A-Line, Bispectral Index, and Estimated Effect-Site Concentrations: A Prediction of Clinical End-Points of Anesthesia

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Autoregressive modeling with exogenous input of middle-latency auditory evoked potentials (A-Line AEP index, AAI) has been developed for monitoring depth of anesthesia. We investigated the prediction of recovery and dose-response relationship of desflurane and AAI or bispectral index (BIS) values. Twenty adult men scheduled for radical prostatectomy were recruited. To minimize opioid effects, analgesia was provided by a concurrent epidural in addition to the general anesthetic. Electrodes for AAI and BIS monitoring and a headphone for auditory stimuli were applied. Propofol and remifentanil were used for anesthetic induction. Maintenance of anesthesia was with desflurane only. For comparison to AAI and BIS monitor parameters, pharmacokinetic models for desflurane and propofol distribution and effect-site concentrations were used to predict clinical end-points (Prediction probability \( P_k \)). Patients opened their eyes at an AAI value of 47 ± 20 and a BIS value of 77 ± 14 (mean ± sd), and the prediction probability for eye opening was \( P_k = 0.81 \) for AAI, \( P_k = 0.89 \) for BIS, and \( P_k = 0.91 \) for desflurane effect-site concentration. The opening of eyes was best predicted by the calculated desflurane effect-site concentration. The relationship between predicted desflurane effect-site concentration versus AAI and BIS was calculated by nonlinear regression analysis \((r = 0.75 \text{ for AAI and } r = 0.80 \text{ for BIS})\). The correlation between BIS and clinical end-points of anesthesia or the desflurane effect-compartment concentration is better than for the AAI.

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A large body of evidence suggests that bispectral index (BIS, Aspect Medical Systems Inc., Newton, MA) of the electroencephalogram (EEG) may help to assess the hypnotic component of anesthesia (1–6). However, middle-latency auditory evoked potentials (AEP), which are currently used to quantify the pharmacodynamic (PD) action of anesthetic drugs (8–11), may detect the transition from unconsciousness to consciousness better than BIS (12). The A-Line AEP monitor (Danmeter, Odense, Denmark, version 1.4) is the first commercially available auditory evoked potential (AEP) monitor designed to measure the depth of anesthesia. It generates an A-line AEP index (AAI), a dimensionless number scaled from 100 (awake) to 0, with values between 15–30 indicating adequate anesthesia.

For inhaled anesthetics, a hysteresis or time lag between end-tidal and brain concentration has been recognized and physiologically modeled (13–14). The transition of anesthetics across the blood-brain barrier requires a certain time. Therefore, equilibrium between plasma and brain concentrations is reached after a time delay that is substance-specific and called “hysteresis,” i.e., the delay between the maximum plasma concentration and the maximum EEG effect. In pharmacokinetic (PK)/PD models, this hysteresis is considered by inclusion of a fictitious compartment, the so-called “effect compartment.”

The reports about the functionality of the AAI in the literature are contradictory. Struys et al. (15) found excellent prediction probabilities for the AAI, as good as for BIS, predicting the level of sedation during propofol administration. However, with inhaled anesthetics more than 0.5 MAC there was no relationship

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between sevoflurane (16) or desflurane concentrations (17) and AAI values.

Therefore, the present study was designed to define the relationship between predicted desflurane effect-site concentrations and AAI or BIS values and to explore the ability of AAI, BIS values, and desflurane effect-site concentration to predict clinically important end-points such as loss of eyelash reflex, eye opening, and tracheal extubation.

Methods

With IRB approval and written informed patient consent, 20 adult male patients scheduled for radical prostatectomy with a normal aural acuity were enrolled in this study. Exclusion criteria were a history of any disabling central nervous or cerebrovascular disease, hypersensitivity to opioids or substance abuse, or a treatment with opioids or any psychoactive medication.

All patients were premedicated with midazolam 7.5 mg orally on the morning before surgery. In the operating room, an IV catheter was inserted into a large forearm vein and standard monitors were applied. An epidural catheter was inserted in the lumbar space and a test dose of 3 mL bupivacaine 0.5% was given. After the skin of the forehead had been degreased with 70% isopropanol, the BIS (BIS Sensor, Aspect), the A-line electrodes (AEP electrodes, Danmeter) and a headphone for the delivery of auditory stimuli were synchronized by time for each device for each individual patient.

The three AEP electrodes were positioned at mid forehead, left forehead (reference), and left mastoid; both forehead electrodes were positioned cranially of the head, left forehead (reference), and left mastoid; both forehead electrodes were positioned cranially of the BIS sensor. Finally, impedances were measured by the internal capabilities of each monitor for each set of BIS sensor. The neurophysiologic electrodes to ensure optimal electrode contact as recommended by the manufacturers. The neurophysiologic electrodes were recorded continuously using an Aspect A-2000 BIS monitor (version XP) and the A-Line AEP monitor (version 1.4).

While oxygen 10 L/min was given by a facemask, anesthesia was induced with a remifentanil infusion (0.4 μg · kg⁻¹ · min⁻¹); 2 min later, 2 mg/kg propofol was given for hypnosis. After loss of consciousness, oxygen was given by facemask ventilation. Patients received 0.5 mg/kg atracurium 3 min before tracheal intubation. The lungs were ventilated to an end-tidal carbon-dioxide concentration of 35 mm Hg. Immediately after tracheal intubation, the desflurane vapor (Devapor, Dräger, Lübeck, Germany) was opened, and desflurane in O₂/air was given for hypnosis. The patient received 12 mL bupivacaine 0.5% epidurally, and the remifentanil infusion was stopped. We chose a combination of epidural analgesia with desflurane anesthesia to obviate the need for opioid analgesia.

Therefore, the desflurane effect on the EEG and the AEP could be studied without considering drug interaction. During maintenance of anesthesia, desflurane was delivered according to individual clinical needs. All patients were assessed for signs of inadequate anesthesia, e.g., hypotension, bradycardia, hypertension, tachycardia movement, or lacrimation. The patient did not receive further bupivacaine epidurally or any opioids during maintenance of anesthesia.

At the end of surgery, defined as the final surgical suture, desflurane delivery was stopped and the fresh gas flow was increased to 10 L/min oxygen while the respirator pattern was unchanged. Simultaneously, complete neuromuscular recovery was ensured by neuromuscular monitoring; i.e., train-of-four and double-burst stimulation monitoring. There was no further stimulation until the spontaneous opening of eyes. The patients were tracheally extubated after awakening from anesthesia and sufficient spontaneous breathing.

End-tidal desflurane concentrations were measured using infrared absorption technology (pm 8050, Dräger) and recorded using the software program Proto 99 (version 1.0.2.0, Dräger); the AAI and BIS values were recorded by Hyperterminal (Microsoft Inc., Redmond, WA). Data were recorded automatically at 5-s intervals. The data evaluation period included the induction of anesthesia and the last 15 min before tracheal extubation. The data sets were synchronized by time for each device for each individual patient.

The propofol effect-site concentrations were calculated using the software program STANPUMP (revision date: December, 1999; copyrighted by S. Shafer, Stanford, CA) using the Dipifusor data set as published by Marsh et al. (18). Desflurane effect-site concentrations were obtained by simultaneous PK modeling (19). To eliminate the hysteresis between the end-tidal concentrations of desflurane and the neurophysiologic effect, an effect compartment was introduced into the model:

\[
\frac{dC_{eff}}{dt} = (C_{et} - C_{eff}) \cdot k_{e0}
\]

where \(C_{et}\) is desflurane end-tidal concentrations, \(C_{eff}\) is desflurane effect compartment concentration, \(k_{e0}\) is first order rate constant determining the efflux from the effect compartment.

The effect-site concentrations were calculated with a \(k_{e0}\)-value of 0.61 L/min as published by Rehberg et al. (20). The relationship between predicted desflurane effect-site concentrations and AAI or BIS was calculated by nonlinear regression analysis by minimizing the squared error between the measured and predicted concentration that necessarily maximizes the coefficient of determination (R), and we therefore report as our objective function based on the Hill equation (21). The computations were performed using...
Results

All participants were ASA physical status II; they were 59.2 ± 10.7 yr old (mean ± sd), weighted 83.2 ± 15.0 kg, and had a height of 172.8 ± 8.1 cm. Mean baseline values before induction of anesthesia were 69 ± 19 for AAI and 93 ± 6 for BIS (Table 1). Two minutes after the start of remifentanil infusion, the AAI and BIS values remained unchanged (69 ± 20 and 93 ± 8, respectively).

Loss of eyelash reflex was observed at a propofol effect-site concentration of 2.1 ± 1.5 μg/mL and was accompanied with a significant reduction of AAI (47 ± 24; P = 0.003) and BIS (75 ± 19; P < 0.001) values (Fig. 1) The P<sub>K</sub> for consciousness versus unconsciousness, i.e., loss of eyelash reflex, was better for BIS (P<sub>K</sub> = 0.90 ± 0.01) than for AAI (P<sub>K</sub> = 0.85 ± 0.05; P < 0.001) (Table 2).

During emergence from anesthesia, i.e., the 15 min preceding tracheal extubation, the mean end-tidal desflurane concentration changed significantly from 3.4 ± 0.7 volume % to 0.8 ± 0.2 volume % at 1 min before extubation (Table 1, P < 0.001). Opening of eyes occurred at a mean end-tidal desflurane concentration of 0.7 ± 0.2 volume %, with an AAI of 47 ± 20 and BIS value of 77 ± 14.

The individual changes of the desflurane concentrations, AAI, and BIS values are shown in Figures 2 and 3. The P<sub>K</sub> value for unconsciousness versus consciousness, i.e., opening of eyes, was better for BIS (P<sub>K</sub> = 0.89 ± 0.03) than for AAI (P<sub>K</sub> = 0.81 ± 0.13; P = 0.011) or the end-tidal desflurane concentration (P<sub>K</sub> = 0.75 ± 0.16; P < 0.001). The P<sub>K</sub> value for the desflurane effect-site concentration was P<sub>K</sub> = 0.91 ± 0.07 (Table 2).

The correlation of BIS and desflurane effect-site concentration (r = 0.80 ± 0.19) was better than the correlation of the AAI value with desflurane effect-site concentration (r = 0.75 ± 0.14) (Fig. 4). The prediction probability (P<sub>K</sub>) was assessed as described by Smith et al. (22). We calculated P<sub>K</sub> values using the Somer’s d cross tabulation statistic on SPSS (version 12; SPSS Inc., Chicago, IL), which was then transformed from the -1 to 1 scale of Somer’s d to the 0 to 1 scale of P<sub>K</sub> as P<sub>K</sub> = 1 – (1 – |Somer’s d|)/2. The P<sub>K</sub> values were computed for the assessments just before and after opening of eyes and tracheal extubation for AAI, BIS, and the desflurane end-tidal and effect-site concentrations. The efficacy of neurophysiologic variables to predict desflurane end-tidal and calculated effect compartment concentrations was also evaluated using prediction probability.
probability for BIS to predict desflurane effect-site concentration was also better ($P_K = 0.77 \pm 0.11$) than for AAI ($P_K = 0.66 \pm 0.10; P = 0.025$) (Table 3).

**Discussion**

We studied AAI and BIS values during emergence from desflurane anesthesia and defined the dose-response relationship between the calculated desflurane effect-site concentrations versus AAI and BIS values. Using prediction probability for important clinical end-points, such as loss of eyelash reflex, opening of eyes, and tracheal extubation, better $P_K$ values were obtained for BIS than for AAI. Interestingly, the best $P_K$ value for opening of eyes was obtained for the predicted desflurane effect-site concentration.

Table 2. Prediction Probability ($P_K$) Values for A-Line Auditory Evoked Potentials Index (AAI), Bispectral Index (BIS), and Anesthetic Concentrations for Clinical End-Points of Anesthesia

<table>
<thead>
<tr>
<th>End-tidal Desflurane concentration</th>
<th>Desflurane effect-site concentration</th>
<th>Propofol effect-site concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of eyelash reflex</td>
<td>0.85 ± 0.05</td>
<td>N/A</td>
</tr>
<tr>
<td>Open eyes</td>
<td>0.81 ± 0.13</td>
<td>0.75 ± 0.16</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

AAI = A-Line AEP Index; BIS = Bispectral index; N/A = not applicable.

**Figure 2.** The individual desflurane end-tidal and effect-site concentrations during the 15 min preceding tracheal extubation.

**Figure 3.** A-Line Auditory Evoked Potentials Index (AAI) and Bispectral Index (BIS) values during the 15 min preceding tracheal extubation.

We chose a combination of epidural analgesia with desflurane anesthesia to obviate the need for opioid analgesia. Therefore, the desflurane effect on the EEG and the AEP could be studied without considering opioid interaction. Furthermore, we studied the predicted desflurane effect during emergence from anesthesia because the possible range of intraoperative desflurane concentrations is limited to avoid intraoperative awareness.

Dose-response curves for BIS and AAI were substantially different (Fig. 4), which is of practical interest for the interpretation of this depth of anesthesia measure. The higher steepness of the slope for AAI means that during decreasing desflurane concentrations the AAI remains unchanged until relatively small concentrations, but this is followed by a sudden, steep increase of the AAI value. In contrast, the BIS...
started to increase at larger desflurane concentrations and had a smoother increase. A previous study with propofol-remifentanil anesthesia yielded a sigmoidal fit between BIS and AAI, thus indicating different dose-response curves for BIS and AAI (23).

The steep increase of the AAI dose-response curve may impressively alert imminent intraoperative awareness, but there are no studies relating AAI values to cerebral information processing or memory formation. In contrast, a fine tuning in a predefined range during general anesthesia, such as 40 to 60 for BIS, aiming to decrease anesthetic drug consumption and to shorten recovery times, may be more difficult to achieve with the AAI. A smoother increase, as found for BIS, may be more favorable for this purpose. Therefore, it is not surprising that the promising results for BIS regarding reduced anesthetic drug consumption and shortened recovery times (1–7) could not be found equally for AAI (24–26).

Our finding that neurophysiologic measures such as BIS and AAI are superior to end-tidal anesthetic drug concentrations for predicting clinical end-points is in concordance with multiple previous reports (27). Better prediction probabilities for BIS than for AAI in our study, compared with similar prediction probabilities for BIS and AAI in the study by Struys et al. (15), may be attributable, in part, to different study designs. In contrast to the more static study design of Struys et al., with a slow stepwise increase of propofol, we chose a dynamic study design with constantly changing desflurane concentrations. Our approach is closer to daily clinical practice, but hysteresis caused by internal smoothing and averaging of the monitor values might have influenced our results.

The most surprising result of our study is that the calculated desflurane effect-site concentration is a better predictor than either BIS or AAI in predicting the spontaneous opening of eyes. The patients opened their eyes at a desflurane effect-site concentration of \(1.3 \pm 0.5\) volume %; the loss of eyelash reflex was observed at a propofol effect-site concentration of \(2.1 \pm 1.5\) \(\mu\)g/mL. The larger variability of the propofol effect-site concentration in contrast to the desflurane effect-site concentration could be explained by the differences in the calculation of effect-site concentrations. For propofol, it is necessary to calculate the plasma concentration based on a three-compartment model first and then the effect-site concentration with a \(k_{eo}\)-value. For volatile anesthetics the calculation of the effect-site concentration is easier because the measured end-tidal concentration could be equated with the plasma concentration. Our results indicate that online calculation of the effect-site concentration of volatile anesthetics on the basis of end-tidal concentrations could be useful in clinical practice.

In conclusion, we found different dose-response relationships between calculated desflurane effect-site concentrations and BIS or AAI values. The more monotonic dose-response curve of the BIS and better prediction probabilities for clinical end-points favors

![Figure 4](image)

**Figure 4.** The individual fit of the A-Line Auditory Evoked Potentials Index (AAI) and Bispectral Index (BIS) values versus the desflurane effect-site concentrations.

<table>
<thead>
<tr>
<th></th>
<th>End-tidal desflurane concentration</th>
<th>Desflurane effect-site concentration</th>
<th>Propofol plasma concentration</th>
<th>Propofol effect-site concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAI</td>
<td>0.64 ± 0.09</td>
<td>0.66 ± 0.10</td>
<td>0.67 ± 0.07</td>
<td>0.74 ± 0.05</td>
</tr>
<tr>
<td>BIS</td>
<td>0.75 ± 0.09</td>
<td>0.77 ± 0.11</td>
<td>0.72 ± 0.09</td>
<td>0.80 ± 0.08</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

AAI = A-Line AEP Index; BIS = Bispectral Index.
BIS compared to AAI for tuning general anesthesia. The calculation of the effect-site concentration of volatile anesthetics could be a useful alternative to the electrophysiological monitors in clinical practice.

References


