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BISPECTRAL INDEX MONITORING

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Monitoring the CNS effects of anesthesia in an objective, reliable fashion has been a holy grail of the specialty for decades. Many previous technologies have been enthusiastically proposed, promoted, and discarded. There has been widespread skepticism regarding the feasibility of monitoring anesthetic depth. Even if such a monitor could be made, would it really be useful in most cases? Sophisticated neurologic monitoring has proved beneficial for a limited subset of surgical applications, but most anesthetics are still provided without any measurement of drug effect on the target organ. Ironically, the most common guide to overall anesthetic effect is usually cardiovascular toxicity.

New monitors are increasingly difficult to justify in this cost-conscious era. Perioperative mortality and serious morbidity rates are rarely attributable to the conduct of anesthesia. Despite dramatic improvements in anesthesia safety, it is unclear whether these benefits are attributable to new monitoring technology, more intense monitoring, newer monitoring standards, or other factors. Most clinicians would agree that anesthetic care has been improved by the addition of new technologies, such as oximetry and capnometry; few would suggest that further progress is unnecessary. In the last few years, more focus has been placed on comprehensive measures of anesthetic outcome, such as efficient use of resources, better patient satisfaction, and more predictable intraoperative and postoperative courses.

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This article provides an updated review of a technology called the Bispectral Index (BIS), a parameter derived from the electroencephalogram (EEG) parameter that was developed specifically to measure patient response during the administration of anesthetics and sedatives. It was approved by the Food and Drug Administration for this use in late 1996; since then, nearly 200 peer-reviewed original articles on BIS have appeared. These studies demonstrate that BIS correlates well with various hypnotic clinical endpoints (e.g., sedation, loss of consciousness, lack of awareness, and memory) and that it can be used effectively to improve patient recovery from anesthesia.[6, 19, 21, 25, 28, 29] Several recent BIS review articles and editorials have appeared.[17, 26, 30] This article provides a broad overview of the clinical development and validation of BIS, and describes how BIS monitoring can be used to improve anesthetic outcomes.

HISTORICAL PERSPECTIVE

Monitoring of the EEG in the operating room has become a well-established procedure for assessing neurologic function in certain high-risk procedures. Since the original descriptions of anesthetic-induced changes in the EEG, numerous studies have reported significant correlation between anesthetic doses and various specific EEG patterns.[7, 18, 51] Several excellent review articles describing the promise and the limitations of EEG monitoring have appeared.[8, 33] Most researchers agree that although the raw EEG may be a useful measure of neurophysiologic function, practical issues preclude its routine use as a monitor of anesthetic effect. More than 15 years ago, Grundy[22] outlined the following factors that limit the use of EEG monitoring during anesthesia:

Expensive, bulky equipment
Need for expert interpretation
Differing effects of various anesthetics
Polypharmacy in clinical practice
Individual variability
Electrically hostile environment
Use of a single EEG channel
Overwhelming amount of data in the raw EEG
Excessive time required to apply electrodes
Difficulty in developing an easily understood data display
Lack of data showing an impact on patient outcomes

Adapted from Grundy BL: EEG monitoring in the operating room and critical care unit: If, when, and what machine? Anesthesiology Reviews 12:73-80, 1985; with permission.

Although significant progress has been made in understanding and overcoming each of these specific limitations, a general perception that these problems still remain insurmountable has long existed in the anesthesia community. One of the greatest challenges facing the introduction of any new EEG monitoring technology is the long legacy of

ineffective products previously touted as monitors of anesthetic depth. The BIS is the first technology to demonstrate that EEG monitoring can be used to assess anesthetic depth in routine clinical practice.

TECHNOLOGIC IMPROVEMENTS

There is a tendency to oversimplify BIS and other processed EEG monitors as boxes with sophisticated algorithms. Many of the problems outlined in the previous list involve the electronic acquisition of artifact-free raw EEG, rapid set-up, and display in a user-friendly format. Any EEG monitor intended for routine operating room use fails unless it first addresses the following fundamental technical issues.

To be useful, the monitor cannot occupy too much of the limited space on an anesthesia machine. It must auto-calibrate and provide accurate physiologic information in seconds in a manner similar to a pulse oximeter or agent analyzer. Advances in microchip technology have eliminated the size and calibration issues for most electronic monitors. The current BIS monitor is a comparatively tiny, free-standing device; and the key circuitry is as small as a brick or plug-in module in many existing, multiparameter monitoring systems.

Another technical hurdle is providing a simple artifact-resistant EEG electrode. The operating room is full of extraneous electrical noise, and detection of the tiny EEG signal requires a dependable, low-impedance electrical contact with the scalp. No matter how good the processing algorithm is, few anesthesiologists would subject patients undergoing routine operations to the traditional gold-cup electrodes, acetone, skin abrasion, and collodion adhesive used by EEG technicians. Bispectral Index monitoring is facilitated by the development of self-prepping electrodes. These devices use a small, plastic sponge embedded in conductive gel to establish good electrical contact with the skin. Electrode impedances less than 5 kohm usually can be achieved without previous skin preparation. The BIS-Sensor uses three or four of these electrodes (to make a single referential lead) on an adhesive strip that also incorporates a printed circuit (Fig. 1). This arrangement allows the monitor to perform an automatic impedance check on each electrode and permits connection to the patient by a single cable. The recommended BIS electrode montage is not part of the standard 10-20 system used in conventional EEG monitoring, but it has the distinct practical advantage of not requiring electrode placement in the hair.

Most EEG processing (e.g., analog to digital conversion, Fourier transformation, bispectral analysis, and so forth) requires substantial computation. Signal-processing software algorithms sample and statistically characterize the vast amount of data contained in the raw EEG signal, and convert it into formats that are understood more easily by the non-EEG expert. Inexpensive semiconductor chips can perform computational tasks that previously required mainframe computers, allowing advanced statistical procedures, such as bispectral analysis, to

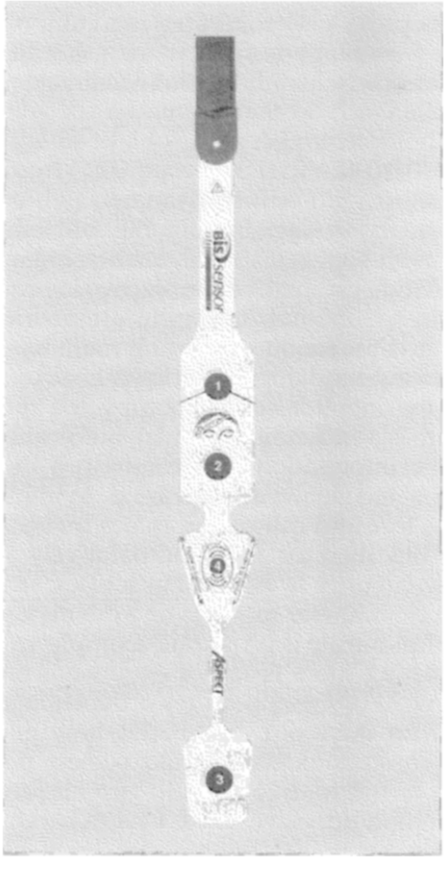

Figure 1. The BIS-Sensor-XP® in its most recent configuration (August, 2001).

be performed in real time.[47] Rampil[41] recently provided a comprehensive review of the basics of EEG processing, including a description of bispectral analysis.

DEFINING THE COMPONENTS OF ANESTHESIA

Until recently, research on depth-of-anesthesia monitors (including the initial research on the BIS) suffered from inadequate or incorrect definitions of the state being measured. General anesthesia aims to produce hypnosis (i.e., sleep, lack of awareness, lack of recall), analgesia (i.e., decreased responses to noxious stimuli), and a quiet surgical field (i.e., lack of movement, muscle relaxation) (Fig. 2). Recent articles and editorials have reviewed the evolution of these components, especially the distinction between hypnosis and analgesia.[40, 51] The distinction be-

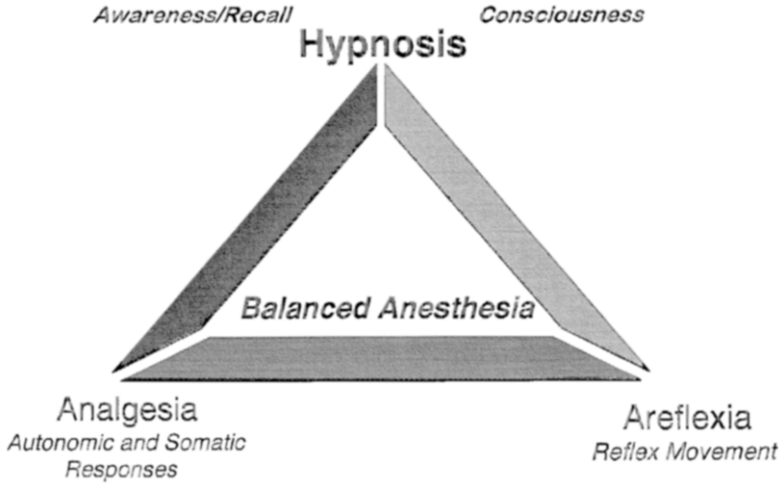

Figure 2. The components of balanced anesthesia.

comes blurry in the operating room, however; patient responses, such as hypertension or movement, do not specifically indicate the need for analgesics versus hypnotics versus vasodilator therapy.

In the initial stages of BIS development, much effort was put unsuccessfully into creating a unique EEG measure that could be used to predict patient movement. The customary way to define *anesthetic potency* for the volatile agents was lack of a movement response to skin incision (i.e., minimum alveolar concentration). Minimum alveolar concentration also was believed to predict amnesia and unconsciousness produced by these drugs. The performance of BIS in these early studies was good for volatile anesthetics but it did not perform as well when the anesthetic included large amounts of opioids.[32, 46] Suppression of movement is largely mediated by anesthetic actions on the spinal cord,[3, 42] and most intravenous hypnotics and analgesics do not have a good correlation between actions on the cord and higher brain centers. Hypnotic drugs, such as thiopental and propofol, may produce sleep and large changes in cortical EEG without suppressing movement; conversely, opioid analgesics may suppress movement at doses that have only small effects on the EEG.[46] The research on BIS was redirected at creating a measure that predicts sedation, hypnosis, awareness, and recall–endpoints likely to be reflected in the cortical EEG.

THEORETIC BASIS FOR THE BISPECTRAL INDEX

Although individual drugs can produce some unique effects on the EEG, the overall pattern of changes is similar for many hypnotic agents.

General anesthesia is associated with a decrease in the average EEG frequency and an increase in the average power. This information can be obtained mathematically from the complex EEG waveform to create the power spectrum. Many attempts have been made to use the power spectrum as a measure of anesthetic effects.[18, 33] The entire power spectrum usually is distilled to a single number that can be used to track the decrease in average EEG frequency (e.g., median frequency, relative δ power, spectral edge, and so forth).

For most anesthetic drugs, however, the changes in frequency and power do not bear a simple, monotonic relationship to dose. For example, low doses of benzodiazepines or propofol usually cause high-frequency activation, resulting in a net increase in power spectrum frequency measures.[51] Large doses of thiopental, propofol, or isoflurane can cause burst suppression and a net decrease in power. Power spectrum-derived measurements most likely become ambiguous when the patient is too lightly or too deeply anesthetized.

The BIS is a single number that incorporates information on EEG power and frequency, but also includes information regarding β activation, burst suppression, and bicoherence. The rationale for BIS and the technical details of its development are presented in more detail elsewhere,[41, 47] but the following three features are worth emphasizing here.

A portion of the cortical EEG reflects activity in deeper structures, and this component changes during sleep. Bispectral analysis determines the components of the EEG that are caused by harmonic and phase relationships (i.e., bicoherence), and can provide more information regarding interactions between cortical and subcortical neural generators. Unique bicoherence patterns in the EEG change with increasing amounts of hypnotic drugs.

The BIS is an empiric, statistically derived measurement. The key hypothesis underlying the development of BIS was that some combination of EEG features (e.g., bispectral, power spectral, or other) could be identified and shown to be highly correlated with sedation and hypnosis, regardless of the agent used to produce that clinical state. The BIS was derived by analyzing a large database of EEGs from subjects who had received one or more of the most commonly used hypnotic agents (Fig. 3). Several EEG features were identified that each characterized some portion of the spectrum of EEG changes as patients went from an awake to a fully anesthetized state. Multivariate, statistical models were used to derive the optimum combination of these features, which then was transformed into a linear, dimensionless scale from 0 to 100 (lower number = more hypnotic effect) (Table 1).[21, 26, 41, 53]

What is a unit of BIS? Todd[53] noted that the BIS is not a real physiologic measurement expressed in mm Hg, μV, or Hz. The same observation could be made about any laboratory assay expressed in arbitrary units (e.g., 1 million U of penicillin). The value of the BIS assay is its ability to quantify changes in the electrophysiologic state of the brain during anesthesia. The BIS correlates with clinical measures of hypnosis, sedation, and recall with high accuracy and reproducibility.

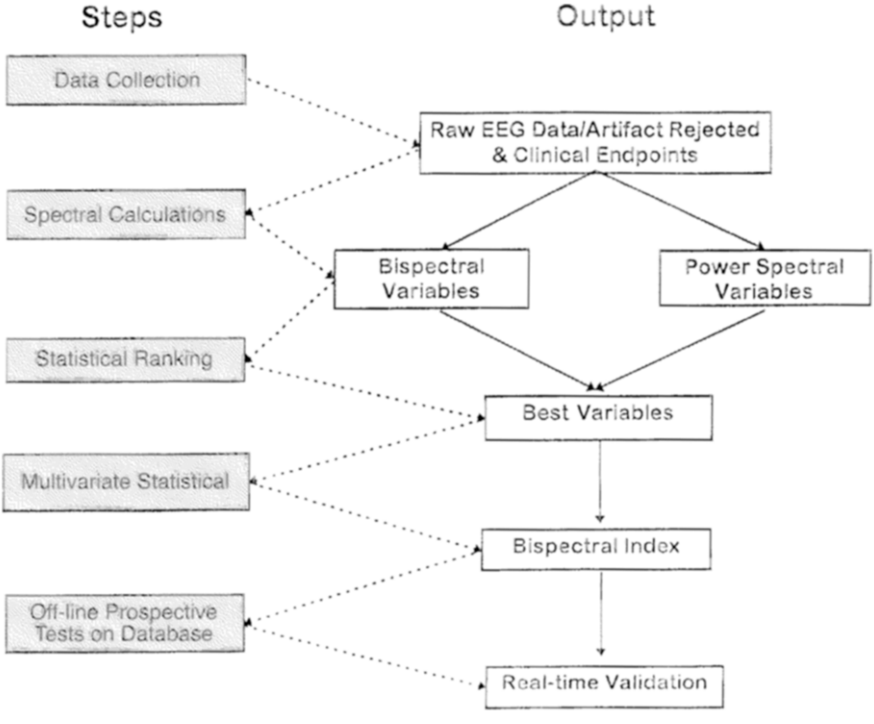

Figure 3. The Bispectral Index (BIS) development process.

Its ability to measure these endpoints is substantially better than assessment by usual clinical signs.

The BIS measures a state of the brain, not a concentration of a particular drug. A low value for BIS indicates hypnosis irrespective of the way it was produced. The BIS can be decreased during natural sleep,[49] although not to the degree (i.e., suppression) caused by high doses of propofol, thiopental, and volatile anesthetics. Alkire[1] has demonstrated that BIS also may be a reflection of the reduced cerebral

Table 1. RELATIONSHIP BETWEEN CLINICAL STATE, PREDOMINANT ELECTROENCEPHALOGRAPHIC PATTERN, AND CORRESPONDING BISPECTRAL INDEX (BIS) RANGES INDUCED BY SEDATIVE AND HYPNOTIC AGENTS

BIS Level	Clinical State	Main EEG Feature
100	Awake Sedated	Synchronized high-frequency activity
60	Moderate hypnotic level	Normalized low-frequency activity (Bispectral feature)
40	Deep hypnotic level	Amount of EEG suppression
0	Isoelectric EEG	Total suppression

metabolic rate produced by most hypnotics. Using positron emission tomography in volunteers receiving isoflurane or propofol, this investigator found a direct correlation between BIS, reduction in whole brain metabolic activity, and degree of sedation.

CLINICAL VALIDATION IN VOLUNTEERS

A series of volunteer trials was conducted to validate BIS as a measure of hypnotic drug effect.[21, 25, 29] Healthy subjects were given increasing doses of propofol, midazolam, isoflurane, or the combinations midazolam-alfentanil, propofol-alfentanil, or propofol-nitrous oxide. The anesthetic agents were increased and decreased in a stepwise fashion, targeting specific effect-site concentrations (Fig. 4). The BIS was measured continuously; at each step, drug concentrations were measured and clinical measurements of sedation, hypnosis, and memory were obtained. The BIS proved to be an extraordinarily good predictor of hypnotic state, and it significantly out-performed measured or targeted drug concentration.[21] For all agents tested, logistic regression curves were constructed to display the probability of response to voice and the probability of free recall as a function of BIS (Fig. 5). Overall, a BIS value

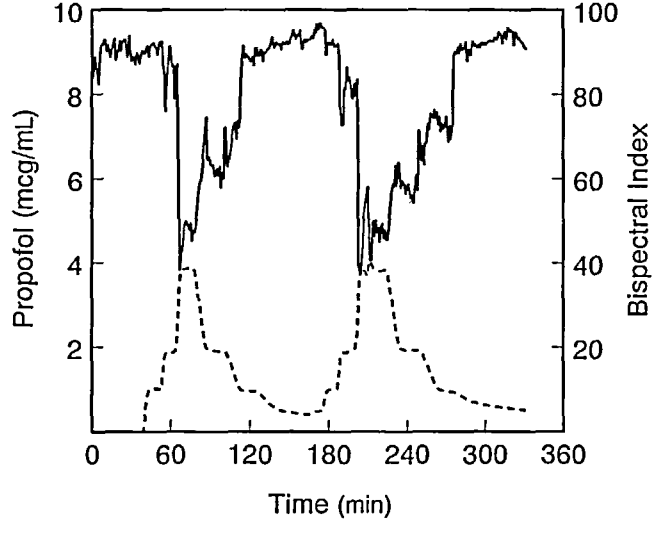

Figure 4. The trend of BIS over time *(solid line)* and its relationship to the predicted effect-site concentration of propofol *(dashed line)* in a single volunteer. A computer-controlled infusion was used to produce different steady-state concentrations of propofol, and BIS was correlated with response to verbal command at each concentration. (*Data from* Kearse LA Jr, Rosow C, Zaslavsky A, et al: Bispectral analysis of the electroencephalogram predicts conscious processing of information during propofol sedation and hypnosis. Anesthesiology 88(1):25–34, 1998.)

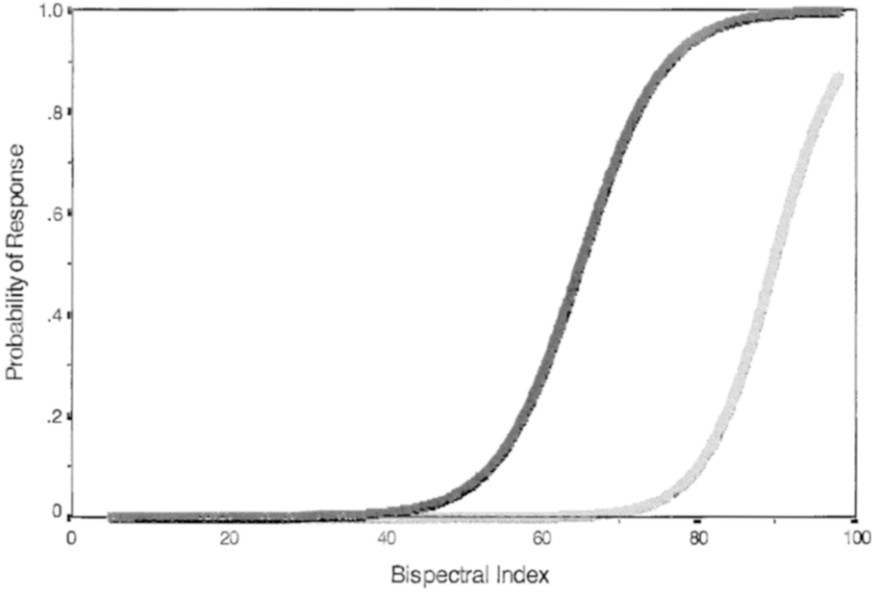

Figure 5. Relationship between BIS and probability of response to verbal command *(black line)* or free recall test *(shaded line)*. Fractional probability of 1.0 = 100%. These relationships were determined using logistic regression analysis for volunteers receiving propofol, isoflurane, or midazolam. (*Data from* Glass P, Bloom M, Kearse LA Jr, Rosow C, et al: Bispectral analysis measures sedation and memory effects of propofol midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology 86:836–847, 1997.)

below 60 is associated with a low probability of response to verbal command. This relationship is nearly identical for all of the hypnotic agents tested, and it does not vary significantly over time or when two anesthetic drugs are combined. Free recall of word or picture cues is lost when the BIS is between 60 and 90, suggesting that memory impairment occurs before loss of consciousness. Lubke et al[36] reported that some residual learning (i.e., implicit memory) can occur at lower BIS levels, although this was not confirmed by Andrade et al.[2]

Caution is warranted about describing BIS as a *predictor* of response. Because BIS is a number derived from the preceding 15 to 30 seconds of EEG data, it is really a measure of the state just before the reading. Under steady-state conditions in a research trial, a given value of BIS predicts subsequent responses to voice command or memory for words. The clinical situation during surgery is different, because future responses depend on the amount of analgesia, changing level of stimulation, and a host of other variables. Brain state, as measured by BIS, may change rapidly in response to strong stimulation.

The volunteer data have been confirmed in other populations undergoing sedation with monitored anesthesia care. Leslie et al[31] reported on

the validity of BIS in volunteers receiving propofol during epidural anesthesia, whereas Liu et al[34, 35] and Avramov and White[4] confirmed these findings in patients sedated with propofol or midazolam. In a large study of the influence of age on hypnotic requirements, Katoh et al[28] demonstrated that the relationship between BIS and the sedative effects of sevoflurane is consistent across a wide range of age groups (Fig. 6). These investigators concluded that BIS predicts depth of sedation better than end-tidal concentration monitoring. The consistent dose-response relationship between BIS and sevoflurane has been confirmed in children by Degoute et al[13] and Denman et al.[14] These studies demonstrate that BIS provides a continuous and consistent age-independent measure of sedation induced by the most widely used sedative-hypnotic agents.

IMPORTANCE OF MONITORING THE HYPNOTIC STATE

Even if a good measuring tool is available, how can it be demonstrated that it is really useful or desirable to monitor hypnosis during anesthesia? Despite the absence of a reliable depth-of-anesthesia measure, anesthesia remains one of the safest and most effective practices in medicine. Some practitioners contend that awareness occurs too infrequently to be of concern and that traditional clinical signs are perfectly adequate measures of patient response. The adequacy of clinical signs is open to debate. There is still significant unpredictability in the delivery of anesthetic care. A small but not insignificant group of patients suffers intraoperative awareness each year, and many more patients undergo

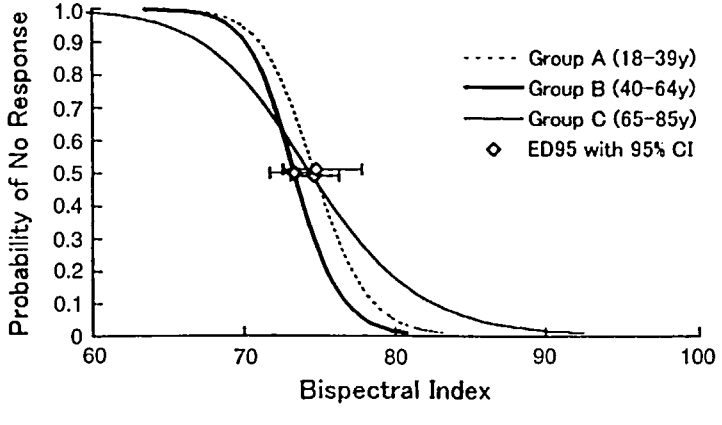

Figure 6. Relationship between BIS and probability of response to verbal command (*fractional* probability of 1.0 = 100%) in patients of various age groups receiving sevoflurane sedation. (*From* Katoh T, Bito H, Sato S: Influence of age on hypnotic requirement, Bispectral Index, and 95% spectral edge frequency associated with sedation induced by sevoflurane. Anesthesiology 92(1):55–61, 2000; with permission.)

prolonged recovery because of a relative overdose of anesthetic drugs used to ensure against intraoperative awareness.

In theory, the use of BIS to monitor brain state, in combination with current monitored parameters and clinical signs, should enable better balancing of hypnotic and analgesic administration. Many published clinical trials have investigated the following proposed benefits of BIS monitoring:

Detection of the return of consciousness intraoperatively
Improved titration of hypnotics based on individual requirements, with a reduction in the incidence of relative underdosing and overdosing
Better recovery, with fewer patients having abnormally long recovery hospital stays
More rational selection of anesthetic interventions (e.g., hypnotics, analgesics, vasoactive drugs).

CLINICAL UTILITY TRIALS IN SURGICAL PATIENTS

Using the isolated forearm technique, Flaishon et al[16] investigated the usefulness of BIS monitoring to predict the recovery of consciousness after induction of anesthesia. After a single bolus dose of propofol or thiopental, BIS was monitored continuously and patients were asked every 30 seconds to squeeze the investigators' fingers. Figure 7 shows

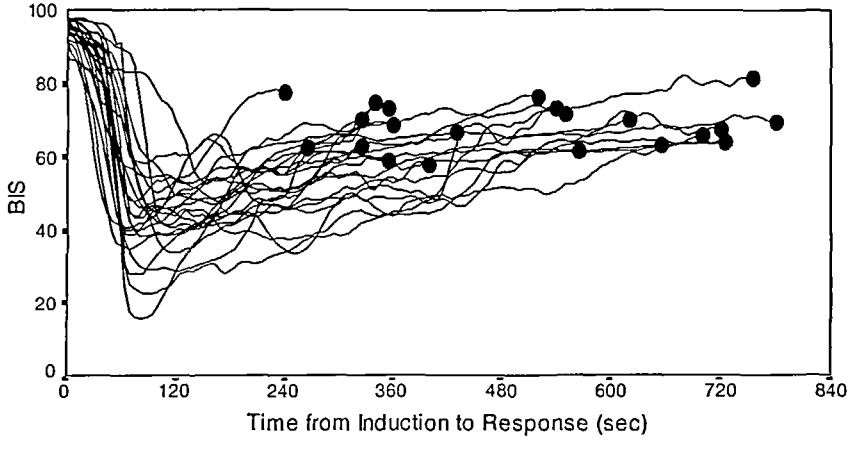

Figure 7. Plot of the BIS over time from induction to recovery of consciousness for subjects receiving a propofol induction dose of 2 mg/kg. Solid circles represent the points when individual subjects responded correctly to the verbal command *squeeze my hand twice.* (*From* Flaishon R, Windsor A, Sigl J, Sebel PS: Recovery of consciousness after thiopental or propofol. Anesthesiology 86(3):613–619, 1997; with permission.)

the BIS data for patients given propofol, 2 mg/kg. Although the intensity and duration of propofol effect varied considerably among patients, the return of response to verbal command occurred consistently when the BIS rose above 60. Changes in blood pressure and heart rate were poor predictors of response. A BIS of less than 65 indicated a probability of less than 5% that consciousness would return within 50 seconds. No patient who responded to verbal command had recall of the episode, confirming the relationships between BIS, responsiveness, and recall observed in the volunteer trials. This study supports the conclusion that a BIS value below 60 is an excellent predictor that a patient is unconscious and will not have recall.

Based on these results, a prospective, multicenter study was undertaken to determine whether the addition of BIS monitoring would improve clinical outcomes relative to standard practice. [19] Nearly 300 patients undergoing general anesthesia for various procedures were studied. The anesthetic technique was standardized for this protocol: a balanced technique using an infusion of propofol, an infusion of alfentanil, and nitrous oxide in oxygen (this technique was selected because it allowed independent titration of hypnosis and analgesia). Two hypotheses underlied this study. During standard practice (i.e., without direct monitoring of hypnosis) patients are given more propofol than needed to produce unconsciousness. Bispectral Index monitoring should reduce propofol usage and improve recovery by making titration more accurate. In skilled hands, this balanced anesthetic technique can produce rapid recovery, so it provides a stringent test of the second hypothesis.

Staff anesthesiologists at four sites participated in this study; all were experienced users of the anesthetic technique. Patients were assigned randomly to BIS versus standard practice groups. The anesthesiologists were told in each case to provide a safe anesthetic with the fastest possible recovery time. In the BIS group, propofol was titrated to produce a BIS between 45 and 60, and this was raised to 60 to 70 during the last 15 minutes of the procedure. In the standard practice group, propofol was titrated by clinical signs, and BIS was not displayed. Alfentanil and muscle relaxants were administered as clinically indicated. Recovery was assessed by study personnel who were blindfolded during the group assignment. The results of this large trial showed that patients monitored by BIS received much less propofol (Fig. 8) and had earlier awakening, faster time to meet postanesthesia care unit discharge criteria, and better global recovery scores (Table 2).[19] There was no increase in unwanted intraoperative events, such as hypotension, hypertension, or movement.

Similar findings using inhalational agents (sevoflurane, desflurane) were reported by Song et al[50] in a prospective, randomized study of female patients undergoing laparoscopic tubal ligation. Compared with standard clinical practice, BIS-guided anesthetic titration resulted in significant (30%-38%) reductions in volatile anesthetic usage and emergence times.

Struys et al[52] conducted a similar comparison trial in 58 patients

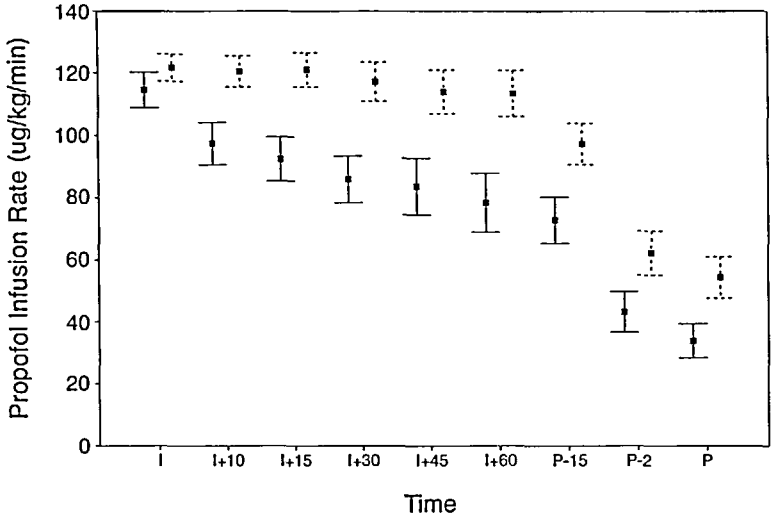

Figure 8. Propofol infusion rates (mean ± 95% confidence interval, in μg/kg/min) at various milestones during surgery in patients randomized to either standard practice *(dashed symbols)* or BIS-monitored *(solid symbols)* treatment groups. I = incision, P = time of propofol discontinuation at end of surgery. (*Data from* Gan TJ, Glass PS, Windsor A, et al, and the BIS Utility Study Group: Bispectral Index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. Anesthesiology 87(4):808–815, 1997.)

receiving computer-controlled propofol infusions for short (~ 30 minutes) surgical procedures. Maintaining a target BIS range of 40 to 60 resulted in a lower incidence of movement events and implicit awareness compared with the standard target-controlled infusion technique. These

Table 2. IMPROVEMENTS IN RECOVERY TIMES ASSOCIATED WITH USE OF BISPECTRAL INDEX (BIS) MONITORING COMPARED WITH STANDARD PRACTICE (SP) IN PATIENTS RECEIVING PROPOFOL, ALFENTANIL, AND NITROUS OXIDE ANESTHESIA

Recovery Endpoint	SP n = 125	BIS n = 115
Opens eyes	10	6*
Responds to commands	10	7*
Extubated	11	7†
Eligible for postanesthesia care unit discharge	38	32‡

Mean recovery time in minutes:
*$P < 0.001$ versus SP.
†$P < 0.01$ versus SP.
‡$P < 0.05$ versus SP.
Data from Gan TJ, Glass PS, Windsor A, et al, and the BIS Utility Study Group: Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. Anesthesiology 87:808–815, 1997.

investigators concluded that the quality of anesthesia was improved using the BIS.

In a similar prospective, randomized, clinical utility study in children undergoing inguinal hernia repairs or tonsillectomies, Bannister et al[6] demonstrated that BIS monitoring was associated with a significant (25%) reduction in sevoflurane administration and a 25% to 40% reduction in recovery times.

Based on these results and several additional prospective, randomized studies that have appeared only in abstract form, it is clear that anesthetic titration using BIS can result in significantly reduced average drug use and faster patient recovery from anesthesia. These benefits are the results of titration and not simply the act of monitoring. A study by Johansen et al[27] of over 1500 patients found that the routine application of BIS monitoring in an operating room improved clinical outcome but only if anesthetic levels were adjusted to maintain a target BIS range of 50 to 65. Applying the BIS monitor without using it to titrate the anesthetic did not confer any recovery improvement relative to unmonitored cases.

INTERPRETATION OF BISPECTRAL INDEX LEVELS DURING ANESTHESIA

The use of any monitor does not obviate the need for critical anesthetic judgment. The clinician should never specify a single blood pressure reading or end-tidal carbon dioxide as optimal for all patients. The data do not suggest that *one BIS fits all*, or that every general anesthetic should be titrated to some specific BIS value. The interpretation of BIS depends on the type of anesthetic and the clinical goals of the anesthetist.

Balanced Anesthesia

In some situations, the clinician can vary the three components of anesthesia (i.e., sleep, analgesia, muscle relaxation) independently. One case might be, for example, a balanced propofol-opioid relaxant technique; assuming that the opioid is used to provide adequate analgesia, BIS can be used to titrate propofol. Similar considerations apply when balanced anesthesia includes a low concentration of potent volatile agent; the inhaled anesthetic is used mainly for its hypnotic effects, and titration of the agent with BIS is likely to be useful.

Inhalational Anesthesia

During a pure inhalational anesthesia (e.g., isoflurane, nitrous oxide, oxygen), titrating the hypnotic effect with BIS may not be possible. In

the absence of an opioid or local anesthetic, the volatile agent usually must be titrated to an analgesic endpoint, and the higher concentrations needed to prevent movement or hypertension may produce low values of BIS. If subanalgesic concentrations of volatile anesthetics are used, BIS values may increase during surgical stimulation. Ropcke et al[43] studied BIS responses in patients who received a pure desflurane anesthetic. Before surgical stimulation 2.2 ± 0.74% desflurane was sufficient to maintain a BIS of 50, whereas 6.8 ± 0.98% desflurane was required to maintain the same target value of BIS during surgery.

Anesthetic Goals

Close titration of hypnosis is not equal for all patients. For the healthy outpatient undergoing a superficial procedure, a light level of hypnosis (i.e., BIS near 60) might be appropriate. The clinician might want a bigger safety margin for a patient undergoing major intraocular surgery. Typical treatment during intraocular surgery involves the use of large anesthetic doses because the consequences of inadequate dosage can be disastrous. The value of BIS in such a case is to allow the clinician to quantify the extra effect he or she is producing. At the other extreme, when BIS is used during monitored anesthesia care, preventing oversedation (BIS < 70) may be the desired goal.

BIS is displayed as a single value and a trend on the monitor. The number is calculated from data gathered over 15 seconds of EEG recording, and this information is updated as a moving average every 2 seconds. Recording the data in this way prevents excessive fluctuations in BIS, and allows a value to be estimated when the signal is interrupted for a few seconds by electrocautery. When abrupt changes occur in hypnotic state (e.g., during induction, rapid emergence), the BIS value lags 5 to 10 seconds behind the clinical change in the patient.

The graphic display of BIS trend over time is particularly useful during maintenance of anesthesia (Fig. 9). Lightening or deepening anesthesia usually manifests as a slow upward or downward trend. Often, the rapid redistribution of a small bolus of propofol can be seen as a short-lived decrease in BIS. When large, abrupt changes in BIS occur, they often are caused by cortical arousal caused by painful surgical stimulation. This situation often occurs when the anesthetic technique relies heavily on hypnotic agents but includes little or no opioid.[23] Even allowing for the 5- to 10-second lag because of signal averaging, surgical stimulation can sometimes produce a rapid increase in BIS before the appearance of other clinical signs, such as hypertension or movement. Clinicians should be cautious when using a particular BIS value in isolation as a predictor of such patient responsiveness, because arousal responses to pain are not well correlated with absolute hypnotic effect. The BIS will track these arousal responses, however.[9]

Cyclic oscillation in BIS under steady-state conditions may provide an indication of the shifting balance between sensory suppression and

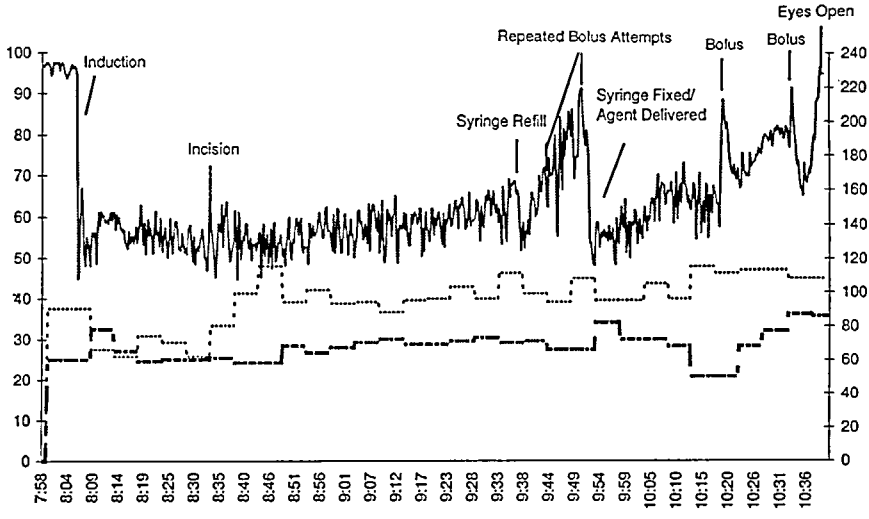

Figure 9. Detection of a malfunctioning infusion pump by the BIS. The graph shows changes in three parameters over time: BIS *(top graph line)* on the left axis, mean blood pressure *(middle graph line)*, and heart rate *(bottom graph line)*, both on the right axis. During this surgical procedure propofol and nitrous oxide were the primary hypnotic agents used. In this case, changes in BIS indicated both the interruption in the propofol infusion and the subsequent response to bolus doses, whereas blood pressure and heart rate did not. (*Data from* Gan TJ, Glass PS, Windsor A, et al and the BIS Utility Study Group: Bispectral Index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. Anesthesiology 87:808-815, 1997.)

stimulation. In volunteer studies, higher BIS variability was observed when only sedatives were used compared with alfentanil used concurrently.

The following physiologic factors also may change the BIS. Cerebral ischemia from any cause can result in a decrease in the BIS if it is severe enough to cause global EEG slowing or suppression. For example, a case report by England[15] described how the BIS can provide information regarding the state of cortical function during hypovolemic cardiac arrest. The frontal montage used for BIS monitoring does not reliably detect episodes of focal ischemia caused by embolic events. It would be inappropriate, for example, to rely on only BIS as a monitor for ischemia during carotid endarterectomy procedures.

Hypothermia (< 33°C) generally results in a significant decrease in BIS levels as brain processes slow. Moderate or profound hypothermia used during cardiac bypass procedures causes suppression of the EEG and low values of BIS. The BIS reflects the synergistic effects of hypothermia and hypnotic drugs. Rewarming during cardiac bypass surgery is usually associated with a rapid rise in the BIS, which is consistent with the previously mentioned correlation between BIS and the cerebral metabolic rate of the brain.

Certain non-EEG electrical signals can corrupt the BIS calculations. Appearance of high-frequency activity from the electromyogram facial (EMG) activity may occur during awakening; EMG is incorporated in several experimental depth-of-anesthesia monitors.[12] The BIS usually increases in conjunction with higher EMG activity, although the presence of EMG is not required for BIS to track the return of consciousness.[16] In this circumstance, administration of a hypnotic or a muscle relaxant can produce a significant drop in BIS. The appearance of EMG activity often occurs during emergence and can be the cause of an elevated value of BIS while the patient remains unresponsive.[11] The EMG contribution is measured and displayed on the monitor and sometimes can be seen in the raw EEG trace.

AWARENESS DURING BISPECTRAL INDEX MONITORING

Awareness with explicit recall during anesthesia is believed to occur in approximately 1 in 500 general anesthetic cases and more frequently during trauma, obstetric surgery, or cardiac surgery.[20] If episodes of awareness without recall (i.e., response to verbal stimulus but no explicit memory of the event) also are considered, the incidence of inadequate anesthesia is probably higher. It is difficult to prove that BIS (or any other monitor) can reduce this risk. As discussed by O'Conner et al,[38] to demonstrate a 50% reduction of awareness with recall (to 1 in 1000 cases), an adequately powered, randomized trial would require over 40,000 patients. It may still be worthwhile to perform such a study in high-risk populations.

Aspect Medical Systems (Natick, MA) has accumulated a large database of anesthetic cases in which BIS monitoring has been used. More than 5000 of these cases were from clinical trials that required completion of case records and recording of continuous BIS trends and raw EEG in archived computer files. More than 10,000 anesthetic cases have been included in independent, investigator-sponsored clinical studies during the past several years. As of January 1, 2001, more than 10,000 BIS monitors have been in routine clinical use, and at least 2.75 million additional anesthetics have been monitored with BIS. Sixty-three cases of possible awareness have been reported to Aspect Medical Systems as of January 1, 2001. In the subset of cases in which access to the trend memory of the BIS monitor was available, it usually could be established that the BIS was greater than 60 close to the time that awareness occurred.[37] Although experience suggests that the risk for intraoperative awareness with BIS values remaining low (< 60) seems to be small, it would be unrealistic to expect that a low value of BIS guarantees lack of awareness. For example, patients with genetically determined low-voltage EEGs or damaged frontal cortices may exhibit abnormal awake EEG patterns that result in an abnormally low BIS.[45]

FUTURE APPLICATIONS OF BISPECTRAL INDEX MONITORING

Most research regarding the use of BIS monitoring has been conducted in volunteers and patients undergoing surgical anesthesia and sedation. Because BIS is an empiric measure, it is only as good as the database from which it is derived. As the use of the technology grows, so will the need to validate it for new anesthetic drugs and new patient populations.

Considering the widespread use of sedation and anesthesia in ICU settings and for procedures performed outside the operating room, many other potential applications must be investigated. In the ICU, excessive sedation has tremendous medical and economic consequences. Initial studies using BIS in the ICU[48] and for conscious sedation in various procedural settings[5, 10, 44] have been promising, and more trials are ongoing to assess the benefits of BIS monitoring for these purposes.

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