Review article

Measuring anesthesia in children using the EEG

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Abstract
Advances in electroencephalogram (EEG) processing have produced new interest in measuring anesthesia using the EEG. There are a number of EEG-based anesthesia ‘depth’ monitors now available and their use in pediatric anesthesia is increasing. Although these monitors have been extensively studied in adults, there are relatively few studies examining their validity or use in children. To some extent we must rely on adult data. However, extrapolation of data from adults to children requires an in depth understanding of the physiology behind the data. The first question is what is being measured. What is anesthesia? A model of anesthesia has several components with arousal as a core component. Arousal can be linked to clinical observations, and correlates with anatomical and physiological studies. The EEG has characteristics that fairly consistently change with arousal during anesthesia, but the relationship between arousal and the EEG is imprecise and drug dependent. This relationship is the basis for using the EEG to measure anesthesia and provides only an indirect measure of consciousness and memory formation. A good understanding of how the EEG is related to anesthesia is essential when interpreting the EEG during anesthesia, and especially when extending the use of the EEG to measure anesthesia in children. Physiological studies in adults and children indicate that EEG-derived anesthesia depth monitors can provide an imprecise and drug-dependent measure of arousal. Although the outputs from these monitors do not closely represent any true physiological entity, they can be used as guides for anesthesia and in so doing have improved outcomes in adults. In older children the physiology, anatomy and clinical observations indicate the performance of the monitors may be similar to that in adults, although the clinical relevance of outcomes may be different. In infants their use cannot yet be supported in theory or in practice.

Keywords: Anesthesia; arousal; electroencephalograph

Introduction
The assessment of anesthesia effect is crucial to ensure anesthesia is adequate. Throughout the history of anesthesia, anesthetists have been striving to
assess, measure and quantify anesthesia. Advances in electroencephalogram (EEG) processing have produced new interest in measuring anesthesia effect. There are now hundreds of publications describing the use of a steadily increasing number of EEG-based anesthesia ‘depth’ monitors. Their use in pediatric anesthesia is also increasing. Although these monitors have been extensively studied in adults, there are relatively few studies in children. Physiological and intervention studies to assess these monitors are not easily performed in children because of methodological and ethical reasons. For pediatric anesthesia we often rely on extrapolation of adult data. Extrapolation of physiological data or application of a technology from one population to another requires an in-depth understanding of the physiology and the principles behind the technology. Measuring anesthesia is not as simple as it seems.

The aim of this review is to discuss what EEG-derived anesthesia depth monitors try to measure, what they actually measure, how we should interpret the outputs, and how differences in a child’s physiology may influence the extension of their use to children.

What is anesthesia?

Before trying to measure anesthesia it is essential to define anesthesia. It is also prudent to speculate how a measure of anesthesia should be presented – is it a binary phenomenon or is it a continuum?

There are a variety of ways of defining general anesthesia. Most of these definitions or models, divide anesthesia into components. One approach is to define anesthesia by the clinical aims of anesthesia; another is to approach the definition from the biochemical and neurophysiologic action of the agents used.

The most practical way to define anesthesia is from the clinical aims of anesthesia which can be regarded as loss of consciousness, amnesia, immobility and a reduction in the reflex autonomic responses associated with nociceptive stimulus (such as hypertension and tachycardia). Like all definitions of anesthesia, a key concept in this definition is that the components of anesthesia are linked to varying degrees. The link may be drug specific. A concentration of drug, which achieves one aim, may or may not always achieve another aim. Similarly measuring one component may, or may not be a reliable reflection of another component.

Anesthesia has also been defined as the triad of hypnosis, analgesia and muscle relaxation. Rees and Gray first mentioned this triad in 1950 (1). This construct is still frequently used as a model of anesthesia effect. It is perhaps most useful for the titration of the anesthetic drugs most frequently used such as opioids, muscle relaxants and volatile agents. However, it is insufficient to explain more complex interactions of anesthetic drugs and effects. The term analgesia should also be avoided. It is more closely related to the relief of pain – a phenomenon in conscious patients rather than during anesthesia. The concept of reducing nociceptive stimulus is a better concept than analgesia when considering anesthesia. Using this triad, hypnosis is a term used to incorporate consciousness, amnesia and modulation of other higher cortical function. This simplistic amalgamation may be unwise, as memory formation and consciousness are complex phenomena that are related but still distinct.

The triad has also been linked to anatomic location – hypnosis being proposed as a cortical function, and immobility and analgesia being a brain stem or spinal cord function. Although increasingly more is known about where anesthetic agents have an effect, any rigid anatomic distinction of anesthetic effect is premature and misleading.

Defining components of anesthesia by the action of specific drugs is also problematic. Some drugs have very specific clinical actions, such as neuromuscular blockers. But other drugs have more complex effects on the different clinical and physiological components of anesthesia. For example, opioids can, in large doses, produce unconsciousness but are far more effective in reducing nociceptive stimulus. Benzodiazepines can produce unconsciousness but are distinctly effective in preventing the laying down of long-term memory.

To explain how anesthesia is measured I shall use a model of anesthesia with six-linked components (consciousness, memory, movement, autonomic reflexes, arousal and nociceptive stimuli). First, there are four endpoints or clinical aims of anesthesia – loss of consciousness, amnesia, lack of movement and the reduction of autonomic reflexes. A balance
of arousal and concentration of various anesthetic drugs, which act directly on these components, determine the state of these components of anesthesia. In turn, a balance of drug concentration and nociceptive stimulus also determine degree of arousal. Finally degree of nociceptive stimulus may also be directly influenced by drug concentration (Figure 1). An important feature of the model is that anesthesia drugs can have direct, and indirect effects at many points in the model.

The concept of arousal is to some extent an abstract construct. We do not know anatomically where arousal is located; however, it may parallel activity in the reticular activating system or other activating systems in the brain stem and thalamus.

**Depth of anesthesia as a construct**

Having established a model of anesthesia, how should a measure of anesthesia be represented? There is an ongoing debate as to whether anesthesia is binary and should be defined as simply ‘adequate’ or ‘not adequate’, or whether some graded scale can be applied to anesthesia – akin to the idea of ‘depth’ (2–7). The original idea of depth of anesthesia dates from when a single drug was used (ether or chloroform). The depth of anesthesia described the predictable order of physiological changes seen as the dose increased. Interestingly the original descriptions describe a series of levels that overlapped rather than a linear scale (8,9). The word depth implies a surface and a linear extension below the surface. This has been reinforced by the use of anesthesia depth monitors with linear outputs. However, describing anesthesia as a linear phenomenon may be problematic. First, as described above, anesthesia has many components – a single linear measure cannot directly represent all components with all combinations of drugs. Secondly, each component of anesthesia should be examined to determine the most appropriate scale. Not all components change in a linear manner. The measure of each component should be determined by the nature of the component. If a component of anesthesia is binary, or categorical, then the measure of anesthesia should be the probability that the patient exists in each state. If the component has ordinal or continuous characteristics then the measure may be represented as a scale or number that correlates with the effect. This is a key concept when assessing anesthesia depth monitor output.

**Memory**

Memory and consciousness are harder to measure than autonomic responses and movement, and it is these components of anesthesia that are of the most interest. There are several components to memory – explicit, implicit, semantic, episodic, short term and long term. Explicit memory, which may be episodic or semantic, is the free, unprompted recall of events. Episodic memory is the recollection of events that have been experienced (I had a coffee for breakfast), while semantic memory is the recollection of facts (the capital of Peru is Lima). Implicit memory refers to changes in performance or behavior that are produced by prior experiences that do not require any conscious or intentional recollection of these events.

The components of memory, together with consciousness, have been described in an ordinal scale. Explicit memory is described as the most sensitive to increasing dose of anesthesia, followed by implicit memory, and lastly consciousness (10,11). Use of this scale would imply that there is no overlap of loss of consciousness before loss of memory. It is unclear if this assumption is justified. There is conflicting evidence for memory formation without consciousness (12). Although the experiments are difficult to perform, it has been suggested that explicit memory formation does not occur in an unconscious patient (13). In contrast there is increasing evidence that
implicit memory formation does occur during unconsciousness (14), although the clinical significance of this implicit memory is uncertain. Similarly implicit memory formation may occur during periods of consciousness for which the patient has no explicit memory. The significance of these memories is also uncertain (15).

If explicit memory does not occur during unconsciousness, and implicit memory is of questionable clinical significance, then it could be argued that memory is not an independent aim or relevant component of anesthesia. If a patient can be shown to be unconscious then assessment of memory may be irrelevant.

**Consciousness**

A measure of consciousness depends on the definition of consciousness. There are a number of definitions of consciousness. The definition may depend on the perspective of the investigator – whether they are theologians, philosophers, psychologists, neurophysiologists or anesthetists. A broad gap remains between the philosophical aspects of consciousness and any anatomical or neurophysiologic explanation of the phenomenon. Although it is clear to an individual that they are conscious, it is surprisingly difficult to determine if somebody else is conscious. The philosophers of mind, John Searle and Thomas Nagel, define being conscious as having three dominant features – subjectivity, unitary nature and intentionality (16). Externally, these can only be measured by the individual’s interaction with their environment. The key indication of being conscious is the ability to respond to the environment in an integrated and intentional manner.

Therefore, it is not surprising that measures of consciousness are usually measures of response to applied stimuli. Unconsciousness may be defined as no coordinated intentional response to a stimulus. In this respect, consciousness is a binary phenomenon; a person is conscious or unconscious. The issue becomes confused when scales use graded stimuli. The Observer’s Assessment of Alertness/Sedation Scale (OAA/S) scale (17), Glasgow Coma Scale and other measures of consciousness use increasingly intense stimuli to illicit a response. The deeply unconscious patient does not respond to an intense painful stimulus but not the human voice. Both patients are unconscious. What the scale is actually measuring is arousal (sometimes called rousability) not consciousness. A low level of arousal results in no response. A higher level of arousal results in response with a lesser stimulus.

A key concept when discussing anesthesia models is the relationship between arousal and consciousness. As shown in Figure 1, the level of arousal and the direct effect of any drug on consciousness, determine whether or not a patient will gain or lose consciousness. Consciousness also has switch-like (or hysteresis) characteristics. The ability to turn on the switch will be determined by the degree of existing arousal and the intensity of the stimulus. The idea of a switch is supported by the observation that once awakened patients tend to stay awake. This hysteresis is difficult to prove experimentally. Hysteresis may be represented in many pharmacokinetic models as a lag from blood to effect site (18). Whether this lag is a pharmacokinetic or pharmacodynamic effect is difficult to determine. Unlike the switch from unconsciousness to consciousness and vice versa, there is less evidence for any pharmacodynamic hysteresis in the effect of anesthetic drugs when a patient remains unconscious (19,20).

In infants there is increasing evidence that the switch to consciousness is particularly evident. When infants are left to awaken slowly they often appear to suddenly regain consciousness from a previously unresponsive state. It is also of interest to note that infants have a rapid transition from a very suppressed EEG during awakening (21,22).

Although consciousness can be defined as a switch or binary phenomenon, the definition of an ‘integrated, intentional response’ is not clear. In practice, a variety of responses are used to define being conscious. These include the OAA/S scale, and the University of Michigan sedation scale, the ability to follow or hold a syringe, eye opening and others (23–26). On close examination the crucial measures within these scales are still very subjective. Lack of clear definition of consciousness makes it a difficult phenomenon to measure. The problem is compounded in children where ability or willingness to follow command is less certain.
The sedated, lethargic or drowsy patient further confuses the issue of measuring consciousness. How do we classify the patient who responds with slurred or incoherent speech? By most definitions these patients are conscious. A sedated but conscious patient is by definition not anesthetized and therefore measuring their degree of sedation is a different question to measuring anesthesia. Although this is an attractive simplification, a measure of sedation is linked to a measure of consciousness as the sedated patient may be on the cusp of unconsciousness. The measurement and definition of sedated states is complex, involving the concepts of alertness and a variety of higher cortical functions and moods. Like anesthesia, sedated states will be dependent on balances of arousal, concentration of drug and strength of stimuli.

Arousal

As mentioned above arousal can be measured indirectly by gauging the response to a stimulus. As response varies with the strength of the stimulus, arousal may be regarded as an abstract but basically, linear construct. It is arousal that sits most comfortably as a linear scale.

The EEG and anesthesia

Having discussed anesthesia from a clinical perspective, it is time to look at the physiology. Which aspect of anesthesia is most likely to be represented in the EEG, and how strong is the association from a physiological perspective? To answer this requires a brief understanding of the neurophysiology of consciousness and the EEG, and also an understanding of how anesthetic drugs interact with the relationship between the EEG and consciousness.

The neuroanatomy of arousal and consciousness

Much of our understanding of the physiology and anatomy of consciousness comes from the studying effects of lesions in particular nerve tracts. Ascending monoaminergic pathways pass from the brainstem and hypothalamus to the cortex and thalamus to increase wakefulness and vigilance. They also increase the responsiveness of the cortical and thalamic neurons to sensory stimuli. Cholinergic pathways from pedunculopontine and laterodorsal tegmental nucleus nuclei and input from the parabranchial nucleus through the paramedian midbrain reticular formation also join these pathways. This is what is known as the ascending arousal system (27).

This arousal system divides. One branch enters the thalamus activating and modulating thalamic relay nuclei, and other thalamic nuclei with extensive and diffuse cortical projections. The other branch travels through the lateral thalamic area where it is joined by basal forebrain and hypothalamic ascending pathways. Together these diffusely innervate the cortex. Lesions in either branch will impair consciousness (27).

There are no clearly defined anatomical locations for consciousness. Consciousness, defined as the ability to respond to the environment in a coordinated intentional manner, is dependent on the diffuse summated activity of both cerebral hemispheres as well as the ascending arousal system. Unconsciousness can be produced by either diffuse injury to the cerebral cortex, or a lesion in the ascending arousal system (27). The state of sedation is characterized by blunting of higher cortical function. Sedation and alertness are therefore also diffusely represented over the cortex.

The EEG and arousal

The EEG recorded on the scalp arises from the summated activity of synaptic potentials in the dendrites of cortical neurons, in particular the pyramidal cells. The origin of the rhythm of the EEG is controversial. A recent popular theory is that the EEG rhythmic activity reflects firing patterns of the thalamocortical system, which in turn are required for arousal and hence consciousness (28). The rhythmic activity is due to the properties of the thalamic relay neurons. Thalamic relay neurons have two modes: burst and transmission. During transmission mode sensory input is passed through the thalamus to the cortex to produce a complex, desynchronized, apparently random EEG. In burst mode, the sensory input is interrupted and the thalamic relay nuclei produce intermittent bursts of output. This can be detected in the EEG by an increase in regular, low frequency signal. The inhibitory neurons that trigger burst mode are gamma-
aminobutyric acid (GABA)-ergic interneurons in the thalamic reticular nuclei. When awake cholinergic inputs from the brain stem keep the thalamic neurons in transmission mode by inhibiting the thalamic reticular nuclei interneurons (27).

However, there is some evidence that not all rhythmic EEG activity is driven by subcortical structures (29). The cortical pyramidal neurons, which are responsible for generating the potentials that form the EEG, can have their firing patterns altered by factors other than the thalamocortical system. Brain slice preparations have demonstrated that anesthetic agents can act directly on cortical neurons to alter their pattern of depolarization (30–32). Similarly hypothermia and metabolic changes can result in a slowing of the EEG through direct action on cortical neurons. There is also evidence that burst suppression, seen in the EEG with high concentrations of anesthetic, is a direct effect of the anesthetic on the cortical neurons (33). The cortex has a high concentration of GABA receptors, so it is not surprising that anesthetics have an action there. Recordings over the scalp will inevitably be contaminated with signal from the muscle [electromyogram (EMG)]. Most EMG signal is in frequency bands higher than the EEG, but some EMG signal is present in the bands used by commercially available anesthesia depth monitors. Like the EEG, anesthetics suppress the EMG (although opioids do not), but unlike the EEG, neuromuscular blocking drugs will suppress the EMG. The influence of the EMG on anesthesia depth monitors remain a controversial area (34).

The neuroanatomy of anesthesia

Studies using functional magnetic resonance imaging (fMRI) and positron emission tomography scanning have increased our understanding of the anatomic link between consciousness and anesthetic action. These studies have found that volatile anesthetics suppress metabolism in the thalamus, cortex and ascending arousal system. Comparing isoflurane, halothane and propofol, halothane is associated with more suppression in the subcortical regions while propofol has a more distinct cortical effect (35–40). Low doses of anesthetic tend to affect association areas of the cortex. Doses sufficient to produce unconsciousness affect both the cortex, thalamus and midbrain reticular formation (41). One fMRI study has also suggested unconsciousness may occur with cortical suppression of activity with no suppression in the thalamus (42). These findings concur with the previously described model of consciousness being susceptible to both thalamic and cortical injury.

**EEG-based anesthesia depth assessment**

Von Maxow first noted the effects of anesthesia on brain waves in 1890 (43). Berger, ‘the father of the EEG’, demonstrated the effect of anesthesia on the EEG in 1933 (44). Increasing the dose of a volatile anesthetic first increases the amplitude of the signal, then with increasing dose the amplitude decreases and the predominant frequencies become slower. After further increases in anesthetic an isoelectric EEG was achieved (45–47).

The EEG can be analyzed using simple or increasingly complex mathematical derivatives. The simplest analysis is to derive the power frequency spectrum – how much power is in each range of frequencies. Although this can be carried out mathematically, it is also the essence of the visual interpretation and description of the EEG as having slow or fast waves.

As described above, thalamic inhibition of the ascending arousal system results in an increase in low frequency EEG signal and a decrease in stimuli to the cortex. Linking the EEG and arousal through a common thalamocortical system is an attractive idea. However, it is not certain that the rhythm of the EEG actually represents activity of the arousal system. As stated above, at least part of the EEG may be generated within the cortex itself. The relationship between firing of thalamic relay neurons and the EEG has been elucidated studying non-rapid eye movement (REM) sleep patterns and wakefulness, or studies in animals with lesions to the anatomical areas or pathways. Changes seen in the sleep–wake system may not be relevant to changes produced by anesthesia. In other words, the slowing of the EEG seen with anesthesia may not be due to the thalamic induced slowing of the EEG seen during non-REM sleep.

Consciousness requires an intact ascending arousal system and intact cerebral cortex. Anesthetic drugs acting on the cortex independently to any
action on the thalamic relay can also produce unconsciousness. In other words, a patient can be unconscious without slowing of the EEG, e.g. with ketamine anesthesia.

The patterns of burst suppression and ‘flat line’ EEG seen with high doses of anesthesia are thought to be due to direct affects of the anesthetic agents on the cortical neurons independent of the thalamocortical system (29).

In summary:
• consciousness requires an intact ascending arousal system and an intact cerebral cortex;
• the EEG rhythm is derived from thalamocortical pathways and/or direct activity of the cortex;
• during non-REM sleep, or with defined anatomic lesions, changes in the thalamocortical component of the ascending arousal pathways produce a slowing of the EEG and loss of arousal;
• during anesthesia, there is a characteristic activation of the EEG then a slowing of the EEG;
• anesthesia may slow the EEG by actions in the thalamocortical component of the ascending arousal system, or by actions directly on the cortex. The differential effect may depend on drug and dose;
• anesthesia may produce decreases in arousal or unconsciousness by actions in the thalamocortical component of the ascending arousal system or by actions directly on the cortex; the differential effect may depend on the drug and dose.

Thus from a physiological basis it is reasonable to assume some link between the EEG and a measure of anesthesia. The component of anesthesia that would be most amenable to measurement would be arousal. However, such a link would have a degree of uncertainty and not be applicable to all situations.

The EEG and children

The normal awake EEG changes with brain maturation. With increasing age the frequency of the awake dominant background activity increases; at 6 months of age the dominant frequency is 5 Hz, from 9 to 18 months 6–7 Hz, at 2 years 7–8 Hz, by 7 years it is 9 Hz and by 15 years of age reaches adult levels at 10 Hz (48,49). Children <5 years old also have specific EEG patterns associated with the transition to, and from, sleep and drowsiness. Children aged 6 months to 4 years have short bursts of 4–8 Hz activity lasting 1–5 s. Also, longer periods of 1- to 3-Hz activity may be seen in 3 months to 5 year old children. This activity is observed maximally at 12 months.

There are only limited reports describing the EEG in children during anesthesia. There are no systematic studies comparing the EEG during anesthesia in adults, children and infants. Sugiyama et al. (50) described a slowing of the EEG with halothane anesthesia in infants, noting that the baseline was already slow in infants. Kitahara et al. (51) found slow waves during halothane anesthesia, and no activation of the EEG with stimulus in younger infants. Another report describes unusual high frequency activity during isoflurane anesthesia in children having cardiac surgery (52). In children aged 6–12 years who were anesthetized with propofol (53), and aged 0.3–13 years with sevoflurane (54) the typical changes seen during anesthesia in adults were noted. The broad age range limits the usefulness of any data from the latter study. Sevoflurane is reported to cause epileptiform movements and EEG changes when given at high concentrations at induction. However, it is unclear if the movement and EEG changes actually represent epileptic activity. Nevertheless, the study of this phenomenon has resulted in numerous studies investigating the EEG of children during induction with sevoflurane and halothane. These studies report a typical increase in total spectral power then a shift to lower frequencies (55,56).

The changes seen in the EEG with maturation, and the lack of systematic evaluation of the EEG in children during anesthesia make it very difficult to presume that the correlation between EEG, arousal and anesthesia that is quite plausible in adults is equally plausible in children. The uncertainty increases as age decreases.

Linking the EEG to clinical anesthesia measures

Advances in computing power have enabled the development of technologies that can rapidly analyze the EEG. As a result several EEG-based anesthesia depth monitors have been produced. The Bispectral Index (BIS) is the most widely studied. Although the exact workings of many of these technologies are not clear, it is possible to...
establish the principles of how they link the EEG to a measure of anesthesia. This is the crucial step in understanding what they actually measure, and therefore what their likely uses and limitations would be. An understanding of the principles behind their functioning is essential before extrapolating their proven or theoretical utility from adults to children.

How do EEG-based anesthesia depth monitors work?

A detailed description of the algorithms for these monitors can be found elsewhere (57–60). In general terms, the EEG signal is collected from a limited array of scalp electrodes. The signal is digitalized and filtered for nonphysiologic artefact. The signal is then analyzed using a variety of mathematical derivatives. For example, Entropy calculates Shannon entropy and BIS computes ratio of power in fast and slow frequencies and the bispectral power (interfrequency harmonics). Burst suppression is also identified and quantified. It is very unclear if the higher orders of mathematical derivatives of the EEG, such as the bispectrum or entropy, actually represent any physiological phenomenon (61,62).

The numbers generated from the signal analysis are then transformed to generate a single value, usually on some arbitrary scale between 0 and 100. For example, entropy uses a simple spline function. BIS uses a proprietary nonlinear algorithm that uses four mathematical derivatives of the EEG. The output value is then averaged and displayed.

The most important step is the transform or algorithm. The algorithm for BIS was determined by retrospective analysis of adult EEG data collected during anesthesia. The final algorithm was created by progressively testing likely algorithms with archival data until the best fit between order of output values and a hierarchy of anesthesia milestones was achieved.

In this review I have not specifically discussed auditory evoked potentials (AEP). Monitors using the AEP measure the response in the EEG to an auditory stimulus. The delay and amplitude in the response signal correlates with arousal and anesthesia drug concentration. As they are a measure of response they are sometimes called active monitors rather than the passive EEG-derived monitors that measure ‘normal’ background EEG. The clinical significance of this distinction is unclear but worthy of future investigation.

How do they relate to anesthesia?

A schematic representation of how EEG-based monitors are related to arousal consciousness or memory formation is depicted in Figure 2. The BIS, and other depth monitors, are derived from the EEG. The EEG pattern is determined in part by both arousal and by direct effects of anesthetic agents. Sensory stimuli and anesthetic drugs determine degree of arousal. Consciousness and memory are dependent on arousal but may also be directly affected by anesthetic drugs. The relationship between EEG and consciousness is therefore indirect. They do not directly measure consciousness. Movement is either purposeful or a direct response to nociceptive stimulus. Movement is even more indirectly related to arousal (Figure 1) and it is thus understandable that EEG correlates very poorly with movement.

The association between BIS (and other EEG-derived anesthesia depth monitors) and arousal, and the indirect association between BIS and consciousness remains valid only if the relative actions of the anesthetic drugs on the EEG, arousal and consciousness are consistent and reproducible. This is the case for isoflurane, propofol, thiopentone and midazolam (Figure 3). The association between BIS and arousal or BIS and consciousness will be less valid for drugs with different relative effects on consciousness, arousal and the EEG. For
example, ketamine, nitrous oxide and halothane (Figure 4) (63–66).

The effect of opioids is more complex. Indirectly, opioids will reduce arousal and BIS by reducing nociceptive stimulus (67,68). In the absence of nociceptive stimulus the evidence for effect of opioids on arousal and BIS is contradictory and dose dependent. Low doses have minimal effect on consciousness or BIS (67,68), but high doses of opioids will cause a decrease in arousal and a fall in BIS, but with a relatively greater fall in arousal than BIS (69–71).

**Uses of EEG-derived anesthesia depth monitors**

In essence, there are two ways to use, an EEG-derived anesthesia depth monitor. First, as a machine that quantifies a component of anesthesia, and secondly as a guide, or arbitrary scale, to guide the anesthetist through anesthesia using particular drugs.

**Measures of arousal**

The component of anesthesia most likely to be represented by the EEG-derived monitors is arousal. As a measure of arousal they can give a fair indication of the possibility that a patient may be conscious or that they may switch to the conscious state with the appropriate stimulus. The mean values associated with consciousness are higher than those associated with unconsciousness but there is a significant degree of imprecision and overlap (23,24,68,69,72–76). The monitors do not provide direct probabilities of consciousness, but having a value beneath a certain cut-off is almost always associated with unconsciousness (e.g. a BIS value of 55). With values above the cut-off the monitors have more difficulty in differentiating consciousness and unconsciousness.

There is other indirect evidence that they give a measure of arousal. At constant levels of stimulation the values will change with anesthesia concentration (73–75) and with constant drug concentration the values will change with stimulus (67,68,77). However, arousal is not a well-defined phenomenon so it is not surprising that it is unclear exactly what the numbers represent in a clinical setting. When the monitors are used for physiological studies this uncertainty must always be highlighted. Similarly as the scales do not represent any defined physiological phenomenon it is more appropriate to regard the data as on an ordinal rather than linear or interval scale.

Finally, the monitors rarely provide any degree of certainty around their measures. An ideal monitor would provide a value that could be directly translated into a clinically meaningful measure, along with the degree of uncertainty around that value.

Another way an anesthesia depth monitor may function is not to be a measure of arousal, but rather
by providing a measure of brain concentration of a drug. This is indeed how some existing monitors may function at very high concentrations of anesthesia. If a patient is unrousable, even with maximal stimulation, then the degree of arousal might be regarded as zero. However, the brain concentration of anesthetic drug may still rise resulting in further change in the EEG. This change in EEG is still a useful information as the higher the brain concentration, the further it must fall before any measurable degree of arousal. At high concentrations of anesthesia and low levels of arousal it is difficult to determine if the changes seen in the EEG are related to changes in arousal or to direct effects of the anesthetic agent on the thalamic (or cortical) neurons producing the EEG. This is particularly the case when burst suppression is occurring.

Anesthesia guides

Although the monitors are imprecise measures of a somewhat abstract construct, it is incorrect to conclude that the monitors are without use. Indeed outcome studies have provided increasing evidence for their use to prevent awareness (78) and improve recovery times and postoperative vomiting (79–81). The logical way to apply these monitors is as a road map to guide the anesthetist through a standard anesthetic using the particular drugs that were used when the algorithms were derived. The number generated to guide the anesthetist can be called a ‘depth of hypnosis’. Hypnosis is a fine term to use, provided it is recognized that hypnosis is not always equivalent to arousal, it is not a linear or interval measure, it has no real or exact physiological meaning, and its validity is drug dependent. The monitors and the term depth of hypnosis should be used with great caution on any other roads apart from that for which they were conceived.

Use in children

In spite of uncertainty surrounding maturational changes in the EEG, and the paucity of data about EEG changes during anesthesia in children, there are several physiological studies indicating that the EEG-derived anesthesia monitors do give some measure of arousal in children (82). Initial studies have shown BIS and Entropy give values that do go down and up as expected during routine anesthesia (26,83,84). Studies have also demonstrated a relationship between anesthetic concentration and BIS, Entropy and Narcotrend values (85–88) – although often these measures were not made at equilibrium (26,83) or multiple measures in the same child were used. The relationships between anesthetic concentration and the EEG-derived values were not as clear in infants (22,89,90), and not clear over all concentrations of sevoflurane (91). A relationship between BIS and sedation scores have also been demonstrated (92–94). As for adults there was considerable overlap in values between conscious and unconscious states (26,54). On closer examination the numbers for BIS and Entropy that occur prior to awakening (a particular state of arousal) differ in infants compared with older children (21,22,90). As in adults the values in children are also agent dependent (63,95,96).

The differences in infants may be due to the immaturity of the EEG or it may be that the nature of arousal in an infant differs from adults (22,82), for example, infants may have a more marked ‘switch’. If the relationship between arousal and consciousness is different in infants, then the relationship between the monitor and consciousness will also be different in infants (Figure 3).

In younger children given constant concentrations of sevoflurane or desflurane the Entropy and BIS values rise as age decreases (90,97). The rise in values appears to be disproportionate to the rise that would be expected when comparing MAC across these age groups (98). The significance of this is uncertain. It may indicate a higher degree of arousal at MAC equivalent doses of anesthesia, or equivalent arousal with MAC equivalent doses of anesthesia but relatively less direct effect of the anesthetic on the EEG in younger children. Both explanations assume that the MAC data are correct. If the former explanation is correct, and there is a higher degree of arousal, there could be an increased risk of consciousness at MAC equivalent doses of anesthesia. This is potentially of considerable relevance to understand awareness in children.

From the limited physiological studies, it can be concluded the EEG provides a similar measure of anesthesia in older children as it does in adults. It is therefore possible that any clinical benefit derived from measuring the EEG which has been proven in
adults, such as improved recovery and reduced awareness, could be translated to children. The only outcome study so far performed during anesthesia in children gave some evidence of a moderate improvement in recovery when BIS-guided anesthesia was used (21). Time to discharge readiness was shorter with BIS-guided anesthesia in older children, but not in younger children. There are no studies evaluating EEG-derived monitors and actual discharge time or postoperative vomiting. It is important to note that EEG-derived benefits seen in adults can only be expected in children if the causes of delayed recovery and postoperative vomiting are similar and the improvements in outcomes are of similar clinical significance.

Awareness occurs in children at least as frequently as in adults (99,100). The utility of EEG-derived monitors to prevent awareness in children is unknown. Results from adult studies demonstrating utility of BIS to prevent awareness may be relevant to some cases of pediatric anesthesia, but it cannot be assumed EEG-derived monitors will always reduce awareness in children. There are indications that awareness has a different etiology in children compared with high-risk adults and, as fewer aware children were paralyzed, awareness may be of different clinical relevance in children (99).

Conclusion

A model of anesthesia has several components. Arousal is a core component that can be linked to clinical, anatomical and physiological observations. The EEG has characteristics that fairly consistently change with arousal during anesthesia, but the relationship between arousal and the EEG is imprecise and drug dependent. This relationship is the basis for using the EEG to measure anesthesia and provides only an indirect measure of consciousness and memory formation. A good understanding of how the EEG is related to anesthesia is essential when interpreting the EEG during anesthesia, and especially when extending the use of the EEG to measure anesthesia in different populations and anesthesia regimens. Physiological studies in adults and children indicate that EEG-derived anesthesia depth monitors can provide an imprecise and drug-dependent measure of arousal. Although the outputs from these monitors do not closely represent any true physiological entity, they can be used as guides for anesthesia and in doing so have improved outcomes in adults. In older children the physiology, anatomy and clinical observations indicate the performance of the monitors may be similar to that in adults, although the clinical relevance of outcomes may be different. In infants their use cannot yet be supported in theory or in practice.

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