ENTROPY INDICES VERSUS THE BISPECTRAL INDEX (BIS) FOR ESTIMATING NOCICEPTION DURING COMBINED PROPOFOL ANESTHESIA AND FEMORAL NERVE BLOCK

Dissertation for the

Doctorate Degree in Medicine

Department of Anesthesiology

and Intensive Care Medicine

Medical University of Graz

Graz, Austria

Emina Talakić

ENTROPIE INDEXE VERSUS BISPECTRAL INDEX (BIS) FÜR DIE SCHMERZEINSCHÄTZUNG WÄHREND DER ANÄSTHESIE MIT PROPOFOL- UND N. FEMORALIS BLOCK

Dissertation zur Erlangung des

Doktorgrades der gesamten Heilkunde

Universitätsklinik für Anästhesiologie
und Intensivmedizin
Medizinische Universität Graz

Emina Talakić

Dank

In erster Linie gilt mein Dank meiner Mutter, die mich stets in meiner Intention, das Medizinstudium zu absolvieren sowie die Dissertation zu schreiben bestärkt und dies durch finanzielle Unterstützung auch ermöglicht hat.

Ich danke **o. Univ. Prof. Dr. Helfried Metzler**, Leiter der Universitätsklinik für Anästhesiologie und Intensivmedizin, für die hervorragende Unterstützung bei der Erstellung dieser Arbeit.

Einen großen Dank spreche ich **Prof. Dr. Ashraf A. Dahaba** für die wissenschaftliche und persönliche Betreuung aus.

Ebenso besonders danke ich **em. Univ. Prof. Dr. Werner F. List**, emeritierter Leiter der Universitätsklinik für Anästhesiologie und Intensivmedizin.

Besonderen Dank spreche ich **OA Dr. Maria Gries** und **OA Dr. Thomas Bössner** für die großzügige Unterstützung bei der klinischen Durchführung dieser Studie.

Für die statistische Auswertung der Daten danke ich besonders **a.o. Univ. Prof. DI Dr. Peter H. Rehak**, Leiter der Abteilung für medizinische Technik und Datenverarbeitung.

Abstract

Background: Consciousness monitoring has become increasingly popular in general anesthesia, and a new technology has recently been introduced with potential advantages over the other available products. Bispectral index (BIS) and state/response entropy (SE/RE) index have been widely used to estimate depth of anesthesia and sedation. In adults, independent of age, adequate and safe depth of anesthesia for surgery is usually assumed when these indices are between 40 and 60. Since its introduction in 1996, the Bispectral Index™ (BIS™) has gained increasing popularity as a monitoring tool for the depth of anesthesia. Many reports on the value of BIS have been published in the literature paradoxically changing or inaccurately indicating the depth of anesthesia.

Methods: Fifty American Society of Anesthesiologists (ASA) classification I-II patients, aged 18-59 years, undergoing general surgery on the lower limb were recruited in the study. We recruited two groups, one group was maintained at BIS around 25 and the other group of 25 patients was maintained at BIS around 50. Exclusion criteria was body mass index <18 or >26 kg m^{-2} and subjects with medical conditions that could affect the level of consciousness such as stroke, stupor or dementia, or patients on treatment with cardiovascular or sedative/hypnotic drugs that might affect BIS monitoring. BIS and Entropy electrodes were placed on patients forehead. For monitoring the level of analgesia we use BIS variability (BIS standard deviation) and Entropy bias (response entropy-state entropy).

Results: There were no significant differences between the demographic data of the 2 groups. Our results indicate no significant differences with increasing degrees of noxious stimulation starting from 10 mA till 80 mA. And there were no significant differences between two groups as well.

Discussion: We demonstrated that neither monitor could successful monitor the depth of analgesia.

Kurzzusammenfassung

Hintergrund: Die Überwachung von Patientinnen und Patienten unter Vollnarkose gewinnt zunehmend an Popularität und die neuersten Technologien bieten viele Vorteile gegenüber anderen bisher verfügbaren Produkten. Der Bispectral Index (BIS) und der state/response Entropie Index werden zunehmend verwendet, um die Tiefe der Anästhesie und der Sedierung zu bestimmen. Bei Erwachsenen, unabhängig vom Alter, wird von einer adäquaten und sicheren Tiefe der Anästhesie ausgegangen, wenn diese Indexe zwischen 40 und 60 liegen. Seit der Einführung dieser für die Bestimmung der Tiefe der Anästhesie entwickelten Überwachungsmöglichkeit, dem Bispectral Index™ (BIS™), gewann diese Methode zunehmend an Popularität in täglicher Verwendung in der Anästhesie.

Methoden: Es wurden fünfzig „ American Society of Anesthesiologists (ASA) classification I-II“ Patienten im Alter zwischen 18-59 Jahren, die einer Operation am unteren Extremitäten unter Anästhesie mit Propofol und N.femoralis Block unterzogen worden sind, in diese Studie rekrutiert. Wir untersuchten zwei Gruppen, eine Gruppe mit BIS Werten von etwa 25 und die andere Gruppe mit BIS Werten von etwa 50. Die Ausschlusskriterien waren body mass index <18 oder >26 kg m² sowie die Personen die in solchen medizinischen Zuständen sind, die einen Einfluss auf das Bewusstsein haben könnten, wie z.B. Insult, Stupor, Demenz oder die Patienten in der Behandlung mit kardiovaskulärer oder sedierend/hypnotischen Medikamenten die einen Einfluss auf BIS monitoring haben könnten. BIS und Entropie Elektroden wurden auf Patienten Stirn platziert. Für die Überwachung der Analgesiestufe, haben wir die BIS Variabilität (BIS Standard Deviation) und Entropie Bias (response und state Entropie) verwendet.

Ergebnisse: Es gab keine signifikante Unterschiede zwischen demographischen Daten in beiden Gruppen. Unsere Ergebnisse deuten auf keine signifikante Unterschiede in beiden Gruppen mit zunehmenden Graden der Stimulation von 10mA bis 80mA.

Diskussion: Wir haben demonstriert, dass keine dieser beiden Monitoren die Tiefe der Analgesie erfolgreich messen können.

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1 Introduction

Clinical evaluation has poor sensitivity and specificity in measuring the depth of anesthesia. It requires knowledge of the dose-response relationship between anesthetic agents and their pharmacodynamic effects. However, the bispectral index (BIS) and the Entropy have been designed to estimate the hypnotic level during the general anesthesia [1].

In anesthesiology, a special automated EEG analysis, the bispectral index (BIS) monitor, has been designed for monitoring the effects of anesthetic/hypnotic drugs. Among the electroencephalographic (EEG)-derived indices, the BIS (Aspect Medical Systems, Newton, MA) is widely used in estimating the hypnotic level during general anesthesia. This index has been proven to be a highly sensitive and specific measure of the anesthetic effect in comparison with other EEG-derived variables [1] [2].

Anesthetic depth can also be measured by means of spectral entropy using the Datex-Ohmeda S/5 Entropy-Module (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland).

It is now possible to acquire and process raw EEG and frontal EMG (fEMG) signals to produce two spectral entropy-based indices (response entropy and state entropy) reflective of nociceptive and hypnotic levels during general anesthesia. EEG signals change from fast wave activity to slow wave activity when anesthesia deepens and the Entropy Module measures the irregularity of the EEG by means of an entropy algorithm to assess the depth of anesthesia.

The State entropy, which is calculated for frequencies ranging from 0.8 to 37 Hz, consists of the entropy of the EEG signal reflecting the patient's cortical activity. Response entropy includes additional higher frequencies up to 47 Hz, reflecting both EEG and fEMG activity. Response entropy becomes equal to state entropy when the EMG power (sum of the spectral power between 32 and 47 Hz) is equal to zero. The difference between response entropy and state entropy serves as an indicator for EMG activation [3].

The definition of inadequate analgesia is still unclear. Various signs such as patient movement, increase in arterial pressure or heart rate (HR), and increase in the release of catecholamine in response to noxious stimulation have all been defined as signs of inadequate analgesia. Motor response to noxious stimulation has been used as one of the indicators of inadequate analgesia. EMG activity reflects sub cortical activity during general anesthesia. According to previous studies, sub cortical structures could be a site of the analgesic effect of anesthetics [4].

Although fEMG has not gained clinical acceptance, it has been reported that fEMG may be of value in assessing adequacy of analgesia [5] [6].

On the other hand the Bispectral algorithm has a new electrode (electrode 4, placed above the eyebrow) in the Quatro sensor dedicated for monitoring fEMG activity as an indicator of inadequate analgesia. According to manufacturer's instructions a high oscillations of the BIS value would indicate inadequate analgesia.

We hypothesize that the difference between response entropy and state entropy, which is the constituent of fEMG, also reflects nociception. It has been reported that sensitivity, specificity and prediction power of the BIS values and corresponding entropy indices for differentiating between consciousness and unconsciousness are high and comparable [7]. However, it is still unclear whether the difference between response entropy and state entropy or the BIS standard deviation for a given period of time can be used as an indicator of an inadequate level of analgesia.

The aim of this study was to compare this two monitoring systems (BIS and entropy) in the assessment of nociception in patients undergoing surgery using a combination of anesthesia with propofol and femoral nerve block.

2 Bispectral Index

The Food and Drug Administration (Rockville, MD) approved in the year 1996 the Bispectral Index as an accepted measure of hypnotic effect of anesthetics and sedative drugs. Up to date, Bispectral Index (BIS) monitor (Aspect Medical Systems, Inc, Newton, MA) increased popularity in daily anesthesia practice and this type of monitoring is used in 160 countries and in 40% of all operating rooms in the US. Worldwide, there are about 12.2. millions of patients monitored by the Bispectral Index [8].

As an EEG processing tool for measuring consciousness, Bispectral analysis is based on EEG assessment, correlating behavioral and prospectively collected clinical data. The material from approximately 1, 500 patients is contained in this database. Although, there are more then 5000 hours of recording during anesthetic administrations [9].

2.1. The BIS-Algorithm

BIS offers values of 0 to 100. It represents a single, dimensionless and continuous number ranging. Isoelectric EEG is associated with 0 and fully awake with 100. Those are integrated measures of cerebral electrical activity. The idea of BIS design was to correlate with hypnotic endpoints and on that way to be able to provide valid information with propofol and with volatile anesthetics as well [10] [11].

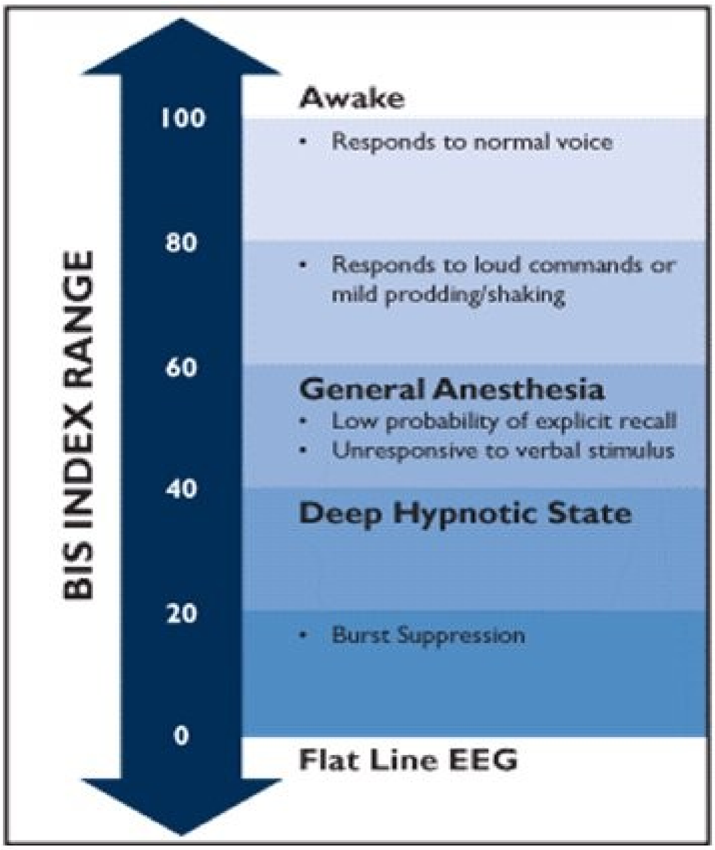

Fig. 1: BIS index ranging

http://www.ispub.com/ostia/index.php?xmlFilePath=journals/ijnm/vol4n1/acubis.xml *last acceded on 2 January 2011*

Bispectral analysis is based upon information from power- or Fourier analysis which transforms EEG signals into waves, each with an amplitude, phase angle and frequency [12] [9] [10].

Typical EEG changes occur during anesthesia. α-waves (7.5-12.5 Hz) predominate in relaxation with the closed eyes. Light anesthesia make a decrease in α-waves and an increase of β-waves (12.5-30 Hz). Slow wave activity - δ waves (1.5-3.5 Hz) and θ waves(3.5-7.5 Hz) becomes more prominent and increases with deepening of anesthesia. It means we have a domination of thalamohippocampal-septal generators of δ and θ activities over the cortical generator of α and β activities. When the consciousness returns, all of these changes are reversed in the same order [2] [14].

2. The recognitions of Artifacts

To make the calculation of the BIS possible, the raw EEG is divided into epochs and each on of them have duration of two seconds. The samples that are supposed to be artifacts, are going to be removed or ignored by consecutive algorithms.

The first step is to detect and if found, to discard the low frequencies. Previously, there is the filter for artifact spikes. Those artifact values are removed and the absent data is interpolated for additionally processing [14].

One of the possible artifacts is the use of electrocautery. It belongs to external artifacts. These signals are easily detected since they exceed the dynamic range of the amplifier. Those EEG epochs having that kind of signals are following excluded [14].

There is also the possibility of enormous transient slow wave activity with a well-defined structure as the resulting signal. For example, moving the orbital or the frontal muscles has an influence on the EEG and it represents an significant source of data artifact. Of course, that kind of data is removed from continuing data analysis [14].

If there is a large difference in the signal of individual EEG epoch from the previous average, it is assumed as an artifact and removed from the real time computing of the bispectral index. This is saved in the matrix for calculating the average. According to this, if the next epoch is still going to be without any changes, the average will be reacting in new direction and after considerable time, the samples will not be declined anymore [9].

Under the names A-1000, A-1050, A-2000, BIS-XP there are multiple available models of bispectral index developed in the course of the years by Aspect Medical Systems. The latest generation of BIS monitors is the Bilateral BIS-Vista The introduction of the new BIS-Vista monitor offers a new proprietary algorithm (version 1.4) as well as some new technical specifications over the latest BIS-XP model such as clear real time EEG waveform display on a wider LCD color screen, and the capability of bilateral monitoring of cerebral hemispheres using either a new BIS-Vista bilateral sensor or the conventional Quatro sensor. You can also retrieve patients data for up to one month using USB-A and USB-B.

The bispectral index (BIS) is a processed EEG parameter quantifying the level of interfrequency phase-coherent synchronization in the signal. The BIS is statistically derived from an empirical database using a complex proprietary algorithm that combines three subparameters into a single metric: Relative BetaRatio, a frequency-domain feature; SynchFastSlow, a bispectral-domain feature; and Burst Suppression, a time–domain feature. None of the BIS disparate descriptors is particular per se, as each has a specific range of effect where it performs best. The BIS algorithm allows the different descriptors to dominate sequentially as the EEG changes its character.

These instruments are different than other several additions, with the goal to increase the quality and safeness of the algorithm, in other words dealing with burst suppression EEG [10] [15].

Also with more active discovering and eliminating EMG activity, further reducing of earliest activation of the EEG seen with some anesthetic agents and in addition capturing of parameter deduced from clinical testing [9] [10] [12].

The side effects reported in certain model, might not necessarily apply to other models [14].

2.3. Other parameters

In addition to bispectral index, there are multiple parameters supplied by the BIS monitor. The EEG is notified as a raw wave with a plotting-rate of 25 mm and amplitude of 25 μV and the EMG power is measured by the BIS monitor in the 70-110 Hz frequency band. The value is voiced in decibel units, with 0.01 μV described as 0 dB. The minimum value notified is 30 dB [8] [9].

The measure of the signal quality for the EEG electrodes is the so called signal quality index (SQI) and it supplies a value from 0 to 100. The calculation is based upon artifact, impedance data and other variables.

Furthermore, there is the spectral edge frequency (SEF) as one more parameter included by the BIS monitor. The SEF_{95} is the frequency where 95% of the total power lies below it and 95% lies above it. 15Hz is the minimal value displayed by the monitor.

The Density Spectral Array (DSA) represents differences in the power spectrum distribution in the course of time as a gray-shaded, two dimensional contour plot. Based on a decibel scale, an amplitude bar shows the total amplitude of the signal. This is displayed beside the DSA plot.

Other parameter, suppression ratio (SR) is the percentage of burst suppression over the last 63-second period and it is a calculated parameter indicating an isoelectric condition [8][9] .

3 The Entropy

In year 1949, Shannon and Weaver determinated the entropy monitor. Furthermore introduced to a power spectrum od a signal by Johnson and Shore in 1984. The idea was pointed to measure the irregularity of the EEG.

Entropy is, if one considers it as a physical category, is in proportion with the logarithm of the number of microstates accessible to a thermodynamic system [15].

This type of monitoring is giving a description of the abnormality, incompatibility and complexity characteristics of a signal.

Entropy is a directly parameter which is able to differentiate between one periodic and one aperiodic signal and owns characteristic that is independent of absolute scales like signal frequency or amplitude of the signal.

This has a considerable value of property in a EEG application. Moreover, interindividual variations are a solid fact in the unequivocal frequencies of the measured EEG rhythms [15].

We have numerous ways of calculating signals, i.e. the entropy. In a given time frame, we can also take into consideration the Shannon entropy, also called information entropy. We can also calculate spectral entropy within a frequency domain. When adjusting and perfecting the speed at which information data is deducted from the signal, it is advisable to build numerous accesses for time and frequency domain [15].

The Datex-Ohmeda Entropy™ Module (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland) applies an algorithm of the kind in its operational software. Terminus a quo of the algorithm lies in the spectral entropy, ensuring a significant advantage, which adds to entropy from whichever noteworthy frequency scope can be expressed separately. For an optimum reaction, the calculations are to be constructed in a specific way which allows the time frame's length of each specific frequency to be severally selected. This directs to a theory refered to as time-frequency balanced spectral entropy [15].

Fig. 2: Entropy anesthesia monitor

http://www.medwrench.com/?equipment.view/equipmentNo/958/Datex-Ohmeda--GE-Healthcare/Compact-Anesthesia-Monitor/ *last accessed on 2 January 2011*

1. State entropy and response entropy

Muscle action creates a grave electromyographic (EMG) component, which is enclosed within a biopotential signal measured from the patient's forehead.

During anesthesia, the EMG's wide noise-like spectrum signal prevails on frequencies higher than 30 Hz. On frequencies lower than 30 Hz the EEG signal component prevails, while it is restrained in the existing biopotential within the electrodes. The EEG signal power decreases exponentially on frequencies higher than 30 Hz [15].

Sudden appearance of the EMG signal data often indicates that the patient is responding to certain external stimulus, such as a painful stimulus, i.e. nociception, caused by a surgical procedure. This kind of response may arise in case of insufficient level of analgesia. If no additional analgesics are administered and the stimulation is persistent, then it is highly likely to conclude that a degree of hypnosis will, at some point, start to lighten [15].

Therefore, EMG provides a quick indication of impending rousing. Significantly, due to the higher frequency of the EMG data signal, the sampling time can be vastly shorter in comparison to the time required for the measurement of the lower frequency EEG signal data. This permits frequent calculations of the EMG data, allowing for better and quicker results of the patient's state and its changes given by the general diagnostic indicator [15].

It is informatory to consider two entropy indicators – one is assigned solely to the dominant EEG frequency; whereas another is assigned to the complete spectrum of frequencies, in which we include here extremely important EEG and EMG factors. State entropy is calculated from 0.8 Hz to 32 Hz frequency ranges; including the dominant EEG range of the spectrum, hence mainly reflecting patient's cortical state. The time windows for State entropy are being elected optimally for each specific frequency factor and range from 60s to 15s in accordance with the previously given explanation under the division Time frequency Balanced Spectral Entropy. It incorporates the dominant EEG and the EMG 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 Hz and 47 Hz, equal to 1.92s [15].

These two entropy parameters should, to the advantage, be normalized in a way that RE becomes equal to SE when the EMG power (sum of spectral power between 32 Hz and 47 Hz) is equal to zero, as the RE-SE-difference then serves as an indicator for EMG activation. We have to highlight frequency range from 0.8. Hz to 32 Hz as R_{low} and the frequency range from 32 Hz to 47Hz as R_{high}; the combined range from o.8. Hz to 47 Hz is denoted by R low+ high [15].

When the EMG activity is present, spectral factors within the range (R_{high}) vary dramatically from zero and hence RE is more prominent than SE.

Having in mind these explanations, SE and RE serve their informational purposes for the anesthesiologists. SE is a secure indicator of the hypnotic effect on the cortex. The time windows for State entropy are to be selected in a manner which removes the transient fluctuations from the collected data. RE, quite opposite, responds faster to occurring changes. A distinctive situation, in which diverse parts of these parameters are demonstrated, is during arousal, when RE ascents at first simultaneously with the muscle activation; few seconds later it is followed by SE [15].

4 Nociception

*„Definition: **Pain** is a combination of sensory (discriminative) and affective (emotional) components. The sensory component of pain is defined as **nociception**. (Rohini Kuner, Universität Heidelberg)"* [16] .

R. Melzack wrote: "Freedom from pain is a basic human right, limited only by our knowledge of how to achieve it." [17]. The most potent analgesic is opiates. However tolerance and systemic side effects such as respiratory depression often limit their effectiveness. Alternate medication for pain control should be possible since neurophysiological studies have demonstrated that nociceptive responses can be modified on a spinal level by a number of non-opiate drugs [18].

According to Subcommittee on Taxonomy of the international Association for the Study of Pain (1994), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [19]. Nociception is the process, which involves the generation of nerve impulses by the peripheral terminals of the small-diameter sensory neurons, the propagation of the impulses to the spinal cord and the release of mediators in the dorsal horn. Nociceptive neurons serve as a vehicle for this type of afferent signalling and also sub-serve other types of communication [20].

5 Patients and Methods

Our study was registered at EudraCT, trial registration number: 2009-015557-21. A prospective clinical consecutive study was conducted after Medical University of Graz ethics committee's approval. All patients who agreed to participate in the study give a written informed consent.

Fifty American Society of Anesthesiologists (ASA) classification I-II patients, aged 18-59 years, undergoing general surgery on the lower limb were recruited in the study. We recruited two groups, one group was maintained at BIS around 25 and the other group of 25 patients was maintained at BIS around 50. Exclusion criteria was body mass index <18 or >26 kg m^{-2} and subjects with medical conditions that could affect the level of consciousness such as stroke, stupor or dementia, or patients on treatment with cardiovascular or sedative/hypnotic drugs that might affect BIS monitoring [13].

BIS-XP 4-electrodes "Quatro" sensor and an Entropy sensor were randomly allocated to be placed either on the left or the right side of the patients' forehead. The sensors were connected to a synchronized Datex-Ohmeda S/5 Entropy-Module and a BIS-XP monitor (software version 3.4). Both monitors were connected to 2 laptop computers. BIS and Entropy recordings were started after verifying a signal quality index (SQI) >95% and electrodes impedance <5 kΩ.

Data was continuously collected and stored in the once every 5 s mode using the hyperterminal connection for the BIS data and the Datex-Ohmeda S/5 collect (software version 4.0), while the BIS smoothing window was set at 30 s.

In addition the BIS-XP monitor calculates the electromyography (EMG) power in the 70-110 Hz frequency band displayed in decibel (dB).

After verifying a successful femoral nerve block (Ropivacaine 0.5%, 30 ml) using a nerve stimulator with 0.1 ms, 0.4 mA stimulations to identify the femoral nerve, and after entering the patients' anthropometric data, a propofol TCI infusion pump incorporating a three-compartment pharmacokinetic algorithm of the Marsh pharmacokinetic model [21] was started.

Patients were spontaneously breathing via a facemask. Propofol TCI is set to reach an effect-site concentration of 3.0 μg ml^{-1} until patients lost their eyelash reflex. A remifentanil 0.15 μg kg^{-1} min^{-1} infusion was started for a Laryngeal Mask Airway (LMA) placement. After capnographic verification of proper LMA placement the lungs were ventilated mechanically with 40% oxygen in air and patients were warmed using a forced-hot-air-blanket. Mean arterial pressure (MAP), heart rate (HR) were recorded. Anesthesia of stable BIS of around 40 was shown to be an adequate surgical anesthesia [22], as there were only 2 reported cases of awareness among 4945 prospectively examined patients when BIS was maintained around 40 [22].

BIS 40 will be subsequently maintained via propofol TCI ±0.2 μg mg^{-1} rate adjustments.

Two silver/silver chloride surface stimulating electrodes were placed 4 cm apart on the ulnar nerve at the wrist and connected to Innervator® NS272 (Fisher & Paykel, Auckland, New Zealand) peripheral nerve stimulator. After switching off the remifentanil infusion for 15 min, the ulnar nerve was stimulated in an ascending sequence of single twitch electric stimulations starting from 10 mA, up till 80 mA for a period of 3 min followed by a 5 min recess. BIS and Entropy baseline data at the ascending sequence stimulating current were recorded.

Fig. 3: Entropy and bispectral electrode on the patient's forehead

6 Statistical Analysis

To date there are no data on BIS monitoring or Entropy as monitors for nociception to allow an *a-priori* sample size calculation. Although a previous study [23] demonstrated that response entropy and state entropy [median, (range)] before skin incision were significantly lower in patients who did not move [29 (15–41) and 24 (14–41)] compared to response entropy and state entropy in those patients who did move [38 (24–53) and 37 (24–52)] respectively, still this was not a suitable base for a sample size estimation [23].

Thus we chose a convenient sample size of 26 patients in a pilot study. Based upon the data obtained from the first 6 pilot patients the final procedure regarding the stimulation schedule and the duration of the recess interval in-between stimulations was developed, as well as a detailed analysis plan for the data obtained from the following 20 patients. Data from the 26 patients was then further examined aiming at identifying possible predictors of nociception and estimating the specificity, sensitivity and cut-off values for detection of nociception.

7 Results

There were no significant differences between the demographic data of the 2 groups.

Our results indicate no significant differences with increasing degrees of noxious stimulation starting from 10 mA till 80 mA.

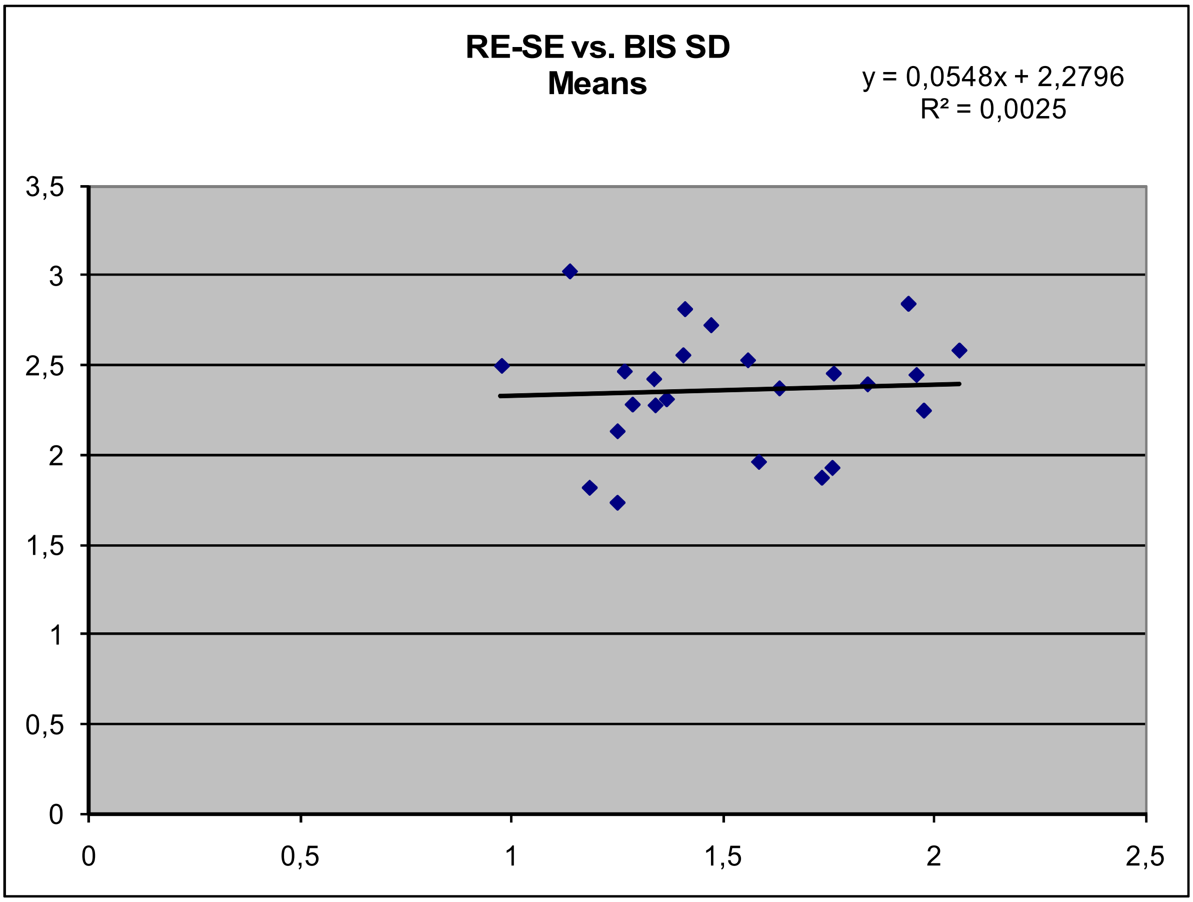

Fig. 4: Correlation between Response Entropy (RE) – State Entropy (SE) versus Bispectral Index Standard Deviation

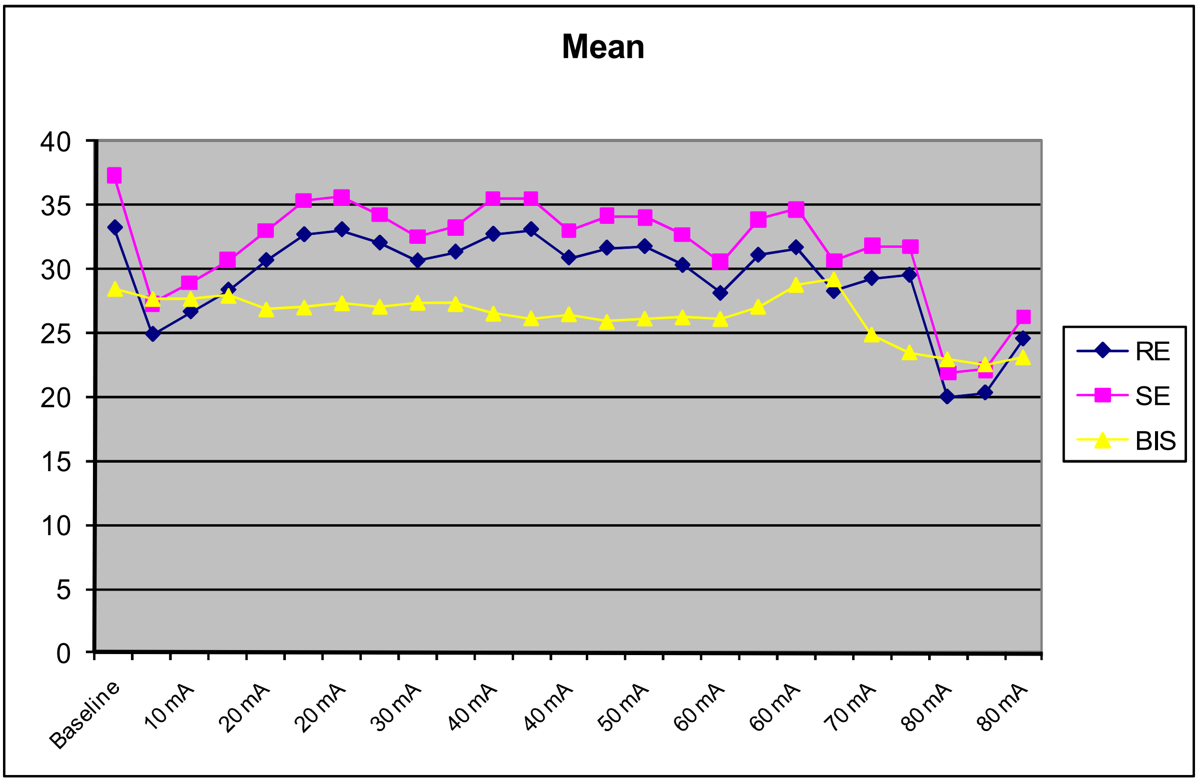

Fig. 5: Mean Response Entropy (RE), State Entropy (SE) and Bispectral Index at various noxious stimulations.

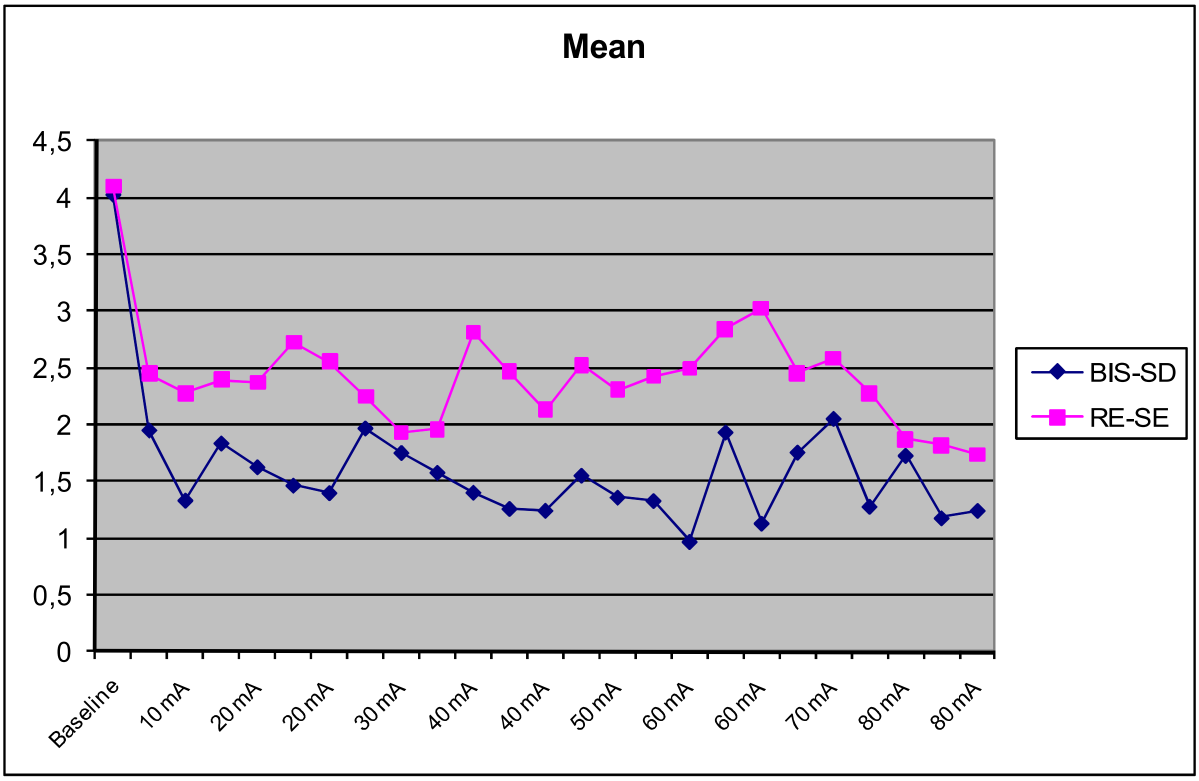

Fig. 6: Mean Response Entropy (RE) - State Entropy (SE) versus Bispectral Index Standard Deviations at various noxious stimulations.

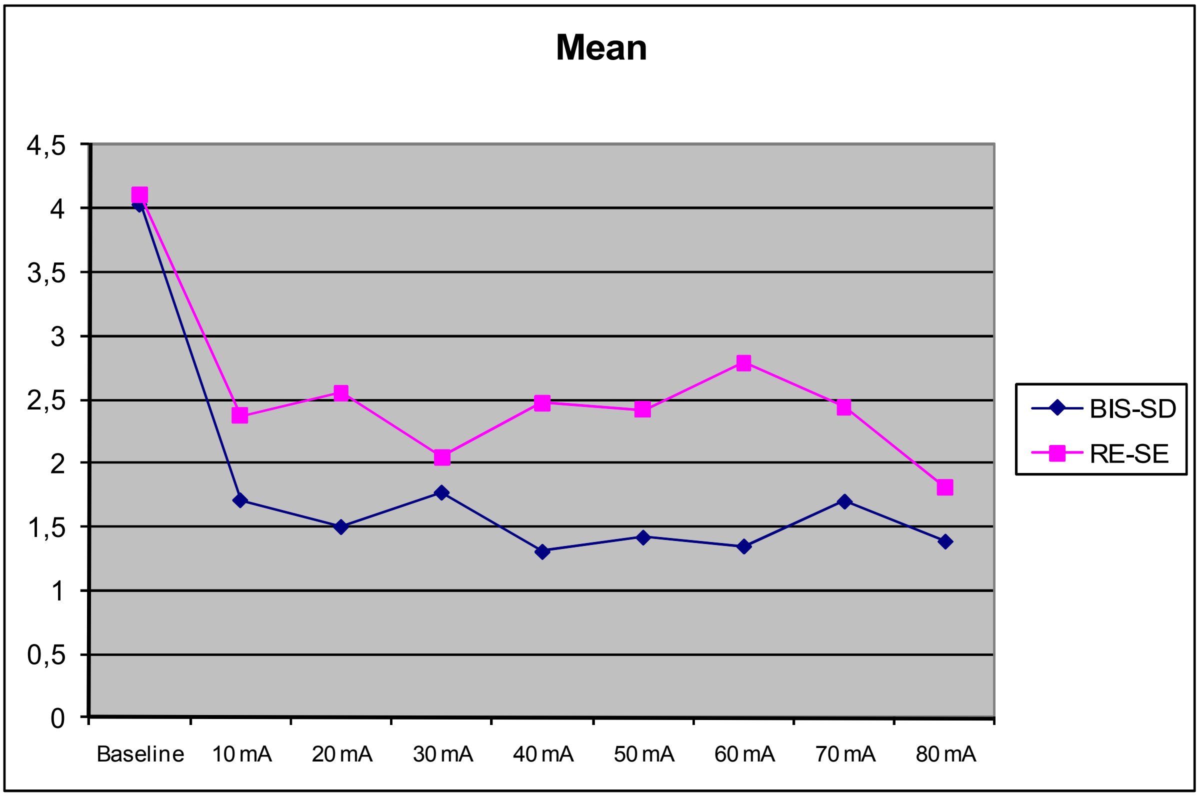

Fig. 7: Mean Response Entropy (RE) - State Entropy (SE) versus Bispectral Index Standard Deviations at various noxious stimulations.

8 Discussion

In the present study, we investigated the accuracy of response entropy minus state entropy and BIS as indicators of nociception to determine whether the difference between response entropy and state entropy can indicate inadequate analgesia. Noxious stimulation was shown to increase response entropy more than state entropy. However, all indices did not always increase when the intensity of noxious stimulus increased. Therefore, neither response entropy and state entropy nor BIS was sufficiently accurate to determine the strength of noxious stimulation.

In another study, there was no linear correlation between BIS and entropy indices above a BIS value of 60 [24]. This was because the BIS values for different levels of anesthesia are calculated with different algorithms [9]. In the present study, most BIS values were between 20 and 80. This suggests that linear correlation between BIS and entropy indices was observed in our study because most of the BIS values were calculated with the same algorithm.

In the present study, the changes in BIS, did not decrease significantly with an increase in noxious stimulation from 10 to 80 mA, whereas both entropy indices did not change significantly. However, BIS values were clinically low in the present study.

Although the prediction of movement in response to skin incision by means of EEG-derived variables [25] [29] [30-33] has been well described, the accuracy of such a prediction has not been established. In the present study, response entropy and state entropy were significantly lower, whereas there was no significant difference in BIS. In the range of propofol anesthesia used in the present study, response entropy and state entropy and BIS did significantly change. This difference between BIS and entropy indices may explain why a significant difference was not observed between movers and non-movers.

In the present study, no EEG variable could differentiate the intensity of electrical stimulation accurately. Although it is uncertain whether the intensity of the electrical stimulus is equal to the strength of noxious stimulation, both BIS and entropy indices seem to be inadequate for quantifying noxious stimulation.

In the present study, BIS increased significantly with electrical stimulation. Therefore, the increase in BIS was thought to be because of a decrease in the level of hypnosis caused by noxious stimulation. However, BIS also increases under light hypnosis because of insufficient administration of hypnotic agents. Ultimately, an increase in BIS during general anesthesia, possibly similar to a change in other EEG derivatives, indicates one of two different anesthetic states: light hypnosis or inadequate analgesia.

In a previous study of a goat brain model, [26] subcortical structures were suggested to be the site of the analgesic effect of anesthetics. In other studies, [27] [28] depression of the motor response to noxious stimulation by general anesthetics was suggested to be caused by immobilization and antinociceptive effects in the spinal cord. Therefore, excitability of subcortical structures evoked by noxious stimulation, with EMG activation taken as the motor response, which increases the difference between response entropy and state entropy, may indicate inadequate analgesia. Thus, we hypothesized that an increase in the difference between response entropy and state entropy, that is, the fEMG activity, could indicate nociception during general anaesthesia. Certainly, in our study, the difference increased significantly after electrical stimulation. However, we concluded that the increase in the difference between response entropy and state entropy merely indicates the motor response to noxious stimulation and is not a direct indication of analgesia per se.

In a previous study measuring the plasma norepinephrine concentration as the stress response during sevoflurane anaesthesia, it was found that a high concentration of sevoflurane could not suppress the adrenergic nervous system responses to surgical noxious stimulation, [34] but it could suppress the motor response to noxious stimulation.

This probably indicates that fEMG is not activated even under inadequate analgesia during high-concentration sevoflurane anaesthesia because of the suppressive effect of sevoflurane on motor response to noxious stimulation. Furthermore, in a previous study, fEMG activity was found to indicate pending arousal during anaesthesia, [35] and recovery from paralysis produces an increase in fEMG [26]. Thus, the absence of fEMG activation after noxious stimulation does not always indicate adequate analgesia, especially during sevoflurane anaesthesia, and fEMG activation does not always indicate inadequate analgesia. Therefore, the difference between the two entropy indices should be interpreted carefully during anaesthesia.

We did not use neuromuscular blocking agents during the study period so that we could observe patient movements after noxious stimulation. Therefore, it is possible that EMG activity after noxious stimulation contaminated our results. Facial muscles have been found to be more resistant than other skeletal muscles to neuromuscular blocking agents, [37] [38] and noxious stimulation has been found to increase the difference between response entropy and state entropy before recovery from paralysis [36]. Furthermore, neuromuscular blocking agents are usually used in clinical anesthesia. Therefore, in evaluating nociception, further studies that incorporate a neuromuscular blocking agent are needed to clarify the role of fEMG activity.

In conclusion, neither BIS nor entropy indices could quantify the intensity of the stimulation. Furthermore, although response entropy increased more than state entropy after noxious stimulation, it is possible that the increase in the difference between these two indices did not always indicate inadequate blockade of noxious stimulation. Therefore, although the increase in the difference seems to be useful in estimating the nociception, the difference should be interpreted carefully during anesthesia.

9 References

[1] MORIMOTO Y, HAGIHIRA S, KOIZUMI Y, ISHIDA K, MATSUMOTO M, SAKABE T. The relationship between bispectral and electroencephalograohic parameters during isoflurane anesthesia. *Anesth Anlag 2004 May;98(5):1336-40*

[2] **G**UGINO LD, **C**HABOT RJ, **P**RICHEP LS, **J**OHN ER, **F**ORMANEK V, **A**GLIO LS. Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane. *Br J Anaesth* 2001 Sep; 87(3):421-8.

[3] **H**enrie JR, **P**arkhouse J, **B**ickford RG. Alteration of human consciousness by nitrous oxide as assessed by electroencephalography and psychological tests. *Anesthesiology* 1961 Mar-Apr; 22:247-59.

[4] **R**ampil IJ, **K**im J, **L**enhardt R, **N**egishi C, **S**essler DI**.** Bispectral EEG index during nitrous oxide administration. *Anesthesiology* 1998; 89: 671-7.

[5] **P**uri GD. Paradoxical changes in bispectral index during nitrous oxide administration. *Br J Anaesth 2001;* 86: 141-2.

[6] **Z**hang C, **D**avies MF, **G**uo TZ, **M**aze MM. The analgesic action of nitrous oxide is dependent on the release of norepinephrine in the dorsal horn of the spinal cord. *Anesthesiology 1999;* 91: 1401-7.

[7] **H**irota K, **K**ubota T, **I**shihara H, **M**atsuki A. The effects of nitrous oxide and ketamine on the bispectral index and 95 % spectral edge frequency during propofol-fentanyl anaesthesia**.** *Eur J Anaesthesiol 1999;* 16: 779-83.

[8] **A**SPECT **M**EDICAL **S**YSTEMS. *BIS quick FAQ.* http://www.aspectmedical.com, 2010

[9] **R**AMPIL IJ. A primer for EEG signals processing in anesthesia. *Anesthesiology 1998;* 89; 980-1002

[10] **S**IGL JC, CHAMOUN NG. An introduction to bispectral analysis fot the electroencephalogram. *J Clin Monit*. *1994;* 10: 392-404

[11] **D**E DEYNE C, **S**TRUYS M. (1996) Cerebral monitoring. *Cur Opin Anaesthesiol* 9: 41-50

[12] **J**OHANSEN JW, **S**EBEL PS. Development and clinical application of electroencephalographic bispectrum monitoring. *Anesthesiology*. *2000;* 93: 1336-44

[13] **D**AHABA AA. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. *Anesth Analg*. *2005;* 101: 765-773

[14] **D**ETSCH O, **S**CHNEIDER G, **K**OCHS E, **H**APFELMEIER G, **W**ERNER C. Increasing isoflurane concentration may cause paradoxical increases in the EEG bispectral index in surgical patients. *Br J Anaesth*. *2000*; 84:33-7

[15] **H**. VIERTIÖ-OJA, **V**.MAJA, **M**. SÄRKELÄ, **P**. TALJA, **N**.TENKANEN, **H**.TOLVANEN-LAAKSO, **M**. PALOHEIMO, **A**.VAKKURI, **A**. YLI-HANKALA and **P**. MERILÄINEN. Description of the EntropyTM algorithm as applied in the Datex Ohmeda S/5TM Entropy Module. *Acta Anaesthesiol Scand 2004;* 48: 154—61

[16] http://www.amca2005.unibe.ch/kas/pres_pdf/20050411_2a_KorhonenIlkka.pdf Detection of nociception during general anaesthesia. **I**lkka **K**orhonen. Research Professor,VTT InformationTechnology, Tampere, Finland

[17] **M**ELZACK R. Psychological aspects of pain, implications for neural blockade. In: Cousins MJ and Brienbaugh PO (eds). Neural blockade in clinical anaesthesia and management of pain. 2nd ed., JB Lippincott. *Philadelphia. 1988;* 845-60

[18] **P**ENN RD, **P**AICE JA, **K**ROIN JS. Octreotide: a potent new non-opiate analgesic for intrathecal infusion. *Pain 1992;* 49: 13-9

[19] **M**ERSKEY H and **B**OGDUSK N. Classification of chronic pain. In: Task Force on Taxonomy. 2nd ed. *Seattle, IASP Press 1994;*

[20] **R**ANG HB, **B**EVAN S, **D**RAY A. Chemical activation of nociceptive peripheral neurons. *British Medical Bulletin 1994;* 47: 534-48

[21] **M**ARSH B, **W**HITE M, **M**ORTON N, **K**ENNY GNC. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth 1991;* 67: 41-8.

[22] **E**KMAN A, **L**INDHOLM ML, **L**ENNMARKEN C, **S**ANDIN R. Reduction in the incidence of awareness using BIS monitoring. *Acta Anaesthesiol Scand 2004:* 48: 20-6.

[23] **T**AKAMATSU I, **O**ZAKI M, **K**AZAMA T. **E**ntropy indices vs the bispectral indexTM for estimating nociception during sevoflurane anaesthesia. *British Journal of Anaesthesia 2006;* 96: 620–6

[24] **V**AKKURI A, **Y**LI-HANKALA A, **T**ALJA P, et al. Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. *Acta Anaesthesiol Scand 2004*; 48:145-53.

[25] **K**ATOH T, **S**UZUKI A, **I**KEDA K. Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. *Anesthesiology 1998;* 88:642-50

[26] **A**NTOGNINI JF, **S**CHWARTZ K. Exaggerated anesthetic requirements in the preferentially anesthetized brain. *Anesthesiology 1993;* 79:1244-9.

[27] **S**AVOLA MK, **W**OODLEY SJ, **M**AZE M, **K**ENDIG JJ. Isoflurane and an alpha 2-adrenoceptor agonist suppress nociceptive neurotransmission in neonatal rat spinal cord. *Anesthesiology 1991*; 75:489-98.

[28] **C**OLLINS JG, **K**ENDIG JJ, **M**ASON P. Anesthetic actions within the spinal cord: contributions to the state of general anesthesia. *Trends Neurosci 1995;* 18:549-53.

[29] **V**ANCLUHENE AL, **S**TRUYS MM, **H**EYSE BE, **M**ORTIER EP. Spectral entropy measurement of patient responsiveness during propofol and remifentanil. A comparison with the bispectral index. *Br J Anaesth 2004;* 93:645-54.

[30] **L**ESLIE K, **S**ESSLER DI, **S**MITH WD, et al. Prediction of movement during propofol/nitrous oxide anesthesia. Performance of concentration, electroencephalographic, pupillary, and hemodynamic indicators. *Anesthesiology 1996;* 84:52-63.

[31] **K**EARSE LA Jr, **M**ANBERG P, **C**HAMOUN N, **D**E BROS F, **Z**ASLAVSKY A. Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia*. Anesthesiology 1994*; 81:1365-70.

[32] **V**ERNON JM, **L**ANG E, **S**EBEL PS, **M**ANBERG P. Prediction of movement using bispectral electroencephalographic analysis during propofol/alfentanil or isoflurane/alfentanil anesthesia. *Anesth Analg 1995;* 80:780-5.

[33] **S**INGH H, **S**AKAI T, **M**ATSUKI A. Movement response to skin incision: analgesia vs. bispectral index and 95% spectral edge frequency. *Eur J Anaesthesiol 1999;* 16:610-14.

[34] **S**EGAWA H, **M**ORI K, **M**URAKAWA M, et al. Isoflurane and sevoflurane augment norepinephrine responses to surgical noxious stimulation in humans. *Anesthesiology 1998;* 89:1407-13.

[35] **S**TRUYS M, **V**ERSICHELEN L, **M**ORTIER E, et al. Comparison of spontaneous frontal EMG, EEG power spectrum and bispectral index to monitor propofol drug effect and emergence*. Acta Anaesthesiol Scand 1998;*42:628-36.

[36] **W**HEELER P, **H**OFFMAN WE, **B**AUGHMAN VL, **K**OENIG H. Response entropy increases during painful stimulation. *J Neurosurg Anesthesiol 2005*; 17:86-90.

[37] **P**ALOHEIMO MP, **W**ILSON RC, **E**DMONDS HL Jr, **L**UCAS LF, **T**RIANTAFILLOU AN. Comparison of neuromuscular blockade in upper facial and hypothenar muscles. *J Clin Monit 1988;* 4:256-60.

[38] **P**ALOHEIMO M. Quantitative surface electromyography (qEMG): applications in anaesthesiology and critical care. *Acta Anaesthesiol Scand Suppl 1990;* 93:1-83.

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