MONITORING CONSCIOUSNESS

Using the Bispectral Index™ (BIS™) brain monitoring system

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MONITORING CONSCIOUSNESS

Using the Bispectral Index™ (BIS™) brain monitoring system during anesthesia

A POCKET GUIDE FOR CLINICIANS

THIRD EDITION

LEARNING OBJECTIVES

After reading this guide, the anesthesia clinician will be able to:

- Describe the link between anesthetic sedative and hypnotic effects, EEG signals, and the Bispectral Index™ value
- Integrate BIS™ monitoring system information during induction, maintenance, and emergence
- Identify special situations that can influence BIS™ monitoring technology
- Formulate responses to sudden BIS™ monitoring system changes occurring during anesthesia
- Summarize the evidence-based impact of using the BIS™ monitoring system during the management of anesthesia care
- Recommend a role for the BIS™ monitoring system in a strategy to reduce the risk of postoperative delirium
- List resources and pathways to access additional clinical support for BIS™ monitoring technology

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EXECUTIVE OVERVIEW AND KEY POINTS

Bispectral Index™ (BIS™) monitoring systems allow anesthesia professionals to access processed EEG information to measure the effect of certain anesthetics during patient care. The clinical impact of the BIS™ monitoring system has been demonstrated in randomized controlled trials that reveal the potential of the BIS™ monitoring system to improve anesthesia care — and patient safety.

Because the BIS™ monitoring system may be new to some anesthesia professionals, it's important to recognize the fundamentals of BIS™ technology and how they relate to the patient's clinical status. The situations and limitations that can influence the BIS™ monitoring value should also be reviewed before using the BIS™ monitoring system information in anesthesia care.

A more in-depth discussion of the following key points can be found in this guide:

- **BIS™ Monitoring Value: A Processed EEG Parameter with Clinical Validation (page 5)**

  The BIS™ monitoring value is the output from advanced EEG signal analysis offered by Covidien LP, a Medtronic company. During signal analysis, multiple characteristics of the EEG are identified. The BIS™ algorithm was developed to quantify the changes in these EEG features that best correlate with drug-induced changes in the clinical state.

- **BIS™ Monitoring System Clinical Range: A Continuum Concept (page 7)**

  The BIS™ monitoring value is a dimensionless number scaled to clinical endpoints as well as specific EEG features. Awake, unsedated, healthy individuals typically have BIS™ monitoring values >90. With progressive deepening of the drug-induced sedative effects, the BIS™ value declines. BIS™ monitoring values should be interpreted with this continuum in mind. A BIS™ monitoring value of 60 has a high sensitivity for identifying drug-induced unconsciousness. However, in some settings and with some combinations of sedatives and analgesics, unconscious individuals may have BIS™ monitoring values >60. BIS™ monitoring values <30 signify increasing amounts of EEG suppression. A BIS™ monitoring value of 0 represents an isoelectric EEG signal.

- **Using the BIS™ Monitoring System During General Anesthesia (page 11**)
  - General anesthesia involves administering anesthetics to induce and maintain unconsciousness. It then requires reducing and/or discontinuing the anesthetics to allow emergence and return of consciousness. Anesthesia professionals should appreciate that in most clinical investigations using the BIS™ monitoring system to guide anesthetic dosing, the primary maintenance anesthetic was adjusted to maintain BIS™ monitoring values <60 during surgery.
  - BIS™ monitoring system information is useful in various clinical situations that develop during anesthesia. Clinicians should be prepared to assess and respond to unexpected changes in the BIS™ monitoring values. Assessment of the BIS™ monitoring system information is best done in conjunction with the other standard hemodynamic parameters as well as the patient assessment and the clinical events.
- **Special Issues Impacting the BIS™ Monitoring System (page 18)**

  It is important to understand that several clinical situations can influence the accuracy of the BIS™ monitoring value as an indicator of anesthetic hypnotic effect. Four key areas include: the influence of muscle tone (EMG) from the forehead muscles; electrical and mechanical artifacts from other medical devices; abnormal EEG states; and certain anesthetic agents and may artifactually elevate BIS™ monitoring values.

Serious clinical conditions requiring prompt response, e.g., hypotension, have been associated with the sudden appearance of low BIS™ monitoring values.

- **Clinical Impact of the BIS™ Monitoring System (page 24)**

  A substantial number of randomized controlled trials demonstrate the impact of BIS™ monitoring-guided anesthesia care on patient outcomes. Compared with standard clinical practice, adjusting anesthetic dosing to maintain BIS™ monitoring values within a target range (45 to 60) has been shown to reduce anesthetic dosing, emergence, and recovery times. BIS™ monitoring system during anesthesia may also be associated with the reduction of the incidence of awareness with recall in adults during general anesthesia and sedation.

- **BIS™ Monitoring System and Postoperative Delirium (page 27)**

  Postoperative delirium is a common surgical complication, occurring in 20% to 60% of patients depending on the patient group and type of surgery. Postoperative delirium is particularly common among older patients. Two randomized clinical trials demonstrated the effectiveness of BIS™ monitoring-guided anesthetic titration in helping reduce the risk of postoperative delirium when compared to routine care. Clinicians may wish to consider this evidence when developing patient-specific strategies to avoid postoperative delirium in the elderly and other patients at risk of delirium.

More recent information and additional clinical, educational and training resources can be accessed at covidien.com/pace/clinical-education/channels/brain-function-monitoring. If you require clinical information on the use of the BIS™ monitoring system, please contact Covidien LP, a Medtronic company at: RMSEducation@Covidien.com.

IMPORTANT INFORMATION ABOUT USING THE BIS™ MONITORING SYSTEM

The BIS™ EEG-based monitoring system is intended for use under the direct supervision of a licensed healthcare practitioner or by personnel trained in its proper use. The system, and all its associated parameters, is intended for use on adult and pediatric patients greater than four years of age within a hospital or medical facility providing patient care to monitor the state of the brain by data acquisition of EEG signals.

The BIS™ monitoring value is one of the output parameters. It may be used to help monitor the effects of commonly used anesthetic agents. Its use with these anesthetic agents: propofol, sevoflurane, desflurane, isoflurane, dexmedotomidine may be associated with a reduction in anesthetic dosing and a reduction in emergence and recovery time.

Use of the BIS™ monitoring value to help guide anesthetic administration may be associated with the reduction of incidence of awareness with recall in adults during general anesthesia and sedation.

BIS™ technology is a processed form of EEG monitoring technology intended for use as an adjunct to clinical judgment and training. Clinical judgment should always be used when interpreting BIS™ monitoring values in conjunction with other available clinical signs. **Reliance on BIS™ monitoring values alone for intraoperative anesthetic management is not recommended.** As with any monitored parameter, artifacts and poor signal quality may lead to inappropriate BIS™ monitoring values. Potential artifacts may be caused by poor skin contact (high impedance), increased muscle tone or rigidity, head and/or body motion, sustained eye movements, improper BIS™ sensor placement, and unusual or excessive electrical interference. BIS™ monitoring values should also be interpreted cautiously with certain anesthetic combinations, such as those relying primarily on either ketamine or nitrous oxide/narcotics to produce unconsciousness. Due to limited clinical experience in the following applications, BIS™ values should be interpreted cautiously in patients with known neurological disorders and those taking psychoactive medications.

THE BIS™ MONITORING VALUE — A CLINICALLY VALIDATED PROCESSED EEG PARAMETER

The BIS™ monitoring value is a processed EEG parameter with extensive validation and demonstrated clinical utility.[1–5] It is derived using a composite of measures from EEG signal processing techniques, including bispectral analysis, power spectral analysis, and time domain analysis. These measures were combined via an algorithm to optimize the correlation between the EEG states and the clinical effects of anesthesia, and to quantify these effects using the BIS™ monitoring value.

The use of the BIS™ monitoring system to guide anesthetic administration and monitor patient status is a clinical decision. It is the responsibility of each clinician to make clinical practice decisions that are in the best interest of the patient.

Today, the BIS™ monitoring system remains the most studied form of consciousness or brain function monitoring used within the clinical context of anesthesia and sedation care. BIS™ monitoring values are the result of two particular innovations: bispectral analysis and the BIS™ monitoring algorithm.

Bispectral analysis is a signal processing methodology that assesses relationships among signal components and quantifies synchronization within signals like the EEG. By quantifying the correlation between all the frequencies within the signal, bispectral analysis yields an additional EEG facet of brain activity.[6]

The BIS™ monitoring algorithm was developed to combine EEG features (bispectral and others) that correlated highly with sedation/hypnosis in EEGs from more than 5,000 adult subjects. The four key EEG features characterizing the full spectrum of anesthetic-induced changes were[7]:

- Degree of high-frequency (14 to 30 Hz) activation
- Amount of low-frequency synchronization
- Presence of nearly suppressed periods within the EEG
- Presence of fully suppressed (i.e., isoelectric, "flatline") periods within the EEG

The algorithm enables the optimum combination of these EEG features to provide a reliable processed EEG parameter of anesthetic and sedative effect — the BIS™ monitoring value (Figure 1).

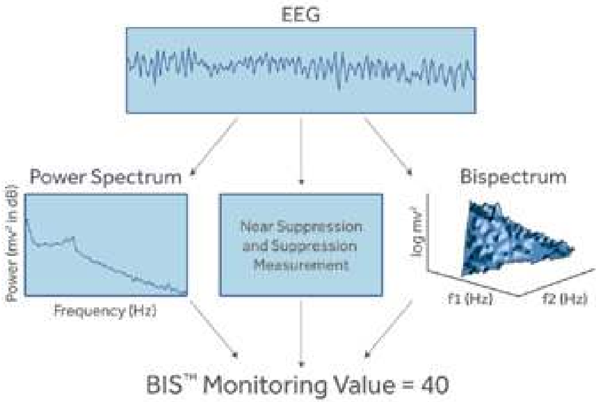


Figure 1. The BIS™ monitoring algorithm, developed through statistical modeling, combines the contribution of each of the key EEG features to generate the scaled BIS™ monitoring value.

THE BIS™ MONITORING VALUE RANGE — A CONTINUUM

The BIS™ monitoring value is a number between 0 and 100 scaled to correlate with important clinical endpoints and EEG states during administration of anesthetic agents (Figure 2).

BIS™ monitoring values near 100 represent an "awake" clinical state while 0 denotes the maximally suppressed EEG effects (i.e., an isoelectric EEG).

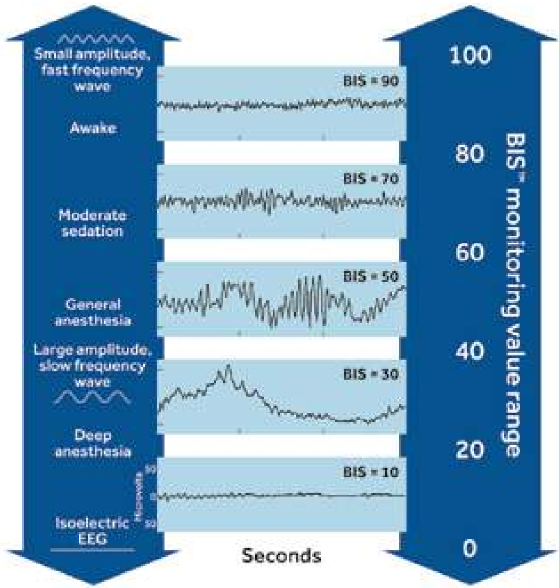


Figure 2. The BIS™ monitoring value is scaled to correlate with important clinical endpoints during administration of anesthetic agent.

It should be noted that the BIS™ monitoring value range represents a continuum that correlates to the clinical state and expected responses of the brain state to the administration of sedative hypnotic drugs. (Figure 3).

BIS™ MONITORING VALUE RANGE	
100	**Awake** Responds to normal voice
80	**Light/moderate sedation** May respond to loud commands or mild prodding/shaking
60	**General anesthesia** ▪ Low probability of explicit recall ▪ Unresponsive to verbal stimulus
40	**Deep hypnotic state**
20	**Burst suppression**
0	**Flatline EEG**

Figure 3. BIS™ monitoring value range: a continuum of clinical state and EEG changes. This chart reflects an established association between clinical state and BIS™ monitoring values. Ranges are based on results from a multicenter study of BIS™ monitoring values involving the administration of anesthetic agents.[8] Recommended BIS™ monitoring values and ranges assume that the EEG is free of artifacts that can affect its performance. Titration of anesthetics to the BIS™ monitoring value should be dependent on the individual goals established for each patient. The goals and associated BIS™ monitoring values may vary over time and in the context of patient status and treatment plan.

As BIS™ monitoring values decrease <70, memory function is markedly impaired and the probability of explicit recall decreases significantly.[9] During sedation care, BIS™ monitoring values >70 may be observed during apparently adequate levels of sedation. At these levels, however, there may be a greater probability of consciousness and potential for recall.[9]

In volunteer studies, a threshold of BIS™ monitoring value <60 has a high sensitivity to reflect unconsciousness.[10,11] As noted previously, the specificity of this threshold value may be dependent on the anesthetic technique utilized — particularly with the combination of opioid analgesics.[8] In prospective clinical trials it has been demonstrated that maintaining BIS™ monitoring values in the range of 45 to 60 ensures adequate hypnotic effect during balanced general anesthesia while improving the recovery process.[1,12] Similarly, in two large prospective trials, maintaining BIS™ monitoring values <60 was associated with reducing the incidence of intraoperative awareness compared to routine standard care.[13,14]

BIS™ monitoring values <40 signify deeper anesthetic effects on the brain state and resultant EEG state. BIS™ monitoring values <40 are associated with negative outcomes. In patients monitored using BIS™, increased stroke, myocardial infarction, and mortality were associated with BIS™ monitoring values <40 for more than 5 minutes.[15] Maintaining BIS™ monitoring values ≤40 during laparoscopic surgery was associated with reduced postoperative cognitive function.[16] At very low BIS™ values, the degree of EEG suppression is the primary determinant of the BIS™ monitoring value.[17] A BIS™ monitoring value of 0 occurs with detection of an isoelectric EEG signal.

BIS™ monitoring value responses are similar when most, but not all, anesthetic agents are administered in increasing amounts. Specifically, the BIS™ monitoring system responses to commonly used hypnotic agents (midazolam, propofol, thiopental, isoflurane) were similar and consistent across all EEG states.[11,18] However, halothane has been found to have higher BIS™ monitoring values at an equipotent minimum alveolar concentration dose.[19] Further, the BIS™ monitoring value responses to ketamine administration are atypical because of the high frequency EEG signature characteristics, unique to this particular drug.[20]

The BIS™ monitoring system responses to administration of analgesic agents that have minimal hypnotic EEG-related effects — opioid analgesics and nitrous oxide — are dependent on the level of concomitant noxious stimulation. The synergistic effects of opioids and maintenance anesthesia agents may allow for a reduced dosing of maintenance drug administration.

BIS™ monitoring values may reflect the reduced cerebral metabolic rate produced by most hypnotics. A significant correlation between BIS™ monitoring values and reduction in whole brain metabolic activity due to increasing anesthetic effect was measured using positron emission tomography (PET; Figure 4).[19] However, factors other than drug administration can influence brain metabolism (e.g., temperature, hypoxia, ischemia) may also produce changes in the BIS™ monitoring value.

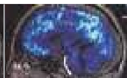
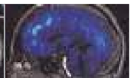
PET				
% BMR	100	64	54	38
BIS™ value	95	66	62	34

Figure 4. Significant correlation is seen between decreasing brain metabolic rate (% BMR = percent of initial whole-brain glucose metabolism measured from PET scan) and increasing anesthetic effect (as measured by decreasing BIS™ monitoring value).[21]

Finally, it is important to note that the BIS™ monitoring value provides a measurement of brain state derived from the EEG changes in response to changes in the brain state. BIS™ monitoring values do decrease during natural sleep as well as during administration of a sedative or an anesthetic agent.[22]

BIS™ MONITORING SYSTEM DURING TYPICAL GENERAL ANESTHESIA

The BIS™ monitoring system provides potentially useful information during each of three phases of a "typical" general anesthetic case:

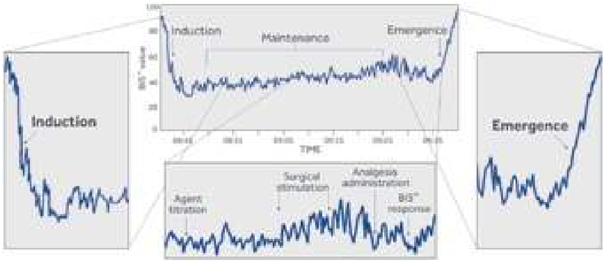
- Induction of anesthesia (including airway management)
- Maintenance of anesthesia
- Emergence from anesthesia

The BIS™ system displays the BIS™ monitoring value as a numerical value, calculated from data gathered over the last 10 to 30 seconds of raw EEG recording and updated every second. Deriving the BIS™ monitoring value from several seconds of EEG data effectively "smooths" the data to prevent excessive fluctuations in BIS™ monitoring values. It also allows a value to be determined even if the EEG signal is briefly interrupted. Most BIS™ systems allow the user to change the smoothing rate to one most appropriate to the current clinical environment.

BIS™ monitoring values, while extremely responsive, are not instantaneously altered by changes in the clinical status. When abrupt changes occur in hypnotic state — for example, during induction or rapid emergence — the BIS™ monitoring value may lag behind the observed clinical state by approximately 5 to 15 seconds depending on the smoothing rate used.

Most BIS™ systems also display a graphical trend of the BIS™ monitoring value plotted over time, every five seconds — the BIS™ monitoring value trend (Figure 5) — which represents the BIS™ monitoring values calculated and plotted throughout the entire monitoring period. Figure 5 uses the BIS™ monitoring value trend to present the information available during each of the three phases of a general anesthetic case.

Figure 5. BIS™ monitoring technology during a general anesthetic case.



BIS™ Monitoring During Induction

- BIS™ monitoring technology may be useful to gauge response to intravenous induction dose.[23]
- BIS™ monitoring system responses are sensitive to agents that influence intravenous induction of anesthesia.[24,25]
- During inhalation induction, BIS™ monitoring values reveals interpatient variability of onset time, as well as the effects of other medications or strategies.[26-28]
- The BIS™ monitoring system can facilitate different strategies for intubation or placement of various airway devices (e.g., laryngeal mask).[29]
- The BIS™ monitoring system responses during intubation are also important. History of and anticipated difficult intubation are risk factors for intraoperative awareness.[28] Prolonged intubation attempts may result in decreased hypnotic effect from the induction agent without obvious somatic movement.
- Because of these considerations, a good strategy is to implement BIS™ monitoring prior to induction along with the standard patient monitors (ECG, blood pressure, SpO_2, capnography) before induction to individualize patient care during both induction and airway management.

BIS™ Monitoring During Maintenance

- In response to noxious stimulation, BIS™ monitoring responses may be observed either parallel with or independent from hemodynamic responses.[23,31,32]
- Clinical trials demonstrate that adjustment of anesthetic dosing to maintain BIS™ monitoring values within a target range of 45 to 60 during anesthesia maintenance results in improved recovery patterns as compared with standard anesthesia care.[1-5]
- BIS™ responses to stimulation may be markedly attenuated in a dose-dependent fashion with opioid administration, e.g., fentanyl or remifentanil.[33]
- BIS™ monitoring value variability — the cyclic oscillation in BIS™ monitoring values during surgery — may be useful to observe. Both short-term BIS™ variability and BIS™-derived EMG activity have been useful in assessing the adequacy of analgesia in surgical patients. In volunteers, opioid analgesia reduced BIS™ variability.[11,34-36]
- Abrupt, unexpected changes in the BIS™ monitoring trend warrant additional assessment and clinical correlation. (Tables 1 and 2.)

BIS™ Monitoring Technology During Emergence

- BIS™ monitoring permits reduction in anesthetic drug dosing in tandem with the decrease in surgical stimulation, promoting a rapid emergence that avoids premature recovery of consciousness as well as delayed emergence from anesthesia.
- The BIS™ monitoring trend will reflect the decreasing hypnotic effect when anesthetic agent delivery is reduced or stopped at the end of surgery.
- BIS™ monitoring values during emergence are variable and:
  - May increase gradually in response to a reduction in anesthetic dose (e.g., end-tidal agent concentration)

- May increase rapidly to values >60 prior to return of consciousness, particularly if EMG tone increases substantially
- Are typically lower immediately after emergence than at baseline, consistent with residual drug effect

- With adequate analgesia, a patient may remain unconscious and display BIS™ monitoring values <60 despite low concentration of hypnotic agent (indicates patient sensitivity to the agent dose) until additional stimulation is provided (e.g., oropharyngeal suctioning, positioning).
- High BIS™ monitoring values in an unresponsive patient could result from EMG artifact or from residual NMB effect.
- The BIS™ monitoring value may abruptly drop after termination of anesthetic administration. This is an EEG phenomenon referred to as paradoxical arousal. The termination of anesthesia would presume the BIS™ value to increase, hence the term paradoxical. There is no clinical correlation and the state resolves spontaneously. This phenomenon happens even when system BIS™ monitoring system is not used. It is only identified by brain monitoring of the patient.

Integrating BIS™ Monitoring System Information During Anesthesia Care

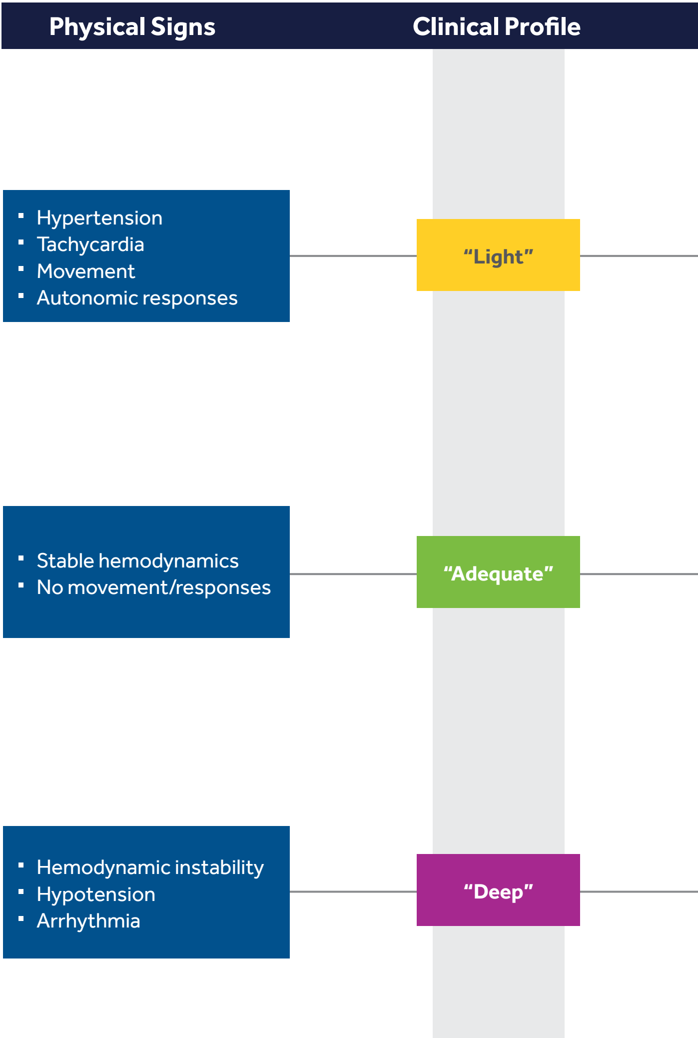
The integration of BIS™ monitoring technology with other traditional monitoring parameters has created new paradigms for intraoperative patient assessment and management.[37-39] Figure 6 outlines conceptual management strategies based on the integration of the clinical profile with BIS™ monitoring data for "balanced" anesthesia techniques utilizing both hypnotic and analgesic components. Using the BIS™ monitoring value in combination with hemodynamic data and patient assessment can facilitate a better-informed selection of sedatives, analgesics, and autonomic agents.

Although a BIS™ monitoring value of 45 to 60 is a typical target during the maintenance phase, the BIS™ monitoring value target range needs to be tailored to the anesthetic technique. For example, during balanced anesthesia including opioid administration to provide adequate analgesia, a target range of 45 to 60 may be very appropriate. However, for anesthesia using little or no opioid or analgesic supplementation, the range will be different. Increasing the hypnotic agent — typically, a volatile anesthetic — to produce acceptable suppression of a noxious stimulation response (e.g., movement) will result in lower BIS™ monitoring values, commonly less than 40.

No single anesthetic technique is appropriate for every patient or clinical situation. That's why the optimum use of BIS™ monitoring to guide anesthesia care will depend on the clinical goals of the anesthesia professional. Given this consideration and agent-specific BIS™ monitoring responses (discussed earlier in greater detail), no single BIS™ monitoring value or range can be recommended as appropriate for all patients, conditions, and anesthetic techniques.

It is important to emphasize that reliance on BIS™ monitoring technology alone for intraoperative anesthetic management is not recommended. Clinical judgment is crucial when interpreting BIS™ monitoring data. Patient assessment should include evaluation of BIS™ monitoring data with hemodynamic and other monitoring data, as well as observation of clinical signs. The BIS™ monitoring value is an additional piece of information to be incorporated with other standard monitoring parameters available for patient assessments.

Figure 6. Anesthesia management strategies using the BIS™ monitoring value.



BIS™ Monitoring Value†	Management Strategy
High value	▪ Assess level of surgical stimulation ▪ Confirm functional delivery of hypnotics/analgesics ▪ Consider ↑ hypnotic/↑ analgesic dosing ▪ Consider antihypertensive administration
Desired range (e.g., BIS™ monitoring value 45 to 60)	▪ Assess level of surgical stimulation ▪ Consider ↑ analgesic dosing ▪ Consider antihypertensive administration
Low value	▪ Consider antihypertensive administration ▪ Assess level of surgical stimulation ▪ Consider ↓ hypnotic/↑ analgesic dosing

BIS™ Monitoring Value†	Management Strategy
High value	▪ Assess level of surgical stimulation ▪ Consider ↑ hypnotic dosing ▪ Consider ↑ analgesic dosing
Desired range (e.g., BIS™ monitoring value 45 to 60)	▪ Continue observation
Low value	▪ Consider ↓ hypnotic dosing ▪ Consider ↓ analgesic dosing

BIS™ Monitoring Value†	Management Strategy
High value	▪ Consider blood pressure support ▪ Assess for other etiologies ▪ Consider ↑ hypnotic/↑ analgesic dosing
Desired range (e.g., BIS™ monitoring value 45 to 60)	▪ Assess for other etiologies ▪ Consider blood pressure support
Low value	▪ Consider ↓ hypnotic/↓ analgesic dosing ▪ Consider vasoactive support ▪ Assess for other etiologies

†Potential impact of artifact should be considered when interpreting BIS™ monitoring values.

SPECIAL ISSUES IMPACTING BIS™ MONITORING TECHNOLOGY

Prospective trials demonstrate that despite the potential for artifact and other issues, reliable BIS™ monitoring values can be obtained throughout many types of clinical cases.[3,13] However, in certain circumstances, BIS™ monitoring values may not be an accurate reflection of the hypnotic state. As noted, BIS™ monitoring technology is an adjunct to clinical judgment, not a substitute for it.

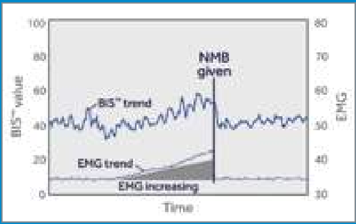
The clinician should be prepared to identify and respond to situations where the underlying EEG signals — and hence the BIS™ monitoring values — may not accurately reflect the clinical endpoints of sedation and hypnosis. For example, BIS™ monitoring values >60 may occur as the result of external artifacts, certain pharmacologic agents, or other unrelated causes rather than reflecting inadequate anesthetic effect and the potential for intraoperative awareness. Similarly, BIS™ monitoring values <40 may develop as a consequence of serious clinical conditions, not merely from the anesthetic hypnotic. As mentioned, alterations in physiologic status that reduce brain metabolism (hypotension, hypoxia, hypothermia, ischemia) may result in decreased BIS™ monitoring values.

A review of published reports of discrepancies between BIS™ monitoring values and clinical judgement provides a comprehensive discussion of the spectrum of possible artifacts and clinical conditions which may impact the displayed BIS™ monitoring values.[40] It is important for clinicians to consider these conditions when evaluating unusual BIS™ monitoring values or trend responses. These conditions are identified within the clinical examples in Figure 7.

Figure 7. Reported factors influencing BIS™ monitoring values.

EMG Artifact and Neuromuscular Blocking Agents (NMB)

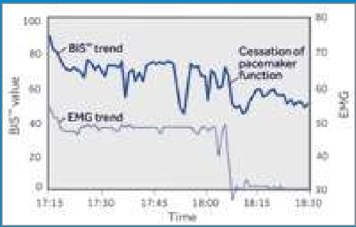
- Excessive muscle tone from forehead muscles may increase BIS™ monitoring values ("EMG artifact").
- NMB agents reduce EMG activity and may result in a decreased BIS™ value.
- During stable anesthesia without EMG artifact, NMB agents have little or no effect on BIS™ monitoring value.



Medical Devices

Electromechanical artifact may, under certain conditions, increase BIS™ monitoring values:

- Pacemakers
- Forced-air warmers applied over the head
- Surgical navigation systems (sinus surgery)
- Endoscopic shaver devices (shoulder, sinus surgery)
- Electrocautery



Serious Clinical Conditions

The following have been associated with low BIS™ monitoring values during the intraoperative period, presumably because of marked reduction in cerebral metabolism:

- Cardiac arrest, hypovolemia, hypotension
- Cerebral ischemia/ hypoperfusion
- Hypoglycemia, hypothermia

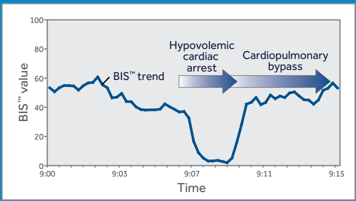
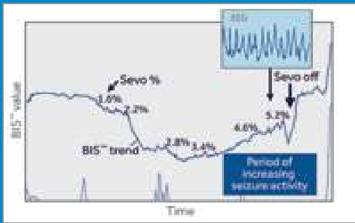


Figure 7. Reported factors influencing BIS™ monitoring values (cont'd.).

Abnormal EEG States

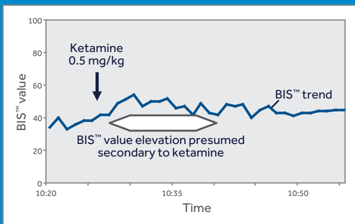
May be associated with low BIS™ monitoring values:

- Postictal state, dementia, cerebral palsy, low-voltage EEG
- Severe brain injury, brain death
- Paradoxical arousal or paradoxical delta
- Increased BIS™ monitoring values may be associated with epileptiform EEG activity.



Certain Anesthetic Agents and Adjuvants

- Ketamine — May transiently increase BIS™ monitoring values due to EEG activation
- Etomidate — Drug-induced myoclonus may transiently increase BIS™ monitoring values



- Halothane — Results in higher BIS™ monitoring values than isoflurane or sevoflurane at equipotent MAC doses
- Isoflurane — Transient paradoxical response to increased dose has been reported
- Nitrous oxide — May have minimal effect on BIS™ monitoring values
- Ephedrine, but not phenylephrine, may increase BIS™ monitoring values

CLINICAL MANAGEMENT — RESPONDING TO SUDDEN CHANGES IN THE BIS™ MONITORING VALUE

When BIS™ monitoring technology is used during anesthesia care, fluctuations in BIS™ monitoring values will likely be observed. Such variability, like a single fluctuation in blood pressure, is not necessarily clinically significant. However, specific consideration should be given to sudden BIS™ monitoring value changes or situations where BIS™ monitoring values seem inappropriately high or low.

For example, changes in the hypnotic state due to changes in dosing of agent delivery will produce changes in the BIS™ monitoring value.

Normally, if the change in anesthetic dosing was incremental — e.g., slight adjustment in the vaporizer setting — subsequent changes in BIS™ monitoring values would be gradual. In contrast, a sudden dramatic change would be unexpected and additional assessment would be appropriate.

Tables 1 and 2 present an assessment process for sudden increases or decreases in the BIS™ monitoring value.

Table 1. BIS™ monitoring increase/high value assessment.

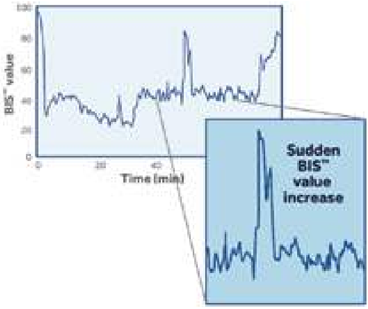
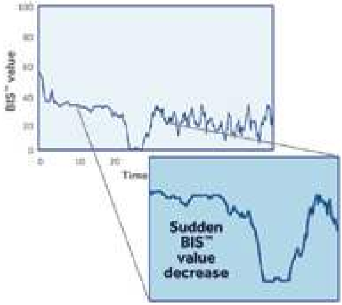
Responding to a Sudden BIS™ Monitoring Value Increase	
	
Examine for the presence of artifacts (EMG, electrocautery, or high-frequency signals)	High-frequency artifacts including those listed may contaminate the EEG signal and bias the BIS™ monitoring value toward a higher level.
Ensure that anesthetic delivery systems are operating properly so that the intended dose of anesthetic agent is reaching the patient	Changes in vaporizer setting, fresh-gas flow rates, intravenous infusion pump setting, and intravenous delivery routes may account for a sudden change in level of anesthetic effect and the resulting BIS™ monitoring value.
Ensure that the anesthetic dose is sufficient	An abrupt change in the BIS™ monitoring value may reflect a new cortical state relative to anesthetic dosing and changes in surgical conditions.
Assess the current level of surgical stimulation	The BIS™ monitoring value may show a transient increase in response to increases in noxious stimulation.

Table 2. BIS™ monitoring decrease/low value assessment.

Responding to a Sudden BIS™ Monitoring Value Decrease	
	
Assess for pharmacologic changes	Bolus administration of intravenous anesthetic, recent changes in inhalation anesthesia, and administration of adjuvant agents (beta blockers, alpha2 agonists) can all result in acute decreases in the BIS™ monitoring value.
Assess the current level of surgical stimulation	The BIS™ monitoring value may show a decrease in response to decreases in noxious stimulation.
Consider decrease as possible response to administration of muscle relaxants	In some situations, the BIS™ monitoring value will decrease in response to administration of neuromuscular blocking agent, especially if excessive EMG was present prior to administration.
Assess for other potential physiologic changes	Profound hypotension, hypothermia, hypoglycemia, or anoxia can produce decreases in the brain state activity.
Assess for emergence from anesthesia	Paradoxical emergence patterns have been described with transient abrupt decreases in the BIS™ monitoring value prior to awakening during inhalation anesthesia. The clinical significance of such changes remains unknown.

THE CLINICAL IMPACT OF BIS™ MONITORING TECHNOLOGY

There is a large and growing body of literature on BIS™ monitoring technology. The practitioner can review this information to ascertain how to use BIS™ technology based on anesthetic agents, drug dosing, and individual patient parameters.

Several large prospective, randomized clinical investigations have measured the influence of BIS™-guided anesthesia care compared with standard practice. In most of these studies, the primary anesthetic was adjusted to maintain BIS™ monitoring values in a "target zone," typically either 40 to 60 or 45 to 60.

The range of observed benefits in clinical trials with certain anesthetic agents includes:

- Reduction in primary anesthetic use[1,4,41]
- Reduction in emergence and recovery time[1,2,4]
- Improved patient satisfaction[2]

Peer-reviewed literature has also reported that, compared to standard anesthesia care, BIS™-guided anesthesia is associated with a reduced risk of:

- Intraoperative awareness and recall[13,14,42]
- Postoperative nausea and vomiting[2,43-45]
- Long-term postoperative cognitive dysfunction[4,46]
- Postoperative delirium[4,46-48]

A 2014 systematic review included 36 trials in which BIS™-guided anesthesia was compared to anesthetic titration based on either clinical signs or end tidal anesthetic gas (ETAG).[5] The resulting analysis found a significant benefit for the use of BIS™ monitoring technology compared to standard practice with respect to multiple outcomes.

BIS™-guided anesthesia was found to significantly reduce the risk of intraoperative awareness in patients at high risk for awareness compared to reliance solely on clinical signs.[5] This effect was seen across 4 studies involving 7761 patients, with an overall OR of 0.24 (95% CI, 0.12-0.48). An equivocal difference was seen in studies comparing BIS™-guided anesthesia to ETAG-guided anesthesia, leading the authors to conclude a large trial comparing these approaches is required.

BIS™-guided anesthesia improved anesthetic delivery, reducing the amount of propofol and of volatile anesthetics consumed.[5] No significant effect was observed for BIS™-guided anesthesia on the requirement for narcotic analgesics during surgery.[5]

BIS™-guided anesthesia care was found to be associated with improved recovery.[5] Early recovery, assessed as time to eye opening, time to response to command, time to extubation, and time to orientation, was reduced by the use of BIS™ monitoring technology. In addition, BIS™-guided anesthesia was associated with reduced time of stay in the postanesthesia care unit and reduced time to discharge.[5]

Best practice statements for brain monitoring

Based on the accumulating scientific evidence, professional societies from around the world have addressed the specific topic of brain monitoring to prevent intraoperative awareness.

The American Society of Anesthesiologists (ASA) recommends that the depth of anesthesia be monitored to reduce the incidence of intraoperative awareness, using clinical signs in conjunction with conventional monitoring systems. The use of brain function monitoring is not recommended for all patients undergoing general anesthesia rather its use should be at the judgement of the physician on a case-by-case basis.[30]

To reduce the risk of intraoperative awareness, the Association of Anaesthetists of Great Britain and Ireland recommends that processed EEG monitoring be used with total intravenous anesthesia (TIVA) and with neuromuscular blocking drugs.[49] The Australian and New Zealand College of Anaesthetists recommend that, during general anesthesia, equipment to monitor the anesthetic effect on the brain be available, especially for patients at high risk of awareness.[50]

The American Association of Nurse Anesthetists (AANA) recommends that medical personnel consider monitoring for level of consciousness in patients at risk for intraoperative awareness.[51] The Association of Perioperative Registered Nurses (ASPAN) states that bispectral index monitoring may be used as an adjunct technology to measure level of sedation.[52]

The Brazilian Consensus on Anesthetic Depth Monitoring suggests brain electrical activity monitoring for high-risk patients under balanced general anesthesia and highly recommends brain electrical activity monitoring for patients under total intravenous anesthesia.[53]

The National Institute for Health and Care Excellence (NICE) recommends BIS™ system monitoring of the depth of anesthesia as an option during general anesthesia for patients at high risk of unintended awareness or at risk of undergoing too-deep anesthesia. BIS™ monitoring technology is also recommended as an option for all patients undergoing intravenous anesthesia.[54]

USING BIS™ MONITORING-GUIDED ANESTHESIA TO REDUCE THE RISK OF POSTOPERATIVE DELIRIUM

Postoperative Delirium

Postoperative delirium (POD) is a complication observed in the days following surgery, most often occurring one to three days after surgery.[55] The incidence of postoperative delirium ranges from 10% to 60% of patients depending on the patient population and the type of surgery.[56] It is the most common surgical complication in older patients.[57]

Older age (age >65 years) is a significant risk factor for POD.[57] Additional risk factors include[57]:

- Preexisting cognitive decline or dementia
- Impaired vision or hearing
- Severe illness
- Frailty
- Presence of infection
- Excess alcohol use
- Certain laboratory or electrolyte abnormalities

Postoperative delirium is associated with increases in both short- and long-term mortality.[48,58] Postoperative delirium was an independent risk factor for mortality three months and six months after surgery,[46,58-60] and was associated with increased mortality rates both in the hospital after major surgery and over a period of 12 to 18 months after cardiac surgery.[58,59] In older patients, POD is also associated with longer hospital stays,[61-63] and higher costs of treatment.[63-65]

Studies using BIS™ monitoring technology to assess anesthetic depth suggest that heavier sedation may be associated with increased risk of POD.[66,67] A significant reduction, 53%, in the incidence of POD was observed in hip fracture patients who received regional anesthesia combined with either light sedation (defined as BIS™ monitoring value ≥80) versus those who received deeper sedation (defined by investigators as a BIS™ monitoring value ~50).[67]

To reduce the incidence of postoperative delirium, the American Geriatrics Society Expert Panel on Postoperative Delirium recommends monitoring the depth of anesthesia during intravenous sedation or general anesthesia using processed EEG monitors.[57]

BIS™ Monitoring Technology and Postoperative Delirium: Evidence

BIS™-guided anesthesia results in lower rates of postoperative delirium compared to routine care.[4,48] Two randomized, controlled trials in 2057 patients have found a reduced incidence of POD among older patients treated with BIS™-guided anesthesia compared to those treated using routine care (Figures 8 and 9). In one study, the median BIS™ monitoring value was significantly lower in the BIS™-blinded group than in the BIS™-guided group.[4] In the

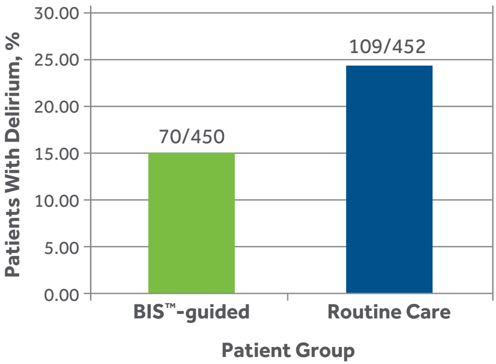


Figure 8. Fewer patients experienced POD with BIS™-guided anesthesia compared to routine care (P = 0.01).[4]

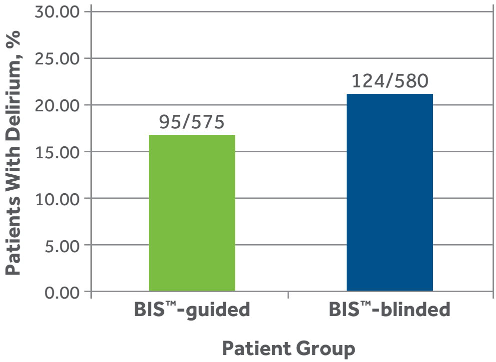


Figure 9. Fewer patients experienced POD with BIS™-guided anesthesia compared to patients whose treating anesthetists were blinded to the BIS™ data (P = 0.036).[48]

second study, BIS™ monitoring values <20 were observed more often in the BIS™-blinded group, leading the authors to hypothesize that the lower incidence of POD observed with BIS™-guided anesthesia may be due to the observed extremely low BIS™ monitoring values.[48] A review of interventions for preventing delirium in hospitalized patients analyzed these two studies and found moderate evidence that BIS™-guided anesthesia reduces the incidence of delirium (RR 0.71, 95% CI 0.60–0.85).[46]

A substudy analysis of data from a larger study found the incidence of POD after cardiac or thoracic surgery was lower in patients treated with BIS™-guided anesthesia than in those treated with end tidal anesthetic concentration (ETAC)-guided protocols.[68,69] The difference approached statistical significance (P = 0.058), leading the authors to propose a large trial to confirm the effectiveness of BIS™-guided anesthesia.[68]

BIS™ Monitoring Technology and Postoperative Delirium: Practice Guidelines

Multiple professional societies have recommended the use of BIS™-monitored anesthesia to reduce POD. The American Geriatrics Society (AGS) recommends the use of processed EEG monitoring as an option to monitor depth of anesthesia in older patients undergoing general anesthesia or intravenous sedation.[57]

The European Society of Anesthesiology recommends (recommendation grade A) monitoring depth of anesthesia to avoid POD. It states that neuromonitoring during surgery can avoid excessive anesthesia depth.[70]

The Brazilian consensus on anesthetic depth monitoring recommends using BIS™ technology to monitor and manage the depth of anesthesia, titrating anesthetics to reduce POD, particularly in older patients.[53]

THE EVOLVING ROLE OF BRAIN FUNCTION MONITORING

Despite remarkable improvements in assessment of cardiovascular and respiratory systems during anesthesia, determining the effect of anesthetics on the central nervous system had remained a challenge. Now, technologies permit routine neurophysiologic monitoring of the CNS for a direct measure of anesthetic effects on the brain.[71] The combination of brain function monitoring with traditional monitoring and assessment of clinical signs can provide the anesthesia professional a more well-informed approach to optimizing both the selection and/or dosing of anesthetic and adjuvant agents for each individual patient.

Optimized anesthesia is important as both inadequate and excessive anesthetic dosing may have negative consequences for the patient. As noted previously, inadequate anesthetic effect is the primary etiology of unintentional intraoperative awareness.[72] Excessive anesthetic depth also has consequences. Excessive anesthetic depth may result in cardiovascular or respiratory depression, and rarely, in cardiac arrest.[73] More recently, new concerns about other consequences of excessive anesthetic effect have appeared. Exposure to high doses of volatile anesthetic is a risk for acute transient epileptiform changes in the EEG.[74] In addition, excessive anesthetic dosing has been associated with an increased risk of POD as well as adverse long-term cognitive and mortality outcomes.[4,48,75,76]

The ability of brain function monitoring to allow the anesthesia professional to monitor patient-specific anesthetic effects on the target organ is important. Avoidance of excessive anesthetic effect reduces the occurrence of prolonged recovery, delayed orientation, and postoperative delirium.[1,2,4,48,77]

As future investigation and clinical experience establish the potential short-term and long-term risks of excessive anesthetic effect, it may become all the more important for anesthesia professionals to better modulate patient exposure to anesthesia. Given the increasing recognition of the consequences of excessive — as well as inadequate — anesthetic dosing, it is likely that more anesthesia clinicians will find it beneficial to integrate brain function monitoring into overall patient management.

SUMMARY

This pocket guide discussed how BIS™ brain function monitoring can be used most effectively during the different phases of anesthesia care. It is important for anesthesia professionals to fully appreciate the applications, limitations, and special considerations for use of BIS™ monitoring technology. Evidence in the literature documents patient benefits in the area of safety, and the improved quality outcomes of anesthesia care resulting from the use of BIS™ monitoring technology. These clinical investigations provide an evidence-based rationale for incorporation of BIS™ monitoring technology as a tool to facilitate intraoperative management with certain anesthetic agents.

Depending on the specific patient characteristics, surgical procedure, and planned anesthetic technique, use of BIS™ monitoring technology may be a very appropriate decision. The decision to use BIS™ monitoring technology should be made on a case-by-case basis by the individual practitioner.

As clinical experience and investigation continue, anesthesia clinicians are encouraged to stay current with available literature regarding the use, benefits, and limitations of BIS™ monitoring technology to guide and optimize patient care.

More recent information and additional clinical, educational and training resources can be accessed at covidien.com/pace/clinical-education/channels/brain-function-monitoring. If you require clinical information on the use of BIS™ monitoring technology, please contact Covidien LP, a Medtronic company at: RMSEducation@Covidien.com.

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