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New Composite Index Based on Midlatency Auditory Evoked Potential and Electroencephalographic Parameters to Optimize Correlation with Propofol Effect Site Concentration

Comparison with Bispectral Index and Solitary Used Fast Extracting Auditory Evoked Potential Index

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Background: **This study investigates the accuracy of a composite index, the A-Line® auditory evoked potentials index version 1.6 ($AAI_{1.6}$; Danmeter A/S, Odense, Denmark), as a measure of cerebral anesthetic drug effect in a model for predicting a calculated effect site concentration of propofol (Ce_{PROP}). The $AAI_{1.6}$ algorithm extracts information from the midlatency auditory evoked potentials, the spontaneous electroencephalographic activity, and the detection of burst suppression. The former version of this monitor, the A-Line® auditory evoked potential index version 1.5, is only based on fast extracted midlatency auditory evoked potential information.**

Methods: **After institutional ethics committee approval (University Hospital, Ghent, Belgium), informed consent was obtained from 13 patients (10 women, 3 men) with an American Society of Anesthesiologists physical status of I, aged 18–65 yr, who were scheduled to undergo ambulatory gynecologic or urologic surgery. The authors evaluated for Bispectral Index, A-Line® auditory evoked potential index, version 1.5, $AAI_{1.6}$ scaled from 0 to 100 and $AAI_{1.6}$ scaled from 0 to 60, the interpatient stability at baseline, the detection of burst suppression, prediction probability, and correlation with Ce_{PROP}, during a constant infusion of 1% propofol at 300 ml/h. The authors developed pharmacodynamic models relating the predicted Ce_{PROP} to each measure of cerebral anesthetic drug effect.**

Results: **Bispectral Index had the lowest interindividual baseline variability. No significant difference was found with prediction probability analysis for all measures. Comparisons for correlation were performed for all indices. The $AAI_{1.6}$ scaled to 60 had a significantly higher correlation with Ce_{PROP} compared with all other measures. The $AAI_{1.6}$ scaled to 100 had a significant higher correlation with Ce_{PROP} compared with the A-Line® auditory evoked potential index version 1.5 ($P < 0.05$)**

Conclusions: **The authors found that the application of $AAI_{1.6}$ has a better correlation with a calculated Ce_{PROP} compared with a solitary fast extracting midlatency auditory evoked potential measure. Whether this improvement in pharmacodynamic tracing is accompanied by an improved clinical performance should be investigated using clinical endpoints.**

PROCESSED analysis of the electroencephalogram or midlatency auditory evoked potentials (MLAEPs) is increasingly accepted as surrogate endpoint for quantification of anesthetic cerebral drug effect. For the electroencephalogram, the Bispectral Index (BIS) incorporated in the A-2000 BIS® monitor (Aspect Medical Systems, Newton, MA) has been proven to have a high sensitivity and specificity to measure anesthetic drug effect.[1–3] For MLAEPs, Jensen *et al.*[4] developed a new method for extracting the MLAEP from the electroencephalogram by using an autoregressive model with an exogenous input (ARX), allowing fast extraction of the raw MLAEP signal. A new monitoring variable called the A-Line® ARX Index, version 1.5 ($AAI_{1.5}$), is incorporated in a recently commercialized monitor called the A-Line® (Danmeter A/S, Odense, Denmark). Various investigators have illustrated its clinical usefulness and limitations.[2,3,5,6]

In previous work, we compared the performance of both systems and found that the correlation between the changes in anesthetic drug effect as measured by BIS or $AAI_{1.5}$ and the propofol effect site concentration (Ce_{PROP}) were accurate, except at baseline and during excessive levels of anesthetic drug effect, as detected by the increasing level of burst suppression.[7] For BIS, better baseline stability (minimal variability in the absence of drugs between individuals) was observed as compared with $AAI_{1.5}$.[7] Excessive levels of anesthetic drug effect remained detectable by the BIS monitor from a burst suppression ratio of 40%, whereby no changes in $AAI_{1.5}$ were observed during increasing levels of burst suppression.[7] This lack of information is caused by the fact that (1) burst suppression ratio does not participate in the calculation of $AAI_{1.5}$ and (2) at patient-specific levels of anesthetic drug effect, the amplitude (latency) of the raw MLAEP wave is reduced (increased) in such a way that it becomes nearly a straight line, limiting its discriminating power.[8,9]

In a recent editorial in ANESTHESIOLOGY, Kalkman and Drummond[10] stated that it might be proven ultimately, if

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we deem the grail of depth of anesthesia monitoring worth pursuing, that the optimal monitor of depth of anesthesia will be one that integrates parameters extracted from both spontaneous and evoked cerebral electrophysiologic signals. Following this philosophy, the first step is to prove that this monitor has a good correlation with cerebral anesthetic drug effect during the administration of a hypnotic drug.[10] Therefore, we hypothesized that the construction of a composite index calculated from the combination of a fast extracted MLAEP, electroencephalogram, and burst suppression might offer a broader range of information on the calculated effect site of propofol—as a pharmacodynamic endpoint of cerebral anesthetic drug effect— compared with an index based on solitary MLAEP or electroencephalographic input. Recently, an upgrade version of the A-Line® has been developed, producing such a composite index, called the A-Line® auditory evoked potential index, version 1.6 ($AAI_{1.6}$; Danmeter).

This study compares the accuracy of the BIS, $AAI_{1.5}$, and $AAI_{1.6}$ in their ability to predict a progressively increasing Ce_{PROP}. Therefore, we evaluated for all measures the stability at baseline (minimal variability in the absence of drug between individuals),[11] accurate detection of burst suppression,[12] prediction probability,[13,14] and correlation with the Ce_{PROP}. We also developed pharmacodynamic models relating the predicted Ce_{PROP} to each measure of cerebral anesthetic drug effect.

Materials and Methods

Clinical Protocol

After institutional ethics committee approval (University Hospital, Ghent, Belgium), informed consent was obtained from 13 patients (10 women, 3 men) with an American Society of Anesthesiologists physical status of I, aged 18–65 yr, who were scheduled to undergo ambulatory gynecologic or urologic 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.

An 18-gauge intravenous line was positioned at a large left forearm vein. Every patient received approximately 100 ml crystalloid fluid during the study period. No fluid load was given before induction. No patient received preoperative medication. No other drugs, including opioids, were given during the study period. All patients maintained spontaneously ventilating (even at high levels of burst suppression) *via* a facemask delivering 100% oxygen at 6 l/min.

Heart rate and noninvasive blood pressure, arterial oxygen saturation, and capnography were recorded at 1-min intervals using an S-5 monitor (Datex, Helsinki, Finland). Capnography was monitored by putting the side stream sample line in the facemask of the patient. This implies the occurrence of an error for quantification of the partial pressure of carbon dioxide, but it enables monitoring of respiratory rate and free airway. A silent operation room was obtained for all patients.

At the start of the study period, 1% propofol was administered at 300 ml/h *via* a computer-assisted continuous infusion device (RUGLOOP**). This system captures all monitored data while driving a Fresenius Modular Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France) *via* an RS-232 interface. During the propofol infusion, the corresponding Ce_{PROP} is calculated in a time-synchronized way by RUGLOOP using a three-compartment model enlarged with an effect site compartment, previously published by Schnider *et al.*[15,16] The calculated Ce_{PROP} was computed to yield a time to peak effect of 1.6 min after bolus injection,[17] as also published by Schnider *et al.*[15,16] and clinically confirmed by Struys *et al.* [18] The propofol infusion was continued at the same speed until burst suppression levels of 80% or higher were achieved. However, infusion was stopped earlier if the mean arterial blood pressure became lower than 50 mmHg.

Before the drug administration was started, all patients were asked to close their eyes and relax for 2 min. During that time, signal quality, impedance of the electrodes, and the adequate detection of all parameters by RUGLOOP were verified. Baseline measures were performed during the first 5 s after starting the pumps, when Ce_{PROP} was 0 in all patients. Averaging of the data was performed using a 10-s interval.

Electroencephalographic and MLAEP Data Collection

BIS-XP (version 4.0) was derived from the frontal electroencephalogram (At-Fpzt) and calculated by the A-2000 BIS® monitor using four BIS® sensor electrodes (Aspect Medical Systems, Inc.). The BIS value ranges from 0 to 100. The smoothening time of the BIS monitor was set at 15 s.

We recorded raw electroencephalographic data including the MLAEP data with a prototype version of the A-Line® monitor. Three electrodes (A-Line® AEP electrodes; Danmeter A/S) were positioned at mid forehead (+), left forehead (reference), and left mastoid (−). Impedance was always lower than 5 kOhm. In this protocol, MLAEP was elicited by a bilateral click at 9 Hz, with a 2-ms duration and an adaptable click intensity set automatically by the monitor according to the measured signal-to-noise ratio (SNR) of the raw MLAEP signal.[19] Artifact rejection and 25- to 65-Hz band-pass filtering was conducted previously to the extraction of the MLAEP.

All raw MLAEP data were stored on a compact flash card (SanDisk, Sunnyvale, CA) connected to the proto-

** RUGLOOP program. Available at: http://www.anesthesia-uzgent.be. Accessed April 11, 2005.

type A-Line®. *Post hoc*, both $AAI_{1.5}$ and $AAI_{1.6}$ were extracted from these data on a time synchronized basis.

The $AAI_{1.5}$ is calculated using a fast extracting method called ARX, enabling us to extract information from the MLAEP within 2–6 s. This protocol has been published elsewhere.[2] The $AAI_{1.5}$ value ranges from 0 to 100.

The $AAI_{1.6}$ is a composite index using three sources of information resulting in an index value ranging between 0 and 100. First, an ARX is used to extract information from the raw MLAEP wave during periods with high SNR. The method used is based on the $AAI_{1.5}$ protocol and is described elsewhere.[4] When the MLAEP is reduced to a flat line, the SNR becomes too low to extract a useful AAI calculation. At that time, the electroencephalographic-based information will determine the $AAI_{1.6}$ calculation. Finally, when burst suppression patterns are detected, this information becomes the major factor in the calculation of the composite index. The $AAI_{1.6}$ is mathematically formulated as

$$AAI_{1.6} = k_0 AAI_{1.5} + k_1 \log\frac{E_{30-47\,Hz}}{E_{10-20\,Hz}} + k_2 BS$$

where $AAI_{1.5}$ is the result of the ARX model. $E_{30-47\ Hz}$ and $E_{10-20\ Hz}$ are the results of a power analysis in the raw electroencephalographic spectrum using higher and lower frequencies, respectively. BS is the percentage of burst suppression patterns detected during the last 30 s. k_0, k_1, and k_2 are functions of the SNR, the detection of iatrogenic artifacts (translated in a signal quality index), and the auditory stimulus intensity. The SNR is determined during the averaging process of the raw signal. It evaluates the detection quality of the signal under investigation. For MLAEP, the occurrence of the electroencephalogram, electromyogram, and other artifacts will induce a lower SNR. For the electroencephalogram, only electromyographic and iatrogenic artifacts will be taken into account. The signal quality index is calculated based on the number (and type) of artifacts during a certain period of time. If the amount of artifacts per period of time is higher than a percentage of this time, no $AAI_{1.6}$ is calculated because it is not reliable. If the number of artifacts per period of time is less than this value, an index is calculated, but the signal quality index bar is decreased on screen, indicating a lower accuracy of the calculated index. When this occurs, an artifact code is transferred to the RUGLOOP program automatically. These data were deleted *post hoc* from further analysis.

The burst suppression parameter is defined as the percentage of time where the power of the electroencephalogram is smaller than 5 μV over a period of time. However, the calculation of burst suppression differs between monitors. For BIS and $AAI_{1.5}$, the burst suppression algorithm details are published previously.[7]

In the $AAI_{1.6}$, the burst suppression detection algorithm is based on a maximum likelihood cumsum algorithm, with variable probability functions, using a preprocessed signal after artifact detection and filtering. The main property of this method is that low-amplitude signal criteria are based on probabilities and not on a fixed number. Second, the signal has no fixed segmentation, allowing a higher time resolution for detecting changes in comparison with other methods as applied in $AAI_{1.5}$ and BIS. Finally, burst suppression is evaluated over a window of 30 s in $AAI_{1.6}$, instead of 22 s in the former version.

Because it might be hypothesized that no additional information on loss of consciousness is revealed for $AAI_{1.6}$ values between 60 and 100,[3] the A-Line® monitor offers the possibility to adjust the range of the index toward a 0–60 scale (defined as $AAI1.6_{60}$). However, by setting all values higher than 60 to 60, it has to be proven that no information on cerebral anesthetic drug effect is lost, which is crucial when using the monitor in a pharmacodynamic protocol or in a clinical setting. Therefore, applicable performance measurements (baseline variability, individualized Spearman rank correlation, prediction probability analysis) were calculated on both scales.

Performance Measures

The significance level was set at 5% unless otherwise reported.

Baseline Variability. The baseline variability is calculated by computing the coefficient of variance on the electroencephalographic data points obtained during the first 5 s of the protocol, before any drug has been delivered. In this setting, the baseline variability will mainly reflect interpatient variability because of the short duration of measurement.

Comparison between $AAI_{1.5}$ and $AAI_{1.6}$. A Pearson correlation was calculated between $AAI_{1.5}$ and $AAI_{1.6}$.

Burst Suppression Detection and Parameter Correlation. The relations between the burst suppression and each measure of anesthetic drug effect are plotted. A Spearman rank correlation was calculated. For each scatterplot, a model was fitted to the data using curve estimation function from Sigmaplot2000® for Windows® (SPSS Inc., Chicago, IL). The curve estimation function produces curve estimation regression statistics and related plots for different curve estimation regression models including linear, logarithmic, inverse, quadratic, cubic, power, compound, S-curve, logistic, growth, and exponential. A separate model is produced for each dependent variable, together with its regression coefficients, predicted values, residuals, and predictive intervals. After this, the most appropriate regression model can be selected.

Prediction Probability. The ability of the different indicators to describe the anesthetic drug effect was evaluated using prediction probability (P_K), which compares the performance of indicators having different units of measurements. P_K was calculated using a custom

spreadsheet macro P_KMACRO, developed by Smith *et al.*[13,14] The P_K value was calculated for every individual patient and for all parameters studied. We evaluated the predictive capacity of BIS, $AAI_{1.5}$, and $AAI_{1.6}$ for detecting the calculated Ce_{PROP}, which has a known correlation with the anesthetic drug effect.[18] The calculated Ce_{PROP} reached at every 5 s was used as an endpoint for P_K calculation. Ce_{PROP} was calculated with a precision of two decimals. A P_K of 1 for BIS, $AAI_{1.5}$, or $AAI_{1.6}$ would mean that BIS, $AAI_{1.5}$, or $AAI_{1.6}$ always decreases (increases) as the patient reaches higher (lower) drug concentrations according to the Ce_{PROP}. Such an indicator can perfectly predict the anesthetic drug concentration. Alternatively, a P_K value of 0.5 would mean that the indicator is useless for predicting anesthetic drug concentration. The jackknife method was used to compute the SE of the estimate, based on the assumption that all assessments were independent.[13,14] After having evaluated normal distribution, a Student *t* test with Bonferroni correction was used to evaluate significant difference between P_K means.

Individualized Spearman Rank Correlation. As an additional nonparametric approach, the Spearman rank correlations between Ce_{PROP} and BIS, $AAI_{1.5}$, or $AAI_{1.6}$ (both scales) were individualized by computing the correlation first for every patient i separately, defined as R_i. The reported Spearman rank correlation, R, is a weighted average of the R_i (weighted according to the number of observations for each patient). In this way, R retained its usual interpretation. The confidence intervals on R were obtained by the bootstrap method in which the hierarchical nature of the data were incorporated by resampling within patients. Equality of two correlation coefficients was tested at the 5% level of significance by constructing the 95% confidence intervals of the difference (confidence intervals were also computed with the bootstrap technique). All bootstrap calculations were based on 10,000 simulation runs.

Pharmacodynamic Modeling

The relation between Ce_{PROP} and the electroencephalographic measures of anesthetic drug effect were analyzed using a sigmoid E_{max} model,

$$\text{Effect} = E_0 + \frac{(E_{max} - E_0) \times Ce_\gamma}{(Ce_{50\gamma} + Ce_\gamma)}$$

where Effect is the electroencephalographic effect being measured (BIS, $AAI_{1.5}$, or $AAI_{1.6}$ [both scales]), E_0 is the baseline measurement when no drug is present, E_{max} is the maximum possible drug effect, Ce is the calculated effect site concentration of propofol, Ce_{50} is the effect site concentration associated with 50% maximal drug effect, and γ is the steepness of the concentration–response relation curve. The model parameters were estimated using NONMEM V (Globomax LLC, Hanover, MD). Interindividual variability was modeled using a log-normal distribution,

$$P_i = P_{tv} e^{-\eta_i}$$

where P_i is the parameter value (E_0, E_{max}, y or Ce_{50}) in the *i*th patient, P_{tv} is the typical value of the parameter in the population, and η is a random variable with a mean of 0 and a variance of ω^2. Individual variability is reported as ω, the SD of η in the log domain, which is approximately the coefficient of variance in the standard domain. Residual intraindividual variability was modeled using a standard additive error model.[20]

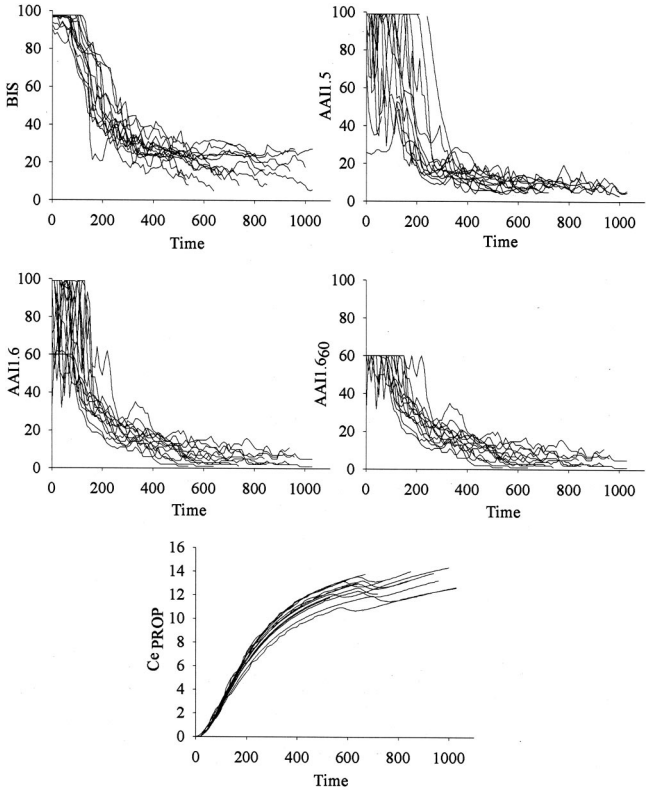

Fig. 1. Raw data of all patients *versus* time. $AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® ARX Index version 1.6 (scaled to 100); $AAI1.6_{60}$ = A-Line® ARX Index version 1.6 (scaled to 60); BIS = Bispectral Index; Ce_{PROP} = effect site concentration of propofol (the disruption in the continuously increasing Ce_{PROP} is due to the inevitable change of the 1% propofol syringe around 600 s.)

Results

The population characteristics were as follows: weight, 64.0 ± 3.8 kg; age, 38 ± 6.0; height, 168 ± 7.8 cm; sex, 10 women and 3 men. All patients remained within a safe hemodynamic and respiratory clinical state.

All measured data were included in the analysis. Figure 1 shows the raw data over time for the four electroencephalographic measures (BIS, $AAI_{1.5}$, $AAI_{1.6}$, $AAI1.6_{60}$) and Ce_{PROP}. All patients remained in a hemodynamic and respiratory safe condition during the study period.

Table 1. Baseline Stability Defined as the Coefficient of Variation of All Measures

	BIS	$AAI_{1.5}$	$AAI_{1.6}$ (Scaled 0–100)	$AAI_{1.6}$ (Scaled 0–60)
Mean ± SD	96.12 ± 2.40	90.06 ± 21.16	87.00 ± 20.60	58.69 ± 8.58
Coefficient of variation	0.02	0.23	0.24	0.15

$AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® Composite Index (both scales); BIS = Bispectral Index.

Performance Measures

The interpatient baseline variability was calculated for all studied electroencephalographic measures (BIS, $AAI_{1.5}$, $AAI_{1.6}$, $AAI1.6_{60}$). The coefficient of variance on the first 5 s of measurement before administration of propofol is shown in table 1.

$AAI_{1.5}$ and $AAI_{1.6}$ (both scaled between 0 and 100) were compared as shown in figure 2. This shows a strong correlation between both AAI versions (Pearson correlation $R = 0.91209833$, $P < 0.001$). We notice a large variability at high values of both parameters and a tendency for $AAI_{1.5}$ to remain on a higher value at higher levels of Ce_{PROP} in comparison with $AAI_{1.6}$. For $AAI_{1.5}$, no data lower than 7 are observed in contrast to $AAI_{1.6}$.

The relations between the percentage of burst suppression and BIS, $AAI_{1.5}$, and $AAI_{1.6}$ are plotted in figure 3 together with the most appropriate curve estimation. For BIS, a cubic polynomial regression curve was considered to be the best fit. For $AAI_{1.5}$ and $AAI_{1.6}$, a sigmoid regression curve with three parameters was selected as the best fit. For $AAI1.6_{60}$, identical results to $AAI_{1.6}$ were found. Therefore, no graph is presented. The Spearman rank correlations between burst suppression and BIS, $AAI_{1.5}$, and $AAI_{1.6}$ are −0.728, −0.551, and −0.871, respectively.

The P_K values for BIS, $AAI_{1.5}$, $AAI_{1.6}$, and $AAI1.6_{60}$ are shown in table 2. The individualized Spearman rank correlations between Ce_{PROP} and BIS, $AAI_{1.5}$, $AAI_{1.6}$, and $AAI1.6_{60}$ are also included in table 2.

Pharmacodynamic Modeling

Figure 4 shows the behavior of the four electroencephalographic measures *versus* Ce_{PROP} for all patients. With increasing Ce_{PROP}, all measures decreased. The relations of Ce_{PROP} to BIS, $AAI_{1.5}$, $AAI_{1.6}$, and $AAI1.6_{60}$ are modeled and shown in figure 5. The typical parameter values for each population model including the coefficient of variance (as a measure for interindividual variability in the standard domain) are found in table 3. The SD for each model (as a measure of the intraindividual variability in the log domain) was 5.63 for BIS, 13.67 for $AAI_{1.5}$, 7.24 for $AAI_{1.6}$, and 4.02 for $AAI1.6_{60}$.

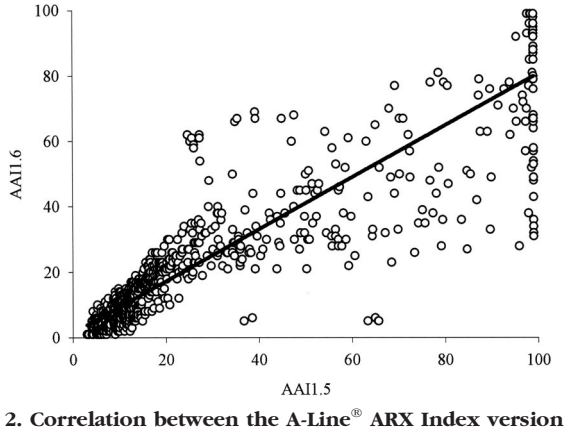

Fig. 2. Correlation between the A-Line® ARX Index version 1.5 ($AAI_{1.5}$) *versus* A-Line® ARX Index version 1.6 ($AAI_{1.6}$). The *black line* shows the most appropriate linear correlation.

Discussion

This study shows that the application of a composite index ($AAI_{1.6}$) based on MLAEPs and spontaneous electroencephalography optimizes the prediction of Ce_{PROP} as compared with a solitary fast extracting MLAEP measure ($AAI_{1.5}$). Comparing several monitors for cerebral hypnotic drug effect demands a systematic approach. The methodology used in this trial is based on a former

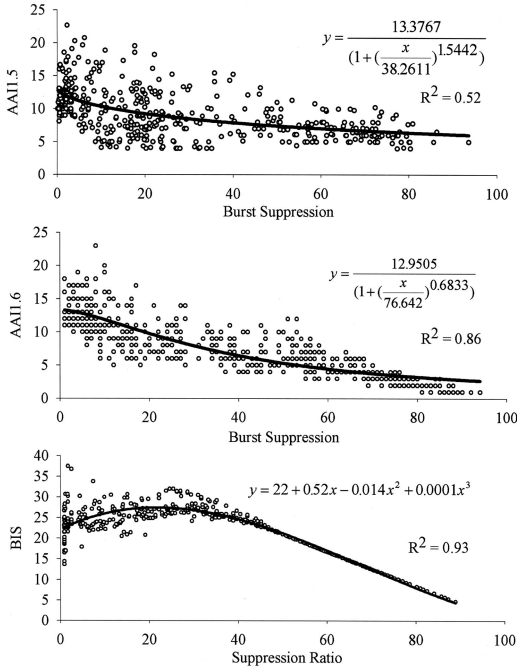

Fig. 3. Correlation between burst suppression and the A-Line® ARX Index are shown for the versions 1.5 ($AAI_{1.5}$) and 1.6 ($AAI_{1.6}$), respectively. The *lower figure* shows the correlation between the suppression ratio *versus* the Bispectral Index (BIS). The *black line* is the most appropriate fitted regression. The regression curve formula is printed in the *right upper corner* of every figure. R^2 = the goodness of fit of the regression curve.

Table 2. Individualized Spearman Rank Correlation Coefficients and Prediction Probability for Each Electroencephalographic Measure of Anesthetic Drug Effect *versus* Propofol Effect Site Concentration

	BIS	$AAI_{1.5}$	$AAI_{1.6}$	$AAI1.6_{60}$
P_K, median (minimum–maximum)	0.91 (0.70–0.98)	0.90 (0.73–0.94)	0.92 (0.75–0.98)	0.89 (0.75–0.97)
Individualized Spearman rank correlation, mean ± SD (95% CI)	−0.686 ± 0.033 (−0.748, −0.618)†	−0.661 ± 0.032 (−0.721, −0.597)*†	−0.753 ± 0.031 (−0.813, −0.691)*†	−0.959 ± 0.005 (−0.967, −0.949)†

* $P < 0.05$ between $AAI_{1.5}$ and $AAI_{1.6}$. † $P < 0.05$ between $AAI1.6_{60}$ and all other measures.

$AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® ARX Index version 1.6 (scaled to 100); $AAI1.6_{60}$ = A-Line® ARX Index version 1.6 (scaled to 60); BIS = Bispectral Index; CI = confidence interval; P_K = prediction probability.

publication from Vanluchene *et al.*,[7] where spectral entropy is compared with BIS and $AAI_{1.5}$.

The A-Line® monitor offers the possibility to reduce the upper scale limit to 60, based on the rationale that values between 60 and 100 suffer from a high interpatient variability and offer no additional information on loss of consciousness.[2] Although this adjustment might be interesting on a clinical level, it is crucial to prove whether this scale is applicable to pharmacodynamic studies investigating subhypnotic levels of anesthesia (when consciousness is not lost), without losing any information on the propofol drug concentration. Therefore, we also investigated the performance accuracy of the $AAI1.6_{60}$ as an individual index.

High baseline variation, as defined by the coefficient of variance, might decrease the predictive ability of the electroencephalogram-derived measures when used to detect cerebral drug effect, as stated by Bruhn *et al.* [11] BIS showed the lowest baseline variability. In contrast, $AAI_{1.5}$ and $AAI_{1.6}$ showed a high but comparable coefficient of variance. We found a major improvement in baseline variability in $AAI1.6_{60}$ in comparison to $AAI_{1.5}$ and $AAI_{1.6}$. Although it is potentially interesting when applying the A-Line® monitor clinically to monitor loss of consciousness, one might question that it does not make sense to reduce baseline variability by cutting of data higher than 60, if this new scale causes a decreased sensitivity for the detection of subhypnotic levels of anesthetic drug effect. This reduced upper limit only makes sense if the other performance measures reveal a beneficial effect.

Burst suppression is a benign electroencephalographic pattern frequently seen in healthy brain at deep levels of anesthesia. Because the detection of burst suppression represents an important component to the level of hypnotic effect, it might be helpful to take into account burst suppression analysis when measuring deep levels of anesthetic drug effect because it might optimize the discriminating power of the investigated index at these levels. For BIS, burst suppression is included in the

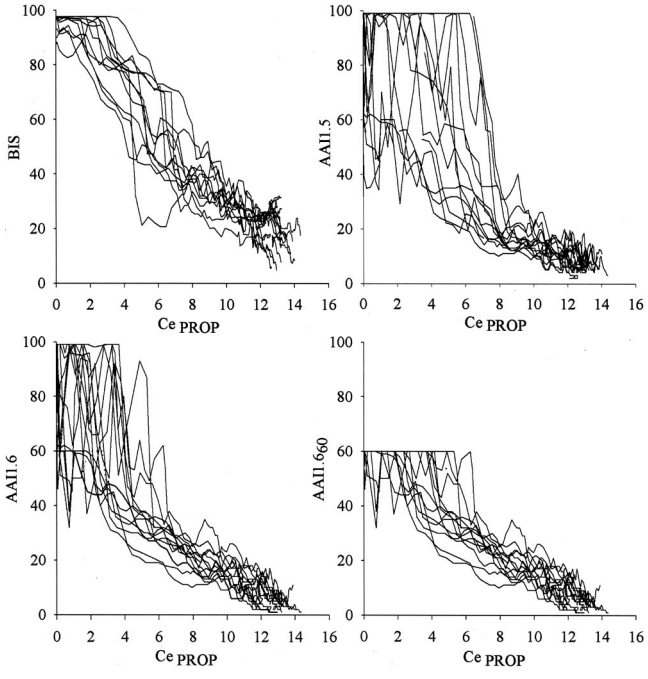

Fig. 4. Raw data of all anesthetic drug effect measures *versus* calculated effect site of propofol (Ce_{PROP}). $AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® ARX Index version 1.6 (scaled to 100), $AAI1.6_{60}$ = A-Line® ARX Index version 1.6 (scaled to 60).

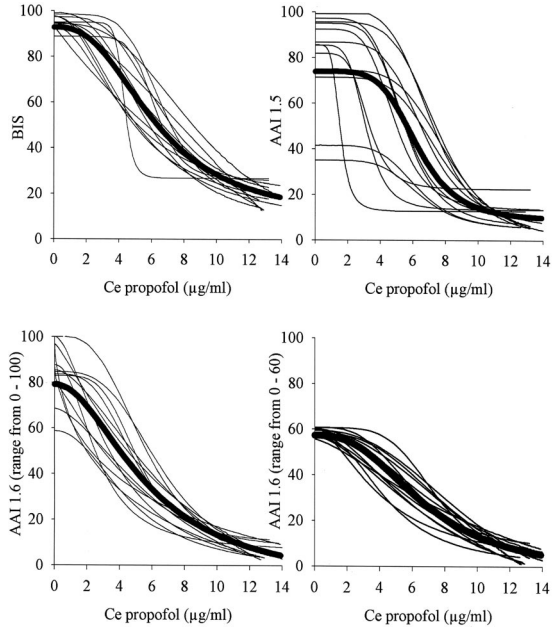

Fig. 5. NONMEM regression of the population data. $AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® ARX Index version 1.6; BIS = Bispectral Index; Ce propofol = effect site concentration of propofol.

Table 3. Typical Values and Coefficients of Variation for Each Electroencephalographic Measure of Anesthetic Drug Effect.

	BIS	$AAI_{1.5}$	$AAI_{1.6}$ (Scaled 0–100)	$AAI_{1.6}$ (Scaled 0–60)
Ce_{50}	6.25 (210%)	6.28 (50%)	5.71 (36%)	6.78 (36%)
E_0	92.90 (66%)	74.00 (50%)	79.20 (59%)	57.40 (4%)
E_{max}	−83.60 (127%)	−65.70 (36%)	−87.50 (31%)	−60.00 (31%)
γ	2.59 (45%)	5.09 (0%)	1.98 (57%)	2.61 (38%)

$AAI_{1.5}$ = A-Line® ARX Index version 1.5; $AAI_{1.6}$ = A-Line® ARX Index version 1.6; BIS = Bispectral Index; Ce_{50} = the effect site concentration associated with 50% maximal drug effect; E_0 = the baseline measurement when no drug is present; E_{max} = the maximum possible drug effect; γ = the steepness of the concentration–response relation.

algorithm. Various authors have found that above a burst suppression ratio of 40%, a linear correlation exists between BIS and burst suppression ratio, indicating that the burst suppression ratio is the only determinant factor for BIS values below 30.[7,21] Our results for BIS, as shown in figure 3, are in agreement with these previously published findings. If burst suppression was excluded from the algorithm, BIS would become very resistant at excessive levels of anesthetic drug effect. In contrast, the calculation of the $AAI_{1.5}$ is only based on the MLAEP. As already observed in previous work, the MLAEP flattens at patient-specific levels of anesthetic drug effect, thereby limiting its discriminating power.[7–9] This phenomenon results in a maximum decreased $AAI_{1.5}$ "plateau" level higher than 0. As shown in figures 2 and 4, the lowest observed $AAI_{1.5}$ values are ceiled around 7. Beyond this level, no additional information on cerebral drug effect can be obtained. When taking in consideration that the ED_{95} for loss of consciousness is around 19 for $AAI_{1.5}$, the discriminating power might become very low after loss of consciousness. For $AAI_{1.6}$, the electroencephalogram and burst suppression are included as a component of the composite index as described in the Materials and Methods section. This results in an increased discriminating power at deep levels of anesthetic drug effect. As shown in figure 3, the absolute values of $AAI_{1.6}$ are able to decrease to 0 at increasing levels of burst suppression. This improvement between $AAI_{1.5}$ and $AAI_{1.6}$ is also reflected in the statistically significant better individualized Spearman rank correlation for $AAI_{1.6}$ (table 2).

When studying performance accuracy, the question is how well the observed measure, which is the electroencephalographic response, predicts the unobserved "underlying" state of the patient, which is represented by the Ce_{PROP}. Therefore, P_K was calculated for BIS, $AAI_{1.5}$, $AAI_{1.6}$, and $AAI1.6_{60}$. The underlying theoretical background of P_K calculations has been published elsewhere.[7] In our study, we did not obtain any significant difference between P_K values, although $AAI_{1.6}$ tended to have the highest median value.

As an additional analysis for correlation between parameters and Ce_{PROP}, we calculated the Individualized Spearman rank correlation coefficients for each measure. This weighted nonparametric statistical approach depicts the nonlinearity in the system much more accurately as compared with P_K analyses. Results confirm the significant increase in correlation between $AAI_{1.6}$ *versus* Ce_{PROP} in comparison to $AAI_{1.5}$, thereby proving that the combination of MLAEP and derived measures from the spontaneous electroencephalogram (power spectrum analysis and burst suppression calculation) increases the accuracy to measure cerebral anesthetic drug effect. Initially, no difference was found between BIS and $AAI_{1.5}$ or between BIS and $AAI_{1.6}$ when scaled to 100. However, when the upper limit of the scale was reduced to 60, remarkable results were observed. Figure 4 shows that a high variability and a high amount of nonlinearity are observed in all measures when scaled to 100. For $AAI_{1.6}$, one can say that the signal between 60 and 100 nearly behaves as "random noise." By eliminating this part of the $AAI_{1.6}$ range, the high variability resulting in a high level of nonlinearity is drastically reduced. This results in a very high individualized Spearman rank correlation as shown in table 2. However, one can raise the question of whether a constant number around 60 offers more information compared with the complete scale, both when predicting propofol anesthetic drug effect and when evaluating a clinical level of sedation before loss of consciousness is obtained. This must be studied in further research. We were not able to evaluate the clinical level of sedation in this population because we wanted to avoid any stimulation during induction.

Figure 5 shows the pharmacodynamic modeling for all measures *versus* Ce_{PROP}. Previously, the relation between measures of anesthetic drug effect and Ce_{PROP} was observed following a sigmoid E_{max} model. Therefore, in our study, the relation between the measures of anesthetic drug effect and Ce_{PROP} was also modeled using a sigmoid E_{max} model, and the model parameters were estimated using a population approach. In NONMEM, the parameters in the individual are weighted in a Bayesian manner toward the mean for the population, based on the variance of the individual parameters. Examining our raw data, we found for all parameters a single sigmoid regression to be adequate for describing the range of concentrations used in this study. When looking at figure 5, one can conclude that the smoothest regression is found in $AAI1.6_{60}$. This is reflected in an optimization of both the interindividual and the intraindividual variability in the population. In table 3, the coefficients of variation of the typical values of the cerebral drug effect measures reveal a major decrease in

the interindividual variability of the slope (γ) when $AAI1.6_{60}$ is compared to $AAI_{1.6}$. Simultaneously, a decrease in intraindividual variability at baseline is observed for $AAI1.6_{60}$, reflected by the lower SD compared with $AAI_{1.6}$. However, we want to stress the fact that the regression analysis for $AAI1.6_{60}$ should be interpreted cautiously because of the effect of rejection of data on the NONMEM analysis. It might cause a distortion on the data input in such a way that the behavior of the population regression is closer to the *a priori* chosen E_{max} model. Further research is needed to clarify whether this result is an artificial overestimation of the performance parameters or whether $AAI1.6_{60}$ is indeed able to maintain a high performance as a hypnotic drug effect monitor.

We conclude that the use of the composite index $AAI_{1.6}$, which combines information from the MLAEP, spontaneous electroencephalogram, and burst suppression, increases the correlation with the cerebral drug effect of propofol as compared with the $AAI_{1.5}$, which is a solitary fast extracted MLAEP index. By adjusting the upper scale limit to 60, the performance measures are optimized even more. However, the implications of this newly chosen upper scale limit should be further explored on both the clinical and the pharmacodynamic level.

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