Technology Overview: Bispectral Index

The assessment of a patient's brain state during surgery has long been an objective of research in the field of automated electroencephalogram (EEG) analysis. Aspect Medical Systems has developed a processed EEG parameter, the Bispectral Index™ (BIS™), to measure the effects of anesthetic agents on the patient's brain. The early versions of the BIS were evaluated using prediction of movement to skin incision at the beginning of a surgical procedure. The movement response is considered by many researchers and clinicians to be a sign of inadequate anesthesia. While numerous individual studies showed these early versions of the BIS to be a good predictor of movement response to incision[1,2] and hemodynamic response to incision[3] and intubation[4] for the specific drug regimens tested, it was not a good predictor of lack of movement across some commonly used drug combinations that include the use of varying doses of opioids. The data supported the view that movement to skin incision is primarily an indicator of inadequate analgesia and may not provide significant information about hypnosis when certain combinations of agents are used[5,6]. It appears that the EEG primarily correlates with the patient's hypnotic state and provides less information about analgesia. Indeed, the BIS was shown to be well correlated with changes in the level of hypnosis produced by anesthetics and sedatives.[7] In response, Aspect Medical Systems redirected its research with the objective of providing an improved means of quantifying the patient's hypnotic state. The Bispectral Index has been developed to monitor the effects of anesthetics and other pharmacological agents on the hypnotic state of the brain.

Introduction

Clinicians administering anesthetics and sedatives need to manage the hypnotic state of their patients. Hypnosis is defined as the impairment of consciousness and memory or oblivion to external stimuli. Patients undergoing surgery or intensive therapy require an adequate level of hypnosis to protect them from stress, awareness and recall of traumatic interventions. It is not currently possible, however, to directly measure the hypnotic state. At lighter levels, an indirect assessment of the hypnotic state is performed clinically by observing physical signs and patient responsiveness to voice or touch. For example, sedation scales such as the Ramsay Scale and the Modified Observer's Assessment of Alertness/Sedation Scale have been used in published studies. Although this approach is adequate in some situations, it has several significant limitations. Assessment using patient responsiveness is not applicable to patients who are incapable of responding. In those patients who are capable of responding, the stimulation caused by the assessment itself may arouse the patient. Also, this approach provides only a subjective, instantaneous assessment of the patient's state.

In response to these limitations, researchers have sought an objective measurement of the hypnotic state that can be acquired continuously without disturbing the patient. Because the spontaneous EEG shows changes with hypnotic state, scientists have examined ways to automate EEG analysis to create a measure (or index) that is indicative of these changes. This paper describes the development of one such EEG measure, the Bispectral Index, presents how the EEG and the index change with hypnotic/sedation state, and demonstrates how using the BIS to guide anesthetic titration can provide clinical utility.

Changes in EEG with Increasing Sedation

EEG sedation measures have been developed based on the observation that the EEG generally changes from a low amplitude, high frequency signal while awake to a large amplitude, low frequency signal when deeply anesthetized. The general, idealized pattern of changes that occur in the EEG as the level of hypnosis is increased is shown in Figure 1. These changes may be described using the frequency bands in Table 1.

Sedatives may increase or decrease the activity in the high frequencies. In an alert subject, muscle activity or "EMG" appears across frequency bands and extends above 30Hz. Much of the decrease of activity in the high frequency band seen with sedative doses is a result of diminished EMG activity. Some sedative doses may also increase medium/high frequency activity or "beta activation". As the doses increase and loss of consciousness is approached, there is an increase in

Frequency Band	Frequency Range (Hz)
Very Low Frequencies (Delta)	0-4 Hz
Low Frequencies (Theta)	4-8 Hz
Medium Frequencies (Alpha)	8-14 Hz
High Frequencies (Beta)	14-30 Hz

Table 1: EEG Frequency Bands

the amplitude of low frequencies and the overall EEG amplitude is typically larger than awake. In deeper hypnotic states, beyond the loss of consciousness, the higher frequencies disappear entirely and the overall amplitude is much larger than awake. At very high doses, all activity may disappear leading to an isoelectric EEG.

Like any other signal, the EEG can be broken down into a series of sine wave components such that when the components are combined together, the original signal is recovered. The decomposition of an EEG signal into its components is typically performed to characterize the signal by a single number or set of numbers that are easily trended over time. These numbers are referred to as processed parameters. Most EEG processed parameters used today are based on a technique called power spectral analysis which represents the amplitudes (or power) of each of the sine wave components as a function of frequency. One commonly used descriptor that attempts to track the changes that occur with increasing levels of hypnosis is the 95% spectral edge frequency (SEF). The 95% SEF is the frequency below which the power spectrum contains 95% of the total power in the EEG. It is an adequate measure of hypnotic/sedation state in some limited situations; however, the 95% SEF becomes less useful when the EEG does not transition smoothly from high frequencies to low frequencies as the anesthetic dose increases.

Bispectral analysis is a method of analysis which examines the relationships or "coupling" among the sine wave components.[8] Specifically, bispectral analysis quantifies the level of synchronization in the EEG, along with the traditional amplitude and frequency

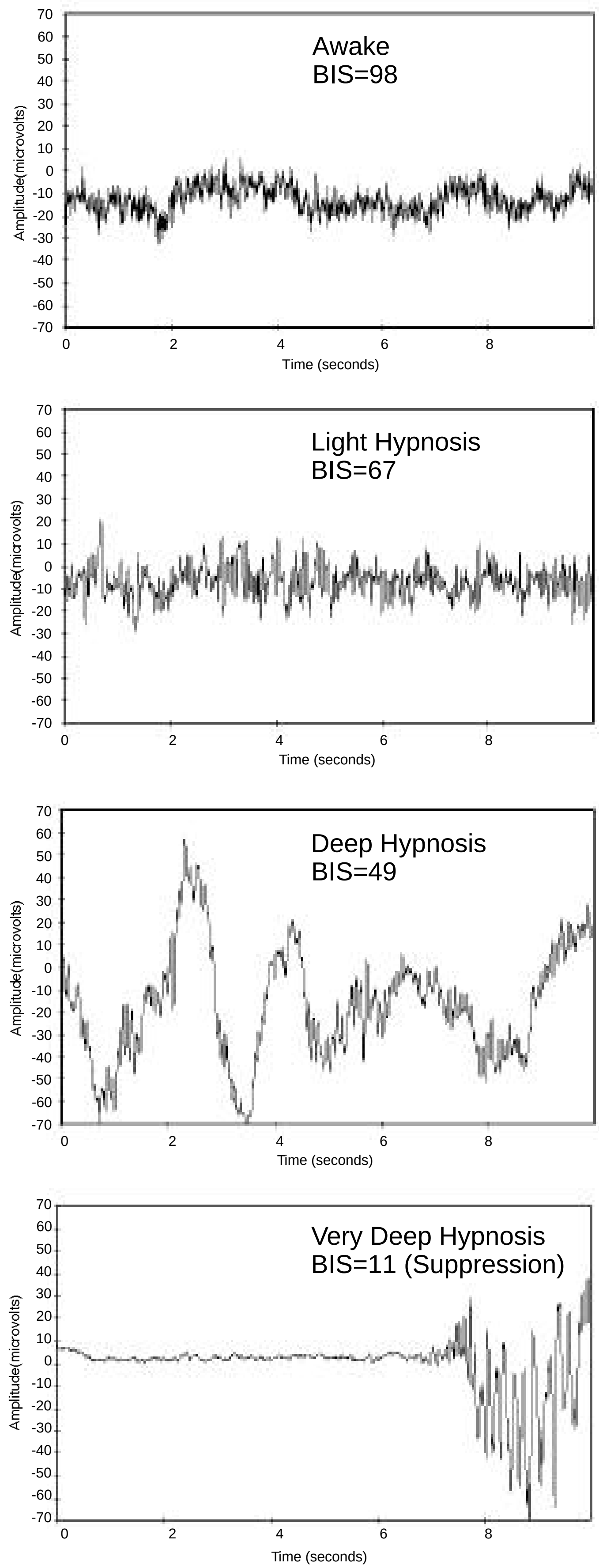

Figure 1: General, idealized pattern of changes in the EEG as the level of hypnosis increases

Hypnotic State/Sedation Level	Score	
Responds readily to name spoken in normal tone	5	
Lethargic response to name spoken in normal tone or says name post-op	4	
Responds only after name is called loudly and/or repeatedly, or opens eyes post-op	3	Conscious
Responds only after mild prodding or shaking	2	Unconscious
Does not respond to mild prodding or shaking	1	
Does not respond to noxious stimulus	0	

Table 2: Hypnotic state/sedation level scoring criteria

parameters. Aspect Medical Systems has reduced the complex data arrays generated from bispectral analysis using a sophisticated algorithm to generate a composite, numerical Bispectral Index which tracks changes in the cerebral state.

Bispectral Index Development

Over several years a large database of high fidelity EEG recordings and clinical records was collected from more than 2000 patients receiving a wide variety of anesthetic regimens. These regimens included the use of isoflurane, propofol, midazolam and sodium thiopental often supplemented with various opioids and nitrous oxide. A subset of this data, the development database, was used to develop and evaluate the index using a learn and test approach. The development database consisted of a segment of recorded EEG and an associated, clinically derived hypnotic state or sedation level. The criteria used to define the sedation level are defined in Table 2. Figure 2 depicts an overview of the index development process. The segments of EEG were used to compute a set of candidate bispectral and power spectral EEG features for evaluation. Those features best able to discriminate between different hypnotic states/sedation levels were combined using multivariate statistical modeling techniques to form a composite index. This index was then prospectively tested on a different subset of Aspect's larger database.

The Bispectral Index is computed real-time using a combination of three analysis steps. The first step is an EEG pre-processor, which breaks the EEG signal down second by second and marks those segments containing artifact that might arise from movement, EMG or electrocautery equipment. Segments of suppressed EEG are also identified. These segments are excluded from further processing. The second step is the calculation of the hypnosis/sedation index by combining selected EEG features using the algorithm which was developed as previously described. In the third step, the hypnosis/sedation index is modified to better reflect the level of suppression in the EEG. The suppression ratio (SR) is computed as the percentage of suppressed EEG in the non-artifact data.[9]

Results from Clinical Validation Studies

The Bispectral Index was developed using only segments of artifact-free, non-suppressed EEG. Figure 3 depicts the distribution of the BIS at different clinically assessed hypnotic states/sedation levels. Lower numbered levels are deeper hypnotically, as defined in Table 2.

The performance of the Bispectral Index was also evaluated on data more representative of the clinical setting. This data consisted of recordings from more than 400 patients totaling more than 1000 hours of EEG data monitored intraoperatively during various anes-

Bispectral Index Development Process

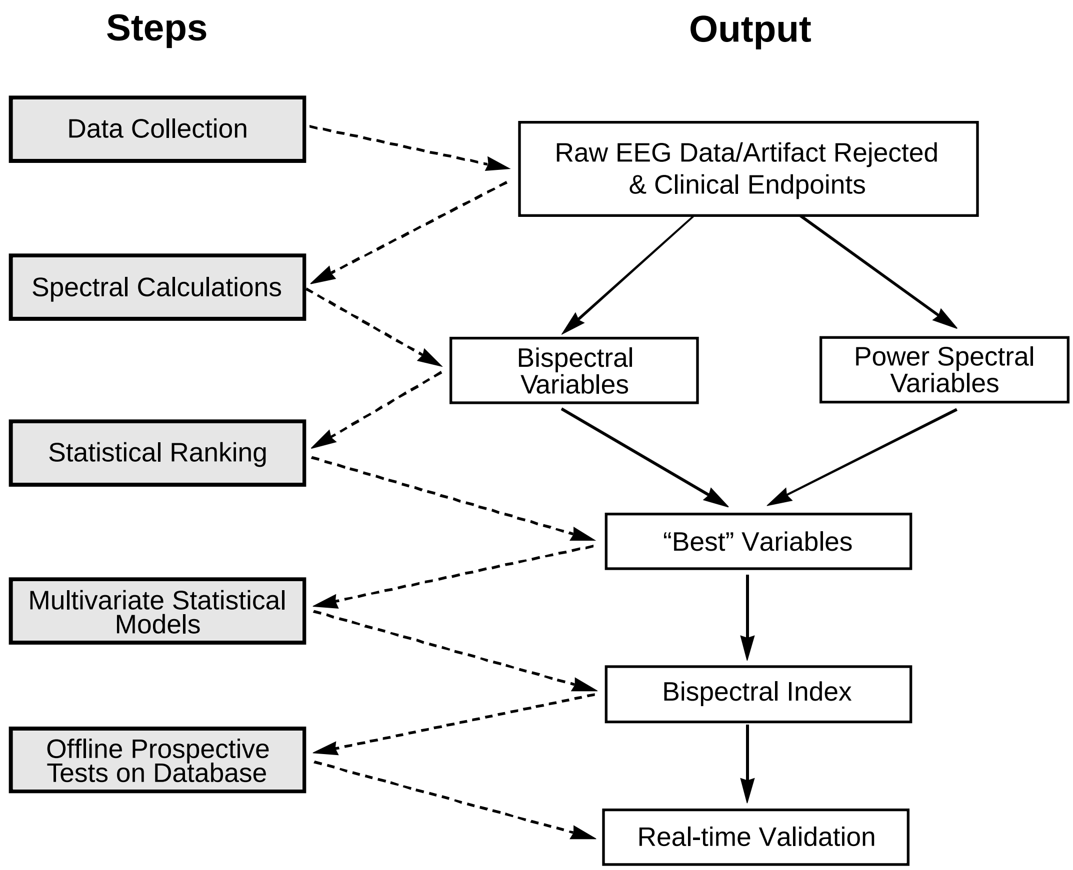

Figure 2: Overview of the process for developing the Bispectral Index

thetic techniques.[7] Noise-corrupted and suppressed EEG as well as artifact-free EEG were part of this data. Key events were recorded by the clinician to assess the level of hypnosis/sedation. Use of this data allowed the full trend during a procedure to be analyzed. Figure 4 presents the range of BIS levels recorded during the various periods of intraoperative procedures contained in the database. Data recordings started while the patients were still awake, but lightly sedated in some cases. Induction resulted in a rapid decrease in the index followed by intubation. The pre-incision period was classified as either light or deep hypnosis depending on the level of effect-site drug concentration during this time period. An effect-site drug concentration is a hypothetical agent concentration at the site of agent action (e.g., the brain). It is computed based upon the pharmacokinetics and pharmacodynamics of a particular agent using a mathematical model. In cases where EEG suppression was present or during very deep anesthesia, as during cardiac procedures, the index was very low. Awakening, or eyes open, occurred at levels similar to initial baseline values.

The relationship between the Bispectral Index and the hypnotic effects provided by propofol, midazolam, methohexitol, isoflurane and sevoflurane have also recently been described in a number of reports.[7,11-16] These studies concluded that the BIS provides a quantifiable measure of the effects of anesthetics on the brain that correlates to the level of consciousness and probability of recall. Values below 70 indicated a very low probability of recall and values below 60 indicated unconsciousness. BIS was also found to be useful as an indication of return of consciousness during general anesthesia.[17]

Results from Clinical Utility Studies

Findings from a randomized multicenter clinical trial conducted to evaluate the utility of BIS monitoring as an adjunct to managing anesthetic drug delivery showed more efficient drug utilization, faster emergence from anesthesia and improved patient recovery.[18-20]

The goal of the study was to minimize the drug delivered while maintaining an adequate hypnotic state.

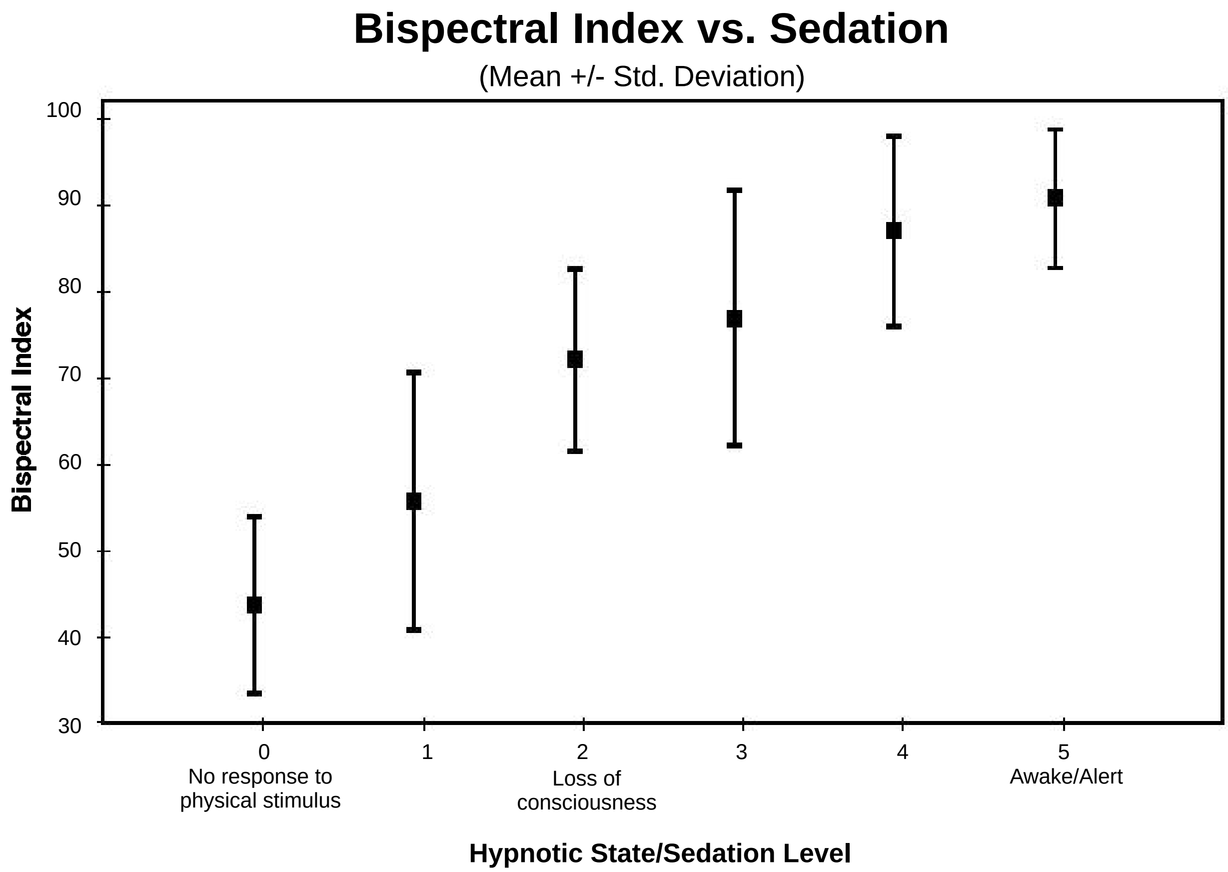

Figure 3: Level of the Bispectral Index at each of the sedation levels

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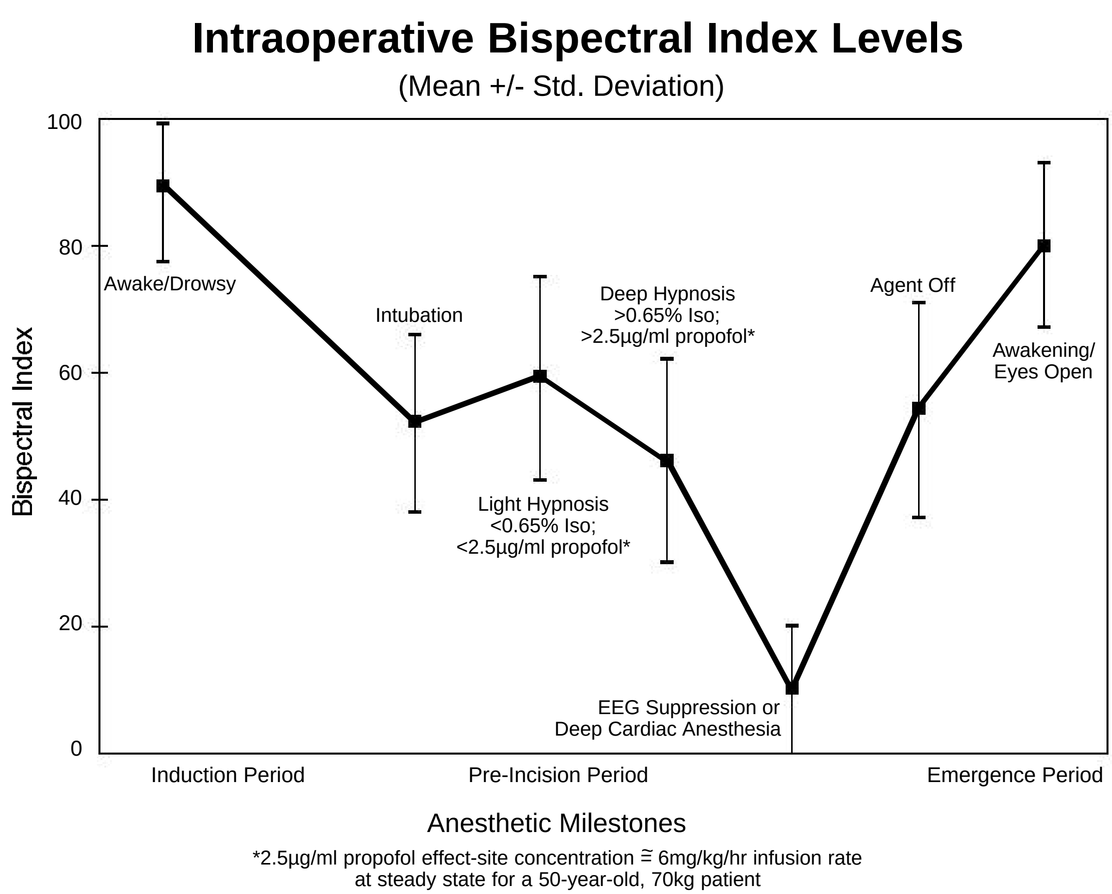
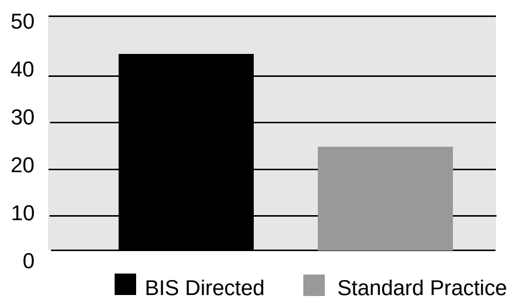


Figure 4: Level of the Bispectral Index at various intraoperative points

Utilizing a propofol/alfentanil/N_2O technique, the researchers documented that compared to standard practice, in the BIS managed patients:

- 35-40% faster wake-up was obtained
- 16% faster eligibility for PACU discharge was achieved
- 13-23% less hypnotic drug was used
- more patients were rated as "excellent-fully oriented" on admission to the PACU, as noted in Figure 5 (43% vs. 23%)

Figure 5: % of patients fully oriented on arrival to PACU



Case Reports

One important application of the BIS is the ability to consistently indicate the return of consciousness after a surgical procedure.[21,22] Figure 6 provides an example of how the Bispectral Index performs during a period of emergence. The recording starts shortly after induction. The expired agent decreased significantly at around 10:30. This resulted in the patient's hypnotic state becoming gradually lighter as reflected by the BIS. Monitoring this trend allows the clinician to anticipate when the patient will recover and hence, titrate drugs better at the end of the procedure. It is also interesting to compare this performance with the 95% SEF. The patient's lightening hypnotic state is detected by the BIS trend at least fifteen minutes earlier than the 95% SEF.

Another important application of the BIS is the ability to track patient arousals intraoperatively. Arousals may be due to an inadequate amount of anesthesia as a result of drug delivery problems or changes in the patient's drug requirements due to altered levels of stimulation or metabolism. Figure 7 represents a case where drug delivery was unintentionally interrupted. The graph shows the Bispectral Index, heart rate (HR) and mean arterial pressure (MAP) over the entire procedure, a total abdominal hysterectomy. The case began with induction at 8:03; the concomitant drop in the BIS reflected the expected deepening of the patient's hypnotic state. Intubation occurred at 8:07. The BIS subsequently increased to 80 and it was discovered that the propofol infusion pump did not switch over to continuous infusion mode after the last bolus as expected. A bolus of propofol was then administered and a constant infusion of propofol was initiated reducing the BIS to the 40's range. The stimulation of incision and the resultant lightening of the patient's hypnotic state are

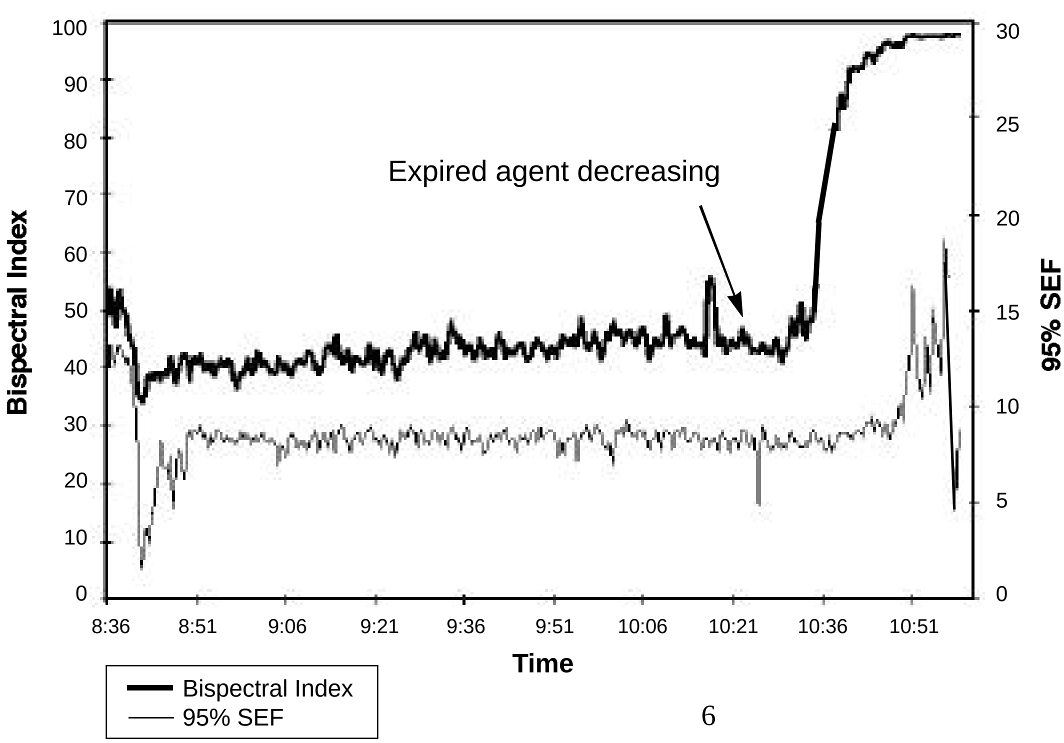


Figure 6: Performance of the Bispectral Index vs. 95% SEF during emergence from an intraoperative procedure

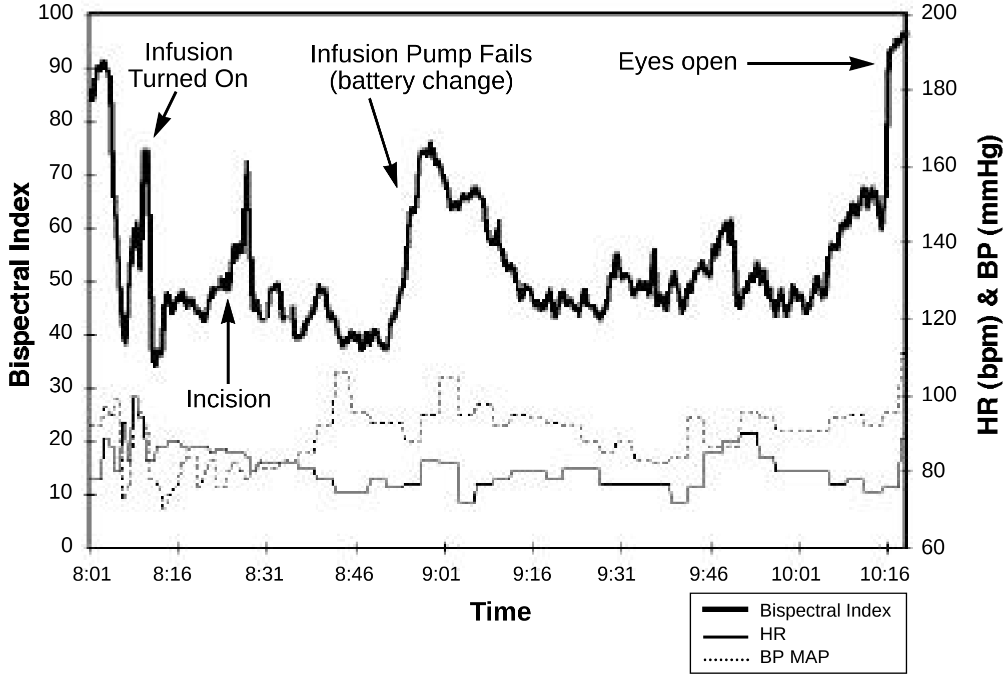


Figure 7: Trend of the Bispectral Index during a procedure with an episode of inadequate drug delivery

indicated by the rise in the BIS. In the middle of the procedure the patient's hypnotic state began to lighten. This is clearly demonstrated by the increasing BIS trend after 8:46. Note that neither heart rate nor blood pressure indicated any clinically significant changes. Based on this early indication of patient emergence, the anesthetist checked the infusion system and discovered that it had stopped functioning. Replacing the batteries and restoring the infusion returned the patient to deeper hypnotic levels. At the end of the case, the index increased rapidly prior to eye opening.

Another example of a patient regaining consciousness is shown in Figure 8. This graph depicts a one-hour intraoperative segment during which the patient underwent a wake-up test during spinal surgery. At 13:22, an attempt to wake the patient was initiated. The index increased to 95, reflecting the patient's lightened hypnotic state, with wake-up occurring shortly thereafter at 13:31.

Conclusion

Aspect Medical Systems has developed a unique processed EEG parameter, the Bispectral Index, that monitors the effects of anesthetics and other pharmacological agents on the hypnotic state of the brain. The

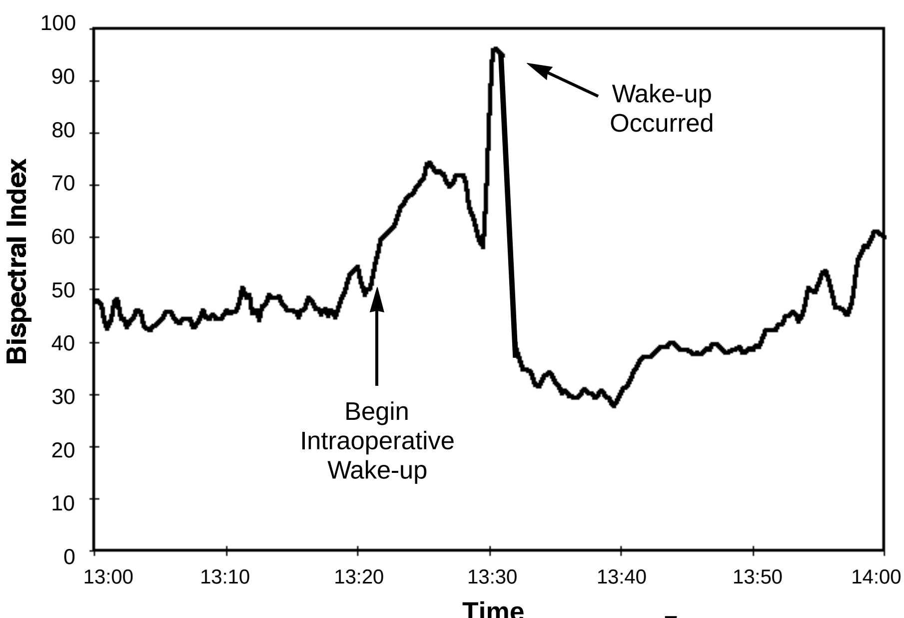


Figure 8: Performance of the Bispectral Index during an intraoperative wake-up test

BIS is the only commercially available technology of this kind that has proven clinical utility.[18,19,20]

Several clinical studies, and a growing body of evidence from routine users have shown that use of the BIS to manage anesthesia leads to:

- less drug usage
- faster wake-up in the OR
- earlier discharge eligibility from the PACU
- higher quality recovery
- significant cost savings

The BIS received marketing clearance as a measure of anesthetic effects in October of 1996.

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