

Anesthesiology  
81:1365-1370, 1994  
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## ***Bispectral Analysis of the Electroencephalogram Correlates with Patient Movement to Skin Incision during Propofol/Nitrous Oxide Anesthesia***

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**Background:** Bispectral analysis is a signal-processing technique that determines the harmonic and phase relations among the various frequencies in the electroencephalogram. Our purpose was to compare the accuracy of a bispectral descriptor, the bispectral index, with that of three power spectral variables (95% spectral edge, median frequency, and relative  $\delta$  power) in predicting patient movement in response to skin incision during propofol-nitrous oxide anesthesia.

**Methods:** Forty-four adult patients scheduled for elective noncranial surgery were studied. Gold cup electroencephalographic electrodes were placed on each patient in a frontoparietal montage ( $F_{p1}$ ,  $F_{p2}$ ,  $P_3$ , and  $P_4$ ) referred to  $C_z$ , and the electroencephalogram was recorded continuously and processed off-line. Conventional frequency bands were used to describe power spectrum variables. Anesthesia was induced with propofol ( $1.5$ – $3.0$   $\text{mg}^{-1} \cdot \text{kg}^{-1}$ ) and maintained with 60% nitrous oxide in oxygen and with propofol at one of three randomized infusion rates (100, 200, or 300  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Inadequate anesthetic depth was defined as patient movement in response to a 2-cm skin incision at the planned site of surgery. Plasma propofol concentrations were measured within 2 min after skin incision.

**Results:** Complete data were available for 38 patients, of whom 17 moved in response to skin incision. Analysis of the

area under the receiver operating characteristic curves showed that only for bispectral index and drug dose group was there a significant predictive relation (area > 0.5). Furthermore, the bispectrum was significantly predictive even after stratification by dose group.

**Conclusions:** The bispectral index of the electroencephalogram is a more accurate predictor of patient movement in response to skin incision during propofol-nitrous oxide anesthesia than are standard power spectrum parameters or plasma propofol concentrations. (Key words: Anesthetics, intravenous: propofol. Monitoring, electroencephalography: bispectral index.)

ALTHOUGH the electroencephalogram (EEG) has been proposed and studied as a method of determining anesthetic depth,<sup>1-4</sup> major limitations restrict its usefulness. Each anesthetic agent alters the EEG in a different fashion,<sup>5-10</sup> making precise correlations between EEG changes and anesthetic depth problematic. The computerized EEG power spectrum and the 95% spectral edge are examples of EEG-derived parameters that have been correlated with blood plasma concentrations of single drugs, but consistent correlations between the EEG and amount of drug administered, plasma concentrations, and responses to different surgical or anesthetic manipulations have not been found.<sup>11-13</sup> No individual EEG profile or set of changes that characterizes adequate anesthesia for all surgical manipulations and procedures has been established.

In previous studies, adequate anesthetic depth has been defined simply as the threshold or level of general anesthesia below which patients move to the noxious stimulus of skin incision.<sup>14,15</sup> Any useful EEG measure of adequate anesthetic depth should correlate with the absence of patient movement to skin incision. Given the lack of a consistent relation between conventional EEG changes and patient responses during anesthesia, we evaluated a new bispectral parameter, the bispectral index of the EEG, as a measure of adequate anesthesia defined by patient movement in response to skin incision.

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Received from the Department of Anesthesia and the Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston; Aspect Medical Systems, Framingham; and the Department of Statistics, Harvard University, Cambridge, Massachusetts. Accepted for publication August 4, 1994. Supported by Aspect Medical Systems.

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Bispectral analysis is a technique that quantifies the nonlinear phase-locking and quadratic energy coupling within various frequencies of the EEG. For example, the technique has established the mutually interdependent harmonic activity of the scalp-recorded EEG, as demonstrated by the relation between the anteriorly predominant  $\beta$  (14–40 Hz) and the posteriorly predominant reactive  $\alpha$  (8–13.5 Hz) activities in normal awake adults.<sup>16</sup> This interrelation among frequency bands of the EEG is altered by natural sleep<sup>16</sup> and varies among individuals and scalp location of the recording electrodes.<sup>17</sup> Because these interdependent EEG harmonics change during transition from alertness to stages of natural sleep, we investigated the EEG bispectral index as a potential measure of patient responsiveness to a specific stimulus during a general anesthetic. The purpose of this study was to compare the accuracy of the bispectral index with that of three power spectrum parameters, median frequency, relative  $\delta$  power, and 95% spectral edge in measuring EEG parameters predictive of patients' movement to skin incision during propofol–nitrous oxide anesthesia.

## Materials and Methods

### Patients

The studies were approved by the Subcommittee on Human Studies at the Massachusetts General Hospital. Informed consent was obtained from 44 adult ASA physical status 1 and 2 patients who were scheduled for elective noncranial surgery. There were 22 women and 22 men, 21–67 (mean 40) yr of age. Patients were excluded from study if they had a history of any neurologic or psychiatric disorders, or if they were taking anticonvulsant medication.

### Anesthesia Management

After patients breathed oxygen for 3 min, anesthesia was induced with a bolus of propofol at 1.5–3 mg<sup>-1</sup> · kg<sup>-1</sup>, and tracheal intubation was completed after a bolus injection of succinylcholine at 1.0–1.5 mg<sup>-1</sup> · kg<sup>-1</sup>. Additional doses of propofol to 0.5 mg<sup>-1</sup> · kg<sup>-1</sup>, were given if required to achieve adequate anesthesia for induction and intubation. Immediately after the propofol bolus was given, an automatic infusion device delivered a constant rate infusion of propofol to each patient at one of three assigned doses (100, 200, or 300  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) based on a computer-generated randomization schedule. After intu-

bation, 60% nitrous oxide in oxygen was added. The skin incision was performed by the surgeon after a period of not less than 10 min to allow for adequate preparation of the surgical area and to establish the full return to strength of the train-of-four peripheral nerve response to stimulation.

### Surgical Stimulus

The initial skin incision was standardized at 2 cm and was made superficially through the dermis, using a number 16 blade for all procedures, except for surgery involving the knees in which a number 11 blade was used. Extension and deepening of the incision for surgical purposes was commenced after 2 min. The second surgical incision was separated in time but not location from the planned total incision.

### Electroencephalography

Five E5 gold cup electrodes (Grass Instrument, Quincy, MA) were placed according to the international 10–20 system in a frontoparietal ( $F_{p1}$ ,  $F_{p2}$ ,  $P_3$ , and  $P_4$ ) montage referred to  $C_z$ . Electrodes were secured with collodion and electrode impedances were kept at less than 2,000  $\Omega$ . The analog EEG was recorded throughout the operation using a prototype portable computer system (B500 Spectral EEG Monitor, Aspect Medical Systems, Framingham, MA) consisting of a modified 386/20-MHz computer (Toshiba, Irvine, CA) with an analogue-to-digital converter. The high- and low-pass filters were 0.25 and 110 Hz.

Data were acquired at 2,048 samples/s and then simultaneously decimated to 128 samples/s with a low-pass filter set at 50 Hz. Each 4-s epoch was analyzed with each successive epoch overlapping the previous one by 3 s. The bispectrum and power spectrum of each successive 4-s epoch were computed. The bispectra of the 60 most recent epochs were averaged and the averaged bispectra were used to compute the bispectral index. The power spectra of the 60 most recent epochs also were averaged, and the averaged power spectrum was then used to compute the power spectral parameters for that period. Four EEG parameters were derived for the two combined frontal to  $C_z$  channels: (1) bispectral index, (2) 95% spectral-edge frequency, (3) median frequency, and (4) relative  $\delta$  power. To assess the quality of the electrographic signal, a 5-min baseline EEG recording with and without the patient's eyes closed was performed before the administration of anesthesia.

## EEG BISPECTRUM CORRELATES WITH PATIENT MOVEMENT

### *Bispectral Index and Power Spectrum*

The bispectral index is a univariate parameter computed from the EEG bispectrum. It was developed using artifact-free EEG recorded from a group of patients ( $n = 195$ ) undergoing one of a series of anesthetic regimens (isoflurane,  $n = 42$ ; isoflurane-alfentanil,  $n = 19$ ; propofol-alfentanil,  $n = 32$ ; propofol-nitrous oxide,  $n = 43$ ; alfentanil,  $n = 15$ ; and propofol,  $n = 44$ ). Using as models previous reports studying the EEG effects of specific drugs, the alfentanil and propofol anesthetic regimens were conducted during volunteer studies in which the amount of drug administered was titrated to specific EEG patterns.<sup>12,\*\*</sup> Propofol was infused in subjects until the EEG revealed an isoelectric interval of 3 s during an EEG burst-suppression pattern. The appearance of prominent EEG  $\delta$ -wave activity defined the "maximum" drug effect in subjects receiving alfentanil infusions. Samples of EEG from these endpoints were classified as representative of nonresponsive states in subsequent development of the algorithms. The other studies were performed during surgical procedures, using movement to incision as evidence of inadequate anesthesia. The patients from this study were included in this learning database.

For each EEG recording, a large set of variables was computed from the bispectrum at specific times corresponding to response endpoints. A subset of these variables that best predicted the specific response (movement *vs.* no movement) to a standardized skin incision or to the specified EEG drug effect was obtained by using a backward stepwise multiple regression. A significance criterion of  $P > 0.005$  was used to eliminate noncontributing variables. A discriminant analysis was then used to compute coefficients for these variables that maximized separation of responders and nonresponders, resulting in a linear bispectral index that maximized the separation of the two response groups. To limit the range of the bispectral index, the linear index was scaled sigmoidally by the following functions:

sigmoidal bispectral index

$$= 1 / (1 + e^{-(\text{linear bispectral index})}) \times 100.$$

This equation limits the possible values of the bispectral index to 0–100. In this article, the sigmoid bis-

pectral index is referred to simply as the "bispectral index."

The following power spectral parameters were computed from each power spectrum; relative  $\theta$  (0.5–3.75 Hz),  $\tau$  (4.0–7.75 Hz),  $\alpha$  (8.0–13.5 Hz), median frequency, and 95% spectral-edge frequency. The relative powers were defined as the power with the respective frequency band to the total power between 0.5 and 30 Hz. The median frequency was defined as the frequency at which half the power was at higher frequencies and half at lower frequencies. The 95% spectral edge is the frequency at which 95% of the total power was at lower frequencies.

### *Definitions of Movers and Nonmovers*

To derive the EEG power spectrum and the bispectral variables, the off-line analysis of EEG records included the 3 min before and after the skin incision. Movers were defined as patients who showed any visible spontaneous muscle movement, whether withdrawal or flexor movement of the arms and legs, frowning of the forehead muscles, or coughing, within 1 min of the 2-cm skin incision. The examiner evaluating the patient's response to skin incision was not blinded to the infusion rate of propofol.

### *Propofol Assays*

Two minutes after the initial skin incision, 10 ml blood was drawn from a brachial vein contralateral to the infusion catheter. The plasma propofol concentration was measured by a liquid chromatographic method (PharmaKinetics Laboratories, Baltimore, MD) that had an interassay variability of less than 8%.

### *Statistical Analysis*

Means of the EEG variables were compared by Student's  $t$  test (two-sided) and analysis of variance, with significance defined as  $P < 0.05$ . Data are presented as mean  $\pm$  standard deviation.

The predictive power of the EEG parameters, propofol dose group, and plasma propofol concentrations was summarized by receiver operating characteristic (ROC) curves. The ROC curve for each measure is a plot of sensitivity (fraction of movers correctly predicted) against  $1 - \text{specificity}$  (fraction of nonmovers correctly predicted) at various threshold values for predicting a positive response. The ROC curve summarizes predictive power at all levels of the threshold, avoiding the problems associated with *post hoc* selection of an optimal cutoff. The methods of Hanley and

\*\* Dyck JB, Varvel J, Hung O, Shafer SL: The pharmacokinetics of propofol *versus* age (abstract). ANESTHESIOLOGY 75:315A, 1991.

**Table 1. Response Rates by Treatment Group**

Low	7 movers	5 nonmovers (57%)
Mid	8 movers	6 nonmovers (56%)
High	2 movers	10 nonmovers (17%)
Combined	17 movers	21 nonmovers

McNeil were used to calculate the areas under the ROC curves and their standard errors,<sup>18</sup> to test for better-than-chance predictive power (an area > 0.5), and to test the significance of the differences between areas under the curve for the various indexes.<sup>19</sup>

To test whether bispectral index was predictive of movement when dose group was known, the area under the ROC curve was calculated for each of the three dose groups separately. The mean of the three areas and its standard error were calculated, and the mean area was compared with 0.5.

All tests on areas of ROC curves are described with one-sided *P* values.

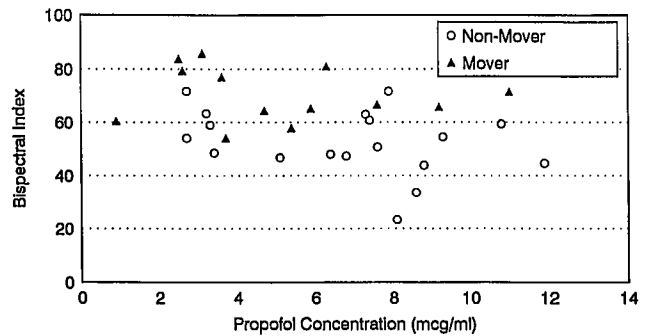
**Results**

Analysis of EEG parameters and patient movement in response to skin incision was performed in 38 patients. In five studies, technical difficulties in obtaining EEG recordings prevented data collection, and in another, the patient was given a muscle relaxant before the incision. Seventeen patients moved and 21 patients did not move in response to the initial skin incision. All patients who coughed or grimaced in response to skin incision also simultaneously had gross muscle movement and were considered movers. Table 1 identifies the distribution of movers and nonmovers among the three groups defined by propofol infusion rate. A comparison of EEG parameters before skin incision in patients who did and did not move reveals no significant

**Table 2. Comparison of Preincision EEG Parameters for Movers and Nonmovers**

	Movers (n = 17)	Nonmovers (n = 21)
Bispectral index	70.0 ± 12.0	54.0 ± 13.0*
95% Spectral edge frequency (Hz)	14.0 ± 4.8	14.0 ± 3.0
Median frequency (Hz)	2.8 ± 3.6	1.7 ± 1.4
Relative delta power (%)	70.0 ± 21.0	74.0 ± 16.0

\* *P* < 0.001.



**Fig. 1. Plasma propofol concentrations determined from blood samples drawn within 2 min of skin incision in movers and nonmovers compared with the bispectral index values immediately before that incision.**

differences in the power spectrum, relative  $\delta$  and 95% spectral-edge parameters (table 2). However, the difference in the bispectrum was significant (*P* = 0.001).

Plasma propofol concentrations were available from 31 patients. In figure 1, movers and nonmovers are identified by their bispectral index and plasma propofol concentration. Mean plasma propofol concentrations for each treatment group are displayed in table 3. The area under the ROC curve was calculated for each of the EEG variables, serum propofol levels, and dose group (table 4). The area under the curve was significantly greater than 0.5 for bispectral index (*P* < 0.001) and for dose group (*P* = 0.018). These findings indicate that each of these measures has significant predictive power. For all other measures, the area was close to 0.5, indicating little diagnostic value. The area under the ROC curve for bispectral index was significantly greater than that for serum propofol level (*P* = 0.035), for relative  $\delta$  (*P* < 0.003) and for spectral-edge and median frequency (*P* < 0.0005). The area for bispectral index was greater than that of dose group, but that difference was not significant (*P* = 0.089).

The mean and standard error of the mean of the areas under the three ROC curves for bispectral index, strat-

**Table 3. Plasma Propofol Concentration and Bispectral Index by Treatment Group**

	Low (100*)	Mid (200*)	High (300*)
Plasma propofol concentration ( $\mu\text{g/ml}$ )	3.9 ± 2.4	6.9 ± 1.5	7.5 ± 3.1
Bispectral index	69.0 ± 11	60.0 ± 10	50.0 ± 14.0
n	11	9	11

\* Propofol infusion rate ( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ).

## EEG BISPECTRUM CORRELATES WITH PATIENT MOVEMENT

**Table 4. Diagnostic Performance for EEG and Dosing Variables**

Variable	ROC Area*
Bispectral index	0.81 ± 0.07
Propofol infusion rate	0.68 ± 0.09
Propofol plasma concentration	0.56 ± 0.10
Relative delta power	0.55 ± 0.10
Median frequency	0.53 ± 0.10
95% Spectral edge frequency	0.50 ± 0.10

\* Area ± SE under receiver operating characteristics curve using Wilcoxon estimate.

ified by dose group, was  $0.80 \pm 0.08$ , which is significantly greater than 0.5 ( $P < 0.001$ ).

## Discussion

As a measure of adequate anesthesia, the EEG parameters were tested against one brief and discrete noxious stimulus. The thresholds for each EEG parameter used in this analysis to determine the predictive powers of these parameters in identifying those patients who would and would not move in response to skin stimulus were derived retrospectively. To assess our results, three potential sources of bias in our methodology must be considered.

First, the algorithms and weighting coefficients of the bispectral index were derived from 195 patients, including the 38 patients in this study. In general, a prediction technique based on a retrospective fit appears to be more accurate for the cases to which it was fitted than for new cases. If the bispectral index had been exclusively fitted to the 38 patients in our study, this bias would be expected to be prominent, whereas, if the bispectral index had been fitted only to the other 157 and applied to these 38 patients, there would be no bias. Our subset was only 19% of an overall group that comprised a heterogeneous population of patients and volunteers anesthetized according to various protocols, each with different endpoints defining patient response. In this situation, the bias is expected to be small, even though it cannot be quantified.

Second, the only experimental variable to which the examiner was not blinded was the dose of propofol administered to each patient. Our data demonstrate that the examiner's observation of whether the patient moved or not in response to skin incision was sufficiently objective that it was not determined by his

knowledge of the dose infused. The test that controlled for dose group confirms the independent predictive power of the bispectral index and suggests that the bispectral index provides information beyond what would be available to a clinician who knows what dose was administered.

Third, the bispectral index demonstrated a stronger significant correlation with patient movement in response to skin incision than did the plasma propofol concentrations. It should be noted, however, that venous blood sampling at a single point in time only estimates effective drug concentrations. More frequent arterial blood sampling may provide a more precise estimate of propofol concentrations and effects, but such sampling was not practical in our clinical setting.

Therefore, our data indicate that the EEG bispectral index may be a sensitive and specific measure of anesthetic adequacy, defined as prevention of movement during and after a 2-cm incision of the skin in patients anesthetized with a propofol infusion and nitrous oxide-oxygen. The bispectral index before skin incision more accurately correlated with patient movement than did 95% spectral edge, relative  $\delta$  power, or measured plasma propofol concentrations. This retrospective study, however, requires further confirmation in prospective studies.

The authors thank Michael Cheng and Mary Farr for their assistance in the preparation of the manuscript.

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