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Comparison of Conventional Averaged and Rapid Averaged, Autoregressive-based Extracted Auditory Evoked Potentials for Monitoring the Hypnotic Level during Propofol Induction

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Background: **The extraction of the middle latency auditory evoked potentials (MLAEP) is usually done by moving time averaging (MTA) over many sweeps (often 250–1,000), which could produce a delay of more than 1 min. This problem was addressed by applying an autoregressive model with exogenous input (ARX) that enables extraction of the auditory evoked potentials (AEP) within 15 sweeps. The objective of this study was to show that an AEP could be extracted faster by ARX than by MTA and with the same reliability.**

Methods: **The MTA and ARX methods were compared with the Modified Observer's Assessment of Alertness and Sedation Scale (MOAAS) in 15 patients scheduled for cardiac surgery and anesthetized with propofol. The peak amplitudes and latencies were recorded continuously for the MTA- and ARX-extracted AEP. An index, AAI, was derived from the ARX-extracted AEP as well.**

Results: **The best predictors of the awake and anesthetized states, in terms of the prediction probability, Pk, were the AAI (Pk [SE] = 0.93 [0.01]) and Na-Pa amplitude (MTA, Pk [SE] = 0.89 [0.02]; ARX, Pk [SE] = 0.87[0.02]). When comparing the AAI at the MOAAS levels 5–3 *versus* 2–0, significant differences were achieved. During the transitions from awake to asleep, the ARX-extracted AEP were obtained with significantly less delay than the MTA-extracted AEP (28.4 s *vs.* 6 s).**

Conclusion: **The authors conclude that the MLAEP peaks and the AAI correlate well to the MOAAS, whether extracted by MTA or ARX, but the ARX method produced a significantly shorter delay than the MTA.**

IT has been shown in several publications that the middle latency auditory evoked potentials (MLAEP) can detect the hypnotic level of a patient undergoing general anesthesia.[1–5] MLAEP are small changes noted on electroencephalogram (EEG) caused by auditory stimuli; averaging the response of many stimuli is required to extract these responses, which are embedded in the background EEG and electromyogram (EMG) activity. The MLAEP is recorded using scalp electrodes, and the acoustical stimuli are given repetitively through a pair of headphones.

To extract the AEP from the background activity, the click stimulus must be repeated 250–1,000 times. This process is called moving time averaging (MTA) and has been used in the majority of studies for the extraction of the AEP. However, its main disadvantage is its long total update delay (30 s to 5 min).[6]

We addressed this problem by applying a more advanced signal-processing tool, the autoregressive model with exogenous input (ARX). The ARX model has previously been applied to the extraction of visual and auditory evoked potentials (AEP).[7,8] The objective of this study was to compare the ARX and MTA methods in terms of update delay of the extracted AEP. The AEP were extracted by both methods during propofol induction in patients scheduled for cardiac surgery, and the AEP peaks and latencies and a derived index (AAI) were compared with the levels 5 to 1 on the Modified Observer's Assessment of Alertness and Sedation Scale (MOAAS)[9] (table 1).

Materials and Methods

Clinical Trial

The study protocol was approved by the local Ethics Committee, and written consent was obtained. Fifteen patients scheduled for elective cardiac surgery were included in the study. Exclusion criteria were age less than 18 yr, neurologic disorders, deafness, mental impairments, and emergency surgery. The patients were premedicated with 0.02 mg/kg intravenous midazolam 15 min before entering the operating room, and electrocardiogram (EKG; DII, V5), invasive blood pressure, Spo_2, and nasopharyngeal temperature were monitored.

The rate of propofol infusion was calculated by the pharmacodynamic model of the TCI-Diprifusor® (Zeneca Ltd., Macclesfield, Cheshire, UK). The target for the plasma propofol concentration was set at 5 μg/ml to be achieved in 5 min, using a ramp infusion. When the patient was at MOAAS level 1, the propofol infusion was set to maintain the estimated plasma concentration achieved at that moment. This infusion rate was maintained until the end of the study, 5 min after the onset of loss of consciousness (LOC). The estimated effect-site concentrations of propofol were calculated by the TCI-

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Table 1. Responsiveness Levels of the Modified Observer's Assessment of Alertness/Sedation Scale (MOAAS)

Level	Response
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

Diprifusor® and registered every minute during the study period. When the patients were asleep, the ventilation was assisted with a mask.

The AEP recordings were initiated 3 min before the anesthetic induction to establish a baseline for the AEP during the awake condition (MOAAS level 5). One of the investigators assigned the MOAAS levels. Blinded to the AEP monitor, he was continuously talking to the patient until loss of response. Then, testing for response to mild shaking and prodding was done at 10-s intervals until loss of response. A second investigator, blinded to the clinical signs of the patient, registered the AAI values that corresponded to the MOAAS levels assigned. When the study finished, the anesthesia continued according to the routines of the department, and surgery began.

Auditory Evoked Potentials Recording and Analysis

The AEP were recorded using the A-Line® (Software version 1.4) AEP monitor (Danmeter, Odense, Denmark). The AEP were elicited with a binaural click stimulus of 65-dB (sound pressure level) intensity, 2-ms duration, and repetition rate of 9 Hz (one click each 110 ms). Three silver-silver chloride electrodes (A-Line®, Danmeter, Odense, Denmark) were positioned at middle forehead (active electrode), left forehead (reference), and the left mastoid (ground). The AEP window was 80 ms, and the preprocessing of the EEG sweeps consisted of artifact rejection and 25–65 Hz finite impulse response (FIR) 170th order band-pass filtering. Artifactual signals were rejected automatically. These are commonly caused by interference from electrical devices in the operating room. The band-pass filter chosen was narrow to minimize spurious EEG signals and facial EMG as much as possible. This ARX-extracted AEP was used to calculate the A-Line ARX Index (AAI), a unitless index ranging from 0 to 99 continuously presented on the A-Line display, which in other studies has been shown to decrease below 28 for MOAAS level 1.[4] The MTA-extracted AEP was obtained off-line *via* specially designed software.

The ARX AEP were extracted over 15 sweeps, producing an update delay of 6 s (15 times at 110 ms, plus 4.35 s in a post-smoothening process), and the MTA AEP were extracted over an average of 256 sweeps, resulting in an update delay of 28.4 s (256 times at 110 ms). During sweeps with artifact contamination, the monitor interrupts its calculations. When "clean" sweeps are detected again, calculations start again from the point of interruption. A more detailed description of the total signal processing can be found elsewhere[8] or in the Appendix.

The amplitudes and latencies of the Na, Pa, and Nb peaks of the AEP were determined manually off-line. This was done for the MTA- and the ARX-extracted AEP by replaying the AEP registration. At each change of MOAAS level, the registration paused, and the peak amplitudes and latencies were measured.

Statistical Analysis

The difference in mean time between the moment when the patient was deemed at MOAAS level 1 and the moment when the Nb latency (estimated by ARX and MTA AEP) became larger than 60 ms was tested using a *t* statistic.

We tested the hypothesis that the latency and amplitude of the same peaks obtained with the ARX and the MTA methods should not be different when measured in either the asleep or awake state for the same patient. This was also tested with a *t* statistic. Mann–Whitney U tests were carried out on each AEP indicator to determine at which successive levels of MOAAS the indicators showed significant differences.

The prediction probability, termed *Pk analysis*,[10] was used in this study to evaluate the indicator's prediction performance related to the MOAAS scale. This method has been applied in several recent articles evaluating different systems for monitoring depth of anesthesia.[11,12] The use of this standardized statistical tool facilitates the comparison among the results of different studies. The Pk ranges from 0 to 1. A value of Pk = 1 means that the x values always predict correctly the order of the y values. A value of Pk = 0.5 means that the x values predict the order of the y values no better than chance (flipping a fair coin)[10].

The Pk was applied to Na, Pa, Nb latencies, Na-Pa amplitudes, the AAI, and the estimated effect-site propofol concentrations (Ce_{prop}; *i.e.*, the x values) in relation to the MOAAS levels (the y values). A power calculation, based on differences in Pk, was carried out to estimate the necessary sample size before commencing the study. Based on previous results[12] for other AEP indicators, it was considered that a difference of less than 0.05 in Pk would not be of clinical importance, and we assumed an estimate of the standard error of Pk (SE) of 0.02, when using the jackknife estimate. The value of clinical importance was chosen from the criteria that it should be considerably larger than the SE. The *t* statistic was then calculated as the quotient between the chosen difference in clinical importance and the SE ($t = 0.05/0.02$). With these characteristics and testing with a statistical significance of $P = 0.01$, a *t* table shows that approximately 15 patients (14 degrees of freedom) should be

Table 2. Mean (SD) Values of all AEP Indicators, AAI, and Ce_{prop} for each Modified Observer's Assessment of Alertness/Sedation Scale (MOAAS) Level

MOAAS	Na Latency MTA (ms)	Pa Latency MTA (ms)	Nb Latency MTA (ms)	Na-Pa Amp MTA (μV)	Na Latency ARX (ms)	Pa Latency ARX (ms)	Nb Latency ARX (ms)	Na-Pa Amp ARX (μV)	AAI (unitless)	Ce_{prop} ($\mu g \cdot ml^{-1}$)
5	22.6 (3.2)*	33.6 (3.6)*	44.5 (4.8)*	1.2 (0.4)*	22.3 (3.5)	32.9 (4.6)*	43.9 (5.4)*	1.3 (0.4)*	81.3 (8.1)*	—
4	25.1 (2.3)	36.1 (4.6)	48.6 (6.6)	1.1 (1.1)*	25.7 (4.6)	38.6 (6.3)	50.8 (6.6)	1.1 (0.8)*	70.3 (15.8)*	0.5 (0.7)*
3	25.9 (3.1)	38.3 (3.9)*	52.9 (5.4)*	0.6 (0.2)*	26.1 (4.8)	39.1 (6.2)*	53.1 (5.1)*	0.6 (0.3)*	53.4 (12.9)*	0.9 (0.3)*
2	27.0 (5.3)	42.4 (4.6)	58.3 (5.2)*	0.3 (0.1)*	29.0 (6.3)	44.8 (5.4)	58.9 (5.9)*	0.3 (0.1)	30.7 (9.5)*	1.3 (0.4)*
1	31.3 (8.8)	47.3 (7.6)	63.1 (6.9)	0.2 (0.1)	31.6 (9.0)	46.0 (8.7)	64.2 (4.8)	0.2 (0.1)	21.1 (6.7)	1.7 (0.6)

Mann-Whitney tests were carried out in order to test significant differences between subsequent MOAAS levels.

AAI = A-Line ARX Index; AEP = auditory evoked potentials; Ce_{prop} = estimated propofol effect-site concentrations; MTA = extracted by Moving Time Average; ARX = extracted by an Autoregressive model with Exogenous input; * = significant difference with subsequently lower MOAAS level ($P < 0.05$).

included in the study. The Pk of the AAI was compared with the remaining AEP indicators; therefore, a Bonferroni correction was applied to the significance levels shown in table 2.

Results

The difference between the moment where the patient was deemed in MOAAS level 1 and the moment when the Nb peak had increased to a latency of 60 ms was calculated for each patient for the ARX and the MTA methods. The means (SD) were 5.4 s (24.7) and 29.8 s (27.2) for the ARX and MTA methods, respectively ($P < 0.05$). The ARX method was significantly faster than the MTA method. Figures 1 and 2 are SPSS (SPSS Inc, Chicago, IL) box plots where the box limits present the 25% and 75% percentiles and the middle line is the median. The whiskers present the minimum and maximum data point, provided that this data point is not an outlier. When the difference between the minimum and maximum exceeds the 25%/75% percentile with 1.5 or 3 box lengths, then the value is marked with an "o" or an "*", respectively. Figure 1 shows the box plots of the AAI and Ce_{prop} *versus* MOAAS scale, and figure 2 shows the box plots of the Na, Pa, Nb latencies and Na-Pa amplitude extracted by ARX and MTA *versus* MOAAS scale. The transition from MOAAS level 5 to 1 caused a significant increase in the latency of the Nb peaks from mean (SD) 43.9 ms (5.4) to 64.2 ms (4.8) for the ARX method and 44.5 ms (4.8) to 63.1 ms (6.9) for the MTA. Table 2 shows the mean and SD of each indicator and the result of the Mann–Whitney U tests for each indicator at successive levels of MOAAS. The AAI, Ce_{prop}, and the MTA-calculated Na-Pa amplitude showed significant differences at all levels of the MOAAS scale, whereas the latency of the Na peaks only showed significant differences at one MOAAS level (5 *vs.* 4) when extracted by MTA.

The difference in means of each AEP indicator extracted by MTA and ARX were tested (*t* test) for each MOAAS level. None of these comparisons produced significant differences ($P < 0.05$).

Table 3 shows the prediction performances, Pk, for the AEP-derived parameters of the MOAAS scale and the Pk for the Ce_{prop} prediction performance of the MOAAS scale. The AAI (Pk [SE] = 0.93 [0.01]) and the Na-Pa amplitudes (MTA Pk [SE] = 0.89 [0.02]; ARX Pk [SE] = 0.87 [0.02]) presented the highest Pk values, followed closely by the Nb latencies (MTA Pk [SE] = 0.79 [0.03]; ARX Pk [SE] = 0.84 [0.02]). The Pk for the AAI was not significantly higher than the Pk values for the Na-Pa amplitudes but was significantly higher than the Pk values for all peak latency measures. The Pk for the Ce_{prop} produced high values as well (Pk [SE] = 0.92 [0.02]). Figure 3 shows examples of AEP extracted simultaneously with the MTA and ARX methods while patients were awake and after propofol induction.

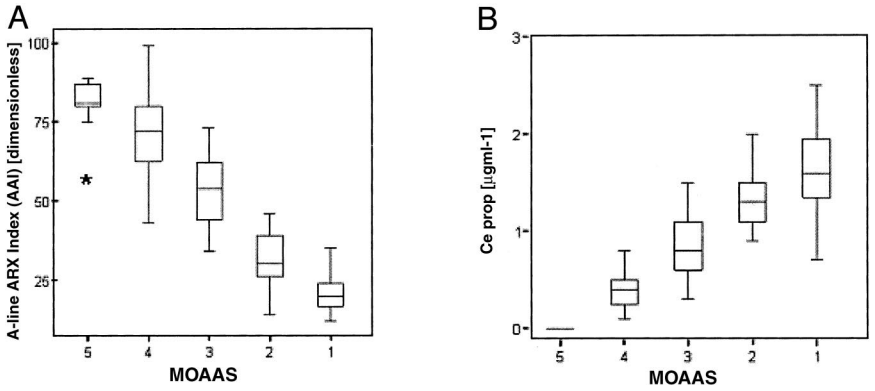

Fig. 1. Box plots with 50% outliers (*o*) and extremes (*) of the A-Line autoregressive model with exogenous input (ARX) index (*A*) and Ce_{prop} (*B*) *versus* Modified Observer's Assessment of Alertness and Sedation scale (MOAAS).

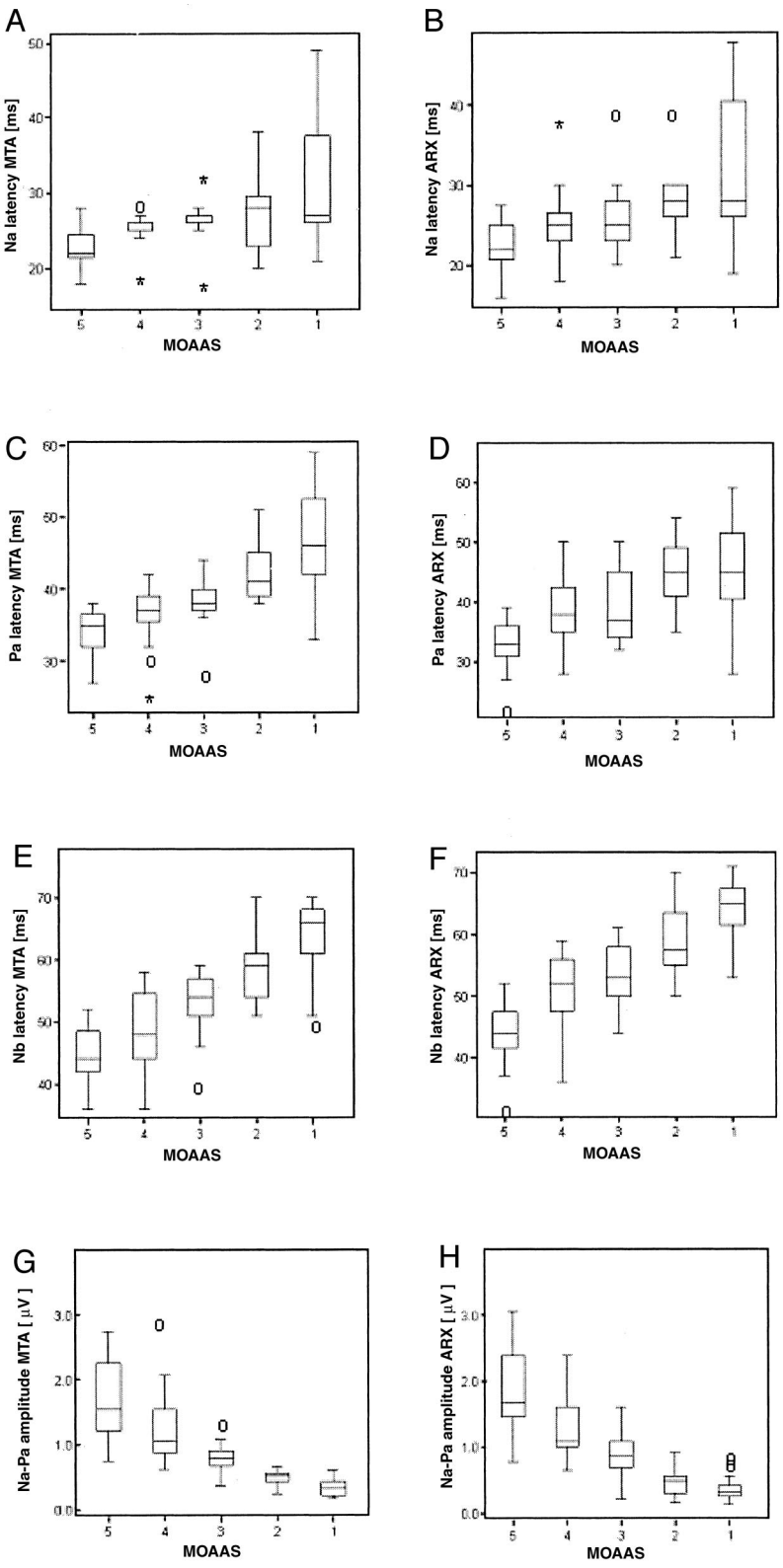

Fig. 2. The figure shows the box plots with the median, 50% outliers (*o*), and extremes (*) of the auditory evoked potentials (AEP) peak amplitudes and latencies *versus* Modified Observer's Assessment of Alertness and Sedation (MOAAS) scale, for moving time averaging (MTA) and autoregressive model with exogenous input (ARX) methods. (*A*) and (*B*) show the Na latencies; (*C*) and (*D*) show the Pa latencies; (*E*) and (*F*) show the Nb latencies; and (*G*) and (*H*) show the Na-Pa amplitudes, in all cases for MTA and ARX, respectively.

Discussion

The purpose of the current study was to compare a new method, ARX, for extraction of the AEP with the classic method, the MTA.

The application of ARX models to physiologic signals was originally described by Cerutti,[13] who extracted visual evoked potentials (VEP) with an ARX model. The model was later applied by Liberatti and Cerutti[14] and by Magni.[15] Although single-sweep analysis was applied to VEP, which have considerably larger amplitudes than

Table 3. The Prediction Probability (Pk) Analysis of the Prediction Performances for AEP Indicators and the Ce_{prop} against the Modified Observer's Assessment of Alertness/Sedation Scale (MOAAS)

	Na Latency MTA	Pa Latency MTA	Nb Latency MTA	Amp Na-Pa MTA	Na Latency ARX	Pa Latency ARX	Nb Latency ARX	Amp Na-Pa ARX	AAI	Ce_{prop}
Pk	0.69	0.80	0.79	0.89	0.63	0.73	0.84	0.87	0.93	0.92
SE	0.04	0.03	0.03	0.02	0.04	0.03	0.02	0.02	0.01	0.02
Significance	—	—	—	NS	—	—	—	NS	—	NS

The Pk value of the AAI was compared with each of the remaining indicators using a *t* test with Bonferroni correction.

AAI = A-Line ARX Index; AEP = auditory evoked potentials; Ce_{prop} = estimated propofol effect-site concentrations; MTA = extracted by Moving Time Average; ARX = extracted by an Autoregressive model with Exogenous input; $P < 0.05$ after Bonferroni correction: significant difference (—); $P > 0.05$ after Bonferroni correction: no significant difference (NS); SE = standard error.

that of AEP, we decided not to attempt single-sweep analysis but rather do a preaveraging of 15 sweeps to improve the SNR of the AEP before applying the ARX model. This is the result of the lower SNR of the AEP as compared with the VEP. An important advantage of the ARX method is that it does not require *a priori* knowledge of the underlying distribution of the analyzed signal. The main disadvantage of the ARX method is that any time-locked signal in the two inputs to the ARX model would be interpreted as an AEP; therefore, preconditioning of the signals and rejection of artifacts are crucial before applying the ARX method.

Our results show that the AEP extracted using the ARX method presented the Na, Pa, and Nb peaks as clearly as the AEP extracted by MTA. We found no significant differences in either peak amplitudes or peak latencies when extracted with ARX or MTA. This is reflected in table 2, where it is also observed that the SD for peak latencies and amplitudes are at the same levels for MTA and ARX. Therefore, we conclude that even though the ARX method uses much fewer sweeps for the extraction of the AEP, the morphology of the AEP remains largely

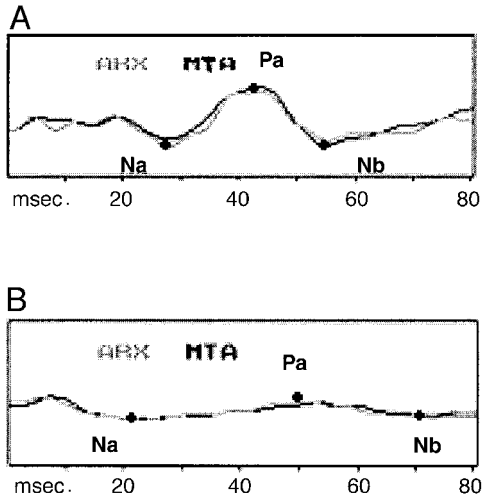

Fig. 3. An auditory evoked potential $(AEP)_{MTA}$ (black) and AEP_{ARX} (gray) registered in an awake patient (*A*) and a patient anesthetized with propofol (*B*). The estimation of the Na, Pa, and Nb peak positions is marked. MTA = AEP extracted by a moving time average; ARX = AEP extracted by an autoregressive model with exogenous input.

unchanged. The highest prediction probability, Pk, between the MOAAS scale and the AEP indicators was obtained by the AAI, although the Pk difference between Na-Pa amplitude (extracted by MTA and ARX) and AAI was not significant. The explanation for the higher Pk values observed using the AAI could be because the AAI reflects the overall changes of the AEP (latency and amplitude changes). Also, the fact that the AAI is automatically obtained whereas the Na, Pa, and Nb latencies were estimated manually could produce some variations and observer bias, especially when the patient is anesthetized and the peak amplitudes are low. Figures 1 and 2 also show that the overlap between indicator values is largest for the short peak latencies (Na and Pa), whereas the latencies of Nb show less overlap between the MOAAS levels 5 and 1, and the amplitudes and AAI do not show any overlap between MOAAS levels 5 and 1. The Ce_{prop} produced a high Pk indicating that the Ce_{prop} arising from the applied ramp infusion scheme of propofol predicted well the MOAAS levels in this patient population. However, this high prediction performance of the drug effect-site concentrations has only been established in single-drug settings, as in this study. The transition from awake to asleep caused a significant increase in the ARX AEP latency of the Nb peak, from a mean of 43.9 ms to a mean of 64.2 ms. These findings are comparable with the findings of Schwender *et al.*,[16] who noted larger Nb latencies were found during maintenance of anesthesia. Also, the Pk values shown in table 3 confirmed that the Na-Pa amplitudes decreased and the Na, Pa, and Nb latencies increased after anesthetic induction with propofol. In this study, MLAEP were monitored to predict movements during isoflurane or propofol anesthesia in patients with epidural analgesia to minimize the effect of pain on the level of consciousness and to inhibit reflex movements in response to pain. It was concluded that an Nb latency threshold of 60 ms was the most significant predictor of movement or no movement.

Mantzaridis *et al.* also mapped the AEP into an index and found that it correlated well with the moment of eye opening after propofol anesthesia, [17,18] and recently they obtained a Pk of 0.82 for sevoflurane concentration as a predictor of the MOAAS score.[19] This AEP index was

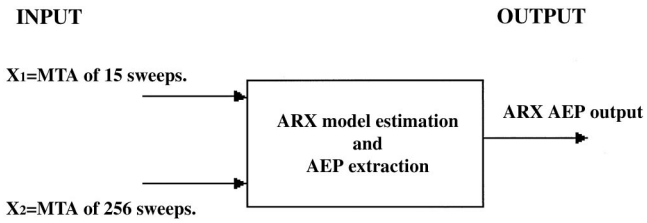

Fig. 4. The ARX model, showing the two inputs: an MTA of 256 sweeps and an MTA of 15 sweeps. The output, ARX AEP, is X_2 filtered by the a and b coefficients obtained for each new sweep. AEP = auditory evoked potentials; MTA = AEP extracted by a moving time average. ARX = AEP extracted by an autoregressive model with exogenous input.

based on an AEP extracted by the MTA method, producing a delay of 36.9 s.[20] Iselin-Chaves *et al.*[21] compared the Pk of two methods, the Bispectral analysis of the EEG (BIS) and Pa and Nb peak amplitudes and latencies of the MLAEP, and found that the MLAEP needed considerable time to produce a response (0.5–5 min to build an average of the AEP).

The method of choice for AEP extraction in those studies was the MTA, which produces a delay of at least 30 s. The delay depends on the number of repetitions of the stimuli. Although the MTA-extracted AEP used in this study produced a shorter delay, this delay is still important when applying the AEP for on-line monitoring in the operating room. Further, optimal performance of the MTA method depends on the following three requirements: (1) the noise in which the AEP is embedded should be a random signal; (2) the desired signal (here, the AEP) should be identical in each sweep, *i.e.*, no changes in amplitude or latency of the peaks may occur over time; and (3) the noise and the desired signal should be independent. If these three requirements are accomplished, it can be shown that the improvement in SNR of the AEP equals the square root of the number of repetitions of the stimuli.[22] However, these three conditions are rarely accomplished when recording evoked potentials. First, the AEP is not identical in each elicited sweep. This is especially evident when a transition from awake to asleep or *vice versa* occurs. Further, the EEG, here considered as the noise, is not totally random; rather, it is quasi-periodic. The assumption of independence is not certain either, as the EEG spectral changes are similar to those of the AEP during transition from awake to asleep. Therefore, beyond a certain number of repetitions of the click stimulus, the SNR of the AEP will not increase with larger number of repetitions. In conclusion, increasing the number of repetitions produces a stable output but does not mean that the output is a more "uncontaminated" AEP.[22]

The results obtained during the transition from the awake to the anesthetized state showed that the ARX-extracted Nb peaks were obtained with less delay than those extracted by MTA (5.4 s *vs.* 29.8 s), which means that AEP monitoring can be carried out on-line and close to real-time in the operating room.

We finally conclude that the Na-Pa amplitudes and Nb latencies of the MLAEP can be used as a reliable indicator of loss of consciousness, independently of whether extracted by MTA or ARX, but the ARX method generates a shorter delay.

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Appendix: Principles of the A-Line Auditory Evoked Potentials Recording and Analysis

The A-Line monitor uses an AEP window of 80 ms. Preprocessing of the EEG sweeps consisted of artifact rejection and 25–65 Hz finite impulse response (FIR) 170th order band-pass (BP) filtering. A narrow BP filter ensures better suppression of noise, but the disadvantage is that the brainstem AEP (BAEP) is suppressed as well because this has larger frequency content than the MLAEP. Thornton *et al.*[23] used a BP filter of 25–125 Hz, whereas Wolf *et al.*[24] chose a BP filter of 25–75 Hz.

Autoregressive with Exogenous Input Model 1

The ARX model is the technology used for night vision in helicopters, where the need is to rapidly extract a stable image from the infrared camera image that is disturbed by the vibration of the helicopter. Similar, the AEP waveform is disturbed by spontaneous EEG and EMG activity, and signal processing should be applied to extract the AEP. The classic method is MTA. The principal disadvantage of the MTA is the need of many repetitions of the stimuli, hence producing a delay of typically 1–5 min. On the other, the ARX model can extract a common component present in two signals obtained by relatively low numbers of repetitions, here 15 and 256 sweeps. Single-sweep analysis has been carried out on VEP by ARX modeling, but as the amplitude of the AEP is much smaller, we applied a preaveraging of 15 sweeps.

The application of ARX modeling for extraction of AEP was originally reported by Jensen *et al.*[25,26]

Definition of the ARX Model

The ARX model has two inputs: the moving time average of the last 15 sweeps (X_1) and the moving time average of the last 256 sweeps (X_2). The average of the 256 sweeps has a better signal-to-noise ratio than the average of 15 sweeps, but the average of 15 sweeps has a shorter delay than the average of the 256 sweeps. The objective of the ARX model is to merge the rapid response from input X_1 with the better SNR of input X_2.

The central equation of the ARX model is:

$$X_1(t) = b_1 \cdot X_2(t) + \ \ldots\ + b_m \cdot X_2(t-m+1) - a_1 \cdot X_1(t-1) - \ \ldots\ - a_n \cdot X_1(t-n) + e \quad (1)$$

where the *a*s and *b*s are the coefficients of the model. The *n* is the model order. By setting up several equations with the same structure as equation 1, but shifted in time, it is possible to determine the coefficients. The coefficients are determined in such a way that the best prediction is obtained in equation 1, in a least mean square sense. When the coefficients of the model are determined, the ARX–AEP is obtained by filtering of input X_2 with the *a* and *b* coefficients. Figure 4 shows the diagram of the ARX model and the AEP extraction.

The principle of the ARX model is that peaks that correlate between the two inputs are used to define the ARX coefficients in such a way that the output is the linear combination of the peaks common in the two inputs. The main advantage of the ARX model is that changes can be traced as rapidly as the changes appear in the input containing the 15 sweeps, but with much less noise than is present in the average of the 15 sweeps. The principal disadvantage of the ARX method is that peak components that correlate between the two inputs arising from noise, *e.g.*, mains, will be modeled as well. For this reason, robust preprocessing is essential before applying the ARX model. The preprocessing should remove 50–60 Hz line interference and reject artifactual signals.

Model Order

The order of the ARX model should ideally be calculated for each sweep, but this is a time-consuming process. Hence, to comply with the need of fast processing time, an average model order of five for *a* and *b* coefficients was implemented in the A-line.

Artifact Rejection and Stability

Input Amplitude. If the amplitude in any sample exceeds 90 μV, then the present sweep and the subsequent three are rejected. The reason for rejecting the following three is because the amplifier may go into saturation, therefore a recovery time is considered.

Pole-zero Analysis. The coefficients of the ARX model are calculated for each sweep. The stability of the ARX model is important to ensure that the ARX-extracted AEP is reliable. Stability is tested by a pole-zero analysis of the ARX polynomial; if a sweep has poles outside the unit circle, then the sweep is rejected. Further, if the amplitude of the ARX-extracted sweep is more than three times that of the MTA-extracted sweep, then the sweep is rejected as well.

Subsequently, the ARX–AEP is smoothed exponentially, using:

$$\text{ARX-AEP}_{\text{mean}} = 0.1\text{ARX-AEP}_{\text{new}} + 0.9\ \text{ARX-AEP}_{\text{old}} \quad (2)$$

SNR Ratio

Even though the data have been BP filtered and data with excessive amplitude have been discarded, the question remains whether the processed data are really an AEP. This problem has been addressed the following way. A block of sweeps was averaged in the conventional way, *i.e.*, synchronized with the acoustic stimulus. The same sweeps were averaged asynchronously. The maximum amplitudes were calculated in the synchronous average (Amp_{sync}) and the asynchronous average (Amp_{async}). The SNR was then defined as:

$$SNR = \frac{Amp_{\cdot sync}}{Amp_{Async}} \quad (3)$$

If no synchronized signal is present, then the maximum amplitude of the synchronized and asynchronized signal will be roughly equal and SNR will converge to 1. If a synchronized signal is present, the SNR will increase. The SNR is typically in the range of 1.5–3 when using 256 repetitions of the stimulus. A limit of 1.45 was defined, which means that sweeps with SNR less than 1.45 are rejected.

This procedure ensures that the processed signal is synchronized to the click stimulus. Such a signal is either an AEP or a muscle reflex, a so-called startle response. However, the startle response is much larger than the AEP; therefore, it can be easily distinguished from the AEP. Thus, this proprietary method is a good quality assurance of whether the displayed signal is an AEP.

Index Calculation

The last step in the A-line signal processing chain is the index calculation, the purpose being a mapping of the AEP into one number, which facilitates an easier clinical interpretation of the AEP. Other groups have suggested strategies for mapping the AEP, the first ones being McGee *et al.*[26] and Thornton.[2]

The index that we have defined is termed the A-Line *ARX index* (AAI), and it is calculated as the sum of absolute differences in the 20- to 80-ms window of the AEP.

The AAI is mostly dependent on the amplitude changes of the AEP. Increasing amplitude will increase the index and *vice versa*. The peak latencies have some influence as well because if the peak latency is increased, then the index will decrease.

The 20-ms start of the window was chosen so as not to include BAEP and auricular muscular artifacts, and the 80-ms end of the window was chosen so as not to include long latency AEP (LLAEP).

The index can also be considered as a differentiation of the signal. The index calculation is a mapping from a two-dimensional space to a one-dimensional one. This is certainly mathematically possible, but information will be lost. However, the important issue is that the information related to the changes in the level of consciousness should be preserved.

Care should be taken not comparing the AAI with other AEP-based indices because an index largely depends on the following characteristics: sampling frequency, AEP window, BP filter, and the method by which the AEP is extracted.