

# Performance of the ARX-derived Auditory Evoked Potential Index as an Indicator of Anesthetic Depth

## A Comparison with Bispectral Index and Hemodynamic Measures during Propofol Administration

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**Background:** Autoregressive modeling with exogenous input of middle-latency auditory evoked potential (A-Line autoregressive index [AAI]) has been proposed for monitoring anesthetic depth. The aim of the current study was to compare the accuracy of this new index with the Bispectral Index (BIS), predicted effect-site concentration of propofol, and hemodynamic measures.

**Methods:** Twenty female patients scheduled for ambulatory gynecologic surgery received effect compartment controlled infusion of propofol. Target effect-site concentration was started at 1.5  $\mu\text{g/ml}$  and increased every 4 min by 0.5  $\mu\text{g/ml}$ . At every step, sedation level was compared with monitoring values using different clinical scoring systems and reaction to noxious stimulus.

**Results:** Bispectral Index, AAI, and predicted propofol effect-site concentration were accurate indicators for the level of sedation and loss of consciousness. Hemodynamic variables were poor indicators of the hypnotic-anesthetic status of the patient. BIS correlated best with propofol effect-site concentration, followed by AAI. Hemodynamic measurements did not correlate well. No indicators predicted reaction to noxious stimulus. Poststimulus, BIS and AAI showed an increase as a result of arousal. This reaction occurred more rapidly with the AAI than with BIS.

**Conclusion:** Bispectral Index, AAI, and predicted propofol

effect-site concentration revealed information on the level of sedation and loss of consciousness but did not predict response to noxious stimulus.

BOTH electroencephalography and middle-latency auditory evoked potentials (MLAEP) have been proposed as monitors of the hypnotic state during anesthesia.<sup>1</sup> The waveforms of both raw measures require real-time quantification to become useful in clinical anesthesia practice. For electroencephalography, the Bispectral Index (BIS) incorporated in the A2000 BIS<sup>®</sup> monitor (Aspect Medical Systems Inc., Newton, MA) has been proven to have a high sensitivity and specificity compared with other processed electroencephalographic variables.<sup>2,3</sup> For MLAEP, Mantzaridis and Kenny<sup>4</sup> extracted a single numerical variable, called the auditory evoked potential (AEP) index, applying a proprietary algorithm that uses a moving time average to extract the AEP waveform followed by the calculation of the sum, over the waveform, of the square root of the absolute difference between every two successive segments of that AEP waveform. As described, this classic moving time average method requires 256 sweeps, each of 144-ms duration, creating a response delay time of 36.9 s. This large number of sweeps is required to obtain an acceptable signal-to-noise ratio for the AEP, and this method is therefore poorly suited to recording changeable AEPs, which is the case during anesthesia. Throughout the last two decades, a number of methods have been applied to facilitate a single-sweep or a few-sweep extraction of the AEP.<sup>5-7</sup> Recently, Jensen *et al.*<sup>8</sup> developed a new method for extracting the MLAEP from the electroencephalographic signal using an autoregressive model with an exogenous input (ARX) adaptive method (more details are provided later in the article). This method allows extraction of the AEP signal within 15-25 sweeps of 110-ms duration, resulting in only a 6-s response delay time. A new variable, called the A-Line ARX Index (AAI), is then calculated from this fast-extracted MLAEP wave. This new technology was incorporated in a recently commercialized system called A-Line<sup>®</sup> (A-Line Monitor; Danmeter A/S, Odense, Denmark).

This ARX-extracted AEP index may be as accurate as and is significantly faster than the 256-sweep moving time average method in detecting arousal reaction after tracheal intubation.<sup>9</sup> Other methods for processed elec-

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troencephalography and MLAEP have been recently proposed,<sup>3,10-12</sup> although only the tested indices, BIS and AAI, have become commercially available.

The purpose of the current study was to test the performance and reliability of BIS, AAI, predicted propofol effect-site concentration, and classic hemodynamic variables as indicators of the level of consciousness (defined by the responsiveness scores of the modified Observer's Assessment of Alertness/Sedation scale [OAA/S]<sup>13</sup> and loss of eyelash reflex). In addition, we tested the ability of the proposed indicators to predict movement as a reaction to noxious stimulus. In an interference analysis, the possible alteration of the BIS value caused by the auditory input ("clicks") from the A-Line<sup>®</sup> monitor was evaluated.

## Methods and Materials

After obtaining approval from the Institutional Ethics Committee (Ghent University Hospital, Gent, Belgium), informed consent was obtained from 20 female patients (American Society of Anesthesiologists physical status I, aged 18–60 yr) scheduled for ambulatory gynecologic surgery. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight, neurologic disorder, and recent use of psychoactive medication, including alcohol.

Propofol was administered *via* a computer-assisted continuous-infusion device to a target effect-site concentration (RUGLOOP<sup>††</sup>) using a three-compartment model enlarged with an effect-site compartment, previously published by Schnider *et al.*<sup>14,15</sup> The target effect-site concentration of propofol (Ce propofol) was computed to yield a time-to-peak effect<sup>16</sup> of 1.6 min after bolus injection, as also published by Schnider *et al.*<sup>14,15</sup> and clinically confirmed by Struys *et al.*<sup>17</sup> Propofol infusion was administered using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France). The computer ran RUGLOOP monitors and drove the pump at infusion rates between 0 and 1,200 ml/h *via* an RS-232 interface. Using this infusion technique, we were able to obtain a steady state condition for propofol at every target concentration after 4-min infusion. The initial propofol target effect-site concentration was set at 1.5  $\mu\text{g/ml}$  and was increased every 4 min by 0.5  $\mu\text{g/ml}$  until loss of all relevant clinical signs was observed (explanation to come). Propofol was infused *via* a large left forearm vein. Every patient received approximately 200 ml of crystalloid fluid during the study period. No fluid load was given before induction. No patient received preanesthetic medication. No other drugs were given. All

patients maintained spontaneous ventilation *via* a face mask delivering 100% oxygen.

Heart rate and noninvasive blood pressure, oxygen saturation, and capnography were recorded at 1-min intervals using an AS3<sup>®</sup> monitor (Datex, Helsinki, Finland). BIS<sup>®</sup> (version 3.4) was derived from the frontal electroencephalography (At-Fpzt) and calculated by the A-2000 BIS<sup>®</sup> monitor using 3 BIS<sup>®</sup>-Sensor electrodes (Aspect Medical Systems, Inc.). The smoothening time of the BIS<sup>®</sup> monitor was set at 30 s. The AAI from the MLAEP was calculated using the A-Line<sup>®</sup> monitor. The MLAEP were elicited with a bilateral click stimulus of 70-dB intensity and 2-ms duration. Three electrodes (A-Line<sup>®</sup> AEP electrodes; Danmeter A/S) were positioned at mid-forehead (+), left forehead (reference) and left mastoid (–). The extraction of the MLAEP using a short moving time average together with an ARX model and the calculations of the AAI are described in Appendix 1, which can be found on the ANESTHESIOLOGY Web site. Figure 1 shows a flow chart of the signal processing.

Before each increase in target concentration (after 4-min infusion at the specific target effect-site concentration), measures of BIS, AAI, hemodynamic variables, level of consciousness (using the modified OAA/S score shown in table 1 and the response to eyelash reflex), and reaction to noxious stimulus were recorded (more details are provided later in the article). The sequence of testing was always the same: first the "electronic indicators," then the eyelash reflex test, followed by the OAA/S score. The response to noxious stimulus was recorded last.

The responsiveness component of the OAA/S scale (table 1) is an assessment procedure involving a presentation of progressively more intense stimulation, ranging from a moderate speaking voice to physical shaking or moderate noxious stimulus (trapezius squeeze) until response is observed. Patients were considered to have loss of consciousness at the transition between level 3 and level 2.

For measuring the reaction to noxious stimulus, a tetanic electrical stimulus (100 Hz, 50 mA) for 2 s was applied to the volar forearm level. To examine the possible change in BIS and AAI as a reaction to the stimulation sequence at each propofol concentration, we recorded latency and peak value of change in BIS and AAI until 1 min after stimulus.

Both BIS and AAI indices were also logged automatically. RUGLOOP digitally recorded the BIS each 10 s, and the A-Line<sup>®</sup> monitor recorded AAI index values nominally each 8 s. The time marks of both systems were synchronized with the manual timing for stimulus and manually recorded events to within  $\pm 1$  s.

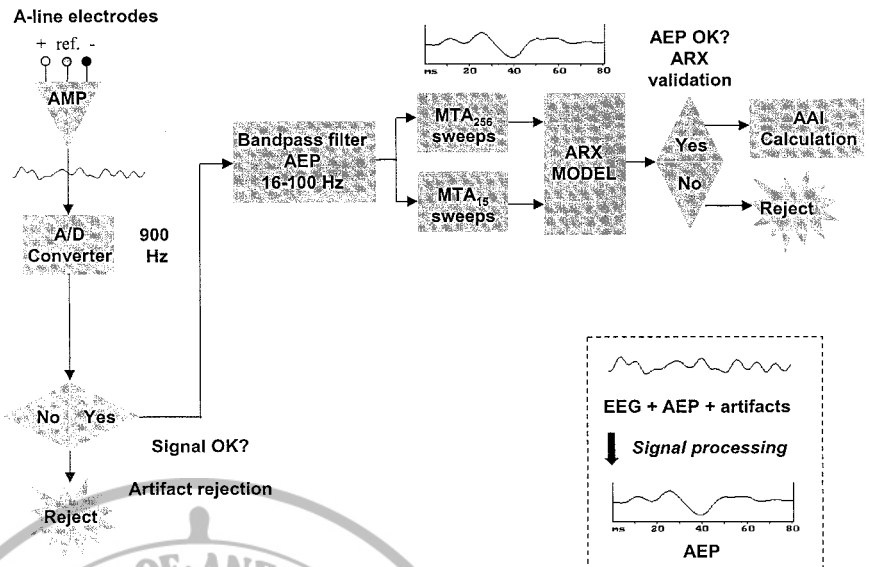
## Statistical Analysis

Significance level was set at 5% unless otherwise reported. Because some of the data violated the normality rules (tested with a chi-square test), we used nonpara-

<sup>††</sup>RUGLOOP, written by T. De Smet and M. Struys. More information is available at <http://allserv.rug.ac.be/~mstruys>.



**Fig. 1.** The A-Line signal processing flow chart. The artifact rejection and bandpass filtering serve for preconditioning of the signal. The core of the A-Line processing is the ARX model. The objective of the ARX model is rapid and robust extraction of the auditory evoked potential (AEP) by merging the information from the two inputs: the moving time averages (MTA) of the 15 and 256 sweeps, respectively. Subsequently, the ARX AEP is validated and the A-Line autoregressive index (AAI) is calculated. AMP = amplification; EEG = electroencephalography.



metric statistics. Spearman rank-order correlation analysis was performed to evaluate the relation between each measure and the propofol effect-site concentration. To evaluate the significance between the obtained Spearman rank correlation coefficients, a specific comparison test, described by Steiger,<sup>18</sup> was used.

To analyze the significant changes in each indicator (BIS, AAI, Ce propofol, heart rate, blood pressure) at different levels of the OAA/S score, a Friedman analysis was used. When  $P$  was  $< 0.05$ , a Wilcoxon signed rank test was used to distinguish significance between specific levels. To determine significant changes in each measurement during loss of eyelash reflex and loss of response to noxious stimulus, a Wilcoxon signed rank test was used.

The ability of the different indicators to describe depth of sedation, loss of consciousness, and response to noxious stimulus was evaluated using prediction probability ( $P_K$ ), which compares the performance of indicators having different units of measurements, as developed by Smith *et al.*<sup>19,20</sup> Consider a predicting indicator such as BIS or AAI and a gold-standard measure of anesthetic depth such as the multilevel OAA/S score or the two-level responsiveness (yes-no) to eyelash reflex or noxious stimulus. Then, a  $P_K$  of 1 for the BIS or AAI indicator would mean that BIS or AAI always increases (decreases) as the patient gets lighter (deeper) according to the gold-standard depth measure. Such an indicator can perfectly predict anesthetic depth. Alternatively, a  $P_K$  value of 0.5 would mean that the indicator is useless for predicting anesthetic depth. A  $P_K$  value of  $-1$  also means a perfect indicator, once the direction of the scale is reversed. For the OAA/S score, a  $P_K$  value was computed for all assessments combined. Similarly,  $P_K$  values for all eyelash reflex responses and response to noxious stimulus assessments were determined. The jackknife method was used to compute the SE of the estimate,

based on the assumption that all assessments were independent. A paired-data jackknife analysis<sup>19,20</sup> was used to evaluate whether the  $P_K$  for one variable was different from another one. Bonferroni correction was used to the paired-data jackknife analysis to correct for multiple comparisons. Significance level was set at 0.01. Prediction probability was calculated using a custom spreadsheet macro,  $P_K$ -MACRO, developed by one of the authors (W. S.). The power on the  $P_K$  values was calculated using a  $t$  statistic defined as the quotient between the difference considered of clinical importance and the SE of the difference between two indicators. Assuming a  $P_K$  difference of 0.05 as being of clinical importance, then 20 patients should be included to find significant differences with a  $P < 0.01$ . The SE assumption was based on previous results of the AAI and other AEP indicators.<sup>10</sup>

After the  $P_K$  analysis, three measures were found to merit further analysis: BIS, AAI, and Ce propofol. For these variables, median effective dose ( $ED_{50}$ ) and  $ED_{95}$  were evaluated using a Probit procedure for the levels of the OAA/S score until loss of consciousness, for loss of eyelash reflex, and for loss of response to noxious stimulus. Goodness-of-fit tests for the Probit analyses are based on the Pearson chi-square test. Large  $P$  values for these tests indicate that the fitted model agrees well with the data.  $P < 0.05$  indicates that the fitted model does not agree well with the data.

**Table 1.** Responsiveness Scores of the Modified Observer's Assessment of Alertness and Sedation Scale<sup>13</sup>

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

We further investigated the performance of the BIS, AAI, and Ce propofol indexes for three binary measures of anesthetic depth: conscious-unconscious as defined by the OAA/S score, presence-absence of eyelash reflex, and response-no response to noxious stimulus. For each of the three indexes and the three binary measures of depth, we computed values of normalized cumulative occurrence, values of sensitivity and specificity, and positive and negative predictive values *versus* index cutoff (threshold) value. For these calculations, we used "positive" to denote a test result that suggested consciousness or responsiveness and "negative" to denote a test result that suggested unconsciousness or nonresponsiveness. We assumed that increases in the BIS and AAI and a decrease in Ce propofol corresponded to an increased likelihood of consciousness or responsiveness. We computed the normalized cumulative occurrence of consciousness-responsiveness as the percentage of such occurrences with index values below the cutoff value for BIS and AAI and above the cutoff value for Ce propofol. Similarly, we computed the normalized cumulative occurrence of unconsciousness-nonresponsiveness as the percentage of such occurrences with index values above the cutoff value for BIS and AAI and below the cutoff value for Ce propofol. We computed sensitivity as the proportion of conscious-responsive patients with positive test results (index value higher than cutoff value for BIS and AAI and lower than cutoff value for Ce propofol). Similarly, we computed specificity as the proportion of unconscious-nonresponsive patients with negative test results (index value lower than cutoff value for BIS and AAI and higher than cutoff value for Ce propofol). We computed positive predictive value as the proportion of patients with positive test results that were correctly diagnosed as conscious or responsive. Similarly, we computed negative predictive value as the proportion of patients with negative test results that were correctly diagnosed as unconscious-nonresponsive.

#### Interference Analysis

We became concerned during the analysis of this study that the auditory input ("clicks") from the A-Line® monitor might significantly alter BIS values because of the presence of the small evoked response in the electroencephalography. Therefore, an interference analysis study was performed. Fifteen female patients with the same inclusion criteria as the main study were included to receive three different concentrations of propofol (1.5–3–4.5 µg/ml) using an effect compartment controlled administration identical to the main study. Randomly in nine patients, both monitors were connected to the patient for 6 min, described as the "on" phase, whereafter the A-Line® "clicks" were disconnected for 2 min, described as the "off" phase. In six patients, the "off" period was maintained during the first 6 min, followed by a 2-min "on" period. In all patients, the se-

quence was repeated three times at the three different propofol target concentrations. The averaged BIS values (obtained using the area under the curve technique) between minutes 5 and 6 after the start of propofol administration were compared with the averaged BIS values between minutes 7 and 8, using a Wilcoxon signed rank test for two related samples.

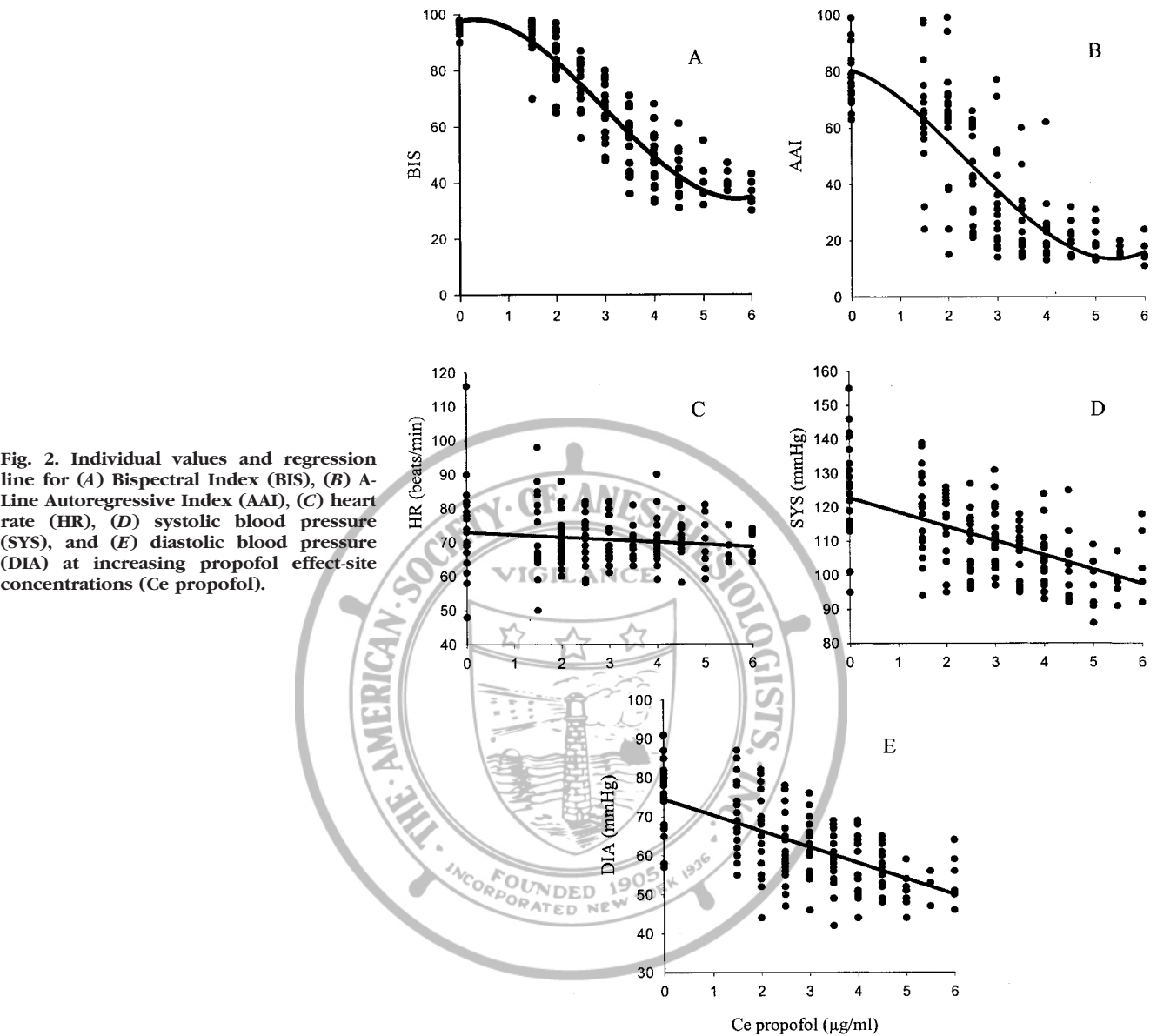
## Results

The demographics (mean ± SD) of the 20 female patients in the main study are as follows: age, 32 ± 5 yr; weight, 63 ± 6 kg; and height, 167 ± 10 cm.

Figure 2 shows the behavior of BIS, AAI, heart rate, and blood pressure at increasing propofol effect-site concentrations. A significant decrease in BIS and AAI was found with increasing propofol concentration. For heart rate, systolic blood pressure, and diastolic blood pressure, less significant changes were found. Considerably less scatter was observed in the BIS results than in the other variables. The Spearman rank-order correlation between the different variables and Ce propofol is shown in table 2. The best correlation was obtained for BIS, followed by AAI. For all hemodynamic variables, we observed a poor correlation with Ce propofol.

With increasing sedation (decrease in OAA/S score from level 5 to level 0), the median BIS decreased from 95 to 48, median AAI decreased from 70 to 19, and Ce propofol increased from 1.5 to 4 µg/ml (median), as shown in Figures 3A–C, respectively. In contrast (figs. 3D–F), only small, if any, changes were observed in heart rate (from 71 beats/min [median] at OAA/S level 5 to 69 beats/min at OAA/S level 0), systolic blood pressure (from 120 to 106 mmHg), and diastolic blood pressure (from 74 to 58 mmHg). For the mean arterial pressure, similar small changes were found (from 88 to 74 mmHg). The AAI (fig. 3B) reached its minimum early compared with the BIS (fig. 3A).

At the moment of loss of eyelash reflex (fig. 4), significant changes in median BIS (from 72 to 64), AAI (from 43 to 22), and Ce propofol (from 2.5 to 3 µg/ml) were found when comparing the values taken at the level just before loss of consciousness and just after loss of consciousness. No hemodynamic variables showed differences at loss of eyelash reflex. No indicators showed significant changes at the moment of loss of response to noxious stimulus (figure 5) when comparing the values taken at the last level before loss of response with the first level after loss of response. The ability of the indicators to predict the OAA/S score, loss of eyelash reflex, and loss of response to noxious stimulus as presented by the  $P_K$  values is shown in table 3. In all tests, a similar performance was found for BIS, AAI, and Ce propofol. A much lower performance was observed for the hemodynamic indicators. The SE for the  $P_K$ s of the OAA/S for BIS



**Fig. 2.** Individual values and regression line for (A) Bispectral Index (BIS), (B) A-Line Autoregressive Index (AAI), (C) heart rate (HR), (D) systolic blood pressure (SYS), and (E) diastolic blood pressure (DIA) at increasing propofol effect-site concentrations ( $C_e$  propofol).

and AAI were 0.015 and 0.013, respectively. By calculating the  $t$  statistic, we found that this study including 20 patients had the power to determine significant differences between indicators of OAA/S score larger than 0.058, which is in accordance with our initial assumption.

**Table 2.** Spearman Rank Correlations between the BIS, AAI, and Hemodynamic Variables and Propofol Effect-site Concentration

	Propofol Effect-site Concentration
Bispectral Index (BIS)	-0.905
A-Line Autoregressive Index (AAI)	-0.794*†
Heart rate (HR)	-0.144*††
Systolic blood pressure (SYS)	-0.477*††
Mean blood pressure (MAP)	-0.484*††
Diastolic blood pressure (DIA)	-0.497*††

\*  $P < 0.05$  between BIS and other measures; †  $P < 0.05$  between AAI and HR, SYS, MAP, and DIA; ††  $P < 0.05$  between HR and SYS, MAP, and DIA.

tion that only difference larger than 0.05 would be considered significantly different.

Because the previous analysis revealed the best performance for BIS, AAI, and  $C_e$  propofol, further examination was warranted. By applying Probit analyses, the effective concentration or index at which 50% ( $ED_{50}$ ) and 95% ( $ED_{95}$ ) of the patients lost response to the OAA/S levels 5, 4, and 3 or eyelash reflex, were calculated (table 4). The complete probability curves for these observations are shown in figures 6A-C for  $C_e$  propofol, BIS, and AAI, respectively. For loss of response to noxious stimulus, the  $ED_{50}$  and  $ED_{95}$  are also shown in table 4, and the probability curves are plotted in figure 6 for  $C_e$  propofol, BIS, and AAI, respectively.

The normalized cumulative occurrence curves for these data are shown in figures 7A-C for BIS, figures



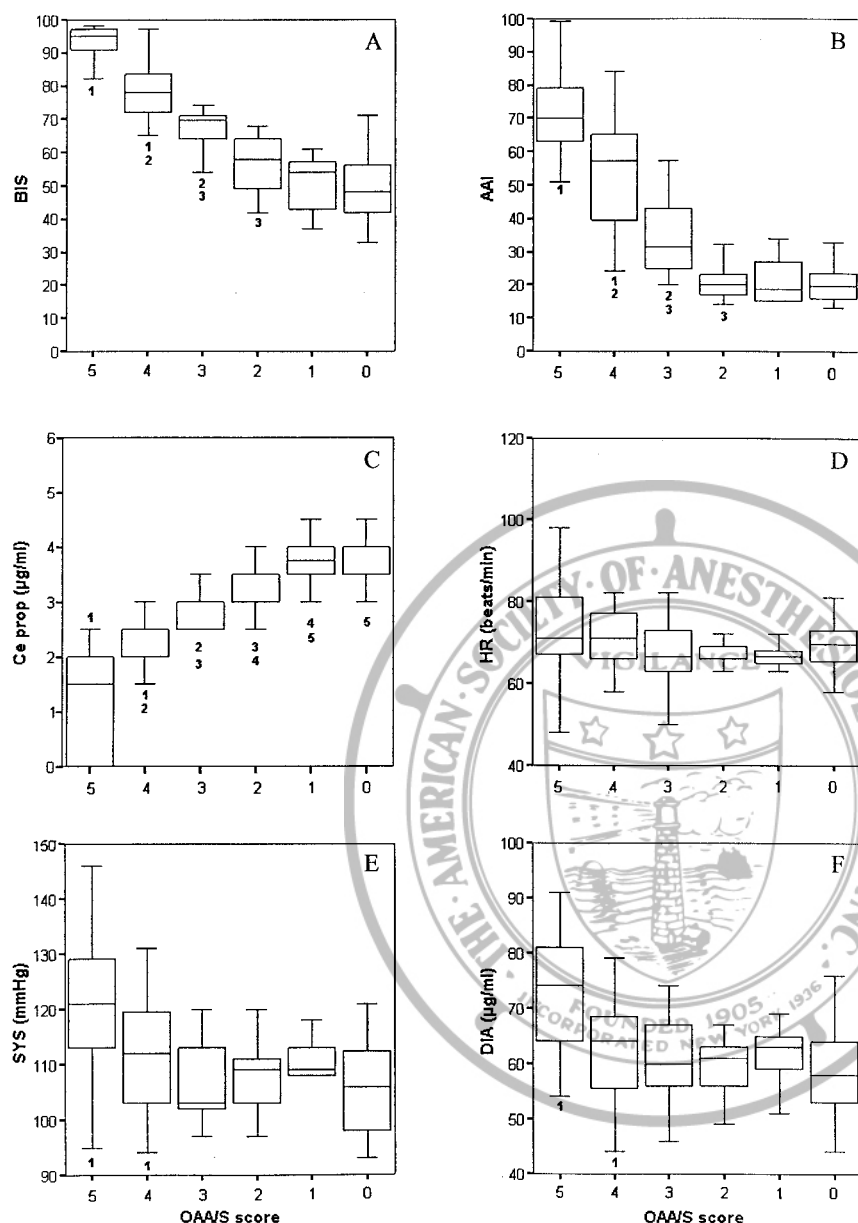


Fig. 3. Boxplot graphics (mean and 25th and 75th percentiles [box top and bottom] and 5th and 95th percentiles [whiskers]) for (A) Bispectral Index (BIS), (B) A-Line Autoregressive Index (AAI), (C) propofol effect-site concentration (Ce propofol), (D) heart rate (HR), (E) systolic blood pressure (SYS), and (F) diastolic blood pressure (DIA) at different levels of the Observer's Assessment of Alertness/Sedation scale (OAA/S). 1 =  $P < 0.05$  between levels 5 and 4; 2 =  $P < 0.05$  between levels 4 and 3; 3 =  $P < 0.05$  between levels 3 and 2; 4 =  $P < 0.05$  between levels 2 and 1; 5 =  $P < 0.05$  between levels 1 and 0.

7D-F for AAI, and figures 8A-C for Ce propofol. The data in figures 7 and 8 are presented for the OAA/S levels (conscious *vs.* unconscious), (loss of) eyelash reflex, and (loss of) response to noxious stimulus. In all figures, no variable provided perfect sensitivity-specificity. Therefore, more in-depth sensitivity-specificity calculations were performed.

Tables 5-7 show the specific sensitivity and specificity values of different cutoff BIS, AAI, and Ce propofol levels to observe loss of consciousness as described by OAA/S, loss of eyelash reflex, and loss of response to noxious stimulus. To be 100% certain of unconsciousness, a BIS value of just less than 55, an AAI of just less than 20, or a Ce propofol value just greater than 3.5  $\mu\text{g/ml}$  was required. All patients were found to be conscious at a BIS value greater than 75, at an AAI value greater than 66,

and at a Ce propofol value less than 2  $\mu\text{g/ml}$ . For all indicators, some overlap between the curves was found.

After stimulus, the maximum mean increases in BIS and AAI until 1 min after stimulus were 8.2 (SD, 5.0) and 15.4 (SD, 11.1), respectively. The mean reaction times until maximum value were 39 s (SD, 12 s) and 20 s (SD, 15 s) ( $P < 0.05$ ) for BIS and AAI, respectively. To illustrate this behavior, the time synchronized averages of the digitally recorded values are shown in figure 9.

#### Interference Analysis

The results for the on-off study at three different propofol steady state concentrations are shown in figure

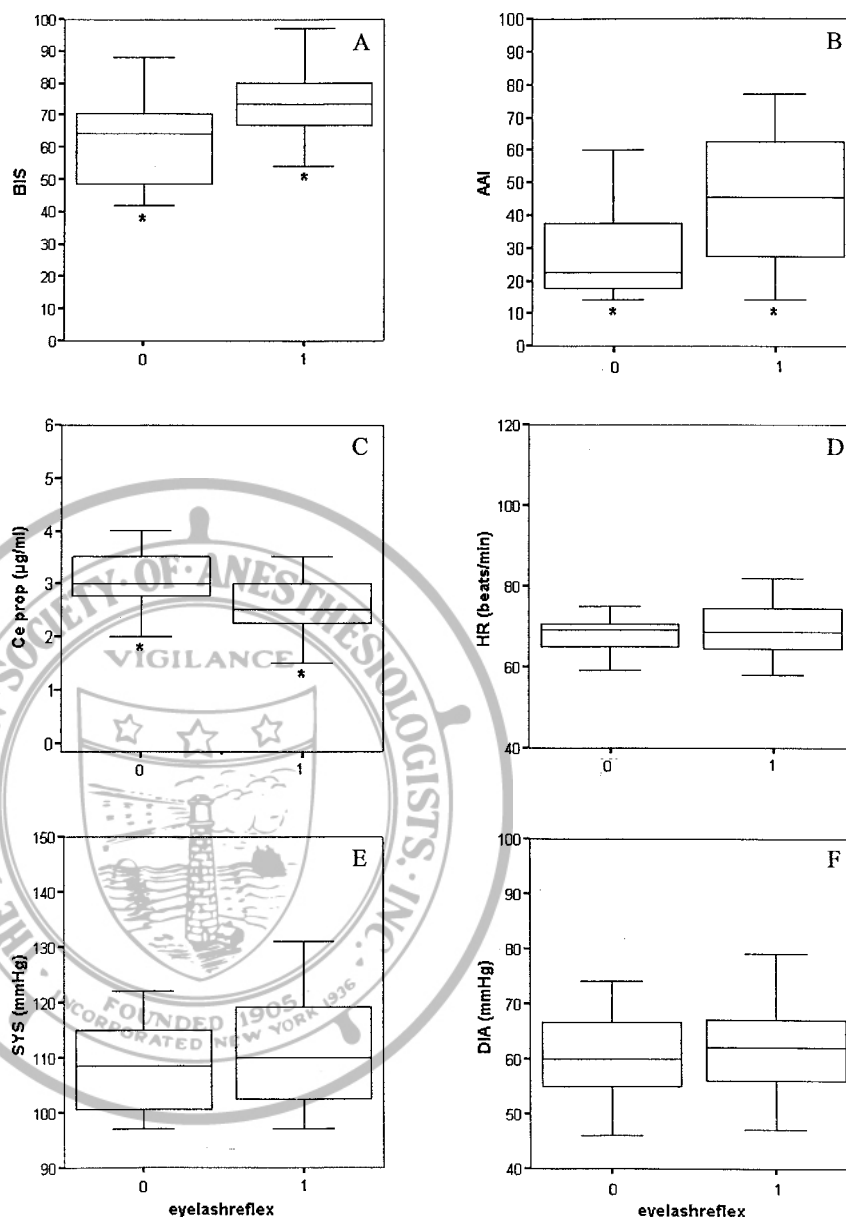


Fig. 4. Boxplot graphics (mean and 25th and 75 percentiles [box top and bottom] and 5th and 95th percentiles [whiskers]) for (A) Bispectral Index (BIS), (B) A-Line Autoregressive Index (AAI), (C) propofol effect-site concentration (Ce propofol), (D) heart rate (HR), (E) systolic blood pressure (SYS), and (F) diastolic blood pressure (DIA) for the last level of response (1) or the first level of no response (0) to eyelash reflex. \* $P < 0.05$  between groups.

10. No significant differences in BIS values between the "on" and "off" periods were found.

## Discussion

The current study demonstrates that a stepwise increase in propofol effect-site concentration (Ce propofol) resulted in a monotonic decrease in BIS and AAI, which correlated well with the level of sedation and loss of consciousness as observed by the OAA/S score and loss of eyelash reflex. In contrast, the changes in hemodynamic measures in our study did not correlate well with changes in Ce propofol or in level of sedation or loss of consciousness. We selected the OAA/S score because it provides a good correlation with sedation and has been tested prospectively.<sup>21</sup> In addition, loss of eye-

lash reflex was used because it is a simple binary variable and is commonly applied by anesthesiologists in clinical practice to detect loss of consciousness.

Although both BIS and AAI indicators seemed to be clinically accurate, the Spearman correlation between BIS and Ce propofol was significantly better than the correlation between AAI and Ce propofol (table 2 and figure 2). This means that a better degree of monotonic relation was found between BIS and Ce propofol compared with AAI and Ce propofol. Recently, Iselin-Chaves *et al.*<sup>11</sup> concluded that the Pearson correlation (measuring the degree of linear monotonic relation) between BIS and a measured steady state concentration of propofol ( $r = -0.8$ ) was significantly better than the correlation between MLAEP latency variables, Pa and Nb latency, and propofol ( $r_{Pa} = 0.68$  and  $r_{Nb} = 0.63$ ). Bonhomme *et*

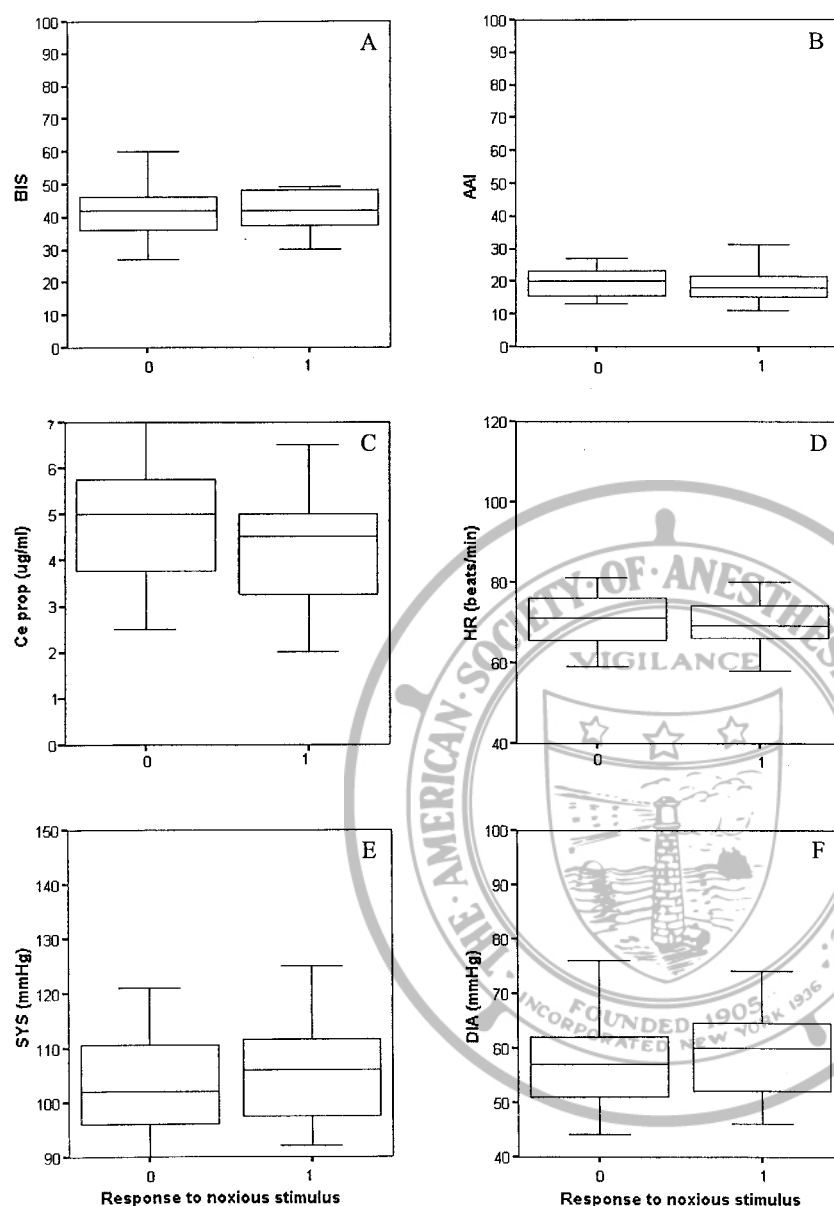


Fig. 5. Boxplot graphics (mean and 25th and 75 percentiles [box top and bottom] and 5th and 95th percentiles [whiskers]) for (A) Bispectral Index (BIS), (B) A-Line Autoregressive Index (AAI), (C) propofol effect-site concentration (Ce propofol), (D) heart rate (HR), (E) systolic blood pressure (SYS), and (F) diastolic blood pressure (DIA) for the last level of response (1) or the first level no response (0) to noxious stimulus. \* $P < 0.05$  between groups.

*al.*<sup>12</sup> found correlation coefficients similar to ours when comparing BIS with another AEP technique called steady state response. The differences in abilities of BIS and AAI to correlate with a range of propofol effect-site concentrations has to do with the fundamental difference in the

signals that are being processed. Although the AAI is a linear mapping of the MLAEP peak amplitudes and latencies, it does not give a linear correlation to the Ce propofol, in contrast with BIS, which was developed using correlation between electroencephalography and

Table 3. Prediction Probability Scores, Mean (SE)

	$P_K$ for OAA/S Score	$P_K$ for Loss of Eyelash Reflex	$P_K$ for Reaction to Noxious Stimulus
Bispectral Index (BIS)	0.93 (0.01)	0.95 (0.02)	0.87 (0.13)
Autoregressive-index (AAI)	0.89 (0.02)	0.94 (0.03)	0.88 (0.13)
Ce propofol	0.91 (0.01)	0.94 (0.03)	0.82 (0.11)
Heart rate (HR)	0.59 (0.04)*	0.61 (0.05)*	0.60 (0.10)
Systolic blood pressure (SYS)	0.72 (0.03)*	0.74 (0.04)*	0.72 (0.03)
Mean blood pressure (MAP)	0.70 (0.04)*	0.65 (0.04)*	0.68 (0.04)
Diastolic blood pressure (DIA)	0.71 (0.04)*	0.53 (0.04)*	0.59 (0.04)

\*  $P < 0.05$  compared with bispectral index.

$P_K$  = prediction probability; Ce propofol = propofol effect-site concentration.



**Table 4.** ED<sub>50</sub> (CI 95%)/ED<sub>95</sub> Values of BIS, AAI, and Ce propofol for Three Levels of the OAA/S Score (Until Loss of Consciousness), Loss of Eyelash Reflex, and Loss of Response to Noxious Stimulus

	BIS	AAI	Ce propofol
Loss of OAA/S 5	85 (82–88)/80	63 (52–75)/40	1.9 (1.4–2.1)/2.9
Loss of OAA/S 4	74 (60–82)/58	39 (30–46)/20	2.7 (2.5–2.9)/3.5
Loss of OAA/S 3	66 (61–70)/52	28 (25–32)/19	3.1 (2.9–3.2)/3.7
Loss of eyelash reflex	71 (63–76)/54	30 (20–39)/11	3.0 (2.7–3.4)/3.9
Loss of response to noxious stimulus	41 (33–47)/20	16 (10–21)/4	5.2 (4.3–7.4)/13.0

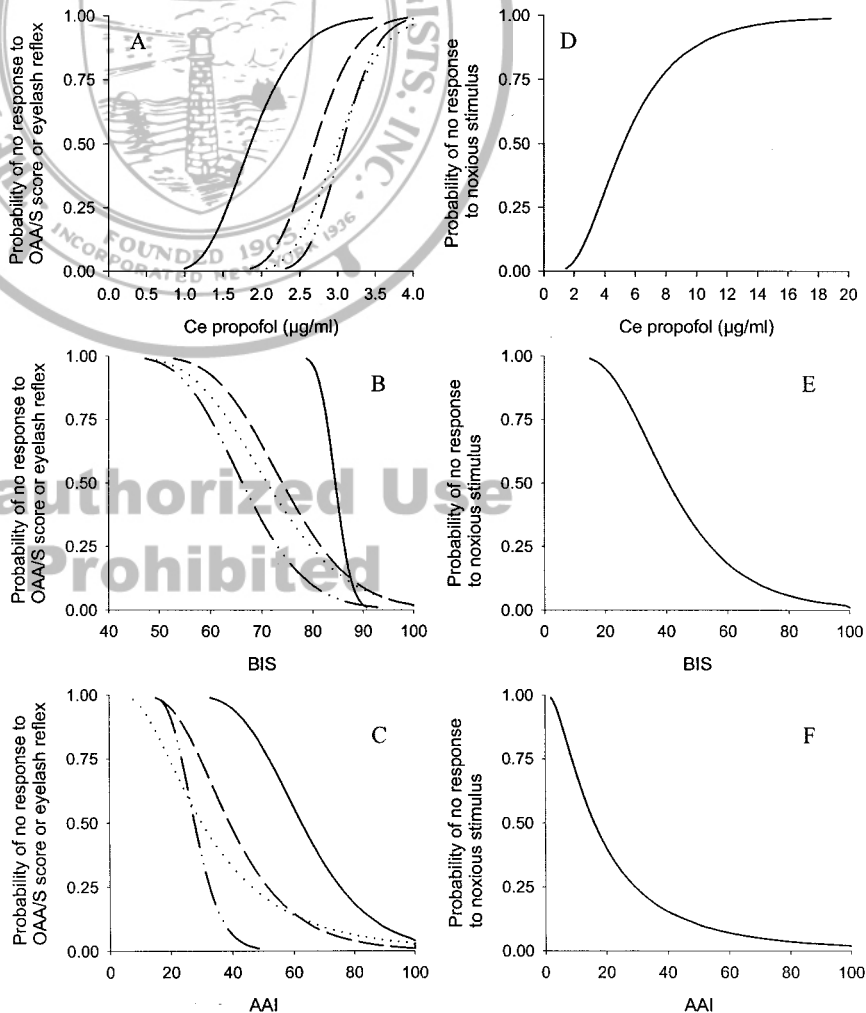
OAA/S = observer's assessment of alertness and sedation; BIS = Bispectral Index; AAI = A-Line autoregressive index; Ce propofol = propofol effect-site concentration.

drug concentrations. One might argue the appropriateness of attempting to develop an anesthetic depth indicator (e.g., cerebrally derived) by establishing a linear relation to anesthetic effect-site concentration. It is known that individuals vary in sensitivity to anesthetics and that anesthetic concentration is not a perfect predictor of an individual's anesthetic depth, especially if the interpretation of concentration value to predict depth is for a population of patients rather than one individual.<sup>22</sup> Therefore, an anesthetic depth indicator

that is developed by crafting it to track concentration is inherently limited. A better strategy for developing an anesthetic depth indicator is to craft the indicator to track the patient's clinically measured anesthetic depth; therefore, we also studied the behavior of the different indicators in that way.

Bispectral Index, AAI, and Ce propofol changed significantly during the transition from a conscious to an unconscious state, as shown in figure 3 for the transition from OAA/S level 3 to level 2 and as shown in figure 4 for loss of eyelash reflex. This is in contrast to previous work from Gajraj *et al.*<sup>23,24</sup> using a mathematically derived single numerical variable from the MLAEP, called the AEP index. During repeated transitions from awake to asleep and nonsteady conditions, they concluded that the AEP index was better able to detect the transition from unconsciousness to consciousness than was BIS (using an A-1000 monitor and software version 3.0).<sup>4</sup> For the hemodynamic data, no changes were observed at loss of consciousness. Once again, this suggests that hemodynamic data are not useful indicators for describing depth of sedation or loss of consciousness, as already stated by other investigators.<sup>25</sup>

**Fig. 6.** Probability of no response to different levels of the Observer's Assessment of Alertness/Sedation scale (OAA/S) (level 5 = straight line; level 4 = dashed line; level 3 = dashed and dotted line) and eyelash reflex (dotted line) as a function of (A) propofol effect-site concentration (Ce propofol), (B) Bispectral Index (BIS), and (C) A-Line Autoregressive Index (AAI). Probability of no response to noxious stimulus as a function of (D) Ce propofol, (E) BIS, and (F) AAI.



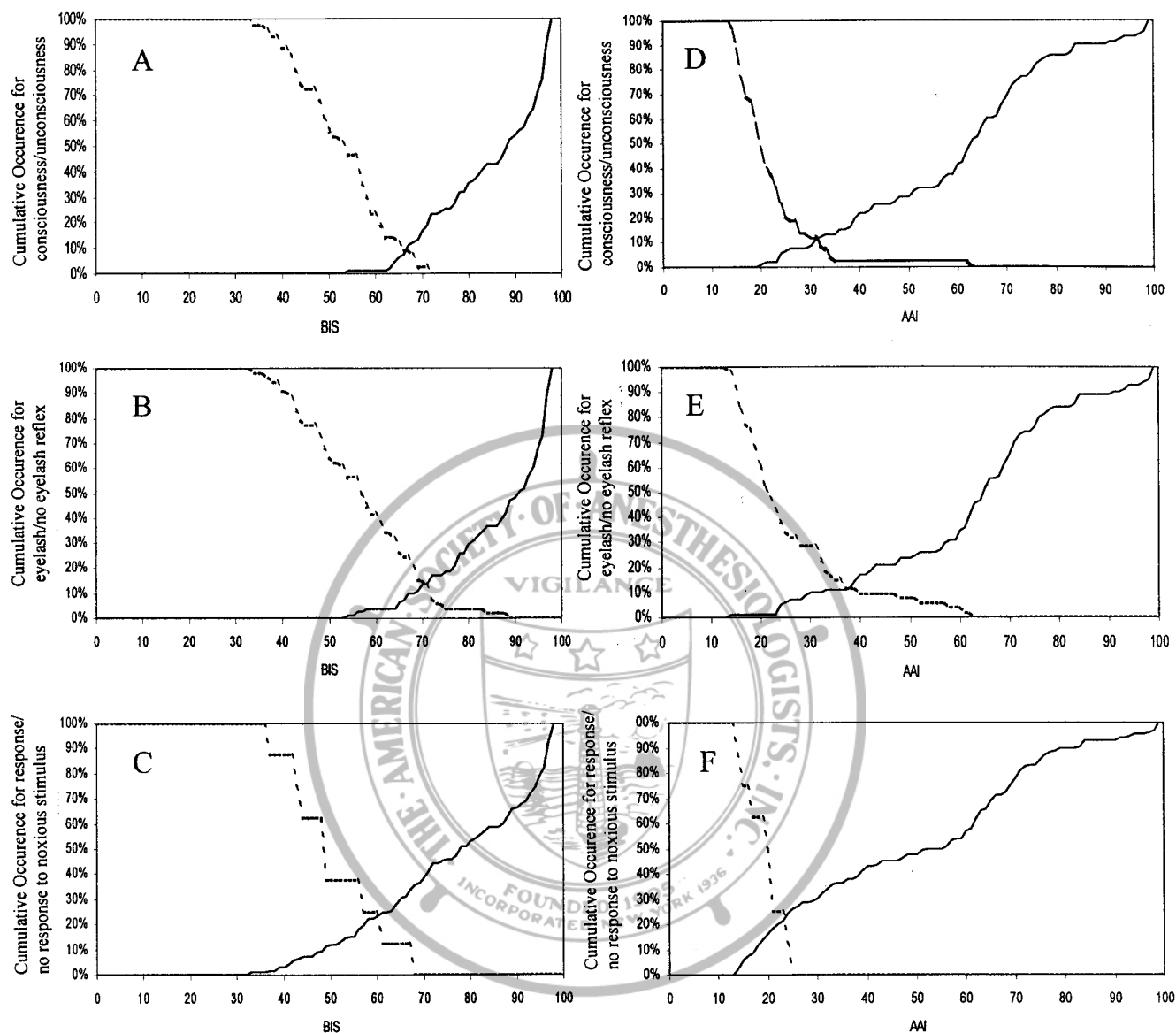


Fig. 7. Cumulative occurrence for consciousness (straight line), unconsciousness (dashed line) described by the Observer's Assessment of Alertness/Sedation Scale (OAA/S; transition from level 3 to level 2) as a function of the (A) Bispectral Index (BIS) and the (D) A-Line Autoregressive Index (AAI). Cumulative occurrence for consciousness (straight line), unconsciousness (dashed line) described by presence-loss of eyelash reflex as a function of (B) BIS and (E) AAI. Cumulative occurrence for response (straight line), no response (dashed line) to noxious stimulus as a function of (C) BIS and (F) AAI.

The correlations between the different indicators and the sedation score are important to observe in assessing their performance accuracy. As shown in figure 3, ordinal values obtained using a responsiveness rating scale such as the OAA/S score may not allow a perfect linear relation between the observed clinical state of the patient and the measured value of the indicator. To account for this, the prediction probability,  $P_K$ , provides a better alternative to investigate the overall relative performance of the different indicators in describing a sedation level or loss of consciousness.<sup>19,20,26</sup> Table 3 shows that BIS, AAI, and  $C_e$  propofol comparably, and reasonably accurately, predicted the level of sedation or loss of consciousness as observed by the OAA/S score or

the loss of eyelash reflex. The performance of the hemodynamic data was significantly worse in predicting the sedation level or loss of consciousness. These performance results indicate that both BIS and AAI are reliable indicators for assessing depth of sedation and loss of consciousness. At the level of significance used in our study, the cerebrally derived indicators, BIS and AAI, were found to be comparable in performance to estimated steady state propofol concentration,  $C_e$  propofol. Our findings agree with those previously found for propofol,<sup>27</sup> as well as the previously published observations between utility of BIS and measured sevoflurane or isoflurane end-tidal concentration.<sup>21,26</sup> This highly predictive accuracy of drug effect-site concentrations has

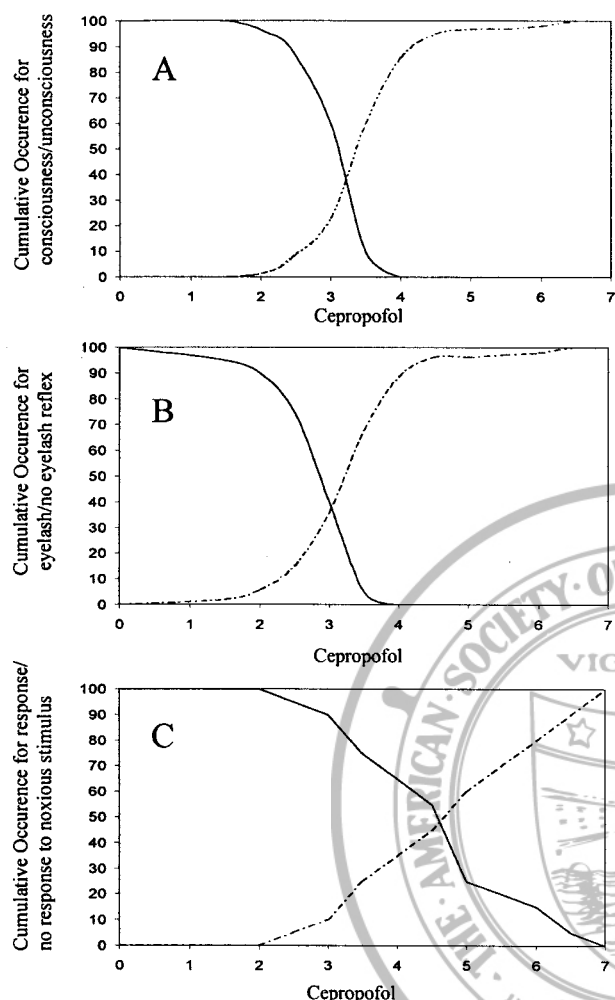


Fig. 8. Cumulative occurrence for (A) consciousness (straight line), unconsciousness (dashed line) as described by the Observer's Assessment of Alertness/Sedation Scale (OAA/S; transition from level 3 to level 2) and (B) as described by presence (straight line), loss (dashed line) of eyelash reflex as a function of the propofol effect-site concentration (Ce propofol). (C) Cumulative occurrence for response (straight line), no response (dashed line) to noxious stimulus as a function of Ce propofol.

only been established during steady state conditions and single-drug settings, as in this study. Additional research should be performed to study the performance of these indicators during multiple drug administration, as well as during non-steady state conditions.

Because BIS, AAI, and Ce propofol were the most accurate indicators that we studied, we examined these in greater depth. As shown in figure 6A and in table 4, higher propofol effect-site concentrations were required to cause loss of response at decreasing OAA/S levels until loss of consciousness. This was correlated with a decrease in BIS (fig. 6B) and AAI values (fig. 6C). The results for Ce propofol and BIS found in this study agree with those previously found by other investigators who used the same scoring systems.<sup>21,26,28,29</sup>

The study was also aimed at observing the sensitivity-specificity characteristics for BIS, AAI, and Ce propofol

in more detail. Recently, Drummond<sup>30</sup> expressed the opinion that a depth of anesthesia indicator should have, at a minimum, a 100% sensitivity (no false-negative results) if what the clinicians seek is a specific numeric threshold ("cutoff value") that can be interpreted to mean "not aware." Ideally, there should be a 100% sensitivity and specificity. Unfortunately, to the best of our knowledge there exists no system or monitor in the real world reaching this level.

In our study (figure 7), because the cumulative occurrence data derived from our population showed some overlap between "conscious" and "not conscious," none of the three "best" indicators was found to be ideal.

Table 5. Specific Sensitivity or Specificity of Different "Cut-off" BIS Levels to Describe Loss of Consciousness as Described by OAA/S, Loss of Eyelash Reflex, and Loss of Response to Noxious Stimulus

Variable	Cut-off Value	Specificity	Sensitivity	Negative Predictive Value	Positive Predictive Value
BIS OAA/S score	100	—	—	0.32	—
	95	—	0.28	0.40	—
	90	—	0.46	0.47	—
	85	—	0.57	0.52	—
	80	—	0.65	0.57	—
	75	—	0.75	0.55	—
	70	0.98	0.84	0.74	0.99
	65	0.91	0.93	0.87	0.96
	60	0.81	0.99	0.97	0.92
	55	0.53	0.99	0.96	0.82
	53	0.53	1.00	1.00	0.82
BIS LER	100	—	—	0.40	—
	95	—	0.32	0.49	—
	90	—	0.52	0.58	—
	85	0.98	0.63	0.63	0.98
	80	0.96	0.70	0.68	0.97
	75	0.96	0.81	0.77	0.97
	70	0.87	0.86	0.81	0.90
	65	0.75	0.94	0.89	0.85
	60	0.62	0.96	0.92	0.80
	55	0.43	0.98	0.96	0.73
	53	0.43	1.00	1.00	0.73
BIS LRNS	100	—	—	0.11	—
	95	—	0.17	0.13	—
	90	—	0.28	0.15	—
	85	—	0.35	0.16	—
	80	—	0.40	0.17	—
	75	—	0.46	0.19	—
	70	—	0.52	0.21	—
	65	0.95	0.59	0.23	0.99
	60	0.95	0.66	0.26	0.99
	55	0.84	0.72	0.28	0.97
	50	0.84	0.77	0.32	0.97
	45	0.74	0.82	0.34	0.96

BIS = Bispectral Index; OAA/S = observer's assessment of alertness and sedation; LER = loss of eyelash reflex; LRNS = loss of response to noxious stimulus.



**Table 6. Specific Sensitivity or Specificity of Different "Cut-off" AAI Levels to Describe Loss of Consciousness as Described by OAA/S, Loss of Eyelash Reflex, and Loss of Response to Noxious Stimulus**

Variable	Cut-off Value	Specificity	Sensitivity	Negative Predictive Value	Positive Predictive Value
AAI OAA/S score	70	—	0.31	0.41	—
	65	—	0.43	0.45	—
	60	0.98	0.58	0.53	0.98
	55	0.98	0.68	0.59	0.98
	50	0.98	0.71	0.62	0.98
	45	0.98	0.75	0.65	0.99
	40	0.98	0.78	0.68	0.99
	35	0.98	0.87	0.78	0.99
	30	0.88	0.91	0.83	0.94
	25	0.81	0.93	0.85	0.91
	20	0.60	0.98	0.96	0.84
	19	0.51	1.00	1.00	0.81
AAI LER	70	—	0.35	0.50	—
	65	—	0.48	0.58	—
	60	0.98	0.65	0.65	0.98
	55	0.94	0.74	0.70	0.95
	50	0.92	0.77	0.72	0.94
	45	0.91	0.79	0.74	0.93
	40	0.91	0.83	0.77	0.93
	35	0.85	0.89	0.83	0.90
	30	0.72	0.90	0.83	0.83
	25	0.68	0.94	0.88	0.82
	20	0.49	0.99	0.96	0.75
	19	0.40	1.00	1.00	0.71
AAI LRNS	70	—	0.19	0.14	—
	65	—	0.26	0.15	—
	60	—	0.36	0.17	—
	55	—	0.42	0.18	—
	50	—	0.44	0.19	—
	45	—	0.46	0.19	—
	40	—	0.48	0.20	—
	35	—	0.54	0.22	—
	30	—	0.60	0.24	—
	25	0.89	0.65	0.25	0.98
	20	0.63	0.74	0.25	0.94
	15	0.26	0.89	0.24	0.90
	13	0.11	0.98	0.50	0.90

AAI = A-Line autoregressive index; OAA/S = observer's assessment of alertness and sedation; LER = loss of eyelash reflex; LRNS = loss of response to noxious stimulus.

However, such monitors might still help provide in the "decision support" during anesthesia. The cutoff values with 100% sensitivity and their corresponding specificity found in this study are shown in tables 5–7.

The study also tested the performance of the indicators to predict movement as a reaction to noxious stimulus. The supramaximal tetanic stimulus used in this study was previously used by other investigators as a substitute for conventional forms of stimulation in humans.<sup>27</sup> As shown in figure 5, no indicator changed significantly when loss of response to noxious stimulus occurred. Other investigators have already observed that measures from the cerebral cortex such as electroencephalography and AEP are poor predictors of response to noxious

stimulus.<sup>31</sup> Likewise, the hemodynamic values recorded in this study were also nonpredictive regarding loss of response to noxious stimulus. Because of the specific design of our protocol, we only observed static hemodynamic values recorded just before the stimulus and not changes in the hemodynamics after each noxious stimulus. Changes in hemodynamics caused by noxious stimulus might indicate stress response or arousal more accurately. Table 3 shows that the  $P_K$  values, which indicate the ability of the variables to predict loss of response to the noxious stimulus, were not significantly better for one indicator over another because of the large SEM values. During propofol-alfentanil anesthesia, Doi *et al.*<sup>32</sup> found a mean  $P_K$  value of 0.54 (SE, 0.10) for BIS to predict movement at the insertion of a laryngeal mask. In contrast to our results, they found a significantly better prediction probability ( $P_K = 0.87$ ; SE = 0.073) for the AEP-derived variable, AEP index, to predict movement at laryngeal mask insertion. They concluded that the ability of the AEP to discriminate between movers and nonmovers in response to a noxious

**Table 7. Specific Sensitivity or Specificity of Different "Cut-off" Levels of Ce Propofol to Describe Loss of Consciousness as Described by OAA/S, Loss of Eyelash Reflex, and Loss of Response to Noxious Stimulus**

Variable	Cut-off Value	Specificity	Sensitivity	Negative Predictive Value	Positive Predictive Value
Ce Propofol OAA/S score	1.5	—	0.22	0.38	—
	2	—	0.44	0.46	—
	2.5	0.98	0.65	0.57	0.98
	3	0.93	0.85	0.74	0.96
	3.5	0.76	0.98	0.94	0.90
	4	0.40	1.00	1.00	0.78
Ce Propofol LER	4.5	0.14	—	—	0.71
	5	0.05	—	—	0.68
Ce Propofol LRNS	1.5	—	0.25	0.46	—
	2	0.98	0.48	0.55	0.98
	2.5	0.94	0.70	0.68	0.95
	3	0.85	0.89	0.83	0.90
	3.5	0.64	0.98	0.97	0.81
	4	0.32	1.00	1.00	0.69
Ce Propofol OAA/S score	4.5	0.11	—	—	0.63
	5	0.04	—	—	0.61
Ce Propofol LRNS	1.5	—	0.13	0.13	—
	2	—	0.27	0.15	—
	2.5	—	0.40	0.18	—
	3	0.95	0.53	0.20	0.99
	3.5	0.89	0.65	0.25	0.98
	4	0.74	0.75	0.27	0.96
	4.5	0.63	0.84	0.33	0.95
	5	0.53	0.91	0.43	0.94
	5.5	0.37	0.95	0.47	0.92
	6.0	0.26	0.97	0.50	0.91
Ce Propofol OAA/S score	6.5	0.16	0.99	0.75	0.90
	7.0	0.06	1.00	1.00	0.90

Ce propofol = propofol effect-site concentration; OAA/S = observer's assessment of alertness and sedation; LER = loss of eyelash reflex; LRNS = loss of response to noxious stimulus.

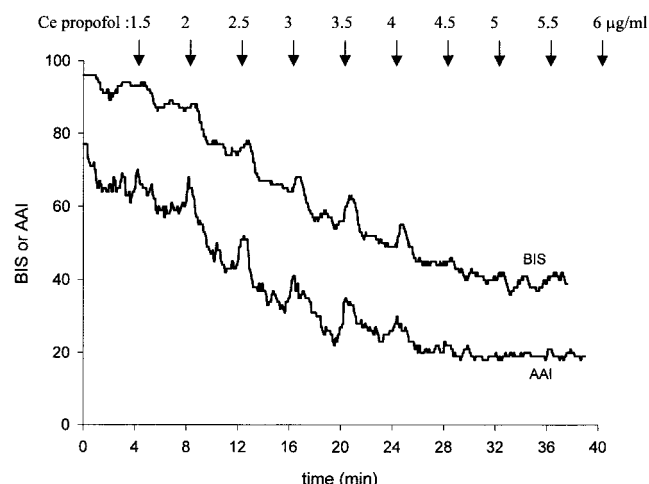


Fig. 9. The time-synchronized averages of the digitally recorded values for Bispectral Index (BIS) and A-Line Autoregressive Index (AAI) taken from all patients at increasing targeted effect-site concentration of propofol (Ce propofol) to illustrate to poststimulus arousal effect every 4 min as an increase of both variables. (Top) The equilibrated Ce propofol at the moment of stimulus are shown.

stimulus is caused by the fact that AEP reflects not only cortical but also subcortical brain activities. In contrast, our results describe no better performance of the AAI than BIS in predicting surgical immobility. No accurate threshold values could be defined for any indicator with acceptable specificity-sensitivity values (tables 5-7). With respect to movement in response to a noxious stimulus, Thornton and Sharpe<sup>33</sup> suggested that various end points such as loss of consciousness and loss of response to a noxious stimulus do not appear to be a part of a single continuum and can occur independently of one other. We suggest that the poor performance of the rostral central nervous system indicators tested here

might support the hypothesis that movement response to a noxious stimulus occurs as a spinal reflex.<sup>34</sup> Only when the information can reach the cerebral cortex *via* afferent central nervous system pathways, changes might be observed in the cerebrally derived indicators (= arousal reaction).<sup>35</sup> This arousal reflex was clearly manifested by both indicators, BIS and AAI, as illustrated in figure 9. The reaction time for detecting arousal was significantly shorter with the AAI than BIS because of the shorter signal acquisition and processing time found with the A-Line<sup>®</sup> monitor compared with the BIS<sup>®</sup> monitor, as previously observed by other investigators.<sup>9</sup>

A limitation of this study is the possible intraobserver bias because of the fact that the observer was not completely blinded to the indicator values when scoring the clinical measures. In addition,  $P_K$  statistics assumed independent data. For the OAA/S score, the assessments were all collinear with depth. In the absence of a comparable statistical test to analyze these data, we have accepted, as have other investigators,<sup>26</sup> the potential bias introduced into our results.

For the interference analysis, the results for the on-off study at three different propofol steady state concentrations are shown in figure 10. No significant differences in BIS values between the "on" and "off" periods were found.

In conclusion, during propofol anesthesia with steady state conditions, we found that BIS, AAI, and Ce propofol were accurate indicators for the level of sedation and loss of consciousness. Hemodynamic variables were poor indicators of the hypnotic-anesthetic status of the patient. BIS correlated best with propofol effect-site concentration, followed by the AAI. Hemodynamic measurements did not correlate well. No indicators revealed any information concerning reaction to noxious stimulus.

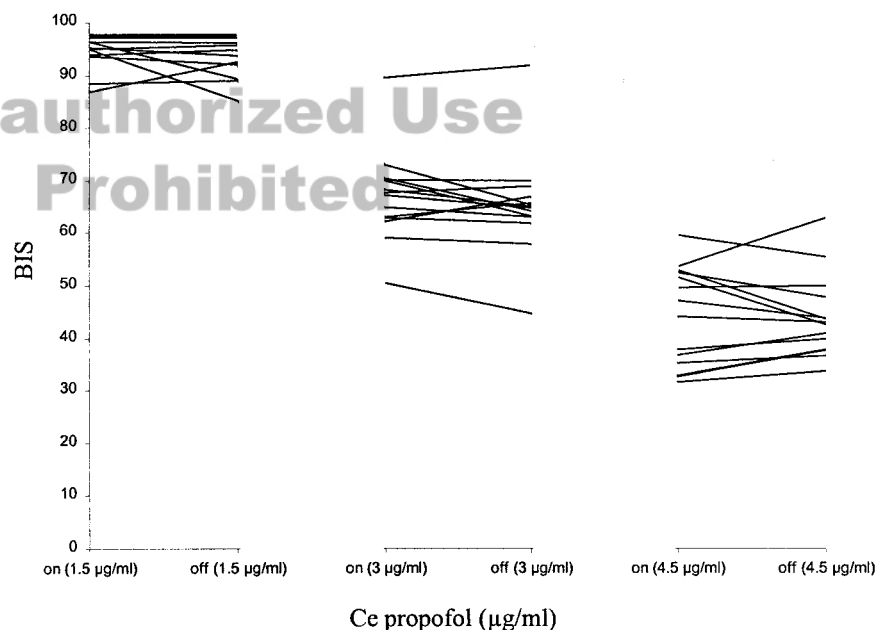


Fig. 10. Results of the interference analysis between the BIS<sup>®</sup> and the A-Line<sup>®</sup> monitors. Averaged BIS values for all patients (n = 15) are shown at three different steady state concentrations of propofol (Ce propofol) in the presence (on) or absence (off) of the auditory stimulus from the A-Line<sup>®</sup> monitor.

After stimulus, BIS and AAI showed an increase as a result of arousal. This reaction occurred more rapidly with the AAI than with BIS.

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