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Evaluation of the Alaris Auditory Evoked Potential Index as an Indicator of Anesthetic Depth in Preschool Children during Induction of Anesthesia with Sevoflurane and Remifentanil

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Background: **Autoregressive modeling with exogenous input of middle latency auditory evoked potentials (A-Line autoregressive index [AAI]) has been proposed for monitoring depth of anesthesia in adults. The aim of this study was to evaluate the performance of the AAI during induction of anesthesia with sevoflurane and remifentanil in pediatric patients.**

Methods: **Twenty preschool children were anesthetized with sevoflurane and remifentanil. AAI, heart rate, and mean arterial pressure were compared for their ability to distinguish between different hypnotic states before inhalation induction and during sevoflurane anesthesia with and without remifentanil infusion. The prediction probability was calculated for discrimination between the predefined case milestones *Awake*, *Spontaneous Eye Closure*, and insertion of a laryngeal mask airway during general anesthesia (*Laryngeal Mask Insertion*).**

Results: **The AAI (mean ± SD) in *Awake* children was 79 ± 10, declining to 59 ± 22 at *Spontaneous Eye Closure* and 34 ± 13 when anesthetized. AAI values significantly overlapped between anesthetic states. For the AAI, the prediction probabilities regarding the ability to discriminate the hypnotic state at the case milestones *Awake versus Spontaneous Eye Closure* and *Awake versus Laryngeal Mask Insertion* were 0.77 and 0.99, respectively. In terms of prediction probability values, heart rate and mean arterial pressure were not indicative for anesthetic states. Remifentanil did not influence the AAI.**

Conclusion: **During induction of pediatric patients with sevoflurane, the AAI is of higher value in predicting anesthetic states than hemodynamic variables and reliably differentiates between the awake and anesthetized states. However, individual AAI values demonstrate significant variability and overlap between different clinical conditions.**

THE availability of new technologies to assess various aspects of the depth of anesthesia has stimulated current revival of interest in monitoring the hypnotic component of general anesthesia.

Middle latency auditory evoked potentials (MLAEPs), extracted from the electroencephalogram 10–100 ms after an auditory signal, represent the earliest cortical response to the acoustic stimulus. Amplitudes and latencies of the MLAEP are influenced by anesthetics and surgical stimuli and are therefore believed to be useful for measuring depth of anesthesia.[1–3]

The A-Line Monitor (Danmeter A/S, Odense, Denmark), a recently commercialized system for depth of anesthesia monitoring, extracts the MLAEP from the electroencephalographic signal by using an autoregressive model with an exogenous input adaptive method. A monitoring variable, the A-Line Autoregressive Index (AAI), is then calculated from the MLAEP.[4]

Several recent studies in adult patients suggested that the AAI might be helpful in distinguishing between the awake and unconscious states[5–8] and for the detection of intraoperative awareness.[9] However, data regarding the ability of the AAI to help to conduct an anesthetic with reduced drug consumption and shortened recovery times when compared to a conventional practice protocol are contradictory.[10,11] Recart *et al.* reported on reduced anesthetic and opioid requirement[12] and improved quality of recovery and more rapidly achieved fast-track eligibility[13] when AAI monitoring was used to guide the anesthetic compared with conventional practice.

The purpose of the current study was to evaluate and compare the performance and reliability of the AAI and hemodynamic variables as indicators of different hypnotic states during induction of anesthesia with sevoflurane and remifentanil in pediatric patients. Our hypothesis was that the AAI is superior to hemodynamic variables for discriminating between anesthetic states during induction of anesthesia with sevoflurane and remifentanil in preschool children.

Materials and Methods

Study Population

After approval by the institutional ethics committee of the University of Regensburg, Germany, and written informed parental consent were obtained, 20 pediatric patients scheduled to undergo ophthalmic surgery (strabismus repair, dacryocystorhinostomy) were enrolled in our study.

Children were considered eligible for enrollment in our study if they had an American Society of Anesthesiologists physical status of I or II, were aged younger than 7 yr, and were scheduled to undergo elective ophthalmologic surgery necessitating general anesthesia. Children were excluded from the study if they had relevant hypacusis or deafness; had significant cardiovascular, respiratory, or neurologic disease; or if they were taking

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Table 1. The University of Michigan Sedation Scale for Children

UMSS	Clinical Features
0	Awake and alert
1	Minimally sedated; tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated; somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated; deep sleep, arousable only with significant physical stimulation
4	Unarousable

UMSS = University of Michigan Sedation Scale.

long-term medication known to affect the central nervous system.

Study Protocol

All children received a standardized anesthetic: Approximately 30 min before induction of anesthesia, oral premedication (2.4 mg/kg ketamine and 0.4 mg/kg midazolam; 0.4 ml/kg of a syrup preparation) was given. Anesthesia was induced with sevoflurane *via* facemask, initially 8 vol% fraction inspired (fresh gas flow, 10 l/min), in oxygen. After the moment of spontaneous eye closure (EC), sevoflurane was administered at 4 vol% for another 2 min, and then a peripheral venous catheter was inserted. If there was no withdrawal reaction to venipuncture and end-tidal sevoflurane was greater than 3%, a laryngeal mask airway (LMA) was inserted immediately after fixation of the intravenous catheter. In case of a withdrawal reaction to venipuncture, the patient was given sevoflurane *via* facemask for another 2 min, and then LMA insertion was performed. Reactions to LMA insertion (movement of limbs, coughing, hemodynamic changes) were specifically noted, and patients were assigned to a level of the University of Michigan Sedation Scale (UMSS)[14] (table 1). In the case of no reaction to LMA insertion, patients were deemed to be anesthetized. After LMA insertion, the end-tidal sevoflurane concentration was reduced to 50% of the minimum alveolar concentration (MAC), corrected for age[15] (fresh gas flow, 0.5 l/min). Then, a slow intravenous bolus injection of 0.5 μg/kg remifentanil was given over 10 s, followed by a continuous infusion at a rate of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Initially, patients breathed spontaneously; if necessary, normocapnia (end-tidal carbon dioxide, 35–40 mmHg) was ensured by manually assisted ventilation. After remifentanil bolus application, controlled ventilation was started. Patients were not paralyzed during the study period.

End-tidal sevoflurane, electrocardiogram, noninvasive blood pressure, capnogram, temperature, AAI, and electromyogram were monitored during anesthesia. The anesthesiologist in charge was not involved in the study and was blinded to the AAI. On arrival of the patient in the induction room, he defined the consciousness state of the child at baseline, using the UMSS.

Auditory Evoked Potential Recording and Analysis and Data Collection

The MLAEPs were recorded using the A-Line (software version 1.4) AEP monitor. To make the monitor applicable to infants and preschool children, we modified its setup as follows: Using a custom-made adapter and a device for click-level reduction, both provided by Danmeter, we connected a commercially available stereo headphone that fits well on the small head of infants or preschoolers (MDR-V150; Sony Germany, Cologne, Germany) to the monitor. Before our study, the modified A-Line system was tested in adults during routine anesthetics with sevoflurane and remifentanil, where AAI values and the MLAEP curves on the monitor remained unaltered when the click-level reduction device was switched on and off.

After the skin was prepared with alcohol and abraded with gauze, three silver–silver chloride electrodes (Medicotest A/S, Olstykke, Denmark) were positioned at the mid forehead (+), left forehead (reference), and left mastoid (−). Electrode placement and skin preparation were performed until the electrodes' impedance was less than 1,000 Ω. The MLAEPs were elicited with a binaural click stimulus of 45 dB above the hearing threshold of an adult with normal hearing, 2 ms in duration, with a repetition rate of 9 Hz. The MLAEP analysis window was 20–80 ms, and the preprocessing of the electroencephalographic sweeps consisted of artifact rejection and 25- to 65-Hz finite impulse response 170th order band-pass filtering. Processing time for the AAI was 30 s for the first signal, and there was a total update delay, defined as the difference between data acquisition and data presentation,[16] of 6 s. Detailed information on the A-Line signal processing have been given by Litvan *et al.*[4] and Struys *et al.*[5]

The AAI was recorded from immediately before the start of inhalational induction of anesthesia until 5 min after the start of the remifentanil infusion. The AAI was specifically noted together with heart rate (HR), mean arterial pressure (MAP), end-tidal sevoflurane concentration, and electromyographic activity at the time of the following case milestones: *Awake*, *Spontaneous EC*, *LMA Insertion*, and after 5 min on remifentanil infusion (remifentanil + 5 min). The UMSS was derived at the case milestones *Awake* and *LMA Insertion*.

Statistical Analysis

All continuous data were tested for normality using the Kolmogorov-Smirnov method and then compared by one-way analysis of variance. *Post hoc* analysis was performed using Dunnett and Bonferroni tests for multiple comparisons where appropriate. *P* values less than 0.05

were considered statistically significant. Data are presented as mean and SD unless otherwise mentioned.

The ability and accuracy of the different indicators to distinguish between *Awake versus EC*, *Awake versus LMA Insertion*, and *EC versus LMA Insertion* were evaluated using the prediction probability (P_K), which compares the performance of indicators having different units of measurements, as described by Smith *et al.*[17] P_K was calculated for all parameters using a custom spreadsheet macro, the P_K-MACRO, described and provided by Smith *et al.*[17] We used the jackknife method to compute the SEM of the estimate. A P_K value of 1.0 means that the parameter (*e.g.*, the AAI) predicts the states (*e.g.*, *Awake vs. EC*) correctly 100% of the time. A P_K value of 0.5 means that the prediction is no better than chance alone. A P_K value of less than 0.5 indicates an inverse relation. The hypnotic states of the patient at the case milestones *Awake* and *LMA Insertion* were described by the UMSS, whereas EC is a simple observational measure that could not be assigned to the UMSS.

Results

The demographics (mean ± SD) of the 20 children in the study are as follows: age, 3.8 ± 0.2 yr; weight, 16.0 ± 4.5 kg; female:male ratio, 14:6.

Before induction of anesthesia (case milestone *Awake*), all children were awake and therefore assigned to levels 0 and 1 of the UMSS. LMA insertion did not lead to clinically visible reactions or alteration of HR or MAP in any patient; therefore, all patients were assigned to UMSS level 4.

A-Line Autoregressive Index and electromyographic (dB) values were statistically different between the case milestones *Awake* (79 ± 11 and 78 ± 17) and *EC* (59 ± 22 and 70 ± 23), *Awake* and *LMA Insertion* (34 ± 13 and 44 ± 25), and *EC* and *LMA Insertion* (Bonferroni corrected; $P < 0.01$). MAP (mmHg) was different between *Awake* (77 ± 11) and *LMA Insertion* (66 ± 10) ($P < 0.03$). Only the AAI was able to distinguish the case milestones *Awake versus LMA Insertion* with a P_K greater than 0.9 (table 2). HR was not found to be indicative for any case milestone.

Individual patient data and box plots (95th, 75th, 50th, 25th, and 5th percentiles) of the observed variables AAI, MAP, and HR at the predetermined case milestones are given in figure 1. Five minutes after the addition of remifentanil to sevoflurane, the AAI remained unaltered compared with the case milestone *LMA Insertion*. The total observation time from the beginning of inhalation induction was 19.5 ± 3.5 min. There was a significant positive Spearman rank correlation between corresponding AAI and electromyographic values ($r = 0.72$, $P < 0.0001$) but no correlation between AAI and non–steady state sevoflurane concentrations.

Table 2. Discrimination of Case Milestones *Awake versus Spontaneous EC, Awake versus LMA Insertion*, and *EC versus LMA Insertion*

Variable	Case Milestones	P_K	SE
AAI	*Awake vs. EC*	0.77	0.08
	Awake vs. LMA Insertion	0.99	0.00
	EC vs. LMA Insertion	0.83	0.07
MAP	*Awake vs. EC*	0.75	0.08
	Awake vs. LMA Insertion	0.80	0.07
	EC vs. LMA Insertion	0.57	0.09
HR	*Awake vs. EC*	0.36	0.09
	Awake vs. LMA Insertion	0.50	0.09
	EC vs. LMA Insertion	0.64	0.09
Electromyographic activity	*Awake vs. EC*	0.61	0.09
	Awake vs. LMA Insertion	0.86	0.06
	EC vs. LMA Insertion	0.77	0.07

Prediction probability (P_K) for the ARX auditory evoked potential index (AAI), mean arterial pressure (MAP), heart rate (HR), and electromyographic activity. Shown are the P_K values with SEs. A P_K value of 1.0 means that the variable always predicts the clinical condition correctly. A P_K value of 0.5 means that the variable predicts the condition no better than by chance (50:50). A P_K value of less than 0.5 indicates an inverse relation.

EC = eye closure; LMA = laryngeal mask airway.

Discussion

Measuring depth of anesthesia in children is, for several reasons, an unsolved problem. First, there is no clear definition of what *depth of anesthesia* really means. Second, in infants and young children, assessment of different hypnotic states is problematic. Regarding the lack of a clear definition of depth of anesthesia and the ability of monitors to measure different components of anesthesia, it is now widely accepted that variables derived from the electroencephalogram or MLAEPs represent the hypnotic component of anesthesia. Regarding the problems of clinical assessment of vigilance states or hypnotic states in children, the development and validation of the UMSS has given a reliable tool to categorize hypnosis.

It has been recently reported that, in adults, MLAEPs are superior to the spontaneous electroencephalogram for discriminating between consciousness and unconsciousness.[3,18] O'Kelly *et al.*[19] used an experimental setup to measure MLAEPs in anesthetized children. In children aged older than 2 yr, monitoring depth of anesthesia by MLAEPs seemed to be as reliable as formerly reported in adults, whereas their monitoring technique did not lead to satisfying results in younger children. The authors speculated that MLAEPs may also be helpful to assess cerebral protection in the perioperative period.

To our best knowledge, this is the first study to investigate the performance of the A-Line AEP monitor and the AAI in children. Until now, the Bispectral Index® monitor (Aspect Medical Systems, Natick, MA) was the only commercially available depth-of-anesthesia monitor that has been evaluated in pediatric patients.[20,21] In contrast to the AAI as a variable derived from the evoked

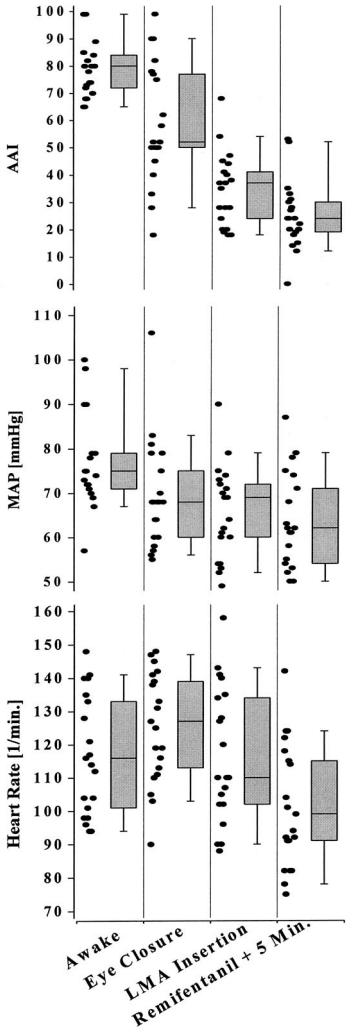

Fig. 1. Individual patient data (*dots*) and box and whisker plots (95th, 75th, 50th, 25th, and 5th percentiles) of parameters Alaris Auditory Evoked Potential Index (AAI), mean arterial pressure (MAP), and heart rate (y-axis) *versus* case milestones (x-axis). LMA = laryngeal mask airway.

electroencephalogram, the Bispectral Index is passively calculated from the electroencephalogram.

In this study, the AAI was superior to HR and MAP for discriminating the hypnotic status of the patients at the case milestones *Awake versus EC*, *Awake versus LMA Insertion*, and *EC versus LMA Insertion*. The AAI values for awake children were similar to the adult data reported by Struys *et al.*[5] and Schmidt *et al.*[7] Litvan *et al.*[22] measured the AAI during sevoflurane induction in adult patients. In their study, mean ± SD AAI values of 77 ± 15 during wakefulness decreased to 23 ± 11 after loss of consciousness (LOC), with a P_K of 1.0 for discriminating the two states. Again, the awake values were almost identical to our data. Unfortunately, we cannot compare the adult LOC data to ours because we do not have an appropriate definition of LOC in infants and small children. Defining the moment of loss of response to verbal commands as the moment of LOC (as in adults) is certainly inappropriate in infants and toddlers. The UMSS[14] helps to evaluate the hypnotic state of the child. However, unconsciousness is likely to be associated with stage 2 of the UMSS, and assignment to this stage requires tactile stimulation. During inhalation induction in children, the transition from consciousness to unconsciousness is frequently accompanied by excitation phenomena, which might be an explanation for the increase of HR at the case milestone *EC* in this study (fig. 1), and additional external stimuli would significantly increase the risk to develop laryngospasm. As a consequence, we choose to define a case milestone at the moment of spontaneous EC, instead of applying the UMSS. On one hand, we do not have a valid tool to define LOC during inhalation induction in young children; on the other hand, we believe that the moment of spontaneous EC is situated very closed to LOC.

Another shortcoming of our study relates to the fact that our patients were premedicated with midazolam and ketamine. Administration of preanesthetic anxiolytic and sedative medication to small children is a standard procedure in our hospital, as it is in most German hospitals. Furthermore, anxiolysis is of importance because anxiety before the induction causes excessive artifact contamination of the MLAEP recording, leading to rejection of the data from AAI processing. The combination of midazolam and ketamine is a common pediatric premedication, and ketamine has been shown to have no effect on MLAEPs[23] or the AAI.[24]

In this study, remifentanil infusion at a rate of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ did not change AAI values under sevoflurane at 50% MAC. There are several possible explanations for this finding: The combination of premedication with midazolam–ketamine and sevoflurane anesthesia at 50% MAC had induced such a deep level of hypnosis that remifentanil did not further contribute to the patient's hypnotic level, the AAI is insensitive to remifentanil in pediatric patients, or both.

Smooth LMA insertion requires deep anesthesia. All patients in our study were assigned to UMSS level 4 during LMA insertion; furthermore MAP and HR remained unaltered by the procedure. Therefore, from the clinical point of view, our patients were anesthetized with an AAI of 34 ± 13.

Anderson *et al.*[25] recently reported the difficulties of using the AAI in a clinical situation of non–steady state pharmacodynamics in adult patients. In their study using an inhalation induction technique with sevoflurane, the mean AAI at the moment of loss of response to verbal command was 39 (range, 24–85) at 2.3 vol% (range, 1.3–4.0 vol%) end-tidal sevoflurane. In our study, the mean AAI at the case milestone *EC* was significantly higher (59; range, 18–99), although end-tidal sevoflurane was higher (4.3%; range, 3.2–5.4%). Because of the hysteresis between non–steady state end-tidal sevoflurane and brain concentration and the large overlap of

AAI values between *Awake*, *EC*, and *LMA Insertion*, like Anderson *et al.*, we could not portray sevoflurane *versus* the AAI in a meaningful manner.

Electromyographic activity can disturb the MLAEP waveform and is therefore displayed on the screen of the A-Line monitor. Excessive artifact contamination of an MLAEP sweep leads to rejection from further analysis.[4] We found a significant positive Spearman rank correlation between AAI and electromyographic values ($r = 0.72$, $P < 0.0001$). Whether there is a dependency between the AAI and measured electromyographic values remains unclear. A possible explanation for our findings could be that electromyographic activity normally decreases with increasing anesthetic depth. Interestingly, Ge *et al.*[26] found a significant decrease in AAI values after administration of vecuronium during isoflurane anesthesia without surgical stimulation in adult patients. Our patients were not paralyzed throughout the study period.

In Germany, the A-Line AEP monitor is licensed for monitoring depth of anesthesia in adult patients only. This should be considered for any criticism regarding the performance and reliability of the AAI in pediatric anesthesia. Furthermore, we used a monitor with a setup that differs from the commercialized version, but these modifications were implemented to improve the performance of the system in infants and small children. A visual assessment of the AEP recording was performed by one of the authors (F. W.) during anesthesia.

In summary, in this study with sevoflurane and remifentanil anesthesia in children, the AAI showed significant decreases between the awake and different deeper hypnotic states and reliably discriminated the hypnotic status of the patients at the case milestones *Awake versus LMA Insertion*. Hemodynamic variables also showed significant differences between hypnotic states but were poor indicators of anesthetic depth. Our data support our initial hypothesis that the AAI is superior to hemodynamic variables for discriminating between anesthetic states during induction of anesthesia with sevoflurane and remifentanil in preschool children. However, the lack of an adequate tool to define LOC during inhalation induction of anesthesia in young children makes it difficult, if not impossible, to comment on the A-Line monitor (or any other device for depth of anesthesia monitoring) with respect to its ability and reliability to discriminate between consciousness and unconsciousness in this patient group.

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