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Review Article

The role and limitations of EEG-based depth of anaesthesia monitoring in theatres and intensive care

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Summary

In this article we will look at some of the principles in processed EEG monitoring as applied to bispectral index (BIS). We outline why BIS should be regarded as a 'memory' monitor which in most circumstances reflects the depth of sedation or anaesthesia in particular patients. Its limitation in paralysed and non-paralysed patients must be understood in order for this monitor to be used safely. Finally, its emerging use in critical care will be explored.

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Introduction to electroencephalography and the bispectral index

Electroencephalography (EEG) was first described in 1875 by Caton, a physician working at Liverpool Royal Infirmary, UK, demonstrating the presence of currents of varying direction detectable on the skull of dogs and apes using a galvanometer and electrodes [1]. Berger later extended this work to the EEG in humans [2]. The effect of certain drugs (scopolamine, barbiturates, morphine, and ether) on EEG was noted around 10 years later [3]. Raw EEG has limited use in the measurement of depth of anaesthesia. The majority of clinicians do not have the time nor the skill to interpret the complexity of the raw data and utilise the information to titrate the delivery of anaesthesia. Thus, efforts were made to compress and simplify the analysis. Numerous monitors have been marketed for this purpose; the most popular include Narcotrend™ (MonitorTechnik, Bad Bramstedt, Germany), M-Entropy™ (GE Healthcare, Helsinki, Finland) and Bispectral Index (BIS™ Medtronic-Covidien, Dublin, Ireland). The most extensively studied (particularly in terms of its effect on the incidence of accidental awareness during general anaesthesia, (AAGA)) is the BIS so this review will concentrate on BIS, but similar principles apply to all EEG-based monitors.

The EEG signal is acquired through gel electrodes placed on the forehead. This is subsequently digitised, amplified and filtered to isolate EEG from other biological potentials such as ECG waveforms, ocular activity and mains power interference. Scalp electromyography (EMG) is part of the device measurement, reported separately [4–7].

The electrode strip can be difficult to apply in certain neurosurgical approaches (yet is particularly useful in neuro-anaesthesia titration, since it is looking at the very organ being operated upon [8]) but has been validated when used across the bridge of the nose because the frontal lobe signals are detectable in this alternative montage [9].

Fourier transformation is used to deconstruct the complex EEG waveform into individual sine waves of differing amplitude or frequency (Fig. 1). The power spectrum is created by plotting the signal power (energy against time) of a given frequency as a graphical display. The 'frequency domain' can be envisaged crudely as the relative proportion of the component waveforms of different frequencies. A 'time domain' can be envisaged as how the pattern of these frequencies change over time. Thus, the numerical BIS value will change over time according to the relative proportions of high vs. low frequency component waveforms within the EEG signal. How the device exactly does that is a commercial secret.

To calculate burst suppression ratio (BSR), EEG activity not exceeding 5.0 mV and lasting longer than 0.5 seconds is identified, and the time spent in this state calculated as a fraction of total time. Burst suppression of the EEG (Fig. 2) may be witnessed during periods of deep anaesthesia as well as hypoxia or brain trauma, but has also been associated with reduced cerebral metabolic activity and can be used to titrate barbiturate coma therapy [10, 11].

The above values are incorporated into the final dimensionless (BIS) number between 0 (cortical electrical silence) and 100 (normal awake activity). This number, averaged over the previous 60 s of data, declines with anaesthesia-induced unconsciousness.

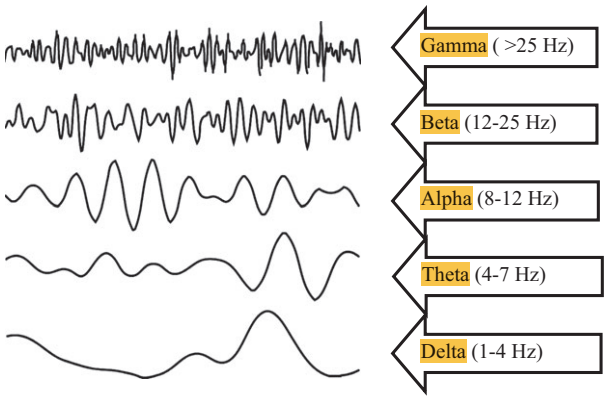


Figure 1 Basic EEG waveforms of the adult human brain; the y-axis is voltage and x-axis time, but neither are drawn quantitatively in this illustrative figure.

Figure 2 Screenshot of BIS (from bilateral leads) following a thiopental bolus. Overall the BIS value is very low at 17 (displayed at panel a), and also demonstrating (panel b) very flat EEG activity with a single burst on a suppressed background EEG (the burst suppression ratio (SR) = 69). Also seen are two 'spectrograms' (panels c), illustrating the power spectrum explained in text. There is no right to left asymmetry apparent.

AAGA without recall

Studies utilising Brice interview methodology [12], actively seek cases of AAGA by semi-direct questioning and yield an incidence of ~1:600 anaesthetics [13–17]. More recently, the 5th National Audit Project (NAP5) demonstrated an overall incidence of ~1:19,000 anaesthetics [18]. The disparity between results and methodologies used has been extensively discussed, with Avidan and Sleigh commenting in an editorial that NAP5 'was reliant on sampling from the population of all GA survivors from 1946 to the present, who had not previously reported any intra-operative recall, and who had also chanced to be exposed to the investigation team' [19]. Importantly, the associated NAP5 Activity Survey reported that only 2.8% of all general anaesthetics involved depth of anaesthesia (DOA) monitoring in the UK [18].

All these awareness statistics relate to AAGA followed by explicit recall. Accidental awareness during general anaesthesia without recall is far commoner than with recall but the only way to study this phenomenon is using the isolated forearm technique (IFT) [20]. The IFT is rightly considered the gold standard measure of wakefulness under anaesthesia. However, NAP5 found that only 0.03% of anaesthetics in the

UK utilise the IFT and subsequently the AAGBI has acknowledged that it might be of use, with careful interpretation of positive responses [21]. Originally described by Tunstall in 1977, an upper limb is isolated from paralysis using a sphygmomanometer cuff. The patient is instructed to move their fingers in a particular manner to detect AAGA [20].

A 2013 single-operator study investigated the ability of BIS to detect intra-operative wakefulness compared with the IFT [22]. Twenty-two women undergoing gynaecological surgery were given total i.v. anaesthesia (TIVA) with target-controlled infusion (TCI) of propofol and remifentanil. Neuromuscular blockade was achieved with atracurium. The TCI was reduced to achieve a BIS of 55–60 (in practice, as evidenced in the paper, this can be notoriously difficult to achieve). The BIS was > 60 during 47 of the 80 appropriate hand movements seen in 16 of the subjects, giving a sensitivity as a diagnostic awareness monitor of 59%. None of the participants reported any intra-operative recall. This paper shows that close control of BIS to within narrow pre-set limits is difficult, and secondly, that BIS is not reliable as an awareness monitor when used in this way and if BIS is kept too close to 60 then wakefulness (albeit without recall) may occur.

Numerous other studies have detected AAGA without recall using the IFT. In one study, 40% of patients demonstrated a positive IFT response 2 min after thiopental administration, falling to 10% after 3 min [23]. None of the patients studied recalled these responses postoperatively. A 2014 study sought to compare BIS values with IFT responses. The results demonstrated positive IFT responses in 30%, 36% and 18% of patients despite mean BIS values of 45, 46 and 48 at laryngoscopy, intubation and skin incision, respectively. When interviewed at 12–24 h after surgery, none of the subjects had recall of intra-operative events [24].

Almost all the authors seem to agree, therefore, that BIS is poor at detecting wakefulness. However, there are several points in mitigation. Induction is a dynamic stage of anaesthesia and it is possible that the BIS is relatively good in the steady state, but poor at tracking rapid changes in anaesthetic depth. Second, it could be argued that since there was no recall in these cases, the BIS had in fact been quite effective. Finally, it is not entirely clear whether the mental state of responsiveness during IFT actually represents 'wakefulness' in the same way as a person who is completely conscious (without drugs). These IFT patients show no spontaneous movements to indicate they are awake [25] and this dichotomy has been argued to represent a distinct mental state (termed 'dysanaesthesia' [26, 27]), which the BIS is not designed to detect.

Using BIS at induction

It can be argued that BIS is validated against postoperative recall as opposed to intra-operative ability to perform motor commands; it should be regarded as a 'recall probability' monitor, not an 'awareness' monitor.

The clinician should consider if the depth of anaesthesia during general anaesthesia, as indicated by BIS, is adequate for any imminent change in the level of surgical (or anaesthetic) stimulus planned. It is known that BIS falls to levels as low as 30 during normal sleep (Fig. 3) [28], yet sleep is an inadequate state to allow surgery to proceed. In other words, the BIS value encompasses several biological brain states, and is not specific for those induced by anaesthesia. Likewise, it is no surprise that a BIS value ~50 immediately before a stimulating event (e.g. laryngoscopy, intubation, skin incision) is potentially inadequate to avoid AAGA. Such stimuli can increase catecholamine release (evidenced by increased blood pressure) and also usually result in an increase in BIS. The redistribution of a single induction dose of intravenous agent

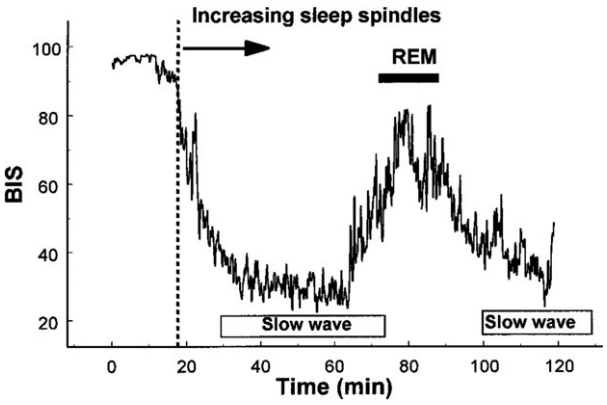


Figure 3 BIS during natural sleep. (Based on [28]). REM is rapid eye movement sleep. The dotted line represents the point at which there is detection of sleep spindles that occur during stage-2 sleep.

and a barely adequate concentration of volatile agent may result in a 'mind the gap' situation as described by the NAP5 authors (the gap referring to any delay between the induction dose of anaesthetic and that used for subsequent maintenance) [18]. In an obstetric IFT study, it was calculated that for the particular combination of drugs used, a BIS value < 27 was required at laryngoscopy if an IFT response was to be eliminated in all patients [24]. More opiate-based anaesthetics (e.g. remifentanil infusion) have fewer variations in BIS (known as 'trend spikes') and result in a smaller increase in BIS following painful stimuli such as intubation. A second dose of induction agent given immediately before intubation or a more opiate-based anaesthetic might consequently result in fewer IFT positive responses.

AAGA with recall

Large multicentred trials have been conducted investigating the use of BIS to prevent AAGA. The B-Aware trial in 2004 recruited 2463 patients and investigated general anaesthesia with neuromuscular blockade (NMB) in patients identified as high risk for AAGA [14]. In all, 13 confirmed cases of AAGA were identified during postoperative interviews, of which two were in the BIS group. Bispectral index-guided anaesthesia thus reduced the risk of AAGA by 82% in this high-risk population. The Swedish SAFE-2 trial [29] showed a 77% reduction in AAGA in the BIS group when compared with a historical control group from the SAFE-1 study [15].

The B-Unaware study recruited 2000 patients considered to be at high risk of AAGA comparing anaesthesia guided by BIS (40–60) or a target end-tidal anaesthetic gas (ETAG) concentration of 0.7–1.3 MAC [16]. Two definite cases of AAGA with explicit recall in postoperative interviews occurred in both groups. The authors subsequently followed this up with a larger three-site study in 2011; the BAG-RECALL trial [30, 31]. Previously identified weaknesses of B-Unaware were addressed, the sample size was three times larger, and the study was conducted over multiple sites. The results showed no significant difference in AAGA between the ETAG and BIS groups, further reinforcing the conclusion that MAC > 0.7 is as effective as BIS in preventing AAGA.

An alarm set to sound when MAC falls < 0.7 seems to be a prudent measure to avoid AAGA. It is less clear if/how this threshold should be adjusted when large doses of opiates are employed. Patients who may not even be able to tolerate (e.g. haemodynamically) MAC values of ~0.7, or those receiving TIVA with NMB, would probably benefit from BIS being employed to minimise AAGA while optimising haemodynamic stability.

The most recent systematic review in 2014 examined randomised controlled trials comparing BIS with standard practice for delivery of anaesthetic [32]: 36 trials were included and the results demonstrated that BIS-guided anaesthesia reduced risk of AAGA in those patients who are at highest risk. However, the same effect was not evident in studies which utilised ETAG monitoring alone. Furthermore, use of BIS reduced consumption of intravenoux and inhaled anaesthetic, as well as reducing postoperative recovery times.

The UK National Institute for Health and Care Excellence (NICE) recommendations in 2012 recommend BIS, E-Entropy, or Narcotrend as an option in any patients considered high risk of over- and under-dosing of anaesthesia, and specifically recommended depth of anaesthesia monitoring in patients receiving TIVA [33]. The NAP5 recommendations were broadly in agreement and recommended routine use for TIVA with NMB.

Pitfalls with BIS

Neuromuscular blockade

A recent study on 11 volunteer anaesthetists assessed the effect of administered suxamethonium and rocuronium on BIS in the absence of any anaesthesia, with IFT utilised for communication [34]. Onset of muscle paralysis resulted in a fall in BIS, and return to previous values upon return of muscle activity. The authors argued that the algorithm upon which the BIS is based must use information from the EMG to derive the BIS statistic. It is not known however, if a strong, painful stimulus would have increased the BIS value in these subjects, which might have confirmed that the BIS was not wholly reliant on EMG activity.

Other studies have also demonstrated that reversal of NMB with sugammadex or neostigmine are followed by rises in BIS value [35]. Sugammadex (which

reverses amino-steroidal NMB agents) has been demonstrated to have no effect on BIS when given to patients receiving a benzylisoquinoline NMB agent [36]. These results underline the likelihood that the EMG does indeed contribute to ~20% of the BIS value in the higher ranges. This is important to remember when dealing with any patient at emergence whose NMB is inadequately reversed: in our institution, a patient with complete residual postop curarisation secondary to unrecognised mivacurium apnoea, had a BIS of 80 (i.e. consistent with a degree of sedation) despite being completely awake.

Ketamine and other agents

Ketamine is decidedly not only a general anaesthetic agent but also has unique dissociative properties which distinguishes it from many other anaesthetic agents. Although logic would suggest concurrent use of ketamine as part of a multimodal anaesthetic would deepen anaesthesia and so lower BIS values, the converse is true [37, 38]. Ketamine's known positive effect on cerebral metabolic rate ($CMRO_2$) may explain the phenomenon, since it has been shown that $CMRO_2$ changes are mirrored by proportional changes in BIS [8], however, this remains unproven. Ketamine may also change the EEG power spectrum by causing a rise in theta activity, and this influences the manner in which the BIS values are calculated by a commercially-secret algorithm. Similar principles probably apply to BIS with dexmedetomidine and xenon anaesthesia [42–46]. Nitrous oxide has no effect on BIS when used as a sole agent or when administered with propofol, but has a small additive effect with sevoflurane. Its use with BIS might result in an unintentionally deep level of anaesthesia. [47, 48].

Tracking the number

The NAP5 reported cases of AAGA where anaesthetists had 'tracked' the BIS value, keeping it at low levels (< 50) albeit achieved using very low anaesthetic concentrations (~0.3 MAC). In one case, it is possible that the BIS had been disconnected during the positioning process which can in itself be stimulating, however, it emphasises the importance of using the BIS value as just one piece of information about the depth of anaesthesia, and that caution is necessary whenever delivered anaesthetic concentrations are low (e.g. < 0.7 MAC). It is vital to keep BIS cables attached, if at all possible, during repositioning (or reattached immediately afterwards) and until any muscle relaxation has been confirmed as fully reversed using a peripheral nerve stimulator. Some authors have tried to combine BIS values quantitatively with other measures to achieve an overall measure of anaesthetic depth [49].

BIS and outcomes

A recent Cochrane review found that the use of BIS decreased postoperative delirium [50]. Studies have also shown that BIS levels correlate with outcome in other ways. A 'triple low' (the combination of a low BIS, low BP, and low MAC) appears to be correlated with a higher mortality [51, 52]. This may indicate excessive sensitivity to anaesthetic in the affected patients, and has been the driver for a large multicentre trial called the Balanced Study which aims to determine the effect of light vs. deep anaesthesia on all-cause mortality at 1 year postoperatively [53].

Bispectral index in ICU

The use of BIS monitoring to assess for recall in anesthetised patients in the operating theatre room for short periods of time is quite different to its use in monitoring critically unwell patients who may be receiving continuous sedation and analgesia in the ICU for prolonged periods of time.

Sedation in ICU

Bispectral index variability is large in the intensive care patient population, where levels of arousal range from almost none at rest to high during nursing procedures, physiotherapy and medical or surgical interventions. Over-sedation in ICU is associated with higher rates of ventilator-associated pneumonia and longer ICU stays [54, 55].

Using BIS in surgical ICU patients receiving continuous infusions of sedatives and NMB can have both economic and patient benefits. One study reported less recall of frightening or painful events during the period of sedation in a BIS-titrated group, with concomitant sedative drug cost savings of $150

(£123, Euros 137) per patient [56]. Using BIS as an objective guide for the dosage of sedating agents can also decrease the medical complications of over-sedation, such as depressed cardiac contractility and hypotension, with a secondary benefit of financial savings from lower drug doses and decreased time to extubation [57, 58].

The BIS and the behaviour pain score were found to be more sensitive when compared with monitoring of vital signs alone in patients undergoing (potentially uncomfortable) procedures [54]. Since the publication of NAP5, where patients receiving paralysis with TIVA were found to be at increased risk of AAGA, many institutions are mandating some form of depth monitoring for such patients in the operating suite [18]. The logic can be extended to patients receiving NMB agents in ICU. This would be particularly important during patient transfers or when painful procedures such as reintubation, tracheostomy, rigid bronchoscopy or prone positioning are to be performed [59–61].

Bispectral index values can vary greatly in patients sedated in the ICU and has been shown in some studies to correlate poorly with the Sedation-Agitation Scale [62–64]. We will consider some of the possible reasons for this wide variation in BIS.

First, unlike those undergoing painful operations, patients on ICU rarely undergo much stimulation, and so require relatively low levels of sedation. Minor interventions can lead to arousal and consequent fluctuating BIS scores. A second reason is the effect of NMB [31]: one study showed that BIS declined in a group of lightly sedated patients who were paralysed with NMB, and subsequently increased when paralysis wore off [65]. The dilemma is which is the 'true' level of BIS that should guide the clinician? The value before or after a stimulation or the value before or after administration of a NMB agent? The authors of the study warned that *"clinicians who determine the amount of sedation in ICU patients solely based on BIS monitoring may expose patients to unnecessary over-sedation"*. Perhaps during periods of low stimulation on ICU, clinicians should aim for slightly higher BIS scores than those needed to prevent recall during stimulating surgery; however, establishing this will need further research.

BIS in neurological disorders

Quite apart from titration of the anaesthetic in patients at high risk for AAGA, BIS can be used to assist therapies for some neurological disorders or yield insight into conscious levels in minimally conscious states. An emerging idea is that minimally conscious patients might actually be 'aware' and the EEG is one way of accessing cognitive function in them [66]. One report used BIS to guide anaesthetic management during necessary dental surgery in persistent vegetative state [67].

A useful application of BIS in ICU is monitoring for seizures that might be subclinical or unrecognised in patients receiving NMB [68]. However, BIS values can be low or high during a seizure, since BIS value depends on the main frequency of the ictal waveform. It is known that facial nerve stimulation affects the EMG and thus the BIS reading (Fig. 4) [69]. Therefore, the resultant muscle activity from a seizure may affect BIS readings, in addition to its effect on EEG alone. One patient in status epilepticus was unarousable with a BIS of 94 [70, 71]. Thus, any sudden unexplained change in BIS might correspond to seizure activity warranting further investigation and/or treatment. Figure 5 illustrates the BIS of a patient in status epilepticus.

Bispectral index monitors can also be used to guide burst suppression therapy, which is the aim during deep coma for the treatment of status epilepticus

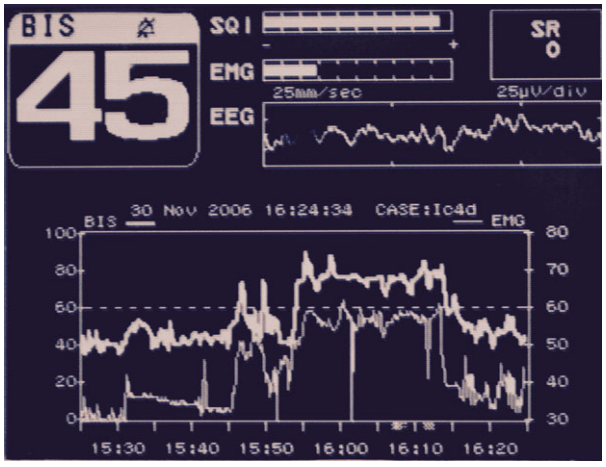


Figure 4 BIS demonstrating facial nerve irritation (upper line represents BIS, lighter lower line represents EMG). Rocuronium was given at 16:11. Based on [69].

or for resistant raised intra-cranial pressure. A burst suppression ratio of 15–30 correlates to 3–5 bursts per minute when recorded on a full EEG, which most neurophysiologists would consider optimal burst suppression for safely minimising $CMRO_2$ [72].

Predicting outcome following cardiac arrest and traumatic brain injury

Bispectral index values fall following cardiac arrest as a consequence of global ischaemia [73]. Mean BIS values in the first 24 h after resuscitation are higher in patients with good outcomes compared with those with poor outcomes [74]. A retrospective evaluation of patients resuscitated from cardiac arrest showed that a form of 'neurocardiac triage' based on very early BIS values is feasible, and may identify patients appropriate for individualised postresuscitation care [75]. In their cohort of 171 patients, those with a BIS < 10 suffered 91% overall mortality (82% due to neurological causes) while BIS > 20 was associated with 36% overall mortality (12% due to neurological causes).

Following traumatic brain injury (TBI), one study found patients with BIS > 60 to have a 30-fold improved survival rate and be 20 times more likely to have a Glasgow Coma Score (GCS) > 8 [76]. In another study of 61 patients with TBI who had no sedation and were admitted to ICU, there was a significant correlation between admission GCS and BIS, although it is unclear how these critically unwell patients with very low GCS reached ICU having not received sedation before admission [77]. Although a high BIS is an encouraging finding in patients not receiving sedation, the sensitivity and specificity is inadequate for it to be a reliable prognostic indicator in TBI.

When managing TBI patients with raised ICP, a low cerebral metabolic rate of oxygen consumption ($CMRO_2$) is beneficial, and a deep induced coma is often used to achieve this. It has been shown that BIS correlates with $CMRO_2$ (Fig. 6) [8, 78]. It is the author's experience (JA) that a sedated and ventilated patient with high ICP > 20 mmHg but paradoxical values of BIS > 40 will often respond to increased sedation with a decline in ICP (providing cerebral perfusion pressure is maintained). Some protocols still include burst suppression in TBI as a tertiary therapy. Titrating to a BIS of < 15 corresponds to burst suppression, although not with 100% sensitivity and specificity [11, 79]. Concordance between BIS and burst suppression pattern should periodically be checked using a formal EEG.

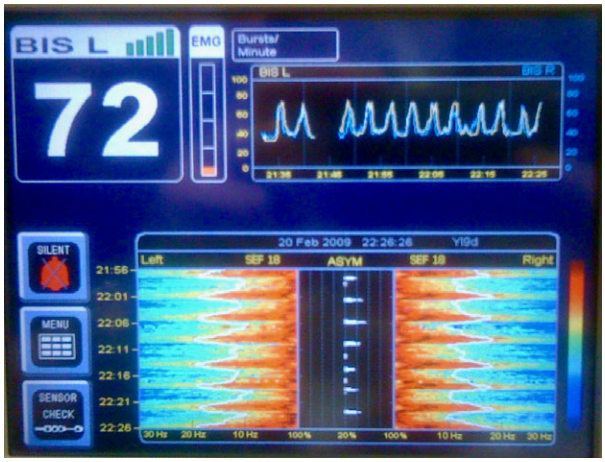


Figure 5 Bilateral BIS demonstrating epileptiform BIS activity in a patient with severe resistant status. It shows BIS fluctuating between 40 and 70 every few minutes.

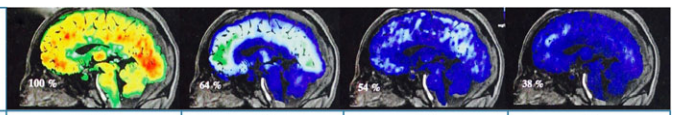
PET				
%BMR	100	64	54	38
BIS	95	66	62	34

Figure 6 PET images demonstrating correlation between brain metabolic rate (BMR) and BIS in a patient undergoing a general anaesthetic with propofol. The bright yellow brain on the left has a baseline BMR of 100% corresponding to an awake BIS of 95. As propofol is increased and the depth of anaesthesia increases (with a corresponding fall in BIS) the brain activity is displayed in bluer colours related to a fall in BMR. Based on [8].

Summary: is BIS useful in ICU?

The potential for artefacts and pitfalls in using BIS in ICU needs to be acknowledged. There have been reports of pacemakers and the use of external rewarming devices resulting in increases in BIS scores [80]. Catecholamine infusions may heighten arousal and consequently increase BIS [81]. Nevertheless, BIS monitoring seems advisable in the ICU to avoid awareness during invasive and stimulating procedures, particularly when NMB is employed. In traumatic brain injury, its use may avoid overly-light sedation in patients with raised ICP. There is evidence of its use as a prognostic tool, but decisions should not be made on BIS values alone. In seizure management, BIS correlates with burst suppression and appears useful in treating status epilepticus; it should be checked against a formal EEG when used for prolonged periods of time in this context.

Summary: is BIS useful in the operating theatre?

There now seems to be consensus that a depth of anaesthesia monitor should be employed when using TIVA coupled with NMB, including for periods of patient transfer. Which monitor to use (or whether to employ IFT) is a secondary question, and amenable to further research. But there seems little other way by which to monitor the drug or the effect of drug in this context.

However, considerably more debate exists around whether to use depth of anaesthesia monitoring during inhalational anaesthesia. Detractors point to the many limitations of BIS [82], whereas proponents point to the many trials and advice from national bodies supporting its use [14, 15, 18, 21]. The main argument making specific monitoring unnecessary is that the end-tidal concentration is an accurate reflection of anaesthetic dose and, therefore, of likely brain effect [30]. The counter-argument is, however, that this does not reflect an individual patient's requirements and the effect of supplementary regional anaesthesia or large-dose opoids. Nevertheless, until the results of studies looking at the effect of depth of anaesthesia on outcome are published, a balanced approach might be to use BIS when: (a) the patient falls into a 'high-risk' category; (b) the patient has had an experience of AAGA or expresses specific fears of such; (c) other measures such as heart rate or blood pressure indicate that very high levels of agent are required; (d) other measures such as blood pressure are unusually low despite low levels of agent (i.e. danger of 'triple low'); or (e) when the patient has brain injury or neurological state impairing consciousness.

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