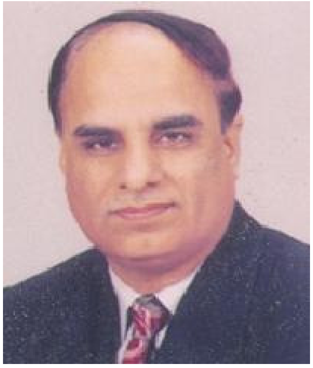
The Indian Anaesthetists' Forum – (www.theiaforum.org) Online ISSN 0973-0311
October 2008(1)

MEASURING DEPTH OF ANAESTHESIA - AN OVERVIEW ON THE CURRENTLY AVAILABLE MONITORING SYSTEMS

V K Grover[1], Neerja Bharti[2]
1. Professor
2. Associate Professor
Department of Anaesthesia & Intensive Care
Post Graduate Institute of Medical Education and Research
Chandigarh-160012, India
Correspondence: Prof. V K Grover
E-mail: vinodkgrover@gmail.com
Phone: 0172-2756505, 0091-9815027833



About the Author: Dr. Vinod Kumar Grover is presently working as Professor, Department of Anaesthesia, Post Graduate Institute of Medical Education & Research (PGIMER), Chandigarh. He is a Graduate from Government Medical College Rohtak, Haryana; did his MD from PGIMER Chandigarh and MNAMS in 1980 from National Academy of Medical Sciences, New Delhi.
Fields of Interest: Neuroanaesthesia, Critical Care and Anaesthesia for Renal Transplant. Started Neuroanaesthesia & Critical Services at Salmaniya Medical Centre, Bahrain, Regional Hospital, Sur, Sultanate of Oman and at Apollo Hospital, Dhaka.

Summary

One of the objectives of modern anaesthesia is to ensure adequate depth of anaesthesia to prevent awareness without inadvertently overloading the patients with potent drugs. In the absence of graded pharmacodynamic measurements, dosing of hypnotics may be inaccurate, which may lead to either delayed recovery or awareness during surgery. Awareness experiences frighten patients and can leave a lifetime of residual emotional and psychological problems. There appears to be increasing evidence that anaesthesia depth monitors reduce the incidence of unexpected intraoperative awareness and also that they improve the quality of anaesthesia.

In this review, the authors critically analyse the use of a number of depth of anaesthesia monitors in light of the most recent literature. Traditional techniques such as clinical parameters, isolated forearm technique, spontaneous surface electromyogram and lower oesophageal contractility together with modern techniques such as heart rate variability, bispectral index, entropy and evoked potentials bring us to the

current state of the art in depth of anaesthesia monitoring. This article reviews information about each of the modern techniques, demonstrating its implementation, and discusses the existing technical problems and clinical challenges, suggesting new techniques necessary for the future development of depth of anaesthesia monitoring and control system.

Introduction

Assessment of the depth of anaesthesia is fundamental to anaesthetic practice. Depth of anaesthesia depends on two antagonizing factors: the anaesthetic, which induces different anaesthesia components to a varying degree depending on the specific drug used; and the surgical stimulation, which may activate the sympathetic nervous system and increase the patient's level of consciousness and somatic and autonomic reactivity. Adequate depth of anaesthesia requires a sufficient amount of the agent to secure unconsciousness and other components of anaesthesia as needed for that particular surgical procedure, without jeopardizing vital organ functions.

Prior to the use of muscle relaxants, maintaining the appropriate depth of anaesthesia was a balance between abolishing movement to pain whilst maintaining adequate respiration. With the absence of movement on incision it was safe to assume that the patient was not aware, however with the use of muscle relaxants it became necessary to be certain that the administered concentration of anaesthetic agent was adequate to prevent awareness. With the emergence of new anaesthetic techniques such as intravenous anaesthesia, the use of potent opiate analgesics, newer volatile agents and more complicated regional nerve blocks, a means of measuring depth of anaesthesia is important.

Depth of anaesthesia is difficult to define, perhaps because increasing anaesthetic concentration is associated with such diverse phenomena as amnesia and loss of cognitive ability, which is balance against the intense arousal that surgical stimulation can induce. Plomley[1], in 1847, was the first to attempt to define depth of anaesthesia. He described three stages: intoxication, excitement and the deeper level of narcosis. In that same year John Snow[2] described 'five degrees of narcotism' for ether anaesthesia. The first three stages encompassed induction of anaesthesia, and the last two represented surgical anaesthesia. In 1937, Guedel[3] defined four stages of anaesthesia on the basis of somatic muscle tone, respiratory parameters and ocular signs. The first stage was later expanded by Artusio[4] into three planes. In plane 3, the patient has complete analgesia and amnesia. The success of using clinical signs to assess ether anaesthetic depth arises partly from the established hypnotic and analgesic effects that ether provides, which differ from those of the current inhaled anaesthetics used in modern anaesthetic practice.

In 1957, Woodbridge[5] defined anaesthesia as having four components; sensory blockade, motor blockade, reflex blockade of autonomic reflexes and loss of consciousness. According to Prys-Roberts[6], common feature of general anaesthesia is suppression of conscious perception of noxious stimuli. Analgesia, autonomic stability and muscle relaxation are desirable but not actual components of anaesthesia. Prys-Roberts divided the noxious stimuli into somatic and autonomic components, which were further, divided into sensory, motor and respiratory, haemodynamic, sudomotor and hormonal (Figure 1). The depth of anaesthesia is determined by the stimulus applied, the response measured, and the drug concentration at the site of action that blunts responsiveness.

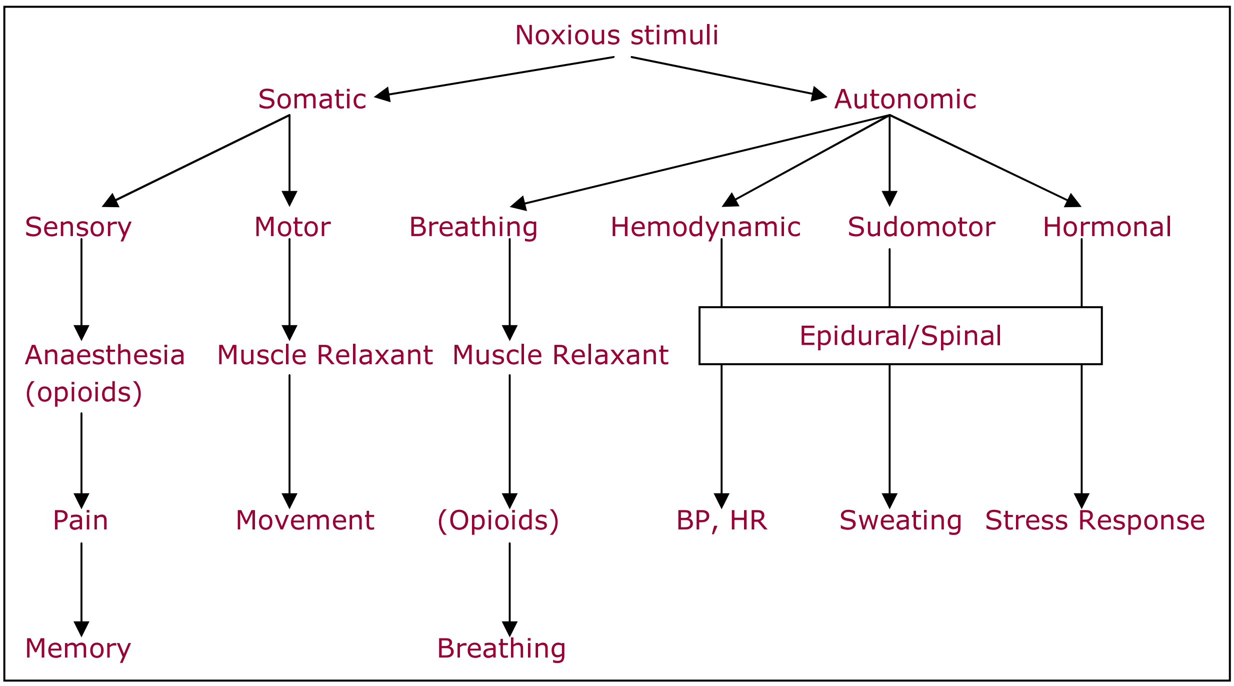


Figure 1: Various noxious stimuli and their effects

Glass in 1988[7], proposed that consciousness can be perceived as a balance within the cortex between depression and excitation. The cortex is primarily depressed by hypnotics, although opioids and nitrous oxide also have sedating properties that depress the cortex. Cortex depression promotes unconsciousness. These effects are opposed by both ambient stimulation and the excitatory effects of pain projected from the thalamus and midbrain on the cortex. Systemic opioids act primarily on the midbrain and thalamus, whereas neuraxial opioids and local anaesthetics act on the spinal cord to attenuate the transmission of painful sensation to the cortex, thereby reducing the amount of hypnotic required to obtain a state of unconsciousness.

The interaction between analgesics and hypnotics is thus fundamental to understanding and defining anaesthetic depth. Following components are needed to define depth of anaesthesia-

- Afferent stimulus
- Efferent response
- Equilibrated concentrations of analgesic components
- Equilibrated concentrations of hypnotic components
- Equilibrated concentrations of other relevant drugs (β-blockers, muscle relaxants, local anaesthetics)
- Interaction surface relating drug interactions to the probability of a given response to a given stimulus

Stimuli can be roughly divided into benign and noxious. Benign stimuli (calling name and light touch) are readily suppressed by hypnotics alone, with minimal need for analgesic drugs. Noxious stimuli (Laryngoscopy, intubation and skin incision) are physically painful and thus responses to noxious stimuli are more readily suppressed in the presence of analgesics.

Responses can be categorized as verbal, purposeful movement, involuntary movement, ventilation, haemodynamic response, sudomotor response, the formation of implicit and explicit memories, and EEG responses. Opioids tend to ablate haemodynamic response before movement, whereas hypnotics tend to ablate movement response before haemodynamic response. Increasingly larger doses of anaesthetic are required to suppress more difficult response (hypertension and tachycardia) to the more profound stimulus (Figure 2).

Depth of anaesthesia can be defined as the probability of non-response to stimulation, calibrated against the strength of the stimulus, the difficulty of suppressing the response, and the drug-induced probability of nonresponsiveness. Anaesthetic depth ranges from a 100% probability of response to a mild stimulus and readily suppressed responses to a 100% probability of nonresponse to profoundly noxious stimuli and responses that are difficult to suppress.

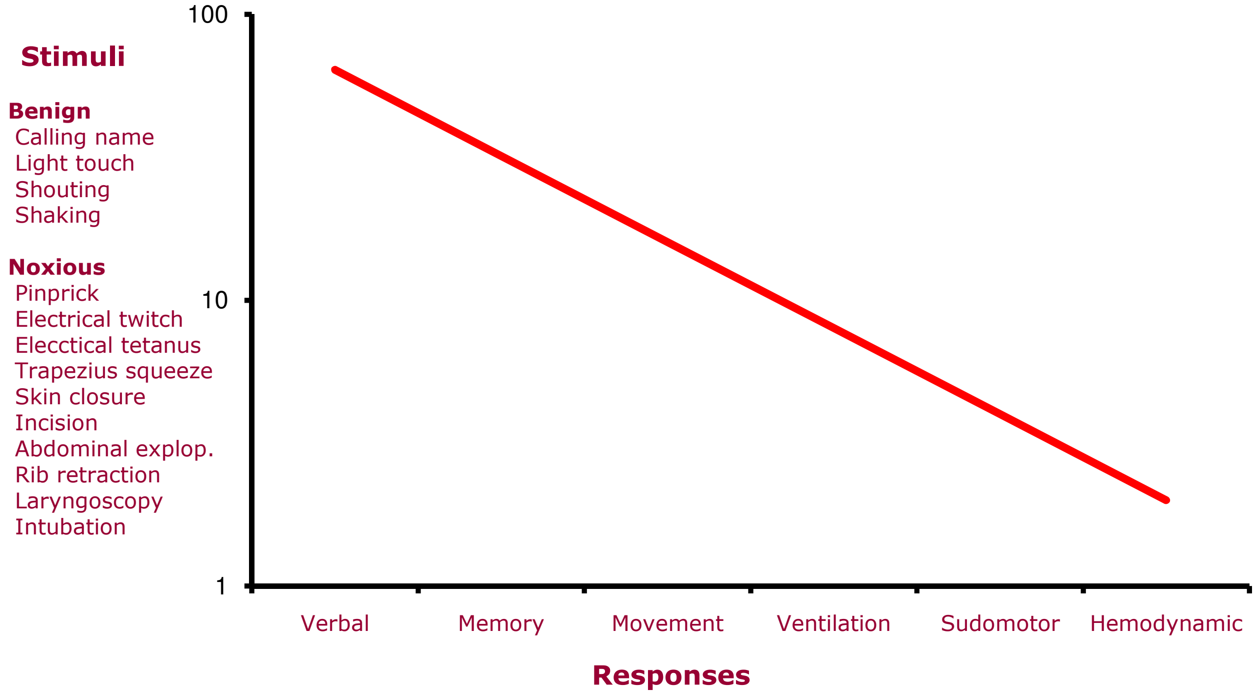


Figure 2. Relationship between relevant stimuli and responses. As the cells progress from left to right and from top to bottom, increasingly larger doses of anesthetic are required to suppress a given response to a given stimulus

Cognition, Memory and Awareness

The effect of anaesthesia on cognition and memory occurs before noticeable autonomic effects. Cognition is described in the terms of short-term and long-term memory. Short-term memory is concerned with learning, decision-making and retrieving information from very large, long-term memory. It is associated with conscious awareness. The long-term memory can be divided into procedural memory - knowing how to do things and, the declarative memory. The declarative memory is further divided into somatic memory - simply remembering the facts without knowing how to learn them and, episodic memory - remembering both the facts and how they were learnt.

Awareness during general anaesthesia can be defined as a degree of consciousness, revealed by the occurrence of explicit or implicit memory of intra-operative events. During such an episode information may be stored temporarily into short-term memory and may or may not be stored permanently into long-term memory. Two clinical signs possibly predicting the recall are movement and autonomic response. The use of muscle relaxants can eliminate the movement response, which leaves the only autonomic activity as a response of intraoperative awareness. Griffith and Jones[8] recognize four stages of awareness. The 4th stage is of conventional deep anaesthesia with no awareness or recall. Postoperatively, an interview can reveal the explicit awareness. Detection of implicit awareness requires psychological testing, which is impractical during routine anaesthesia.

The overall incidence of intraoperative awareness with recall is about 0.2 – 3%[9], but it may be >40% in certain high risk patients, like, those with multiple trauma, caesarean section, cardiac surgery and haemodynamically unstable patients[10]. For many patients, the experience of awareness may not leave prolonged after-effects; in some, however, a post-traumatic stress disorder marked by repetitive nightmares, anxiety, irritability, a preoccupation with death, and a concern with sanity can develop[11].

Specific Drugs and Clinical Situations

Inhalational Agents

Volatile anaesthetics cause a lack of movement response to noxious stimuli by action at the spinal cord and create loss of consciousness at a supraspinal, cortical site of action. The purposeful movement of any part of the body in response to noxious stimuli is one of the most useful clinical sign of depth of anaesthesia. Using this movement to quantitate anaesthetic response induced by potent inhaled anaesthetics, Eger et al[12] defined MAC as the minimum alveolar concentration of inhaled anaesthetic required to prevent 50% of subjects from responding to a standard painful stimulus (initial skin incision) with "gross purposeful movement." Later on, MAC has been expanded as, MAC- intubation (inhibit movement and coughing during intubation), MAC-incision (prevent movement during initial surgical incision), MAC-bar (prevent adrenergic response to skin incision) and MAC-awake (allow opening of the eyes on verbal command during emergence) by evaluating other clinical end-points or stimuli[13-15].

MAC provides the best available method to monitor continuous brain concentration of volatile anaesthetics provided adequate time is allowed for equilibration between alveolus, blood and effect site. The MAC curves (representing the relationship between the concentration of anaesthetic agent and the probability of response) are located from left to right in the order: MAC-awake < MAC-incision < MAC-intubation < MAC-bar[16]. The

MAC-awake and MAC-incision curves are so steep that the difference between MAC 5% and MAC 95% is approximately 0.2% for halothane[17]. The MAC-bar curve is much less steep, which means that very high concentrations are needed to eliminate the catecholamine response[14]. Tracheal intubation represents stronger noxious stimuli than all surgical stimuli, therefore, MAC curves for various intraoperative stimuli falls between MAC-incision and MAC-intubation. In unstimulated patients both explicit and implicit memory may be absent at end-tidal concentration of inhalational agents equal to MAC-awake[18].

In contrast to somatic reflexes, haemodynamic responses to noxious stimuli do not correlate well with end-tidal drug concentration. Consequently the relationship between somatic (movement) and autonomic (haemodynamic) responses is poor during inhalational anaesthesia. Inhalational agents including nitrous oxide are considered additive in their actions and contribution to MAC but it must not be forgotten that their pharmacokinetics are different depending on relative solubility. MAC can be changed with the use of other anaesthetics, opioids and CNS drugs[19]. Numerous altered physiological states and pathological states may also change the requirement of inhaled anaesthetics. MAC is increased by hyperthermia, hyperthyroidism, alcoholism and acute administration of dextroamphetamine and decreased by increasing age, hypothermia, severe hypotension, hypoxia and acidosis, pregnancy, sedative drugs including α_2-agonists, systemic and epidural opiates, ketamine and intravenous local anaesthetics[20].

Hypnotics

These are commonly used for induction of anaesthesia as a single intravenous bolus. The depth of anaesthesia increases rapidly (causing loss of consciousness), peaks and then decreases as plasma concentration declines due to rapid redistribution of the drug. The CNS depression lags behind the plasma concentration manifesting as hysteresis on curves plotting against plasma concentration. Clinical end points that are useful in assessing depth of anaesthesia during induction include - loss of verbal responsiveness, loss of eye lash reflex, loss of corneal reflex and absence of movement in response to squeezing the trapezious muscle. Because they do not provide sufficient analgesia, the haemodynamic response to major noxious stimuli is great even when large doses are given. Therefore, assessment of depth of anaesthesia using clinically relevant noxious stimuli (laryngoscopy/intubation) requires the concurrent administration of other analgesic and adjuvant drugs (opioids/nitrous oxide, muscle relaxants) to provide haemodynamic control.

The use of intravenous hypnotics for maintenance of anaesthesia is becoming more common with the introduction of propofol. Unfortunately there is no equivalent of measuring end-tidal volatile agent concentration. Although, commercially available target-controlled infusion systems using propofol, estimate a plasma concentration using a pharmacokinetic model, estimated blood concentrations do not correlate well with measured values due to inter-patient pharmacokinetic variability. Also the clinical effects of a particular drug concentration vary between patients[21]. The accurate assessment of depth of anaesthesia during intravenous anaesthesia is difficult and care in preventing awareness, especially with the use of muscle relaxants, is important. Sear et al[22] proposed the concept of minimum infusion rate (MIR) to compare the anaesthetic requirements of intravenous anaesthetics during total intravenous anaesthesia (TIVA), They calculated the 50% effective dose (ED50) and 95% effective dose (ED95) infusion rates using the movement response to skin incision, which were analogous to MAC. Unfortunately, the MIR is also affected by pharmacokinetic properties of the drug, age and physical status of the patient and the use of other drugs (opioids, N_2O) in addition to the anaesthetic requirement or responsiveness of the CNS.

In clinical practice, intravenous hypnotics are frequently combined with other drugs (opioids, nitrous oxide, and potent inhaled anaesthetics) to prevent haemodynamic response to strong clinical stimuli such as laryngoscopy and intubation. Kazana and coworkers[23] demonstrated that a steady-state fentanyl plasma concentration of 3 ng/mL decreased Cp50 values of propofol by 50-55% for intense noxious stimuli.

Narcotics (Opioids)

Various narcotics like morphine, fentanyl, alfentanil, sufentanil and remifentanil have been used in higher dosage to provide anaesthesia in patients with severe valvular or congenital heart disease because of their ability to maintain cardiovascular stability[24,25]. However, they provide incomplete hypnotic effects even at very large doses when used as sole anaesthetics. In a study, using high dose fentanyl induction in patients for cardiac anaesthesia, Stanley et al[25] found that even increasingly large doses of fentanyl could not always produce a complete anaesthetic state in all subjects. Wynandas and colleagues[26] demonstrated that even extremely high concentration of fentanyl (15 ng/mL) did not eliminate haemodynamic responses to defined surgical stimuli (skin incision, sternotomy, aortic root dissection) in 20% of patients undergoing coronary artery surgery. Murphy and Hug[27] demonstrated a ceiling to the enflurane-sparing effect of fentanyl. McEvan et al[28] also found very similar results with isoflurane. The maximal MAC reduction was 82% at a steady state fentanyl concentration of 10.6 ng/mL. In current clinical practice, high-dose opioids are supplemented either with amnesic drugs (benzodiazepines) or low concentrations of potent inhalational anaesthetics.

The Cp50 values (Steady-state plasma concentration of the drug which will prevent purposeful movement to noxious stimuli in 50% population) of opioids were calculated for three clinical events: intubation, skin incision and skin closure. The relationship curves of alfentanil show that intubation requires significantly higher concentration of alfentanil than skin incision and skin closure[29]. The minimum infusion rate of opioids during surgery has been titrated to the following end points: Increase in SBP >15 mmHg above normal value, HR >90 beats/min in absence of hypovolaemia, somatic response (body movements, swallowing, coughing, grimacing or eye opening), and the autonomic signs of inadequate anaesthesia (lacrimation, flushing, sweating). If any clinical sign occurred, the infusion rate has increased by 20-30% and a small bolus dose was given.

TECHNIQUES FOR MONITORING DEPTH OF ANAESTHESIA

The precise titration of anaesthetic agents is necessary to avoid the consequences of a too light depth of anaesthesia such as unexpected intraoperative awareness, as well as a too deep level of anaesthesia, which can be deleterious in terms of postoperative morbidity and mortality. The ideal monitoring should fulfil the following criteria - It should be applicable for any type of anaesthesia, the monitor must have an extremely high sensitivity, and finally, the monitoring device must be economic.

There are various subjective and objective methods of assessing depth of anaesthesia (Table 1). Subjective methods rely on the movement and autonomic response to stimuli and depend on the opinion and experience of an anaesthetist. The objective methods rely on the sensitivity of the monitor.

A. Subjective methods

1. Autonomic response
2. Patient Response to Surgical Stimulus (PSRT) Scoring system
3. Isolated forearm technique

B. Objective methods

1. Spontaneous surface electromyogram (SEMG)
2. Lower oesophageal contractility (LOC)
3. Heart rate variability (HRV)
4. Electroencephalogram and derived indices
   - Compressed spectral array/ Spectral edge frequency/ Median frequency
   - Bispectral index
   - Entropy
   - Narcotrend index
   - Patient state index
   - Snap index
   - Cerebral state index
5. Evoked potentials
   - Somatosensory evoked potentials
   - Visual evoked potentials
   - Auditory evoked potentials
   - Auditory evoked potential index
   - A-Line autoregressive index

Table 1: Methods of assessing depth of anaesthesia

SUBJECTIVE METHODS

1. Autonomic response

Even today many anaesthesiologists rely on parameters of the autonomic nervous system, such as blood pressure and heart rate to decide if a patient is adequately anaesthetized. Sudden hypertension and/or tachycardia, sweating, tearing or mydriasis may indicate lightening of anaesthesia. Although, the measurement of clinical parameters provides useful information regarding the adequacy of analgesia and depth of anaesthesia, this must be taken into context with the surgical procedure and the anaesthetic technique, as cardiovascular parameters alone are poor predictors of the hypnotic state. Tachycardia secondary to anti-cholinergic drugs like atropine make the heart rate uninterpretable, and beta- adrenergic blocking drugs, opiates and regional anaesthetic techniques will obtund the sympathetic nervous system response to pain. A wide range of other events like, hypotension, dehydration, hypoxia, hypo or hyperthermia, sudden massive blood loss etc may also lead to such haemodynamic changes. Factors like, built of the patient, baseline tone, drugs like, anti-hypertensive agents, inotropes and vasodilators may also affect blood pressure and heart rate. Beside this various drugs used in anaesthesia like muscle relaxants and opioids may suppress these responses but not produce hypnosis.

2. Patient Response to Surgical Stimulus (PRST) Score

PRST score, based on autonomic changes in response to surgical stimulus is a poor indicator of depth of anaesthesia[30]. It has been proven that haemodynamic responsiveness to noxious stimuli does not necessarily signify awareness, nor does lack of haemodynamic changes guarantee unconsciousness[31]. Case reports have described cases of explicit awareness during anaesthesia, evident on electroencephalographic monitoring minutes before any significant cardiovascular changes occurred[32]. In most of the cases of ASA closed claim for recall during anaesthesia, there was no concomitant autonomic sign[33]. Among the patients with recall during anaesthesia, 15% showed hypertension, 7% showed tachycardia and only 2% showed movement[33]. In a study conducted by Vernon et al[34], it has been shown that pre-incision haemodynamic variables did not predict patient response to skin incision.

3. Isolated Forearm Technique (IFT)

In this method a tourniquet is placed on an arm of the patient before administration of a muscle relaxant and inflated above systolic pressure to exclude its effect. The arm is therefore free to move during anaesthesia. Ischaemia has to be prevented by periodically releasing the tourniquet, usually before topping up the muscle relaxant. Patient may then be asked to move his fingers to check adequacy of depth of anaesthesia. A purposeful movement of the arm either spontaneously or in response to verbal command indicates light anaesthesia, although not necessarily explicit awareness[35]. This method has been used previously as a means of detecting awareness during caesarian section under general anaesthesia and during clinical trials assessing rates of awareness. Some would argue that response to command during surgery is a late sign when attempting to prevent awareness however not all patients responding have any recall. Russell[36] showed that the incidence of movement with IFT can vary with the choice of anaesthetic. The incidence of purposeful movement was 44% after nitrous oxide and fentanyl anaesthesia, but it was only 7% after continuous infusion of etomidate and fentanyl.

Despite a simple technique, IFT has some limitations, like – non specific startle response may be interpreted as consciousness; levels of anaesthesia needed to prevent movements in patients using IFT are significantly higher than those routinely used, since the advent of muscle relaxant; patients have reported that they heard commands to move the isolated arm, but were unable to do so, even though nerve stimulator suggested that the arm was not paralysed[37].

OBJECTIVE METHODS

Without objective monitoring depth of anaesthesia is a dimensionless concept, and the subjective descriptors 'too light', 'too deep' or 'enough' are not helpful for any rigorous assessment of where the patient is on the continuum.

1. Spontaneous Surface Electromyogram (SEMG)

In patients who are not completely paralysed, spontaneous surface electromyogram (SEMG) can be recorded from various muscle groups, especially facial, abdominal and neck muscles. Frontalis muscle is innervated by a branch of the facial nerve and is less affected by the neuromuscular blockade. A stick on electrode positioned over the frontalis muscle can record the frontalis electromyogram (FEMG). The level of FEMG has been observed to fall during anaesthesia and to rise to pre-anaesthetic levels just before awakening[38]. However, the scales were not absolute and there may be variability in response. The FEMG together with EEG provide better results. The ABM monitor system (Datex) records both EEG indices and FEMG via the same electrodes[39].

2. Lower Esophageal Contractility (LOC)

The non-striated muscles in the lower half of oesophagus retain their potential activity even after full skeletal muscle paralysis by neuromuscular blocking agents. Measurements of lower oesophageal contractility (LOC) provide two prime derivatives:

(i) Spontaneous lower oesophageal contractions (SLOC):

These are non-propulsive spontaneous contractions originated in the vagal motor nuclei and adjacent reticular activating system in the brain stem and is mediated by efferent vagal pathways. The frequency of these movements is increased as the dose of the anaesthetic is reduced.

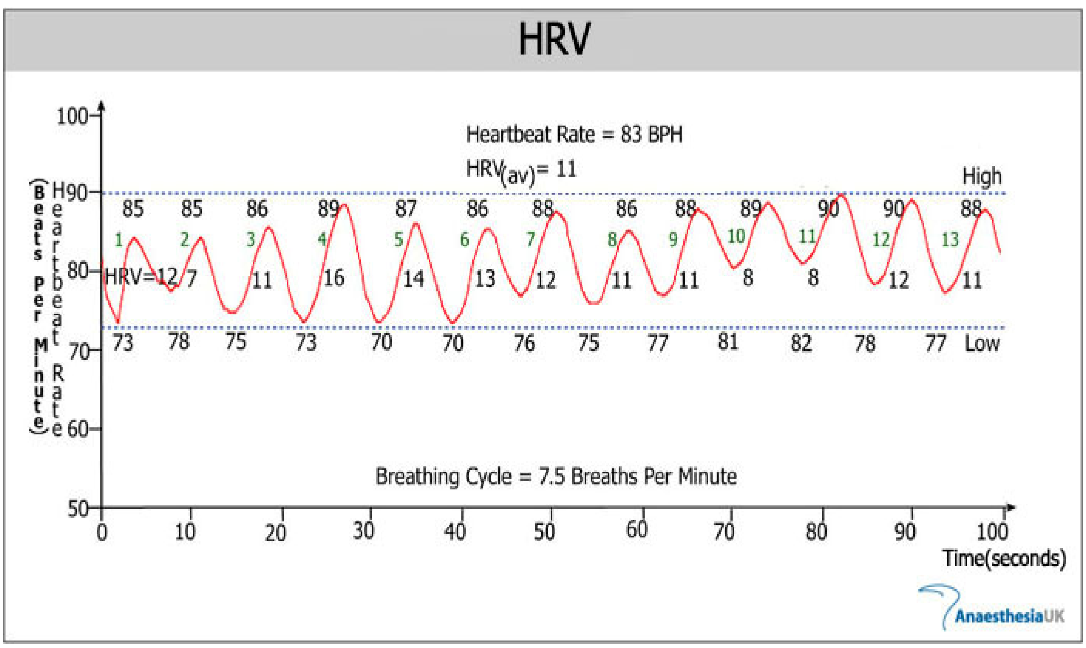
(ii) Provoked lower oesophageal contractions (PLOC):

The brief inflation of small balloon in the lower oesophagus provokes a secondary peristaltic response, which increases in amplitude as anaesthetic depth decreases. Evans and colleagues[40,41] were the first to propose that depth of anaesthesia might be measured by the degree of spontaneous contractions of lower oesophagus. Sessler et al[42] demonstrated that the absence of spontaneous contractions of the lower esophageal sphincter 6 min before skin incision correlated well with no movement on incision in subjects given halothane anaesthesia but not with N_2O/opioid anaesthesia. Erikson et al[43] found that SLOC frequency did not predict movement in unparalysed patients given isoflurane. A wide variation in responses between individuals reduces the sensitivity and specificity of the method. The method has distinct disadvantages: the monitoring catheter can not be placed prior to and used during induction of anaesthesia, the contraction intensity can be affected by the location of the catheter tip, and the frequency of SLOC is reduced by anticholinergic drugs.

3. Heart Rate Variability (HRV)

Sakuma et al[44] investigated beat to beat variability of heart rate and observed that it may provide information, which would be useful for monitoring depth of anaesthesia. The special analysis of HRV revealed 3 components: low frequency fluctuations; believed to be circadian, Medium frequency fluctuations; attributed to baroreceptor reflex, and High frequency fluctuations; coincides with the frequency of ventilation, in which heart rate increases during inspiration and decreases during expiration, through a predominantly parasympathetic reflex connecting stretch receptors in the lungs and aorta to vagal motor neurons innervating the heart. This is called as respiratory sinus arrhythmia (RSA). It is typically characterized by greater than 10% variation in the ECG P-wave interval over 5 minutes. RSA is easily visible on an ECG monitor that is time locked to an ECG R-wave peak, but is difficult to distinguish with a rolling display. Pomfrett and colleagues[45] reported, using on line analysis of RSA, reduction in RSA during anaesthesia together with increase in RSA during recovery. Various studies[46,47] have shown that changes in the level of RSA mirror changes in anaesthetic level. In addition, surgical stimulation during light anaesthesia elicits a greater increase on RSA than seen during lightening anaesthesia alone. The 'Fathom' monitor (Amtec Medical Limited) is based on the use of HRV as a method of assessing anaesthetic depth. At this stage, experience with the Fathom monitor is very limited.

Although, measurement of vagal tone using HRV has been described as an important window into the activity of the nervous system, it depends on an intact autonomic nervous system and healthy myocardial conducting system. Moreover, confounding effects of multiple factors influencing HRV in the perioperative setting make interpretation of data difficult and limit this methodology. Beta-blockers, conduction abnormalities, autonomic neuropathy and sepsis all cause problems. Atropine in pharmacologically relevant doses serves to attenuate, but not abolish, changes in HRV. Because of the ongoing progress in monitoring with regard to acquisition and computer-based analysis of HRV data, it seems at least possible to measure HRV routinely in the perioperative setting. However, the need for standardization requires large prospective and standardized trials.



Heart rate variability (HRV) at respiration frequency of 7.5 breaths/ min

4. Electroencephalogram and Derived Indices

In 1937, Gibbs et al[48] reported that anaesthetics changed EEG activity from low-voltage fast waves to high-voltage slow waves and postulated that the EEG could be used to measure the effect of anaesthesia. However, the raw EEG is a complex small (1-50 µv) voltage deflection, which does not correlate with specific underlying events. The electronic filtering of EEG with the integrated amplitude of EEG waveform provides better indication of the level of brain activity. The cerebral function monitor (CFM) gives a single trace of integrated EEG amplitude; increasing level of cerebral activity appears as a broadening of the trace, which ranges from 5-18 µv peak to peak amplitude. The cerebral frequency analysing monitor (CFAM) filters the EEG into five frequency bands and adds one extra trace demonstrating periods of burst-suppression. The main drawback of these monitors is that they are influenced by diathermy and the periods of poor electrode contact. They can be unreliable, especially when using inhalational anaesthetic agents and the response to increasing depth of anaesthesia is biphasic, complicating dose-response interpretation.

The modern EEG monitors process and obtained EEG analog signals over a period of time and display the information in the form of histograms as compressed spectral array (CSA) or single-figure numeric indices, like: Spectral edge frequency (SEF), Median frequency (MF) and Bispectral index (BIS).

Compressed Spectral Array (CSA)

The CSA has been used to monitor the depth of anaesthesia[49]. During deeper anaesthesia the peaks of CSA shifts from higher frequencies to low frequency activity. While at recovery, there is a progressive increase in the amount of high frequency activity with a corresponding decrease in low frequency activity. Although the CSA is considered more compact than the raw EEG, it is still a complex display that takes time to comprehend, and changes within it are difficult to quantify.

Spectral Edge Frequency & Median Frequency

The spectral edge frequency is that below which 95% of EEG power is located. The median frequency is described as, above and below which 50% of EEG power spectrum is distributed. Both SEF and MF have been correlated to clinical signs using numerous anaesthetic agents.[50,51] Although, these parameters predicted imminent arousal with sensitivities of 90% and specificities of 82-90%, they were unable to predict the response to skin incision and the development of memory.

Bispectral Index (BIS)

BIS is a statistically based, empirically derived complex parameter that is composed of a combination of time domain, frequency domain and high order spectral sub parameters. It is unique in the sense that it integrates several disparate descriptors of the EEG into a single variable, based on a large volume of clinical data to synthesize a combination that correlates behavioural assessments of sedation and hypnosis, yet is insensitive to the specific anaesthetic or sedative agent chosen. BIS is a numerical index, ranges from 100 (awake) to 0 (isoelectric EEG). The BIS correlates well with the level of the responsiveness (responsiveness scores of modified observer's assessment of alertness / sedation level) and provide an excellent prediction of the level of consciousness with propofol, midazolam and isoflurane anaesthesia[52]. After administration of a hypnotic drug, the BIS index decreases gradually from an awake value of 100. The loss of consciousness will tend to occur at BIS values between 70 and 80. BIS values of 40-60 reflect adequate hypnotic effect for general anaesthesia with reasonably rapid recovery to consciousness. A BIS index less than 40 represents deep hypnosis. Various studies[53-55] have shown that BIS also correlates with the haemodynamic response to intubation, patient's response to skin incision and verbal command during inhalational as well as total intravenous anaesthesia. BIS is a useful monitor to adjust the anaesthetic dosages with decreased incidence of haemodynamic disturbances and leads to improved recovery[56]. It reduces the cost by decreasing anaesthetic use and reducing stay in PACU, and provides a useful guide for titration of anaesthetic agents in cardiac surgery, elderly and paediatric patients.[57,58]

In spite of its excellent usefulness, BIS have some shortcomings. BIS is a cortical function indicator that does not directly reflect the activity of the subcortical structures, including the spinal cord, that primarily mediate motor response to a noxious stimulus; thus, BIS may not be reliable for predicting responsiveness to noxious stimuli. The presence of senile dementia may be a confounding factor in interpretation of BIS value. In some instances BIS has been observed to increase with the use of N_2O and ketamine[59,60]. Infusion of esmolol can also alter the BIS index during stimulation with relevant noxious stimuli (tracheal intubation)[61]. Mathew and colleagues[62] showed that in patients undergoing cardiopulmonary bypass with constant effect-site concentrations of fentanyl and midazolam, hypothermia decreased the BIS index by $1.12/^0C$ decline in temperature. BIS response is less reliable with a high dose opioid technique[63]. Because the reduced hypnotic dose in high-dose opioid techniques results in less profound hypnotic EEG drug effect. BIS index is most accurate when used with anaesthetics consisting of a low or moderate dose of opioid analgesic and a hypnotic drug titrated to the BIS response.

2000 BIS-XP Monitor (Aspect Medical Inc., Newton, MA, USA)

Entropy

Entropy monitoring is based on acquisition and processing of raw EEG and FEMG signals by using the entropy algorithm. EMG can be separated from EEG due to its faster frequency. Entropy of the signal has been shown to drop when a patient falls asleep and increase again when the patient wakes up[64]. The commercially available Datex-Ohmeda module calculates entropy over time windows of variable duration and reports two separate numerical values on a scale between 0 and 100. The maximum value of the response entropy (RE) is 100, and the maximum value of the state entropy (SE) is 91. Numbers close to 100 mean that the patient is conscious, and numbers close to zero denote very 'deep' anaesthesia. A clinically practical level of anaesthesia is achieved when the value is between 40 and 60. At this point, unintended awareness is extremely unlikely; on the other hand, recovering from anaesthesia is not unnecessarily prolonged. When the RE and SE values are identical (subtracted value 0-3), the level of anaesthesia can be considered 'adequate'. A slow increase in the difference between the RE and SE values during anaesthesia is a sign of frontal muscle EMG activity, which in turn is a sign of 'inadequate' anaesthesia. It is typical for the RE and SE values to differ during intubation, when it is a case of nociception, and during recovery at the end of anaesthesia when the diminishing effect of the drugs on the nervous system can be seen as activation of the frontal muscle. This is a sign of imminent regaining of consciousness. Entropy charts the level of consciousness just as reliably as BIS[65]. The functionality of the monitor has been validated for propofol, thiopental, sevoflurane and desflurane anaesthesia. The entropy indices are found to be less interfered with the electrocautery unit than BIS during intraoperative period[66]. However, like other monitors measuring consciousness on the basis of EEG, entropy is also unreliable during high-dose opioid anaesthesia. Furthermore, it should be taken into account that even when using entropy, a sudden pain stimulus during an operation may unexpectedly change the anaesthesia into 'inadequate'. The difference between the RE and SE values does not necessarily predict a situation like this. Entropy has not yet been reliably validated in ketamine anaesthesia either; thus its dependability is uncertain in this situation.

The Datex Monitor screen trends showing entropy along with ECG, SpO_2, End-tidal CO_2

The Entropy sensor attached to a patient

Narcotrend Index

The Narcotrend® is an EEG monitor designed to measure the depth of anaesthesia and has been developed at the University Medical School of Hannover, Germany. The raw EEG signal is recorded by standard ECG electrodes for single- and double-channel registration. After artifact exclusion and fourier transformation, a multivariate statistical algorithm transforms the raw EEG data in a 6-letter classification of the depth of anaesthesia: A(awake), B(sedated), C(light anaesthesia), D(general anaesthesia), E(general anaesthesia with deep hypnosis), F(general anaesthesia with increasing burst suppression). The system included a series of sub-classifications resulting in a total of 14 possible sub-stages: A, B0–2, C0–2, D0–2, E0–1, and F0–131[67]. In the most recent version (4.0) of the Narcotrend® software, the alphabet-based scale has been "translated" into a numerical scaling index system which called as the Narcotrend® index. This is scaled quantitatively similar to BIS scale viz. 0 (deeply anaesthetized) to 100 (awake). Kreuer S et al[68] demonstrated that an increase of the hypnotic component of anaesthesia as indicated by BIS is accompanied by corresponding effects as displayed by the Narcotrend® during propofol-remifentanil anaesthesia. Narcotrend® has also been used in children during propofol/remifentanil anaesthesia and sevoflurane anaesthesia[69,70]. It is found to reduce propofol consumption and shorten recovery time as compared to a conventional clinical practice. In a recent study, however, Narcotrend® is found unable to differentiate reliably between conscious and unconscious patients during general anaesthesia using neuromuscular blocking agents.[71]

Patient State Index

The patient state index (PSI) has a range of 0–100, with decreasing values indicating decreasing levels of consciousness or increasing levels of sedation, similar to BIS, entropy, and Narcotrend®. The derivation of the PSI is based on the observation that there are reversible spatial changes in power distribution of quantitative EEG at loss and return of consciousness. The PSI algorithm, calculated via a proprietary algorithm by a high-resolution 4-channel EEG monitor after advanced artifact rejection The PSI monitor, initially called the Patient State Analyzer (PSA) 4000 from Physiomatrix, is now known as the SED Line monitor from Hospira, Inc., the newest generation of the device. The SED Line system provides the clinician the option of storing and downloading patient data for future use as well as monitoring bilateral brain function and symmetry with a density spectral array (DSA) display. Drover and colleagues[72] compared standard practice to PSI-guided (target level of 25-50) propofol titration of propofol – alfentanil – nitrous-oxide anaesthesia in a multicenter, prospective, randomized study. The group titrated with PSI guidance received less propofol and emerged more quickly from anaesthesia as compared to control group. Chen et al[73] compared the PSA monitor with BIS monitor in patients receiving propofol, fentanyl, desflurane, and nitrous-oxide anaesthesia. The results were similar with both the monitors. However, no clinical trial or comparative study has found that examined the impact of PSI monitoring on the incidence of intraoperative awareness.

Snap Index

The SNAPII monitor (Everest Biomedical Instruments, Chesterfield, MO) is the first commercial EEG-monitoring tool to use Personal Digital Assistant computer technology. It samples raw EEG signals and uses its own unique algorithm, analyses both high-(80-420 Hz) and low- (0-20 Hz) frequency components of the signal. This is termed as the 'Snap index', and it range from 100 (arbitrarily representing the fully awake state) to 0 to provide functional data points for patient management. The first version of Snap monitor was introduced in 2002, and so far there has been little experience with the Snap device reported in the literature. There is no clinical evidence that Snap is superior to other EEG devices in generating more specific information about 'depth of anaesthesia'. One study has reported a mean Snap index of 71 to be predictive of a loss of consciousness in 95% of elective surgery patients[74]. Same author, in a recent study, however, compares Snap with BIS, and concluded that Snap index tracks loss of consciousness and emergence from sevoflurane and sevoflurane/nitrous oxide anaesthesia. They further observed that the Snap index returns to baseline before awakening, whereas the BIS index remains below baseline at awakening, suggesting that the Snap index may be more sensitive to unintentional awareness[75].

Cerebral State Index (CSI)

The Cerebral State Monitor (Danmeter A/S, Odense, Denmark) is a handheld device that analyses the frequency shifts that take place in the EEG signal as the level of consciousness changes and presents a CSI scaled from 0 to 100. In addition, it also provides EEG suppression percentage and a measure of EMG activity. The EEG waveform is derived from the signal recorded between the frontal and mastoid electrodes. The performance of the CSI is based on the analysis of the frequency content (2-35 Hz) of the EEG signal. The energy of the EEG is evaluated in specific frequency bands. These are used to define two energy ratios called alpha (α) and beta (β). Both of these show a shift in energy content from the higher to the lower frequencies during anaesthesia. The relationship between these quantities is also analyzed as a separate parameter (α-β shift). The monitor also on-line evaluates the amount of instantaneous burst suppression (BS) in each thirty-second period of the EEG. The four parameters (α_{ratio}, β_{ratio}, α-β shift & BS) are used as input to a fuzzylogic classifier system that calculates the CSI. The CSI is a unit-less scale from 0 to 100, where 0 indicates a flat EEG and 100 indicate EEG activity corresponding to the awake state. The range of adequate anaesthesia is designed to be between 40 and 60. The EMG bar shows the energy of the EMG level in the 75–85 Hz frequency band. EMG activity is expected to be present when the patient is awake. When the patient is asleep, EMG activity can increase due to (i) reflex reactions to painful stimuli during surgery, (ii) lack of muscular relaxation, (iii) muscular rigidity caused by some opioids (analgesics) and, (iv) presence of large external electrical fields, e.g. diathermy. The monitor also shows a BS% indicator to show periods when the EEG is iso-electric during last 30 seconds. Anderson RE et al[76] reported that CSI correlated well with BIS and show similar patterns and numerical values in day-surgery anaesthesia without muscle relaxation, however, which monitor is the more dependable remains to be established in such subset of patients. In a recent study[77], it has been further found that the CSI detects well the graduated levels of propofol anaesthesia when compared with the propofol effect site concentration and the OAAS score, and it behaves as other depth of anaesthesia monitors with a progressive decrease during propofol induction, but loss of consciousness with N_2O results no change in CSI[78].

Evoked Potentials (EPs)

Evoked potentials (EPs) show the response of more localised areas of the brainstem, mid brain and cerebral cortex to specific stimuli. EPs represents a time versus voltage relationship that can be quantitated by measuring the post-stimulus latency and inter-peak amplitudes in the waveform. Three types of evoked responses have been investigated as possible measures of depth of anaesthesia monitoring.[79]

Somatosensory evoked potential (SEP): SEP is recorded over the somatosensory cortex in response to tibial, peroneal or median nerve stimulation.

Visual evoked potentials (VEP): VEP is recorded over occipital cortex in response to photic stimulation (using flashing lights) of the eyes. They have been used to monitor function during surgery for lesions involving the pituitary gland, optic nerve and chiasma.

Auditory evoked potential (AEP): AEP is recorded at primary auditory cortex in response to auditory canal stimulation by audible clicks.

Audible clicks → acoustic nerve (I) → cochleae nucleus (II) → superior olivary nucleus (III) → inferior colliculus (IV) → Medial geniculate nucleus (V) → primary auditory cortex (VI).

AEP is the most commonly used EP for assessment of anaesthetic depth. It may be divided into three parts (Figure 3) depending upon the time and the site of origin.

- Brain stem AEP is represented by I – VI numerals and extends from 0 - 10 ms after the stimulus. These waves represent the process of stimulus transduction in the brainstem.

- Early cortical response or middle latency AEP (extends from 15-80 ms after stimulus), marked by the waves N0, P0, Na, Pa and Nb, are thought to originate from the medial geniculate body and the primary auditory cortex, and

- Late cortical response or long latency AEP (extends from 80-100 ms after stimulus), consists of waves P1, N1, P2 and N2. It reflects the neural activity of the frontal cortex and association areas.

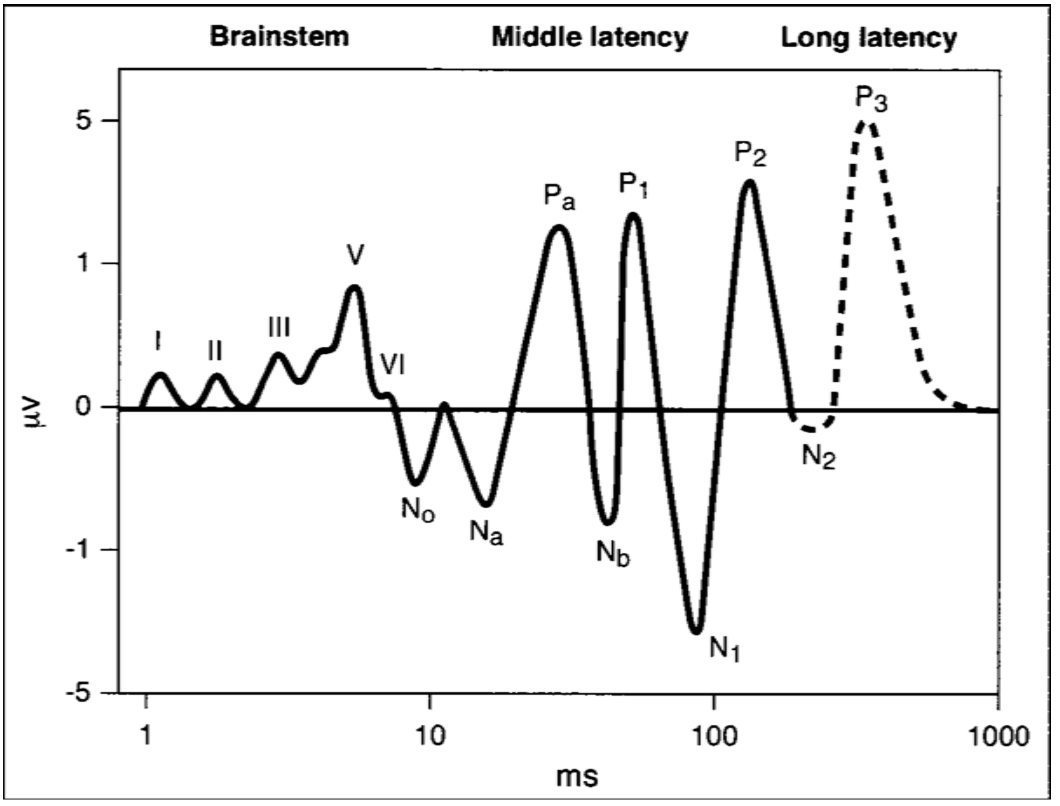


Fig. 3. Schematic representation of the auditory evoked response.

The increasing end-tidal concentration of potent inhaled anaesthetics (halothane, enflurane, isoflurane) increases the latencies and decreases the amplitudes of SEP, VEP and AEP[80]. In contrast N_2O produces a dose-related decrease in the amplitude of VEP & SEP, but no effect on latency. Opioid in clinically relevant concentrations produce minimal changes in EPs[81]. Thomton et al[82] have demonstrated the change in specific components of AEP during anaesthesia and recovery. Potent inhalational agents tend to increase the latencies of brain stem AEP waves III and V as anaesthetic deepens. They also increased the latency and decreased the amplitude of early cortical AEP. Intravenous barbiturates also increased the latency of brain stem components III & V, but other intravenous anaesthetics (etomidate, propofol, althesin) do not change the brain stem response, but change the cortical latency and amplitude in similar manner.

Using evoked potentials to monitor depth of anaesthesia entails some technical, clinical and practical complexities of recording evoked responses. Many confounding artefacts can alter evoked potentials: stimulus characteristics (intensity, duration, inter-stimulus interval), electrode placement, technique, age and gender of the subject and choice of anaesthetic drugs[83].

Middle latency auditory evoked potentials (MLAEP)

Thomton and Sharpe[84] investigated the use of MLAEP in the detection of awareness by focusing on the latencies and amplitude of Pa and Nb waves. Thereafter several studies have suggested the use of MLAEP as an effective indicator of depth of anaesthesia[85-87]. MLAEPs have been shown to be significantly affected by anaesthetic hypnotic drugs in a graded, reversible, and a nonspecific manner. Hypnotic anaesthetic drugs decrease the amplitudes and increase the latencies of Pa and Nb waves. Recent studies have shown that MLAEP derivatives confirm high level of sensitivity and specificity as in case of BIS[87]. MLAEPs have inconveniences that to date have limited their clinical use[88]. These limitations include; considerable time needed to produce a response (0.5-5min), complex setup, need for intact hearing, and lack of a univariate parameter calibrated to the anaesthetic state.

Auditory evoked potential index (AEPI)

This has been derived from auditory evoked potentials and represent as a single numerical variable for monitoring depth of anaesthesia[89]. The auditory evoked potential index reflects the morphology of the AEP curves and is calculated from the amplitude difference between successive segments of the curve. A moving time average of AEP index is obtained at 3 sec intervals. AEP index of 37 was 100% specific and 52% sensitive for unconsciousness. It correlated best with BIS to distinguish awake from sleep state[90]. AEP index monitor obtains the response from subcortical pathways that may partly reflect the activity of the subcortical structures, including the spinal cord. Therefore, AEP index is a better predictor of movement response to noxious stimuli than BIS.[91]

Gajraj et al[92] compared the AEPI, SEF, MF and BIS during target controlled infusions of propofol and found, of the four measurements, AEP index was the best and highly sensitive for distinguishing the transition from unconsciousness to consciousness.

A-Line autoregressive index (AAI)

Jensen and coworkers[93] developed a new adaptive method for extracting the MLAEP from EEG signal that involves an autoregressive model with an exogenous input (ARX) to allow extraction of the AEP signal within 15-25 sweeps of 110-msec duration. The A-Line monitor (Danmeter A/S, Odense, Denmark) calculates the A-Line ARX index (AAI) from the fast-extracted MLAEP waveform analysis. The AAI, like the BIS index, ranges from 100 (awake) to 0 (deep hypnotic effect). Struys and colleagues[94] compared this AAI technique with BIS index in patients receiving target control propofol infusion and found that both were accurate indicators of the level of sedation and loss of consciousness. Neither methodology predicted reaction to noxious stimuli. In a recent study Schmidt et al[95] found that BIS index and AAI were superior to haemodynamic variables and classic single-parameter EEG variable (MLAEP) in discriminating between unconscious and awake states during transitions from wakefulness to unconsciousness.

Conclusion

At present, no monitoring system has been found to measure the depth of anaesthesia reliably for all patients and all anaesthetic agents. All available monitors are no predictors, whether depth of anesthesia is sufficient for the next painful surgical stimulus. They can only monitor the anaesthetic state at the time of measurement. There is no "golden number" predicting absolutely safely that the patient is in adequate anaesthesia. The anaesthetist must consider any technique for monitoring of the depth of anaesthesia as an additional help in improving care for his patient.

We hope that the dynamic growth in microcomputer technology will allow us a greater scope to interpret our observations of the anaesthetic state in near future. Position emission tomography (PET) scanning revealed that propofol anaesthesia has a widespread suppressive effect on cerebral metabolism. This approach may lead to the adoption of a standard, absolute scale of anaesthetic depth; against which other measures can be calibrated. However, it is an invasive method and can not be used in routine cases. Ultra sensitive super conducting quantum interference device (SQUIDS) is a non-invasive method, which measures functional activity of brain. Although expensive at present, this may provide the ultimate monitor to the anaesthetists. It is capable of determining not just anaesthetic depth but also awareness, anoxia, ischaemia and unusual pathology. If monitoring depth of anaesthesia will become simple, safe, and economic, each anaesthesia will be monitored for its depth, as today each patient needs pulseoxymetry.

References

1. Plomley F: Operations upon the eye (letter). Lancet 1847; 1: 134.
2. Snow J. On the inhalation of the vapors of ether in surgical operations. Containing a description of the various stages of etherization, and a statement of the result of nearly eighty operations in which ether has been employed in St. George's and University College Hospitals. John Churchill, London, 1947. Reproduced by Lea and Febiger, Philadelphia, 1959.
3. Guedel AE. Inhalational anesthesia. A fundamental guide. Macmillan, New York, 1937.
4. Artusio JF, Jr. Di-ethyl ether analgesia: A detailed description of the first stage of ether analgesia in man. J Pharmacol Exp Ther 1954; 111: 343.
5. Woodbridge PD. Changing concepts concerning depth of anaesthesia. Anaesthesiology1957;18:536
6. Prys-Roberts C. Anaesthesia: A practical or impossible construct (editorial). Br. J Anaesth 1987; 59: 1341.
7. Glass PS: Anaesthetic drug interactions: An insight into general anaesthesia – its mechanism and dosing strategies. Anaesthesiology 1998; 88: 5-6.
8. Griffith D, Jones JB. Awareness and memory in anaesthetized patients. Br J Anaesth 1990; 65: 603.
9. Liu WHD, Thorp TAS, Graham GSG, et al. Incidence of awareness with recall during general anaesthesia. Anaesthesia 1999; 46: 435.
10. Dierdof SF, Awareness during anaesthesia. Anesth Clin N Am. 1996; 14: 369.
11. Ghoneim MM, Block RI: Learning and memory during general anaesthesia, an update. Anaesthesiology 1997; 87:387.
12. Eger EI II, Saidman IJ, Brandstater B. Minimum alveolar anesthetic concentration: A standard of anesthetic potency. Anesthesiology 1965; 26: 756.
13. Yakaitis RW, Blitt CD, Angiulo JP. End-tidal halothane concentration for endotracheal intubation. Anesthesiology. 1977; 47: 386.
14. Roizen MF, Horrigan RW, Frazer BM. Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision-MAC BAR. Anesthesiology 1981; 54: 390.
15. Stoelting RK, Longnecker DE, Eger EI II. Minimum alveolar concentrations in man on awakening from methoxyflurane, halothane, ether and fluroxene anaesthesia: MAC awake. Anaesthesiology 1970; 33:5.

16. Zbinden AM, Maggiorini M, Petersen-Felix S, Lauber R, Thomson DA, Minder CE. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anaesthesia. 1 motor reactions. Anesthesiology 1994; 80: 253.
17. Stanski DR. Monitoring depth of anesthesia. In Miller RD, ed. Anesthesia, New York: Churchill Livingstone 1990; 1001-1029.
18. Chortkoff BS, Eger EI II, Bennett HL, et al. Learning of matter of fact information is suppressed at MAC-awake. Memory and awareness in anaesthesia. Third Int Symposium, Rotterdam 1995; 36 (Abstract).
19. Cullen DJ. Drugs and anesthetic depth, p 287. In Smith NT, Miller RD, Corbascio AN (eds): Drug interactions in anesthesia. Lea and Febiger, Philadelphia 1981.
20. Quasha AL, Eger EI II, Tinker JH: Determination and application of MAC. Anaesthesiology 1980; 53:315.
21. Sneyd JR. How low can we go? British Journal of Anaesthesia 2003; 91: 771-72
22. Sear JW, Phillips KC, Andrews CJH, Prys-Roberts C. Dose-response relationships of infusions of althesin or methohexitone. Anesthesia 1983; 38: 931.
23. Kazana T, Ideka K, Morita K. Reduction by fentanyl of the Cp50 values of propofol and haemodynamic responses to various noxious stimuli. Anesthesiology 1997; 87: 213.
24. Lowenstein E. Morphine anesthesia – a prospective (editorial). Anesthesiology 1971; 35: 563.
25. Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth analg 1978; 57: 411.
26. Wynandas JE, Wong P, Townsend GE, et al. Narcotic requirements for intravenous anaesthesia. Anesthesia Analgesia 1984; 63: 101.
27. Murphy MR, Hug CC, Jr. The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 1982; 57: 485.
28. McEvan AI, Smith C, Dyar O, et al. Isoflurane minimum alveolar concentration reduced by fentanyl. Anesthesiology 1993; 78: 864.
29. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect. The comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 1985; 62: 234.
30. Evans JM, Davies WL. Monitoring anaesthesia. Clin Anesth 1984; 2: 243-262.
31. Hug CC. Does opioid anesthesia exist? Anesthesiology 1990; 73: 1-4.

32. Trillo-Urrutia L, Fernandez-Galinski S, Castano-Santa J. Awareness detected by auditory evoked potential monitoring. British Journal of Anaesthesia 2003;91: 290-92
33. Domino KB, Posner KL, Caplan RA, Cheney FW. Awareness during anesthesia. A closed claims analysis. Anesthesiology 1999; 90: 1053-1061.
34. Vernon JM, Lang E, Sebel PS, Manberg P. Prediction of movement using bispectral electroencephalographic analysis during propofol/alfentanil or isoflurane/alfentanil anesthesia. Anesth Analg 1995; 80: 780-785.
35. Tunstall ME. Detecting wakefulness during general anesthesia for caesarean section. British Medical Journal 1977; 1: 1321.
36. Russell IF. Comparison of wakefulness with two anaesthetic regimens: Total IV balanced anaesthesia.Br J Anaesth 1986; 58: 965.
37. Russell IF. Auditory perception under anaesthesia. Anaesthesia 1979; 34: 211.
38. Herregots L, Rolly G, Mortier E, Bogaert M, Mergaert C. EEG and SEMG monitoring during induction and maintenance of anesthesia with propofol. International Journal of clinical Monitoring and Computing 1989; 6: 67-73.
39. Kay B. The anaesthesia and brain monitor (ABM). Acta Anaesthesia Belgica 1984; 535: 167-174.
40. Evan JM, Davies WL, Wise CC. Lower oesophageal contractility: A new monitor of anesthesia. Lancet 1984; 1: 1157.
41. Evans JM, Bithell JF. Vlachonikolis IG. Relationship between lower oesophageal contrability, clinical signs and halothane concentration during general anesthesia and surgery in man. Br J Anesth 1987; 59: 1346-1355.
42. Sessler DI, Sten R, Lofsson CI, chow F. Lower esophageal contractility predicts movement during skin incision in patients anesthetized with halothane, but not with nitrous oxide and alfentanil. Anesthesiology 1989; 70: 42-46.
43. Erickson JP, Foss J, Kuni DR. A controlled trial of efficacy of lower esophageal contractility as a measure of depth of anesthesia. Anesthesiology 1987; 67: A672.
44. Sakuma Y, Ueda Y, Kiode M. R-R interval variation and autonomic nervous function under general anesthesia. Masui 1989; 34: 223-227.

45. Pomfrett LJD, Sneyd JR, Beech M, Healy TEJ. Variation in respiratory sinus arrhythmia may reflect levels of anaesthesia. Br J Anaesthesia 1991; 67: 6216.
46. Healy TEJ, Bellman MH, Pomfrett CJD. Respiratory sinus arrhythmia indicates light anaesthesia during caesarean section. Anesth Analg 1994; 78: S156.
47. Pomfrett CJD, Barric JR, Healy TEJ. Respiratory sinus arrhythmia reflects surgical stimulation during light enflurane anaesthesia. Anesth analg 1994; 78: S 334.
48. Gibbs FA, Gibbs EL, Lenox WG. Effect of electroencephalogram of certain drugs which influence nervous activity. Arch Intern Med 1937; 60: 154.
49. Pichmayer I, EEG atlas for anaesthesiologists. Berlin: Springerverlag 1987.
50. Schwilden H. Use of median EEG frequency and pharmaco-kinetics in determining depth of anaesthesia. Balliere's Clinical Anaesthesiology 1989; 3: 603-621.
51. Rampil IJ, Sasse FJ, Smith NT, Hoff BH, Flemming DC. Spectral edge frequency-a new correlate of anesthetic depth. Anesthesiology 1980; 53: S12.
52. Glass P S, B Marc, K Lee et al. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane and alfentanil in healthy volunteers. Anaesthesiology 1997;86: 836-847.
53. Kearse Jr. LA, Manberg P, Debros F, Chamoun N, Sinai V. bispectral analysis of the encephalogram during induction of anesthesia may predict hemodynamic responses to laryngoscopy and intubation. Electroenceph Clin Neurophysiol 1994; 90: 194-200.
54. Kearse Jr LA, Manberg P, Chamoun N, Debros F, Zaslavsky A. Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia. Anesthesiology 1994; 8111: 365-70.
55. Flaishon R, Windsor A, Sigl J, Sebel PS. Recovery of consciousness after thiopental or propofol. Bispectral index and the isolated forearm technique. Anesthesiology 1997; 86: 613-619.
56. Song D, Joshi GP, White PF. Titration of volatile anesthetic using bispectral index facilitates recovery after ambulatory anesthesia. Anesthesiology 1997; 87: 842-848.
57. Laussen PC, Murphy JA, Zurakowski D, Sullivan LJ, McGowan Jr. FX, Demaso DR. Bispectral index monitoring in children undergoing mild hypothermic cardiopulmonary bypass. Paediatr Anaesth 2001; 11: 567-573.

58. Renna M, Venturi R. bispectral index and anaesthesia in the elderly. Minerva Anesthesiol 2000; 66: 398-402.
59. Monika N, et al. Ketamine causes a paradoxical increase in Bispectral index. Anesthesiology 1997; 87: A502.
60. Puri GD. Paradoxical changes in bispectral index during nitrous oxide administration. Br J Anesth 2001; 86: 141-142.
61. Menigaux C, Guignard B, Edam F et al, Esmolol prevents movement and attenuates the BIS response to orotracheal intubation Br J Anaesth 2002; 89: 857.
62. Mathew JP, Weathersax KJ, East CJ, et al. Bispectral analysis during cardiopulmonary bypass: the effect of hypothermia on the hypnotic state. J Clin Anesth 2001; 13: 301.
63. Glass PSA, Gan TJ, Howell S, et al. Drug interactions: Volatile anesthetics and opiates. J Clin Anesth 1997; 9: 18S.
64. J Bruhn, H Röpcke and A Hoeft, "Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia", Anesthesiology 2000; 92: 715–726.
65. Bonhomme V, Deflandre E, Hans P. Correlation and agreement between bispectral index and state entropy of the electroencephalogram during propofol anaesthesia.Br J Anaesth 2006; 97: 340-46.
66. Alkire MT, Barker SJ, Haier RJ, et al. A position emission tomography study of cerebral metabolism in a volunteer during propofol anesthesia. Anaesth Analg 1994; 78: S5.
67. Schultz B, Schultz A, Grouven U. Sleeping stage based systems (Narcotrend), In, New Aspects of High Technology in Medicine 2000. Eds. Bruch HP, Kockerling F, Bouchard R, Schug-Pab C. Bolognia, Monduzzi Editore, pp. 285–91.
68. Kreuer S, Biedler A, Larsen R, et al. The Narcotrend™ – a new EEG monitor designed to measure the depth of anaesthesia. A comparison with bispectral index monitoring during propofol remifentanil-anaesthesia. Anaesthetist 2001; 50: 921–25.
69. Weber F, Pohl F, Hollnberger H, Taeger K. Impact of the Narcotrend Index on propofol consumption and emergence times during total intravenous anaesthesia with propofol and remifentanil in children: a clinical utility study. Eur J Anaesthesiol 2005; 22:741-47.
70. Weber F, Hollnberger H, Gruber M, et al. The correlation of the Narcotrend Index with end-tidal sevoflurane concentrations and hemodynamic parameters in children. Paediatr Anaesth 2005; 15:`727-32.

71. Russell IF. The Narcotrend 'depth of anaesthesia' monitor cannot reliably detect consciousness during general anaesthesia: an investigation using the isolated forearm technique. Br J Anaesth 2006; 96: 346-52.
72. Drover DR, Lemmens HJ, Pierce ET, et al. Patient state index: titration of delivery and recovery from propofol, alfentanil, and nitrous oxide anaesthesia. Anesthesiology 2002; 97: 87-89.
73. Chen X, Tang J, White PF, et al. A comparison of patient state index and bispectral index values during the perioperative period. Anesth Analg 2002; 95: 1669–74.
74. Wong CA, Fragen RJ, Fitzgerald PC, McCarthy RJ. The association between propofol-induced loss of consciousness and the SNAPTM index. Anesth Analg 2005; 100: 141–48.
75. Wong CA, Fragen RJ, Fitzgerald P, McCarthy RJ. A comparison of the SNAP II and BIS XP indices during sevoflurane and nitrous oxide anaesthesia at 1 and 1.5 MAC and at awakening. Br J Anaesth 2006; 97: 181-86.
76. Anderson RE, Jacobsson JG. Cerebral state monitor, a new small handheld EEG monitor for determining depth of anaesthesia: a clinical comparison with the bispectral index during day-surgery. Eur J Anaesthesiol 2006; 23: 208-12.
77. Jensen EW, Litvan H, Revuelta M, et al. Cerebral state index during propofol anesthesia: a comparison with the bispectral index and the A-line ARX index. Anesthesiology 2006; 105: 28-33.
78. Anderson RE, Barr G, Jakobsson JG. Cerebral state index during anaesthetic induction: a comparative study with propofol or nitrous oxide. Acta Anaesthesiol Scand 2005; 49: 750-53.
79. Grundy BL. Evoked potential monitoring. In Blitt ED (ed): Monitoring in Anesthesia and Critical Care Medicine. New York, Churchill Livingstone, 1985, p 345.
80. Sebel PS, Ingram DA, Flynn PJ, et al. Evoked potentials during isoflurane anesthesia. Br J Anesth. 1986; 58: 580.
81. Schwender D, Rimkus T, Haessler R, Klasing S, Po¨ppel E, Peter K: Effects of increasing doses of alfentanil, fentanyl and morphine on mid-latency auditory evoked potentials. Br J Anaesth 1993; 71:622– 8.
82. Thomton C, Newton DEF. The auditory evoked response: a measure of depth of anaesthesia. Balliere's Clinical Anaesthesiology 1989; 5: 559-585.

83. Grundy BL. Evoked potential monitoring. P 345. In monitoring in Anesthesia and Critical Care Medicine. Churchill Livingstone, New York, 1985.
84. Thomton C, Sharpe RM. Evoked responses in anaesthesia. Br. J. Anesth. 1998; 81: 771-781.
85. Schwender D, Kaiser A. Klasing S, Peter K, Poppil E. Mid-latency auditory evoked potentials and explicit and implicit memory in patients undergoing cardiac surgery. Anesthesiology 1994; 80: 493-501.
86. Newton DE, Thomton C, Konieczko KM, Jordon C, Webster NR, et al. Auditory evoked response and awareness: A study in volunteers at sub-MAC concentrations of isoflurane. Br J Anaesth 1992; 69: 122-129.
87. Schraag S, Bothner U, Gajraj R, Renny GNC, Geogieff M. The performance of electroencephalogram Bispectral index and auditory evoked potential index to predict loss of consciousness during propofol infusion. Anesth Analg 1999; 89: 1311-1315.
88. Iselin-Chaves IA, Maolem HF, Gan TG, et al. Changes in the auditory evoked potentials and the bispectral index following propofol or propofol and alfentanil. Anesthesiology 2000; 92:1300.
89. Mantzaridis H, Kenny GN. Auditory evoked potential index: A quantitative measure of changes in auditory evoked potentials during general anaesthesia. Anaesthesia 1997; 52: 1030-1036.
90. Doi M, Gajraj RJ, Mantzaridis H, Kenny GNC. Relationship between calculated blood concentration of propofol and electrophysiological variables during emergence from anaesthesia: comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index. Br J Anaesth 1997; 78: 180-184.
91. Mantzaridis H, Kenny GH. Auditory evoked potential index: A quantitative measure of changes in auditory evoked potentials during general anesthesia. Anesthesia 1997; 52: 1030.
92. Gajraj RJ, Doi M, Mantzaridis H and Kenny GNC. Analysis of the EEG bispectrum, auditory evoked potentials and EEG power spectrum during repeated transitions from consciousness to unconsciousness. BJA 1998; 80: 46-52.
93. Jensen EW, Nygaard M, Hennenberg SW. On line analysis of middle latency auditory evoked potentials (MLAEP) for monitoring depth of anesthesia in laboratory rats. Med Eng Phys 1998; 20: 722.
94. Struys MMRF, Jensen EW, Smith W, et al. Performance of the ARX-derived evoked potential index as an indicator of anesthetic depth. Anesthesiology 2002; 96: 803.

95. Schmidt GN, Bischoff P, Standl T, et al. ARX-derived auditory evoked potential index and bispectral index during the induction of anesthesia with propofol and remifentanil. Anesth Analg 2003; 97: 139.