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Auditory Evoked Potential Index Predicts the Depth of Sedation and Movement in Response to Skin Incision during Sevoflurane Anesthesia

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Background: **The auditory evoked potential (AEP) index, which is a single numerical parameter derived from the AEP in real time and which describes the underlying morphology of the AEP, has been studied as a monitor of anesthetic depth. The current study was designed to evaluate the accuracy of AEPindex for predicting depth of sedation and anesthesia during sevoflurane anesthesia.**

Methods: **In the first phase of the study, a single end-tidal sevoflurane concentration ranging from 0.5 to 0.9% was assigned randomly and administered to each of 50 patients. The AEPindex and the Bispectral Index (BIS) were obtained simultaneously. Sedation was assessed using the responsiveness portion of the observer's assessment of alertness–sedation scale. In the second phase of the study, 10 additional patients were included, and the 60 patients who were scheduled to have skin incisions were observed for movement in response to skin incision at the end-tidal sevoflurane concentrations between 1.6 and 2.6%. The relation among AEPindex, BIS, sevoflurane concentration, sedation score, and movement or absence of movement after skin incision was determined. Prediction probability values for AEPindex, BIS, and sevoflurane concentration to predict depth of sedation and anesthesia were also calculated.**

Results: **The AEPindex, BIS, and sevoflurane concentration correlated closely with the sedation score. The prediction probability values for AEPindex, BIS, and sevoflurane concentration for sedation score were 0.820, 0.805, and 0.870, respectively, indicating a high predictive performance for depth of sedation. AEPindex and sevoflurane concentration successfully predicted movement after skin (prediction probability = 0.910 and 0.857, respectively), whereas BIS could not (prediction probability = 0.537).**

Conclusions: **Auditory evoked potential index can be a guide to the depth of sedation and movement in response to skin incision during sevoflurane anesthesia.**

SEVERAL electroencephalographic variables have been studied as a monitor of depth of sedation or anesthesia.[1–8] However, the use of scalp-recorded electroencephalographic variables is still controversial, especially as a predictor of movement.[3–6, 8] The auditory evoked potential (AEP) is another possible monitor of anesthetic depth. Middle latency AEPs have been reported to correlate well with depth of anesthesia[9] and to demonstrate the consciousness of anesthetized patients.[10,11] A recent study reported that 40 Hz middle latency AEP activity was especially accurate in predicting wakeful response during desflurane and propofol anesthesia in volunteers.[12] However, these middle latency AEP values are usually obtained intermittently, and their waveforms can be difficult to interpret in clinical situations. To address this problem, the AEPindex, which is derived from the AEP in real time, was recently proposed as a single value (ranged from 0 to 100) for monitoring depth of anesthesia.[13–17] The AEPindex reflects the shape of AEP waveforms and is calculated from the amplitude difference between successive 0.56-ms segments of the curve.[13]

Recent studies have reported that the AEPindex discriminates between consciousness and unconsciousness better than other electroencephalographic variables during propofol sedation.[14,15] Furthermore, the AEPindex predicts movement on insertion of the laryngeal mask airway during propofol and alfentanil anesthesia.[16] These results show that the AEPindex might be a useful predictor of both sedation and movement in response to several noxious stimuli.

It is not known whether the AEPindex correlates with volatile anesthetic–induced sedation and anesthesia. The current study was designed to evaluate the efficacy of the AEPindex for predicting the depth of sedation and depth of anesthesia as defined by movement in response to skin incision during sevoflurane anesthesia. Simultaneous with AEPindex measurement, we also recorded the Bispectral Index (BIS) to compare the predictive abilities of these two indices.

Materials and Methods

Participants

After obtaining approval from the ethics committee (Committee on Human Research, Hamamatsu University School of Medicine, Hamamatsu, Japan) and informed consent, we studied 60 patients (17 men, 43 women), all classified as American Society of Anesthesiologists physical status I or II, who were scheduled for elective noncranial surgery with skin incision longer than 5 cm. Patients ranged in age from 21 to 69 yr (mean age ± SD, 47.2 ± 11.8 yr). Fifty of the 60 subjects participated in the first phase (assessments of the depth of sedation) and

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Table 1. Responsiveness Scores of the Modified Observer's Assessment of Alertness/Sedation Scale (OAA/S)

Responsiveness	Score
Responds readily to name spoken in normal tone	5 (alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapetius squeeze	1
Does not respond to painful trapetius squeeze	0

the second phase (assessments of the depth of anesthesia), while an additional 10 patients participated in the second phase only. Exclusion criteria were a history of esophageal reflux or hiatal hernia, drug or alcohol abuse, significant obesity (body mass index > 30), and contraindication for inhalational induction. Patients fasted for at least 8 h before surgery and received no premedicant drugs.

Study Design

The depth of sedation was evaluated at subminimum alveolar concentration end-tidal concentrations of 0.5, 0.6, 0.7, 0.8, and 0.9%. The concentration range was based on data from a previous study.[8] Each of the first 50 patients in the study was randomly administered one of the aforementioned five concentrations. After maintaining the end-tidal sevoflurane concentration for 15 min, the depth of sedation was assessed using the responsiveness component of the Observer's Assessment of Alertness/Sedation (OAA/S) rating scale (table 1).[18] This assessment procedure involves introduction of progressively more intense stimulation, ranging from a moderate speaking voice to physical shaking or moderate noxious stimuli (trapezius squeeze) until a response is observed. These stimuli were applied at 15-s intervals. All assessments of sedation level were performed by one investigator to minimize interobserver variability. The AEPindex and BIS were simultaneously recorded from just before the administration of sevoflurane until anesthesia depth assessments. The AEPindex and BIS values were calculated at 1 min before the assessment of depth of sedation and the patients' movements by averaging the 15-s interval values to that point. After the first 50 patients in the study had undergone the various sedation measurements, the depth of anesthesia was evaluated at anesthetizing concentrations of 1.6, 1.8, 2.0, 2.2, 2.4, and 2.6%. This range was chosen to supply both adequate and inadequate levels of anesthesia and was based on data from previous minimum alveolar concentration studies.[19,20] An additional 10 patients who were only assessed for the depth of anesthesia were also given one of the aforementioned six concentrations. In all 60 patients, movement in response to skin incision was observed to assess the depth of anesthesia.

Acquisition of Auditory Evoked Potentials

The AEPs were obtained using a similar system to that described in previous studies[10,13,14] from three disposable silver-silver chloride electrodes (Zipprep; Aspect Medical Systems, Natick, MA) placed on the right mastoid (+), middle forehead (−), and Fp2 as a reference. The amplifier was custom-built with a 5-kV medical grade isolation. It had a common mode rejection ratio of 170 dB with balanced source impedance, input voltage noise of 0.3 mV (10 Hz to 1 kHz rms), and current input noise of 4 pA (0.05 Hz to 1 kHz rms). A third-order Butterworth analog band-pass filter with a bandwidth of 1–220 Hz was used. The clicks were 70 dB above the normal hearing level with a duration of 1 ms. They were presented at a rate of 6.9 Hz to both ears using a standard molded earplug. The amplified electroencephalogram was sampled at a frequency of 1,778 Hz by a 12-bit analog-to-digital converter (PCM-DAS08; Computer Boards Inc., Mansfield, MA) and was processed in real time by a microcomputer (T2130CT; Toshiba, Tokyo, Japan). AEPs were produced by averaging 256 sweeps of 144-ms duration. The time required for a full update of the signal was 36.9 s, and the AEPs were obtained at intervals of 3 s. The AEPindex is a mathematical derivative that indicates the shape of the AEP. The value was calculated as the sum of the square root of the absolute difference between every two successive 0.56-ms segments of the AEP waveform (see Appendix).[13]

Bispectral Index Analysis

The BIS was obtained from four electrodes (Zipprep) placed bilaterally on the outer malar bone (At1 and At2), with Fpz as the reference and Fp1 as the ground. The impedance of the electrodes was confirmed to be less than 2,000. The BIS was measured using an electroencephalographic monitor (A-1000, version 3.2, Aspect Medical Systems), requiring at least 30 s to be fully updated. Values were stored automatically on the microcomputer at 5-s intervals.

Anesthetic Techniques

All patients breathed through a face mask connected to a semiclosed anesthetic circuit. Fresh gas flow into the anesthetic circuit was 6 l/min. To prevent contamination of end-tidal samples with inspired gas, dead space was augmented at the sampling port (between the mouthpiece and Y piece) with tubing having an internal volume of 60 ml. For analysis, gas was drawn continuously at a flow rate of 200 ml/min from the sampling port located between the face mask and the dead space. The concentrations of carbon dioxide, sevoflurane, and oxygen were measured continuously using an infrared anesthetic gas analyzer (Ohmeda 5250 RGM, Louisville, KY), which was calibrated before anesthesia was administered for each patient using a standard gas mixture.

Anesthesia was induced with sevoflurane and oxygen,

first during spontaneous ventilation and then during assisted ventilation as required to maintain an adequate tidal volume for the accurate measurement of end-tidal anesthetic concentration. The end-tidal carbon dioxide concentration was kept between 35 and 45 mmHg during the study period. The inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration at a constant, predetermined value. After maintaining the end-tidal sevoflurane concentration for 15 min, depth of sedation was assessed. After these assessments, the inspired sevoflurane concentration was increased for tracheal intubation. Vecuronium (0.02 mg/kg) was administered for precurarization, and then paralysis was induced with 1.5 mg/kg succinylcholine, followed by tracheal intubation. Immediately after tracheal intubation, the inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration at a constant, predetermined value. Movement in response to skin incision was tested after maintaining the end-tidal concentration at a constant value for more than 15 min. Any visible spontaneous muscle movement, such as withdrawal or flexor movement of the arms or legs, frowning of the forehead muscles, or coughing, was considered movement. The AEPindex and BIS were recorded before assessing the patient's movement in response to skin incision. Residual neuromuscular blockade was assessed by train-of-four stimulation of the ulnar nerve. We confirmed that the response to train-of-four stimulation did not fade and the first twitch height at skin incision was not different from that recorded before administration of a muscle relaxant.

Additional Experiment

To determine the possibility that the repetitive stimuli used to evoke the AEP may interfere with or alter the BIS, we studied an additional 10 patients (three men, seven women). These patients ranged in age from 25 to 65 yr (mean age ± SD, 42.8 ± 17.0 yr). Anesthetic technique was performed in the same manner as previously described, and the inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration of 0.7% and, after tracheal intubation, 2.0%. After maintaining the end-tidal sevoflurane concentration at 0.7% for 15 min, the BIS value was recorded (control). After this assessment, the clicks were started, the AEPindex was monitored for 15 min, and the BIS value was recorded (BIS 1). After the clicks were stopped for 15 min, the BIS value was again recorded (BIS 2). BIS was continuously monitored from just before administration of sevoflurane until obtaining the last BIS value (BIS 2), and the AEPindex system was only placed on a patient before administration of sevoflurane and only operated while the BIS value was obtained, which was simultaneously recorded with the AEPindex (BIS 1). After tracheal intubation, the inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration of 2.0%. BIS values at each state were recorded using the same method as those recorded at 0.7%.

Statistical Analysis

The statistical data analysis was performed using StatView 4.54 (Abacus Concepts, Berkeley, CA). Kruskal-Wallis analysis of variance was used to determine significant changes in AEPindex or BIS and in sevoflurane concentration at different sedation scores. At $P < 0.05$, Bonferroni correction to the Mann–Whitney rank sum test was used to distinguish differences between sedation score groups. Furthermore, Spearman rank-order correlation analysis was performed to evaluate the relation between sedation scores and the AEPindex, BIS, or sevoflurane concentration. Kruskal-Wallis analysis of variance was also used to determine significant changes in AEPindex at different sevoflurane concentrations. The efficacy of the AEPindex, BIS, and sevoflurane concentration at predicting depth of sedation and movement in response to skin incision was evaluated using prediction probability (Pk), which compares the performance of indicators having different units of measurement. The mathematical basis of Pk was described by Smith *et al.*[21] A Pk value of 1 means that the values of the predicting variable (*e.g.*, anesthetic depth indicator) always correctly predict the value of the variable to be predicted (*e.g.*, true observed anesthetic depth). A Pk value of 0.5 means that the values of the indicator predict no better than a 50–50 chance. A Pk value was computed for all 50 sedation assessments combined. Similarly, Pk values for all 60 skin incision assessments combined were determined. The jackknife method was used to compute the standard error of the estimate, based on the assumption that the 50 assessments and the 60 skin incisions were independent. The predictive performance of AEPindex, BIS, and sevoflurane were compared. A paired-data jackknife analysis[21] was used to determine whether the Pk value for one indicator differed from that of another indicator. For multiple comparisons, we used Bonferroni correction to the paired-data jackknife analysis. Pk was calculated using a custom spreadsheet macro, PKMACRO.[21]

For each AEPindex, BIS, and sevoflurane concentration, we estimated the median effective dose (ED_{50}) values for preventing response to three nonnoxious stimuli (verbal command in normal tone, loud, or repeated verbal command and verbal command after mild prodding or shaking) using a logistic regression analysis described by Waud.[22] The ED_{50} values for three nonnoxious stimuli were computed by Waud's technique.[22] Similarly, ED_{50} values for preventing movement after skin incision were estimated. The ED_{95} value was calculated directly from the best-fitting logistic curve. $P < 0.05$ was considered significant.

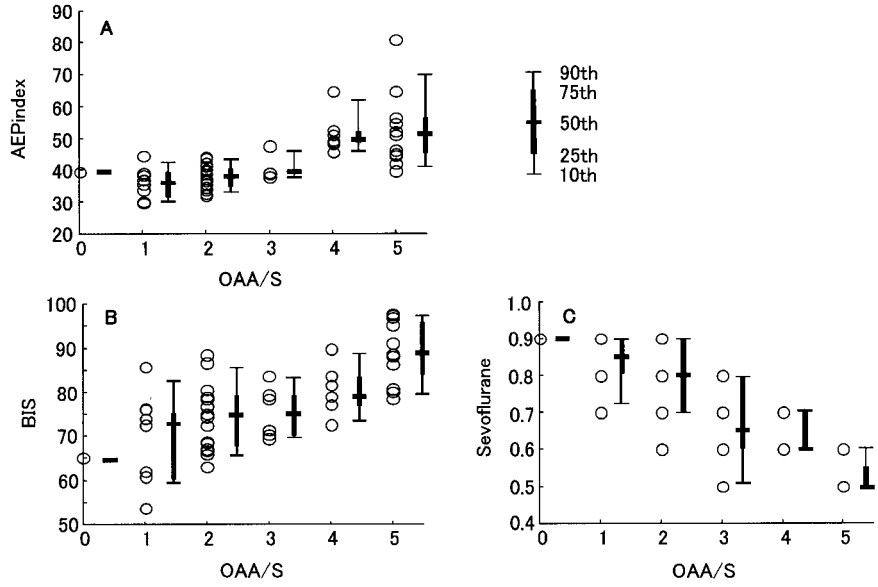

Fig. 1. (*A*) Auditory evoked potential (AEP) index, (*B*) Bispectral Index (BIS), and (*C*) sevoflurane concentration at different observers' assessments of alertness and sedation (Observer's Assessment of Alertness/Sedation [OAA/S]) scores during sevoflurane-induced sedation. The values are either median (25th–75th, 10th–90th percentile interval) or individual.

Results

Figure 1 shows the AEPindex, BIS, and sevoflurane concentration at different observer's assessment of alertness and sedation scores. Only one patient did not respond to painful trapezius squeeze (OAA/S = 0). AEPindex, BIS, and sevoflurane concentration changed significantly with increasing sedation. The AEPindex values decreased from 51.7 (median) at an OAA/S of 5 to 36.4 at an OAA/S of 1. No significant difference in AEPindex values was observed between an OAA/S of 0 and OAA/S of 1. The BIS values decreased from 88.7 at an OAA/S of 5 to 65.2 at an OAA/S of 0, and sevoflurane concentration increased Spearman correlation coefficients from 0.5 to 0.9 between AEPindex, BIS, or sevoflurane concentration, and the sedation scores were 0.74 ($P < 0.0001$), 0.68 ($P < 0.0001$), and −0.83 ($P < 0.0001$), respectively. The Pk values (based on all 50 assessments), which indicate the probability of correctly predicting the rank order of the OAA/S, were 0.870 ± 0.025 (SEM) for sevoflurane concentration, 0.820 ± 0.033 for AEPindex, and 0.805 ± 0.042 for BIS. All indicators predicted sedation level significantly better than a 50–50 chance. No significant difference in Pk values was observed.

Figure 2 shows the relations between AEPindex and the probability of response to three nonnoxious stimuli. Table 2 lists the ED_{50} and ED_{95} values of sevoflurane concentration, AEPindex, and BIS for three nonnoxious stimuli and skin incision.

The Pk value, which indicates the probability of correctly predicting whether a patient will move in response to skin incision, was 0.910 ± 0.041 for AEPindex, 0.857 ± 0.046 for sevoflurane concentration, and 0.537 ± 0.078 for BIS. AEPindex and sevoflurane concentration predicted movement after skin incision better than chance alone, whereas BIS could not predict movement. The Pk values for AEPindex and sevoflurane concentration differed significantly from that of BIS. No significant difference in Pk values was observed between AEPindex and sevoflurane concentration. Because AEPindex was shown to be a reliable predictor of movement, the ED_{50} value of AEPindex for skin incision was determined to be 37.7 (95% confidence interval, 36.3–39.1). The ED_{95} of AEPindex was 32.7. Figure 3 shows the relations between AEPindex and the probability that movement after skin incision will occur. It was not possible to relate BIS and the probability of movement using logistic regression analysis.

The scatter diagram in figure 4 shows the relation among AEPindex, end-tidal sevoflurane concentration (from sedation level to anesthesia level), and response to loud verbal command, or movement in response to skin incision. The solid lines represent third-order polynomial regression curves of the sedation and anesthesia ranges. When end-tidal sevoflurane concentration increased from 0.5 to 0.8%, the AEPindex values decreased almost linearly from 51 (median) to 37.2. The AEPindex showed

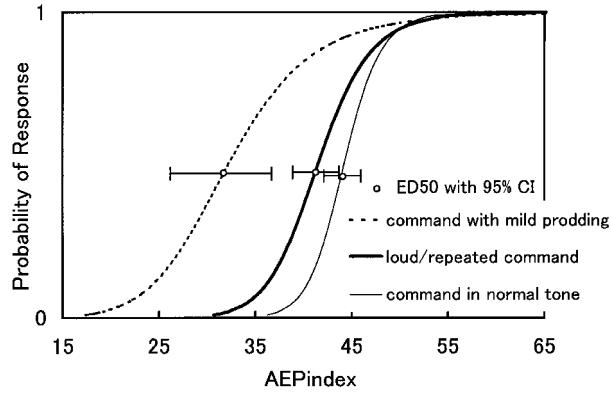

Fig. 2. Probability of response to three kinds of nonnoxious stimuli as a function of the auditory evoked potential (AEP) index. The values are median effective doses with 95% confidence intervals (CI).

Table 2. ED_{50} and ED_{95} Values of the Sevoflurane Concentration, AEP Index, and Bispectral Index for Three Types of Nonnoxious Stimuli and Skin Incision: ED_{50} (95% Confidence Interval)/ED_{95}

Type of Stimuli	Sevoflurane	AEP Index	BIS
Command in normal tone	0.63 (0.59–0.68)/0.81	44.2 (42.1–46.3)/38.9	81.6 (77.9–85.3)/68.8
Loud and/or repeated verbal command	0.70 (0.65–0.74)/0.86	41.5 (39.2–43.7)/34.1	77.7 (73.3–82.0)/60.9
Loud repeated command after mild prodding or shaking (tactile stimuli)	0.89 (0.79–0.98)/1.19	32.1 (26.8–37.5)/21.7	63.4 (55.1–71.7)/46.6
Skin incision	2.03 (1.91–2.17)/2.70	37.7 (36.3–39.1)/32.7	—

AEP = auditory evoked potential; BIS = Bispectral Index.

no further decrease beyond 0.8% in patients who did not undergo tracheal intubation. The AEPindex also decreased with an increase in end-tidal sevoflurane concentrations from 1.6 to 2.6% in patients who underwent tracheal intubation.

Additional Experiment

The BIS values at sevoflurane end-tidal concentration of 0.7% were 77.6 ± 7.6 (mean ± SD) in the control (BIS before the clicks), 77.8 ± 6.6 in BIS 1 (BIS during the clicks), and 78.0 ± 6.4 in BIS 2 (BIS after the clicks). No significant differences were observed between each state. BIS values at sevoflurane end-tidal concentration of 2.0% were 47.0 ± 14.8 in the control, 46.5 ± 15.8 in BIS 1, and 46.8 ± 15.9 in BIS 2. No significant differences were observed between each state.

Discussion

The Pk value for AEPindex for sedation score was 0.82. The good correlation between AEPindex and depth of sedation, coupled with the excellent Pk value, indicates that AEPindex is a reliable guide to the depth of sedation. No significant difference in the Pk values was observed among indicators. These findings suggest that the utility of the AEPindex, not only to predict whether patients are conscious (usually defined as an OAA/S = 3, 4, or 5) or unconscious (OAA/S = 0, 1, or 2), but also to predict sedation level, is similar to that of the end-tidal sevoflurane concentration or BIS when sevoflurane is administered alone.

The correlation between AEPindex and the probability of response to normal verbal commands showed a similar pattern, but the response probability significantly shifted to the left when verbal commands were given in a loud voice or repeated. The AEPindex responses to verbal commands after tactile stimuli shifted significantly further to the left (fig. 2). A similar pattern appeared with respect to the relations between sevoflurane concentration or BIS and probability of response to these verbal stimuli (not shown), with these findings corresponding with those of the previous study.[8] The ED_{50} of AEPindex for preventing response to loud or repeated verbal commands was 41.5 (95% confidence interval, 39.2–43.7). In a study in which alternating periods of consciousness and unconsciousness were produced by target-controlled infusions of propofol during spinal anesthesia, Gajraj *et al.*[15] reported that the mean value of the AEPindex during periods of unconsciousness was 37.6 (SD, 6.5); however, these investigators did not report the ED_{50} value. In our study, because the mean value of the AEPindex for preventing response to loud or repeated verbal commands was 37.2 (SD, 4.2), the AEPindex value for preventing response to a verbal com-

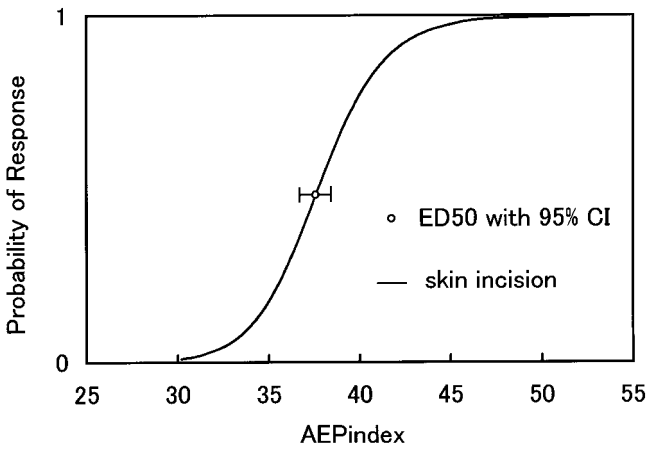

Fig. 3. Probability of movement after skin incision as a function of the auditory evoked potential (AEP) index. The value is the median effective dose with a 95% confidence interval (CI).

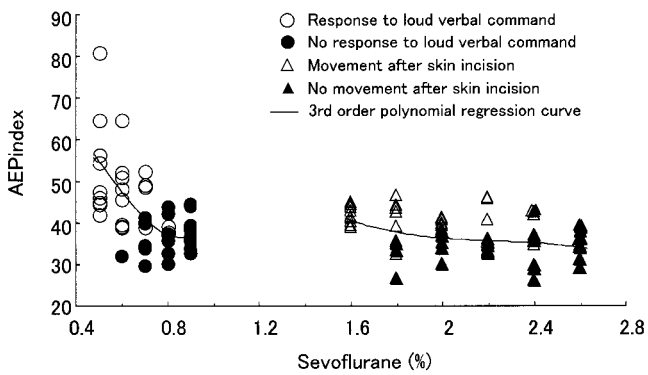

Fig. 4. Scatter diagram showing the relation among auditory evoked potential (AEP) index, end-tidal sevoflurane concentration, and response to loud verbal command, or movement in response to skin incision. Open symbols denote either responders or movers, whereas filled symbols denote either nonresponders or nonmovers.

mand during sevoflurane sedation may be similar to that during propofol sedation.

The AEPindex successfully predicted movement after skin incision just as did sevoflurane concentration, whereas BIS alone could not predict movement better than chance. Although previous studies reported that BIS could predict movement in response to skin incision,[3–6] we did not find any difference in BIS values between movers and nonmovers. This is consistent with a report by Katoh *et al.*,[8] who administered sevoflurane as a single anesthetic agent in the same manner as in this study; however, only an electroencephalographic monitor was used. They suggested that BIS is a cortical function indicator that does not directly reflect the activity of the subcortical structures, including the spinal cord, that primarily mediate motor response to a noxious stimulus; thus, BIS may not be reliable for predicting responsiveness to noxious stimuli. On the other hand, as AEPindex, even recorded at the scalp, could predict movement in response to skin incision, we could at least conclude that it reflects more than cortical function. The AEPindex is the monitor that obtains the response evoked by the stimulation (clicks); this response depends on subcortical pathways and may partly reflect the activity of the subcortical structures, including the spinal cord. In the first report of AEPindex as a predictor of movement, Doi *et al.*[16] reported that the AEPindex predicted movement in response to insertion of the laryngeal mask airway during propofol and alfentanil anesthesia. They reported that the ED_{50} and ED_{95} values preventing movement in response to laryngeal mask airway insertion were 45.4 and 33.1, respectively. Anesthesia was induced using a target-controlled infusion of propofol with a target blood concentration of propofol of approximately 6 g/ml, after confirmation of loss of consciousness, loss of eyelash reflex, and adequate jaw relaxation. According to the current study, the ED_{50} value preventing response to normal verbal commands (44.2) was less than the ED_{50} value of 45.4 that prevented movement in response to laryngeal mask airway insertion during propofol and alfentanil anesthesia. When the AEPindex value during sevoflurane anesthesia was 45.4, more than 50% of patients would respond to command in normal tone. This inconsistency suggests that the AEPindex may be affected by the balance of anesthetic agents used and the degree of stimulation of the patient.

The ED_{50} and ED_{95} values of the AEPindex for preventing movement in response to skin incision (37.7 and 32.7, respectively) were greater than those for preventing response to verbal commands after tactile stimuli (32.1 and 21.7, respectively; table 2). The AEPindex values of anesthesia level of sevoflurane concentration were not necessarily less than those of sedation level (fig. 4). The AEPindex value at sevoflurane end-tidal concentrations of 0.9% (38.3 [3.9], mean [SD]) was significantly less than that at sevoflurane end-tidal concentrations of 1.6% (41.5 [2.2]; fig. 4). Although we did not measure the AEPindex values at high sevoflurane end-tidal concentrations (1.6–2.6%) without tracheal intubation, we observed linear decreases of the AEPindex values with increases of sevoflurane concentration when inspired sevoflurane concentration was increased for tracheal intubation after depth of sedation was assessed. In this process, we did not observe biphasic changes of the AEPindex values. This suggests that the presence of the endotracheal tube is responsible for the higher AEPindex at a sevoflurane concentration of 1.6%. These findings suggest that the AEPindex may be a monitor of arousal level that indicates a dynamic balance between the strength of stimuli and the potency of anesthetic agents. In the current study, we were unable to compare AEPindex values among different stimulation states; further investigations into this matter are needed.

Finally, since we simultaneously monitored and recorded AEPindex and BIS in the current study, the repetitive stimuli used to evoke the AEP might have the possibility to interfere with or alter the BIS and final results. In our additional experiment, at least at sevoflurane end-tidal concentrations of 0.7% and 2.0% (thought to be the nearest concentrations of minimum alveolar concentration awake and minimum alveolar concentration), the clicks to evoke the AEP did not change the BIS values. However, because these results did not completely refute that performing an evoked response introduces a contaminating artifact into the spontaneous electroencephalogram consisting of the 6.9-Hz fundamental (the clicks were presented at a rate of 6.9 Hz) and a series of harmonics, the performance of the BIS in this study must be assessed carefully.

The current study demonstrates that the AEPindex can be a guide to the depth of sedation and movement in response to skin incision during sevoflurane anesthesia. Although further investigations are required to assess the ability of the AEPindex to predict sedation and anesthesia produced by different drugs, or during different stimulation states, the AEPindex has different possibilities for predicting anesthetic depth from surface electroencephalographic parameters.

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Appendix: Calculation of an Auditory Evoked Potential Index

Traditionally, AEPs are analyzed mostly in terms of amplitudes and latencies of the various peaks. Spectral analysis with the fast Fourier transformation has also been used. However, a single number, reflecting the morphology of the AEP, is highly desirable.

From a mathematical point of view, the problem can be defined as mapping a two-dimensional vector into a one-dimensional space. Obviously, this is not possible. A data reduction technique that will take only the relevant features of the AEP into account is required. It was observed that when patients lost consciousness, the amplitudes of the AEP peaks were reduced and their latencies were increased (fig. 5). Those changes were occurring almost simultaneously and in the same direction in all patients; therefore, a measurement that would reflect those changes could be promising.

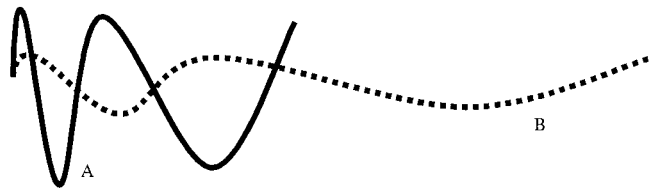

Fig. 5. (*A*) Typical auditory evoked potential waveform of a patient who is conscious. (*B*) Typical auditory evoked potential waveform of a patient who is anesthetized. The latencies of the wave peaks are increased, and the amplitudes are decreased.

Figure 6 is a schematic representation of those changes. A sinusoidal signal is sampled at two successive points, A and B. The sampling interval is t_s. V is the voltage difference between A and B at any given frequency and amplitude. When the frequency increases and the amplitude remains constant, V increases ($V_2 > V_1$, curve b). Similarly, when the frequency remains constant and the amplitude increases, V also increases ($V_3 > V_1$, curve c). Finally, when both the frequency and the amplitude increase, the voltage difference between A and B increases even more ($V_4 > V_1$, curve d).

An empirical algorithm, based on those observations, was developed. It calculates the sum of the square roots of the difference between every two successive points in the curve and produces a single number that reflects the "curviness" of the AEP. This number is called the *AEPindex* and is given by the following equation:

$$\text{AEPindex} = k \sum_{i=1}^{255} \sqrt{|V_i - V_{i+1}|}$$

where $V_1 \ldots V_{256}$ describes an averaged AEP curve as stored in the computer memory, and k is a scaling constant equal to 0.25. This scaling constant was determined empirically to provide an AEPindex approximately equal to 100 in fully alert volunteers. The units of this constant are reciprocals of the square root of volt because the AEPindex is dimensionless. The square root of the absolute difference between two successive points (and not simply their absolute difference) was selected to enhance the resolution of the algorithm in lower frequencies and amplitudes.

The AEPindex is calculated every 3 s and plotted on the screen. When the patient is awake, the AEPindex is approximately 80–90. During surgical anesthesia, it is 35–40. On recovery, it returns to values slightly lower than the awake ones.

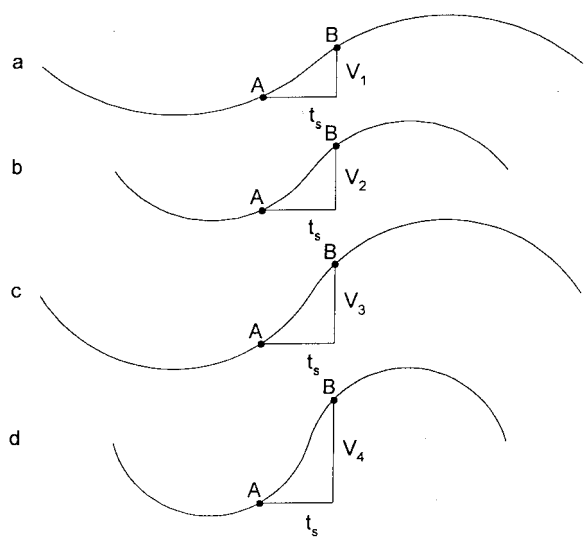

Fig. 6. Principle of the auditory evoked potential index calculation. The x-axis represents time, and the y-axis represents voltage.