REVIEW ARTICLE

Different Conditions That Could Result in the Bispectral Index Indicating an Incorrect Hypnotic State

Ashraf A. Dahaba, MD, MSc, PhD

Department of Anaesthesiology and Intensive Care Medicine, Graz Medical University, Graz, Austria.

Since its introduction in 1996, the Bispectral Index (BIS) has gained increasing popularity in daily anesthesia practice. However, numerous reports have been appearing in the literature of paradoxical BIS changes and inaccurate readings. The purpose of this review is to assess the utility of BIS monitoring through examining the various published reports of all BIS values not coinciding with a clinically judged sedative-hypnotic state, whether arising from an underlying pathophysiology of electroencephalographic (EEG) cerebral function or because of shortcomings in the performance and design of the BIS monitor. High electromyographic activity and electric device interference could create subtle artifact signal pollution without their necessarily being displayed as artifacts. This would be misinterpreted by the BIS algorithm as EEG activity and assigned a spuriously increased BIS value. Numerous clinical conditions that have a direct effect on EEG cerebral function could also directly influence the BIS value.

(Anesth Analg 2005;101:765–73)

Awareness during general anesthesia can be a very unpleasant experience or could even result in tragic consequences. In October 1996, the Food and Drug Administration (Rockville, MD) approved the Bispectral Index (BIS) monitor (Aspect Medical Systems, Newton, MA) as an accepted measure of the hypnotic effect of anesthetics and sedative drugs. Since its introduction, BIS monitoring has gained increasing popularity in daily anesthesia practice. However, a series of reports have been appearing in the literature of various instances of paradoxical BIS changes and inaccurate readings.

The complete details of the BIS algorithm's core technology have not been published. All we know is that the BIS monitor is a "black box" headset and that the BIS value is merely a reflection of a "head-related" biosignal that correlates with changes in certain hypnotic drug effects. Thus, the BIS cannot be considered a true reflection of the depth of anesthesia nor an independent measure of electroencephalographic (EEG) cerebral function.

The purpose of this review is to assess the utility of BIS monitoring by examining the various published reports of all BIS values not coinciding with a clinically judged sedative-hypnotic state, whether arising from an underlying pathophysiology of EEG cerebral function or because of shortcomings in the performance and design of the BIS monitor.

Several models of the BIS are still being used, namely, the A-1000, A-1050, A-2000, and, lately, the BIS-XP. Among these models there are numerous software algorithm revisions and iterations. We must emphasize that the reported performance of a certain BIS model might not necessarily apply to other models. Furthermore, we emphasize that, obviously, the electrophysiological changes in extreme situations, such as hypoglycemic coma or hypovolemic cardiac arrest, cannot be rigorously tested in controlled studies as being a definitive cause of accompanying BIS changes. Thus, the explanations we present for these particular situations are speculations based on electrophysiological changes in similar studies.

Basic Structure

To understand the BIS as an EEG-derived variable, we have to first understand the fundamental EEG changes that occur with the deepening of propofol target-controlled infusion (TCI) or sevoflurane anesthesia (Fig. 1). During relaxation with the eyes closed, there is an α (7.5–12.5 Hz) wave predominance. Light anesthesia is accompanied by a decrease in the α and an increase in β (12.5–30 Hz) power. With deepening of anesthesia, slow wave activity—namely δ (1.5–3.5 Hz) and θ (3.5–7.5 Hz) waves—increase and become

Accepted for publication March 14, 2005.

Address correspondence and reprint requests to Dr. Ashraf A. Dahaba, Department of Anaesthesiology and Intensive Care Medicine, Graz Medical University, Auenbruggerplatz 29, A-8036, Graz, Austria. Address e-mail to ashraf.dahaba@meduni-graz.at.

DOI: 10.1213/01.ane.0000167269.62966.af

0003-2999/05

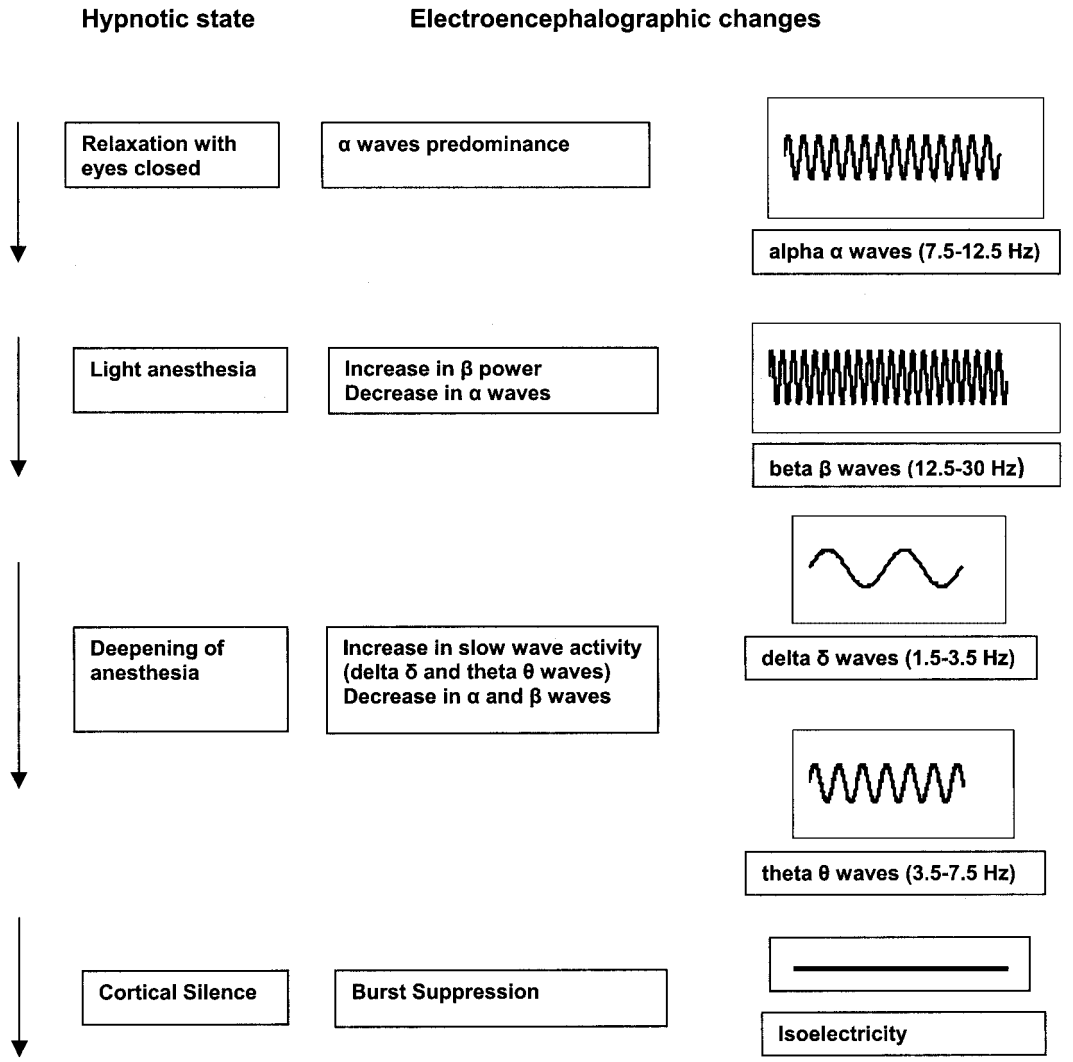

Figure 1. Electroencephalographic changes with deepening of anesthesia.

more prominent, with a simultaneous decrease in the α and β activities in all regions. This represents a decrease in the cortical generator of α and β activities, with a shift toward control by the thalamo-hippocampal-septal generators of δ and θ activities. All these changes are reversed in the same order with the return of consciousness (1).

The BIS is a dimensionless number ranging from 100 (fully awake) to 0 (isoelectric EEG). The BIS is the weighted sum of three descriptors (Fig. 2): Relative BetaRatio, a frequency-domain feature, is the EEG spectral power log ($P_{30-47\ Hz}/P_{11-20\ Hz}$), SynchFastSlow, a bispectral-domain feature, is the bispectral power wave band log ($B_{0.5-47\ Hz}/B_{40-47\ Hz}$), and Burst Suppression is a time-domain feature that quantifies the extent of isoelectrical silence. None of these disparate descriptors is particular *per se* because each has a specific range of effect at which they perform best. BetaRatio is the most influential during light hypnotic states; SynchFastSlow predominates during surgical levels of anesthesia; and Burst Suppression detects very deep anesthesia. The BIS analysis uses a proprietary algorithm that allows the different descriptors to sequentially dominate as the EEG changes character with increasing depth of anesthesia (2).

Paradoxical BIS Changes with Anesthetics

Nitrous Oxide (N_2O)

The first report of paradoxical BIS changes was that of the BIS (A-1000) paradoxically declining, 6 min after N_2O discontinuation, from a mean value of 95–81 (3), and from >90 to 30–50 in another report (4) (Table 1). The simultaneously recorded real time EEG showed an increase in the δ and θ activities (3). This could be attributed to N_2O's peculiar withdrawal-suppression EEG phenomenon, in

Table 1. Effect of Anesthetic Agents, Electric Devices, Different Clinical Conditions, Abnormal EEG Patterns, EMG Activity, and NMBD

Effect (references)	BIS model	BIS change	Explanation
Paradoxical BIS changes with anesthetics			
N_2O termination (3, 4)	A-1000 (3.22), A-1000	Paradoxical BIS ↓	δ, θ waves ↑
Ketamine (7, 11)	A-1050, A-2000 (3.4)	Paradoxical BIS ↑	β waves ↑, δ waves ↓
Isoflurane (13)	A-1000 (3.12)	Paradoxical BIS ↑	α, β waves ↑
Halothane (15, 16)	BIS-XP (4.0), A-1000 (3.21)	High BIS	Different cortical effect
Electric device interference with BIS monitoring			
Atrial pacer (28)	A-1050	BIS ↑	Electric interference
Warming blanket (29, 30)	A-1000 (3.12), A-2000	BIS ↑	Air vibrations
Endoscopic shaver (31)	A-2000	BIS ↑	Shaver oscillations
Electromagnetic system (32)	A-2000	BIS ↑	Electromagnetic interference
Effect of different clinical conditions			
Hypoglycemia (35, 36)	A-2000, BIS-XP	BIS ↓	δ, θ waves ↑, α waves ↓
Cardiac arrest (38, 39)		BIS ↓	Cerebral perfusion ↓
Hypovolemia (40)		BIS ↓	Cerebral perfusion ↓
Cerebral ischemia (41, 42)	A-2000 (2.1)	BIS ↓	Cerebral perfusion ↓
Hypothermia (43)	A-1050	BIS ↓	Isoflurane enhancement
Hypothermia (45)	A-1000	BIS ↓	Propofol enhancement
BIS values modified by abnormal EEG patterns			
Post-ictal (49, 50, 51)	A-1000 (3.31), BIS-XP	Low BIS	δ waves ↑
Alzheimer dementia (53)	A-2000 (4.0)	Low BIS	β waves ↓
Cerebral palsy (54)	A-2000 (3.21)	Low BIS	Abnormal mental function
Severe brain injury (55)	A-2000 (3.4)	Low BIS	Neurological damage
Brain death (56)	A-2000	BIS 0	Isoelectricity
Low-voltage EEG (61)	A-1000 (3.11)	Low BIS	Genetically determined
Effect of EMG and NMBD			
NMBD (73, 74, 75)	A-1000 (3.22), A-2000 (3.12), A-2000 (2.1)	BIS ↓	Alleviating EMG artifact
Succinylcholine (78)	A-1000 (3.31)	BIS ↓	Artifact

EEG = electroencephalographic; EMG = electromyographic; NMBD = neuromuscular blocking drugs; BIS = Bispectral Index.

which 7–10 min from N_2O's sudden discontinuation, an "overswing" of paroxysmal bursts of low-frequency δ and θ waves was shown to diffusely occur throughout the EEG recording, a pattern very similar to that of deep anesthesia (5).

However, N_2O has a weak cortical action, because it acts mainly through activating the descending inhibitory noradrenergic pathway in the brainstem and spinal cord (6). This effect is completely undetectable by the algorithm that computes the BIS. That is why N_2O, both as a sole anesthetic and as an adjunct to IV anesthesia, was shown, in several studies, to result in loss of consciousness without a noticeable change in the BIS A-1000 values (7–9).

Ketamine

Ketamine does not follow the basic EEG pattern of general anesthesia, as it was shown to cause an opposite effect of an increase in the β range activity accompanied by a reduction in the δ power (10). This odd EEG pattern would be reflected by BIS monitoring, as the BIS A-1050 (7) and the BIS A-2000 version 3.4 (11) were reported to paradoxically increase after ketamine administration.

Inhaled Anesthetics

An increase in isoflurane concentrations from 0.79% to 1.26% was shown to cause a "paradoxical arousal reaction" as it results in an increase in the α and the β waves in a pattern similar to that of light anesthesia (12). A similar paradoxical arousal in the mean BIS (A-1000 version 3.12) value from 35 to 46 was reported with the increase of isoflurane concentrations from 0.8% to 1.6%. BIS returned to baseline values with the return to 0.8% (13).

Different inhaled anesthetics have different EEG "signatures." For instance, clinical concentrations of halothane produce slow waves and fast "spindle" EEG rhythms, whereas sevoflurane produces sharp, slow EEG waves with relatively few fast rhythms (14). Consequently, BIS values are not the same for equipotent concentrations of different inhaled anesthetics. With the BIS-XP version 4.0 (15), and BIS A-2000 version 3.21 (16), the mean BIS value of 57 with halothane was significantly higher than a mean BIS value of 32–33 for equipotent sevoflurane (15) or isoflurane concentrations (16). This indicates that the BIS algorithm, which was not written or validated for halothane, does not accurately reflect the hypnotic effect of

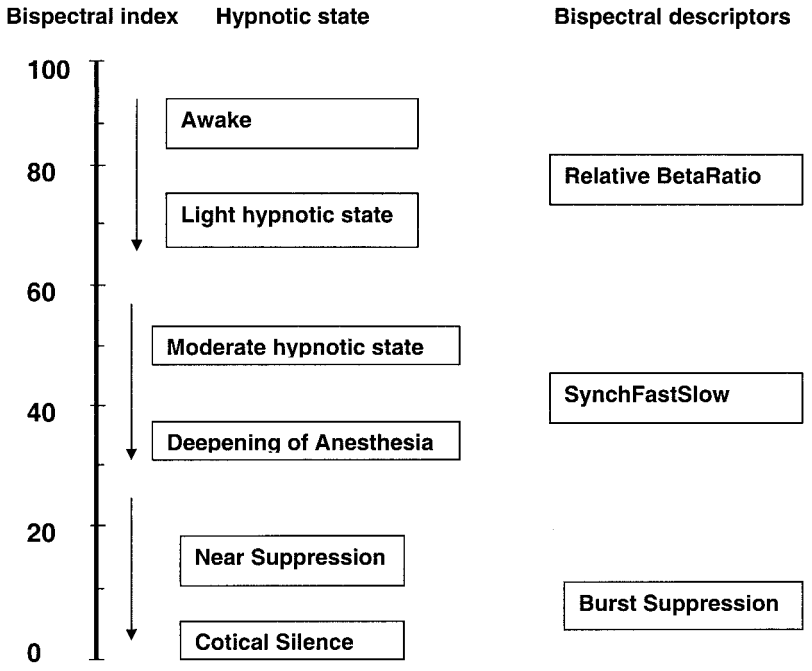

Figure 2. Bispectral Index depth of anesthesia monitoring.

halothane anesthesia and may lead to inadvertent halothane overdose.

Propofol

In 2 volunteers, the BIS (A-1000 version 3.22) was reported to remain unchanged at 35–40 with escalating propofol TCI, despite the simultaneously recorded raw EEG indicating burst suppression (17). The authors of the report speculated that BIS 35–40 could be the "range of uncertainty" or a "blind spot" between the BetaRatio and the Burst Suppression descriptors, where the BIS algorithm could be less sensitive to propofol effect.

The Opioid Effect

Opioid doses of almost 5 times the analgesic concentrations would be required for the appearance of a noticeable EEG depression (18). Unlike IV or inhaled anesthetics, opioids in analgesic concentrations produce minimal or no electrophysiological alterations on the cerebral cortex. This is because "noncortical" structures that are undetectable by the EEG, such as the locus coeruleus-noradrenergic system, are involved in the mechanism of opioid drug effect (19). At constant propofol TCI, remifentanil in escalating concentrations did not change BIS (A-1000 version 3.12) values (20), nor did remifentanil step-by-step reductions change the BIS (A-1000 version 2.0) values (21). This clearly indicates that the BIS monitor is not capable of detecting a direct opioid cortical EEG effect.

However, opioids could still influence BIS monitoring by another peculiar effect, as the addition of fentanyl, sufentanil, remifentanil or alfentanil to TCI propofol resulted in loss of consciousness at smaller propofol effect site concentrations and consequently at higher BIS A-1000 version 3.12 (22), A-2000 version 3.4 (23), and A-1050 (22–25) values. This clearly shows that the hypnotic effect of propofol is enhanced by μ agonist opioids. However, BIS does not show this increased hypnotic effect and would only reflect the lower propofol requirements and hence higher BIS values, which may lead to an inadvertent anesthetic overdose.

Opioids could still directly influence BIS monitoring in a totally different manner, namely, through the attenuation of responses to noxious stimuli. Under constant propofol TCI, μ agonist opioids attenuated increases in BIS (A-1000) in response to tracheal intubation (20), to the pinning of the Mayfield head holder fixator (26), and to endotracheal suction (27). This means that BIS values under a constant level of an anesthetic regimen not only indicate a certain level of hypnosis but also reflect the degree of opioid-induced inhibition of response to noxious stimuli. If BIS suddenly increases in response to a noxious stimulus, this could be a cortical arousal reaction reflecting a deficit in the analgesic component of anesthesia that would require increasing the analgesic doses.

Electric Device Interference with BIS Monitoring

In addition to electrocautery, interference from several electric devices could directly affect BIS monitoring (Table 1). During cardiac surgery under fentanyl-isoflurane anesthesia, BIS (A-1050) increased from 50

to 90 each time atrial pacing was started and decreased when pacing was discontinued. During pacing, the BIS signal quality bar showed poor signal quality indicating that electric interference was responsible for the observed artifact (28).

However, the BIS signal quality bar might not always be helpful, as in numerous occasions when the subtle signal pollution was not detected by the signal quality bar nor displayed as artifacts. For instance, BIS A-1000 version 3.12 (29) and BIS A-2000 (30) were reported to falsely increase from <56 to 70–90 when a forced-air-warming blanket, placed directly on a patient's forehead, was switched on. BIS returned to 35–60 when it was switched off (29,30). Similarly, BIS (A-2000) suddenly increased from 40 to 62 with the start of endoscopic shoulder shaver oscillations and decreased after the shaver device was switched off (31). Furthermore, an otorhinolaryngology positioning system, which created a 20-cm electromagnetic field around the patient's head, was reported to increase the BIS (A-2000) from 40–45 to 60–90 when switched on. BIS immediately decreased to 28–32 with switching the system off (32).

In all the above-mentioned reports, the BIS signal quality indicator displayed "optimal signal quality" in all patients (29–32), whereas, in some cases, the simultaneously displayed raw EEG showed fast moving waves of high amplitudes resembling those of the awake state (30). This clearly indicates that the air-warming-blanket vibrations (30), the shoulder shaver oscillations (31), and the electromagnetic field (32) could have all created minimal vibrations or frequencies in the BIS electrodes simulating the EEG waves of light anesthesia or an awake state. None of these subtle signal pollutions was detected by the BIS monitor and hence were not displayed as artifacts, thus opening the potential for inadvertent anesthetic overdose.

Effect of Different Clinical Conditions on BIS Monitoring

Hypoglycemia

Hypoglycemia of 72 mg/dL causes a small increase in the low-frequency δ and θ waves (Table 1). This proceeds to a widespread increase in the δ and θ waves at 54 mg/dL blood glucose level (33). With a further decrease to 32 mg/dL, the increase in the δ and θ waves is associated with a significant decrease in α waves, a pattern very much similar to that of general anesthesia (34). It comes as no surprise that BIS could reflect these EEG changes, as in 2 separate reports with BIS A-2000 (35) and BIS-XP (36), 2 hypoglycemic coma patients with 35 mg/dL (35) and 21 mg/dL blood glucose levels (36) were reported to manifest BIS values as low as 45. BIS rapidly increased to 80 along with the increase of blood glucose levels and the return of consciousness (35,36). Thus, blood glucose levels should be considered as a contributing factor during interpretation of the BIS values.

Hypovolemic Cardiac Arrest

Real time EEG monitoring is not a part of routine anesthesia monitoring. Thus, there are very few documented cases of EEG changes during the pericardiac arrest period. In one rare, recorded case, real time EEG showed generalized isoelectricity 10 s after the onset of asystole. Low-voltage, high-frequency EEG activity began to return 15–20 s after manual chest compression restored cerebral perfusion and oxygenation with the essentially "standing by" well-oxygenated arterial blood. Return of cardiac rhythm was associated with the return of normal EEG signal (37). Unlike real time EEG, with the increasing use of BIS monitoring in routine anesthesia, we are encountering more cases of documented BIS "witnessed cardiac arrests." In two reported cases, hypovolemic cardiac arrest evoked a parallel decrease in the BIS values to zero with an isoelectric EEG. As arterial blood pressure was restored by volume replenishment, BIS score increased to premorbid levels (38,39). A major difference between BIS monitoring in the first case and real time EEG was that the decrease and increase in BIS lagged 2 min behind the arterial blood pressure, because of the 60-s delay of the "smoothing algorithm" used to calculate the BIS value (38). However, this was not observed in the second case as the gradual decrease of arterial blood pressure over 20 min minimized the lag between the decrease in arterial blood pressure and the decrease in BIS score (39).

BIS changes could even precede hemodynamic changes. In an interesting report, BIS was shown to decrease from a steady value of 35 to 20, 10 min before the decrease of arterial blood pressure from 120/70 to 65/30 in a patient with fatal major bleeding in an aortic graft (40). This BIS "prodromal" change was attributed to the BIS early detection of propofol pharmacokinetics alteration before the actual decrease of arterial blood pressure (40).

Cerebral Ischemia

BIS was shown to successfully reflect the global cerebral ischemia of asystole (38,39) as well as other forms of localized cerebral ischemia and brain injuries. In 2 case reports, BIS decreased from 40–60 to <10 with carotid artery clamping (41,42). The fact that the BIS did not subsequently increase revealed an intracerebral hemorrhage in the first case (41) and severe cerebral ischemia in the second case (42). The BIS (A-2000 version 2.1) later returned to normal values with the restoration of normal cerebral circulation (42).

Hypothermic Cardiopulmonary Bypass (CPB)

In a large group of patients ($n = 100$), during hypothermic CPB under constant isoflurane anesthesia, BIS (A-1050 version 3.3) was estimated to decrease by 1.12 BIS units for each degree Celsius decrease in body temperature (43). Hypothermia produces a linear decrease in inhaled anesthetic requirements. In fact, hypothermia itself serves as a complete anesthetic at 20°C (44). This is attributed to the increase in the solubility of inhaled anesthetics in the lipid membrane with lower temperature, resulting in larger concentrations of anesthetics being available at a cellular level (44), which would result in a BIS decrease.

Similarly, under constant propofol-alfentanil anesthesia, a mean BIS (A-1000) value of 41 was significantly lower during hypothermic CPB than a mean BIS value of 49 during normothermic CPB (45). Hypothermia (25°–27°C) was shown to significantly increase serum propofol concentrations through a decrease in hepatic microsomal enzyme activity and a decrease in propofol biotransformation (46), which would consequently result in a BIS decline.

However, this effect was not consistent among different reports, as during hypothermic CPB ($n = 12$), BIS (A-1000 version 3.12) slightly decreased with decreasing temperature. A possible reason for not finding a consistent association between BIS and temperature could be that the sample size was too small to demonstrate such an effect (47).

BIS Values Modified by Abnormal EEG Patterns

Post-Ictal EEG Patterns

After fully regaining consciousness after electroconvulsive therapy, patients in the post-ictal state display a peculiar EEG pattern in the form of very slow δ waves, a pattern very much resembling deep anesthesia (48) (Table 1). The BIS monitor reflected this "post-ictal suppression state" as patients awakened from propofol anesthesia at drastically low mean BIS (A-1000 version 3.31) values of 45–57 (49,50). Some patients could even open their eyes at a BIS value as low as 7 (50). This post-ictal suppression does not depend on the hypnotic used, as in patients regaining consciousness after electroconvulsive therapy under methohexital anesthesia, the BIS-XP (A-2000) values were still <60 in 75% of the patients at eye opening (51).

Neurological Disorders

The BIS algorithm was developed from volunteers with normal EEG, thus neurological disorders that manifest abnormal EEG patterns would probably affect the BIS monitoring. In patients with Alzheimer's type dementia, who show reduced power in the β band (52), the mean awake BIS (A-2000 version 4.0) was 89 compared with a mean BIS value of 95 in control elderly patients (53). Whereas the mean BIS (A-2000 version 3.21) values both at sevoflurane 1% and after emergence from anesthesia were significantly lower in cerebral palsy mentally retarded children compared with normal children (54). Furthermore, 24 h after all sedative drugs were withdrawn, the mean BIS (A-2000 version 3.4) value was 43 in comatose state intensive care unit (ICU) patients who did not later recover from severe brain injury, whereas the mean BIS value was 63 in those comatose state patients who did later recover from severe brain injury (55).

A BIS (A-2000) value of 0 was shown to accurately indicate brain death (56). However, unlike brain death, cortical cognition of painful stimuli could persist in some permanent vegetative state subjects (57). In a permanent vegetative state patient undergoing dental surgery, BIS (A-1000 version 3.2) values before anesthetic induction were 74–85, indicating neurological damage. BIS decreased to 40–42 with sevoflurane administration and later increased to 98–100 after termination of anesthesia, resembling that of a normal subject (58). This clearly indicates that the BIS is not robust enough to distinguish between integrated and nonintegrated cortical neuron activity. In other words, a high BIS score indicates that the overall level of cortical activity is high, which in a normal subject implies wakefulness, but in a subject with chronic brain disease does not necessarily indicate integrated or meaningful cortical activity.

Low-Voltage EEG

Genetically determined low-voltage EEG variant is defined as EEG amplitude of <20 mV over all head regions. This is a normal variant that occurs in 5%–10% of the population and is not associated with any brain dysfunction (59). The gene responsible for this variant is localized on the distal part of chromosome 20q (60). In an interesting case of a fully conscious volunteer exhibiting an unreasonably low awake BIS (A-1000 version 3.11) value of 40 on 2 separate sessions 3 days apart, a 16-lead EEG showed a genetically determined low-voltage EEG (61). Because the BIS algorithm was developed from volunteers with normal EEG, it is therefore expected that the BIS be misled by this abnormal EEG pattern. Thus, it is essential to confirm a normal BIS value in all patients before induction of anesthesia.

The low-voltage EEG is not restricted to the genetically determined variant, as it could also be drug-induced. The mean BIS (A-1000 version 3.31) value plummeted paradoxically during the remifentanil washout phase in 6 patients (62). The same effect was

reported with 2 different inhaled anesthetics as BIS (A-1050 version 3.4) values decreased from 40–50 to 27–28 during the washout phase of 1.5%–1.6% sevoflurane and the washout phase of 0.9% isoflurane (63). In all of the above-mentioned patients, the simultaneously recorded raw EEG showed a very low-voltage EEG ($\leq$15 μV) that was misinterpreted by the BIS monitor as burst suppression (62,63). Unfortunately, a normal BIS value before induction of anesthesia cannot guarantee a normal BIS performance with this form of drug-induced low-voltage EEG.

Artifact Signals During Isoelectricity

BIS electrodes are intended to detect cortical EEG signals. However, in the absence of EEG signals, as in brain dead subjects, or extreme EEG suppression of deep hypothermia, the BIS algorithm is very vulnerable to a wide range of artifact signals. This was shown in 2 confirmed brain dead subjects (56,64), in whom the BIS score increased from 0–5 to 38. The BIS being exactly synchronized with the subjects' electrocardiography (ECG) signals indicated that the BIS algorithm misinterpreted their ECG signal as EEG activity (56,64).

A similar effect was demonstrated in a 2-mo-old patient undergoing cardiac surgery. During complete isoelectric EEG suppression of deep hypothermic (18°C) circulatory arrest, BIS (A-2000) abruptly increased from 0 to 98–100, indicating radiofrequency pollution. After 10 min of rewarming, BIS returned to 40, indicating that rewarming resulted in resumption of EEG activity that enabled the BIS to discount the radiofrequency noise in the algorithm and appropriately reinterpret the EEG signal (65).

Awareness and Explicit Recall with Different BIS Revisions

A case of explicit recall of intraoperative events under sevoflurane-N_2O anesthesia was reported at a BIS (A-2000) value of 47 (66). Using Tunstall isolated forearm technique (67), 8 patients were reported to be wakeful during propofol-alfentanil anesthesia at BIS (A-1000 version 3.1) values of 50–60, as indicated by purposefully squeezing the anesthesiologist's hand (68). This indicates that a BIS value of around 50 seems to be inadequate in preventing an explicit recall or an awareness reaction. However, when BIS (A-2000 version 3.4) was maintained at a lower BIS level of 40–60, there were only 2 reported cases of awareness among 4945 prospectively examined patients (69) and only 2 cases of awareness in another group of 1225 patients (70). This implies that with lower BIS values of around 40 there would be far less incidence of awareness or recall.

According to the manufacturer, the latest algorithm revision (BIS-XP version 4.0) is a major revision intended to make the BIS more resistant to electrocautery and electromyography (EMG) artifacts. However, 3 volunteers, under propofol-midazolam anesthesia, were recently reported to remain responsive to verbal command at a BIS-XP value of as low as 40 (71). This indicates that the latest algorithm iteration could have resulted in the new BIS-XP providing lower values than the previous BIS models for the same hypnotic level. This may well be the case, as our research group (72) demonstrated, with 2 simultaneously placed BIS monitors, that the mean BIS-XP (version 4.0) value of 33 was significantly lower than the mean BIS (A-2000 version 3.4) value of 40. This clearly indicates that, in addition to all the above-mentioned factors, the choice of the BIS model is a major factor that would greatly influence the interpretation of the BIS value.

Effect of EMG Activity and Muscle Relaxants

High EMG activity and neuromuscular blocking drugs (NMBD) could significantly influence BIS monitoring (Table 1). BIS A-1000 version 3.22 (73) and BIS-XP A-2000 version 3.12 (74) increased from 24–54 to 84–90 with high EMG activity, and later decreased to 30–58 with NMBD administration (73,74). Whereas in ICU patients with high EMG activity, NMBD caused a significant decrease in the mean BIS (A-2000 version 2.10) value from 67 to 43 (75). Furthermore, in 5 confirmed brain dead subjects, BIS increased from 0 to >90 with high EMG activity, before decreasing to 0 with NMBD administration (56).

EMG activities are artifact signals that occur within the frequency "range of interest" of the bispectrum, because the EMG frequencies overlap the BIS algorithm's BetaRatio in the 30- to 47-Hz range. The $EMG_{30-47\ Hz}$ portion was estimated to be one-tenth the magnitude of the $EEG_{30-47\ Hz}$ signal (76). Contamination of BIS by EMG activity is therefore inherent in the calculation of the BIS because EMG frequencies could simulate the 30- to 47-Hz component of the BetaRatio typically associated with awake or light levels of anesthesia. This would be misinterpreted by the BIS algorithm as EEG activity and assigned a spuriously increased BIS value, making deeply anesthetized patients appear more awake than they really are. The administration of NMBD, in that case, would decrease the BIS value by alleviating the artifact and unveiling the true calculated BIS. However, in the absence of EMG activity, the BIS A-1000 version 3.3 (77) and BIS-XP version 4.0 (72) mean value of 40 was unaltered by NMBD administration under propofol TCI anesthesia.

NMBD could still influence BIS monitoring in another manner. Messner et al. (78) volunteered to receive succinylcholine while being fully awake, demonstrating the BIS (A-1000 version 3.31) artifactually decreasing to 33 and to 9 on repeated administration.

In conclusion, high EMG activity and electric device interference could create subtle artifact signal pollution without being necessarily displayed as artifacts. This would be misinterpreted by the BIS algorithm as EEG activity and assigned a spuriously increased BIS value. Numerous clinical conditions that have a direct effect on EEG cerebral function could also directly influence the BIS value.

References

1. Guingo LD, Chabot RJ, Prichep LS, et al. Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflorane. Br J Anaesth 2001;87:421–8.
2. Rampil IJ. A primer for EEG signal processing in anesthesia. Anesthesiology 1998;89:980–1002.
3. Rampil IJ, Kim J, Lenhardt R, et al. Bispectral EEG index during nitrous oxide administration. Anesthesiology 1998;89:671–7.
4. Puri GD. Paradoxical changes in bispectral index during nitrous oxide administration. Br J Anaesth 2001;86:141–2.
5. Henrie JR, Parkhouse J, Bickford RG. Alteration of human consciousness by nitrous oxide as assessed by electroencephalography and psychological tests. Anesthesiology 1961;22:247–59.
6. Zhang C, Davies MF, Guo TZ, Maze MM. The analgesic action of nitrous oxide is dependent on the release of norepinephrine in the dorsal horn of the spinal cord. Anesthesiology 1999;91:1401–7.
7. Hirota K, Kubota T, Ishihara H, Matsuki A. The effects of nitrous oxide and ketamine on the bispectral index and 95% spectral edge frequency during propofol-fentanyl anaesthesia. Eur J Anaesthesiol 1999;16:779–83.
8. Barr G, Jakobsson JG, Oewall A, Anderson RE. Nitrous oxide does not alter bispectral index: study with nitrous oxide as sole agent and as an adjunct to i.v. anaesthesia. Br J Anaesth 1999;82:827–30.
9. Coste C, Guignard B, Menigaux C, Chauvin M. Nitrous oxide prevents movement during orotracheal intubation without affecting BIS value. Anesth Analg 2000;91:130–5.
10. Hering W, Geisslinger G, Kamp HD, et al. Changes in the EEG power spectrum after midazolam anaesthesia combined with racemic or S– (+) ketamine. Acta Anaesthosiol Scand 1994;38:719–23.
11. Vereecke HEM, Struys MMRF, Mortier EP. A comparison of bispectral index and ARX-derived auditory evoked potential index in measuring the clinical interaction between ketamine and propofol anesthesia. Anaesthesia 2003;58:957–61.
12. Clark DL, Hosick EC, Adam N, et al. Neural effects of isoflurane (Forane) in man. Anesthesiology 1973;39:261–70.
13. Detsch O, Schneider G, Kochs E, et al. Increasing isoflurane concentration may cause paradoxical increases in the EEG bispectral index in surgical patients. Br J Anaesth 2000;84:33–7.
14. Constant I, Dubois M, Piat V, et al. Changes in electroencephalogram and autonomic cardiovascular activity during induction of anesthesia with sevoflurane compared with halothane in children. Anesthesiology 1999;91:1604–15.
15. Edwards JJ, Soto RG, Thrush DM, Bedford RF. Bispectral index scale is higher for halothane than sevoflurane during intraoperative anesthesia. Anesthesiology 2003;99:1453–5.
16. Davidson AJ, Czarnecki C. The bispectral index in children: comparing isoflurane and halothane. Br J Anaesth 2004;92:14–7.
17. Bruhn J, Bouillon TW, Shafer SL. Onset of propofol-induced burst suppression may be correctly detected as deepening of anaesthesia by approximate entropy but not by bispectral index. Br J Anaesth 2001;87:505–7.
18. Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology 1991;74:53–63.
19. Pan Y, Li D, Chen S, Pan H. Activation of μ-opioid receptors excites a population of locus coeruleus-spinal neurons through presynaptic disinhibition. Brain Res 2004;997:67–78.
20. Guignard B, Menigaux C, Dupont X, et al. The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation. Anesth Analg 2000;90:161–7.
21. Schmidt GN, Bischoff P, Standl T, et al. Narcotrend, bispectral index, and classical electroencephalogram variables during emergence from propofol/remifentanil anesthesia. Anesth Analg 2002;95:1324–30.
22. Lysakowski C, Dumont L, Pellegrini M, et al. Effects of fentanyl, alfentanil, remifentanil, and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia. Br J Anaesth 2001;86:523–7.
23. Struys MMRF, Vereecke H, Moerman A, et al. Ability of the bispectral index, autoregressive modeling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil. Anesthesiology 2003;99:802–12.
24. Mi WD, Sakai T, Singh H, et al. Hypnotic endpoints vs. the bispectral index, 95% spectral edge frequency and median frequency during propofol infusion with or without fentanyl. Eur J Anaesthesiol 1999;16:47–52.
25. Kodaka M, Okamoto Y, Handa F, et al. Relation between fentanyl dose and predicted EC_{50} of propofol for laryngeal mask insertion. Br J Anaesth 2004;92:238–41.
26. Hans P, Brichant JF, Dewandre PY, et al. Effects of two calculated plasma sufentanil concentrations on the hemodynamic and bispectral index responses to Mayfield head holder application. J Neurosurg Anesthesiol 1999;11:81–5.
27. Brocas E, Dupont H, Paugam-Burtz C, et al. Bispectral index variations during tracheal suction in mechanically ventilated critically ill patients: effect of an alfentanil bolus. Intensive Care Med 2002;28:211–3.
28. Gallagher JD. Pacer-induced artifact in the bispectral index during cardiac surgery. Anesthesiology 1999;90:636.
29. Guignard B, Chauvin M. Bispectral index increases and decreases are not always signs of inadequate anesthesia. Anesthesiology 2000;92:903.
30. Hemmerling TM, Fortier JD. Falsely increased bispectral index values in a series of patients undergoing cardiac surgery using forced-air-warming therapy of the head. Anesth Analg 2002;95:322–3.
31. Hemmerling TM, Migneault B. Falsely increased bispectral index during endoscopic shoulder surgery attributed to interferences with the endoscopic shaver device. Anesth Analg 2002;95:1678–9.
32. Hemmerling TM, Desrosiers M. Interference of electromagnetic operating systems in otorhinolaryngology surgery with bispectral index monitoring. Anesth Analg 2003;96:1698–9.
33. Bjorgaas M, Sand T, Vik T, Jorde R. Quantitative EEG during controlled hypoglycaemia in diabetic and non-diabetic children. Diabet Med 1998;15:30–7.
34. Tribl G, Howorka K, Heger G, et al. EEG topography during insulin-induced hypoglycemia in patients with insulin-dependent diabetes mellitus. Eur Neurol 1996;36:303–9.
35. Wu CC, Lin CS, Mok MS. Bispectral index monitoring during hypoglycemic coma. J Clin Anesth 2002;14:305–6.
36. Vivien B, Langeron O, Riou B. Increase in bispectral index (BIS) while correcting a severe hypoglycemia. Anesth Analg 2002;95:1824–5.

37. Lasasso TJ, Muzzi DA, Meyer FB, Sharbrough FW. Electroencephalographic monitoring of cerebral function during asystole and successful cardiopulmonary resuscitation. Anesth Analg 1992;75:1021–4.
38. Engl MR. The changes in bispectral index during a hypovolemic cardiac arrest. Anesthesiology 1999;91:1947–8.
39. Azim N, Wang CY. The use of bispectral index during a cardiopulmonary arrest: a potential predictor of cerebral perfusion. Anaesthesia 2004;59:610–2.
40. Honan DM, Breen PJ, Boylan JF, et al. Decrease in bispectral index preceding intraoperative hemodynamic crisis: evidence of acute alteration of propofol pharmacokinetics. Anesthesiology 2002;97:1303–5.
41. Billard V. Brain injury under anesthesia: is monitoring of the EEG helpful? Can J Anaesth 2001;48:1055–60.
42. Merat S, Levecque JP, Le Gulluche Y, et al. BIS monitoring may allow the detection of severe cerebral ischemia. Can J Anaesth 2001;48:1066–9.
43. Mathew JP, Weatherwax KJ, East CJ, et al. Bispectral analysis during cardiopulmonary bypass: the effect of hypothermia on the hypnotic state. J Clin Anesth 2001;13:301–5.
44. Antognini JF. Hypothermia eliminates isoflurane requirements at 20°C. Anesthesiology 1993;78:1152–6.
45. Schmidlin D, Hager P, Schmid ER. Monitoring level of sedation with bispectral EEG analysis: comparison between hypothermic and normothermic cardiopulmonary bypass. Br J Anaesth 2001; 86:769–76.
46. Russell GN, Wright EL, Fox MA, et al. Propofol-fentanyl anaesthesia for coronary artery surgery and cardiopulmonary bypass. Anaesthesia 1989;44:205–8.
47. Doi M, Gajraj RJ, Mantzaridis H, Kenny GN. Effects of cardiopulmonary bypass and hypothermia on electroencephalographic variables. Anaesthesia 1997;52:1048–55.
48. Small JG. Psychiatric disorders and the EEG. In: Niedermeyer E, Lopes da Silva, eds. Electroencephalography: basic principles. Clinical applications and related fields. 4th ed. Baltimore: Lippincott Williams & Wilkins, 1999:608.
49. Gunawardane PO, Murphy PA, Sleigh JW. Bispectral index monitoring during electroconvulsive therapy under propofol anaesthesia. Br J Anaesth 2002;88:184–7.
50. Nishihara F, Saito S. Pre-ictal bispectral index has a positive correlation with seizure duration during electroconvulsive therapy. Anesth Analg 2002;94:1249–52.
51. White PF, Rawal S, Recart A, et al. Can the bispectral index be used to predict seizure time and awakening after electroconvulsive therapy? Anesth Analg 2003;96:636–9.
52. Holschneider DP, Leuchter AF, Uijtdehaage SHJ, et al. Loss of high-frequency brain electrical response to thiopental administration in Alzheimer's-type dementia. Neuropsychopharmacology 1997;16:269–75.
53. Renna M, Handy J, Shah A. Low baseline bispectral index of the electroencephalogram in patients with dementia. Anesth Analg 2003;96:1380–5.
54. Choudhry DK, Brenn BR. Bispectral index monitoring: a comparison between normal children and children with quadriplegic cerebral palsy. Anesth Analg 2002;95:1582–5.
55. Fabregas N, Gambus PL, Valero R, et al. Can bispectral index monitoring predict recovery of consciousness in patients with severe brain injury? Anesth Analg 2004;101:43–51.
56. Vivien B, Paqueron X, Le Cosquer P, et al. Detection of brain death onset using the bispectral index in severely comatose patients. Intensive Care Med 2002;28:419–25.
57. Katayama Y, Tsubokawa T, Yamamoto T, et al. Characterization and modification of brain activity with deep brain stimulation in patients in a persistent vegetative state: pain-related late positive component of cerebral evoked potential. Pacing Clin Electrophysiol 1991;14:116–21.
58. Pandit JJ, Schmelzle-Lubiecki B, Goodwin M, Saeed N. Bispectral index-guided management of anaesthesia in permanent vegetative state. Anaesthesia 2002;57:1190–4.
59. Niedermeyer E. The normal EEG of the waking adults. In: Niedermeyer E, Lopes Da Silva F, eds. Electroencephalography: basic principles, clinical applications and related fields. 4th ed. Baltimore: Lippincott Williams & Wilkins, 1999:163.
60. Steinlein O, Anokhin A, Yping M, et al. Localization of a gene for human low-voltage EEG on 20q and genetic heterogeneity. Genomics 1992;12:69–73.
61. Schnider TW, Luginbuehl M, Petersen-Felix S, Mathis J. Unreasonably low bispectral index values in a volunteer with genetically determined low-voltage electroencephalographic signal. Anesthesiology 1998;89:1607–8.
62. Muncaster ARG, Sleigh JW, Williams M. Changes in consciousness, conceptual memory, and quantitative electroencephalographical measures during recovery from sevoflurane- and remifentanil-based anesthesia. Anesth Analg 2003;96:720–5.
63. Hagihira S, Okitsu K, Kawaguchi M. Unusually low bispectral index values during emergence from anesthesia. Anesth Analg 2004;98:1036–8.
64. Myles PS, Cairo S. Artifact in the bispectral index in a patient with severe ischemic brain injury. Anesth Analg 2004;98:706–7.
65. Mychaskiw G, Heath BJ, Eichhorn JH. Falsely elevated bispectral index during deep hypothermic circulatory arrest. Br J Anaesth 2000;85:798–800.
66. Mychaskiw G II, Horowitz M, Sachdev V, Heath BJ. Explicit intraoperative recall at a bispectral index of 47. Anesth Analg 2001;92:808–9.
67. Tunstall ME. The reduction of amnesic wakefulness during Caesarean section. Anaesthesia 1979;34:316–9.
68. Schneider G, Wagner K, Reeker W, et al. Bispectral index (BIS) may not predict awareness reaction to intubation in surgical patients. J Neurosurg Anesthesiol 2002;14:7–11.
69. Ekman A, Lindholm ML, Lennmarken C, Sandin R. Reduction in the incidence of awareness using BIS monitoring. Acta Anaesthesiol Scand 2004;48:20–6.
70. Myles PS, Leslie K, McNeil J, et al. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet 2004;363:1757–63.
71. Vuyk J, Lichtenbelt BJ, Vieveen J, et al. Low bispectral index values in awake volunteers receiving a combination of propofol and midazolam. Anesth Analg 2004;100:179–81.
72. Dahaba AA, Mattweber M, Fuchs A, et al. Effect of different stages of neuromuscular block on the bispectral index and the bispectral index-XP under remifentanil propofol anesthesia. Anesth Analg 2004;99:781–7.
73. Bruhn J, Bouillon TW, Shafer SL. Electromyographic activity falsely elevates the bispectral index. Anesthesiology 2000;92: 1485–7.
74. Baldesi O, Bruder N, Velly L, Gouin F. Spurious bispectral index values due to electromyographic activity. Eur J Anaesthesiol 2004;21:324–5.
75. Vivien B, Di Maria S, Ouattara A, et al. Overestimation of bispectral index in sedated intensive care unit patients revealed by administration of muscle relaxants. Anesthesiology 2003;99: 9–17.
76. Sleigh JW, Steyn-Ross DA, Steyn-Ross ML, et al. Comparison of changes in electroencephalographic measures during induction of general anaesthesia: influence of the gamma frequency band and electromyogram signal. Br J Anaesth 2001;86:50–8.
77. Greif R, Greenwald S, Schweitzer E, et al. Muscle relaxation does not alter hypnotic level during propofol anesthesia. Anesth Analg 2002;94:604–8.
78. Messner M, Beese U, Romstoeck J, et al. The bispectral index declines during neuromuscular block in fully awake persons. Anesth Analg 2003;97:488–91.