Monitoring depth of anaesthesia by EEG

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Key points

Clinical signs of inadequate depth of anaesthesia are unreliable.

No single EEG-derived parameter exists which has a threshold value that defines when all patients may be at risk of awareness.

Bispectral index reflects the pharmacodynamic effect of hypnotic agents on the cortical EEG.

Auditory evoked potentials may facilitate individualised depth of anaesthesia monitoring.

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Depth of anaesthesia and awareness

Depth of anaesthesia is a dynamic balance between effect-site concentration of hypnotic and analgesic drugs, and intensity of surgical stimulation. Awareness during surgery is one of the most feared complications of anaesthesia but excessive depth of anaesthesia is equally undesirable, given the narrow therapeutic index of anaesthetic drugs and the reduced physiological reserve of many patients. The quoted incidence of awareness with explicit recall in non-cardiac and non-obstetric surgery is 0.07–0.2%, increasing to 0.4% for emergency Caesarean section performed under general anaesthesia and 1.1–1.5% for cardiac surgery.

Awareness refers to the capacity to perceive and process incoming sensory information and thus be cognisant of one's environment. In the context of anaesthesia, it is often defined as the ability to respond purposefully to intra-operative stimuli, and is usually assessed by the ability to obey commands. This implies processing and understanding of sensory input, as distinct from reflex movements which are mediated at a spinal or brainstem level. Such a definition is useful when attempting to quantify the occurrence of apparent intra-operative awareness but suffers the obvious drawback that it cannot be used in paralysed patients. Anaesthetists have traditionally relied upon signs of autonomic stress (tachycardia, hypertension, lachrymation, sweating) to indicate inadequate depth of anaesthesia in paralysed patients but these are neither sensitive nor specific markers, either in isolation or when combined in a scoring system.

Patients may have spontaneous or prompted memory for intra-operative events. Such memory is said to be explicit. 'Recall' is synonymous with explicit memory. Implicit memory describes a process whereby patients may have no conscious recollection for intra-operative events but may nevertheless demonstrate evidence of intra-operative memory processing at a subconscious level. It is suggested that this can have a deleterious effect on behaviour, emotions and thought processes, although the patient does not connect any such disturbances to a memory of intra-operative awareness. The distinction made between intra-operative awareness and postoperative ability to remember being aware raises the contentious issue of which is more important. In studies using the isolated forearm test, patients who have clearly been able to respond to commands intra-operatively may subsequently demonstrate neither explicit nor implicit memory for intra-operative awareness.

As the brain is the target organ of drugs that produce general anaesthesia, it is logical that changes in neurophysiological parameters might provide indicators of anaesthetic depth. The characteristics of the ideal depth of anaesthesia monitor are listed in Table 1. This article describes the EEG techniques available for monitoring depth of anaesthesia, highlighting their strengths and shortcomings.

The EEG as a monitor of anaesthetic depth

The EEG is a surface recording of summed electrical potentials arising from the dendritic fields of the pyramidal neurones in the cerebral cortex. In its unprocessed form, it requires specialised expertise to interpret and the raw EEG is not a practical tool for monitoring depth of anaesthesia. Increasingly sophisticated, automated analysis of various EEG components has generated several potential quantitative descriptors of anaesthetic depth. There are two generic problems with

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Table 1 Properties of the ideal depth of anaesthesia monitor

Attribute	Notes
Increases patient safety	Reduces the risk of awareness and recall
Independent of agent used	
No hysteresis	Patient should regain consciousness at the same value as they lost consciousness
Good sensitivity and specificity	No overlap in ranges of values representing consciousness and unconsciousness
Predictive of awareness	Good resolution in the stage of anaesthesia just before consciousness is reached
Predictive of lightening anaesthesia	During stable stimulation, the monitor should reflect changing effect site concentrations, to allow anticipation of changes in conscious level
Proportionately sensitive to stimuli	Reflects the magnitude of partial reversal of anaesthesia by noxious stimuli of varying strengths
Minimal response time	Rapid reflection of abrupt changes in conscious level (e.g. in response to sudden changes in surgical stimulation)
Easy to use	
Inexpensive	

processed EEG technologies. First, different anaesthetic agents generate different EEG patterns or signatures. Second, various pathophysiological events also affect the EEG (e.g. hypoxia, hypotension, hypercarbia). Such events may modify both the patient's level of consciousness and the expected EEG signature that any given anaesthetic agent generates, thus confounding interpretation.

Time domain analysis

This refers to analysis of the EEG that examines voltage changes over time. It was first used intra-operatively in the 1950s when it was observed that the electrical power (which is proportional to the square of the voltage) in the EEG was associated with changes in the rate of administration of thiopental or ethyl ether. From this earliest processed EEG technique evolved the cerebral function monitor (CFM), which was initially used to monitor 'cerebral function' (undefined) in intensive care patients but was subsequently investigated as a monitor of depth of anaesthesia. The monitor records the voltage of the filtered EEG, acquired from a single pair of bilateral parietal electrodes. Voltage is plotted continuously on a semilogarithmic scale against a compressed time axis (6–30 cm h^{-1}). The voltage measured is a composite function of both amplitude and frequency. The height of the base of the trace from the X-axis indicates EEG activity, whilst the width of the trace represents its variability.

The CFM has not proved useful as a monitor of anaesthetic depth for several reasons. The response to increasing depth of anaesthesia is biphasic, complicating dose–response interpretation. Values similar to those seen in awake patients may be seen in anaesthetised individuals, whilst recovery from anaesthesia does not necessarily occur near baseline values. Additionally, burst suppression at deep levels of anaesthesia is characterised on the EEG by periods of normal or high voltage activity alternating with periods of low or no activity. As the CFM provides a smoothed running average of the EEG voltage, early burst suppression artificially elevates the reading, producing an apparent, paradoxical rise in 'cerebral function'.

Frequency domain analysis

The raw EEG can be processed by fast Fourier transformation into its component sine waves. These can be further analysed with respect to three features: (i) frequency distribution; (ii) power contained within different frequencies (a function of wave amplitude); and (iii) phase relationships between waves of different frequencies. Traditional power spectral analysis investigates the relationship between power and frequency over a short time period (epoch). A graph of power versus frequency forms a spectral array. The spectral arrays from successive epochs can be superimposed upon each other to build up a composite display of changes in the location of power within different frequencies over time. Such rolling visual summaries effectively display raw EEG data that have been transformed with minimal loss of information. They are compact, indicate trends and, because different frequency bands are considered independently, changes occurring in one part of the frequency spectrum are immediately apparent. This is in contrast to the CFM where they can be cancelled out by changes in other parts of the spectrum. So, for example, in a CFM trace generated by EEG waves of 6 Hz, 9 Hz and 12 Hz, an increase in the amplitude (power) of the 6 Hz wave coupled with a decrease in that of the 12 Hz wave might produce no net change in overall voltage and hence no change in the trace. In a spectral array, both the decrease in 12 Hz power and the increase in 6 Hz power would be obvious.

The method of display of spectral arrays is of relevance (Fig. 1). The compressed spectral array (CSA) is obtained by superimposing linear plots of successive epochs of time on each other, generating a 3-dimensional 'hill and valley' display. However, as successive epochs are added to the display, information can

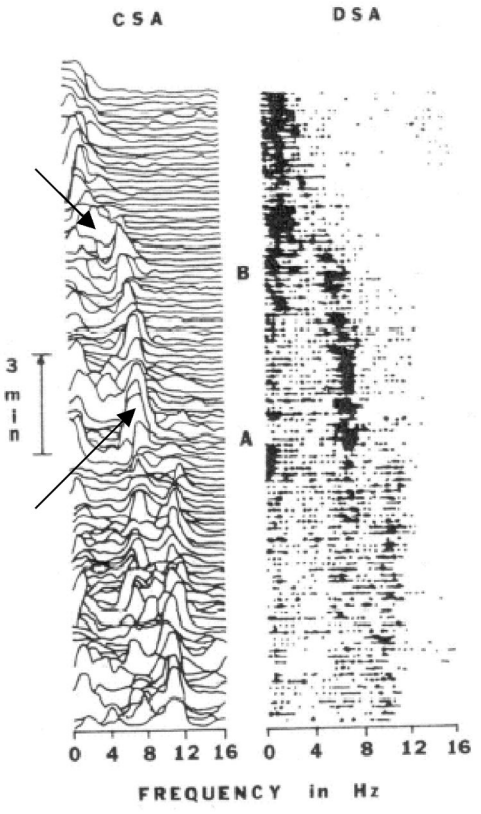

Fig. 1 Compressed and density spectral arrays. Compressed spectral array and density spectral array, recorded simultaneously during deepening halothane/nitrous oxide anaesthesia. The most recent epochs are at the top of the traces. A shift in EEG power from the 8–12 Hz region through the 4–8 Hz region to the 0–4 Hz region is discernible. Truncated 'hills' of power are seen in the CSA trace (arrows), with more recent data partially obscured behind them, a problem not encountered with the DSA display, where high density shading reflects the concentration of EEG power. (Adapted from Levy WJ *et al. Anesthesiology* 1980; **53**: 223–36, with permission).

become hidden behind 'hills' of increased power at particular frequencies. In order to reduce this problem, some displays arbitrarily truncate the peaks of high-amplitude activity, consequently affecting legibility of the trace. The density spectral array (DSA) is a 2-dimensional plot of the same information, using shading instead of relief to demarcate superimposed graphs of successive epochs. This results in a display that is easier to read and that does not compromise data interpretation.

The effects of different anaesthetic agents on the EEG power spectrum have been thoroughly investigated and some general trends are discernible, such as the shift of power to lower frequencies with increasing depth of anaesthesia. However, there remain the problems of great interindividual variability, interagent variability and the confounding effects of other pathophysiological processes such as hypoxia, hypotension and hypercarbia. Moreover, the traditional frequency bands used to describe the EEG (α, β, θ, δ) are based on awake or natural sleep traces; their relevance to anaesthesia is assumed but uncertain.

Further difficulties with using power spectral analysis to monitor anaesthetic depth have arisen with the use of univariate descriptors of the power spectrum, such as peak power frequency, median frequency (MF) and spectral edge frequency (SEF). These indices represent attempts to simplify quantitation of the EEG to a single number, whose physiological significance remains unknown. The MF describes the frequency above and below which lies 50% of the power in that epoch. The SEF identifies the frequency below which 90% or 95% of the total power in the epoch lies (SEF_{90} and SEF_{95}). These are therefore measures of central tendency and the upper limits of dispersion respectively and, as such, should only be used to describe unimodal frequency distributions that change slowly over time. As power spectra are often multimodal, these univariate descriptors fail to convey the complexities of the EEG during anaesthesia. As a result, both MF and SEF, show limited correlation with inhalational agent concentrations, so that the dose–response profile is difficult to interpret. This problem is further exacerbated by wide interpatient variability in values at equivalent anaesthetic concentrations. Neither MF nor SEF are suited to the recognition of deep anaesthesia, as burst suppression may produce a paradoxical rise in their values. Finally, the values for SEF are influenced by the frequency range sampled by the equipment, which varies between manufacturers.

Bispectral analysis

Traditional power spectral analysis does not consider the phase relationships between the component waves of different frequencies that make up the composite EEG. Bispectral analysis combines traditional power spectral analysis with interrogation of these phase relationships. It also incorporates a number of other EEG subparameters to produce a proprietary combination of derived EEG descriptors. BIS was developed by recording EEG data from healthy adults, who underwent repeated transitions between consciousness and unconsciousness, using several different anaesthetic regimens. The raw EEG data were time stamped at various clinical end-points. Offline analysis identified those features of the EEG recordings that best correlated with clinical depth of sedation/anaesthesia and these were

then fitted to a model by multivariate logistic regression. The resulting algorithm generates the bispectral index (BIS). In calculating BIS from raw EEG, the relative weighting of the various subparameters changes, as some descriptors correlate better with clinical measures of light sedation whilst others correlate better with deeper levels of reduced consciousness. The BIS algorithm was initially validated prospectively on a second cohort of healthy volunteers and, subsequently, on various patient groups. It has been refined on several occasions. The monitor generates a dimensionless number on a continuous scale of 0–100, with 100 representing normal cortical electrical activity and 0 indicating cortical electrical silence. The monitor displays a real-time EEG trace, acquired from a triple electrode frontotemporal montage. The display also shows a signal quality index and an indicator of electromyographic (EMG) interference.

Bispectral analysis is the first processed EEG technique to be correlated with behavioural assessments of level of consciousness, irrespective of the hypnotic, or combination of hypnotics, used to produce that state. BIS thus demonstrates a dose–response relationship with inhalational and hypnotic intravenous agents, such as propofol and midazolam, which is independent of the agent(s) being used and correlates with clinical assessments of level of consciousness. However, in the absence of surgical stimulation (conditions applying during most early studies), the use of opioids produces clinical changes in depth of sedation or anaesthesia that are not reflected by decreases in BIS. This is a major drawback of using BIS to assess depth of balanced anaesthesia, as it does not fully reflect the synergistic effect of opioids with hypnotic agents. Nevertheless, when opioids are used during surgery, BIS values do decrease, perhaps illustrating the counteraction of arousal by pain. Not surprisingly, BIS is not able to predict movement in response to surgical stimulation; the anatomical site of generation of such reflexes is likely to be at the level of the spinal cord and therefore unlikely to register on the cortical EEG.

Because there is no 'gold standard' monitor against which to compare BIS, studies have used predictive probability outcome measures, i.e. the likelihood of various clinically relevant endpoints occurring (loss of consciousness, recovery of consciousness, postoperative recall, suppression of learning) at different BIS values. From these various studies, broad guidelines have emerged to aid interpretation of BIS values (Table 2). The probability of postoperative recall is very low when BIS is kept < 60 intra-operatively. Studies comparing BIS-titrated anaesthesia with clinical judgement of anaesthetic requirements show reduced anaesthetic consumption and slightly quicker awakening using BIS, supporting the suggestion that, in trying to ensure lack of awareness, we tend towards excessively deep anaesthesia. However, BIS values tend to display considerable variability within study populations, so that, for example, one patient may be unresponsive to command at a BIS of 75, but another may still be responsive at a BIS of 70. This makes it difficult to identify sensitive and specific threshold values that arewidely applicable. No BIS value predicts an individual's threshold for loss or recovery of consciousness. Moreover, many published BIS studies have controlled for surgical stimulus by excluding it, so the applicability of BIS values taken from these studies to patients undergoing surgery remains uncertain.

Table 2 Suggested interpretation of BIS values

100–85	Awake, aware, capable of memory processing and explicit recall
85–60	Increasing sedation and impairment of memory processing. Rousable in response to stimulation
60–40	Surgical anaesthesia. Decreasing probability of postoperative recall. Auditory processing and reflex movement still occurs
40–0	Increasing frequency of burst suppression. BIS of 0 indicates cortical electrical silence

BIS is therefore best described as a monitor of the depth of the hypnotic component of anaesthesia or sedation. It appears to track the effect-site concentration of hypnotic drugs and their effect on the cortical EEG. BIS values discriminate between awake and asleep states but with considerable overlap of values and no clear-cut transition between awake and asleep values at the end of surgery. This is in keeping with BIS reflecting gradually decreasing effect site concentrations at the end of anaesthesia.

Nitrous oxide, at inspired concentrations of up to 50%, does not reduce baseline BIS values. Furthermore, the addition of nitrous oxide to established anaesthesia has little or no effect on BIS in the absence of surgical stimulation. However, during surgery, the antinociceptive effects of nitrous oxide may be responsible for the observed decrease in BIS. Ketamine causes EEG activation, complicating BIS interpretation. The influence of pre-existing neuropathology on BIS values is unknown. As with any EEG signal, BIS is subject to interference and artefact, particularly from EMG activity, which can artificially elevate the recorded BIS. As the BIS algorithm is based on healthy adult EEG data, it cannot automatically be extrapolated to young children, as the paediatric EEG only approaches the adult pattern by about 5 years of age.

However, early investigations suggest that BIS may be valid in children older than 2 years of age. Investigations of BIS as a continuous monitor of sedation in adult intensive care have concluded that it is a useful reflector of the great interindividual variations in pharmacokinetics and pharmacodynamics of sedatives in critically ill patients. However, comparative studies using either the Ramsey sedation score (itself not validated) or the Sedation-Agitation Score have generated unimpressive correlation statistics. There is methodological dissatisfaction with comparing serial, cross-sectional, subjective observations of patient comfort with a quasi-continuous monitor of cortical activity, and it is unsurprising that there is limited correlation between the two. Investigations into its role in paediatric intensive care are ongoing; early studies on convenience samples comparing BIS with the COMFORT paediatric sedation scoring system again suggest limited correlation.

Two large studies are shortly due to report on the definitive question of whether BIS monitoring actually reduces the real incidence of awareness during anaesthesia; both the Australasian 'B-Aware' trial (2500 patients) and the American AIM trial (> 20 000 patients) are powered to detect significant reductions in the incidence of awareness. Interim analyses have suggested that statistical significance is likely to be achieved.

Auditory evoked potentials

This monitoring technique isolates the neurophysiological signal generated during transmission of a repetitive auditory stimulus to the auditory cortex by repeatedly sampling the EEG during stimulus presentation. The repeated sampling allows the signal to be extracted from the background EEG noise. The signal is acquired using EEG electrodes located on the mastoid processes, a midline reference electrode and a ground electrode.

The auditory evoked potential (AEP) is a composite waveform that can be plotted against time. The brainstem AEP (1–10 msec latency) and the late cortical AEP (50–500 msec latency) do not correspond with depth of anaesthesia but the early cortical signal (mid-latency auditory evoked potential [MLAEP], 10–50 msec latency) does. The mid-latency section of the AEP waveform comprises two nadirs (Na and Nb) and an intervening peak (Pa). It is the amplitude and latency of the Pa and Nb components that are analysed. Anaesthetic agents decrease the amplitude and increase the latency of the MLAEP in a dose-dependent, but agent-independent, manner.

The raw waveform is difficult to analyse in real time and subject to interobserver variability. The auditory evoked potential index (AEP_{index}) is a parameter derived by summing the square root of the difference in amplitude between successive 0.56 msec segments of the MLAEP. This can be calculated online and presented as a running average that can be updated approximately every 30 sec. As a rough guide, an AEP_{index} of ≥ 80 would be expected in awake patients and ≤ 50 in anaesthetised ones. Unlike BIS, the transition from asleep to awake is characterised by a sudden increase in AEP_{index}.

AEPs discriminate between the awake and the anaesthetised state better than BIS values, as there is less overlap between the ranges of values in conscious and anaesthetised patients. Nevertheless, interindividual variability in the MLAEP latency at which consciousness is lost is sufficient to make it difficult to define a sensitive and specific cut-off point. However, AEPs appear to demonstrate minimal hysteresis within an individual, so that the MLAEP values at loss and recovery of consciousness are well conserved during repeated transitions. This raises the theoretical possibility of defining individualised thresholds for loss and recovery of consciousness.

Monitors that process the amplitude and latency changes to the Pa and Nb waves of the AEP using proprietary algorithms to generate an indexed score between 0–100 are now being marketed.

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See multiple choice questions 76–79.