Pseudo", as the TCI evoked steady state is only based on a population prediction, not on an actual individual measurement of drug concentrations in the patient.

Nevertheless, TCI technology is commonly available to all anesthesiologists and therefore, allows a close approximation of “real” steady state anesthesia. By using the most recent TCI models in our protocols, we aim for a high reproducibility of our results. It also allows a better comparison between anesthetic conditions in our patients, and eventually between the monitors tested.

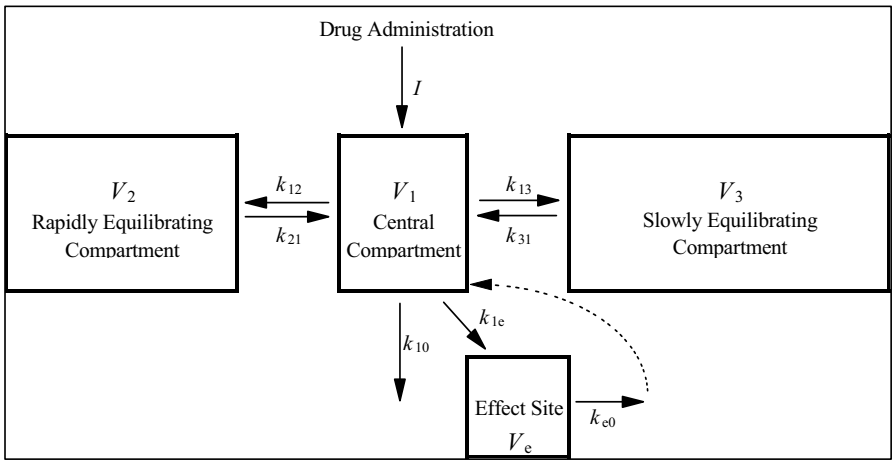


Figure 12: Schematic presentation of the three compartmental PKPD model enlarged with an effect-site compartment.
“I” is the injection of a dose of a drug that immediately disperses towards three compartments, according to the balance between “distribution volume” and “equilibration constants”. V_1,V_2,V_3 ,V_e are the respective distribution volumes of compartment 1(central), 2 (rapidly equilibrating), 3 (slowly equilibrating) and the effect-site. All k values are the equilibration constants that eventually will define the changing concentration in the central (plasma) compartment over time. The elimination constant, that reflects the final excretion of drug out of the system, is k_{10}.

The behavior of the effect-site concentration is only determined by the k_{e0}, which reflects the speed of drug elimination out of the effect-site. The amount of drug, eliminated from the effect-site compartment, is not returning to the central compartment, but is definitely excreted. As the amount of drug lost by this route is considerably smaller, compared to the total elimination, this error is considered to be acceptable.

2.4.3 The models for remifentanil and propofol

All PKPD models used in this study are based on the three compartmental model, enlarged with an effect-site compartment. (Figure 12)

2.4.3.1 Marsh, Schnider, ke0 and time to peak effect

For propofol, the first model used in clinical practice, was a three compartmental pharmacokinetic model defined by **Marsh** et al.(177,204) The Marsh model uses only weight as covariate between patients. Originally, no pharmacodynamic information was included for model building. Therefore, one could only target the plasma concentration. Schuttler et al calculated a ke0 of 0.26 min^{-1} for propofol from a separate population and combined this with Marsh pharmacokinetics. This combined PKPD model was commercialized in a TCI pump called Diprifusor (Cardinal Health, Alaris, Ohio, Il, USA). It was only intended for applications using propofol of the brand Diprivan® (AstraZeneca, Loughborough, Leicestershire, United Kingdom).

Schnider et al, showed that age had a significant effect on the distribution volume and the clearance of the rapidly equilibrating compartment, in a population of 24 adult patients with a large age difference (21 to 81 years).(178,179) This resulted in a more rapid increase of propofol concentrations in the central compartment at the beginning of the infusion, and a more rapid decrease at the end of the drug administration, compared to the Marsh model. With these findings, Schnider et al, created a new PKPD model including age, weight and lean body mass as a covariate for predicting plasma concentration. Both PK and PD data were obtained from the same patient population. The pharmacodynamic measurements were performed with a surrogate EEG derived index, called semilinear canonical correlation. The ke0 of the Schnider model is 0.456 min^{-1}.

Minto et al described an alternative approach for calculating ke0, based on the observation of the time to peak effect.(205) After a bolus injection of propofol, a time delay is observed until maximum clinical hypnotic effect is obtained. At that point the theoretical plasma and effect-site concentration are at equilibrium. This “time to peak effect” allows to depict the initial increasing slope of the effect-site concentrations, resulting in the prediction of an individualized ke0. Minto et al. showed that “time to peak” for propofol was 1.6 minutes. When using Schnider pharmacokinetics, this method results in a mean ke0 of 0.357 min^{-1}. The Schnider model with time to peak effect algorithm is commercially available in several open TCI systems. Recently, the “time to peak effect” method has been implemented on the Marsh model, resulting in a **Modified Marsh model**.(205)

Whenever TCI administration was needed for the studies in this thesis, we preferred to use the Schnider model, with the time to peak effect algorithm of Minto for ke0 prediction. At the time of study inclusions, this choice was rather arbitrary, as no solid proof was available that this model was superior for describing the clinical hypnotic drug effect. Still, we had several arguments to favor this option.

1) The Schnider TCI model is available for all anesthesiologists as it has been implemented in commercialized infusion pumps. Consequently, our results have both scientific and clinical value.

2) The Schnider model has been developed using the “semilinear canonical correlation” as a pharmacodynamic endpoint. This is an independent EEG derived parameter as it is not included in the pharmacodynamic measures that we aimed to compare in our studies. If we had used a PKPD model that was developed with one of the neurophysiological measures under investigation, it could have caused an intrinsic advantage for that specific measure, resulting in a better correlation with Ce_{PROP}. By using the Schnider model, the chance for an intrinsic bias for one of the indices under investigation remains limited.

3) For the studies in steady-state conditions (Study 1, 4 and 5) the potential error in the PKPD model will have little influence on our conclusions as we focus on the differences in neurophysiological response between several predicted steady-state concentrations of propofol, in a “step up” procedure. If the model under- or overestimates Ce_{PROP} at step one, it will probably result in a comparable under- or overestimation of Ce_{PROP} at step two and three. In contrast, the difference in drug effect between steps remains equally informative.

4) For the studies in non steady-state conditions (Study 2,3 and 6), more dramatic errors between the predicted Ce_{PROP} and the actual hypnotic drug effect may occur, especially during the first minutes of drug administration. For this problem, one should distinguish between the errors on a pharmacokinetic level versus those on a pharmacodynamic level.

On a pharmacodynamic level, the Schnider model was validated as an acceptable descriptor of hypnotic drug effect, using BIS as a reflection of the cerebral hypnotic drug effect.(176)

On the pharmacokinetic level, a recent article of Prof. M. Struys provides some arguments to prefer the Schnider pharmacokinetics with the time to peak effect algorithm, as the resulting ke0 better approximates the time course of drug effect during non steady state conditions.(206,207) As this information was not yet available at the time of performing our studies, our decision was fully based on the other arguments listed here.

5) Finally, we preferred to use the Schnider model as it was the only available model at the time of study inclusions, that combined pharmacokinetic and pharmacodynamic data from one single population sample. In contrast, the Marsh model had been developed combining PK data from one sample, with PD data from a second sample of the population. The approach of implementing a ke0, obtained in one study, on a PK model derived from a different sample of patients can result in poor predictability of the final model, as shown by Gentry et al for thiopental, (208) and Wakeling et al. for propofol. (209)

As an illustration we listed all parameters for the currently available propofol PKPD models:

Model Marsh et al.,(204) : Vc = 0.228 * weight (litres * kg). k10 = 0.119/min. k12 = 0.112/min. k13 = 0.0419/min. k21 = 0.055/min. k31 = 0.0033/min. k41 = 0.26/min.

Modified Model Marsh et al.,(204): Vc = 0.228 * weight (litres * kg). k10 = 0.119/min. k12 = 0.112/min. k13 = 0.0419/min. k21 = 0.055/min. k31 = 0.0033/min. *k41 for tPeak = 1.6 min.(205)*

Model Schnider et al.,: Vc = 4.27. V2 = 18.9-0.391 * (age-53). V3 = 238. cl1 = 1.89 + 0.0456 * (weight-77) - 0.0681 * (lbm-59) + 0.0264 * (height-177). cl2 = 1.29 - 0.024 * (age-53). cl3 = 0.836. *k41 for tPeak = 1.6 min.*(179,205)

2.4.3.2 Minto

For remifentanil, Minto et al. have developed a PKPD model, including weight, length, age and lean body mass as covariates.(205,210,211) In agreement with the short acting pharmacological profile, this model is characterized by a small central volume of distribution (around 25L) and a large elimination clearance (about 3L/min). The influence of lean body mass is more important than weight as such. This is reflected in the clinical experience with remifentanil. If remifentanil is given to the obese patient, using a traditional pump, the anesthetist should calculate the dose rather with “lean body mass” in stead of using “total body weight”.

The model parameters for remifentanil are summarized here:(210)

A = (age-40). L = (lbm-55)
Vc = 5.1 - 0.0201 * A + 0.072 * L
Cl1 = 2.6 - 0.0162 * A + 0.0191 * L
V2 = 9.82 - 0.0811 * A + 0.108 * L
Cl2 = 2.05 - 0.0301 * A
V3 = 5.42
Cl3 = 0.076 - 0.00113 * A
k41 = 0.595 - 0.007 * A

2.5 Statistical methodology

Although statistical methods used in this thesis are explained in the respective “methods and materials” sections of the publications, two advanced analyzing techniques will be discussed more in depth, as they are not widely known by many researchers.

2.5.1 Prediction probability (P_K)

A recurrent problem in the datasets presented in this thesis is the need for a measure of accuracy for different dependent variables (= indices of cerebral hypnotic drug effect, using different units and scales) to predict the same ordinal independent variable (=observed anesthetic drug effect). In the setting of this thesis, a candidate anesthetic depth indicator is judged against a "gold standard" endpoint of hypnotic drug effect. As explained before, the clinical endpoints of anesthetic effect are either dichotomous, when evaluating the response to a single stimulus, or polytomous at best, when evaluating the response to a sequence of gradually more intense stimuli. Additionally, the “golden standard” might be a drug effect-site concentration too.

Warren Smith suggested the use of prediction probability (P_K) as an objective measure of accuracy for comparing monitors of hypnotic drug effect.(212,213) P_K is a rescaled version derived from Kim’s dy.x measure of association that generalizes non-parametric receiver operating characteristic (ROC) area for a polytomous ordinal variable. The original output of Kim’s measure of association ranged between 1 and -1, reflecting a direct or reverse correlation in the behavior between variables. In contrast, P_K ranges between 0 and 1. If P_K has a value of 1, it means that the indicator predicts the observed anesthetic depth perfectly. If P_K has a value of 0.5, it means that the indicator predicts no better than a 50:50 chance. P_K was developed to avoid the negative values of Kim’s measure of association. These are not valid in the setting of neurophysiologic monitoring, as we expect the index to evolve in a monotonous way, when the anesthetic state is intensified.

According to Warren Smith, P_K avoids many shortcomings of other measures. For example, as a nonparametric measure, P_K is independent of scale units and does not require knowledge of underlying distributions or efforts to linearize or to otherwise transform scales. Furthermore, P_K can be computed for any degree of coarseness or fineness of the scales for anesthetic depth indicator value and observed anesthetic depth. Consequently, P_K fully uses the available data without imposing additional arbitrary constraints, such as the dichotomization of either scale. And finally, P_K can be used to perform both grouped- and paired-data statistical comparisons of anesthetic depth indicator performance.(212,213) An important shortfall of P_K is that data must be gathered via the same response-to-stimulus test procedure and over the same distribution of anesthetic depths. Therefore, P_K results can not be compared between studies using different independent variables. Additionally, very high P_K results can be obtained easily when endpoints are chosen wide apart in the clinical spectrum of hypnotic drug effect. For example, the P_K for an anesthetic depth indicator that has to predict “the awake patient” at one hand, versus the “unresponsive patient to a painful stimulus” at the other hand, will probably be 1. Such a result does not allow a subtle comparison between measures. Therefore, apart from the analyzing technique chosen, the methodology for data acquisition is equally important when evaluating the clinical use of monitors.

The algorithm for P_K calculation has been distributed freely by Warren Smith as an "Excel®" macro, which has become widespread in the world of pharmacological and neurophysiologic research centres.

2.5.2 Non Linear Mixed Effects Modeling (NONMEM)

Non Linear Mixed Effect Modeling (NONMEM) is a computer program that originally has been developed by Stuart Beal and Lewis Sheiner at the University of San Francisco (UCSF), California. It is currently distributed by "Globomax", a subdivision of "Icon's development solutions" (Ellicott City, MD, USA). It has been developed to allow "non-linear mixed effects modeling" on a dataset, as an advanced alternative for the classic "naive pooled approach" or the intermediate "two stage approach" for population data analysis. Due to the background of both inventors, the program is currently mainly applied in pharmacokinetic and pharmacodynamic model building. However, in theory, any dataset in which the underlying relationship can be expressed as a mathematical model can be investigated by NONMEM.

A limited amount of competitive software is currently available for mixed effect modeling, but NONMEM appears to have become the "standard" for phase 1 and 2 pharmacological research. It is an important analyzing method for drug approval procedures as defined by the Food and Drug Administration in the USA.

What are mixed effects? And what makes them so important that they are included in the programs' name? To answer this question, some background information is mandatory.

The result of any scientific experiment can be characterized as arising from a fundamental relationship. The purpose of the experiment is usually to deduce this underlying relationship. This is called the "structural model". It is in fact a mathematical equation that relates the input (the dependent variable) to the output (the independent variable). In a population of individuals, the structural model includes certain "fixed effects". Fixed effects are features that you can determine or measure in the individuals, such as weight, height, gender etc… The fixed effects help the model account for how individuals vary within the population. Hypothetically, if we know all "fixed effects" that determine the variability between individuals we should be able to construct a mathematical equation that perfectly predicts the outcome of an identical experiment in any individual.

However, in any scientific experiment, there are also "random effects". They are called "random" because they can not be predicted in any way. One kind of random effect is the unexplained differences between individuals. This is caused by the natural reality of "biological variability", which can not be considered as noise in the dataset as it will never be possible to avoid it. A second random effect is caused by residual error in the measurement. This is noise in the dataset that can theoretically be minimized by improved measurement methods. Although both versions of random effects can not be predicted, they arise from a distribution that is, in theory, identifiable by exploring the dataset. The MEM in NONMEM stands for "mixed effects modeling". That means that NONMEM enables to estimate both "fixed effects" (e.g. how do weight and age affect pharmacokinetics?), and

two versions of “random effects”: the intra-individual variability (noise) versus the interindividual variability (biological variability). These random effects can not be predicted in advance (they are random!). But we can use NONMEM to estimate the magnitude (variance) of the random effects. (e.g. “How much variability is there in the measurements, once the fixed effects are accounted for?” or “How much does clearance in the population vary, once the fixed effects are accounted for?”) For variance estimation, NONMEM typically considers the “random” distributions to be normal, with a mean of 0.

In this thesis, we used NONMEM to explore the pharmacodynamic relationship between several neurophysiologically derived indices of cerebral hypnotic drug effect (= dependent variable) with the calculated effect-site concentration of propofol (= independent variable). This relationship classically is described by a sigmoidal E_{max} model. This model is determined by four variables. The baseline effect (E_0), the maximum effect (E_{max}), the effective dose compatible with 50% of the maximum effect (ED_{50}) and the slope of the sigmoidal curve. We used NONMEM to estimate the typical values for these four variables. Additionally, we quantified the intra- and interindividual variability, by estimating the respective variances for these random effects. Finally, NONMEM provides a tool (called “the objective function”) that allows us to compare several estimated models on the same dataset, in order to determine the most optimal parameter estimation. Greatly simplified, the “objective function” should be minimized, as it reflects the mathematical process that aims to minimize the -2 log likelihood of the fit of the model to the observed dataset. We used this method in our studies to find the optimal set of parameters for describing a sigmoidal E_{max} model within our dataset.

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Chapter 3
Studies performed in this thesis

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3.1 Study 1: The ability of BIS, ARX derived auditory evoked potentials and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil

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3.1.1 Introduction

An adequate monitor of hypnotic drug effect is able to discriminate between the presence and absence of clinical signs of hypnotic drug effect. The validation for AAI in propofol mono-anesthesia conditions was already published by Struys et al.(1) Other authors however indicated that during combined administration of opioids and hypnotics, the threshold compatible with the "point of loss of consciousness" shifted to higher values for BIS and AAI, whereas it decreased for Ce_{PROP}[#]. Consequently, questions were raised if this shift in threshold was accompanied by a decreased sensitivity or predictive value of these indices to detect progressively increasing levels of hypnotic drug effect.(2-4)

Therefore, we investigated the ability of the AAI to discriminate several clinical endpoints of hypnotic drug effect in pseudo-steady state anesthesia, both during mono-anesthesia with propofol, as during combined remifentanil-propofol administration. The independent clinical endpoints were defined as: the "loss of response to name calling" as described by a transition from level 3 to 2 on the OAA/S scale, the "loss of eyelash reflex" and the "loss of response to a painful stimulus".(5) We compared the performance of AAI to detect these clinical endpoints with BIS and Ce_{PROP}. The quality of this study results from the TCI "pseudo" steady state conditions, maintained during clinical measurements. Moreover, by comparing three groups with different doses of remifentanil, a potential impact of the potentiating interaction between remifentanil and propofol, on the detection sensitivity of the tested monitors could be explored.

A second reason for the high value of our study is the specific choice for advanced statistical analysis of the dataset. We used prediction probability (P_K) analysis, Probit analysis and thorough sensitivity/specificity analysis. P_K analysis is developed by Smith et al to allow comparison between dependent variables with different units of measure, in their ability to detect multiple (polytomous) independent variables.(6,7) This methodology is explained more in depth, both in the "statistical analysis" section of the manuscript (p804), as in chapter 2 of this thesis.

In an appendix, we used an ordinal logistic regression model to prove that the prediction probability for detection of the OAA/S scale improves by combining neurophysiologic measures (BIS or AAI) with pharmacologic predictions (Ce_{PROP} and Ce_{REMI}), as compared to the solitary measurement of these independent variables. This additional result proves that combining AAI or BIS with TCI technology is worthwhile, as this approach results in an improved anesthetic drug titration.

[#] Ce_{PROP} = the predicted effect-site concentration of propofol, as calculated by the PKPD model of Schnider

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3.1.2 Manuscript

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Ability of the Bispectral Index, Autoregressive Modelling with Exogenous Input–derived Auditory Evoked Potentials, and Predicted Propofol Concentrations to Measure Patient Responsiveness during Anesthesia with Propofol and Remifentanil

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Background: **This study was conducted to compare the performance accuracy of the independent variables Bispectral Index (BIS), A-Line ARX index (AAI), and predicted propofol effect-site concentration (CePROP) to measure the dependent variables of loss of responses to different stimulation defined as loss of response to verbal command (LOR_{verbal}), eyelash reflex (LOR_{lash}), and noxious stimulus ($LOR_{noxious}$) during stepwise increased levels of propofol infusion with and without remifentanil.**

Methods: **Forty-five patients were randomly allocated to one of three groups (0, 2, and 4 ng/ml remifentanil) to receive graded CePROP and predicted effect compartment controlled remifentanil (CeREMI). At every step, the ability to respond to verbal command using the Observer's Assessment of Alertness/Sedation Scale (OAA/S), eyelash reflex, and electrical tetanic noxious stimulus were compared against BIS, AAI, and CePROP. Prediction probability and sensitivity/specificity were calculated.**

Results: **Increasing CeREMI increased BIS and AAI values at LOR_{verbal} and LOR_{lash} and decreased CePROP. Similar findings were found for $LOR_{noxious}$. The overall prediction probability to measure the hypnotic component of anesthesia remained accurate in the three groups for BIS, AAI, and CePROP. Combined information from CePROP, CeREMI, and BIS or AAI increased the overall prediction probability for predicting the OAA/S scale and LOR_{lash}. Less accuracy to $LOR_{noxious}$ was found in all independent variables.**

Conclusions: **Although BIS, AAI, and CePROP were influenced by remifentanil during propofol administration, their ability to detect OAA/S and LOR_{lash} remained accurate. Improved performance is obtained when BIS and AAI are measured in conjunction with drug targeted effect-site concentrations. Remifentanil decreases the ability of these independent variables to detect $LOR_{noxious}$.**

BOTH electroencephalography- and midlatency auditory evoked potential (MLAEP)–derived variables have been proposed as measures of the hypnotic state during anesthesia.[1] For the electroencephalography, the Bispectral Index (BIS) incorporated in the A-2000 BIS® monitor (Aspect Medical Systems, Inc., Newton, MA) has been proven to have a high sensitivity and specificity to measure anesthetic drug effect, compared with other processed electroencephalographic variables.[2–4] Previously, MLAEP has been used by various investigators to study anesthetic depth.[5] Recently, Jensen *et al.*[6,7] developed a new method for extracting the MLAEP from the electroencephalographic signal by using an autoregressive model with an exogenous input (ARX) adaptive model. This method allows extraction of the MLAEP signal within 15–25 sweeps of 110 milliseconds' duration each, resulting in only a 6- to 15-s response delay time. A new monitoring variable, called the A-Line ARX index (AAI), is then calculated from this fast extracted MLAEP wave. This new technology is incorporated in a recently commercialized system called A-Line® (Danmeter A/S, Odense, Denmark). Recently, Struys *et al.*[8] compared the accuracy of both BIS and AAI for measuring loss of responses to different stimulation defined as loss of verbal command (LOR_{verbal}), loss of eyelash reflex (LOR_{lash}), and loss of response to noxious stimulus ($LOR_{noxious}$) during steady state propofol administration. We found that BIS, AAI, and predicted effect-site concentration of propofol (CePROP) revealed a similar level of information on LOR_{verbal} and LOR_{lash} but did not predict $LOR_{noxious}$. Also, AAI has recently been shown to reliably assess the level of consciousness during propofol,[8,9] sevoflurane,[10] and midazolam[11] anesthesia. The BIS correlated better to propofol plasma concentrations than AAI, but AAI correlated better than BIS to the clinical signs during recovery from propofol anesthesia.[11]

In previous work done with the AAI, propofol was administered solely. Although a clear pharmacodynamic interaction between remifentanil and propofol has been described,[12] controversy still exists on the influence of opiates on the accuracy of both BIS and MLAEP to measure loss of response to different stimulation.[13–16] During remifentanil monoinfusion, AAI measured changes in patients' level of arousal better than BIS.[17] However, in this study, a different electrode position was used, where the AEP was recorded between a frontal (+) and an occipital electrode (−). It is possible that a change in

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montage such as this could lead to significantly different results compared with those from the current study.

A fundamental question is whether the electroencephalograph- or AEP-derived variables can be used to optimize drug delivery. A first step to answer this question is to examine the performance and accuracy of these monitors under various conditions and to compare them with the accuracy and usefulness of on-line calculated drug effect-site concentration. A secondary question is how opiates affect these performance parameters. This study was conducted to assess the performance accuracy of the AAI to reflect the hypnotic component of anesthesia and to measure loss of responses to different stimulation defined as LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$ during stepwise increased levels of propofol infusion with and without remifentanil. The performance of AAI was compared with that of BIS and CePROP.

Materials and Methods

After Institutional Ethics Committee (Ghent University Hospital, Gent, Belgium) approval, informed consent was obtained from 45 female patients with American Society of Anesthesiologists class I, aged 18–60 yr, who were scheduled to undergo ambulatory gynecologic surgery. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight, neurologic disorder, and recent use of psychoactive medication, including alcohol. They were randomly allocated to one of the three groups. In all groups, patients received a "staircase" computer-controlled infusion of propofol targeting the effect compartment. Initially, an effect-site concentration of 1.5 μg/ml was targeted in the group without remifentanil, and 1 μg/ml was targeted in the two other groups; this was increased every 4 min by 0.5 μg/ml until loss of response to all relevant clinical measures of anesthetic depth was observed. In the 0 ng/ml remifentanil group, no remifentanil was given. In the 2 ng/ml and 4 ng/ml remifentanil groups, an effect compartment controlled infusion of remifentanil was started 4 min before the start of propofol. Calculated remifentanil effect-site concentrations (CeREMI) of 2 and 4 ng/ml were targeted, respectively.

Propofol and remifentanil were administered *via* a computer-assisted continuous infusion device to a target effect-site concentration (RUGLOOP**) using a three-compartment model enlarged with an effect-site compartment. For propofol, the pharmacokinetic–dynamic model previously published by Schnider *et al.*[18,19] was used. For remifentanil, the pharmacokinetic–dynamic model previously published by Minto *et al.*[20,21] was used. CePROP was computed to yield a time-to-peak effect[22] of 1.6 min after bolus injection, as also published by Schnider *et al.*[18,19] and clinically confirmed by Struys *et al.*[23] For remifentanil, a $t_{1/2}k_{e0}$ of 1.020619 min was applied as published by Minto *et al.*[20,21] Propofol and remifentanil infusion were administered using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France). RUGLOOP steers the pump at infusion rates between 0 and 1,200 ml/h *via* an RS-232 interface. By using this infusion technique, we were able to obtain a steady state condition for both propofol and remifentanil at every target level after 4 min of infusion. Hereby, steady state is defined as the equilibration between the calculated plasma and effect-site concentration of the drug. Remifentanil and propofol were infused *via* a large left forearm vein. Every patient received approximately 200 ml crystalloid fluid during the study period. No fluid load was given before induction. No patient received preanesthetic medication. No other drugs were given. All patients maintained spontaneous ventilation *via* a facemask delivering 6 l/min O_2.

Table 1. Responsiveness Scores of the Modified Observer's Assessment of Alertness/Sedation Scale[24]

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Heart rate and noninvasive blood pressure, oxygen saturation measured by pulse oximetry (Spo_2), and capnography were recorded at 1-min intervals using an AS3 monitor (Datex, Helsinki, Finland). BIS (version 3.4) was derived from the frontal electroencephalogram (At-Fpzt) and calculated by the A-2000 BIS® monitor using a BIS-Sensor® (Aspect Medical Systems, Inc.). The smoothening time of the BIS® monitor was set at 15 s. The AAI from the MLAEP was calculated using the A-Line® monitor. The MLAEPs were elicited with a bilateral click stimulus of 70 dB in intensity and 2 ms in duration. Three electrodes (A-Line AEP electrodes; Danmeter A/S) were positioned at the mid forehead (+), left forehead (reference), and left mastoid (−). The extraction of the MLAEP using a short moving time average technique together with an ARX model and the calculations of the AAI are described elsewhere.[8]

Ten seconds before each increase in CePROP (after 4 min of infusion at the specific target effect-site concentration), the independent variables of response (BIS, AAI, and CePROP) were recorded. Immediately after that, patient responsiveness to different stimuli was tested using the dependent variables eyelash reflex, Observer's

** RUGLOOP, written by Tom De Smet, M.Sc. (Medical Engineer, DEMED Engineering, Temse, Belgium), and Michel M. R. F. Struys, M.D., Ph.D. (Professor of Anesthesia, Ghent University, Gent, Belgium). More information available at http://www.anesthesia-uzgent.be.

Assessment of Alertness/Sedation Scale (OAA/S[24]; table 1), and response to electrical tetanus (at 100 Hz and 50 mA for 2 s; applied to the volar forearm level) assessments, in that order. Verbal stimulation proceeded noxious stimulus. Patients were considered responsive to verbal stimulus if their OAA/S value was 3, 4, or 5 and were considered unresponsive to verbal command at OAA/S values of 0, 1, and 2. Transition between a responsive and an unresponsive state was defined as loss of response to verbal command (LOR_{verbal}). Loss of response of eyelash reflex was defined as LOR_{lash}. Patients were considered responsive to noxious stimulus if they responded to the tetanic electrical stimulation, regardless of whether they responded to trapezius squeeze during the OAA/S assessment. Loss of response to tetanic stimulus was defined as $LOR_{noxious}$.

Both BIS and AAI indices were also logged automatically. RUGLOOP digitally recorded the BIS index every 10 s, and the A-Line monitor recorded AAI index values nominally every 6 s. The time marks of both systems were synchronized with the manual timing for stimulus and manually recorded events to within ±1 s.

Statistical Analysis

The significance level was set at 5% unless otherwise reported. The ability of the independent variables (BIS, AAI, and CePROP) to detect the level of OAA/S, LOR_{lash}, and $LOR_{noxious}$ was evaluated using prediction probability (P_K), which compares the performance of independent variables with different units of measure, as developed by Smith *et al.*[25,26] Consider a variable such as BIS or AAI and a "definitive standard" measure of anesthetic depth such as the multilevel OAA/S score or the two-level responsiveness (yes/no) to eyelash reflex or noxious stimulus. Then, a P_K of 1 for the BIS or AAI variable would mean that BIS or AAI always increases (decreases) as the anesthesia gets lighter (deeper) according to the definitive standard depth measure. Such an independent variable can perfectly measure anesthetic depth. Alternatively, a P_K value of 0.5 would mean that the independent variable is useless for measuring anesthetic depth. For the OAA/S score, a P_K was computed for all OAA/S levels combined. Similarly, P_K values for LOR_{lash} and $LOR_{noxious}$ were determined. The jackknife method was used to compute the SE of the estimate, based on the assumption that all assessments were independent.[25,26] A Student *t* test with Bonferroni correction was used to evaluate whether the P_K for one variable was different from another one. Significance level was set at 0.0167. Prediction probability was calculated using a custom spreadsheet macro, P_KMACRO, developed by Smith *et al.*[25,26] The P_K value was calculated for each independent variable in each group. A P_K analysis for each independent variable with the three groups pooled was performed.

To study whether the combined information from BIS and AAI together with the drug effect-site concentrations offers more accurate information than the independent variables alone, two new composite variables have been designed based on the combined information from BIS + CePROP + CeREMI and AAI + CePROP + CeREMI, and a P_K analysis was performed on both composite variables. The OAA/S score was used as clinical comparator. The P_K on the combined information was calculated using ordinal logistic regression, as described in the Appendix.

The power on the P_K values was calculated using a *t* statistic defined as the difference considered of clinical importance divided by the SE of the difference between two independent variables. Assuming a P_K difference of 0.05 as being of significant with an SE of 0.02, 15 patients should be included to find significant differences with $P < 0.025$ (Bonferroni correction for two *t* tests). Previous assumption were based on previous results of the AAI and other AEP-independent variables.[27]

By applying Probit analyses, the effective concentration or index at which 50% (ED_{50}) and 95% (ED_{95}) of the patients reached LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$ were calculated for all independent variables. For all independent variables, ED_{50} and ED_{95} values were compared between groups using one-way analysis of variance statistics. If significant, an unpaired two-sided Student *t* test with Bonferroni correction was used ($P < 0.0167$).

We calculated cutoff (threshold) values for the ability of the BIS, AAI, and CePROP to detect LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$ in each group. For these calculations, we used "positive" to denote a test result that suggested responsiveness and "negative" to denote a test result that suggested nonresponsiveness. We assumed that increases in the BIS and AAI and a decrease in CePROP corresponded to an increased likelihood of responsiveness. We computed sensitivity as the proportion of responsive patients with positive test results (value higher than cutoff value for BIS and AAI and lower than cutoff value for CePROP). Similarly, we computed specificity as the proportion of nonresponsive patients with negative test results (value lower than cutoff value for BIS and AAI and higher than cutoff value for CePROP). We computed the cutoff values for each independent variable and specificity at a level of 100% sensitivity and at which the sum of sensitivity and specificity were highest. The same sensitivity/specificity analyses were performed for composite variables.

Results

The demographics (mean ± SD) of the 45 female patients in the three groups are shown in table 2. No significant demographic differences were found between groups.

Figures 1A and B show the behavior of BIS and AAI

Table 2. Antropometry

	0 ng/ml Remifentanil	2 ng/ml Remifentanil	4 ng/ml Remifentanil
Age, yr	33 ± 5	33 ± 5	34 ± 4
Weight, kg	63 ± 10	66 ± 11	65 ± 9
Height, cm	167 ± 6	168 ± 6	167 ± 6

versus CePROP and CeREMI. The correlation coefficient between BIS and the drug effect-site concentrations (r = 0.92) was significantly higher than for AAI (r = 0.82). In all groups, a stepwise increase in CePROP resulted in a monotonic decrease in the OAA/S score. BIS and AAI decreased in all groups with decreasing OAA/S scores, as shown in figure 2.

Figures 3A–C show the behavior of BIS, AAI, and

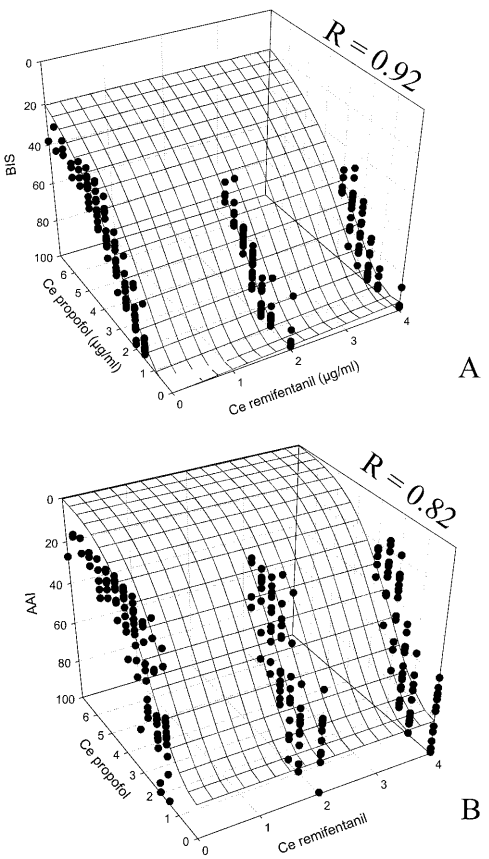

Fig. 1. Nonlinear regression analysis from the raw data from all groups (0, 2, and 4 ng/ml remifentanil effect-site concentration [Ce]) at different propofol effect-site concentrations. (*A*) Correlation with the Bispectral Index (BIS); (*B*) correlation with the A-Line ARX index (AAI).

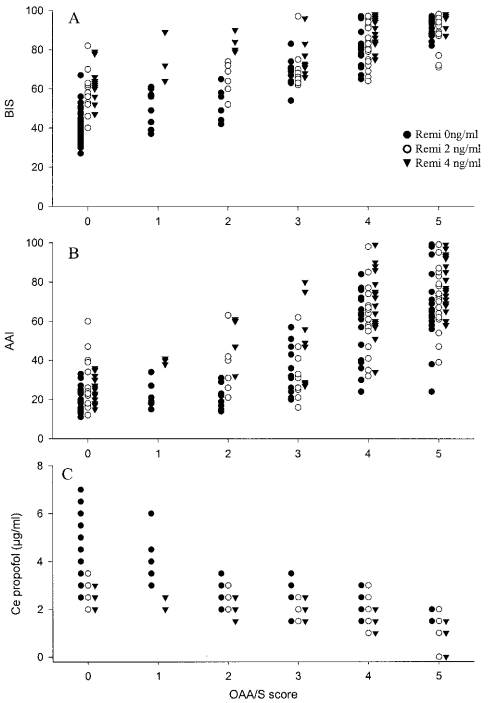

Fig. 2. Raw data at every Observer's Assessment of Alertness/Sedation Scale (OAA/S) score for Bispectral Index (BIS; *A*), A-Line ARX index (AAI; *B*), and propofol effect-site concentration (Ce; *C*). Data from the 0 ng/ml remifentanil (Remi) group are presented as *black circles*, data from the 2 ng/ml remifentanil group as *white circles*, and data from the 4 ng/ml remifentanil group as *black triangles*.

CePROP at LOR_{lash}. For all independent variables, a significant decrease of the variable values between the responsive and unresponsive state was observed in all groups. The BIS, AAI, and CePROP values at $LOR_{noxious}$ are plotted in figures 3D–F. In all groups, all independent variables changed significantly.

By applying Probit analyses, the effective BIS, AAI, or CePROP at which 50% (ED_{50}) and 95% (ED_{95}) of the patients produced a LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$ were calculated and are shown in table 3. For all three groups, the probability curves for the observations at LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$ are shown in figures 4A–C for BIS, in figures 4D–F for AAI, and in figures 5A–C for CePROP.

The ability of the BIS, AAI, and CePROP to predict the level of the OAA/S, LOR_{lash}, and $LOR_{noxious}$ as presented by the P_K values is shown in table 4. Overall, similar performances were found for BIS, AAI, and CePROP. A P_K analysis for each independent variable with the three groups pooled revealed similar ability to detect both the

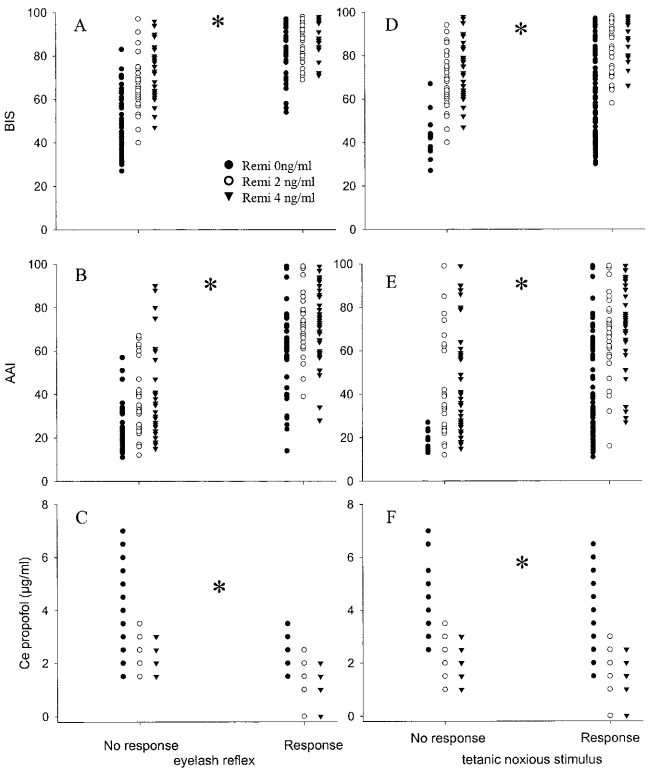

Fig. 3. (*A–C*) Raw data for (no) response to eyelash reflex for Bispectral Index (BIS), A-Line ARX index (AAI), and propofol effect-site concentration (Ce). (*D–F*) Raw data for (no) response to noxious stimulus for BIS, AAI, and propofol effect-site concentration. *$P < 0.05$ for each group between the responsive and non-responsive states. Data from the 0 ng/ml remifentanil (Remi) group are presented as *black circles*, data from the 2 ng/ml remifentanil group as *white circles*, and data from the 4 ng/ml remifentanil group as *black triangles*.

OAA/S levels and LOR_{lash}. In contrast, the overall ability for detection of $LOR_{noxious}$ was lower when pooling the groups together.

By calculating the *t* statistic, we found that this study including 15 patients for each group had the power to determine significant differences between independent variables to predict OAA/S larger than 0.052, which is in accordance with our initial assumption that only differences larger than 0.05 would be considered significantly different.

The P_K values to detect the OAA/S level using the combinations of input variables were better compared to the P_K values of pooled data for BIS, AAI, and CePROP alone. For the composite index using the combination BIS + CePROP + CeREMI, the P_K value was 0.91 (SE = 0.01), and for the composite index using the combination AAI + CePROP + CeREMI, it was 0.93 (SE = 0.01) to detect the OAA/S level.

We also performed more in-depth sensitivity/specificity analysis. Within the three groups, table 5 shows the cutoff values for each independent variable at which the sum of the sensitivity and specificity was the highest, representing the independent variable value where the

Table 3. ED_{50} (95% CI)/ED_{95} Values of BIS, AAI, and EC_{50} (95% CI)/EC_{95} Propofol for All Groups at LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$

	Group I: 0 ng/ml Remifentanil	Group II: 2 ng/ml Remifentanil	Group III: 4 ng/ml Remifentanil
LOR_{verbal}			
AAI	26 (25–28)/20*§	33 (31–34)/18*§	40 (39–42)/25*§
BIS	61 (60–62)/55*§	66 (65–68)/58*§	77 (75–78)/65*§
CePROP	2.9 (2.7–3.1)/3.8*‖	2.4 (2.2–2.6)/3.1*‖	2.0 (1.8–2.2)/2.7*‖
LOR_{lash}			
AAI	34 (33–36)/21†‡	56 (55–58)/44†‡	56 (54–58)/32†‡
BIS	67 (65–68)/55*‡	80 (79–82)/66*‡	84 (82–85)/71*‡
CePROP	2.8 (2.5–3.0)/3.4†	1.8 (1.7–2.0)/2.6†	1.7 (1.6–1.9)/2.5†
$LOR_{noxious}$			
AAI	16 (15–17)/11*‡	42 (40–44)/23*‡	55 (53–57)/27*‡
BIS	41 (40–43)/29*‡	72 (70–73)/56*‡	85 (84–87)/68*‡
CePROP	4.1 (3.8–4.4)/6.6*#	1.8 (1.4–2.1)/3.8*#	1.3 (1.1–1.5)/3.3*#

* $P < 0.0167$ for ED_{50} levels between all groups. † $P < 0.0167$ for ED_{50} levels between group I *vs.* II and I *vs.* III. ‡ $P < 0.0167$ for ED_{95} levels between all group. § $P < 0.0167$ for ED_{95} levels between group I *vs.* III and II *vs.* III. ‖ $P < 0.0167$ for ED_{95} levels between group I *vs.* III. # $P < 0.0167$ for ED_{95} levels between group I *vs.* II and I *vs.* III.

AAI = A-Line ARX index; BIS = Bispectral Index; CePROP = calculated propofol effect-site concentration; LOR_{lash} = loss of eyelash reflex; $LOR_{noxious}$ = loss of response to electrical tetanic stimulus; LOR_{verbal} = loss of response to verbal command.

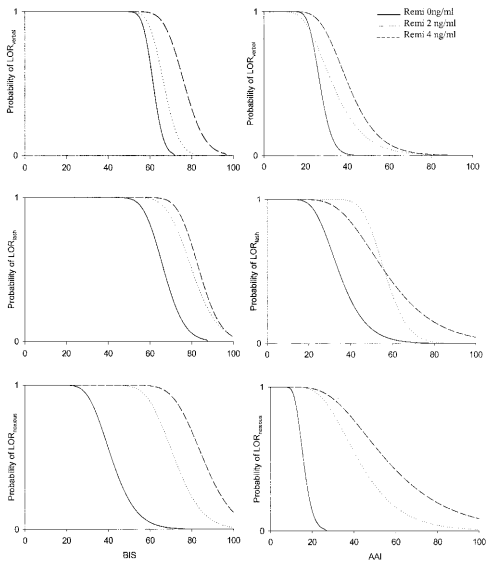

Fig. 4. Probability of loss of response to verbal commend (LOR_{verbal}), eyelash reflex (LOR_{lash}) and a tetanic electrical stimulus ($LOR_{noxious}$) as a function of Bispectral Index (BIS) and A-Line ARX index (AAI). Data from the 0 ng/ml remifentanil (Remi) group are presented as a *solid line*, data from the 2 ng/ml remifentanil group as a *dotted line*, and data from the 4 ng/ml remifentanil group as a *dashed line*.

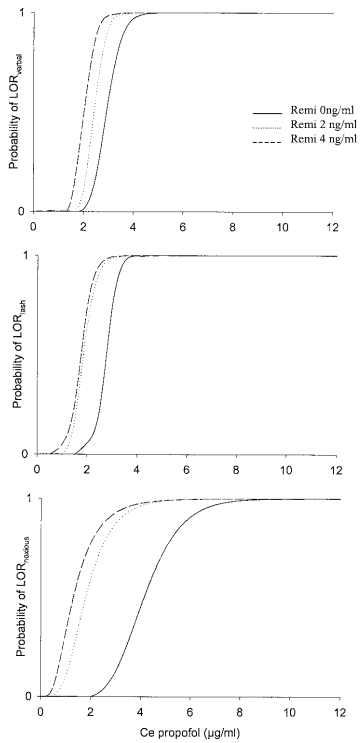

Fig. 5. Probability of loss of response to verbal commend (LOR_{verbal}), eyelash reflex (LOR_{lash}), and a tetanic electrical stimulus ($LOR_{noxious}$) as a function of the propofol effect-site concentration (Ce). Data from the 0 ng/ml remifentanil (Remi) group are presented as a *solid line*, data from the 2 ng/ml remifentanil group as a *dotted line*, and data from the 4 ng/ml remifentanil group as a *dashed line*.

overall "errors" are minimized.[28] Table 6 shows the different cutoff values and their specificity at level of 100% sensitivity. When using the combined information of BIS or AAI together with CePROP and CeREMI, the sensitivity/specificity profiles were more accurate. For both combinations, the best sensitivity-*versus*-specificity combinations were found at 100% sensitivity for 82% specificity.

Table 7 shows at which average OAA/S score at LOR_{lash} and $LOR_{noxious}$ occurred in each of the three groups. The OAA/S is an ordinal scale, but it was considered continuous to be able calculate an average of OAA/S score with a decimal value.

Discussion

This study was conducted to compare the performance accuracy of the independent variables BIS, AAI, and CePROP to measure anesthetic depth and how opiates quantitatively influence this information. Therefore, we observed the influence of remifentanil on the accuracy of the AAI, a new index calculated from the MLAEP, to reflect the hypnotic component of anesthesia (measured by the different levels of the OAA/S) and to measure loss of responses to different stimulation defined as LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$ during stepwise increased levels of propofol infusion with and without remifentanil. The performance of AAI was compared with that of BIS and CePROP.

In previous work, our group concluded that, during propofol anesthesia (without opiates) under steady state conditions, BIS, AAI, and CePROP were accurate independent variables to measure the hypnotic component of anesthesia and loss of responsiveness to different stimuli. Hemodynamic variables did not perform accurately enough to measure the hypnotic–anesthetic status of the patient. BIS correlated best with CePROP, followed by the AAI. Hemodynamics did not correlate well.[8] To study the hypnotic component of anesthesia, two clinical measures (also called dependent variables) were used. We selected the OAA/S score because it provides a good correlation with a clinical reflection of the hypnotic component of anesthesia and has been

Table 4. Prediction Probability (P_K) Described as Mean (SE) for Each Independent Variable (BIS, AAI, and CePROP) Using OAA/S, LOR_{lash}, and $LOR_{noxious}$

	0 ng/ml Remifentanil	2 ng/ml Remifentanil	4 ng/ml Remifentanil	Pooled Data
OAA/S				
AAI	0.88 (0.02)	0.87 (0.02)	0.88 (0.02)	0.87 (0.01)
BIS	0.93 (0.01)	0.90 (0.02)	0.88 (0.02)	0.90 (0.01)
CePROP	0.92 (0.02)	0.92 (0.03)	0.92 (0.02)	0.90 (0.01)
LOR_{lash}				
AAI	0.94 (0.02)	0.96 (0.02)	0.87 (0.04)	0.94 (0.01)
BIS	0.96 (0.02)	0.92 (0.03)	0.94 (0.04)	0.95 (0.01)
CePROP	0.94 (0.02)	0.95 (0.02)	0.94 (0.02)	0.93 (0.01)
$LOR_{noxious}$				
AAI	0.87 (0.04)*	0.86 (0.04)*	0.81 (0.05)*	0.72 (0.03)
BIS	0.88 (0.05)*	0.86 (0.05)	0.86 (0.04)*	0.75 (0.03)
CePROP	0.83 (0.06)	0.86 (0.04)*	0.87 (0.04)*	0.72 (0.03)

* $P < 0.05$ compared to pooled data P_K.

AAI = A-Line ARX index; BIS = Bispectral Index; CePROP = calculated propofol effect-site concentration; OAA/S = Observer's Assessment of Alertness/Sedation Scale; LOR_{lash} = loss of eyelash reflex; $LOR_{noxious}$ = loss of response to electrical tetanic stimulus.

tested prospectively.[29] Also, loss of eyelash reflex was used because it is a simple binary variable and commonly applied by anesthesiologists in clinical practice to detect loss of consciousness.[14]

In all groups, a stepwise increase in CePROP resulted in a monotonic decrease in BIS and AAI as shown in figure 1. Similar to our previous work using propofol alone,[8] the correlation between BIS and the combined drug effect-site concentrations was higher than for the AAI. In all groups, a monotonic decrease in both BIS and AAI was observed at decreasing OAA/S levels as shown in figure 2. Similar findings were found for LOR_{lash}, as seen in figures 3A–C.

LOR_{verbal} and LOR_{lash} were reached at higher independent variable values in a dose-dependent manner when adding remifentanil. This can be concluded from the Probit analyses shown in figure 4 and the extracted ED_{50} and ED_{95} as seen in table 3. Although some differences between groups for the ED_{50} and ED_{95} did not reach the level of significance, a clear trend could be observed. Our results are in contrast with the findings from Iselin-Chaves *et al.*,[30] who reported no significant influence of opiates on the BIS and MLAEP to detect the probability of loss of consciousness and lack of recall by using the OAA/S score. However, they used lower concentrations of opiates (50 and 100 ng/ml alfentanil; potency ratio alfentanil:remifentanil around 40:1). Recently, Mi *et al.*[14] also found that when applying fentanyl pretreatment during propofol administration, the hypnotic endpoints were achieved at higher BIS values. The addition of remifentanil potentiates the effect of propofol. LOR_{verbal} and LOR_{lash} were detected at lower CePROP in the 2 and 4 ng/ml remifentanil groups compared to the 0 ng/ml remifentanil group, as shown in figure 5. Also, EC_{50} and EC_{95} propofol decreased significantly or tended to decrease in a remifentanil dose-dependent matter, as also described previously by others.[31]

A possible bias might have been caused by the influence of opiates on the clinical dependent variables. Both

Table 5. Cutoff Values (Sensitivity [%]–Specificity [%]; Sum of Sensitivity + Specificity [%]) at Maximum Level of Sensitivity + Specificity whereby Sensitivity > Specificity

	0 ng/ml Remifentanil	2 ng/ml Remifentanil	4 ng/ml Remifentanil
LOR_{verbal}			
AAI	29 (91–91; 182)	42 (82–81; 163)	41 (93–86; 179)
BIS	61 (99–94; 193)	64 (95–76; 171)	79 (85–82; 167)
CePROP	3.5 (99–76; 175)	3.0 (98–57; 155)	2.5 (96–64; 160)
LOR_{lash}			
AAI	34 (90–88); 178)	47 (96–82; 178)	47 (96–77; 173)
BIS	67 (90–88; 178)	75 (89–85; 174)	84 (89–87; 176)
CePROP	3.0 (92–85; 177)	2.5 (98–68; 166)	2.0 (87–83; 170)
$LOR_{noxious}$			
AAI	20 (76–64; 140)	40 (92–71; 163)	59 (84–67; 151)
BIS	44 (84–71; 155)	75 (76–71; 147)	90 (77–73; 150)
CePROP	4.0 (80–71; 151)	2.5 (88–50; 138)	2.5 (95–40; 135)

AAI = A-Line ARX index; BIS = Bispectral Index; CePROP = calculated propofol effect-site concentration; LOR_{lash} = loss of eyelash reflex; $LOR_{noxious}$ = loss of response to electrical tetanic stimulus; LOR_{verbal} = loss of response to verbal command.

Table 6. Cutoff Values (Specificity) at Level of 100% Sensitivity

	0 ng/ml Remifentanil	2 ng/ml Remifentanil	4 ng/ml Remifentanil
LOR_{verbal}			
AAI	19 (58%)	15 (5%)	26 (41%)
BIS	53 (58%)	61 (52%)	65 (55%)
CePROP	4.0 (39%)	3.5 (14%)	3.0 (23%)
LOR_{lash}			
AAI	23 (63%)	38 (59%)	27 (37%)
BIS	53 (46%)	68 (65%)	70 (53%)
CePROP	3.5 (63%)	3.0 (32%)	2.5 (53%)
$LOR_{noxious}$			
AAI	13 (14%)*	15 (7%)	26 (27%)
BIS	29 (7%)	57 (21%)	65 (27%)
CePROP	7.0 (7%)	3.5 (21%)	3.0 (13%)

* At the 98% sensitivity level.

AAI = A-Line ARX index; BIS = Bispectral Index; CePROP = calculated propofol effect-site concentration; LOR_{lash} = loss of eyelash reflex; $LOR_{noxious}$ = loss of response to electrical tetanic stimulus; LOR_{verbal} = loss of response to verbal command.

Table 7. Averaged OAA/S Score at LOR_{lash} and $LOR_{noxious}$

Group	OAA/S Level at LOR_{lash}	OAA/S Level at $LOR_{noxious}$
0 ng/ml Remifentanil	3.6	0.87
2 ng/ml Remifentanil	4.2	3.4
4 ng/ml Remifentanil	4.1	4.0

* Average of 15 patients.

LOR_{lash} = loss of eyelash reflex; $LOR_{noxious}$ = loss of response to electrical tetanic stimulus; OAA/S = Observer's Assessment of Alertness/Sedation scale.

OAA/S (from level 2 to 0) and eyelash reflex use tactile stimuli, which might have been lost earlier when adding remifentanil. To demonstrate this, the averaged OAA/S scores at LOR_{lash} and $LOR_{noxious}$ were calculated and are shown in table 7. LOR_{lash} results showed some increase. A clear increase in the OAA/S value is observed when remifentanil is added. In the 2 and 4 ng/ml remifentanil groups, several patients were still responsive at $LOR_{noxious}$. This resulted in larger transitions when the transition between the response and the unresponsive state, for example, from OAA/S 3 to OAA/S 0 without passing through OAA/S levels 2 or 1, causing an increase in averages. This finding obviously confirms that remifentanil blocks the response to pain, without causing LOR_{verbal} and LOR_{lash}, but proves also that it might be difficult to quantify the dependence of the electronic independent variables such as BIS and AAI to opiates because the definitive standard to which they were compared changed its behavior through the groups. This fact highlights that care should be taken when validating loss of response to different stimuli by using OAA/S score or eyelash reflex when opioids are administered. However, because no better validated clinical scoring techniques exist at this moment, we have to accept this possible bias.

Skepticism still exists in the literature regarding the accuracy of cerebrally derived parameters to measure anesthetic depth when adding opiates. Several articles suggested a weaker correlation between BIS and CePROP in the presence of opiates.[14,32,33] Although they state that this might reveal the importance of an analgesic component on the efficacy of depth-of-anesthesia electronic monitors, these studies did not apply specific statistical techniques such as prediction probability[25] or specificity/sensitivity calculations.[1] Also, one should clearly differentiate the phenomenon of the influence of opiates on the changes in cutoff values for LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$ and the overall change in accuracy of these anesthetic depth independent variables when adding opiates.

The prediction probability, P_K, provides a good alternative to investigate the overall relative performance of the different independent variables to measure the hypnotic component of anesthesia and loss of responsiveness to different stimuli.[25] For BIS, Lysakowski *et al.*[34] found no decrease in P_K when adding clinical dosages of fentanyl, alfentanil, remifentanil, or sufentanil *versus* placebo during propofol administration. Iselin-Chaves *et al.*[16] studied the influence of different dosages of alfentanil on the accuracy of both BIS and nonprocessed MLAEP during propofol administration and found no differences in P_K between groups. In their study, BIS performed better than MLAEP. In our study, as indicated in table 4, the performance results indicate that both BIS and AAI are reliable independent variables for assessing the level of OAA/S and LOR_{lash} and did not decrease by the addition of remifentanil. Before being able to conclude that the ability to measure the hypnotic component remained intact, a P_K analysis with the three groups pooled was needed. As seen in table 4, the P_K remained similar to the group-based P_K for both OAA/S and LOR_{lash}, indicating an overall equal accuracy of the independent variables with and without the addition of opiates.

At the level of significance used in our study, BIS and AAI were found to be comparable in performance to the estimated steady state propofol concentration, CePROP. When drug effect-site concentrations are known, one might argue that it only make sense to measure BIS or AAI if the combined information offers more accuracy in measuring depth of anesthesia than a single measure alone. *Vice versa*, it might be asked whether drug effect-site concentrations offer additional information for the clinician when BIS or AAI is used. However, it must be stated that electroencephalographic and MLAEP monitors can be attached to the patient at any random time, whereas calculation of drug effect-site concentration requires knowledge of the complete administration history. As none of the independent variables in the present study gave a P_K larger than 0.9, when pooling the data from the three groups into one, it could be interesting to explore whether a new independent variable defined as a composite of the electronic independent variables and the anesthetics concentrations would produce a larger P_K when predicting the OAA/S. Therefore, we calculated the P_K value for the combined information from both BIS + CePROP + CeREMI and AAI + CePROP + CeREMI using ordinal logistic regression to develop a predicted OAA/S score (see Appendix). For both combinations, the overall prediction probability for predicting the levels of OAA/S increased (or tended to increase) compared to the pooled P_K data.

Because the P_K concept was developed to generalize nonparametric receiver operating characteristic curves area to polytomous ordinal patient state,[26] we thought it was interesting to observe some specific sensitivity/specificity characteristics for BIS, AAI, and CePROP. Statistically speaking, the most frequently applied combined sensitivity/specificity lies at the elbow of the receiver operating characteristic curve, where the sum of both sensitivity and specificity is the highest.[28] However, as defined by J. Drummond[35] recently, a depth of anesthe-

sia–independent variable should have, at a minimum, a 100% sensitivity (no false negatives) if what the clinicians seek is a specific numeric threshold (cutoff value) that can be interpreted to mean "not aware." Therefore, we observed the influence of remifentanil on the cutoff value for LOR_{verbal} and LOR_{lash} and the corresponding sensitivity/specificity profiles for BIS, AAI, and CePROP at the two important points of the receiver operating characteristic curves: (1) highest sum of sensitivity and specificity and (2) level of 100% sensitivity. For both BIS and AAI, the cutoff values at LOR_{verbal} and LOR_{lash} revealing the highest sum of sensitivity/specificity clearly increased in a dose-dependent manner during remifentanil addition. However, the changes in the values of the highest sum were minimal and similar between the different anesthetic depth–independent variables, as observed in table 5. This means that the addition of remifentanil did not decrease the overall sensitivity/specificity profiles of the tested independent variables when observing the cutoff value at the level of maximum combined sensitivity and specificity. As shown in table 6, the cutoff values detecting LOR_{verbal} and LOR_{lash} at the 100% sensitivity level were influenced by the addition of remifentanil. For BIS, a trend toward higher cutoff values at the 100% sensitivity level was observed at LOR_{verbal} and LOR_{lash}. For AAI, the cutoff value only increased in the 4 ng/ml remifentanil group when observing LOR_{verbal} and slightly increased between the 0 and 2 ng/ml remifentanil groups, between the 0 and 4 ng/ml remifentanil groups, and when observing LOR_{lash}. The CePROP cutoff values decreased at this 100% sensitivity level when adding remifentanil. For all independent variables, the influence of remifentanil on the specificity at a level of 100% sensitivity was calculated. For the AAI, a clear decrease in specificity was observed in the 2 ng/ml remifentanil group when observing LOR_{verbal}, and a decrease between the 2 and 4 ng/ml remifentanil groups was seen when observing LOR_{lash}. This might be caused by the severity of the used statistical criterion, where one outlier might cause a dramatic decrease in specificity at the 100% sensitivity level. No decrease in specificity was observed between groups for BIS when observing LOR_{verbal} and LOR_{lash}. Inconsistencies are found in the data for CePROP when comparing the specificity results obtained by LOR_{verbal} with these obtained by using LOR_{lash}. Better sensitivity/specificity profiles were obtained when the information from drug concentrations and BIS or AAI were used together.

This study also tested the influence of opiates on the performance of the independent variables to predict $LOR_{noxious}$. The supramaximal tetanic stimulus used in this study was previously used by others as a substitute for conventional forms of stimulation in humans.[36] In previous work, when only using propofol without opiates, we observed that measures from the cerebral cortex such as BIS and AAI were poor predictors for $LOR_{noxious}$.[8] The overall accuracy for $LOR_{noxious}$ tended to be lower for all independent variables compared with their hypnotic prediction accuracy. The P_K values were lower, however, because of the larger SE, not statistically significant at the level of significance used in our study. Sensitivity/specificity profiles for all independent variables in the three groups were calculated at the two classic points. As seen in table 5, the values of the highest sum of sensitivity and specificity to $LOR_{noxious}$ were lower compared with the values for the detection of LOR_{verbal} and LOR_{lash}. Also, the cutoff values at the point of highest sensitivity/specificity were clearly influenced by the addition of remifentanil in a dose-dependent manner. At the level of 100% sensitivity to detect $LOR_{noxious}$, a very low specificity and a clear influence of remifentanil on the cutoff values was observed (table 6).

A strong interaction between propofol and remifentanil is observed at the ED_{50} and ED_{95} levels when studying the analgesic component of this interaction at $LOR_{noxious}$, as plotted in figure 5 and table 3. This interaction is more pronounced than the hypnotic interaction between remifentanil and propofol, resulting in the fact that in this "staircase study," patients in the 2 and 4 ng/ml remifentanil groups might reach $LOR_{noxious}$ before reaching LOR_{verbal} and LOR_{lash}, as shown in table 7. Similar findings were observed for fentanyl and propofol by Smith *et al.*[37] and by Katoh *et al.*[38] for fentanyl and sevoflurane.

In conclusion, we found that although BIS, AAI, and CePROP were increased by remifentanil during propofol administration, their ability to detect OAA/S and LOR_{lash} remained accurate. Improved performance is obtained when BIS and AAI are measured in conjunction with drug effect-site concentrations. Remifentanil decreases the ability of these independent variables to detect $LOR_{noxious}$.

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Appendix: Definition of an OAA/S Predictor Based on Combinations of AAI/BIS, Propofol, and Remifentanil Effect Concentrations

Methods

Two composite indexes were defined to study whether the combined information BIS + CePROP + CeREMI or AAI + CePROP + CeREMI offers more accuracy in loss of response to hypnotic stimuli than a single measure alone (BIS, AAI, CeREMI, and CePROP). The composite index was defined as an OAA/S predictor based on combined information from the data set BIS + CePROP + CeREMI or AAI + CePROP + CeREMI. The method of choice for designing a composite index was the ordinal logistic regression. The ordinal logistic regression has the advantage, as compared with multiple linear regression, that the output variable is ordinal. An ordinal variable is a categorical variable that has three or more levels of natural ordering, such as awake, drowsy, asleep, and deep asleep. This is suitable for the kind of data from this study because the OAA/S scale is ordinal and not linear. Two models were proposed: model A, where the input variables are BIS, CePROP, and CeREMI; and model B, where the input variables are AAI, CePROP, and CeREMI. The composite index is the output variable that in both models is a prediction of the OAA/S as shown in figures 6 and 7. The composite index is therefore ordinal in the 0–5 range as the OAA/S.

An ordinal logistic regression model was calculated by using SPSS software (SPSS Inc., Chicago, IL), which also provides a more detailed description of the method. The model is composed of constants, θ_i, factors, β_n, and a link function, here the "logit." The constants are associated with the ith event, which in the current study refers to the level of OAA/S.

The factors are obtained from each covariable (input), which here are BIS, AAI, CePROP, and CeREMI at every jth sample in time. Hence, the two models are defined in equations 1 and 2

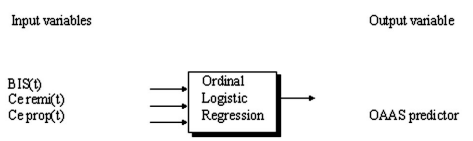

Fig. 6. Model A for calculating the Observer's Assessment of Alertness/Sedation Scale (OAA/S) predictor from the combined information Bispectral Index (BIS) + propofol effect-site concentration (CePROP) + remifentanil effect-site concentration (CeREMI).

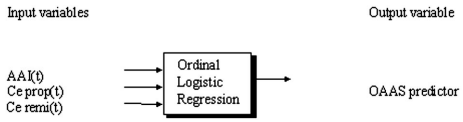

Fig. 7. Model B for calculating the Observer's Assessment of Alertness/Sedation Scale (OAA/S) predictor from the combined information A-Line ARX index (AAI) + propofol effect-site concentration (CePROP) + remifentanil effect-site concentration (CeREMI).

$$g(\text{OAAS ij}) = \theta i + \beta_{remi}\text{Ce Remi}_i + \beta_{Ceprop}\text{Ceprop}_j + \beta_{bis}\text{BIS}_j \quad (1)$$

$$g(\text{OAAS ij}) = \theta i + \beta_{remi}\text{Ce Remi}_j + \beta_{Ceprop}\text{Ceprop}_j + \beta_{AAI}\text{AAI}_j. \quad (2)$$

The accumulated probability of being at or lower than the ith level of OAA/S at the jth sample in time, γ_{ij}, is now calculated as

$$\gamma_{ij} = \frac{e^{g(\text{OAASij})}}{1+e^{g(\text{OAASij})}} \quad (3)$$

Example: The following state has been recorded: remifentanil = 0 ng/ml, propofol = 4 μg/ml, AAI = 25. When using these data as input to model B, the corresponding probabilities for OAA/S 0, 1, 2, 3, 4, and 5 are 0.7944, 0.8867, 0.9620, 0.9935, 0.9998, and 1. The model output is always the OAA/S level, where the accumulated probability exceeds 0.67. In this example, the predicted OAA/S is 0 because the first probability (0.7944) is larger than 0.67.

Table 8. Ordinal Logistic Regression of Model A (BIS)

Predictor	Value	SD	Z	*P*
θ_1	−3.718	1.851	−2.01	0.045
θ_2	−2.995	1.850	−1.62	0.105
θ_3	−1.832	1.853	−0.99	0.323
θ_4	−0.109	1.868	−0.06	0.954
θ_5	3.228	1.896	1.70	0.089
βremi	0.9548	0.1163	8.21	0.000
βprop	2.6277	0.3395	7.74	0.000
βbis	−0.10034	0.01779	−5.64	0.000

Test that all slopes are zero: *P* value < 0.001.

θ_{1-5} = constants of the ordinal logistic regression model used in the prediction of the OAA/S levels 1 to 5; βremi = coefficient of the ordinal logistic regression model multiplied with the remifentanil (remi) effect-site concentration in the prediction equation; βprop = coefficient of the ordinal logistic regression model multiplied with the propofol (prop) effect-site concentration in the prediction equation; βbis = coefficient of the ordinal logistic regression model multiplied with the BIS in the prediction equation; SD = standard deviation.

Table 9. Ordinal Logistic Regression of Model B (AAI)

Predictor	Value	SD	Z	*P*
θ_1	−9.265	1.117	−8.29	0.000
θ_2	−8.559	1.094	−7.83	0.000
θ_3	−7.386	1.057	−6.99	0.000
θ_4	−5.583	1.009	−5.53	0.000
θ_5	−1.9793	0.9563	−2.07	0.038
βremi	1.0143	0.1194	8.50	0.000
βprop	3.0479	0.3091	9.86	0.000
βAAI	−0.064	0.0097	−6.61	0.000

Test that all slopes are zero: *P* value < 0.001.

θ_{1-5} = constants of the ordinal logistic regression model used in the prediction of the OAA/S levels 1 to 5; βremi = coefficient of the ordinal logistic regression model multiplied with the remifentanil (remi) effect-site concentration in the prediction equation; βprop = coefficient of the ordinal logistic regression model multiplied with the propofol (prop) effect-site concentration in the predication equation; βAAI = coefficient of the ordinal logistic regression model multiplied with the AAI in the prediction equation; SD = standard deviation.

Results

Tables 8 and 9 show the parameters of the ordinal logistic regression for models A and B, with the corresponding levels of significance for each constant and factor as well as the *P* value for the whole model. A *P* value less than 0.05 means that the parameter is significant in the model. Both models were statistically significant. The OAA/S values predicted by the two models were compared with the measured OAA/S and evaluated using the P_K analysis, shown in table 10.

Table 10. Prediction Probability (P_K of the Indices

Model	P_K (SE)
Model A (BIS + CePROP + CeREMI)	0.91 (0.01)
Model B (AAI + CePROP + CeREMI)	0.93 (0.01)

AAI = A-Line ARX index; BIS = Bispectral Index; CePROP = calculated propofol effect-site concentration; CeREMI = calculated remifentanil effect-site concentration.

3.2 Study 2: Spectral entropy as an electroencephalographic measure of anesthetic drug effect. A comparison with bispectral index and processed mid-latency auditory evoked response

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3.2.1 Introduction

The clinical validation reveals much practical information on the performance of AAI and BIS. The prediction probability calculations in study 1 suggest that AAI,BIS and Ce_{PROP} are equally adequate to describe the studied clinical endpoints of anesthesia. However, the methodology of our first study did not allow to depict more subtle differences between both cortical (EEG) and subcortical (MLAEP) derived indices. One could question if MLAEP derived information adds anything supplemental to the indices derived from spontaneous EEG (e.g. BIS, or the more recently commercialized "State Entropy" (SE) and "Response Entropy" (RE)). It would be very odd that two surrogate indices of hypnotic drug effect, using entirely different neurophysiologic principles, perform similarly over a wide range of drug effects. Some studies describe a better correlation of MLAEP derived indices with loss and return of consciousness, compared to BIS.(1,2) In contrast, BIS would have a better correlation with the hypnotic drug concentration.(2-4) As such we had to find a more adequate model for comparing subtle differences between monitors.

We chose to use a continuously available, pharmacologic endpoint as the dependent parameter: the predicted effect-site concentration of propofol (Ce_{PROP}). In this study, we calculated the corresponding Ce_{PROP} simultaneously with a constant infusion of propofol 1% at 300ml/h. AAI, BIS, RE and SE were tested in their ability to detect the gradual transition from "fully awake" towards "maximal suppressed EEG". For the first time, our study introduced a specific scientific setting as a benchmark for comparing monitors of the hypnotic component of anesthesia. More protocols have been performed in this thesis using the same methodology. But more importantly, other research centers have reproduced this methodology for validating monitors of the hypnotic component of anesthesia.(5)

This study includes advanced statistical methods for comparing monitor performance. The "baseline variability" depicts the variation in measurements found in the awake patient. Baseline variability should be as low as possible.(6) The very deep levels of anesthesia are depicted by the correlation between the respective indices and the percentage of burstsuppression patterns as measured by every device. The "all round" performance is depicted by P_K analysis. We also introduced the individualized Spearmann rank correlation, as an alternative approach for P_K as it depicts the non-linearities in the dataset better. Finally, we estimated models of the relationship between every measurement and Ce_{PROP} using non linear mixed effect modeling (NONMEM).(cf. "statistical methods" section in the manuscript and chapter 2)

With these methods, we found some important weaknesses for AAI in comparison with BIS, RE and SE. The P_K values and Individualized Spearmann Rank Correlations were all within acceptable range, indicating high "all round performance". All indices also correlated acceptably with Ce_{PROP} as described by a sigmoidal E_{max} relationship using NONMEM. But for AAI, baseline variability was excessively high, and AAI is not able to discriminate between very deep levels of anesthesia. Conclusion of our study: AAI has a problem at the two extremes of the depth of the anesthesia spectrum.

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3.2.2 Manuscript

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Spectral Entropy as an Electroencephalographic Measure of Anesthetic Drug Effect

A Comparison with Bispectral Index and Processed Midlatency Auditory Evoked Response

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Background: **The authors compared the behavior of two calculations of electroencephalographic spectral entropy, state entropy (SE) and response entropy (RE), with the A-Line® ARX Index (AAI) and the Bispectral Index (BIS) and as measures of anesthetic drug effect. They compared the measures for baseline variability, burst suppression, and prediction probability. They also developed pharmacodynamic models relating SE, RE, AAI, and BIS to the calculated propofol effect-site concentration (Ce_{prop}).**

Methods: **With institutional review board approval, the authors studied 10 patients. All patients received 50 mg/min propofol until either burst suppression greater than 80% or mean arterial pressure less than 50 mmHg was observed. SE, RE, AAI, and BIS were continuously recorded. Ce_{prop} was calculated from the propofol infusion profile. Baseline variability, prediction of burst suppression, prediction probability, and Spearman rank correlation were calculated for SE, RE, AAI, and BIS. The relations between Ce_{prop} and the electroencephalographic measures of drug effect were estimated using nonlinear mixed effect modeling.**

Results: **Baseline variability was lowest when using SE and RE. Burst suppression was most accurately detected by spectral entropy. Prediction probability and individualized Spearman rank correlation were highest for BIS and lowest for SE. Nonlinear mixed effect modeling generated reasonable models relating all four measures to Ce_{prop}.**

Conclusions: **Compared with BIS and AAI, both SE and RE seem to be useful electroencephalographic measures of anesthetic drug effect, with low baseline variability and accurate burst suppression prediction. The ability of the measures to predict Ce_{prop} was best for BIS.**

THE regularity of the background electroencephalogram alters with changing levels of consciousness. Recently, different entropy concepts have been applied to describe the "amount of order" in the electroencephalogram.[1–3] One of these, Shannon entropy, has been shown to be a useful measure of anesthetic drug effect.[3] Shannon entropy measures the predictability of future amplitude values of the electroencephalogram based on the probability distribution of amplitude values already observed in the signal. Unfortunately, Shannon entropy as described is not normalized to the total power of the electroencephalogram. Therefore, its absolute value may vary between individuals because of interindividual differences in signal strength, precluding routine clinical use. To overcome these shortcomings, spectral entropy has been developed. The spectral entropy is obtained by applying the Shannon entropy concept to the power distribution of the Fourier-transformed signal, which has been normalized to unit power. Spectral entropy permits separation of the contributions from different frequency ranges. For example, using spectral entropy, one can separate the high-frequency contribution (> 32 Hz, which is likely electromyographic) from the low-frequency contribution (< 32 Hz, which is likely encephalographic). The detailed spectral entropy algorithm is published elsewhere.[4] Recently, this technology has become commercially availably (M-ENTROPY module; Datex-Ohmeda, Helsinki, Finland). In this device, two spectral entropy indicators are considered, state entropy (SE), calculated over the frequency range (0.8–32 Hz) that is likely dominated by the encephalogram, and response entropy (RE), calculated over the frequency range (0.8–47 Hz) that includes both the electroencephalogram and electromyogram. Sudden appearance of the electromyographic signal data often indicates that the patient is responding to some external stimulus, such as a painful stimulus, *i.e.*, nociception, due to some surgical event.[5,6] Such a response may result in arousal if the level of analgesia is insufficient. In theory, in the nonparalyzed patient's electromyogram can provide a rapid indication of impending arousal.

Processed analysis of the electroencephalogram or midlatency auditory evoked potential (MLAEP) is increasingly applied as a surrogate endpoint for quantification of anesthetic drug effect. Because of the difficulties of analyzing raw waveforms for both electroencephalogram and MLAEP during anesthesia, extraction and presentation of this information necessitates computational analysis of the raw signal. The A-Line® ARX Index (AAI)

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is derived from the MLAEP and has been validated as a measure of anesthetic drug effect during propofol administration.[7]

The most widely adopted electroencephalographic measure of anesthetic drug effect is the Bispectral Index (BIS). The BIS has been extensively studied and validated over the past 10 yr as a measure of anesthetic drug effect.[7]

We evaluated the four electroencephalographic measures of drug effect for stability at baseline (minimal variability in the absence of drug between individuals[8]), accurate detection of burst suppression,[9] prediction probability,[10,11] and correlation with the propofol effect-site concentration. We also developed pharmacodynamic models relating the predicted effect-site propofol concentration to each measure of drug effect.

Materials and Methods

After institutional ethics committee approval (Ghent University Hospital, Gent, Belgium), written informed consent was obtained from 10 patients with American Society of Anesthesiologists physical status I who were aged 18–45 yr and scheduled to undergo ambulatory gynecologic or urologic surgery. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight, neurologic disorder, and recent use of psychoactive medication, including alcohol.

All patients received a continuous infusion of propofol at 50 mg/min (Diprivan 1%; AstraZeneca, London, United Kingdom) using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France). To ensure synchronized data recording, all monitor and infusion data were continuously captured by the computer running RUGLOOP II** *via* multiple RS 232 interfaces. By tracking the infused propofol volume continuously, RUGLOOP II calculated the corresponding effect-site concentration using the three-compartment model enlarged with an effect compartment previously published by Schnider *et al.*[12,13] The calculated effect-site propofol concentration (Ce_{prop}) was computed to yield a time-to-peak effect of 1.6 min after bolus injection,[14] as also published by Schnider *et al.*[12,13] and clinically confirmed by Struys *et al.*[15] Propofol was infused *via* a large left forearm vein. Every patient received approximately 100 ml crystalloid fluid during the study period. No fluid load was given before induction. No patient received preanesthetic medication. No other drugs were given. All patients maintained spontaneous ventilation *via* a facemask delivering 100% O_2. Before starting the drug administration, all patients were asked to close their eyes and relax for 2 min. Thereafter, baseline measures were taken. The operating room was kept silent to avoid noise-related stimulation and artifact.

The propofol infusion was continued until a burst suppression level of 80% or higher was achieved on the BIS® monitor (Aspect Medical Systems, Inc., Newton, MA) or the mean arterial blood pressure decreased below 50 mmHg.

Heart rate, noninvasive blood pressure, oxygen saturation measured by pulse oximetry (Spo_2), and capnography were recorded at 1-min intervals using an S-5 monitor; Datex-Ohmeda). All data were recorded continuously on one computer using RUGLOOP software *via* multiple RS-232 connections. Averaging of the data was performed using 10-s intervals.

Electroencephalographic and MLAEP Data Collection

The SE and RE were calculated using the M-ENTROPY module. The SE value ranges from 91 to 0, and the RE value ranges from 100 to 0. Both entropy values were derived from the frontal electroencephalogram and electromyogram using three electrodes. SE is computed over the frequency range from 0.8 to 32 Hz. It includes the electroencephalogram-dominant part of the spectrum. The time windows for SE are chosen optimally for each particular frequency component and range from 60 s to 15 s. RE is computed over a frequency range from 0.8 to 47 Hz. It includes both the electroencephalogram-dominant and the electromyogram-dominant parts of the spectrum. The time windows for RE are chosen optimally for each frequency, with the longest time window equal to 15.36 s and the shortest time window, applied for frequencies between 32 and 47 Hz, equal to 1.92 s. The RE equals the SE when no electromyographic activity is detected. The description of the full algorithm is described elsewhere.[4]

The AAI (version 1.5) from the MLAEP was calculated using the A-Line® monitor (Danmeter A/S, Odense, Denmark). The AAI value ranges from 100 to 0. The MLAEPs were elicited with a bilateral click stimulus of 70-dB intensity and 2-ms duration. Three electrodes (A-Line® AEP electrodes; Danmeter A/S) were positioned at mid forehead (+), left forehead (reference), and left mastoid (−). The extraction of the MLAEP using a short moving–time average technique together with an ARX model and the calculations of the AAI have been described previously.[16]

The BIS (BIS® version 4.0, XP) was derived from the frontal electroencephalogram and calculated by the A-2000 BIS® monitor using the 4 BIS®-Sensor electrodes (Aspect Medical Systems). The BIS value ranges from 100 to 0. The smoothening time of the BIS® monitor was set at 15 s.

All electroencephalographic data were gathered by computer concurrently with the hemodynamic data and drug infusion information.

** De Smet T, Struys M: RUGLOOP program. Available at: http://www.anesthesia-uzgent.be. Accessed February 25, 2004.

Performance Measures

Baseline Variability. Baseline variability is calculated by computing the coefficient of variation (CV) on the electroencephalographic data points obtained during the first 5 s of the protocol, before any drug has been delivered.

Burst Suppression. The burst suppression ratio (BSR) of the electroencephalogram is measured by all three monitors. For the M-ENTROPY module, burst suppression calculation starts by subtracting a local average from each signal sample to eliminate baseline fluctuations. The signal is then divided into two frequency bands by elliptic filters. Cutoff frequencies of the low-pass and high-pass filters are 20 and 75 Hz, respectively. The low-frequency band is used to detect the burst suppression pattern, and the high-frequency band is used to detect artifacts. An energy operator is applied to estimate signal power in both bands in each 0.05-s epoch. Suppression is detected if the estimated signal power is below a fixed threshold at least for 0.5 s and there is no artifact. The BSR is the percentage of 0.05-s epochs in the past 60 s that were considered suppressed. More detailed information on the burst suppression calculation used in the entropy module is described elsewhere.[17]

For the A-Line® monitor, the raw signal is passed though a preprocessing process to reject artifacts. It then passes through a low-pass filter with a cutoff frequency of 32 Hz, yielding the electroencephalogram signal. The filtered signal then is divided in segments of 500 ms, where the mean value is removed to filter out low frequencies. If a segment has a determined percentage of samples with amplitudes less than 3.4 μV, it is considered as a segment with suppression. The burst suppression is considered as the percentage of segments with suppression during 20 s.

For the BIS® monitor, after preprocessing for artifact detection/correction, the log power of 1-s electroencephalogram epochs in two frequency bands (2–30 and 31–40 Hz) is calculated, and suppression is declared if a weighted sum of these bands is less than a threshold. Hereby, the threshold is adaptive (within a narrow range) based on the statistics of the electroencephalogram. The suppression detection algorithm processes the electroencephalogram in overlapping 1-s epochs offset every 0.5 s. A given 0.5 s of electroencephalogram is determined to be suppressed if suppression was detected for either of the 2 overlapping 1-s epochs that contained it. The suppression ratio is the percentage of 0.5-s epochs in the past 63 s that were considered suppressed.

The relation between the burst suppression and its related electroencephalographic measure (SE, RE, AAI, and BIS) was plotted. For each electroencephalographic measure, a model was fitted to the data using the curve estimation function from SPSS version 12 (SPSS Inc., Chicago, IL). The curve estimation procedure produces curve estimation regression statistics and related plots for different curve estimation regression models, including linear, logarithmic, inverse, quadratic, cubic, power, compound, S-curve, logistic, growth, and exponential. A separate model is produced for each dependent variable together with its regression coefficients, predicted values, residuals, and prediction intervals. After this, the most appropriate regression model can be selected.

Prediction Probability. For each electroencephalographic measure of anesthetic drug effect, we calculated the prediction probability (P_K) developed by Smith *et al.*[10,11] P_K was calculated as the Somers d statistic using SPSS version 12, with the electroencephalographic measure set as the independent variable and the Ce_{prop} as the dependent variable. (We recognize that this is physiologically backward in that the propofol effect-site concentration drives the electroencephalographic response. However, for the purpose of this analysis, the question is how well the observed measure, which is the electroencephalographic response, predicts the unobserved "underlying" state of the patient, which is the Ce_{prop}). The Somers d statistic was then rescaled from the -1 to $+1$ range of the Somers d statistic to the 0 to 1 range of P_K, $P_K = 1 - (1 - |\text{Somers d}|)/2$. Then, a P_K of 1 for the electroencephalographic measure means that this measure always decreases (increases) as the patient reaches higher (lower) drug concentrations according to the effect-site propofol concentration. Alternatively, a P_K value of 0.5 means that the measure is useless for predicting anesthetic drug effect. Individual values were calculated for each measure, and the average, minimum, and maximum P_K values were then tabulated for each electroencephalographic measure of anesthetic drug effect.

Individualized Spearman Rank Correlation. In addition, a nonparametric alternative was investigated. The Spearman rank correlations between Ce_{prop} and SE, RE, AAI, and BIS were individualized in the sense that they were first computed for each patient i separately, say R_i. The reported Spearman rank correlation, R, is a weighted average of the R_i (weighted according to the number of observations for each patient). In this way, R retained its usual interpretation. The confidence intervals on R were obtained by the bootstrap method[18] in which the hierarchical nature of the data was incorporated by resampling within patient. Equality of two correlation coefficients was tested at the 5% level of significance by constructing the 95% confidence intervals of the difference (confidence intervals were also computed with the bootstrap technique). All bootstrap calculations were based on 10,000 simulation runs.

Pharmacodynamic Modeling

The relation between propofol effect-site concentration and the electroencephalographic measures of anes-

thetic drug effect was analyzed using a sigmoid E_{max} model:

$$\text{Effect} = E_0 + (E_{max} - E_0)\frac{Ce^{\gamma}}{Ce_{50}^{\gamma} + Ce^{\gamma}},$$

where Effect is the electroencephalographic effect being measured (SE, RE, AAI, BIS), E_0 is the baseline measurement when no drug is present, E_{max} is the maximum possible drug effect, C_e is the calculated effect-site concentration of propofol, Ce_{50} is the effect-site concentration associated with 50% maximal drug effect, and γ is the steepness of the concentration-*versus*-response relation. The model parameters were estimated using NONMEM V (GloboMax LLC, Hanover, MD). Interindividual variability was modeled using a log-normal distribution:

$$P_i = P_{TV}e^{-\eta_i},$$

where P_i is the parameter value (E_0, E_{max}, γ, or Ce_{50}) in the ith patient, P_{TV} is the typical value of the parameter in the population, and η is a random variable with a mean of 0 and a variance of ω^2. Individual variability is reported as ω, the SD of η in the log domain, which is approximately the CV in the standard domain. Residual intraindividual variability was modeled using a standard additive error model. Parameters were evaluated by comparing the log-likelihood values (the NONMEM objective function), with improvement of 3.84 in −2LL with the addition of a single parameter considered statistically significant.[19]

Results

The population characteristics were as follows: weight, 62.0 ± 3.8 kg; age, 37.7 ± 16.2 yr; height, 165 ± 6.5 cm; sex, 8 men/2 women. All measured data were included in the analysis. Figures 1 and 2 show the raw data over time for the four electroencephalographic measures of drug effect (SE, RE, AAI, and BIS) and Ce_{prop}. (In fig. 2, the disruption in the continuous increasing Ce_{prop} is due to the inevitable change of the 1% propofol syringe around 600 s.)

Performance Measures

The baseline variability before administration of propofol is shown in table 1. The smallest variability in baseline values as defined by the CV was found for both spectral entropy measures (SE and RE), followed by BIS. AAI had the largest baseline variability.

The correlation between the burst suppression calculation and its related electroencephalographic measures of anesthetic drug effect is observed in figures 3 and 4. As seen in figure 3, for both spectral entropy indicators, a monotonic nonlinear decrease in entropy (quadratic polygonal curve, goodness-of-fit R^2 for SE = 0.72 and for RE = 0.71) was observed with increased levels of burst suppression. Spearman rank correlation coefficients

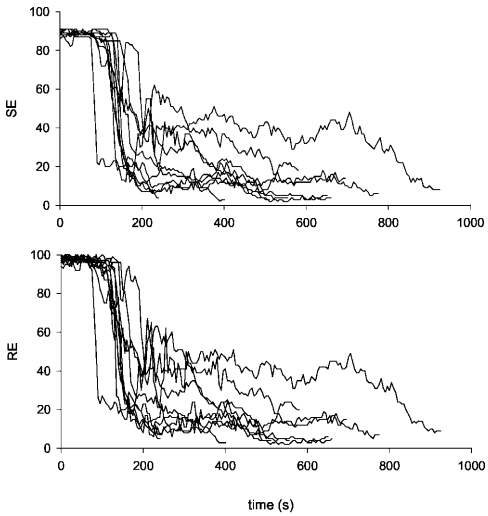

Fig. 1. Individual raw data for state (SE) and response entropy (RE) *versus* time.

were −0.62 and −0.63 for SE and RE, respectively. Figure 4 shows the behavior of the AAI and BIS with increasing levels of BSR. For AAI, no correlation between AAI and the AAI burst suppression could be obtained. For BIS, no accurate correlation could be obtained between BIS and the BSR when all data were included. At a BSR greater than 40, a linear correlation was found.

The P_K values for SE, RE, AAI, and BIS are shown in table 2. The individualized Spearman rank correlations between Ce_{prop} and SE, RE, BIS, and AAI are shown in table 2.

Pharmacodynamic Modeling

Figure 5 shows the behavior of SE and RE *versus* Ce_{prop} for all patients. With increasing Ce_{prop}, both SE and RE decreased monotonically. Similar findings were observed for both AAI and BIS, as seen in figure 6. For the spectral entropy, the difference between RE and SE decreased nonlinearly toward 0 with increasing Ce_{prop} (fig. 7).

The relations of Ce_{prop} to SE and RE are plotted in figure 8. The relations of Ce_{prop} to BIS and AAI are shown in figure 9. The parameter values for each population model including the CV (as a measure of interindividual variability in the standard domain) are found in table 3. The SD for each model (as a measure of the intraindividual variability in the log domain) was 7.1 for SE, 6.8 for RE, 4.8 for AAI, and 4.5 for BIS.

Discussion

In this study, we compared two measures of spectral entropy, SE and RE, with BIS and AAI as a measures of

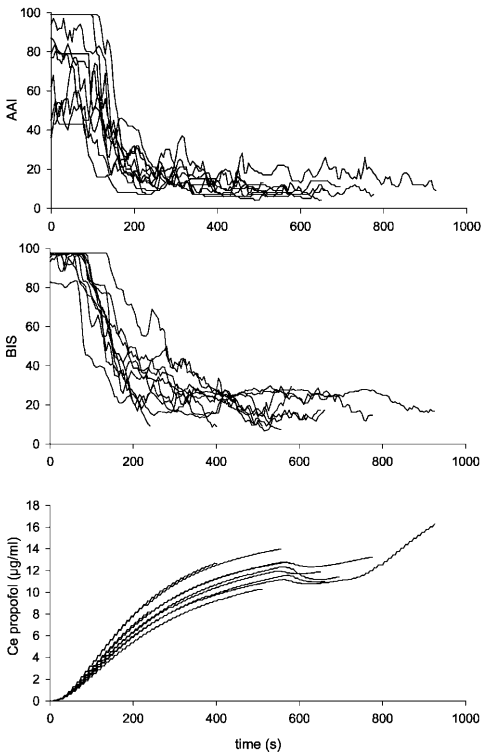

Fig. 2. Individual raw data for Bispectral Index (BIS) and A-Line® ARX Index (AAI) and propofol effect-site concentration (Ce propofol) *versus* time. (The disruption in the continuous increasing Ce propofol is due to the inevitable change of the 1% propofol syringe around 600 s.)

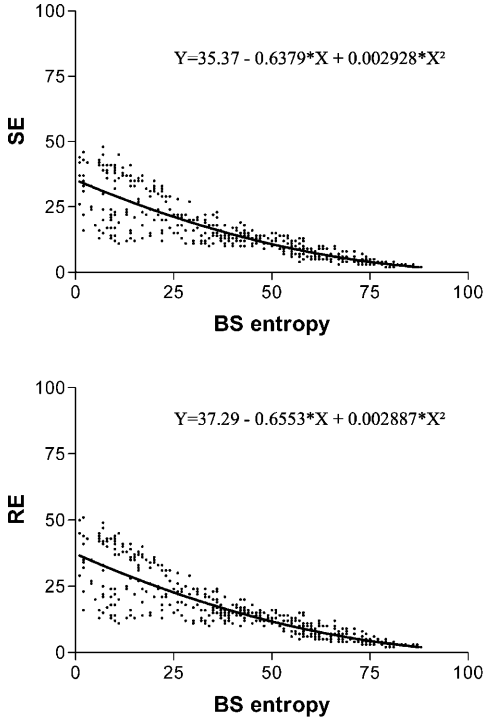

Fig. 3. Behavior of state (SE) (*A*) and response entropy (RE) (*B*) *versus* the burst suppression (BS) ratio as measured by the entropy module for all individual patients (*dots*) and its regression line (*bold line*).

anesthetic drug effect during increasing Ce_{prop}. Also, the stability at baseline and the correlation of burst suppression and its related measures of anesthetic drug effect on the electroencephalogram were tested for the three devices.

Baseline stability was calculated for all measures as seen in table 1. Baseline stability and baseline variation can profoundly affect electroencephalographic-based pharmacodynamic parameter estimation and the usefulness of the processed electroencephalogram or MLAEP as a measure of the arousal state of the central nervous system (depth of anesthesia).[8] Therefore, variation and stability at baseline were measured within our study population by calculating a CV on the data before administering any drug in stable conditions. Both spectral entropy measures showed the highest baseline stability among patients followed by BIS. High levels of baseline variation were found for the AAI. Baseline variation might decrease the predictive ability of the univariate parameter, as stated by Bruhn *et al.*[8]

Table 1. Baseline Stability Defined as the Coefficient of Variation of All Measures

	SE	RE	AAI	BIS
Mean ± SD	89.2 ± 1.4	97.5 ± 1.9	73.0 ± 23.1	95.6 ± 4.6
Coefficient of variation	1.610	1.955	31.697	4.801

AAI = A-Line® ARX Index; BIS = Bispectral Index; RE = response entropy of the spectral entropy; SE = state entropy of the spectral entropy.

Burst suppression represents a benign pattern frequently seen in healthy brain at deep levels of the hypnotic component of anesthesia. It can be identified in the raw electroencephalogram and is composed of episodes of electrical quiescence (the suppression) alternated with high-frequency, high-amplitude electrical activity (the bursts). Increasing anesthetic drug concentration causes increased duration of the suppression periods. Burst suppression patterns of the electroencephalogram are classically quantified as BSR defined as the percentage duration of suppression/duration of the epoch.[8,20,21]

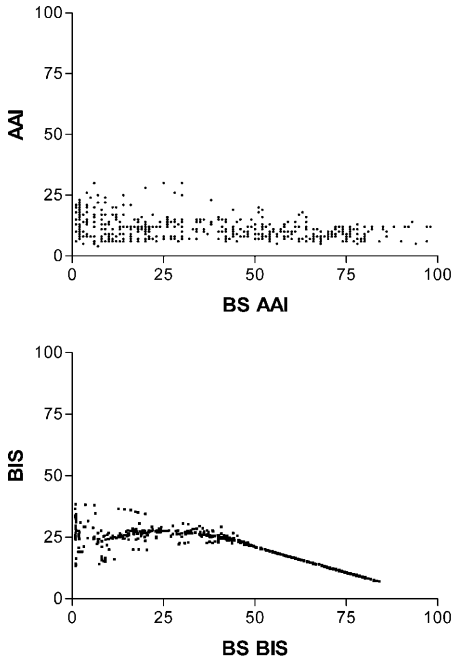

Fig. 4. Behavior of Bispectral Index (BIS) (*A*) and A-Line® ARX Index (AAI) (*B*) *versus* the burst suppression (BS) ratio as measured by the BIS® or AAI monitor (*A* and *B*, respectively) for all individual patients (*dots*).

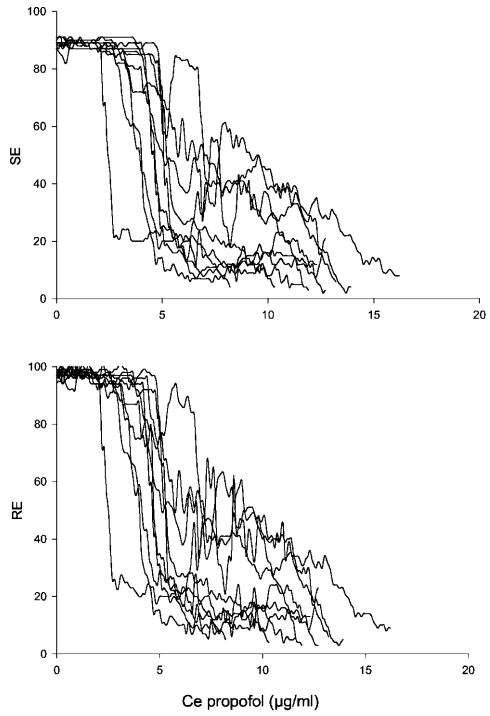

Fig. 5. Individual raw data for state (SE) and response entropy (RE) *versus* propofol effect-site concentration (Ce propofol).

Because the detection of burst suppression represents an important electroencephalographic component to measure deep levels of anesthesia, its correlation to its univariate parameter is important and must be investigated. Figure 3 shows the correlation between SE and RE and its BSR. As the suppression part of the burst suppression is classified as highly regular, the spectral entropy algorithm correctly classifies increasing burst suppression as increasing anesthetic drug effect. As a result, a clear correlation between BSR and SE or RE was found. For MLAEP, it has been published previously that MLAEP lacks accuracy in detecting deepening of the hypnotic–anesthetic level because of a flat MLAEP signal after loss of consciousness.[16] Because AAI is derived from the MLAEP, no BSR was calculated on the original evoked potential signal. As a result, no correlation between AAI and BSR was found. It might be argued that the detection of electroencephalographic burst suppression beside the MLAEP-derived AAI might solve the problem of lack of accuracy at deep levels of anesthesia, which might be revealed in further studies. For BIS, the onset of burst suppression was not correctly detected by BIS as long as BSR was less than 40%, although burst suppression is a part of the BIS® algorithm. Above a BSR of 40, a linear correlation was found between BIS and BSR, as seen in

Table 2. Spearman Rank Correlation Coefficients and Prediction Probability for Each Electroencephalographic Measure of Anesthetic Drug Effect *vs.* Propofol Effect-site Concentration

	SE	RE	AAI	BIS
P_K, median (minimum–maximum)	0.86 (0.60–0.96)	0.89 (0.67–0.96)	0.87 (0.81–0.99)	0.91 (0.72–0.94)
Individualized Spearman rank correlation, mean ± SD (95% CI)	−0.841 ± 0.014 (−0.864, −0.808)*	−0.860 ± 0.013 (−0.882, −0.831)	−0.869 ± 0.010 (−0.883, −0.844)	−0.891 ± 0.011 (−0.907, −0.865)

* $P < 0.05$ between Bispectral Index (BIS) and other measures.

AAI = A-Line® ARX Index; CI = confidence interval; P_K = prediction probability; RE = response entropy of the spectral entropy; SE = state entropy of the spectral entropy.

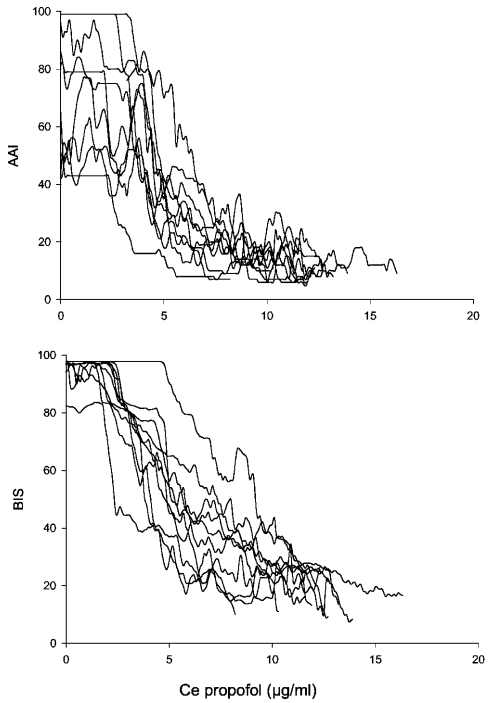

Fig. 6. Individual raw data for Bispectral Index (BIS) and A-Line® ARX Index (AAI) *versus* propofol effect-site concentration (Ce propofol).

figure 8. Others have also found that onset of propofol-induced burst suppression may be correctly detected as deepening of anesthesia by approximate entropy, another form of entropy calculation, but not by BIS.[22] The

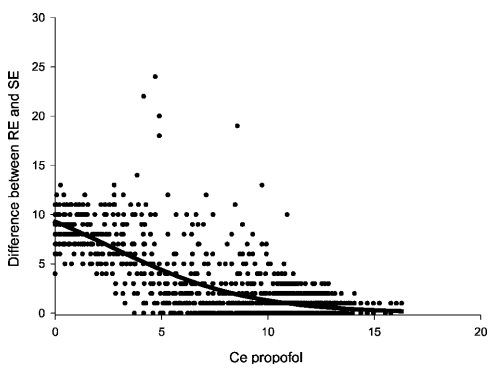

Fig. 7. Difference between response (RE) and state entropy (SE) *versus* the propofol effect-site concentration (Ce propofol) and its regression analysis.

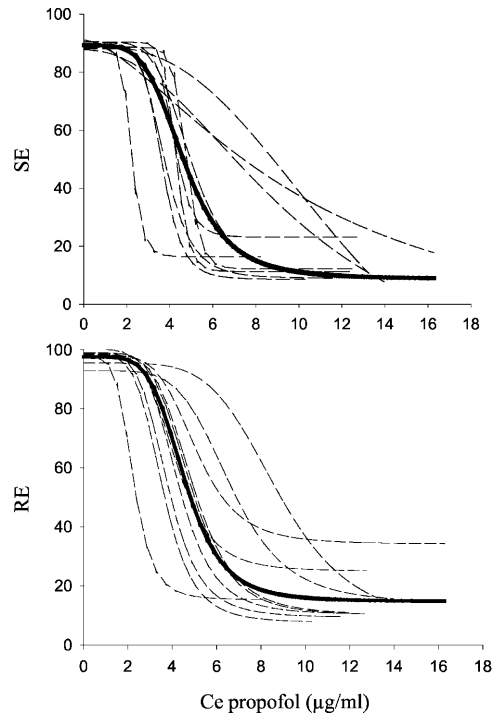

Fig. 8. The relation between propofol effect-site concentration and the state (SE) and response entropy (RE) modeled using nonlinear mixed effect modeling. The individual patients are represented as *dotted lines*, and the typical population curve is plotted as a *straight line*.

same authors found also that BSR is the only determinant for BIS values below 30.[21]

When studying performance accuracy, the question is how well the observed measure, which is the electroencephalographic response, predicts the unobserved "underlying" state of the patient, which is represented by the propofol effect-site concentration. Therefore, P_K was calculated for SE, RE, AAI, and BIS. P_K, a rescaled variant of the $d_{y,x}$ measure of association of Kim, generalizes nonparametric receiver operating characteristics curve area to a polytomous ordinal patient state. It shows the correlation between the value of the electroencephalographic measure of anesthetic drug effect and the calculated effect-site concentration of propofol, taking into account both desired performance and the limitations of the data.[10,11] That is, given two randomly selected electroencephalographic-derived data points with distinct anesthetic drug concentration, P_K is the probability that the indicator describes correctly which of the data points is the one with the higher (or lower) anesthetic drug concentration.[2] To avoid an overwhelming influ-

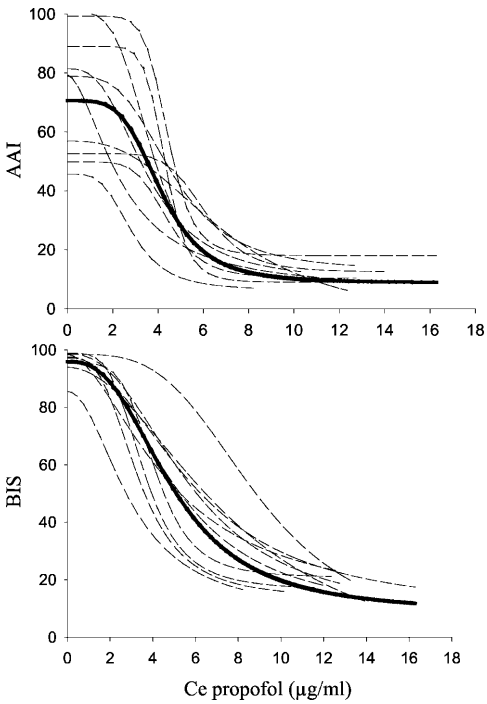

Fig. 9. The relation between propofol effect-site concentration and the Bispectral Index (BIS) and A-Line® ARX Index (AAI) modeled using nonlinear mixed effect modeling. The individual patients are represented as *dotted lines*, and the typical population curve is plotted as a *straight line*.

ence of patient individual variability on the P_K calculation, estimation was performed on an individual patient basis. Although all four measures tended to have similar median P_K values, the range between the minimum and maximum observed was more wider for both entropy measures than for AAI and BIS. Alternatively, a nonparametric approach was used to measure the performance of SE, RE, AAI, and BIS using the individualized Spearman rank correlation. The individualized Spearman rank correlation between the four electroencephalographic measures of drug effect and Ce_{prop}, as shown in table 2, revealed similar findings as P_K. Even more, a significantly lower value for SE compared with BIS was found.

Table 3. Typical Values and Coefficient of Variation for Each Electroencephalographic Measure of Anesthetic Drug Effect

	SE	RE	AAI	BIS
Ce_{50}	4.68 (36%)	4.55 (35%)	4.15 (31%)	4.92 (34%)
E_0	89.3 (24%)	97.6 (3%)	70.6 (28%)	95.9 (4%)
E_{max}	−80.6 (28%)	−82.9 (11%)	−61.8 (31%)	−87.5 (11%)
γ	4.59 (39%)	5.33 (0%)	4.26 (51%)	2.69 (32%)

AAI = A-Line® ARX Index; BIS = Bispectral Index; Ce_{50} = the effect site concentration associated with 50% maximal drug effect; E_0 = the baseline measurement when no drug is present; E_{max} = the maximum possible drug effect; γ = the steepness of the concentration-*vs.*-response relation; SE = state entropy of the spectral entropy; RE = response entropy of the spectral entropy.

Figures 5 and 6 show the raw data for each patient for each electroencephalographic measure of anesthetic drug effect during increasing Ce_{prop}. Figure 7 shows the difference between SE and RE in relation to Ce_{prop}. Previously, using the ABM-2 monitor (Datex-Ohmeda), Struys *et al.*[6] demonstrated that frontal electromyographic activity decreases with increasing propofol drug concentrations and *vice versa*. However, at higher drug concentration, the frontal electromyogram disappeared, making it useless for measuring excessive levels of anesthesia. As seen in figure 7, the difference between RE and SE approached zero in a concentration-dependent manner. It has also been reported that electromyographic activity can be used to detect pending arousal during anesthesia.[5] Because no arousal stimuli were included in the study protocol, this must be investigated in further research.

Figures 8 and 9 show the pharmacodynamic modeling for all measures *versus* Ce_{prop}. Previously, the relation between measures of anesthetic drug effect and Ce_{prop} was observed following a sigmoid E_{max} model.[2,3,6,23,24] Therefore, in our study, the relation between the measures of anesthetic drug effect and Ce_{prop} was also modeled using a sigmoid E_{max} model, and the model parameters were estimated using a population approach. In NONMEM, the parameters in the individual are weighted in a Bayesian manner toward the mean for the population, based on the variance of the individual parameters.[19] The results for each measures of anesthetic drug effect are shown in figures 8 and 9. As shown in table 3, the typical values for each measures of anesthetic drug effect revealed that for both RE as SE, steeper regression curves were seen than for both BIS and AAI, indicating a less graded response in most patients. The measures of individual variability were smaller for BIS and AAI than for SE and RE.

Although the use of a sigmoid E_{max} model is classically proposed in the literature,[2,3,6,23,24] one might criticize this approach. For the entropy of electroencephalography, Steyn-Ross *et al.*[25] discovered that the entropy might decrease discontinuously at the moment of induction into unconsciousness. They even concluded that this discontinuous step change in cortical entropy suggests that the cortical phase transition is analogous to a first-order thermodynamic transition in which the comatose–quiescent state is strongly ordered, whereas the active cortical state is relatively disordered. Recently, Bruhn *et al.*[26] found that two successive sigmoidal curves (instead of one) were useful in describing the pharmacodynamic behavior of two computerized electroencephalographic measures during isoflurane anes-

thesia. Although examination of our raw data suggests that a single sigmoidal relation is adequate for the range of concentrations studied in this experiment, we cannot rule out the possibility that studies exploring a larger range of concentrations may necessitate different models to accurately characterize the relation between effect-site propofol concentration and electroencephalographic response.

In conclusion, when comparing the performance of two spectral entropies, SE and RE, with AAI and BIS as measures of anesthetic drug effect, it was found that baseline variability was lowest when using SE and RE, followed by BIS. AAI showed high baseline variability. Correlation between the burst suppression calculation and both RE and SE were observed. For BIS, suppression ratio values greater than 40% are linearly correlated with BIS values. For values less than 40%, no correlation with BIS was found. No correlation was obtained between the burst suppression calculation and the AAI. Although all within acceptable range, prediction probability and individualized Spearman rank correlation were highest for BIS and lowest for SE. Population pharmacodynamic modeling of each measure *versus* Ce_{prop} using a sigmoid E_{max} model revealed that for both RE as SE, steeper curves were seen than for both BIS and AAI, indicating an less graded response in most patients. The measures of intraindividual variability were smaller for BIS and AAI than for SE and RE.

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3.3 Study 3: 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

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3.3.1 Introduction

Our former study revealed that AAI has problems of large population variability in the awake patient. This was confirmed by Kreuer et al.(1) Also the lack of descriptive capacity at deep levels of anesthesia was confirmed by other studies.(2) This observation re-activated the debate on whether mid-latency auditory evoked potentials (MLAEP) as a neurophysiologic parameter adds much information to the indices obtained from spontaneous EEG. In an editorial of anesthesiology, reflecting on the first AAI validation study by Struys et al,(3) Kalkmann et al. suggested that it might be beneficial to combine “the best of both worlds”.(4) However, at that time not much scientific foundation was available to underpin this statement.

In view of this debate, the inventors of AAI addressed the problems by introducing a drastic change in the algorithm for AAI calculation. The new AAI (version 1.6) is a composite index combining information obtained from MLAEP, spontaneous EEG and the burstsuppression percentage. The index was incorporated in a new commercialized model of the A-Line® monitor. Originally, the new monitor was called A-Line® (version 1.6). More recently, it was decided to change the name in AEPmonitor/2. Confusingly, the index is officially called AAI, even though it cannot be compared with the former version of AAI, using solitary MLAEP.

As an additional innovation, the upper scale limit was decreased from 100 to 60, in order to decrease baseline variability. This was no rescaling with changed units of measurement, but rather an elimination of all data points above 60. The inventors chose this value of 60 based on the sensitivity/specificity calculations from our study 1.(3) They concluded from these results that values above 60 always indicate “awake” patients with a 100% sensitivity. Although the change in scale seems harmless, we wanted to validate this intervention as a different index, as the “allround” behavior can be altered by changing scale.

Additionally, an acoustic stimulus volume controller was implemented as a technical solution for electromyographic interferences called “startle response”. This topic will be addressed more extensively in a next publication.

We validated the new version of the AEP monitor/2 by comparing it with the old version of the AAI and BIS in a comparable “benchmark” protocol, as used for the second trial.(5) We demonstrated a clear improvement on the baseline variability, especially when the upper scale limit of 60 was applied. However, bispectral index (BIS) still performed better at baseline. The discriminating power at deep levels of anesthesia was significantly improved by the inclusion of additional electroencephalographic derived information next to MLAEP. As such we proved that “the best of both worlds” indeed increased the descriptive capacity for the hypnotic component of anesthesia. Although the improvement is a clinically important finding, we couldn’t exclude a potential decreased sensitivity at sedation levels of anesthesia when the scale was reduced to 60. In contrast, other authors have recently successfully used the AEP monitor/2 in sedation protocols.(6-8)

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3.3.2 Manuscript

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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

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Background: **This study investigates the accuracy of a composite index, the A-Line® auditory evoked potentials index version 1.6 ($AAI_{1.6}$; Danmeter A/S, Odense, Denmark), as a measure of cerebral anesthetic drug effect in a model for predicting a calculated effect site concentration of propofol (Ce_{PROP}). The $AAI_{1.6}$ algorithm extracts information from the midlatency auditory evoked potentials, the spontaneous electroencephalographic activity, and the detection of burst suppression. The former version of this monitor, the A-Line® auditory evoked potential index version 1.5, is only based on fast extracted midlatency auditory evoked potential information.**

Methods: **After institutional ethics committee approval (University Hospital, Ghent, Belgium), informed consent was obtained from 13 patients (10 women, 3 men) with an American Society of Anesthesiologists physical status of I, aged 18–65 yr, who were scheduled to undergo ambulatory gynecologic or urologic surgery. The authors evaluated for Bispectral Index, A-Line® auditory evoked potential index, version 1.5, $AAI_{1.6}$ scaled from 0 to 100 and $AAI_{1.6}$ scaled from 0 to 60, the interpatient stability at baseline, the detection of burst suppression, prediction probability, and correlation with Ce_{PROP}, during a constant infusion of 1% propofol at 300 ml/h. The authors developed pharmacodynamic models relating the predicted Ce_{PROP} to each measure of cerebral anesthetic drug effect.**

Results: **Bispectral Index had the lowest interindividual baseline variability. No significant difference was found with prediction probability analysis for all measures. Comparisons for correlation were performed for all indices. The $AAI_{1.6}$ scaled to 60 had a significantly higher correlation with Ce_{PROP} compared with all other measures. The $AAI_{1.6}$ scaled to 100 had a significant higher correlation with Ce_{PROP} compared with the A-Line® auditory evoked potential index version 1.5 ($P < 0.05$)**

Conclusions: **The authors found that the application of $AAI_{1.6}$ has a better correlation with a calculated Ce_{PROP} compared with a solitary fast extracting midlatency auditory evoked potential measure. Whether this improvement in pharmacodynamic tracing is accompanied by an improved clinical performance should be investigated using clinical endpoints.**

PROCESSED analysis of the electroencephalogram or midlatency auditory evoked potentials (MLAEPs) is increasingly accepted as surrogate endpoint for quantification of anesthetic cerebral drug effect. For the electroencephalogram, the Bispectral Index (BIS) incorporated in the A-2000 BIS® monitor (Aspect Medical Systems, Newton, MA) has been proven to have a high sensitivity and specificity to measure anesthetic drug effect.[1–3] For MLAEPs, Jensen *et al.*[4] developed a new method for extracting the MLAEP from the electroencephalogram by using an autoregressive model with an exogenous input (ARX), allowing fast extraction of the raw MLAEP signal. A new monitoring variable called the A-Line® ARX Index, version 1.5 ($AAI_{1.5}$), is incorporated in a recently commercialized monitor called the A-Line® (Danmeter A/S, Odense, Denmark). Various investigators have illustrated its clinical usefulness and limitations.[2,3,5,6]

In previous work, we compared the performance of both systems and found that the correlation between the changes in anesthetic drug effect as measured by BIS or $AAI_{1.5}$ and the propofol effect site concentration (Ce_{PROP}) were accurate, except at baseline and during excessive levels of anesthetic drug effect, as detected by the increasing level of burst suppression.[7] For BIS, better baseline stability (minimal variability in the absence of drugs between individuals) was observed as compared with $AAI_{1.5}$.[7] Excessive levels of anesthetic drug effect remained detectable by the BIS monitor from a burst suppression ratio of 40%, whereby no changes in $AAI_{1.5}$ were observed during increasing levels of burst suppression.[7] This lack of information is caused by the fact that (1) burst suppression ratio does not participate in the calculation of $AAI_{1.5}$ and (2) at patient-specific levels of anesthetic drug effect, the amplitude (latency) of the raw MLAEP wave is reduced (increased) in such a way that it becomes nearly a straight line, limiting its discriminating power.[8,9]

In a recent editorial in ANESTHESIOLOGY, Kalkman and Drummond[10] stated that it might be proven ultimately, if

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we deem the grail of depth of anesthesia monitoring worth pursuing, that the optimal monitor of depth of anesthesia will be one that integrates parameters extracted from both spontaneous and evoked cerebral electrophysiologic signals. Following this philosophy, the first step is to prove that this monitor has a good correlation with cerebral anesthetic drug effect during the administration of a hypnotic drug.[10] Therefore, we hypothesized that the construction of a composite index calculated from the combination of a fast extracted MLAEP, electroencephalogram, and burst suppression might offer a broader range of information on the calculated effect site of propofol—as a pharmacodynamic endpoint of cerebral anesthetic drug effect—compared with an index based on solitary MLAEP or electroencephalographic input. Recently, an upgrade version of the A-Line® has been developed, producing such a composite index, called the A-Line® auditory evoked potential index, version 1.6 ($AAI_{1.6}$; Danmeter).

This study compares the accuracy of the BIS, $AAI_{1.5}$, and $AAI_{1.6}$ in their ability to predict a progressively increasing Ce_{PROP}. Therefore, we evaluated for all measures the stability at baseline (minimal variability in the absence of drug between individuals),[11] accurate detection of burst suppression,[12] prediction probability,[13,14] and correlation with the Ce_{PROP}. We also developed pharmacodynamic models relating the predicted Ce_{PROP} to each measure of cerebral anesthetic drug effect.

Materials and Methods

Clinical Protocol

After institutional ethics committee approval (University Hospital, Ghent, Belgium), informed consent was obtained from 13 patients (10 women, 3 men) with an American Society of Anesthesiologists physical status of I, aged 18–65 yr, who were scheduled to undergo ambulatory gynecologic or urologic surgery. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight, neurologic disorder, and recent use of psychoactive medication, including alcohol.

An 18-gauge intravenous line was positioned at a large left forearm vein. Every patient received approximately 100 ml crystalloid fluid during the study period. No fluid load was given before induction. No patient received preoperative medication. No other drugs, including opioids, were given during the study period. All patients maintained spontaneously ventilating (even at high levels of burst suppression) *via* a facemask delivering 100% oxygen at 6 l/min.

Heart rate and noninvasive blood pressure, arterial oxygen saturation, and capnography were recorded at 1-min intervals using an S-5 monitor (Datex, Helsinki, Finland). Capnography was monitored by putting the side stream sample line in the facemask of the patient. This implies the occurrence of an error for quantification of the partial pressure of carbon dioxide, but it enables monitoring of respiratory rate and free airway. A silent operation room was obtained for all patients.

At the start of the study period, 1% propofol was administered at 300 ml/h *via* a computer-assisted continuous infusion device (RUGLOOP**). This system captures all monitored data while driving a Fresenius Modular Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France) *via* an RS-232 interface. During the propofol infusion, the corresponding Ce_{PROP} is calculated in a time-synchronized way by RUGLOOP using a three-compartment model enlarged with an effect site compartment, previously published by Schnider *et al.*[15,16] The calculated Ce_{PROP} was computed to yield a time to peak effect of 1.6 min after bolus injection,[17] as also published by Schnider *et al.*[15,16] and clinically confirmed by Struys *et al.* [18] The propofol infusion was continued at the same speed until burst suppression levels of 80% or higher were achieved. However, infusion was stopped earlier if the mean arterial blood pressure became lower than 50 mmHg.

Before the drug administration was started, all patients were asked to close their eyes and relax for 2 min. During that time, signal quality, impedance of the electrodes, and the adequate detection of all parameters by RUGLOOP were verified. Baseline measures were performed during the first 5 s after starting the pumps, when Ce_{PROP} was 0 in all patients. Averaging of the data was performed using a 10-s interval.

Electroencephalographic and MLAEP Data Collection

BIS-XP (version 4.0) was derived from the frontal electroencephalogram (At-Fpzt) and calculated by the A-2000 BIS® monitor using four BIS® sensor electrodes (Aspect Medical Systems, Inc.). The BIS value ranges from 0 to 100. The smoothening time of the BIS monitor was set at 15 s.

We recorded raw electroencephalographic data including the MLAEP data with a prototype version of the A-Line® monitor. Three electrodes (A-Line® AEP electrodes; Danmeter A/S) were positioned at mid forehead (+), left forehead (reference), and left mastoid (−). Impedance was always lower than 5 kOhm. In this protocol, MLAEP was elicited by a bilateral click at 9 Hz, with a 2-ms duration and an adaptable click intensity set automatically by the monitor according to the measured signal-to-noise ratio (SNR) of the raw MLAEP signal.[19] Artifact rejection and 25- to 65-Hz band-pass filtering was conducted previously to the extraction of the MLAEP.

All raw MLAEP data were stored on a compact flash card (SanDisk, Sunnyvale, CA) connected to the proto-

** RUGLOOP program. Available at: http://www.anesthesia-uzgent.be. Accessed April 11, 2005.

type A-Line®. *Post hoc*, both $AAI_{1.5}$ and $AAI_{1.6}$ were extracted from these data on a time synchronized basis.

The $AAI_{1.5}$ is calculated using a fast extracting method called ARX, enabling us to extract information from the MLAEP within 2–6 s. This protocol has been published elsewhere.[2] The $AAI_{1.5}$ value ranges from 0 to 100.

The $AAI_{1.6}$ is a composite index using three sources of information resulting in an index value ranging between 0 and 100. First, an ARX is used to extract information from the raw MLAEP wave during periods with high SNR. The method used is based on the $AAI_{1.5}$ protocol and is described elsewhere.[4] When the MLAEP is reduced to a flat line, the SNR becomes too low to extract a useful AAI calculation. At that time, the electroencephalographic-based information will determine the $AAI_{1.6}$ calculation. Finally, when burst suppression patterns are detected, this information becomes the major factor in the calculation of the composite index. The $AAI_{1.6}$ is mathematically formulated as

$$AAI_{1.6} = k_0 AAI_{1.5} + k_1 \log \frac{E_{30-47\,Hz}}{E_{10-20\,Hz}} + k_2 BS$$

where $AAI_{1.5}$ is the result of the ARX model. $E_{30-47\ Hz}$ and $E_{10-20\ Hz}$ are the results of a power analysis in the raw electroencephalographic spectrum using higher and lower frequencies, respectively. BS is the percentage of burst suppression patterns detected during the last 30 s. k_0, k_1, and k_2 are functions of the SNR, the detection of iatrogenic artifacts (translated in a signal quality index), and the auditory stimulus intensity. The SNR is determined during the averaging process of the raw signal. It evaluates the detection quality of the signal under investigation. For MLAEP, the occurrence of the electroencephalogram, electromyogram, and other artifacts will induce a lower SNR. For the electroencephalogram, only electromyographic and iatrogenic artifacts will be taken into account. The signal quality index is calculated based on the number (and type) of artifacts during a certain period of time. If the amount of artifacts per period of time is higher than a percentage of this time, no $AAI_{1.6}$ is calculated because it is not reliable. If the number of artifacts per period of time is less than this value, an index is calculated, but the signal quality index bar is decreased on screen, indicating a lower accuracy of the calculated index. When this occurs, an artifact code is transferred to the RUGLOOP program automatically. These data were deleted *post hoc* from further analysis.

The burst suppression parameter is defined as the percentage of time where the power of the electroencephalogram is smaller than 5 μV over a period of time. However, the calculation of burst suppression differs between monitors. For BIS and $AAI_{1.5}$, the burst suppression algorithm details are published previously.[7]

In the $AAI_{1.6}$, the burst suppression detection algorithm is based on a maximum likelihood cumsum algorithm, with variable probability functions, using a preprocessed signal after artifact detection and filtering. The main property of this method is that low-amplitude signal criteria are based on probabilities and not on a fixed number. Second, the signal has no fixed segmentation, allowing a higher time resolution for detecting changes in comparison with other methods as applied in $AAI_{1.5}$ and BIS. Finally, burst suppression is evaluated over a window of 30 s in $AAI_{1.6}$, instead of 22 s in the former version.

Because it might be hypothesized that no additional information on loss of consciousness is revealed for $AAI_{1.6}$ values between 60 and 100,[3] the A-Line® monitor offers the possibility to adjust the range of the index toward a 0–60 scale (defined as $AAI1.6_{60}$). However, by setting all values higher than 60 to 60, it has to be proven that no information on cerebral anesthetic drug effect is lost, which is crucial when using the monitor in a pharmacodynamic protocol or in a clinical setting. Therefore, applicable performance measurements (baseline variability, individualized Spearman rank correlation, prediction probability analysis) were calculated on both scales.

Performance Measures

The significance level was set at 5% unless otherwise reported.

Baseline Variability. The baseline variability is calculated by computing the coefficient of variance on the electroencephalographic data points obtained during the first 5 s of the protocol, before any drug has been delivered. In this setting, the baseline variability will mainly reflect interpatient variability because of the short duration of measurement.

Comparison between $AAI_{1.5}$ and $AAI_{1.6}$. A Pearson correlation was calculated between $AAI_{1.5}$ and $AAI_{1.6}$.

Burst Suppression Detection and Parameter Correlation. The relations between the burst suppression and each measure of anesthetic drug effect are plotted. A Spearman rank correlation was calculated. For each scatterplot, a model was fitted to the data using curve estimation function from Sigmaplot2000® for Windows® (SPSS Inc., Chicago, IL). The curve estimation function produces curve estimation regression statistics and related plots for different curve estimation regression models including linear, logarithmic, inverse, quadratic, cubic, power, compound, S-curve, logistic, growth, and exponential. A separate model is produced for each dependent variable, together with its regression coefficients, predicted values, residuals, and predictive intervals. After this, the most appropriate regression model can be selected.

Prediction Probability. The ability of the different indicators to describe the anesthetic drug effect was evaluated using prediction probability (P_K), which compares the performance of indicators having different units of measurements. P_K was calculated using a custom

spreadsheet macro P_KMACRO, developed by Smith *et al.*[13,14] The P_K value was calculated for every individual patient and for all parameters studied. We evaluated the predictive capacity of BIS, $AAI_{1.5}$, and $AAI_{1.6}$ for detecting the calculated Ce_{PROP}, which has a known correlation with the anesthetic drug effect.[18] The calculated Ce_{PROP} reached at every 5 s was used as an endpoint for P_K calculation. Ce_{PROP} was calculated with a precision of two decimals. A P_K of 1 for BIS, $AAI_{1.5}$, or $AAI_{1.6}$ would mean that BIS, $AAI_{1.5}$, or $AAI_{1.6}$ always decreases (increases) as the patient reaches higher (lower) drug concentrations according to the Ce_{PROP}. Such an indicator can perfectly predict the anesthetic drug concentration. Alternatively, a P_K value of 0.5 would mean that the indicator is useless for predicting anesthetic drug concentration. The jackknife method was used to compute the SE of the estimate, based on the assumption that all assessments were independent.[13,14] After having evaluated normal distribution, a Student *t* test with Bonferroni correction was used to evaluate significant difference between P_K means.

Individualized Spearman Rank Correlation. As an additional nonparametric approach, the Spearman rank correlations between Ce_{PROP} and BIS, $AAI_{1.5}$, or $AAI_{1.6}$ (both scales) were individualized by computing the correlation first for every patient i separately, defined as R_i. The reported Spearman rank correlation, R, is a weighted average of the R_i (weighted according to the number of observations for each patient). In this way, R retained its usual interpretation. The confidence intervals on R were obtained by the bootstrap method in which the hierarchical nature of the data were incorporated by resampling within patients. Equality of two correlation coefficients was tested at the 5% level of significance by constructing the 95% confidence intervals of the difference (confidence intervals were also computed with the bootstrap technique). All bootstrap calculations were based on 10,000 simulation runs.

Pharmacodynamic Modeling

The relation between Ce_{PROP} and the electroencephalographic measures of anesthetic drug effect were analyzed using a sigmoid E_{max} model,

$$\text{Effect} = E_0 + \frac{(E_{max} - E_0) \times Ce_\gamma}{(Ce_{50\gamma} + Ce_\gamma)}$$

where Effect is the electroencephalographic effect being measured (BIS, $AAI_{1.5}$, or $AAI_{1.6}$ [both scales]), E_0 is the baseline measurement when no drug is present, E_{max} is the maximum possible drug effect, Ce is the calculated effect site concentration of propofol, Ce_{50} is the effect site concentration associated with 50% maximal drug effect, and γ is the steepness of the concentration–response relation curve. The model parameters were estimated using NONMEM V (Globomax LLC, Hanover, MD). Interindividual variability was modeled using a lognormal distribution,

$$P_i = P_{tv} e^{-\eta_i}$$

where P_i is the parameter value (E_0, E_{max}, y or Ce_{50}) in the *i*th patient, P_{tv} is the typical value of the parameter in the population, and η is a random variable with a mean of 0 and a variance of ω.[2] Individual variability is reported as ω, the SD of η in the log domain, which is approximately the coefficient of variance in the standard domain. Residual intraindividual variability was modeled using a standard additive error model.[20]

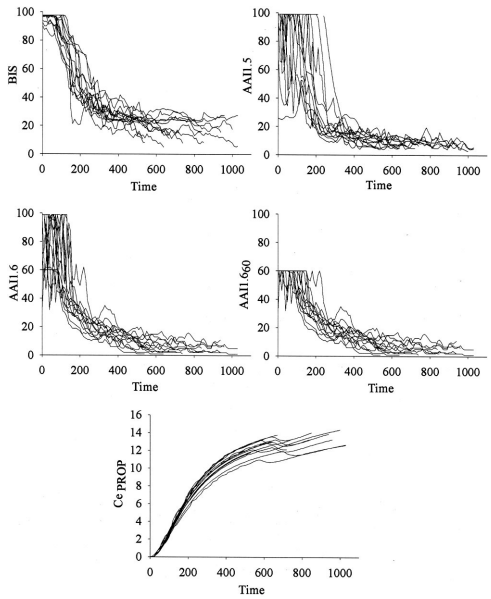

Fig. 1. Raw data of all patients *versus* time. $AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® ARX Index version 1.6 (scaled to 100); $AAI1.6_{60}$ = A-Line® ARX Index version 1.6 (scaled to 60); BIS = Bispectral Index; Ce_{PROP} = effect site concentration of propofol (the disruption in the continuously increasing Ce_{PROP} is due to the inevitable change of the 1% propofol syringe around 600 s.)

Results

The population characteristics were as follows: weight, 64.0 ± 3.8 kg; age, 38 ± 6.0; height, 168 ± 7.8 cm; sex, 10 women and 3 men. All patients remained within a safe hemodynamic and respiratory clinical state.

All measured data were included in the analysis. Figure 1 shows the raw data over time for the four electroencephalographic measures (BIS, $AAI_{1.5}$, $AAI_{1.6}$, $AAI1.6_{60}$) and Ce_{PROP}. All patients remained in a hemodynamic and respiratory safe condition during the study period.

Table 1. Baseline Stability Defined as the Coefficient of Variation of All Measures

	BIS	$AAI_{1.5}$	$AAI_{1.6}$ (Scaled 0–100)	$AAI_{1.6}$ (Scaled 0–60)
Mean ± SD	96.12 ± 2.40	90.06 ± 21.16	87.00 ± 20.60	58.69 ± 8.58
Coefficient of variation	0.02	0.23	0.24	0.15

$AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® Composite Index (both scales); BIS = Bispectral Index.

Performance Measures

The interpatient baseline variability was calculated for all studied electroencephalographic measures (BIS, $AAI_{1.5}$, $AAI_{1.6}$, $AAI1.6_{60}$). The coefficient of variance on the first 5 s of measurement before administration of propofol is shown in table 1.

$AAI_{1.5}$ and $AAI_{1.6}$ (both scaled between 0 and 100) were compared as shown in figure 2. This shows a strong correlation between both AAI versions (Pearson correlation $R = 0.91209833$, $P < 0.001$). We notice a large variability at high values of both parameters and a tendency for $AAI_{1.5}$ to remain on a higher value at higher levels of Ce_{PROP} in comparison with $AAI_{1.6}$. For $AAI_{1.5}$, no data lower than 7 are observed in contrast to $AAI_{1.6}$.

The relations between the percentage of burst suppression and BIS, $AAI_{1.5}$, and $AAI_{1.6}$ are plotted in figure 3 together with the most appropriate curve estimation. For BIS, a cubic polynomial regression curve was considered to be the best fit. For $AAI_{1.5}$ and $AAI_{1.6}$, a sigmoid regression curve with three parameters was selected as the best fit. For $AAI1.6_{60}$, identical results to $AAI_{1.6}$ were found. Therefore, no graph is presented. The Spearman rank correlations between burst suppression and BIS, $AAI_{1.5}$, and $AAI_{1.6}$ are −0.728, −0.551, and −0.871, respectively.

The P_K values for BIS, $AAI_{1.5}$, $AAI_{1.6}$, and $AAI1.6_{60}$ are shown in table 2. The individualized Spearman rank correlations between Ce_{PROP} and BIS, $AAI_{1.5}$, $AAI_{1.6}$, and $AAI1.6_{60}$ are also included in table 2.

Pharmacodynamic Modeling

Figure 4 shows the behavior of the four electroencephalographic measures *versus* Ce_{PROP} for all patients.

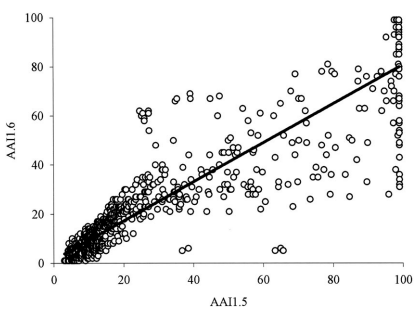

Fig. 2. Correlation between the A-Line® ARX Index version 1.5 ($AAI_{1.5}$) *versus* A-Line® ARX Index version 1.6 ($AAI_{1.6}$). The *black line* shows the most appropriate linear correlation.

With increasing Ce_{PROP}, all measures decreased. The relations of Ce_{PROP} to BIS, $AAI_{1.5}$, $AAI_{1.6}$, and $AAI1.6_{60}$ are modeled and shown in figure 5. The typical parameter values for each population model including the coefficient of variance (as a measure for interindividual variability in the standard domain) are found in table 3. The SD for each model (as a measure of the intraindividual variability in the log domain) was 5.63 for BIS, 13.67 for $AAI_{1.5}$, 7.24 for $AAI_{1.6}$, and 4.02 for $AAI1.6_{60}$.

Discussion

This study shows that the application of a composite index ($AAI_{1.6}$) based on MLAEPs and spontaneous electroencephalography optimizes the prediction of Ce_{PROP} as compared with a solitary fast extracting MLAEP measure ($AAI_{1.5}$). Comparing several monitors for cerebral hypnotic drug effect demands a systematic approach. The methodology used in this trial is based on a former

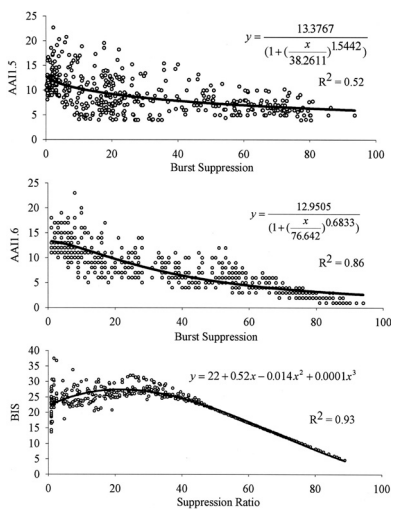

Fig. 3. Correlation between burst suppression and the A-Line® ARX Index are shown for the versions 1.5 ($AAI_{1.5}$) and 1.6 ($AAI_{1.6}$), respectively. The *lower figure* shows the correlation between the suppression ratio *versus* the Bispectral Index (BIS). The *black line* is the most appropriate fitted regression. The regression curve formula is printed in the *right upper corner* of every figure. R^2 = the goodness of fit of the regression curve.

Table 2. Individualized Spearman Rank Correlation Coefficients and Prediction Probability for Each Electroencephalographic Measure of Anesthetic Drug Effect *versus* Propofol Effect Site Concentration

	BIS	$AAI_{1.5}$	$AAI_{1.6}$	$AAI1.6_{60}$
P_K, median (minimum–maximum)	0.91 (0.70–0.98)	0.90 (0.73–0.94)	0.92 (0.75–0.98)	0.89 (0.75–0.97)
Individualized Spearman rank correlation, mean ± SD (95% CI)	−0.686 ± 0.033 (−0.748, −0.618)†	−0.661 ± 0.032 (−0.721, −0.597)*†	−0.753 ± 0.031 (−0.813, −0.691)*†	−0.959 ± 0.005 (−0.967, −0.949)†

* $P < 0.05$ between $AAI_{1.5}$ and $AAI_{1.6}$. † $P < 0.05$ between $AAI1.6_{60}$ and all other measures.

$AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® ARX Index version 1.6 (scaled to 100); $AAI1.6_{60}$ = A-Line® ARX Index version 1.6 (scaled to 60); BIS = Bispectral Index; CI = confidence interval; P_K = prediction probability.

publication from Vanluchene *et al.*,[7] where spectral entropy is compared with BIS and $AAI_{1.5}$.

The A-Line® monitor offers the possibility to reduce the upper scale limit to 60, based on the rationale that values between 60 and 100 suffer from a high interpatient variability and offer no additional information on loss of consciousness.[2] Although this adjustment might be interesting on a clinical level, it is crucial to prove whether this scale is applicable to pharmacodynamic studies investigating subhypnotic levels of anesthesia (when consciousness is not lost), without losing any information on the propofol drug concentration. Therefore, we also investigated the performance accuracy of the $AAI1.6_{60}$ as an individual index.

High baseline variation, as defined by the coefficient of variance, might decrease the predictive ability of the electroencephalogram-derived measures when used to detect cerebral drug effect, as stated by Bruhn *et al.* [11] BIS showed the lowest baseline variability. In contrast, $AAI_{1.5}$ and $AAI_{1.6}$ showed a high but comparable coefficient of variance. We found a major improvement in baseline variability in $AAI1.6_{60}$ in comparison to $AAI_{1.5}$ and $AAI_{1.6}$. Although it is potentially interesting when applying the A-Line® monitor clinically to monitor loss of consciousness, one might question that it does not make sense to reduce baseline variability by cutting of data higher than 60, if this new scale causes a decreased sensitivity for the detection of subhypnotic levels of anesthetic drug effect. This reduced upper limit only makes sense if the other performance measures reveal a beneficial effect.

Burst suppression is a benign electroencephalographic pattern frequently seen in healthy brain at deep levels of anesthesia. Because the detection of burst suppression represents an important component to the level of hypnotic effect, it might be helpful to take into account burst suppression analysis when measuring deep levels of anesthetic drug effect because it might optimize the discriminating power of the investigated index at these levels. For BIS, burst suppression is included in the

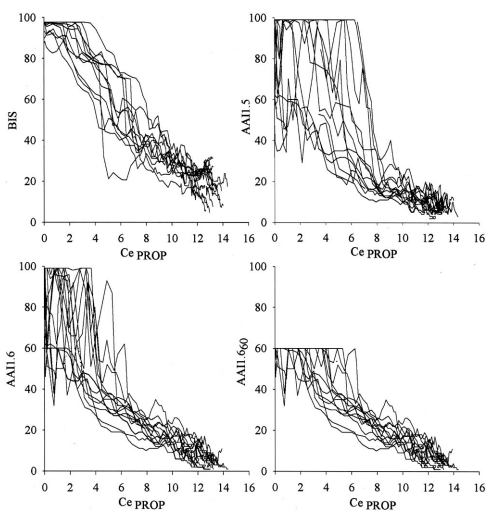

Fig. 4. Raw data of all anesthetic drug effect measures *versus* calculated effect site of propofol (Ce_{PROP}). $AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® ARX Index version 1.6 (scaled to 100), $AAI1.6_{60}$ = A-Line® ARX Index version 1.6 (scaled to 60).

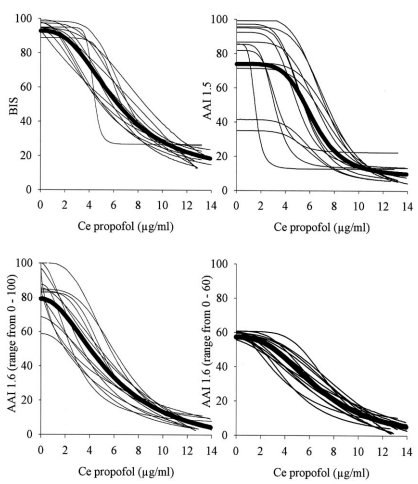

Fig. 5. NONMEM regression of the population data. $AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® ARX Index version 1.6; BIS = Bispectral Index; Ce propofol = effect site concentration of propofol.

Table 3. Typical Values and Coefficients of Variation for Each Electroencephalographic Measure of Anesthetic Drug Effect.

	BIS	$AAI_{1.5}$	$AAI_{1.6}$ (Scaled 0–100)	$AAI_{1.6}$ (Scaled 0–60)
Ce_{50}	6.25 (210%)	6.28 (50%)	5.71 (36%)	6.78 (36%)
E_0	92.90 (66%)	74.00 (50%)	79.20 (59%)	57.40 (4%)
E_{max}	−83.60 (127%)	−65.70 (36%)	−87.50 (31%)	−60.00 (31%)
γ	2.59 (45%)	5.09 (0%)	1.98 (57%)	2.61 (38%)

$AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® ARX Index version 1.6; BIS = Bispectral Index; Ce_{50} = the effect site concentration associated with 50% maximal drug effect; E_0 = the baseline measurement when no drug is present; E_{max} = the maximum possible drug effect; γ = the steepness of the concentration–response relation.

algorithm. Various authors have found that above a burst suppression ratio of 40%, a linear correlation exists between BIS and burst suppression ratio, indicating that the burst suppression ratio is the only determinant factor for BIS values below 30.[7,21] Our results for BIS, as shown in figure 3, are in agreement with these previously published findings. If burst suppression was excluded from the algorithm, BIS would become very resistant at excessive levels of anesthetic drug effect. In contrast, the calculation of the $AAI_{1.5}$ is only based on the MLAEP. As already observed in previous work, the MLAEP flattens at patient-specific levels of anesthetic drug effect, thereby limiting its discriminating power.[7–9] This phenomenon results in a maximum decreased $AAI_{1.5}$ "plateau" level higher than 0. As shown in figures 2 and 4, the lowest observed $AAI_{1.5}$ values are ceiled around 7. Beyond this level, no additional information on cerebral drug effect can be obtained. When taking in consideration that the ED_{95} for loss of consciousness is around 19 for $AAI_{1.5}$, the discriminating power might become very low after loss of consciousness. For $AAI_{1.6}$, the electroencephalogram and burst suppression are included as a component of the composite index as described in the Materials and Methods section. This results in an increased discriminating power at deep levels of anesthetic drug effect. As shown in figure 3, the absolute values of $AAI_{1.6}$ are able to decrease to 0 at increasing levels of burst suppression. This improvement between $AAI_{1.5}$ and $AAI_{1.6}$ is also reflected in the statistically significant better individualized Spearman rank correlation for $AAI_{1.6}$ (table 2).

When studying performance accuracy, the question is how well the observed measure, which is the electroencephalographic response, predicts the unobserved "underlying" state of the patient, which is represented by the Ce_{PROP}. Therefore, P_K was calculated for BIS, $AAI_{1.5}$, $AAI_{1.6}$, and $AAI1.6_{60}$. The underlying theoretical background of P_K calculations has been published elsewhere.[7] In our study, we did not obtain any significant difference between P_K values, although $AAI_{1.6}$ tended to have the highest median value.

As an additional analysis for correlation between parameters and Ce_{PROP}, we calculated the Individualized Spearman rank correlation coefficients for each measure. This weighted nonparametric statistical approach depicts the nonlinearity in the system much more accurately as compared with P_K analyses. Results confirm the significant increase in correlation between $AAI_{1.6}$ *versus* Ce_{PROP} in comparison to $AAI_{1.5}$, thereby proving that the combination of MLAEP and derived measures from the spontaneous electroencephalogram (power spectrum analysis and burst suppression calculation) increases the accuracy to measure cerebral anesthetic drug effect. Initially, no difference was found between BIS and $AAI_{1.5}$ or between BIS and $AAI_{1.6}$ when scaled to 100. However, when the upper limit of the scale was reduced to 60, remarkable results were observed. Figure 4 shows that a high variability and a high amount of nonlinearity are observed in all measures when scaled to 100. For $AAI_{1.6}$, one can say that the signal between 60 and 100 nearly behaves as "random noise." By eliminating this part of the $AAI_{1.6}$ range, the high variability resulting in a high level of nonlinearity is drastically reduced. This results in a very high individualized Spearman rank correlation as shown in table 2. However, one can raise the question of whether a constant number around 60 offers more information compared with the complete scale, both when predicting propofol anesthetic drug effect and when evaluating a clinical level of sedation before loss of consciousness is obtained. This must be studied in further research. We were not able to evaluate the clinical level of sedation in this population because we wanted to avoid any stimulation during induction.

Figure 5 shows the pharmacodynamic modeling for all measures *versus* Ce_{PROP}. Previously, the relation between measures of anesthetic drug effect and Ce_{PROP} was observed following a sigmoid E_{max} model. Therefore, in our study, the relation between the measures of anesthetic drug effect and Ce_{PROP} was also modeled using a sigmoid E_{max} model, and the model parameters were estimated using a population approach. In NONMEM, the parameters in the individual are weighted in a Bayesian manner toward the mean for the population, based on the variance of the individual parameters. Examining our raw data, we found for all parameters a single sigmoid regression to be adequate for describing the range of concentrations used in this study. When looking at figure 5, one can conclude that the smoothest regression is found in $AAI1.6_{60}$. This is reflected in an optimization of both the interindividual and the intraindividual variability in the population. In table 3, the coefficients of variation of the typical values of the cerebral drug effect measures reveal a major decrease in

the interindividual variability of the slope (γ) when $AAI1.6_{60}$ is compared to $AAI_{1.6}$. Simultaneously, a decrease in intraindividual variability at baseline is observed for $AAI1.6_{60}$, reflected by the lower SD compared with $AAI_{1.6}$. However, we want to stress the fact that the regression analysis for $AAI1.6_{60}$ should be interpreted cautiously because of the effect of rejection of data on the NONMEM analysis. It might cause a distortion on the data input in such a way that the behavior of the population regression is closer to the *a priori* chosen E_{max} model. Further research is needed to clarify whether this result is an artificial overestimation of the performance parameters or whether $AAI1.6_{60}$ is indeed able to maintain a high performance as a hypnotic drug effect monitor.

We conclude that the use of the composite index $AAI_{1.6}$, which combines information from the MLAEP, spontaneous electroencephalogram, and burst suppression, increases the correlation with the cerebral drug effect of propofol as compared with the $AAI_{1.5}$, which is a solitary fast extracted MLAEP index. By adjusting the upper scale limit to 60, the performance measures are optimized even more. However, the implications of this newly chosen upper scale limit should be further explored on both the clinical and the pharmacodynamic level.

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3.4 Study 4: A comparison of bispectral index and ARX-derived auditory evoked potential index in measuring the clinical interaction between ketamine and propofol anesthesia

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3.4.1 Introduction

As an additional validation, we investigated the performance of A-Line® auditory evoked potential Index (AAI) for measuring the hypnotic component of “difficult anesthetic molecules”. Generally, anesthetic cerebral drug effects are considered to be mediated by the gamma amino butyric acid (GABA) receptor (e.g. this is the case for propofol). However, a secondary pathway, mediated by the N-methyl D-Aspartate (NMDA) receptor can also produce clinical anesthesia. A typical NMDA dependent molecule that is used in clinical practice is ketamine.

Ketamine is a dissociative anesthetic drug that disrupts the transfer of sensory input to the association areas in the brain. In other words, the patient remains capable to receive sensory input, but the brain is not able to organize this in a comprehensive way. Therefore, the patient will be “unconscious” of his sensory experiences. An interesting side-effect for anesthesia practice is that the patients keep breathing spontaneously, and that the hemodynamic impact of ketamine is low. As ketamine evokes EEG changes resembling to epileptic insults, all EEG derived indices become distorted.(1) Schwender had studied the effect of ketamine on raw MLAEP, but no information was available on the performance of AAI during ketamine administration.(2,3)

We studied the effects of ketamine on the first version of the A-Line® auditory evoked potential Index (AAI), during a steady state propofol anesthesia that was obtained by TCI technology. We compared AAI with simultaneous measurements of BIS.

We found that ketamine had no effect on the mean AAI in the population, although it has a known clinical potentiating effect on propofol. Therefore, a perfect measure of the cerebral hypnotic drug effect should decrease due to this interaction.(4) Mean BIS was increased, which confirmed results of other authors.(4) As an additional finding we found an increase in variability of AAI after ketamine administration. We hypothesized that this could be caused by an increase in electromyographic interference.

We conclude that neither AAI nor BIS were able to detect the potentiating hypnotic effects of ketamine during propofol anesthesia. As the mean AAI remains constant, one might consider that AAI is safer to use during anesthesia involving ketamine, as it has a potentially lower incidence of false high “awareness” detection in this setting, compared to BIS.

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3.4.2 Manuscript

Anaesthesia, 2003, **58**, pages 957–961

MAIN ARTICLE

A comparison of bispectral index and ARX-derived auditory evoked potential index in measuring the clinical interaction between ketamine and propofol anaesthesia

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Summary

We evaluated the effects of a bolus (0.4 $mg.kg^{-1}$) and continuous infusion (1 $mg.kg^{-1}.h^{-1}$) of ketamine on Bispectral Index (BIS) and A-Line® ARX Index (AAI) during propofol anaesthesia. We included 15 ASA I patients scheduled for general anaesthesia. Induction was performed by infusion of propofol at 100 $ml.h^{-1}$ until loss of consciousness. Both BIS and AAI monitors responded appropriately at that time. The calculated effect site concentration of propofol at loss of consciousness was maintained by means of a computer controlled infusion system. A 'pseudo' steady-state effect site concentration was reached after 4 min. After 1 min of baseline measurements, ketamine was administered. BIS values increased from the 3rd to the 8th min after the administration of ketamine. The AAI showed no significant increase or decrease, but between-patient variability increased.

Keywords *Monitoring*: Auditory evoked potentials. Bispectral index. *Anaesthetic drugs*: Ketamine. Propofol.

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***RUGLOOP, written by T. De Smet and M. Struys. More information is available at http://www.anesthesia-uzgent.be.*
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Ketamine used as an adjuvant during propofol anaesthesia has potentiating effects on clinical signs like 'unresponsiveness to verbal command' and 'loss of eyelash reflex' [1]. However, the dissociative state of anaesthesia evoked by ketamine is characterised by confusing effects on both the electroencephalographic (EEG) and auditory evoked potential monitors [2–4]. For the EEG, bispectral index (BIS) incorporated in the A-2000 BIS® monitor (Aspect Medical Systems Inc., Newton, MA) has been proven to have a high sensitivity and specificity to measure anaesthetic drug effect, compared with other processed EEG variables [5, 6]. With respect to auditory evoked potentials, Jensen *et al.* developed a new method for extracting the middle latency auditory evoked potentials (MLAEP) from the EEG signal by employing an autoregressive model with an exogenous input (ARX) adaptive model. This method allows extraction of the MLAEP signal within 15–25 sweeps of 110 ms duration each, resulting in only a 6–15-s response delay time [7, 8]. A new monitoring variable, called the AAI (A-Line ARX-Index), is then calculated from this fast extracted MLAEP wave. The calculations of the AAI are described elsewhere [9, 10]. This new technology is incorporated in a recently commercialised system, called A-Line®. (Developed and distributed by Danmeter A/S, Odense, Denmark).

As the clinical signs of the hypnotic state seem to be potentiated by ketamine, one might hypothesise a reduction in the measured BIS value or a decrease in amplitude and latency of the MLAEP curves, resulting in a lower AAI. However, several authors have described an apparently contradictory rise in BIS values when ketamine is administered as an adjuvant to anaesthesia [1, 11, 12]. Schwender *et al.* investigated the effects of ketamine induction on the MLAEP and concluded that

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ketamine had no influence on amplitudes or latencies of the peaks of MLAEP [2]. However, no data are available for the AAI. Therefore, we determined to investigate the effects of ketamine administration on the AAI during steady-state propofol anaesthesia.

Methods

After local Ethics Committee approval and written informed consent, 15 ASA I patients, aged 18–60 years, scheduled for general surgery were included. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight, neurological disorders, and recent use of psycho-active medication, including alcohol.

For induction, a continuous infusion of propofol was started at 100 $ml.h^{-1}$ until loss of consciousness (LOC) using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base 1 (Fresenius Vial Infusion Systems, Brézins, France). As this pump was controlled using a computer-assisted infusion device (RUGLOOP**) we were able to track the calculated plasma and effect-site propofol concentration. Both concentrations of propofol were computed using a three-compartment pharmacokinetic-dynamic model enlarged with an effect-site compartment, previously published by Schnider *et al.* [13]. Effect site concentration was computed to yield a time to peak effect of 1.6 min after bolus injection [13]. At loss of consciousness (LOC), defined by the clinical signs of 'loss of eye-lash reflex' and 'loss of response to name calling', the calculated effect site concentration was recorded and the propofol infusion system was adjusted to an effect compartment controlled infusion device using the same pharmacological model [13]. The target effect site concentration was set at the same effect site concentration as recorded at LOC. This infusion profile was continued throughout the study period. Using this method, we were able to reach and maintain a stable ('pseudo steady-state') and comparable hypnotic level between and within patients at 4 min after LOC (2.5 times 'time to peak effect'). We refer to this as a 'pseudo' steady-state as it is the best approximation of a real pharmacodynamic steady state available at this time. The time between the 4th and 5th min after LOC was used as baseline registration. At the 5th minute after LOC, a bolus of ketamine (0.4 $mg.kg^{-1}$) was administered over 5 s followed by a continuous infusion of 1 $mg.kg^{-1}.h^{-1}$ for 17 min. Ketamine was administered as described previously by Hirota *et al.* [4].

Heart rate and non-invasive blood pressure, SpO_2 and capnography were recorded at 1-min intervals using an AS3 monitor (Datex, Helsinki, Finland). BIS (version 3.4) was derived from the frontal EEG (At-Fpzt) and calculated by the A-2000 BIS monitor using a BIS sensor (Aspect Medical Systems, Inc., Newton, MA). The smoothening time of the BIS monitor was set at 15 s. The AAI from the MLAEP was calculated using the A-Line® monitor (version 1.5; Danmeter A/S, Odense Denmark). The MLAEP were elicited with a bilateral click stimulus of 70 dB intensity and 2 ms duration. Three electrodes (A-Line AEP electrodes, Danmeter A/S, Odense Denmark) were positioned at mid forehead (+), left forehead (reference) and left mastoid (–). The extraction of the MLAEP using a short Moving Time Average (MTA) technique together with an ARX model and the calculations of the AAI are described else where [9].

All haemodynamic data together with BIS and AAI indices were logged automatically. RUGLOOP recorded the BIS every 10 s, and the A-Line monitor recorded AAI values nominally each second. The AAI was averaged afterwards within 10-s intervals.

Statistical analysis

Significance level was set at 5% unless otherwise reported. For statistical comparison with baseline values, all recorded BIS and AAI values were averaged every minute. As a baseline, we calculated the average AAI and BIS during the last minute of steady state before the administration of ketamine. Normality of all data was tested with the Kolmogorov–Smirnov test. Mean and standard deviation (SD) of all the minute-by-minute data was calculated. A paired *t*-test with Bonferroni correction was performed to evaluate any significant difference between the baseline BIS and AAI and the consecutive minute-by-minute values, with significance level set at 0.003. For BIS and AAI, coefficient of variance (CV) between baseline and each consecutive minute-by-minute data point was compared. To evaluate the stability of depth of anaesthesia at baseline we compared the first and last datapoint during the 4th min of 'pseudo' steady-state with a paired *t*-test for both AAI and BIS.

Results

Demographic data are shown in Table 1.

Figure 1A,B shows the raw data, respectively, for BIS and AAI vs. time. Whereas BIS appears to increase for a period after the ketamine bolus, this is not true for AAI. Both the within- and between-individual variability appear to be smaller for BIS than for AAI.

Table 1 Patients' demographic data.

Variable	Mean (SD)
Age; years	40.63 (15.66)
Height; cm	172.25 (7.89)
Weight; kg	67.81 (16.20)

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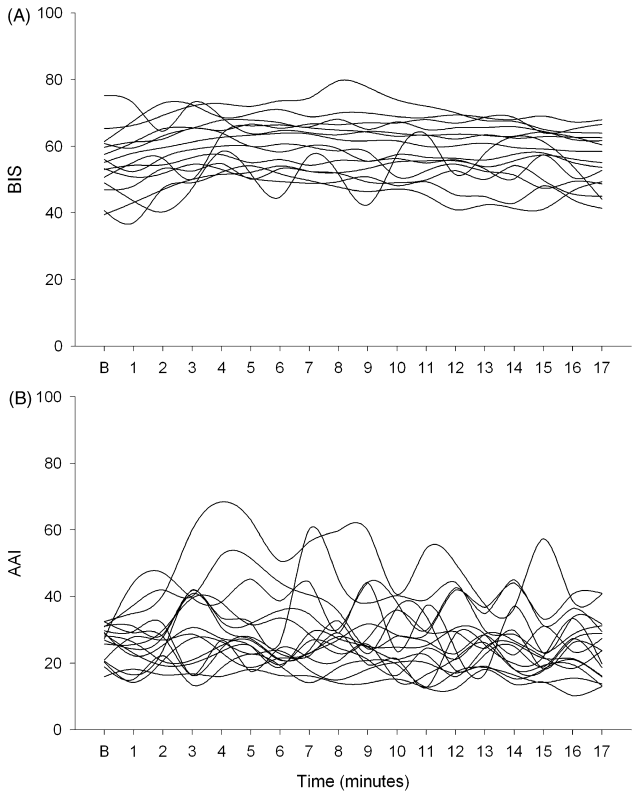

Figure 1 Raw data of the individual profiles of BIS (1A) and AAI (1B) vs. time. Baseline (B) is calculated from the data during pseudo steady-state anaesthesia, 4 min after loss of consciousness. At 1 min, a bolus of ketamine was administered and a continuous infusion started.

Figure 2A,B shows the minute-by-minute calculations of the mean (SD) for BIS and AAI. For the mean BIS, a significant increase is observed after the start of ketamine administration from 3 min to 8 min, as shown in Fig. 2A. However, from 9 min until the end of the procedure, a constant decrease in mean is observed. The minute-by-minute mean AAI reveals no systematic pattern and there is no statistically significant difference with respect to baseline (Fig. 2B).

For both BIS and AAI, the corresponding coefficient of variance (CV) is indicated above every SD bar in Fig. 2A, B. The CV for BIS did not change after the start of the ketamine administration compared to baseline. In contrast, the CV for AAI revealed a stable increase after ketamine.

The first and last value of the AAI and BIS during baseline measurements did not differ significantly for any of the study patients.

Discussion

Ketamine has unique features within the spectrum of anaesthetic drugs. It has both hypnotic and analgesic effects which, in combination with steady-state propofol anaesthesia, have an additive effect on the clinical signs of the hypnotic component of anaesthesia [1, 3, 4]. In contrast to other drugs used in anaesthesia, the hypnotic effect of ketamine is based on a dissociative mechanism. This term refers to the original suggestion that ketamine does not block the sensory input at spinal or brainstem levels, but interrupts afferent impulses in the diencephalon and in the association area of the cortex (limbic system) [14]. Previously, various authors have studied the electroencephalographic behaviour of ketamine. Corssen *et al.* showed that ketamine 1 $mg.kg^{-1}$ i.v. caused heightened theta activity on the EEG [14]. Schwender *et al.* found no effect of a ketamine induction (2 $mg.kg^{-1}$ i.v.) on the MLAEP [1].

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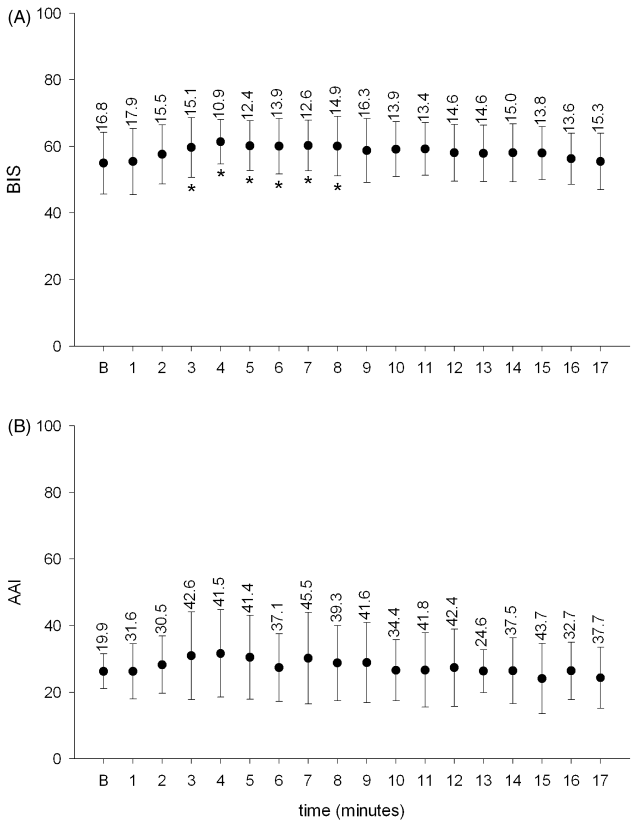

Figure 2 Plots of mean (SD) BIS (2A) and AAI (2B) vs. time. The coefficient of variance (CV) is noted above every SD bar. Baseline (B) is calculated from the data during pseudo steady-state anaesthesia, 4 min after loss of consciousness. At 1 min a bolus of ketamine was administered and a continuous infusion started. *Significant difference with respect to baseline.

Recently, processed EEG and MLAEP derived indicators such as BIS and AAI have been applied in clinical practice as a measure of anaesthetic depth [9]. Therefore, we studied the behaviour of both indices during ketamine administration. It was observed that BIS values increased significantly from the 3rd min until the 8th min after the administration of ketamine, followed by a subsequent decrease for the rest of the study period. This increase was consistent in all patients, reflected by a stable CV compared to baseline, as shown in Fig. 2A. The initial increase in BIS values might be related to the temporary high ketamine concentration after the bolus injection. Our dosage scheme was used previously to investigate the behaviour of ketamine on BIS [4]. The pharmacokinetic profile of this scheme does not evoke stable plasma concentrations in the patient. This might explain the secondary decrease after the initial increase in BIS. Our results are in agreement with Hirota *et al.* [4], who concluded that ketamine increased BIS during propofol–fentanyl anaesthesia despite a deepening level of hypnosis.

In contrast with the BIS, the mean AAI showed no significant change after ketamine administration. Although this is in agreement with previous reports using raw MLAEP [2], the increase in CV suggests an enlarged interindividual variability and less stability in the AAI trends. This makes interpretation of the individual AAI more difficult. In previous reports, an increased instability of the MLAEP during ketamine administration was not observed. However, in these studies a long average time of 2 min was required to obtain one clinically usable AEP signal, possibly resulting in less fluctuating data [2]. Our AAI data were recorded using a fast extracted MLAEP signal, resulting in only a 6-s delay and continuous data generation.

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The results of BIS and AAI might be caused by instability in the propofol plasma and effect site concentrations due to a hypothetical interaction of ketamine on the pharmacokinetic characteristics of propofol. This protocol was not designed to demonstrate such an interaction. Moreover, we put every effort into avoiding disequilibrium in the effect site concentration of propofol before and during the delivery of ketamine. We took care to deliver the best approximation of a pharmacodynamic steady state by using effect compartment controlled target-controlled infusions as described previously. By comparing the first and the last baseline BIS and AAI values, we have additional confirmation of a clinically comparable depth of anaesthesia during the study period.

The variety of mechanisms and sites of action of hypnotic drugs can partly explain some of the phenomena that we have demonstrated. BIS and AAI were developed as monitors for the mechanisms that create a hypnotic state, but the question remains as to whether they are capable of evaluating all sites of action of the different hypnotics. BIS evaluates the raw EEG signal. A moderate dose of ketamine produces dominant frontal rhythmic theta activity with increases in amplitude [3, 15]. This may evoke an increase in BIS that is not compatible with the clinical signs.

The methods applied in this study demand the simultaneous use of both BIS and A-Line monitoring. Other studies have demonstrated that the auditory stimuli provoked by the A-line monitor do not influence the BIS or the clinical signs of depth of anaesthesia [16,9].

Our study could not demonstrate a significant change in mean AAI after ketamine administration. This does not prove that ketamine does not influence the primary processing of the AEP. As an increase in CV was detected after ketamine injection, we suspect a fluctuation in the primary sensory cortex or at a lower level. As the cause of this phenomenon remains unclear, further investigations are mandatory.

We conclude that, in our study, BIS and AAI failed to describe the clinical interaction between ketamine and propofol anaesthesia. Mean BIS values were increased consistently and mean AAI showed no significant change after the administration of ketamine. The variability of BIS remained stable. In contrast, the coefficient of variance of AAI increased significantly, making interpretation of the individual AAI more difficult.

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3.5 Study 5: The Effects of Ketamine and Rocuronium on the A-Line® Auditory Evoked Potential Index, Bispectral Index, and Spectral Entropy Monitor during Steady State Propofol and Remifentanil Anesthesia

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3.5.1 Introduction

This study expands the problem of “difficult molecules” to a more general predicament for AAI, BIS or Spectral Entropy (SE and RE). The problematic conditions for EEG and MLAEP derived monitors are characterized by “high-frequency” interferences in the raw EEG. These conditions can be both drug induced (e.g. by ketamine, cf. study 5) or by electrophysiological interferences (e.g. by the EMG).(1-7)

Neuro-muscular blocking agents (NMBA), such as rocuronium, are commonly used to obtain immobility during surgery. As NMBA abolish all electrical signal transition from the neurons to the muscles, a general muscular paresis sets in, characterized by a complete inhibition of the EMG. It has been shown that both the EMG activity as well as the administration of NMBA can interfere with electroencephalographic or mid-latency auditory evoked potentials monitoring.(5,7-9) Mostly, EMG and NMBA respectively cause an increase/decrease in the EEG and MLAEP derived index calculations. Apparently, there is always some EMG activity included in the index algorithm calculations. It remains a challenge to filter this EMG interference more accurate.

Our main study goal was to exclude whether the increased variability for AAI, after ketamine administration, as demonstrated by Vereecke et al,(1) could be partially caused by an electromyographic alteration. Our hypothesis was based on the clinical impression that the administration of ketamine in a spontaneously breathing patient activated the EMG. Additionally, we found in the scientific literature that the basic locomotor rhythmicity in cats was N-Methyl D-Aspartate (NMDA) receptor dependent.(10) We felt these observations were sufficiently important for performing a new study combining the effects of ketamine and rocuronium.

After implementing a “steady-state” anesthesia with remifentanil and propofol, we randomized 42 patients in four groups. In a time synchronized way, the patients received ketamine (Group Ket), rocuronium (Group Roc) or both (Group Roc+Ket). The fourth group was a control group that received no additional medication. This setup allowed conclusions on several additional research questions that had not yet been answered:

1. What is the effect of ketamine on the new composite index $AAI_{1.6}$?
2. What is the effect of ketamine on the SE and RE?
3. What is the effect of solitary rocuronium on the new $AAI_{1.6}$?
4. What is the effect of solitary rocuronium on SE and RE?

We performed a within and between group analysis. From this, we concluded that the effects of ketamine are independent of the changes in EMG. Rocuronium does not abolish or reduce the effects of ketamine on any monitor. Therefore or primary hypothesis was rejected. We also found that rocuronium decreases all indices except SE, indicating the inclusion of EMG information in most index calculations. The increasing effect of solitary ketamine on BIS, RE and SE has been confirmed in our study. Monitoring the hypnotic component of anesthesia remains a challenge for NMDA dependent anesthesia.

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3.5.2 Manuscript

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The Effects of Ketamine and Rocuronium on the A-Line® Auditory Evoked Potential Index, Bispectral Index, and Spectral Entropy Monitor during Steady State Propofol and Remifentanil Anesthesia

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Background: **The authors studied the effects of ketamine and rocuronium on the Bispectral Index, A-Line® auditory evoked potential index, state entropy, and response entropy during a calculated steady state anesthesia with propofol and remifentanil.**

Methods: **After ethics committee approval, 42 patients were allocated to four groups. Baseline measurements were performed after implementing a calculated steady state anesthesia with propofol and remifentanil. The control group received no additional medication. The ketamine group received a bolus and continuous infusion of ketamine. The rocuronium group received a bolus of rocuronium. The rocuronium–ketamine group received both. All data were stored during 15 min after baseline. After inspection of the raw data, the authors conducted an explorative statistical analysis.**

Results: **No significant changes were found in the control group for any of the monitors. Mean values decreased in the rocuronium group for the A-Line® auditory evoked potential index, Bispectral Index, and response entropy, but not for state entropy. In the ketamine group, the A-Line® auditory evoked potential index and Bispectral Index did not change significantly, but state and response entropy increased. In the rocuronium–ketamine group, the A-Line® auditory evoked potential index and Bispectral Index did not decrease as found in the rocuronium group. Response and state entropy increased significantly.**

Conclusions: **The response of all monitors after ketamine administration is not affected by simultaneous administration of rocuronium. Interpretation of all studied indices must be done cautiously while taking into account the clinical setting during measurement.**

THE Bispectral Index (BIS), response entropy (RE), state entropy (SE), and a recent version of the A-Line® auditory evoked potential index (AAI1.6) have all been investigated as surrogate endpoints of hypnotic drug effect. Previously, their behavior during propofol and remifentanil infusion was studied.[1–4] However, little literature is available on the behavior of the new AAI1.6 in combined anesthesia conditions.

Several reports have been published on the behavior of indices derived from electroencephalography and midlatency auditory evoked potentials (MLAEPs) during clinical conditions characterized by an increased high-frequency electrical activity in the power spectrum of the electroencephalogram.[5–11] These conditions can be both drug induced (*e.g.*, by ketamine) or caused by electrophysiologic interference (*e.g.*, by electromyography).[5–12]

Ketamine is a dissociative anesthetic drug, inhibiting the *N*-methyl-D-aspartate receptor. On the raw electroencephalogram, ketamine evokes an epileptiform activation with high-frequency features.[13] This distortion interferes with the fast extracting index calculations as demonstrated by an increase in mean BIS, RE, and SE.[14] The mean values of the former version of the A-Line® auditory evoked potential index, which is based solely on MLAEP, is not affected by ketamine administration.[5] The effects of ketamine have not yet been studied for the new version of the A-Line® monitor (Danmeter A/S, Odense, Denmark), which calculates a composite index (AAI1.6) extracted from the electroencephalogram, MLAEP, and burst suppression.

Because the *N*-methyl-D-aspartate receptor modulates the basic locomotor rhythmicity in cats, one could hypothesize that the change in the electroencephalographic spectrum evoked by ketamine might be partially derived from altered muscular activity.[15] Few data are available in current literature on the spectral characteristics of the frontal and retroauricular electromyographic activity in both the awake and anesthetized conditions. However, because other facial muscle groups are able to evoke an electrical activity with a power spectrum ranging from 0.4 to 512 Hz, we can expect a potential overlap of electromyographic activity with the frequency domains used for any of the investigated index calculations.[16] Because the detection of the electromyogram is not standardized between monitors, electromyographic activity might be present while going unnoticed by any of the monitors under investigation. Only the administration of a neuromuscular blocking agent (NMBA) is able to exclude all electromyographic interferences, in both the high- and low-frequency bands of the power spectrum analysis.

The aim of this study was to investigate whether the effects of ketamine on BIS, AAI1.6, SE, and RE are influenced by the simultaneous administration of rocuronium during propofol and remifentanil pseudo–steady state anesthesia. To answer this question, we performed a two-step analysis on one control group and three study

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groups receiving rocuronium, ketamine, or both. For each group, we compared the changes of the studied indices over time *versus* their respectively baseline values. Second, we performed a time-synchronized analysis between groups to find significant differences between the control group and the respective study groups.

Materials and Methods

This study was evaluated and approved by the institutional ethics committee (University Hospital, Ghent, Belgium). After obtaining written informed consent, 42 patients, all with American Society of Anesthesiologists physical status I or II, aged 18–65 yr, and scheduled to undergo gynecologic, urologic, or plastic surgery, were included. Premedication with benzodiazepines or anxiolytic drugs was not allowed. Exclusion criteria were anxiety necessitating benzodiazepines, the use of psychoactive drugs, a history of hearing disorders, or a neuromuscular disease.

A silent operation room was obtained for all patients. Electroencephalographic and MLAEP-derived measures, hemodynamic and ventilation parameters, and accelerometry were monitored as described in a later section. Induction was performed through an 18-gauge intravenous line, placed in a forearm vein. We took care not to infuse more than 200 ml of crystalloids before and during the study period to avoid excessive hemodynamic interference.

Anesthetic Drug Administration

Propofol and remifentanil administration was performed by a Fresenius Base A modular infusion pump (Fresenius Vial Infusion Systems, Brézins, France) connected *via* an RS-232 interface to a computer running $RUGLOOP_{II}$.‖ This computer-assisted continuous infusion device captured all monitored data while driving the pumps and calculating all pharmacokinetic–pharmacodynamic parameters in a time-synchronized way. Averaging of the data was performed using a 10-s interval.

After appropriate preoxygenation, remifentanil was targeted to a 2-ng/ml effect site concentration using the pharmacokinetic–pharmacodynamic model published by Minto *et al.*[17,18] After 2 min of remifentanil infusion, 1% propofol was started at a constant speed of 300 ml/h until loss of consciousness was detected, evaluated by the clinical signs of "loss of eye lash reflex" and "loss of response to name calling." At that point, the calculated effect site concentration of propofol, using the pharmacokinetic–pharmacodynamic model published by Schnider *et al.*,[19,20] was locked and maintained in $RUGLOOP_{II}$ as published previously.[5]

After insertion of a laryngeal mask and implementation of volume-controlled ventilation with the Datex ADU ventilator (Datex, Helsinki, Finland), ventilation parameters were adjusted to target an end-tidal carbon dioxide tension between 35 and 38 mmHg. After controlled ventilation was commenced, a 10-min equilibration period was maintained (more than three times the time to peak effect for propofol and remifentanil) to reach and maintain a pharmacokinetic–pharmacodynamic pseudo–steady state for both propofol and remifentanil calculated effect site concentrations. We carefully selected this level of anesthetic drug effect because it is a relevant situation for clinical anesthetic practice compatible with a surgical level of anesthesia.

Group Randomization

Baseline measurements were registered during 1 min after the equilibration period, and randomization was performed. The patients were allocated to one of four groups. The first group was the control group (CONTROL), meaning that no additional medication was administered during the study period. The second group (KET) received a bolus of ketamine (0.4 mg/kg) followed by a continuous infusion of ketamine ($1\ mg \cdot kg^{-1} \cdot h^{-1}$). The third group (ROC) received a single bolus of rocuronium (0.9 mg/kg), and the fourth group (ROC + KET) received both rocuronium and ketamine simultaneously in the same dose as mentioned above. After administration of the study drug according to randomization, all measurements were logged into the computer for a 15-min study period. After this study period, the laryngeal mask was replaced by an endotracheal tube if necessary, and surgery was commenced.

Electroencephalographic Measures

The BIS XP® (Aspect Medical Systems, Newton, MA), spectral entropy (Datex-Ohmeda, Helsinki, Finland), and A-Line® monitors (Danmeter A/S) were attached to the patients. For BIS, a BIS® sensor (Aspect Medical Systems) was attached to the right side of the patient's forehead. For A-Line®, three electrodes (A-Line® auditory evoked potential electrodes; Danmeter A/S) were positioned at the mid-forehead (+), left forehead (reference), and left mastoid (−). For RE and SE, we used an Entropy Sensor® (Datex-Ohmeda) attached to the left side of the head. The Entropy Sensor® was always attached closest to the eyebrow, the BIS® electrode was attached higher on the forehead, and the A-Line® auditory evoked potential electrodes were attached in between both.

The BIS was derived from the frontal electroencephalogram (At-Fpzt) and calculated by the BIS XP® monitor (Aspect Medical Systems). The smoothing time of the BIS® monitor was set at 15 s.

The AAI1.6 was calculated using version 1.6 of the A-Line® auditory evoked potential index monitor (Danmeter). The algorithm extracts information from the

‖ $RUGLOOP_{II}$, written by Tom De Smet, M.Sc., and Michel M. R. F. Struys, M.D., Ph.D. More information available at: http://www.anesthesia-uzgent.be. Accessed January 5, 2006.

electroencephalogram, burst suppression, and MLAEP as described elsewhere.[1] MLAEPs were elicited with headphones producing a bilateral click stimulus of variable click intensity and 2-ms duration. The click intensity is automatically adjusted according to the measured signal-to-noise ratio to avoid interfering startle responses. By using an autoregression method with exogenous input, the AAI1.6 can be calculated within a short delay time of approximately 6 s.

Response entropy and SE are calculated using the Datex M-Entropy® module (Datex). The algorithm has been published elsewhere.[21]

Hemodynamic and NMBA Monitoring

Electrocardiogram, capnography, oxygen saturation, and noninvasive blood pressure measurements were monitored by the Datex S5® monitor (Datex) and automatically logged into $RUGLOOP_{II}$. The hemodynamic data were averaged every minute.

An accelerometry monitor (S5® module; Datex) was positioned at the nervus ulnaris on the contralateral side of the intravenous line to detect the train-of-four percentage on the musculus adductor pollicis. After the patient had lost consciousness, a train-of-four percentage calculation was performed every 10 s to evaluate the curarization level during the study period. The accelerometry was calibrated in all patients according to the manufacturer's guidelines before any NMBA was administered.

Statistical Analysis

The significance level was set at 5% unless otherwise reported. Significant difference in demographic characteristics was tested using an analysis of variance with a Dunnett multiple comparisons test if appropriate. Statistical analysis was performed in an exploratory setting. This means we decided which statistical test to use after having inspected the raw data first.

There is no statistical accepted standard for analysis of trend data. All regression models become very complex, without any assumption about the development of data over time. In our case, such a model would need 16 parameters (16 time points), 3 parameters per group (with one reference group), and 15 times 3 parameters for all possible interactions between time and groups. Moreover, one could argue that the correlation between values within each patient would also have to be considered.

For these reasons, we chose to analyze the data in two steps. In the first step, we analyzed differences within each group (or, more precisely, if there were differences with respect to baseline). In a second analysis, we investigated whether there were differences between groups, without taking into account the time points.

For every individual patient, the raw data obtained from the studied monitors were averaged on a minute-by-minute basis starting with the baseline measurements resulting in one mean BIS, AAI1.6, RE, and SE per minute. By using an individual mean per minute, the natural fluctuation of the raw data obtained from all tested monitors is included in the analysis. Moreover, a change in response of a studied monitor must be consistent during the main part of every minute before it will trigger the statistical test to indicate significant difference. These individual means were averaged within every study group (CONTROL, ROC, KET, and ROC + KET), resulting in a group mean of means and SD for every studied minute. The statistical tests for the within- and between-group analyses were chosen after inspection of the raw data and after testing of normality using the Kolmogorov-Smirnov test.

For the within-group analysis, we performed a repeated-measures analysis of variance with Dunnett *post hoc* test for multiple comparisons to be able to detect significant differences between the baseline means of AAI1.6, BIS, SE, and RE and the consecutive minute-by-minute means within the CONTROL, ROC, KET, and ROC + KET groups ($P < 0.05$).

In a second analysis (the between-group analysis), we compared the results of the control group with the respective study groups in a time-synchronized way. We compared all study groups *versus* CONTROL, ROC *versus* ROC + KET, and KET *versus* ROC + KET. All of the baseline values were subtracted from the respective mean value of every consecutive minute to better reflect the amount of change *versus* baseline and to avoid the drawback of large baseline variability in the data set. For every comparison, the absolute difference of the means with the corresponding 95% confidence interval, based on the t distribution, was calculated. When the confidence interval of the difference of the means includes zero, the measured difference of means between the studied groups is based on coincidence. When zero is not included in the interval, the measured difference between means is statistical significant ($P < 0.05$).

The detection of electromyographic activity is not comparable between devices because a different definition is used in every monitor. Moreover, in some patients, conflicting results in detection of electromyographic activity were seen between monitors. Therefore, we only present electromyographic measurements results in a descriptive manner.

Results

Forty-two patients were included in this study. One patient was excluded *post hoc* because of a failure in the train-of-four measurement. Demographic data are shown in table 1. No significant differences were found between groups considering age, weight, height, lean body mass, body surface area, ideal body weight, and the proportion of males *versus* females.

Table 1. Demographic Data

	n	Age ± SD, yr	Weight ± SD, kg	Length ± SD, cm	BMI ± SD, kg/m^2	Sex, M/F
CONTROL	10	38 ± 10.1	78.3 ± 12.4	173.7 ± 13.2	25.9 ± 3.1	6/4
ROC	11	34.7 ± 7.3	70.4 ± 16.7	176 ± 7.8	22.6 ± 4.1	7/5
KET	10	37.8 ± 11.2	75.3 ± 19.2	174.6 ± 13.2	24.3 ± 3.2	5/5
ROC + KET	10	36.9 ± 10.8	72.4 ± 15.3	171.5 ± 6.5	24.4 ± 3.8	4/6

BMI = body mass index; CONTROL = control group; KET = ketamine group; n = total number of patients; ROC = rocuronium group; ROC + KET = rocuronium–ketamine group.

Hemodynamic parameters did not change in a clinically significant way for any group. The train-of-four percent was 0 for all patients receiving rocuronium from minute 3 until the end of the study period, indicating a clinical comparable drug effect of rocuronium during measurements.

The results for the within-group analysis are depicted in figures 1–4 for AAI1.6, BIS, RE, and SE, respectively. In CONTROL, no significant differences were found for all monitors when comparing baseline values with the consecutive minute means. In ROC, a significant decrease was seen for AAI1.6, BIS, and RE but not for SE. In KET, a significant increase was seen for RE and SE but not for AAI1.6 and BIS. Although the mean BIS showed an increasing trend after administration of ketamine, this trend never reached significance because of a wide range of BIS responses within our population. In ROC + KET, the mean RE and SE increased significantly. In ROC + KET, AAI1.6 decreased, but the decreasing response of RE and BIS seen after monoadministration of rocuronium disappeared after ketamine was associated. BIS did not increase significantly in the ROC + KET group. Again, this was probably caused by the large SDs reflecting major differences in response between patients in this study group.

Figures 5–8 show the results for the comparison of the absolute change from baseline between all study groups for AAI1.6, BIS, RE, and SE, respectively. Five comparisons were made: CONTROL *versus* KET, CONTROL *versus* ROC, CONTROL *versus* ROC + KET, ROC *versus* ROC + KET, and KET *versus* ROC + KET.

When comparing CONTROL *versus* KET, the absolute change from baseline of the AAI1.6 was comparable at all times. For BIS, RE, and SE, the absolute change from baseline was significantly larger for KET compared with CONTROL, during a considerable duration of time.

When comparing CONTROL *versus* ROC, AAI1.6, RE, and SE did not change significantly from baseline in ROC compared with CONTROL. For BIS, only on minute 6 was the absolute change from baseline significantly larger in ROC compared with CONTROL.

The comparison between CONTROL *versus* ROC + KET showed no difference in changes from baseline for AAI1.6 and BIS. RE and SE had a significantly larger change from baseline in ROC + KET compared with CONTROL during several minutes.

When comparing ROC *versus* ROC + KET, AAI1.6 and BIS did not show a significant change from baseline. RE and SE had a significantly larger change from baseline in ROC + KET compared with ROC during several minutes.

When comparing KET *versus* ROC + KET, no differences were found in the absolute changes from baseline for AAI1.6, RE, and SE between groups. For BIS, the changes from baseline were significantly larger in KET compared with ROC + KET from minute 3 to minute 8.

Persistent electromyographic activity was detected throughout the study period in two patients of the CONTROL group. One case was detected by the A-Line®, and one was detected by the entropy monitor. For the KET group, no major electromyographic activity was detected by any monitor; however, the difference between RE and SE gradually increased during the study period from a mean difference of 1.3 to 2.2. For the ROC + KET group, no electromyogram was registered by the A-Line® or BIS®, but on the entropy monitor, a comparable gradual increase in mean difference between RE and SE was seen (from 1.13 at baseline to 2.26 at minute 15). For the ROC group, both the A-Line® and the entropy monitor detected electromyography in the same patient from baseline to minute 2 of the study period. The BIS® monitor did not detect any electromyographic activity in any of the studied patients.

One patient of the ROC group kept showing electromyographic activity throughout the study period on the A-Line® monitor, even after the administration of rocuronium. This electromyographic activity was not detected by BIS® or entropy. Unfortunately, a failure in the train-of-four monitor made it impossible to evaluate the intensity of the NMBA effect in this particular patient. Therefore, we excluded this patient from the analysis.

Discussion

In this study, the response of four electroencephalographic and MLAEP-derived depth of anesthesia monitors have been investigated in clinical anesthetic conditions, during which ketamine and rocuronium were administered in a solitary or combined way. The response of all monitors was compared with baseline values (within-group analysis) and with a control group, receiving a comparable calculated steady state anesthesia as given in all study groups (between-group analysis).

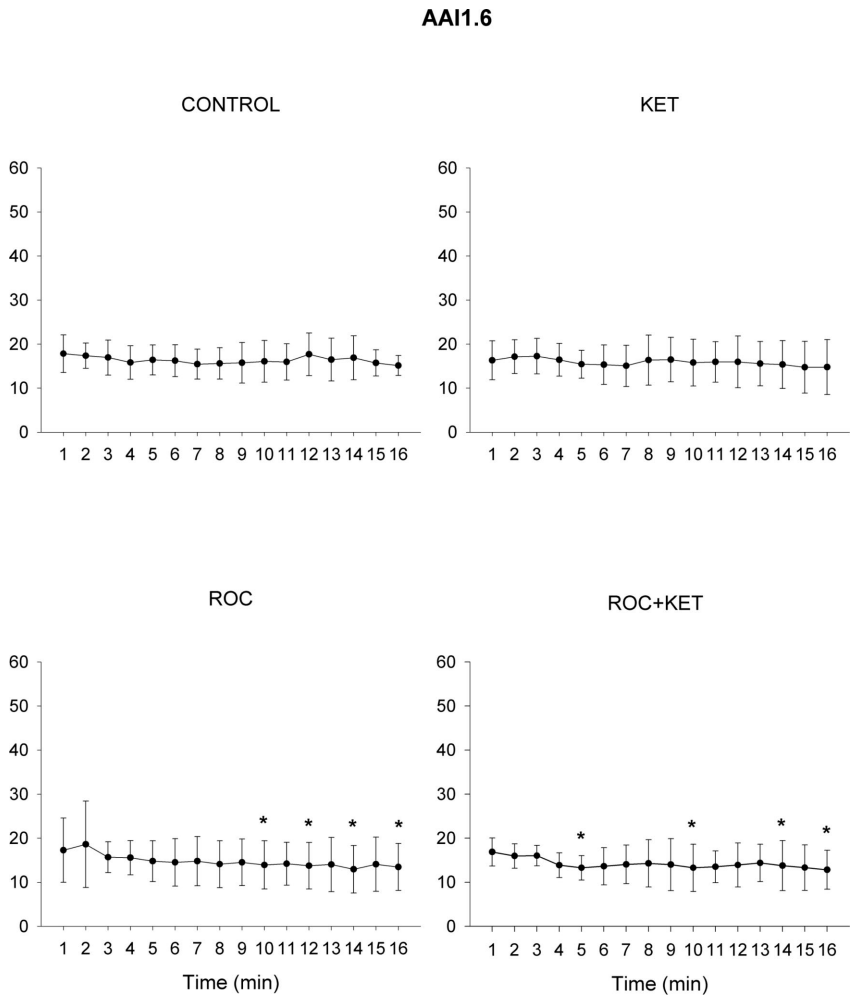

Fig. 1. Mean A-Line® auditory evoked potential index, version 1.6 (AAI1.6), is depicted for every study group, calculated on a minute-by-minute basis with respective SDs, from minute 1 (baseline) to minute 16. CONTROL, KET, ROC, ROC + KET = results of the control, ketamine, rocuronium, and combined rocuronium–ketamine groups, respectively. * $P < 0.05$.

For the CONTROL group, all monitors remained unaltered after baseline measurements, indicating a comparable clinical and pharmacologic calculated steady state anesthesia between patients during the study period.

In the KET group, the within-group analysis suggested that AAI1.6 and BIS were not affected significantly by ketamine. In contrast, RE and SE showed an increasing response after solitary ketamine administration.

One could speculate that the addition of electroencephalogram-extracted information to the MLAEP-derived information, as done for AAI1.6, does not alter the index behavior compared with the former version of the A-Line® monitor, which was based on MLAEP alone.[5] However, it is inherent in the new algorithm that the electroencephalogram-derived information only becomes an important covariate for index calculations in conditions with low signal-to-noise ratios for MLAEP detection.[1] In our setting, all environmental interference was avoided, causing a high signal-to-noise ratio, which might have been sufficient to avoid the use of electroencephalogram-derived information. As such, we can not exclude the occurrence of a more pronounced effect

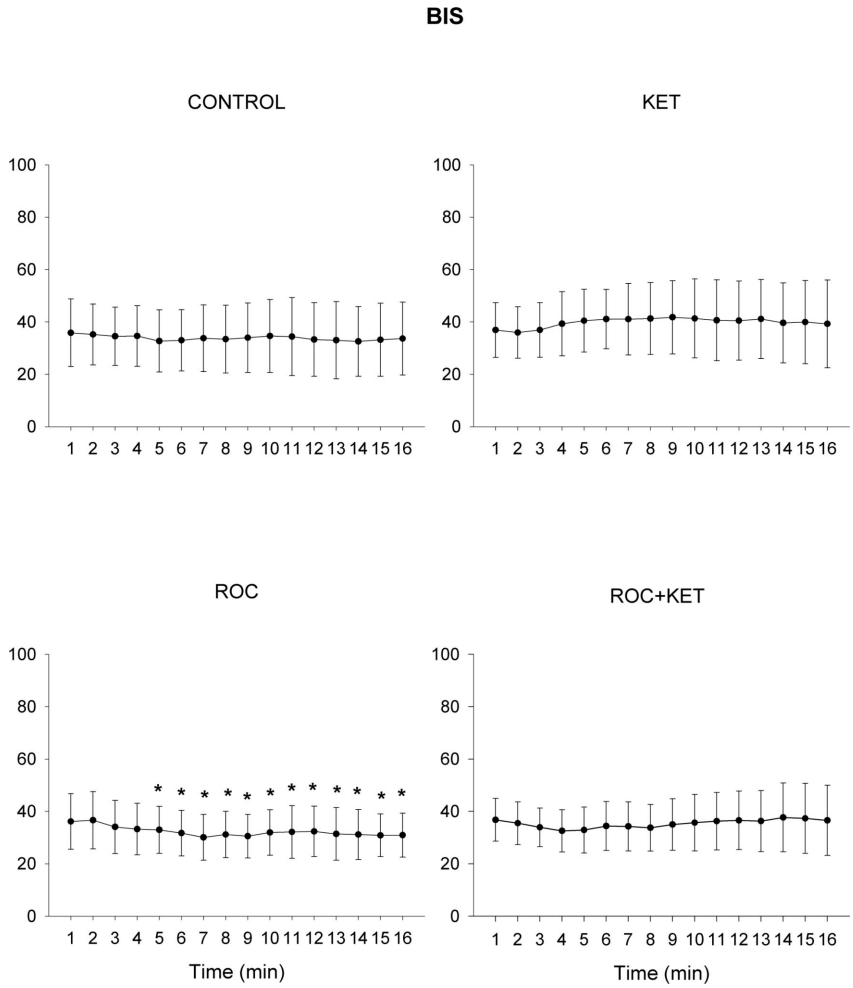

Fig. 2. Mean Bispectral Index (BIS) is depicted for every study group, calculated on a minute-by-minute basis with respective SDs, from minute 1 (baseline) to minute 16. CONTROL, KET, ROC, ROC + KET = results of the control, ketamine, rocuronium, and combined rocuronium–ketamine groups, respectively. * $P < 0.05$.

of ketamine during more challenging conditions for MLAEP extraction (*e.g.*, during surgery).

For BIS, the result of the within-group analysis of KET is in contrast with older publications indicating an increase in BIS after ketamine administration.[5,14] Although figure 2 shows a clear increasing trend for BIS in KET, this trend is not significant because of the large SDs, which are a reflection of the large variability in BIS responses within our population. In contrast, the between-group analysis has more power to detect significant differences compared with the within-group analysis, due to the elimination of the baseline variability in the data set. This was done by subtracting the baseline mean from the mean of every studied minute. As such, this new data set reflects the absolute change from baseline. In figure 6, this resulted in a significantly larger change from baseline for BIS in KET compared with CONTROL during several minutes. The less pronounced effects of ketamine on BIS in our study compared with the known literature are probably related to the deeper level of anesthesia chosen in our study. Because no surgical stimulation was present during measurement,

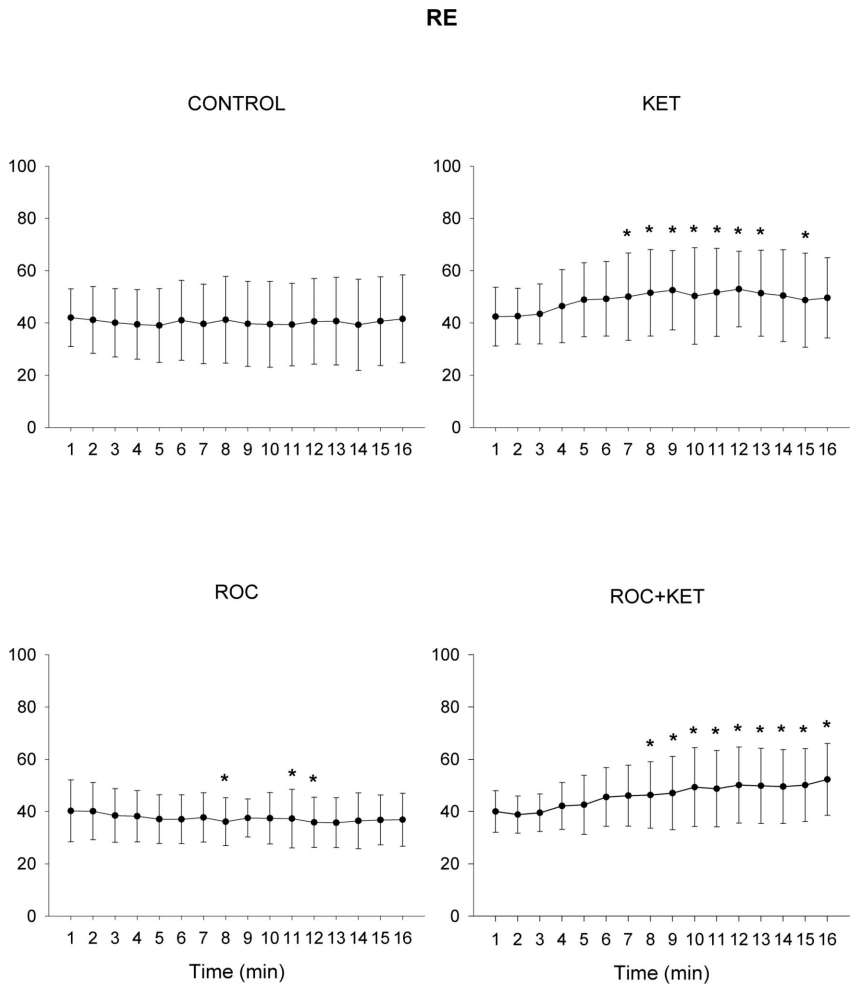

Fig. 3. Mean response entropy (RE) is depicted for every study group, calculated on a minute-by-minute basis with respective SDs, from minute 1 (baseline) to minute 16. CONTROL, KET, ROC, ROC + KET = results of the control, ketamine, rocuronium, and combined rocuronium–ketamine groups, respectively. * $P < 0.05$.

the combination of remifentanil and propofol evoked a moderate level of burst suppression patterns in some patients during the study period. The number of patients with burst suppression was comparable between groups, being 3, 4, 4, and 3 patients for CONTROL, ROC, KET, and ROC + KET, respectively. It has been shown before that BIS loses monotonicity when a suppression rate is detected between 0 and 40%.[1] At that time, an increased interindividual variability in BIS calculations is present compared with lighter levels of anesthesia.[1] This increased variability, which does not occur for the other studied monitors, might explain the limited response of mean BIS after ketamine administration in our study population.

In the ROC group, rocuronium decreased the AAI1.6 and the RE compared with baseline in the within-group analysis, but this effect could not be confirmed by the between-group analysis. When comparing CONTROL *versus* ROC, AAI1.6, RE, and SE did not change significantly from baseline in ROC compared with CONTROL.

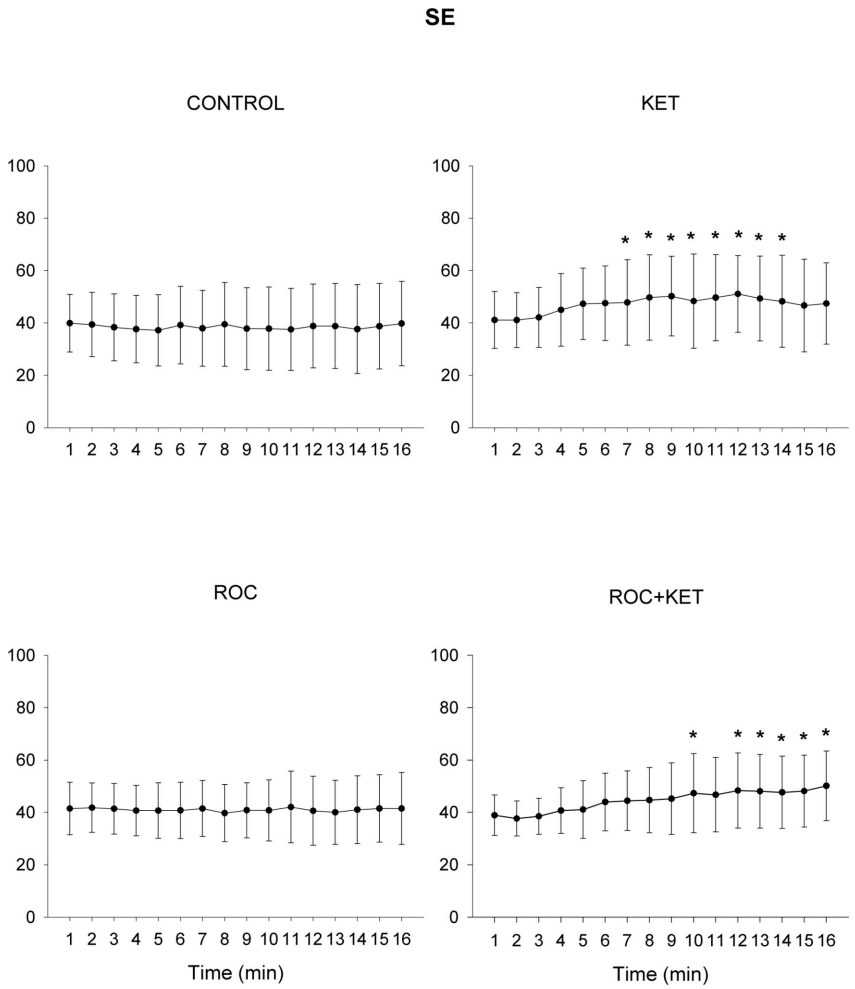

Fig. 4. Mean state entropy (SE) is depicted for every study group, calculated on a minute-by-minute basis with respective SDs, from minute 1 (baseline) to minute 16. CONTROL, KET, ROC, ROC + KET = results of the control, ketamine, rocuronium, and combined rocuronium–ketamine groups, respectively. * $P < 0.05$.

This was in contrast to our findings in the within-group analysis for AAI1.6, BIS, and RE. Apparently, the electromyogram is a main portion of the baseline interindividual variability of AAI1.6, BIS, and RE. By eliminating the baseline variability in our between-group analysis, the test does not detect any difference anymore between CONTROL and ROC. These findings suggest that the effect of rocuronium on the mean values of AAI1.6, RE, and BIS is mainly caused by a drastic reduction in interindividual variability. For BIS, the decreasing effect in ROC is more pronounced compared with the other monitors. Therefore, it is reflected in both the within- and between-group analyses. These results are in agreement with the literature.[7,9,12]

In the ROC + KET group, the AAI1.6 remained sensitive for the decreasing effects of rocuronium in the within-group analysis. For RE and SE, rocuronium was not able to abolish or dampen the effects of ketamine. These results suggest that the distortions in the RE and SE calculations evoked by ketamine are independent of the electromyographic activity.

For BIS, the within-group analysis was not able to

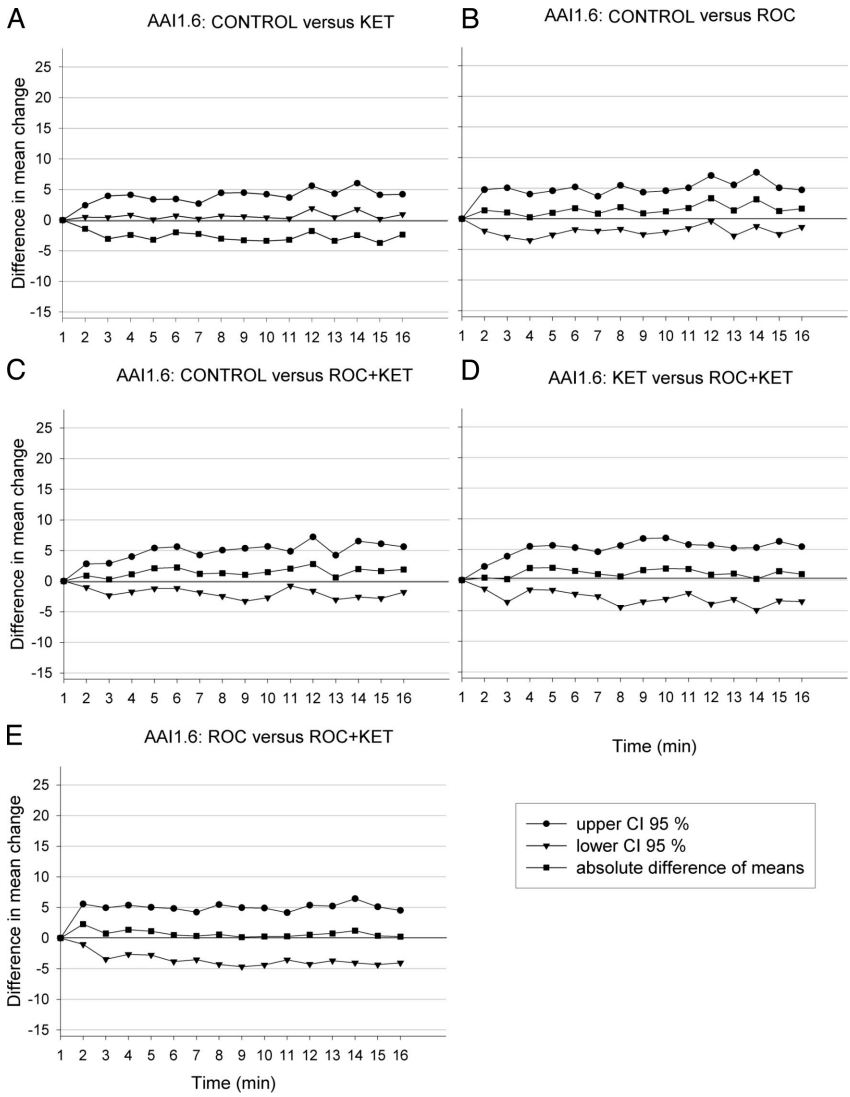

Fig. 5. Between-group comparison for the A-Line® auditory evoked potential index, version 1.6 (AAI1.6). Minute 1 is the baseline measurement. The *axis* shows the absolute difference of the mean change from baseline between the compared groups for every studied minute, together with the corresponding 95% confidence interval (CI). CONTROL = control group; KET = ketamine group; ROC = rocuronium group; ROC + KET = combined rocuronium–ketamine group.

detect any change in ROC + KET. Again, this is probably due to the wide variety in BIS responses in our population. However, the comparison between KET and ROC + KET indicated a larger change from baseline in KET compared with ROC + KET at the beginning of the study period. From minute 9 through minute 15, no differences were found between KET and ROC + KET. Although not significantly different from baseline, a progressive higher trend was seen near the end of the study period for ROC + KET compared with CONTROL. By combining these findings, we conclude that ketamine still has an increasing effect on BIS calculations; however, this effect is much smaller at

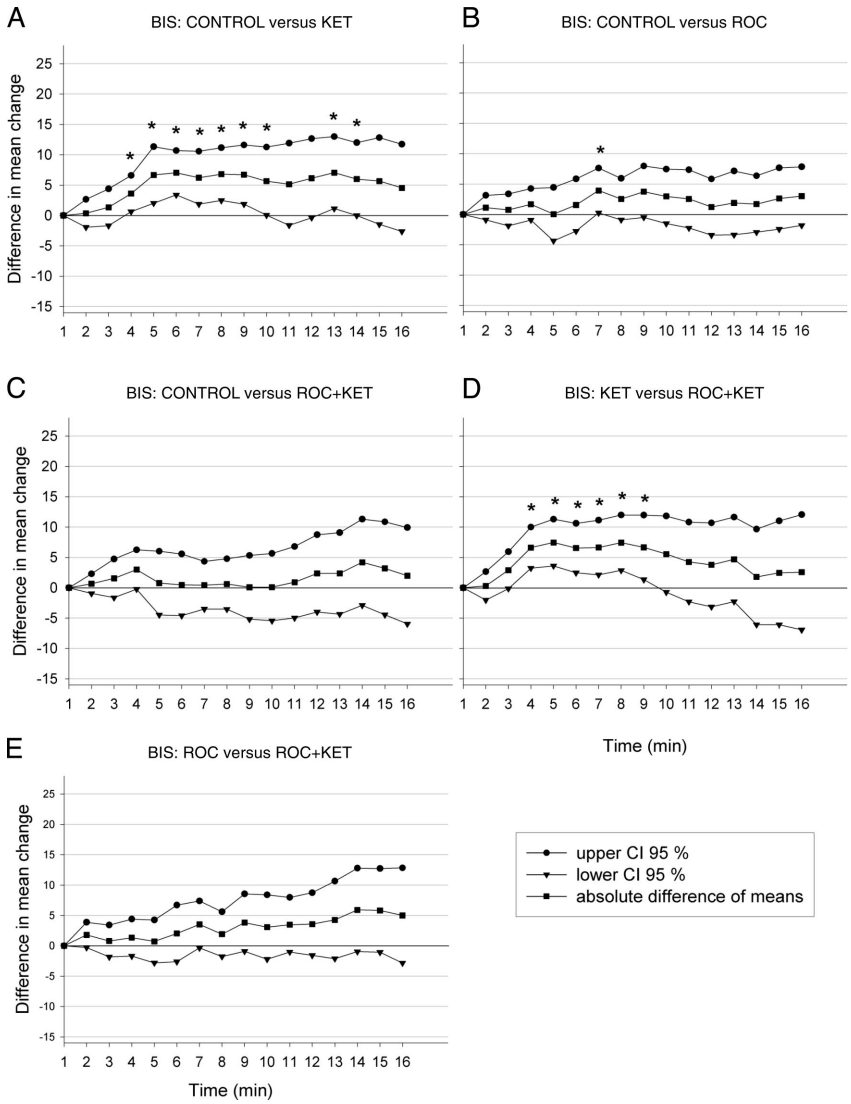

Fig. 6. Between-group comparison for the Bispectral Index (BIS). Minute 1 is the baseline measurement. The *axis* shows the absolute difference of the mean change from baseline between the compared groups for every studied minute, together with the corresponding 95% confidence interval (CI). CONTROL = control group; KET = ketamine group; ROC = rocuronium group; ROC + KET = combined rocuronium–ketamine group. * $P < 0.05$.

deep levels of anesthesia compared with the known effects from the literature.[5]

All electroencephalographic and MLAEP-derived depth of anesthesia monitors are characterized by a large interindividual and intraindividual variability. A major reason for this variability is the occurrence of electromyographic activity. In our study, electromyographic activity was detected only by the A-Line® and entropy monitor in a limited number of patients. This was probably caused by a lower electromyographic activity at deep levels of anesthesia compared with other studies performed at lighter levels of anesthesia, during an ongoing surgical

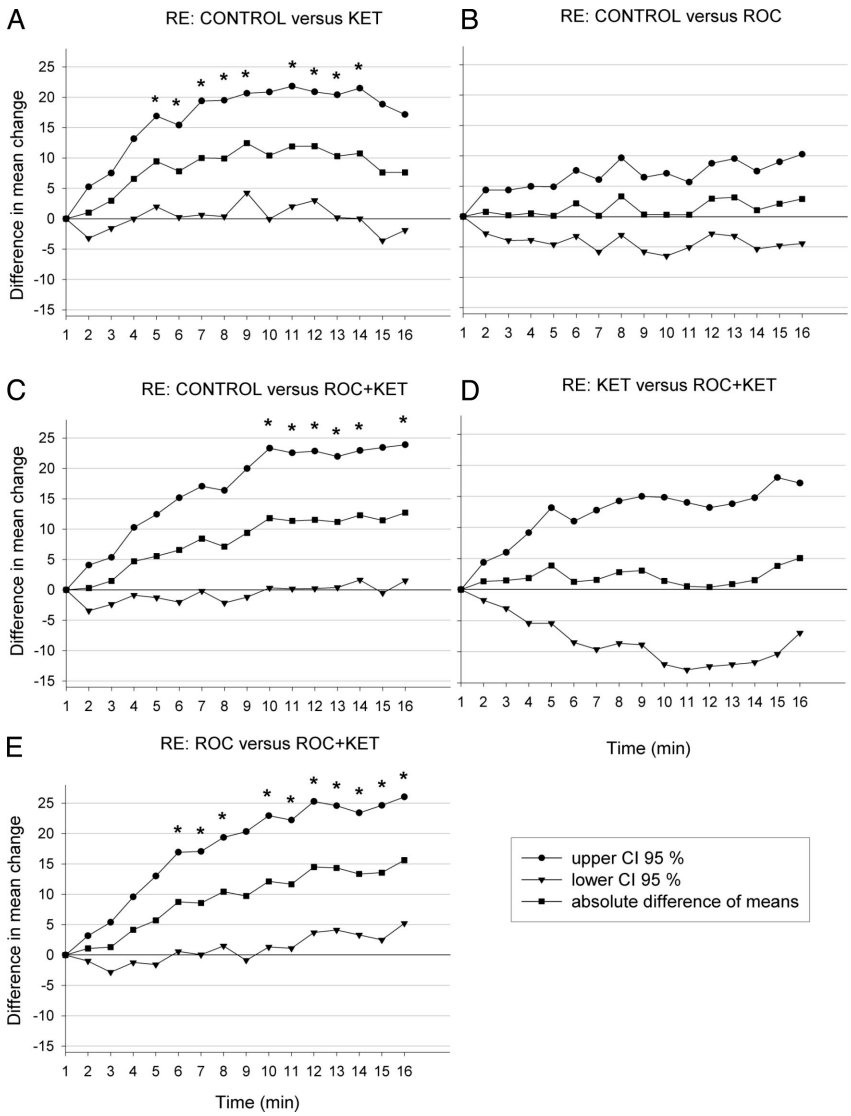

Fig. 7. Between-group comparison for the response entropy (RE). Minute 1 is the baseline measurement. The *axis* shows the absolute difference of the mean change from baseline between the compared groups for every studied minute, together with the corresponding 95% confidence interval (CI). CONTROL = control group; KET = ketamine group; ROC = rocuronium group; ROC + KET = combined rocuronium–ketamine group. * $P < 0.05$.

procedure or in the awake patient.[8] However, anesthesiologists should also be aware of the fact that all studied monitors define the electromyogram in a different frequency band of the power spectrum, ranging from 70 to 110 Hz, 65 to 85 Hz, and 32 to 47 Hz for BIS, AAI1.6, and the entropy monitor, respectively. Although a limited number of data are available in the current literature, one can speculate that electromyographic activity occurs in a much wider range and still can distort index calculations at times where no electromyogram detection is present.

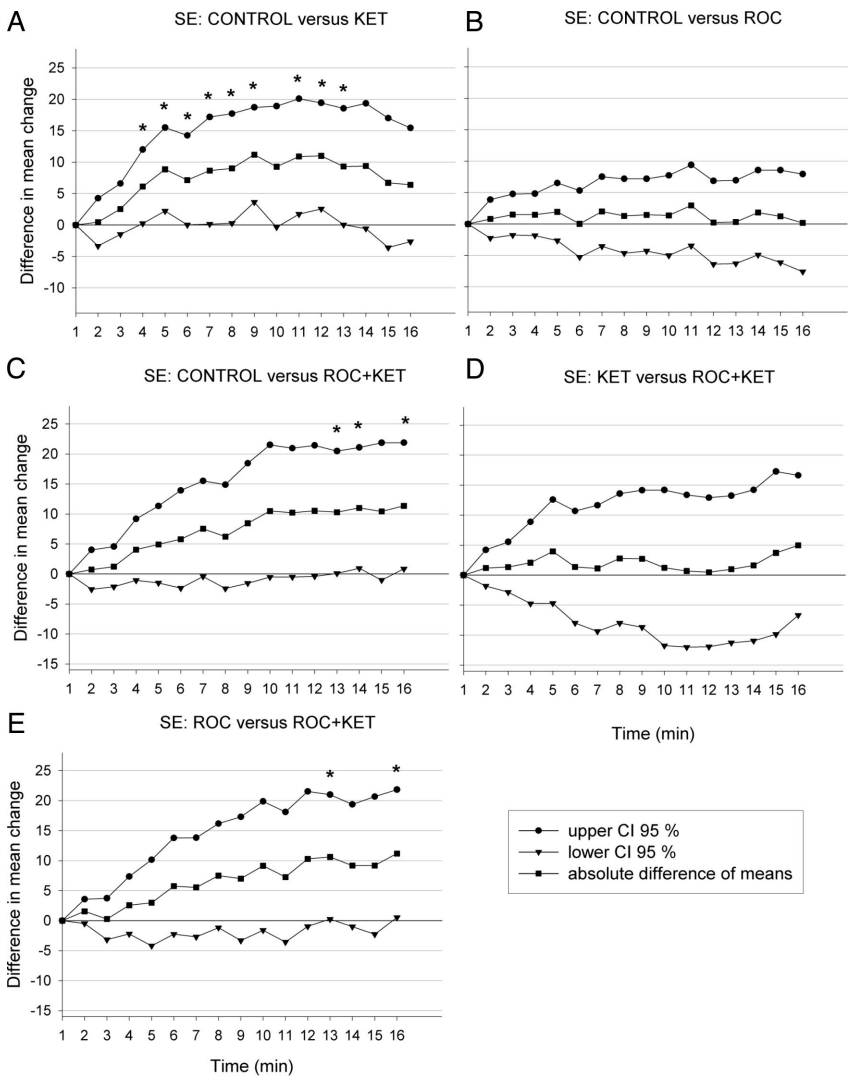

Fig. 8. Between-group comparison for the state entropy (SE). Minute 1 is the baseline measurement. The *axis* shows the absolute difference of the mean change from baseline between the compared groups for every studied minute, together with the corresponding 95% confidence interval (CI). CONTROL = control group; KET = ketamine group; ROC = rocuronium group; ROC + KET = combined rocuronium–ketamine group. * $P < 0.05$.

The entropy monitor defines the electromyogram between 32 and 47 Hz in the power spectrum. This frequency domain is included in the algorithm for the calculation of RE, which is propagated by the company commercializing the monitor, as a fast-responding depth of hypnosis index or even as an indicator of arousal. By including a part of the electromyogram in the algorithm, the decreasing RE after solitary rocuronium administration is to be expected. However, if a depth of hypnosis monitor detects the administration of a nonhypnotic NMBA, this drawback might cause a need for redefining cutoff values of the depth of hypnosis indices, whether a NMBA is in use or not. At this time, no commercially available electroencephalogram or MLAEP-derived mon-

itor is able to detect or filter all of the interfering electromyographic activity in a sufficiently accurate way. As such, it is our opinion that the electromyogram should be considered as noise in the data until more evidence is available to support the use of the electromyogram as an indicator of arousal or the hypnotic component of anesthesia. At this time, no evidence exists to support the 32- to 47-Hz frequency band as superior to the other frequency bands, as an indicator of arousal.

Because the effects of ketamine were larger on RE compared with SE, a progressive increase in the difference between RE and SE was seen over time in both KET and ROC + KET. This gives the impression of an increased electromyographic activity. Because rocuronium is not able to reduce the increasing RE in ROC + KET, we consider this progressive increasing difference between RE and SE to be a result of the electroencephalographic alterations evoked by ketamine, not by electromyographic activation.

As a general remark on the results of this study, we must consider the fact that the inconsistent significant levels over time, which are seen in several comparisons, can be related to the limitations in group size combined with the large biologic variability of the studied indices. The fact that the difference in a comparison is not considered to be significant does not always mean that there is no difference. We might have simply missed it.

Statistical analysis for this study was performed in an exploratory, rather than a confirmatory, setting. This means that we decided which statistical test to use after inspecting the raw data first. Although this methodology might be prone to bias, we preferred to do so because we could not be sure how the model would behave in advance. Moreover, because the biologic variability of electroencephalographic and MLAEP-derived indices is large, we preferred to proceed with statistical analysis only after we found a meaningful trend in the raw data. The interpretation of our results should be considered with this drawback in mind.

In conclusion, we investigated the effects of ketamine and rocuronium on four electroencephalographic and MLAEP-derived parameters. Ketamine has no effect on AAI1.6 calculations during anesthetic conditions with a high signal-to-noise ratio for MLAEP extraction. AAI1.6, BIS, and RE decrease after rocuronium administration. RE and SE increase after ketamine administration, independent of the effects of rocuronium. In our population, BIS has a less pronounced response compared with the known literature, after the administration of ketamine. We hypothesize that this is caused by the higher variability of BIS calculations at deep levels of anesthesia compatible with burst suppression patterns.

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3.6 Study 6: Cerebral State Index during Steady State Propofol and Remifentanil Anesthesia. A comparison with Bispectral Index and the A-Line® ARX Index

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3.6.1 Introduction

In comparison with EEG derived hypnotic drug effect monitors, the additional value of MLAEP as an endpoint of hypnotic drug effect, remains debatable.(1-4) The AAI technology has reached a high level of performance, although remaining practical issues might hamper commercial success, compared to the EEG indices. The use of headphones disrupts the verbal communication between the patient and the anesthesiologist, which is indicated by many users to be an important drawback. Secondly, MLAEP can not be used in patients with important hearing deficits. Additionally, loud acoustic stimuli applied for a long time might appear harmful for the patient's hearing. Therefore, MLAEP derived indices should be used with caution during long procedures, or for monitoring sedation at the intensive care. Finnally, As long as no high quality outcome and macro-economical studies are performed, it remains difficult to evaluate the balance between costs and gain of the AAI.

After a thorough evaluation of our study results, and discussing the formerly mentioned practical issues within the consortium,,Danmeter has chosen to abandon the MLAEP as a source of information, and developed a new EEG based index, called the cerebral state index (CSI). The CSI has been developed using raw binary files registered with the AEP monitor/2, containing all electroencephalographic data of one of our studies.(5) The CSI algorithm is based on a combination of "neural networking" and "fuzzy logic" technology.(cf. appendix of the manuscript) Due to the development process, CSI is the first electroencephalographic monitor using the same electrode position as the AEP monitor/2. Theoretically, with this parameter, we will be able to perform trials that compare AAI, with a simultaneously extracted EEG derived index using identical electrode positions. This creates possibilities for the future, to investigating the additional value of MLAEP versus EEG, as a measure of cerebral hypnotic drug effect. Of course, CSI needs to be validated first, both at a clinical and pharmacological level.

We validated CSI in a **retrospective database** of raw EEG samples. We reused all the raw data files containing EEG and MLAEP, obtained during our former validation studies, published by Struys et al.(6) and by Vereecke et al.(7) By doing so, the CSI algorithm has been validated, both on a clinical level (detecting the level of OAA/S SCALE), as on a pharmacological level (detecting the Ce_{PROP}). Moreover, in this study, we used the composite index AAI as a validated pharmacodynamic reflection of cerebral hypnotic drug effect. Therefore, this study is an example of how AAI can be applied for further pharmacologic and neurophysiologic developments.

Within the limitations of the retrospective methodology, we concluded that CSI is a promising index, performing adequately for detecting both clinical and pharmacological endpoints of hypnotic drug effect. More prospective clinical validation is mandatory, as our methodology excludes the evaluation of potential shortfalls of hardware and software of the commercialized "cerebral state monitor" (Danmeter, Odense, Denmark). In fact we only validated the "CSI algorithm".

The CSI validation study has won the "best clinical trial" award 2006 of the Belgian Society of Anesthesia and Resuscitation (BSAR).

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3.6.2 Manuscript

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Cerebral State Index during Propofol Anesthesia

A Comparison with the Bispectral Index and the A-Line ARX Index

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Background: **The objective of this study was to prospectively test the Cerebral State Index designed for measuring the depth of anesthesia. The Cerebral State Index is calculated using a fuzzy logic combination of four subparameters of the electroencephalographic signal. The performance of the Cerebral State Index was compared with that of the Bispectral Index and the A-Line ARX Index.**

Methods: **This study applied raw data from two previously published clinical protocols. The patients in protocol 1 were given a continuous propofol infusion, 300 ml/h, until 80% of burst suppression occurred. In protocol 2, a stepwise increased target-controlled infusion of propofol was administered to patients until loss of response to noxious stimuli while the Observer's Assessment of Alertness and Sedation was registered every 4 min. The Cerebral State Index was calculated off-line from the recorded electroencephalographic data. The Spearman rank correlation coefficient between electronic indices and the effect site concentration of propofol was calculated along with the prediction probability of each index to predict the Observer's Assessment of Alertness and Sedation level.**

Results: **The Spearman rank correlation coefficients between the Cerebral State Index, Bispectral Index, and A-Line ARX Index and the propofol effect site concentration were −0.94, −0.89, and −0.82, respectively, in protocol 1, whereas the prediction probability values between the Cerebral State Index, Bispectral Index, and A-Line ARX Index and the Observer's Assessment of Alertness and Sedation score in protocol 2 were 0.92, 0.93, and 0.91, respectively.**

Conclusion: **The Cerebral State Index detects well the graduated levels of propofol anesthesia when compared with the propofol effect site concentration and the Observer's Assessment of Alertness and Sedation score.**

MONITORING depth of anesthesia is gaining increased importance. A number of methods have been suggested, most of them based on the analysis of the electroencephalographic signal. These methods can in general be classified into those that analyze the spontaneous electroencephalographic activity and those that measure the response of the electroencephalographic signal to acoustic stimuli, auditory evoked potentials (AEPs).

In spontaneous electroencephalogram analysis, initial methods analyzed one single computerized parameter, such as the spectral edge frequency,[1] but during the past decade, a multiparametric approach has been favored in some methods, such as the clustering analysis of subparameters of the electroencephalogram proposed by Thomsen and Prior[2] or the Bispectral Index (BIS®; Aspect Medical Systems, Inc., Newton, MA) validated in numerous publications and calculated by using four subparameters of the electroencephalographic signal.[3–5]

For the AEP, the particular component that correlates to the depth of anesthesia is the midlatency auditory evoked potential (MLAEP). The MLAEP is allegedly superior to the spontaneous electroencephalographic methods, at least in the early works where the AEP was compared with single parametric analysis of the electroencephalograph.[6] However, the multiparametric analyses have been shown to have as good a correlation to depth of anesthesia as the MLAEP.[7–9] Recently, Jensen *et al.*[10] developed a composite index, the A-Line ARX Index, version 1.6 (AAI1.6), based on a combination of MLAEP and spontaneous electroencephalographic data. For the MLAEP part of this algorithm, a previously validated method for fast extraction based on an autoregressive model with an exogenous input adaptive model was used.[10] If the MLAEP quality is too low, spontaneous electroencephalographic components are used. The AAI1.6 is commercially implemented in the AEP Monitor/2 (Danmeter A/S, Odense, Denmark).[11]

All mentioned derived electroencephalographic and MLAEP indices assume an underlying mathematical function governing the relation between the electroencephalogram and the clinical state of the patient. This might possibly result in less accurate functioning at specific anesthetic states, *e.g.*, causing plateau levels or other less reactive periods in the index at specific levels of the hypnotic component of anesthesia.[12,13]

A different method for system identification using neural networks and fuzzy logic has been applied increasingly in medical technology, where it provides decision support and expert systems with powerful reasoning capabilities.[14,15] Fuzzy reasoning allows the implementation of very complex processes, where a simple mathematical model cannot be obtained. Fuzzy logic can also be successfully applied to highly nonlinear processes,

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where it is observed to greatly simplify the modeling. The advantage of this approach is that it does not assume any underlying mathematical function governing the relation between the electroencephalogram and the clinical state of the patient. It might be hypothesized that this offers modeling advantages because it rather uses clinical data to determine the values of the fuzzy rules to achieve the best fit between the subparameters of the electroencephalogram and the anesthetic depth.

A new index, the Cerebral State Index (CSI), defined by two of the authors (E.W.J. and P.M.), is based on the combination of four subparameters of the electroencephalographic signal. Three of these are derived from spectral analysis of the electroencephalogram, and the fourth is the burst suppression ratio (BS%) calculated by the monitor.

These parameters are used as inputs to an Adaptive Neuro Fuzzy Inference System (ANFIS),[16,17] which optimizes the rules governing the relation between the input parameters using a least mean squares approach. The mathematics is described in detail in the accompanying appendix. Recently, the CSI has been implemented in a commercially available monitor, the Cerebral State Monitor (Danmeter A/S).

The objective of this study was to prospectively test the correlation of the CSI with the effect site concentration of propofol and with patient state of responsiveness to verbal command as assessed by the Observer's Assessment of Alertness and Sedation (OAA/S) scale. The performance of the CSI was also compared with that of the BIS and AAI indexes in the same patient populations.

Materials and Methods

The raw data from two previously published studies were used. Both patient databases were exclusively obtained at Ghent University Hospital (Gent, Belgium). For all patients in both protocols, informed consent was obtained after approval from the institutional ethics committee.

Protocol 1 studied deep anesthetic levels reaching high levels of burst suppression during propofol administration.[11] Protocol 2 studied the correlation between different clinical levels of responsiveness as measured by the OAA/S scale[18] *versus* the electroencephalogram during steady state propofol administration.[7] Because the raw electroencephalographic data, vital signs, and pharmacologic data were recorded online and stored electronically in a time-synchronized way, it was possible to reanalyze the raw electroencephalographic data without the requirement of including new patients.

Clinical Protocols

In both protocols, exclusion criteria were weight less than 70% or more than 130% of ideal body weight, neurologic disorder, and recent use of psychoactive medication, including alcohol.

Table 1. Responsiveness Scores of the Modified OAA/S Scale

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Response only after name is called loudly and/or repeatedly
2	Response only after mild prodding or shaking
1	Response only after painful trapezius squeeze
0	No response after painful trapezius squeeze

OAA/S = Observer's Assessment of Alertness and Sedation.

Protocol 1 (Deep Anesthesia Reaching High Levels of Burst Suppression). The population for this study protocol was formed by 13 patients (10 women, 3 men; American Society of Anesthesiologists physical status I; aged 18–65 yr) scheduled to undergo ambulatory gynecologic or urologic surgery. Before drug administration was started, all patients were asked to close their eyes and relax for 2 min. After this time, baseline measurements were taken. All patients then received a continuous infusion of propofol at 300 ml/h. Infusion was continued until a burst suppression level of 80% or higher was achieved. However, propofol infusion was stopped earlier if the mean arterial blood pressure became lower than 50 mmHg.

Protocol 2 (OAA/S Levels). The study population was formed by 20 female patients (American Society of Anesthesiologists physical status I; aged 18–60 yr) scheduled to undergo ambulatory gynecologic surgery. All patients received an effect site compartment target-controlled infusion of propofol. The initial propofol effect site concentration (Ce prop) was set at 1.5 μg/ml and increased every 4 min by 0.5 μg/ml until an OAA/S level of 0 was reached. The level of consciousness, assessed through the OAA/S score, was recorded along with the electronic indices before each increase in effect target concentration. Table 1 describes the OAA/S score levels and their clinical interpretation.

In both protocols, a similar clinical setting was used. Propofol was administered as the only drug, through a large left forearm vein, and infusion was conducted *via* the computer-assisted continuous-infusion device RUGLOOP II (Demed Engineering, Temse, Belgium). This device drove a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France) through an RS-232 interface. To determine Ce prop, the software uses a three-compartment model enlarged with an effect site compartment, previously published by Schnider *et al.*[19,20] The calculated Ce prop was computed to yield a time to peak effect of 1.6 min after bolus injection,[21] as also published by Schnider *et al.*[19,20] and clinically confirmed by Struys *et al.*[22] Heart rate and noninvasive blood pressure, pulse oximetry, and capnography were recorded at 1-min time

intervals using an S5® monitor (Datex-Ohmeda, Helsinki, Finland). All patients maintained spontaneous ventilation *via* a facemask delivering 100% oxygen.

Electroencephalographic Measurements

In both protocols, the BIS and the raw electroencephalographic signal with the AEP signal embedded were simultaneously acquired for all patients. The BIS XP® (version 4.0) was derived from the frontal electroencephalogram (At-Fpzt) and calculated by the A-2000 BIS® Monitor using four BIS®-Sensor electrodes (Aspect Medical Systems, Inc.). The smoothening time of the BIS® monitor was set at 15 s. The raw electroencephalographic signal corresponding to each patient was recorded using the A-Line Monitor (Scientific Version; Danmeter A/S) with three electrodes positioned at midforehead (+), left forehead (reference), and left mastoid (−) along with headphones to deliver a train of bilateral clicks at a frequency of 9 Hz with a 2-ms duration and an adaptable intensity set automatically by the monitor.

The electroencephalographic signal was sampled at 900 Hz and band-pass filtered in the 0.5- to 45-Hz band. The AAI1.6 was calculated off-line based on the raw MLAEP data. For all calculations, the AAI has been scaled to a 0–60 interval (AAI_{60}). This scale provides the best stability in the awake state, as proven by Vereecke *et al.*[11] The CSI was calculated off-line from the raw electroencephalographic records. Mathematical details from this technology are given in the appendix. It has already been shown that the embedded AEPs resulting from the click stimuli have no effect on the BIS,[23] which includes the β ratio in its calculation. Although an influence of the AEP in the raw signal cannot be excluded, in general, the signal-to-noise ratio between the AEP and the electroencephalographic signal is less than 1 to 30; therefore, the influence of the clicks is assumed to be less than approximately 3% of the final value.

The burst suppression values were taken from the specific parameters calculated by each monitor: the suppression ratio (SR) provided by the BIS and BS% for the AAI_{60} and CSI calculations.

Statistical Analysis

Comparison between CSI, BIS, and AAI. In protocol 1, a linear regression and its corresponding correlation coefficient was calculated between CSI and BIS. A nonparametric approach, the Spearman rank correlation, *R*, was calculated to study the relation between Ce prop and CSI, BIS, or AAI. The Spearman rank correlation was calculated on pooled data.

The relation between Ce prop and the electroencephalographic measures of anesthetic drug effect was analyzed using a sigmoid E_{max} model,

$$\text{Effect} = E_0 + \frac{(E_{max} - E_0) \times C_{e\gamma}}{(C_{e50\gamma} + C_{e\gamma})},$$

where Effect is the electroencephalographic effect being measured (CSI), E_0 is the baseline measurement when no drug is present, E_{max} is the maximum possible drug effect, Ce is the calculated effect site concentration of propofol, Ce_{50} is the effect site concentration associated with 50% maximal drug effect, and γ is the steepness of the concentration–response relation curve. The model parameters were estimated using NONMEM V (Globomax LLC, Hanover, MD). The parameters for the BIS and AAI_{60} have already been estimated for this population by Vereecke *et al.*[11] The relation between Ce prop and CSI was calculated using the same NONMEM V specifications as described by Vereecke *et al.*[11]

In protocol 2, the ability of the CSI, BIS, and AAI to predict the response to verbal command, as defined by the OAA/S scale, was evaluated using prediction probability (P_K). Prediction probability was calculated using a custom spreadsheet macro, P_KMACRO, developed by Smith *et al.*[24,25] The P_K value was calculated as the mean from pooled data of all patients. A P_K of 1 for the CSI indicator would mean that CSI always decreases (increases) as the patient reaches deeper levels of anesthesia according to the OAA/S scale. Such an indicator can perfectly predict the anesthetic state. Alternatively, a P_K value of 0.5 would mean that the indicator is useless for predicting the depth of anesthesia. The jackknife method was used to compute the SE of the estimate.[24,25] After having evaluated normal distribution, a Student *t* test with Bonferroni correction was used to evaluate significant difference between the P_K means. A Friedman analysis was conducted, and if $P < 0.05$, a Wilcoxon signed rank sum test was used to test for significance between the electronic indices at adjacent OAA/S levels (5 *vs.* 4, 4 *vs.* 3 . . .).

Results

Protocol 1

All data from the published study[11] were included in the analysis.

Figure 1 shows a pooled scatter plot of the raw data for all patients. A relation between Ce prop and the electronic indices, CSI, BIS, and AAI_{60}, is hereby shown in plots A, B, and C, respectively. The behavior of the two spontaneous electroencephalographic indices, CSI and BIS, were comparable, as shown in figure 2. The equation for the regression line was CSI = 1.02 BIS ($P < 0.05$ for linearity). Table 2 shows the results of the Spearman rank correlation between propofol and the three indices. The CSI showed a significantly higher correlation than the other two indices.

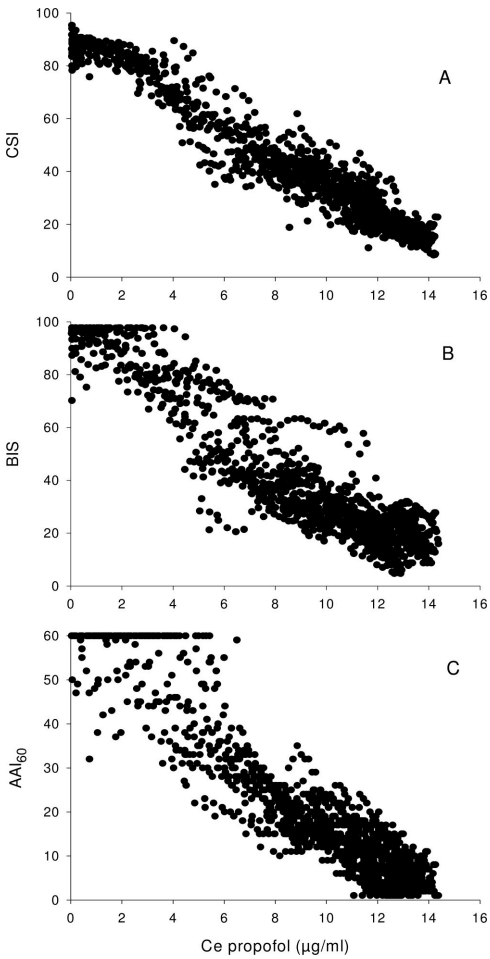

Fig. 1. Raw data of all patients for the three electronic indices (Cerebral State Index [CSI, *A*]; Bispectral Index [BIS, *B*]; and A-Line ARX Index version 1.6, scaled to 60 [AAI_{60}, *C*]) *versus* propofol effect site concentration (Ce propofol) for the data recorded according to protocol 1.

The high concentrations of propofol caused considerable amount of burst suppression, as shown in figure 3. Figure 3A shows CSI *versus* its BS%, where the relation is almost linear when BS% is larger than 60. The equation for the regression line, assuming BS% > 1, is shown to have a significant ($P < 0.05$) linear fit to the data. Less linearity is seen for the BIS and AAI_{60} in figures 3A and B, respectively.

The NONMEM analysis (fig. 4) showed that for this population, the typical values (coefficient of variation) for the sigmoid E_{max} model between Ce prop and CSI

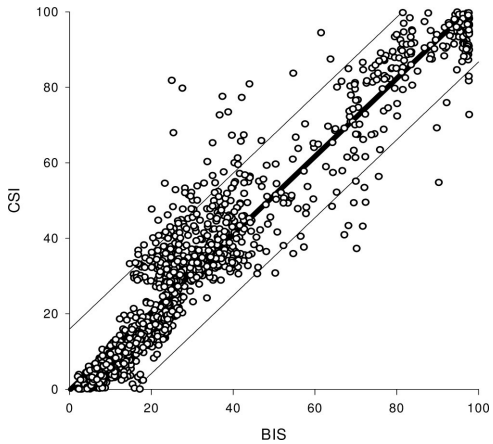

Fig. 2. Linear regression (*thick line*) and 95% confidence interval (*thin lines*) between the Cerebral State Index (CSI) and the Bispectral Index (BIS) values for the data recorded according to protocol 1. The regression followed the equation CSI-1.02 BIS.

were C_{50} = 9.85 (65%), E_0 = 94 (4.6%), E_{max} = −100 (110%), and γ = 3.45 (31%). The SD, depicting the residual intraindividual variability, was 6.79.

Protocol 2

All raw data from the published study were included.[7] Figure 5 shows the CSI, BIS, and AAI_{60} *versus* OAA/S. To compare the different adjacent OAA/S levels for all three indices, a Mann–Whitney U test was applied. The results are shown in table 3. The table shows that in general the BIS and AAI were able to distinguish between OAA/S levels 5 to 2. For the CSI, a smoother drop was observed between level 3 and 2, whereas at deeper anesthesia, the CSI was the only parameter that showed significant differences between OAA/S levels 0 and 1.

Table 4 lists the P_K values of the OAA/S for CSI, BIS, and AAI_{60}. All P_K values were above 0.9, and there were no significant differences between the P_K values of the three electronic indices.

Table 2. Spearman Rank Correlations for the Three Electronic Indices *vs.* Propofol Effect Site Concentration According to Protocol 1

Index	Spearman Rank Correlation
BIS	−0.818*
AAI_{60}	−0.887*
CSI	−0.943*

* Correlation is significant at the 0.01 level.

AAI_{60} = A-Line ARX Index scaled to 60; BIS = Bispectral Index; CSI = Cerebral State Index.

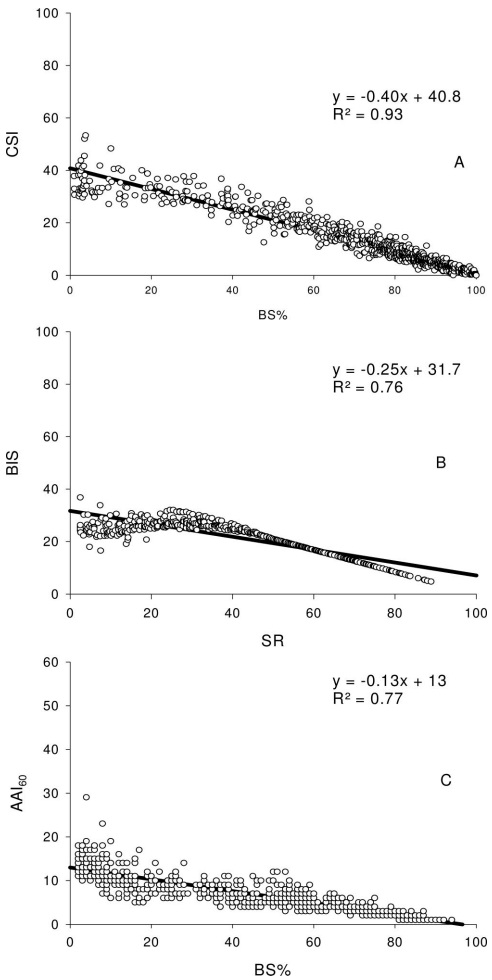

Fig. 3. The relation between the Cerebral State Index (CSI, *A*); Bispectral Index (BIS, *B*); and A-Line ARX Index version 1.6, scaled to 60 (AAI_{60}, *C*), and burst suppression, measured as the burst suppression percentage (BS%) for the CSI and AAI_{60} and as the suppression ratio (SR) for the BIS.

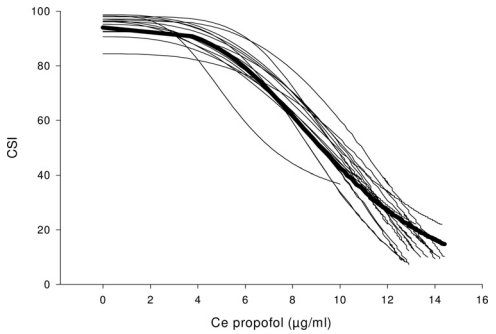

Fig. 4. Sigmoid E_{max} model of the Cerebral State Index (CSI) *versus* propofol effect site concentration (Ce propofol). The *thin lines* represent individual patient fits, whereas the *bold line* represents the typical curve of the population data.

Discussion

The core of the CSI signal processing algorithm is fuzzy logic based. The power of fuzzy logic lies in its ability to perform reasonable and meaningful operations on concepts that cannot be easily codified using a classic logic approach. Such modifications allow for a much more flexible and widespread use of reliable and consistent logic in a variety of applications.

Classic logic relies on something being either true or false. Therefore, either something completely belongs to a set or it is completely excluded from it. Fuzzy logic broadens this definition of membership. The basis of the logic is fuzzy sets. Unlike in "crisp" sets, where membership is full or none, an object is allowed to belong only partly to one set. The membership of an object to a particular set is described by a real value from a range between 0 and 1. Such logic allows a much easier application of many problems that cannot be easily implemented using the classic approach, which only allows a single object to be a member of two mutually exclusive—in the "crisp" sense—sets.

The most common use of fuzzy logic lies in the field of control systems, although the theory seems to have big potential in the different fields of artificial intelligence. The large computational burden of fuzzy logic systems is only justified if a model describing the relation between input and output does not exist. This is the case in the current application, where the relation between the input parameters (β ratio, α ratio, the difference between the two, and BS%) and the clinical state is unknown; therefore, no model is available, which means that the neuro-fuzzy method offers a fast and robust alternative to establish the causal relation between inputs and output. This causal relation may well incorporate nonlinear relations between the linear input parameters, β and α ratio.

When validating a depth of anesthesia monitor, it can only be called accurate if it (1) provides an accurate correlation with cerebral drug effect reflected by its effect site concentration, (2) correlates well with the clinical state of the patients, and (3) informs the clinician when excessive levels of anesthesia are present. In this study, these three aspects were tested using existing databases. The propofol effect site concentration has shown a good correlation to anesthetic depth in several studies, in particular in controlled patient groups; therefore, it was used in this study to evaluate the performance of the CSI as a cerebral drug effect monitor in

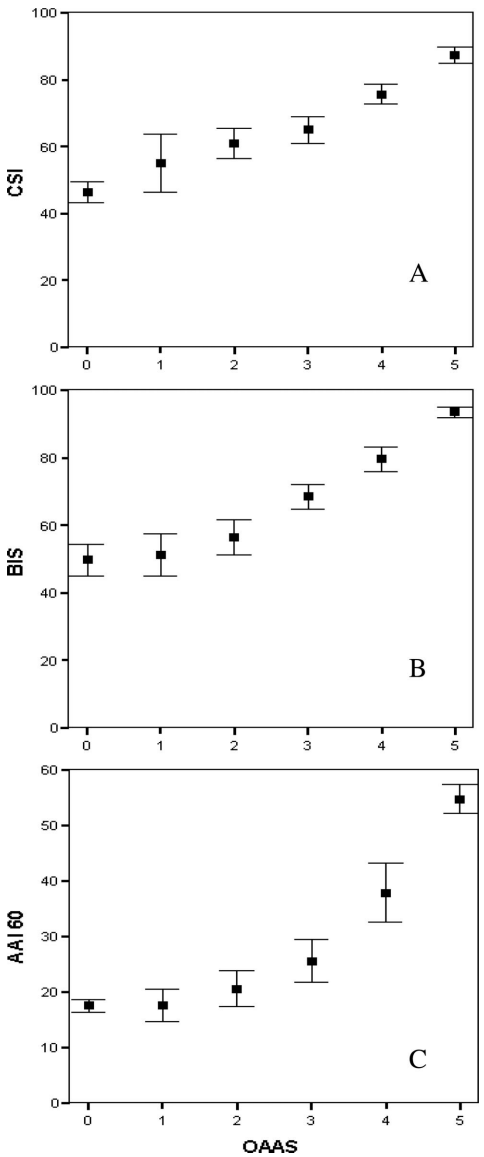

Fig. 5. Mean and 95% confidence interval for Cerebral State Index (CSI, *A*); Bispectral Index (BIS, *B*); and A-Line ARX Index version 1.6, scaled to 60 (AAI_{60}, *C*) *versus* the Observer's Assessment of Alertness and Sedation Scale (OAAS), according to protocol 2.

comparison to BIS and AAI_{60}.[7–9,26] Even more important, a depth of anesthesia monitor should first of all correlate well with the clinical state of the patient, with minimum time delay and variation. To investigate this, we selected the OAA/S score because it provides a good correlation with a clinical reflection of the hypnotic component of anesthesia and has been tested prospectively,[27] although it has its limitations, as we pointed out in a previous article.[28] Burst suppression represents a benign pattern frequently seen in a healthy brain at deep levels of the hypnotic component of anesthesia. It can be identified in the raw electroencephalogram and is composed of episodes of electrical quiescence (the "suppression") alternated with high-frequency, high-amplitude electrical activity (the "bursts"). Increasing anesthetic drug concentration causes increased duration of the suppression periods. Burst suppression patterns of the electroencephalogram are classically quantified as the percentage duration of suppression over a given time period. Because the detection of burst suppression represents an important electroencephalogram component to measure deep levels of anesthesia, its correlation to its univariate parameter is important and must be investigated[9]

The current study demonstrated that both a continuous (protocol 1) and a stepwise increase (protocol 2) in Ce prop resulted in a monotonic decrease in the CSI. These results are comparable with those of our previous study,[7,8] where it was shown that AAI and BIS decrease during increased Ce prop. In protocol 1, CSI showed the highest correlation to the effect site concentration of propofol. The highest concentration of Ce prop was 14 μg/ml which resulted in CSI values approximately from 10 to 20. The higher correlation might be because the

Table 3. Mann–Whitney U Test Results (*P* Values) for Significant Differences between the Values of the Three Electronic Indices to Predict Adjacent OAA/S Levels from Protocol 2

OAA/S	BIS	AAI_{60}	CSI
5 *vs.* 4	< 0.05	< 0.05	< 0.05
4 *vs.* 3	< 0.05	< 0.05	< 0.05
3 *vs.* 2	< 0.05	< 0.05	0.101
2 *vs.* 1	0.186	0.209	0.257
1 *vs.* 0	0.530	0.956	< 0.05

All *P* values are two-tailed. $P < 0.05$: significant difference.

AAI_{60} = A-Line ARX Index scaled to 60; BIS = Bispectral Index; CSI = Cerebral State Index; OAA/S = Observer's Assessment of Alertness and Sedation.

Table 4. Prediction Probability (P_K) for the Electronic Indices to Predict OAA/S Levels from Protocol 2

	P_K for OAA/S Levels
BIS	0.93 (0.01)
AAI_{60}	0.91 (0.01)
CSI	0.92 (0.01)

Results are shown as mean (SD) jackknife estimate.

AAI_{60} = A-Line ARX Index scaled to 60; BIS = Bispectral Index; CSI = Cerebral State Index; OAA/S = Observer's Assessment of Alertness and Sedation.

CSI system was partially trained with propofol data, so the pharmacologic relation is already installed in the system. More research must be done to test the behavior of the CSI when other drugs and drug combinations are used. The behaviors of the two indices derived from the spontaneous electroencephalogram, CSI and BIS, are shown in figure 2 to be similar. In this study, a nearly pure linear relation was found between CSI and BIS. Although scientifically not that important, it is interesting from a clinical point of view to have values in the same range with different monitors when indicating identical clinical hypnotic–anesthetic states. Although the overall correlation between CSI and BIS is high, individual variations were present, *e.g.*, a CSI value of 35 simultaneously with a BIS of 70, or *vice versa*, a BIS value of 30 while the CSI was 80. Those individual values are difficult to account for with the current study design; however, it could be due to interference from electromyography in either device. In the awake state, there was a high clustering of data with values of both CSI and BIS above 90. It cannot be ruled out that the CSI has some influence of facialis electromyography. This should be explored in a study where neuromuscular blocking agents are administered.

As said, the behavior of the index at levels of burst suppression was studied. The linear regressions between the indices and their burst suppression shows the highest linearity for CSI, also at low values of BS%, than the corresponding linear regression between BIS and the suppression ratio calculated by the BIS® monitor. The relation between BIS and the suppression ratio seems to be biphasic, as published previously,[11] which in turn may indicate a better detection of the onset of suppression by the CSI. The AAI_{60} has less correlation, but monophasic, to the BS% because the BS% has less weight in the AAI algorithm. As shown in figure 5 and table 3, a decrease in the OAA/S score resulted in a monotonic decrease in the three indices, CSI, BIS, and AAI_{60}. A difference between the ability to differentiate the adjacent levels of the OAA/S scale was significant. As seen in previous work,[11] BIS and AAI revealed relevant information until loss of consciousness but did not become significant at deeper levels of anesthesia because of the wide variability among patients. The CSI was less significant at the intermediate levels 2 and 3 but was able to distinguish the lowest levels of the OAA/S scale, indicating both loss of responsiveness to verbal and tactile stimuli.

The P_K is widely used to investigate the overall relative performance of the different electroencephalogram-derived indices to measure the hypnotic component of anesthesia.[24,25] Therefore, P_K analysis was conducted on the study data of protocol 2. Table 4 shows that the CSI has a similar performance to BIS and AAI_{60} in terms of predicting the clinical state of the patient assessed by the OAA/S scale. Interestingly, the P_K value for AAI_{60} (0.91), hereby using the new composite index based on MLAEP and electroencephalographic components, performed somewhat better than the original solitary used fast extracting AEP index (AAI version 1.4, scaled from 0 to 100) as published in the original article[7] using the same data sets (P_K = 0.89).

In conclusion, this study shows that the CSI produces a highly significant correlation with the propofol effect site concentration and has a high P_K for the OAA/S. Further studies are needed to validate the CSI to establish its reliability in clinical practice applying other types of anesthetics and other patient groups.

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Appendix

The CSI

The objective of the Cerebral State Index (CSI) is to monitor the level of consciousness during general anesthesia. The CSI is a unitless scale from 0 to 100, where 0 indicates a flat electroencephalographic signal and 100 indicates the awake state. The range of adequate anesthesia is designed as the 40–60 range (table A1).

The CSI requires three electrodes positioned at the middle forehead, left forehead, and left mastoid. Alternatively, the right forehead and right mastoid can be used.

Methods of the CSI

The CSI is calculated based on four subparameters of the electroencephalogram: β ratio, α ratio, β ratio $-$ α ratio, and burst suppression, defining an index from 0 to 100. The novelty of the CSI is that a fuzzy inference system was used to define the index.

The particular method used was the Adaptive Neuro Fuzzy Inference System (ANFIS). The ANFIS was trained with prerecorded electroencephalographic data, where 20 were from propofol and remifentanil anesthesia, 15 were from propofol infusion until 80% of burst suppression occurred, and 15 were from sevoflurane anesthesia, giving a total of 50 patients. The total number of training points was more than 200,000, sufficient to achieve convergence for the 104 parameters in the 4 input 2 membership ANFIS model. All data were recorded at Gent University Hospital (Ghent, Belgium).

Table A1. Definition of CSI Range

CSI	Clinical State
90–100	Awake
80–90	Drowsy
60–80	Light anesthesia or sedation
40–60	Range considered as adequate for surgical anesthesia
10–40	Deep anesthesia, in most cases accompanied by burst suppression
0–10	The BS% is larger than 75. When CSI is below 3, the electroencephalograph is practically isoelectric.

BS% = burst suppression ratio; CSI = Cerebral State Index.

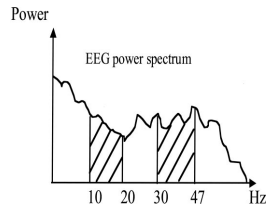

Fig. A1. Power spectrum of the electroencephalographic signal (EEG) showing the bands used for the calculation of the β ratio.

During burst suppression, the α and β ratios are no longer monotonously decreasing as a function of anesthetic depth, and therefore, they cannot be used in the calculation of the final index. Figure A1 shows the power spectrum of the electroencephalographic signal with the bands of the β ratio marked.

The four subparameters were defined as follows:

$$\beta\text{ratio} = \log \frac{E_{30-42.5\text{Hz}}}{E_{11-21\text{Hz}}}$$

$$\alpha\text{ratio} = \log \frac{E_{30-42.5\text{Hz}}}{E_{6-12\text{Hz}}}$$

$$(\beta - \alpha)\text{ratio} = \log \frac{E_{6-12\text{Hz}}}{E_{11-21\text{Hz}}}$$

Burst suppression (BS%): defined as the percentage of time in a 30-s window where the amplitude of the electroencephalographic signal was less than 3.5 μV.

ANFIS Model Structure. Each of the three energy ratios correlates individually to the depth of anesthesia. This has been shown in numerous publications. However, by combining the parameters, a higher correlation coefficient can be reached. An intuitive explanation to this fact is that the ANFIS system, shown in figure A2, automatically uses the best parameter, meaning that when one fails, another might still be a good correlate. The burst suppression parameter indicates deep anesthesia; in this case, the weight on the spectral parameters will be less because they are not good correlates during deep anesthesia with burst suppression due to the nonstationary nature of the electroencephalogram in this situation. The structure of the ANFIS systems ensures that each linguistic term is represented by only one fuzzy set. The parameters of the ANFIS model were determined by training using 50 patients anesthetized with propofol, remifentanil, and inhalational agents. The total update delay of the index is approximately 15 s.

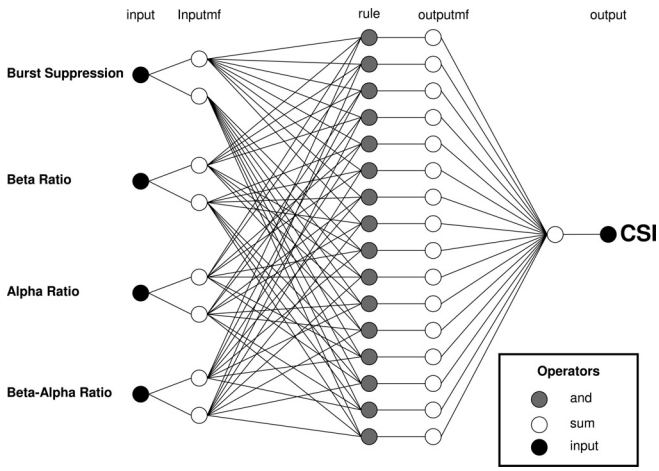

Fig. A2. The Adaptive Neuro Fuzzy Inference System (ANFIS) structure. CSI = Cerebral State Index; inputmf = input membership function; outputmf = output membership function.

Chapter 4
Final discussion and future perspectives

Chapter 4 Final discussion and future perspectives

When Thornton et al, in 1983, first described the dose dependent changes in the auditory evoked potentials (AEP), or more specifically, in the mid-latency auditory evoked potentials (MLAEP), she suggested this phenomenon could be a useful tool for quantifying the cerebral effects of hypnotic drugs.(1-4) It took more than 20 years to overcome the major drawbacks and reach this goal.

At first, multiple methods were developed to improve the extraction speed of MLAEP from the raw electroencephalogram. Various mathematical approaches were applied to the raw MLAEP wave in order to reduce observers bias and convert the complex and rapid changes of MLAEP waves into one single number.(5-11) This single number is much easier to interpret by an anesthesiologist without specific theoretical background on MLAEP behavior. If the number goes down, the patient is more asleep, and vice versa.

This thesis is the result of intense collaboration between engineers, developing both hard- and software, and anesthesiologists, with an interest in clinical pharmacology and neurophysiology. This cooperation started with the original study of Erik Weber Jensen, who worked at the Polytechnic University of Catalonia, Centre of Research in Biomedical Engineering, Barcelona, Spain. He applied an autoregressive model with exogenous input (ARX) on raw MLAEP, to allow a faster detection of changes in MLAEP.(12,13) It allowed extraction of MLAEP derived information with a delay of only 6 seconds. No former MLAEP derived index or spontaneous electroencephalographic derived index could respond this fast to changes in cerebral hypnotic drug effect. Therefore, the new index was a promising tool for anesthesia applications.

At first this technology was only tested on rats. However, for human applications, more severe regulations on hardware quality and safety need to be fulfilled, as dictated by European regulation authorities. The development of such a device is expensive and demands special expertise, which could be provided by the medical industry only. Danmeter, located in Odense, Denmark, agreed to support the development of such a hardware device, called A-Line®, and aimed to commercialize the technology, after human validation. During this validation and optimization process, different names were given to both the monitor, and the MLAEP derived A-Line ARX index (AAI). At first, Alaris® (now incorporated in the "Cardinal Health" industrial group) was the global distributor of the A-Line® monitor, while Danmeter only focused on production. At that time the name of the monitor was: "Alaris® A-Line Monitor" or "Alaris® AEP monitor". Since the implementation of the AAI version 1.6, the monitor is called "AEP monitor/2", and is now (again) distributed by Danmeter. AAI has been used in many studies as an abbreviation of both "A-Line® ARX Index" and "A-Line® Auditory Evoked Potential Index". The algorithms of the consecutive versions $AAI_{1.5}$ and $AAI_{1.6}$, are completely different. Their behavior as a measure for cerebral drug effect is incomparable. Confusingly, the basic name of both versions remained "AAI". All these changes happened over a 6 years period. This might induce confusion for anesthesiologists with less expertise in the subject. Nowadays, the AEP monitor/2 becomes more widespread. Therefore, a consensus on the exact name will be increasingly important.

As an independent partner of the consortium, the department of anesthesia of the University Hospital Ghent, has become involved in the clinical validation process for human applications of AAI. At the start, no consensus was available on the minimal quality levels that should be met by a depth-of-anesthesia monitor to guarantee safety in the general population. This lack of regulations has led to an explosive growth of new indices, based on several neurophysiologic principles. They all claim to have sufficiently adequate correlation with the hypnotic component of anesthesia. However, the “validation processes” of these devices are very diverse and often not comparable. Therefore, we aimed to construct a systematic methodology, for validating and comparing different indices of the hypnotic component of anesthesia, independent of their neurophysiologic background. This methodology had to be sufficiently reproducible, in order to allow other researchers to compare future indices in the same way.

Our strategy includes several steps:

1) The AAI must be able to discriminate several **clinical endpoints** of anesthesia that are routinely used in anesthesia practice. The sensitivity for this measurement must be maintained, both in mono-anesthetic conditions, as during combined effects of hypnotics and analgesics. This validation step was the target of our first study.

2) As neurophysiologic measures are also indicated as pharmacodynamic endpoints of cerebral drug effect, new indices of the hypnotic component of anesthesia, should have a close correlation with the effect-site concentrations of anesthetic hypnotic drugs. As the detection of clinical endpoints of anesthesia is susceptible to observers bias, the **pharmacological validation** allows a more objective comparison of different monitors of cerebral hypnotic drug effect. This step in the validation process was the target of our second publication.

3) The effects of **difficult molecules**, such as ketamine, nitrous oxide and xenon, should be explored. The classic hypnotic drugs use a molecular mechanism based on the gamma-amino butyric acid (GABA) receptor action. However, some molecules evoke clinical anesthetic effects by means of an alternative pathway. For these molecules, the N-Methyl-D-Aspartate (NMDA) receptor appears to be a key player in the effectuation of anesthesia. In our research group, we chose to test the effects of ketamine, a clinically relevant NMDA inhibitor, on the first version of AAI and bispectral index. The results are found in our fourth publication. We found that no EEG or MLAEP derived index is able to detect the potentiating interaction between propofol and ketamine adequately.

4) The potential **mechanical or physiologic interferences** must be depicted as thoroughly as possible. Many of these problems only arise once a monitor is implemented in clinical practice. It was already published in the scientific literature, that electromyographic (EMG) interference is a general problem for all EEG and MLAEP derived measurements. For AAI, Ge et al. confirmed that AAI was reduced by vecuronium, a neuro-muscular blocking agent. This study strongly suggests

that EMG interferences determines part of the AAI calculation. We obtained much information on the interference of EMG on AAI in our fifth study.(14)

With these steps, we present a reproducible strategy to compare the behavior of EEG and MLAEP derived indices during total intravenous anesthesia. Our methodology has received a very positive response at international congresses. Recently, other research centers published comparable validation protocols.(15,16) As our protocols have been designed in cooperation, and with extensive feedback from international partners, both from the academic and the industrial world, we feel to have made a substantial contribution to the construction of an objective benchmark for monitors of the hypnotic component of anesthesia.

Prior to the start of the consortium, its participants agreed to implement a gentleman's agreement. All costs for the studies were covered by institutional funding. Danmeter delivered the necessary hardware for AEP monitoring. The results of the studies were reported to Danmeter before the date of publication, in order for them to allow adaptations in marketing strategy, or to develop improvements on the technology. On the other hand, the rights of publishing the results and the ownership of the data remained with the independent researcher. In order to avoid conflicts of interest, the company that has a commercial interest in the device could not interfere with the format or the content of the publication.

During the first validation session, we observed some drawbacks for AAI, in comparison with other EEG derived indices. Our results suggest that MLAEP derived information depicts a rather "limited" range of hypnotic drug effect compared to EEG derived indices. The consortium generated several suggestions that could help to improve the performance of the ARX technology. Some of these suggestions were addressed by the manufacturer, and implemented in a new monitor, called the AEP monitor/2. This new device contains both hard- and software improvements.

The most apparent adaptation in the AEP monitor/2 was the use of **a new algorithm for AAI calculation**, called AAI version1.6 ($AAI_{1.6}$). The source of information on cerebral drug effect was expanded from solitary MLAEP to a composite index that combines both MLAEP and EEG derived information. This drastic change was also supported by additional findings of other authors. It has been stated in literature that MLAEP derived indices appear to correlate better with loss and return of consciousness, rather than with the effect-site concentration of a hypnotic drug.(17-20) Although these statements are not fully confirmed yet, it suggests that combining information from MLAEP and EEG might result in a high performance index that combines the best of both worlds.

At deep levels of anesthesia, MLAEP is reduced to a flat line that does not contain information anymore. By including EEG in the AAI calculation, the lack of descriptive capacity at deep levels of anesthesia might be resolved. In our third study we used the same validation method as described for the first validation to compare the old version of AAI ($AAI_{1.5}$) with the new version ($AAI_{1.6}$) and with bispectral index (BIS). This study revealed a marked improvement of the descriptive capacity of AAI at deep levels of anesthesia. By

reducing the upper scale limit from 100 to 60, the baseline variability was also reduced drastically. However, in the awake patients BIS remained the more constant parameter. Due to the proven improvements in the new system, it was decided to continue the validation process with the new index $AAI_{1.6}$.

In our fifth trial we combined ketamine and rocuronium to explore the interacting effect of both molecules on $AAI_{1.6}$. Apart from the main investigation question, whether the effect of ketamine on EEG registration was partially mediated by EMG interference, we simultaneously could explore the effects of solitary administered rocuronium and the effects of solitary ketamine on the $AAI_{1.6}$. The results of this study indicate that the new version of AAI has not resolved the problem for measuring the effects of NMDA dependent hypnotic drug effects. Moreover, the effects of rocuronium suggest a persistent interfering effect of EMG, but this interference was comparable to the EEG derived indices.

After our experimental validation process, the question whether MLAEP is able to extract different information on cerebral hypnotic drug effect compared to EEG is not yet answered. However, the performance of the $AAI_{1.6}$ has reached a comparably high performance level as found for BIS and Spectral Entropy. Still, many pharmacologic and physiologic factors determine the behavior of the measurement of raw EEG and MLAEP. Some of the potential causes for unexpected behavior have been studied in this thesis. The main message to the clinical anesthesiologist remains to be vigilant when using a monitor for the hypnotic component of anesthesia. One must always be aware that unexpected values of an EEG or MLAEP derived index do not always mean “unexpected changes in drug effect”. Therefore, the interpretation of EEG and MLAEP derived parameters must always be correlated to the patients’ condition at the time of measurement.
Meanwhile, additional clinical validation and outcome studies remain mandatory in order to decide whether measuring the hypnotic component of anesthesia is worth the effort. In this view, for AAI, several important questions are yet to be answered.

1) The AAI must be sensitive for all **commonly used anesthetics**. In our validation process, we only focused on intravenous anesthesia with propofol, or the combination of propofol and remifentanil. Eventually, it will be mandatory to develop a comparable strategy for the effects of inhalation anesthesia. However, some practical problems of inhalation anesthesia might limit the methodological possibilities. It appears problematic to evoke a gradual transition from “fully awake” to “deep sedation”, by means of inhalation anesthetics. Not all inhalation anesthetics are advised for mask induction, due to irritating bronchial effects. Moreover, we have to cope with the safety issue concerning excitatory symptoms in the patients, at light levels of anesthesia. Additionally, it is not easy to evoke excessive burstsuppression levels using inhalation anesthetics alone, without important hemodynamic or respiratory side effects. Therefore, we will never be able to evaluate such a wide range of hypnotic drug effects in one pharmacological validation study. The validation of effects of inhalational hypnotics on EEG and MLAEP derived indices will need a different approach compared to the validation process described in this thesis.

2) Once AAI is validated in a controlled scientific setting, the performance in **clinical anesthesia conditions** must be confirmed. The clinical practice of anesthesia has much more confounding variables compared to a scientific setting. A scientific experiment aims to limit the "unknown" covariates that might interfere with the measurement. Therefore, it is not guaranteed that a device will have a comparable efficacy in clinical practice compared to the results in a controlled scientific experiment.

3) Although a measurement might have a high performance in the above test phase, eventually, it must be studied whether the new technology **improves the outcome** of the patient. During this validation, it should be determined whether the use of AAI improves quality of anesthesia or if it decreases recovery times. Is it possible to avoid awareness by using AAI? To answer such questions, large numbers of patients are needed. Therefore, it is often necessary to perform this validation in multicentre trials.

4) Every measurement costs money to the patient and to society. Therefore the costs must be balanced to the gains. In my personal opinion, outcome and macro-economic **cost-effectiveness** studies for AAI must be considered in a broader context. Do we improve the outcome by quantifying the hypnotic component of anesthesia? How much do we want to pay for that improvement? Until today, this remains a topic of debate and further study, both for EEG as well as MLAEP derived indices.

Why use the AAI today? The value of using any monitor of hypnotic drug effect results probably from the additional vigilance provided to the anesthesiologist. Although "false positive" and "false negative" measurements can occur, an alarm will prompt the anesthesiologist to check all parameters of the patient. This additional check might just make the difference between "awareness" or "no awareness". Perhaps this mechanism partially explains the large decrease of awareness in a high risk population monitored by BIS.(21) Both EEG and MLAEP derived indices are prone for measurement errors, but apparently, this does not exclude a spectacular result on the clinical endpoint of "awareness". Therefore, it remains interesting to proceed with the research on outcome.

At an academic level, the search for new indications for AAI in anesthesia has already began. Bonhomme et al have studied the potential use of AAI, as a quantification of "nociception", in addition to a BIS guided anesthesia.(22) Although our studies indicate a low accuracy for predicting response to a painful stimulus, we did not investigate the magnitude in change of AAI at the onset of a sustained painful stimulus (such as surgery). Bonhomme states that this might contain additional information on the degree of nociception versus antinociception. Much work still needs to be done in order to confirm this theory.

Why not using the A-Line® machine today? The AAI technology has reached a high level of performance. But some practical issues might hamper commercial success. The use of a headphone disrupts the verbal communication between the patient and the anesthesiologist at the time of anesthesia induction. Although the time of personal contact in anesthesia

practice is often limited, many anesthesiologists indicate that this is an important drawback. Indeed, during the induction most patients have a certain degree of fear. It can be very therapeutic, if the anesthesiologist verbally reassures his patient. A potential solution for this problem is the use of bone conduction to transduce the acoustic stimulus towards the nervus acousticus. In that way the headphones might become unnecessary. This technology deserves further exploration.

The application of loud acoustic stimuli for a long duration might appear harmful. Although this is not yet a proven fact, MLAEP derived indices should be used with caution during long procedures, or for monitoring sedation at the intensive care.

Until now the A-line® is only available as a "stand-alone" machine. This might be unpractical for ergonomics in the operation theatre. A module version that can be combined with the other monitoring parameters might decrease the resistance for using a monitor for the hypnotic component of anesthesia.

For now, the cost of any monitor of the hypnotic component of anesthesia remains high. This is an important limitation for more general use of these devices, as many hospitals question the cost-benefit ratio.

These practical issues have been discussed within the consortium, after a thorough evaluation of our study results. As a response, Danmeter has chosen to abandon the MLAEP as a source of information, and developed a new EEG based index, called the cerebral state index (CSI). It was developed, using raw EEG data that was gathered during our A-Line® validation process. Therefore, it must be measured by using the same electrode positions as the AAI. Moreover, the manufacturer chose to make this device as small as possible (handheld device) to cope with ergonomics. The price is also much lower compared to BIS and Spectral Entropy, thus better coping with the economical issues.

In view of this (commercially driven) decision of Danmeter, one could wonder if there is any future in MLAEP? I think there is. On an academic level, the CSI opens additional perspectives for exploring the additional value of MLAEP versus EEG. As CSI (a cortically derived index) can be extracted post hoc from the raw AEP monitor/2 registrations (including subcortical MLAEP), researchers now have a strong tool for quantifying both cortical and subcortical responses in a time and location synchronized way. In order to optimize the output of a solitary MLAEP derived index, we had to combine both cortical (EEG + burstsuppression) and subcortical (MLAEP) derived information. However, it can not be excluded that both entities enclose a different kind of information on the patients' anesthetic state. One important difference of maintaining MLAEP as a monitor of cerebral hypnotic drug effect could be the faster response time for detecting changes in the clinical condition of the patient? Moreover, if the "nociception" theory of Bonhomme et al appears feasible, one might wonder if we could combine both cortical and subcortical derived information into a single monitoring device, correlating respectively to the "hypnotic" level of anesthesia (the cortical component), as well as the "analgesic" component of anesthesia (the subcortical component). Probably, these fundamental questions can only be fully explored, once the

correlation between the respective neurophysiological measurements and the clinical phenomenon of consciousness are better understood (e.g. with neuro-imaging techniques?).

This future perspective depends on many unknown factors. But every technological achievement of today at one point started as a sci-fi idea. For now, we can only keep on measuring, and finish what we started in the first place. Isn't that the secret to all success?

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Summary

The exact physiologic and anatomical mechanism of “consciousness” is yet insufficiently understood. However, in anesthesia, empirical methods were able to optimize many techniques for interfering with “consciousness”. One goal of an adequate anesthesia is to maintain a sufficient level of hypnotic drug effect. In order to avoid insufficient or excessive drug administration, indirect or “surrogate” measures of the hypnotic component of anesthesia have been developed, based on alterations in spontaneous electroencephalogram (EEG) or mid-latency auditory evoked potentials (MLAEP).

The MLAEP are elicited by headphones, producing repetitive auditory stimuli. The electrical activity evoked by these stimuli can be measured by means of three electrodes on the patients forehead. This thesis investigates the performance of a new fast extracting MLAEP technology (called ARX) to monitor the hypnotic component of anesthesia. The fast extraction time is a major advantage for monitoring sudden changes in pharmacological condition during anesthesia. A commercialized index, using ARX technology, is called the A-Line® auditory evoked potential index (AAI). The AAI is a single numerical quantification of the changes in the main components of MLAEP with a minimal processing delay of 6 seconds.

This thesis includes a search for reproducible ways to compare EEG or MLAEP derived indices of hypnotic drug effect. In two separate trials, we compared the ability of AAI to detect both clinical and pharmacological endpoints of cerebral hypnotic drug effect, with other surrogate measures of hypnotic drug effect. Secondly, we evaluated the ability of AAI to detect “difficult molecules” such as ketamine, that has a specific effect on EEG. The result of this first validation phase, showed serious drawbacks for AAI at baseline and at very deep levels of anesthesia. Therefore, we participated in the development of a new algorithm for AAI, combining both EEG and MLAEP derived information in a composite index ($AAI_{1.6}$).

The $AAI_{1.6}$ was evaluated in a second validation process, which showed a major improvement in comparison with the old version of AAI (version 1.5), based on solitary MLAEP. The effects of difficult molecules on $AAI_{1.6}$ was reevaluated, in a trial combining ketamine, with a neuromuscular blocking agent (rocuronium).

Although the use of MLAEP for clinical anesthesia goals is optimized significantly, practical issues remain, such as the need for a normal hearing threshold. Therefore, commercial success might be limited. A new EEG derived index, called the cerebral state index (CSI), is developed using raw EEG datasets from our AAI validation studies. We validated CSI, both on clinical and pharmacological level, as it might be a helpful tool for exploring the additional value of evoked potentials versus spontaneous EEG.

Samenvatting

De exacte fysiologische en anatomische achtergrond van “bewustzijn” is onvoldoende gekend. Nochtans zijn op empirische basis meerdere anesthesie technieken ontwikkeld, die gericht inwerken op “bewustzijn”. Een belangrijk doel van anesthesie, is het onderhouden van een adequaat niveau van hypnotisch effect. Om insufficiënte of excessieve hypnotische effecten te vermijden, zijn indirecte of “surrogaat” metingen van de hypnotische component van anesthesie ontwikkeld, gebaseerd op veranderingen in het spontane elektro-encefalogram (EEG) en de mid-latente akoestisch uitgelokte hersenpotentialen (MLAEP).

De MLAEP worden uitgelokt door het toedienen van repetitieve akoestische stimuli via een hoofdtelefoon. De daardoor verwekte elektrische hersenpotentialen, kunnen gemeten worden via drie elektroden op het hoofd van de patiënt. Wij onderzochten de prestaties van een nieuwe techniek voor snelle MLAEP extractie (ARX genaamd), om de hypnotische component van anesthesie te meten. De korte berekeningstijd is een groot voordeel in snel veranderende farmacologische condities zoals anesthesie. Een gecommercialiseerde index, gebruik makend van ARX, is beschikbaar onder de naam, “A-Line® auditory evoked potential Index” (AAI). AAI is een numerieke vereenvoudiging van de veranderingen in de componenten van MLAEP, met een berekeningsvertraging van slechts 6 seconden.

Deze thesis omvat een zoektocht naar reproduceerbare vergelijkingsmethodes, om EEG en MLAEP afgeleide monitors aan elkaar te toetsen. In twee studies vergeleken we AAI met andere metingen van hypnotisch effect, in hun capaciteit om zowel klinische, als farmacologische eindpunten van anesthesie te detecteren. Vervolgens bestudeerden we de effecten van “moeilijke molecules”, zoals ketamine, op AAI. Ketamine heeft een gekend verstorend effect op EEG. Deze validatie onthulde enige zwakheden voor AAI. De meting van wakkere patiënten was te variabel en de meting van diepe anesthesie was ongevoelig. Daarom participeerden wij in de ontwikkeling van een nieuw algoritme voor AAI, waarbij EEG en MLAEP afgeleide informatie verenigd werden in een “samengestelde” index $AAI_{1.6}$.

De $AAI_{1.6}$ onderging een tweede validatie, welke een duidelijke verbetering toonde ten opzichte van de oudere AAI (versie 1.5). Het effect van moeilijke molecules werd geëvalueerd voor $AAI_{1.6}$ in een studie, waar spierverslappers met ketamine gecombineerd werden.

Hoewel de toepasbaarheid van MLAEP in de klinische praktijk is verbeterd, blijven praktische hinderpalen een commercieel succes in de weg staan. De EEG datasets uit onze AAI validatie, werden daarom gebruikt ter ontwikkeling van de Cerebral State Index (CSI), een nieuwe EEG afgeleide index. CSI werd zowel klinisch als farmacologisch gevalideerd. Het gebruik van CSI kan een nuttig werktuig worden om de additionele waarde van MLAEP versus spontaan EEG in anesthesie omstandigheden verder te exploreren.

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Wetenschappelijke Prijs

Prijs voor de beste publicatie in de categorie Clinical Research van de Society for Anesthesia and Resuscitation of Belgium voor 2006: Cerebral State Index during Propofol Anesthesia
Erik W. Jensen, Hector Litvan , Mirem Revuelta, Pere Caminal, Bernardo E. Rodriguez, Hugo Vereecke, Michel MRF Struys

Lidmaatschap wetenschappelijke verenigingen en dienstverlening m.b.t. mijn functie

- Lid van de SARB (Society of Anaesthesia and Resuscitation of Belgium) sinds 2001
- Lid van de ESA (European Society of Anaesthesiologists) sinds 2004
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List of Abbreviations

AAI	A-Line ® auditory evoked potentials index
$AAI_{1.5}$	A-Line ® auditory evoked potentials index, version 1.5
$AAI_{1.6}$	A-Line ® auditory evoked potentials index, version 1.6
AEP	Auditory evoked potentials
AEPex	Auditory evoked potential index
ARX	Autoregressive Model With Exogenous Input
ASSR	Auditory Steady State Response
AUC	Area under the curve
BAEP	Brainstem Auditory Evoked Potentials
BIS	Bispectral Index
CePROP	Effect-site concentration of propofol
CeREMI	Effect-site concentration of remifentanil
CI	Confidence interval
CMRR	Common Mode Rejection Ratio
CpPROP	Plasmaconcentration of propofol
CpREMI	Plasmaconcentration of remifentanil
CSI	Cerebral State Index
CUN	Canonical Univariate
ED50	Effective dose to obtain drug effect in 50% of the population
ED95	Effective dose to obtain drug effect in 95% of the population
EEG	Electroencephalogram
Emax	Model of drug effect that describes a sigmoidal relationship between concentration and effect with a maximum limit
EMG	Electromyogram
f	Frequency
FFT	Fast Fourier Analysis
Hz	Hertz
ke0	Equilibration constant reflecting the elimination speed of a drug out of the effect-site
LLAEP	Long-latency auditory evoked potentials
LOE	Loss of eyelash reflex
$LOR_{NOXIOUS}$	Loss of response to noxious stimulus
LOR_{VERBAL}	Loss of response to a verbal command
LOR_{Lash}	Loss of response to eyelash reflex
LORN	Loss of response to noxious stimulus
MAC	Minimal Alveolar Concentration
MF	Median Frequency
MLAEP	Mid-latency auditory evoked potentials
MTA	Moving Time Average
MTA_{15}	Moving Time Average, extracted from 15 sweeps
MTA_{256}	Moving Time Average, extracted from 256 sweeps
N_20	Nitrous Oxide (Laughing Gas)
NMBA	Neuro Muscular Blocking Agent
NMDA	N-Methyl D-Aspartate
NONMEM	Non Linear Mixed Effects Modeling
OAA/S	Observers Assesment of Alertness and Sedation Scale
P	Probability

PD	Pharmacodynamics
Pk	Prediction Probability
PK	Pharmacokinetics
pKa	Ionization Constant (kinetics, chemistry)
PKPD	Pharmacokinetic-pharmacodynamic
θ	Phase
RE	Response Entropy
SD	Standard deviation
SE	State Entropy
SEF95%	Spectral edge frequency 95%
SNR	Signal-to-noise ratio
SR	Suppression Ratio
SSEP	Somato-sensory evoked potential
TCI	Target controlled infusion
VEP	Visual evoked potential
WT	Wavelet transformation