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Bilateral Bispectral Index Monitoring During Suppression of Unilateral Hemispheric Function

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Abstract

Bispectral Index (BIS) has been used to monitor level of “sedation” based on the electroencephalogram (EEG). Patients evaluated for surgery to control a seizure disorder undergo Wada testing, during which one hemisphere is rendered functionally inactive after injecting a short-acting barbiturate. We surmised that the BIS values would reflect these functional changes. Eight epileptic patients were enrolled. A full array of 21 EEG electrodes and 2 BIS XP (Quatro) strips over each frontal region of the scalp were applied. The EEG was continuously recorded. BIS values from each hemisphere were recorded every minute. Angiography was performed by advancing a catheter into each internal carotid artery. Amobarbital or methohexital was injected until the patient developed a hemiparesis. The EEG confirmed a significant lateralized cortical effect of the barbiturate. Repeated measures analysis of variance was used to analyze the differences between the BIS values from monitor electrode strips placed on the left (left BIS) and the right (right BIS) sides of the head as well as the differences in the left and right BIS values before and after each injection of the barbiturate. Injection of barbiturate into either the left or right internal carotid artery produced a significant change on the 21-electrode EEG. However, there was no difference between left BIS to right BIS values ($P = 0.84$). With repeated injections of barbiturates, some patients became sedated. At these times, both left BIS and right BIS values decreased together before and after injection of barbiturate. The BIS monitor was unable to distinguish significant hemispheric EEG and clinical functional changes except when the patient became sedated.

The Bispectral Index (BIS) (Aspect Medical Systems Inc., Newton, MA) has been used to monitor the level of “sedation” and may be used to determine “awareness” during surgery (1). Because BIS values are derived from the electroencephalogram (EEG), it was surmised that BIS would reflect significant functional and EEG changes (2). We tested this hypothesis in patients being evaluated for surgery to control a seizure disorder. These patients undergo Wada testing (3). During this test, the patient is awake and not sedated so that an accurate

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functional assessment can be performed. A catheter is advanced from the femoral artery in the groin selectively into one and then the other internal carotid artery (ICA). To localize a patient's language and memory, a short-acting barbiturate, amobarbital (4) or methohexital (5), is injected through the catheter to produce transient focal neuronal dysfunction in the distribution of the middle cerebral artery of the ipsilateral hemisphere. To ensure that the barbiturate has actually been delivered to the brain regions under investigation, as well as to ensure that all language and memory testing takes place while the barbiturate is effective, the functional consequence of each injection is confirmed by real-time continuous EEG monitoring and real-time motor-strength testing. A standard 21-channel EEG will demonstrate transient, lateralized, and localized δ frequency slowing that is maximal in the frontotemporal regions and clears as the barbiturate loses its effect. Simultaneous motor-strength testing will demonstrate a transient contralateral hemiparesis that will precede the resolution of δ slowing on EEG.

We hypothesized, that with two BIS monitors, one on each side of the forehead, we would see statistically significant changes in BIS values over time and as a function of which hemisphere had been affected by the injected barbiturate. Using standard 21-channel EEG and bilateral BIS monitoring from the left and right forehead, we evaluated 8 epileptic patients undergoing Wada testing with selective intracarotid injections of either amobarbital (4) or methohexital (5).

Methods

Eight patients gave informed and written consent for this IRB-approved prospective study. Age, sex, race, site of pathology, and medical history were recorded. All patients enrolled in the study were scheduled for Wada testing. This test is given to patients with uncontrolled seizures before planned resection of brain tissue containing epileptogenic foci. The Wada test determines if memory and/or language would be impaired after this operation (6). It has been suggested that this test may even be predictive of seizure outcome postoperatively (7).

Each patient was brought to the holding area where 21 gold-plated electrodes were placed on the head in the International 10–20 system of electrode placement and recorded digitally with an EEG machine (Xltek EP16, Oakville, Ontario, Canada). In addition, BIS monitor electrode strips (Quatro: part #186-0106) were placed on the forehead bilaterally and symmetrically except for electrode #1, for which 1 electrode was located just below the other as shown in Figure 1. Two BIS A-2000 XP monitors (P/N 185-0070, host version 3.21) were used to record BIS values. BIS values were recorded both manually and electronically (by configuring the RS232 output from the BIS XP monitor) to a file using the program HyperTerminal (Hilgraeve, Monroe, MI). This file was subsequently read using Excel (Microsoft, Redmont, WA). The BIS monitors and the EEG machine were synchronized in time for proper data analysis.

The patient was then brought into the angiography suite. No conscious sedation or other form of anesthesia was given for Wada testing in order that an accurate functional examination of language, memory, and motor strength could be obtained. Vital signs were taken as per usual protocol under the direction of the neuroradiologist. A catheter was inserted percutaneously into the femoral artery and then selectively advanced over a guidewire into the ICA. A cerebral angiogram was obtained before injection of the short-acting barbiturate. A selective injection of non-ionic iodinated contrast was performed to: 1) verify the position of the catheter, 2) determine the extent of cross-filling through the anterior communicating artery, and 3) verify the absence of vascular abnormalities which may impair the results of the study. In addition, this injection of contrast served as a control for the BIS values obtained subsequently, because the patient was fully awake during this part of the procedure. After the contrast injection, approximately 100–125 mg of amobarbital or 2–4 mg of methohexital was injected directly into the ICA over approximately 5 s. In each patient, the hemisphere thought to have the

epileptogenic focus was injected first followed by the contralateral hemisphere. EEG monitoring occurred throughout the procedure and was used to confirm decreased cerebral cortex functioning. The duration of the barbiturate effect was monitored continuously by its EEG effect and motor testing and lasted approximately 5–12 min when amobarbital was injected and 4–7 min with methohexital. A few of the patients became sedated after the last injection of amobarbital.

The motor examination was performed by having the patient raise his/her arms. Strength was measured on a scale of 0–5 with “0” as no muscle movement, “1” as very slight movement but not even in the plane of gravity, “2” movement in the plane of gravity, “3” movement against gravity, “4” movement and strength against some resistance, and “5” normal strength against normal resistance. The opposite hemisphere was injected only after the EEG had recovered to baseline. This took approximately 7–14 min depending on whether methohexital or amobarbital was used. The procedure took approximately 30–40 min for the evaluation of each hemisphere. The absence or presence of collateral circulation was recorded. EEG was used to confirm focal, localized suppression of cerebral activity.

To test speech and language, patients were requested to follow two verbal commands (e.g., Point to your ear.), name two real (e.g., spoon) and four pictured (e.g., bicycle) objects, repeat phrases, and answer brief questions (e.g., Are 2 pounds of flour heavier than 1?). The verbal commands and object-naming stimuli also served as memory items. Patients were instructed to remember these items for later testing. Only items presented during a hemiparesis strength rating of $<3/5$ were considered valid for memory testing. After full neurologic recovery (typically 10 min from the initial injection), patients were requested to recall memory items, or, if necessary, to select the items presented previously from a series of multiple-choice arrays.

Data from the BIS monitors were analyzed at 1-min intervals. Bilateral BIS scores were recorded before, during, and after injections to each side of the brain. BIS values are reported as mean $\pm$ 1 sd. All the data from the eight patients were combined into one database for statistical analysis. Repeated measures analysis of variance was used to analyze differences between the two BIS monitors as well as changes in BIS scores before and after left- and right-sided injections of barbiturate. A P value ≤ 0.05 was considered significant for all analyses. These data were compared with EEG monitoring and functional testing of motor strength, which were recorded by video and handwritten accounts.

The presence of drowsiness was also recorded. In one patient, an injection of barbiturate was repeated to the same hemisphere because it was believed that the study was inaccurate because of the patient's inattention. In two other patients, it was necessary to repeat the injection because of ambiguous clinical neuropsychometric results. These data were not excluded from the study.

Results

Eight patients scheduled for Wada testing as an evaluation preceding epilepsy surgery agreed to participate in this study from 7/22/03 to 10/7/03. They ranged in age from 23 to 52 yr. The study included three men and five women. Other periprocedural values are listed in Table 1. Despite their seizure history, all were healthy with the exception of one patient who had a history of hypertension, idiopathic peripheral neuropathy, and Raynaud syndrome. Five patients had seizures originating from the right hemisphere and three from the left. A complete angiogram was performed from each ICA. Only one patient had cross-filling between the cerebral hemispheres with unilateral ICA injection of radiographic dye. Each patient received bolus injections of either amobarbital (3 patients) or methohexital (5 patients) to each side of the brain for a total amount of medication listed in Table 2. Amobarbital or methohexital was used based on the preference of the neurologist.

BIS values were obtained from each side of the forehead from 2 BIS EEG electrode strips (Fig. 1). The type and amount of sedative-hypnotic (amobarbital or methohexital) are presented in Table 2. The average BIS values before injection of barbiturate and with left side, right side, and no injections of barbiturate are presented in Table 3.

After an injection of barbiturate into the ICA, patients developed corresponding focal slowing (δ frequency) on the EEG and a contralateral hemiplegia (Fig. 2). No changes on the EEG or BIS values were seen during the angiogram when non-ionic contrast was injected (Fig. 3 shows approximate time of angiograms). The EEG was most sensitive to barbiturate injections and localized changes persisted beyond the recovery from clinical neurologic deficits. BIS values remained unchanged between the two sides of the frontal area, but tended to decrease symmetrically when repeated injections of barbiturate led to sedation or during times between testing when the patient became drowsy. An example of the plotted values is shown in Figure 3. Vital signs throughout the procedure demonstrated no obvious changes.

Left and right BIS scores decreased after injection of either barbiturate compared with BIS values before injection. This decrease was not significant ($P = 0.08$) (Table 3). However, the decrease was the same for left BIS and right BIS regardless of the side of ICA injection ($P = 0.84$). At the conclusion of testing, 1 patient who received multiple injections of sedative-hypnotic during the study became sedated and her BIS scores decreased to values in the 60s for both BIS monitors despite the near-return of her EEG to baseline. These were the lowest BIS values seen in the study.

Discussion

During Wada testing, the EEG interpreted by standard visual inspection was both sensitive and specific regarding regional cerebral dysfunction induced by the barbiturate. The EEG demonstrated unilateral, focal δ frequency slowing which correlated with contralateral hemiparesis as well as a variable amount of artifact produced by electromyography and patient movement. It was hoped that the BIS monitor might also reflect this electrophysiologic response to unilateral ICA injection of barbiturate and therefore substitute for the full EEG. Right and left BIS scores, however, did not reflect the unilateral absence of cortical functioning, as was our original hypothesis.

Regardless of whether right- or left-sided injections of sedative-hypnotic were given, both BIS values tended to decrease slightly (Table 3). These changes, however, were neither statistically significant ($P = 0.08$) nor clinically significant (91 ± 9 and 92 ± 5 , right and left sides, respectively). In particular, decreases in BIS values occurred symmetrically after several injections of a barbiturate caused the patient to become sedated, even though the patient's neurologic function had returned to baseline. While the patient was becoming sedated, the EEG demonstrated a resolution of focal slowing and, as one would anticipate, mild diffuse slowing associated with drowsiness. This happened despite the patient's ability to move the previously paretic limb and the near-return of his/her EEG to baseline. Although we did not evaluate the BIS monitor as a measure of sedation, based on our data, it may be concluded that it is inappropriate for evaluating hemispheric functioning.

The failure of the BIS to detect EEG alterations produced by ICA barbiturate may simply reflect the fact that, whereas the BIS was designed to detect anesthetic-induced alterations in EEG that correlate with intraoperative awareness or level of sedation, its design does not permit detection of the type of EEG changes that occur during Wada test, even though those changes appear prominent to visual inspection of the standard 21-lead EEG. The BIS combines time-domain measures, frequency-domain parameters, and high-order spectral subparameters into a single metric. These measures, and the manner in which they combine to generate the BIS

score, were derived empirically, based on many anesthetic administrations (2). The details of the algorithms used by the BIS are proprietary and have not been fully disclosed.

A strength of the BIS algorithm is that its output is a single, easily understood integer value, between 0 and 100. This attractive simplicity, along with the ease of use of the device itself, makes it tempting to propose that the BIS monitor might serve as a more generally applicable monitor of cerebral function. The proprietary nature of the underlying algorithm makes it difficult to evaluate scientifically the suitability of the BIS for clinical applications beyond those for which it was designed and validated. Whereas the standard EEG itself is well understood and characterized in human disease and diverse clinical settings, the “bispectral index” is, in part, a “black box.” Based on published information, one cannot determine how clinically significant features of EEG signals will be represented in the BIS score, and to what extent data reduction to a single, easily appreciated integer value may be appropriate or deceptive in a given clinical application.

Having said that, we will speculate on why the BIS monitors failed to reflect significant clinical and electrophysiologic changes induced during Wada testing. Perhaps the placement of the electrode strips is important to determine an effect of unilateral barbiturate injection (Fig. 1). However, Shiraishi et al. (8) demonstrated that there was a statistically significant correlation of BIS values between frontal and occipital placement of BIS electrode strips, obviously a widely discrepant difference in electrode strip placement compared with the symmetrical placement of our electrodes. In addition, as previously discussed, the bilateral electrode strips were placed so that the central lead (#1) was shared between them. Whereas the central electrode certainly records electrical activity from both hemispheres, the lateral electrode (#3) does not, and therefore the lateral frontotemporal activity seen with the full EEG electrodes should have been reflected in the BIS EEG.

Furthermore, it is impossible to know with certainty the degree to which artifacts due, for example, to muscle activity, electrical interference, or patient movement, may go undetected by the BIS device and confound the BIS value (9-12). Indeed, reports suggesting that neuromuscular blockade may, itself, reduce the BIS values reasonably call into question the extent to which BIS may be assessing things other than cerebral activity (13,14). Indeed, Wada testing may be a particularly hostile environment for the BIS monitor to generate a meaningful score because the patient is awake and moving, and therefore there is considerable muscle activity.

To determine the contribution of muscle electrical activity in calculating BIS values, Greif et al. (15) anesthetized 10 volunteers and paralyzed them to 7 different degrees of neuromuscular blockade using mivacurium. They were unable to find any systematic effect of muscle blockade on BIS values. However, others have found different results. For example, paralysis alone, in fully awake individuals (13) or in patients sedated in an intensive care environment, can reduce BIS values to levels consistent with anesthetic levels of sedation (14). Our patients were not paralyzed with muscle relaxants.

Another explanation lies in how the BIS monitor processes EEG data. Morimoto et al. (16) recently analyzed the EEG signal from the BIS monitor. For BIS values >60, BetaRatio, defined by Rampil (2) as the logarithm of the ratio of the EEG spectral power in the 30- to 47-Hz band to the EEG spectral power in the 11- to 20-Hz band, linearly correlated with BIS values ($r = 0.90$; $P < 0.01$) (16). The high-frequency band may reflect muscle as well as cerebral activity. If the EEG spectral power in the high- and low-frequency bands change to the same degree, then there will be no change in the BetaRatio.

In view of these considerations, reliable extrapolation of clinical experience from standard EEG interpretation to the BIS should not be reasonably expected.

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Figure 1.

Placement of Bispectral Index (BIS) XP electrodes. Two strips of BIS XP electrodes were placed over each side of the forehead. They were labeled left and right. We show both electrode strips in this figure. The electrodes were numbered 1 through 4. Electrodes 1 and 3 are active and record the electroencephalogram. Electrode 2 is the reference electrode and electrode 4 is used to measure eye movement artifact.

Figure 2.

Electroencephalogram (EEG) recorded with 10-20 system of electrode placement. The filter settings were 1–70 Hz. Only 8 midline electrodes from right (even numbers) and left (odd numbers) are shown for illustrative purposes. Two different epochs of EEG are shown: baseline before and just after injection of methohexital into the right internal carotid artery. After an injection of methohexital, there is significantly more slowing of the EEG on the right with more δ - θ activity of large amplitude and increased muscle artifact compared with changes on the left. Associated with these EEG changes is the development of a left hemiplegia (strength 0/5) with normal strength on the right (motor strength on the left is shown below the EEG). The scales for time and voltage amplitudes are shown on the figure.

Figure 3.

All bilateral Bispectral Index (BIS) values for right and left injections. This is a continuous recording of BIS values from both hemispheres for the same patient as illustrated in Figure 2: the right BIS values are represented by the dashed line with the open diamonds, and the left, by the continuous line with the solid squares. The solid bars are the times of injection of methohexital and are so labeled. BIS values are unitless. The open stars are the approximate times of the cerebral angiograms first from the right internal carotid artery, second from the left internal carotid artery. Figure 2 is taken from the beginning of the right injection. Time is denoted in minutes along the x axis.

Table 1

Perioperative Values

Age, yr (sd)	41 (9)
Sex, % male/female	37.5/62.5
Race	
Caucasian	37.5 (4)
Hispanic	12.5 (1)
Asian	37.5 (3)
Lateralization of language	
Left hemisphere	87.5 (7)
Right hemisphere	0
Bilateral	12.5 (1)
Lateralization of memory	
Unilateral, left	12.5 (1)
Unilateral, right	25.0 (2)
Nonlateralizing	62.5 (5)

Data are percentage (number of patients) unless otherwise indicated.

Table 2

Seizure Location with Type and Amount of Sedative-Hypnotics Injected in the Eight Patients

Patient	SH	Injection amount, left (mg)	Injection amount, right (mg)	Seizure locus
1	A	125	125	LT
2	M	10	7	LT
3	A	125	250	RT
4	M	7	9	LO+RT
5	M	8	6	RT
6	M	7	7	RT
7	A	125	225	RT
8	M	125	125	RT

SH = sedative hypnotic, A = amobarbital, M = methohexital, LT = left temporal, RT = right temporal, LO = left occipital.

Table 3**Bispectral Index (BIS) Values**

	Left BIS score	Right BIS score
Preinjection ^a	94 ± 3	94 ± 3
Left side injection	92 ± 5	91 ± 9
Right side injection	91 ± 5	91 ± 4

Values are mean ± sd.

^aPreinjection describes the time before intracarotid artery injections of barbiturates into the left and right internal carotid arteries (ICA). The “left side injection” and “right side injection” refer to the BIS values immediately after the injection of barbiturate into either the left ICA (left side injection) or right ICA (right side injection). There was no significant difference between left and right BIS scores ($P = 0.84$) before (preinjection) or after (left side injection or right side injection) injection of barbiturate. However, there was a nonstatistically significant difference between the average preinjection BIS scores and average left side injection and right side injection ($P = 0.08$).