

Comparison of Bispectral Index and Composite Auditory Evoked Potential Index for Monitoring Depth of Hypnosis in Children

Heleen J. Blussé van Oud-Alblas, M.D., Jeroen W. B. Peters, Ph.D.,† Tom G. de Leeuw, M.D.,‡ Dick Tibboel, M.D., Ph.D.,§ Jan Klein, M.D., Ph.D.,‖ Frank Weber, M.D.#*

Background: **In pediatric patients, the Bispectral Index (BIS), derived from the electroencephalogram, and the composite A-Line autoregressive index (cAAI), derived from auditory evoked potentials and the electroencephalogram, have been used as measurements of depth of hypnosis during anesthesia. The performance and reliability of BIS and cAAI in distinguishing different hypnotic states in children, as evaluated with the University of Michigan Sedation Scale, were compared.**

Methods: **Thirty-nine children (aged 2–16 yr) scheduled to undergo elective inguinal hernia surgery were studied. For all patients, standardized anesthesia was used. Prediction probabilities of BIS and cAAI *versus* the University of Michigan Sedation Scale and sensitivity/specificity were calculated.**

Results: **Prediction probabilities for BIS and cAAI during induction were 0.84 for both and during emergence were 0.75 and 0.74, respectively. At loss of consciousness, the median BIS remained unaltered (94 to 90; not significant), whereas cAAI values decreased (60 to 43; $P < 0.001$). During emergence, median BIS and cAAI increased from 51 to 74 ($P < 0.003$) and from 46 to 58 ($P < 0.001$), respectively. With respect to indicate consciousness or unconsciousness, 100% sensitivity was reached at cutoff values of 17 for BIS and 12 for cAAI. One hundred percent specificity was associated with a BIS of 71 and a cAAI of 60. To ascertain consciousness, BIS values greater than 78 and cAAI values above 52 were required.**

Conclusions: **BIS and cAAI were comparable indicators of depth of hypnosis in children. Both indices, however, showed considerable overlap for different clinical conditions.**

ELECTROENCEPHALOGRAPHY-DERIVED variables, such as the Bispectral Index (BIS; Aspect Medical Systems Inc., Newton, MA) and midlatency auditory evoked potentials (MLAEPs), have been proposed as measures of the hypnotic state during anesthesia. The BIS is an empirically derived multifactorial electroencephalographic parameter that relies on the correlation of the phases between frequency components of the electroencephalogram.[1] In adult patients, several studies have demonstrated that the use of BIS during anesthesia can decrease drug requirements,[2–5] decrease the incidence of intraoperative awareness,[6,7] and lead to a faster recovery.[3,5] Despite the much smaller number of pediatric outcome studies using BIS, there is evidence that these positive effects of BIS-guided anesthesia can also be found in children.[8–10]

Midlatency auditory evoked potentials, extracted from the electroencephalogram 10–100 ms after an auditory signal, represent the earliest cortical response to an acoustic stimulus. Amplitudes and latencies of the MLAEPs are influenced by anesthetics and surgical stimuli and are therefore believed to be useful in measuring the level of hypnosis during anesthesia.[11] The AEP Monitor/2 (Danmeter A/S, Odense, Denmark), a recently commercialized system for monitoring hypnosis levels of anesthesia, extracts MLAEPs from the electroencephalographic signal using an autoregressive model with an exogenous input adaptive method (ARX).[12] A monitoring variable indicating the patient's hypnotic state, the composite A-Line ARX Index (cAAI), is then calculated from the MLAEP and the electroencephalogram.[13] Specifically, the cAAI is preferably derived from the MLAEP, but in case of low MLAEP signal quality, it is entirely based on the spontaneous electroencephalogram. The majority of previous studies in adults investigated the A-Line Monitor (Danmeter A/S), which is a former version of the AEP Monitor/2 and is entirely based on MLAEP information. These studies suggest that the AAI might be helpful in distinguishing between the awake and unconscious state and in the detection of intraoperative awareness with recall.[14–16] In addition, the use of the A-Line monitor has been shown to decrease anesthetic delivery and may lead to faster postoperative recovery in adult patients.[3,5,17]

More recent studies in adults comparing the usefulness of BIS and cAAI demonstrated that both monitors were comparable indicators of depth of hypnosis.[13,18] Whereas BIS has been studied extensively in pediatric patients, there are only two published studies investigating the cAAI in children.[19,20] Weber *et al.*[20] demonstrated in an outcome study in children undergoing strabismus repair that cAAI-guided anesthesia resulted in lower propofol consumption and shorter recovery times. Furthermore, a study from Ironfield *et al.*[19] suggested that in children during sevoflurane-based anesthesia, the cAAI is a poor predictor of depth of anesthesia

* Research Fellow, † Senior Investigator, ‡ Staff Anesthesiologist, Department of Anesthesiology, § Professor of Research Intensive Care in Childhood, Department of Pediatric Surgery, # Head, Division Pediatric Anesthesiology, Erasmus Medical Center–Sophia Children's Hospital. ‖ Professor and Head, Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands.

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Address correspondence to Dr. Blussé van Oud-Alblas: Department of Anesthesiology, Erasmus Medical Center, Dr. Molewaterplein 60, 3015 GJ Rotterdam, The Netherlands. h.blussevanoudalblas@erasmusmc.nl. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

compared with the BIS. Whether this applies to other volatile anesthetics remains unknown. The main purpose of the current study was to compare the performance of the BIS and the cAAI with respect to their ability to distinguish between different hypnotic states, as evaluated by the responsiveness scores to the University of Michigan Sedation Scale (UMSS).[21] We hypothesized that prediction probabilities, which were calculated as the primary outcome parameter, were equal for both monitors.[22,23] Second, we investigated sensitivity and specificity characteristics for both the BIS and the cAAI in children.

Materials and Methods

Study Population

After approval from the institutional ethics committee (Erasmus Medical Center, Rotterdam, The Netherlands) and written informed parental consent, 47 children scheduled to undergo elective inguinal hernia repair were enrolled in the study. Children were considered eligible for enrollment if they had an American Society of Anesthesiologists physical status classification of I or II, were older than 2 yr, and were scheduled to undergo elective inguinal hernia repair. Children were excluded from the study if they had hypacusis or deafness, significant cardiovascular, respiratory, or neurologic disease, or if they were taking medication affecting the central nervous system.

Study Protocol

All patients received a standardized anesthetic regimen. No premedication was administered before induction. In accordance with hospital standards, EMLA cream (Eutectic Mixture of Local Anesthetics; AstraZeneca BV, Zoetermeer, The Netherlands) was applied locally to the skin at least 30 min before induction of general anesthesia to facilitate placement of an intravenous catheter. In the induction room, a pulse oximetry sensor was applied and intravenous access was secured. Anesthesia was induced with fentanyl (2 μg/kg) and a bolus of propofol (3–5 mg/kg). After loss of consciousness (LOC), defined as loss of eyelash reflex, manual ventilation *via* a facemask was established, and a laryngeal mask airway (*LMA Unique*™; The Laryngeal Mask Company Limited, Oxon, United Kingdom) was inserted. Patients ventilated spontaneously. Anesthesia was maintained with isoflurane with 30% oxygen in air. After induction, patients received a caudal block using 0.2% plain ropivacaine, and rectal acetaminophen and diclofenac were administered for both intraoperative and postoperative pain treatment. Thereafter, patients were transferred to the operating room. Anesthesia was maintained with isoflurane, adjusted to the age-corrected 1 minimal alveolar concentration.[24] In addition, 1 μg/kg fentanyl was administered as needed. In cases of hypoventilation, controlled ventilation was begun to maintain an end-tidal carbon dioxide tension of 35–45 mmHg. During maintenance of anesthesia, all patients were assessed for signs of inadequate anesthesia, defined as sudden increases in either systolic blood pressure by more than 15%, or heart rate by more than 15% in the absence of hypovolemia, or other autonomic signs such as sweating or flushing, and somatic responses such as movement or swallowing.

At the end of surgery, isoflurane was discontinued, and the laryngeal mask was removed. Patients awoke in the recovery room and were discharged when they were pain free and fully awake.

In addition to BIS and cAAI, electrocardiogram, heart rate, noninvasive blood pressure, end-tidal carbon dioxide, oxygen saturation *via* pulse oximetry, end-tidal concentration of isoflurane, and rectal temperature were monitored continuously during anesthesia. All data were collected in 5-s intervals (Rugloop; Demed, Temse, Belgium) and synchronized (Labgrab; Demed) on a laptop computer.

Measurements

The attending anesthesiologist, blinded to BIS and cAAI monitoring, assessed the patient's level of consciousness using the UMSS (table 1). The study period started just before induction of anesthesia and was continued until the return of consciousness (ROC). ROC was defined as eye opening, purposeful movement, or age-appropriate phonation. The following specific case milestones for UMSS assessment were defined *a priori*: awake, LMA insertion, at caudal block placement, and at surgical incision. During surgery, the UMSS was assessed every 5 min. During the emergence phase, the UMSS was assessed every 2 min. During emergence from inhalation anesthesia, the transition from unconscious to conscious is frequently accompanied by excitation phenomena, and additional external stimuli could significantly increase the risk of developing laryngospasm. Therefore, if patients were in the excitation phase, UMSS assessment was not performed. In addition, the following events were specially registered: (1) loss of consciousness (case milestone LOC); (2) return of consciousness (case milestone ROC); and (3) patient movement in response to

Table 1. The University of Michigan Sedation Scale for Children

Score	Responsiveness
0	Awake and alert
1	Minimally sedated; tired/sleepy, appropriate response to verbal conversation 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

LMA, caudal block placement, or surgical stimuli, indicating a low level of anesthesia.

Electroencephalographic and Auditory Evoked Potential Recording

The principal investigator supervised recording of all data and was blinded to BIS and cAAI values. Values were recorded with a BIS® monitor (A-2000, version 3.2; Aspect Medical Systems, Newton, MA) and an AEP Monitor/2 (Danmeter A/S; software version 1.6). Before induction of anesthesia, a pediatric four-sensor BIS® probe (BIS® Pediatric Sensor; Aspect Medical Systems International BV, De Meern, The Netherlands) was attached to the left side of the patient's forehead for BIS registration. For the AEP Monitor/2, a headphone for auditory stimuli and three disposable electrodes (A-Line AEP electrodes; Danmeter A/S) were positioned at the midforehead (+), right forehead (reference), and right mastoid (−). The sensors and headphone were removed after patients regained consciousness.

According to recent recommendations by the manufacturer of the AEP Monitor/2 and based on the results of a study by Vereecke *et al.*,[13] we decided to analyze our cAAI data on a scale of 0–60 (all values above 60 are set to 60). cAAI levels higher than 45 indicate wakefulness, whereas levels between 15 and 25 are considered to reflect surgical anesthesia. The BIS ranges from 0 to 99. According to the manufacturer, values above 90 indicate wakefulness, and the target range for a patient during general anesthesia is 40 to 60.

For both BIS and cAAI, electrode impedances were considered acceptable if they were below 10 kΩ. The principal investigator checked impedances at the beginning and end of the recording period. When unreliable registration of the electroencephalographic parameters was suspected, corrective actions were performed. The smoothening time of the BIS® monitor was set at 15 s. The MLAEPs were elicited with a binaural click stimulus of 2 ms in duration, with a repetition rate of 9 Hz. The MLAEP analysis window was 20–80 ms. Detailed information on cAAI signal processing has been shown by Vereecke *et al.*[13] Just before induction of anesthesia, BIS and cAAI measurements were started to obtain awake baseline values. Measurements continued until the patient was awake in the recovery room.

Statistical Analysis

All continuous data were tested for normality using the Kolmogorov-Smirnov method. For data sets that followed a normal distribution, parametric tests were used. For all other data sets, the appropriate nonparametric tests were applied. For multiple comparisons of interindividual data, Friedman repeated-measures analysis of variance on ranks with subsequent all pairwise multiple comparison procedures (Tukey test) was applied. Data were analyzed using SPSS version 12.0.1 (SPSS Inc., Chicago, IL) and MedCalc® version 9.3.1 (MedCalc Software, Mariakerke, Belgium). A *P* value smaller than 0.05 was considered statistically significant.

Ordinal values as provided by the UMSS may not demonstrate a perfect linear relation between the observed sedation level of the patient and BIS and cAAI. To account for this, the prediction probability (P_k), which compares the performance of indicators having different units of measurements or different data types (*i.e.*, continuous *vs.* ordinal or categorical data), provides a better alternative to investigate the overall relative performance of the different indicators in describing a sedation level. P_K was calculated using a custom spreadsheet macro, P_K MACRO (written in Microsoft Excel; Microsoft Corp., Redmond, CA), described and provided by Smith *et al.*[22,23] A P_K value of 1 means that the value of the predicting variable (*e.g.*, depth of hypnosis indicator such as BIS or cAAI) always correctly predicts the variable to be predicted (*e.g.*, the hypnotic state). Alternatively, a P_K value of 0.5 means that the predictive indicator is not better than chance alone; a P_K value below 0.5 indicates an inverse relation. To assess the relation between BIS and cAAI *versus* UMSS, P_K data were analyzed for the periods of (1) preanesthetic wakefulness to postoperative ROC (overall period), (2) the induction phase (the period from induction of anesthesia until placement of LMA), and (3) the emergence phase (from the termination of surgery to ROC). P_K values of paired BIS and cAAI data were calculated for every individual patient. Then a Mann–Whitney U test was used to evaluate whether the individual P_K for BIS differed from that of cAAI. A Friedman test was used to calculate whether individual P_K for BIS and cAAI were different for the aforementioned study periods.

It is known that there is a time delay in signal processing for both BIS and cAAI. To deal with this problem, comparison of BIS and cAAI values at LOC and ROC were performed. For LOC, awake values *versus* values at LOC and 30 s thereafter (LOC_{30}) were used. For ROC, we used values 5 min before ROC *versus* ROC and 30 s thereafter (ROC_{30}).

We further investigated the performance of BIS and cAAI for determining consciousness–unconsciousness. Values of cumulative occurrence, sensitivity and specificity, and positive and negative predictive values were calculated. For these calculations, we used independent data for consciousness and unconsciousness (*i.e.*, a single median BIS and cAAI value for each patient). *Positive* denotes a test result that suggests consciousness, whereas *negative* denotes a test result that suggests unconsciousness. We computed the cumulative occurrence of consciousness (*i.e.*, the number of BIS and cAAI data points below a previously chosen cutoff value) as the percentage of such occurrences with index values below the cutoff (threshold) value for BIS and cAAI. Similarly, we computed the cumulative occurrence of unconsciousness as the percentage of such occurrences with index values above the cutoff values for BIS and cAAI. Sensitivity was computed as the proportion of conscious patients with positive results (index value higher than various cutoff values for BIS and cAAI); specificity is the proportion of unconscious patients with negative test results (index value lower than the cutoff values for BIS and cAAI). Positive predictive values were computed as the proportion of patients with positive test results that were correctly diagnosed as conscious. Negative predictive values were defined as the proportion of patients with negative test results that were correctly diagnosed as unconscious. This approach has previously been described by Struys *et al.*[16]

Results

Forty-five patients were recruited for the study; 6 patients were excluded from the study because of violation of the anesthesia protocol (*e.g.*, use of muscle relaxants). Therefore, data of 39 patients were analyzed. The demographics (mean ± SD) are as follows: age, 6.2 yr (SD, 3.3 yr); weight, 20 kg (SD, 10.4 kg); and female:male ratio, 15:24.

In 21 patients, BIS and AEP sensors were applied before induction to obtain awake BIS and cAAI values; in 18 children, either the parents did not allow the sensors to be applied before induction of anesthesia or the children were afraid and agitated. Because of excessive artifact contamination, awake BIS values were obtained in 10 children, and awake cAAI values were obtained in 20 children.

Before induction of anesthesia (case milestone Awake), all children were fully awake and therefore assigned to level 0 of the UMSS. After induction of anesthesia, LMA insertion led to clinically visible reactions and heart rate alterations in four patients; therefore, these patients were assigned to UMSS level 3. Patients without clinically visible reactions or heart rate alterations were assigned to UMSS level 4.

The ability of BIS and cAAI monitoring to predict the UMSS score, as presented by the P_K values, is shown in table 2. The performance of BIS did not differ from that of the cAAI ($P = 0.244$). However, overall P_k values for both BIS and cAAI were higher than P_k values for the induction and emergence phases separately (BIS $P < 0.001$, cAAI $P = 0.007$). In addition, for both BIS and cAAI, P_k values for the induction phase were higher than for the emergence phase ($P < 0.001$).

With increasing sedation (increase in UMSS score from level 0 to level 4), the median BIS decreased significantly from 79 to 40 ($P < 0.001$), and the median cAAI decreased from 60 to 19 ($P < 0.001$; fig. 1). During induction (case milestone Awake to LOC), we observed a significant decrease in median cAAI values (60 to 43; $P <$ 0.001), whereas median BIS values remained unaltered (94 to 90; not significant). Median BIS and cAAI values for case milestone LOC were also computed with a time delay of 30 s (case milestone LOC_{30}). Significant changes in median BIS (94 to 36; $P = 0.008$) and cAAI (60 to 35; $P < 0.001$) were found when comparing awake values and values at LOC_{30}. During the emergence phase, median BIS and cAAI increased from 51 to 74 ($P < 0.001$) and from 46 to 58 ($P = 0.03$), respectively, when comparing the values taken at 5 min before ROC with values 30 s after ROC.

The cumulative occurrence curves are shown in figure 2 for BIS and in figure 3 for cAAI. Sensitivity and the corresponding specificity, and positive and negative predictive values for both the BIS and the cAAI at different cutoff values are displayed in tables 3 and 4.

Table 2. Prediction Probabilities for the University of Michigan Sedation Scale

	UMSS		
	cAAI	BIS	*P* Value
Overall	0.9 ± 0.08	0.91 ± 0.1	NS
Induction phase	0.84 ± 0.08	0.84 ± 0.04	NS
Emergence phase	0.74 ± 0.02	0.75 ± 0.02	NS

Data are presented as mean ± SE.

P values: Bispectral Index (BIS) *vs.* composite A-Line ARX Index (cAAI), Mann–Whitney U test.

NS = not significant; UMSS = University of Michigan Sedation Scale.

Discussion

This study was conducted to compare the performance accuracy of BIS and cAAI, which are both inde-

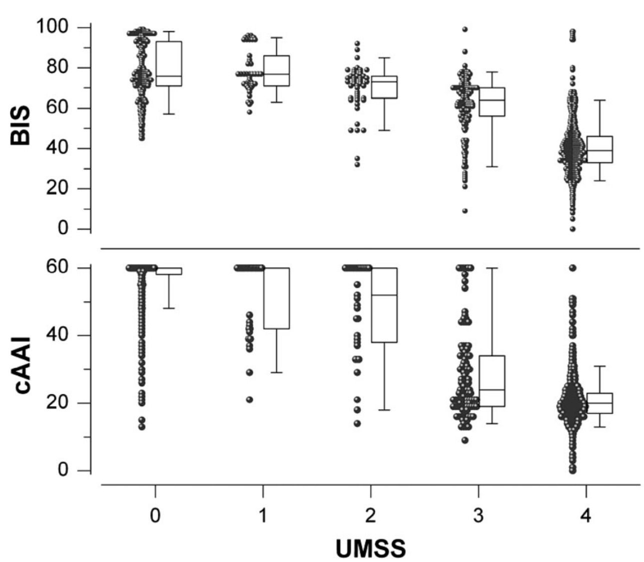

Fig. 1. Box plot graphics (median and 25th and 75th percentiles [*box top* and *bottom*] and 5th and 95th percentiles [*whiskers*]) and individual patient data for Bispectral Index (BIS), and composite A-Line ARX Index (cAAI) at different levels of the University of Michigan Sedation Scale (UMSS).

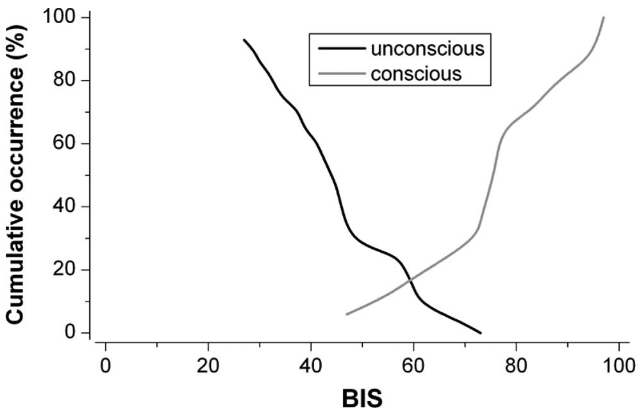

Fig. 2. Cumulative occurrences for consciousness and unconsciousness as a function of the University of Michigan Sedation Scale for the Bispectral Index (BIS).

pendent variables used to measure hypnosis depth, in pediatric patients. Both monitors performed equally in predicting sedation levels, as evaluated by the UMSS. Also, P_K values comparing overall relative performance were equal between the two monitors. However, it is noteworthy to mention that P_k values are only one single performance parameter for comparing depth of anesthesia monitors and that, therefore, caution must be taken not to misinterpret our results as being indicative for equal performance of the cAAI and the BIS.

Not surprisingly, we observed higher P_K values during the induction period than during emergence for both indices. This is in accord with previously published work by Klockars *et al.*[25] Overall P_k values for both monitors, *i.e.*, from preanesthetic wakefulness until postoperative ROC, were higher than P_k values during either the induction or emergence phases (table 2). This finding may at least partly be explained by the fact that intraoperatively all UMSS scores were 4, because patients who did not respond to surgical stimuli were assigned to this level.

Our results are in contrast to a previous study by Ironfield *et al.*[19] comparing BIS and cAAI in children

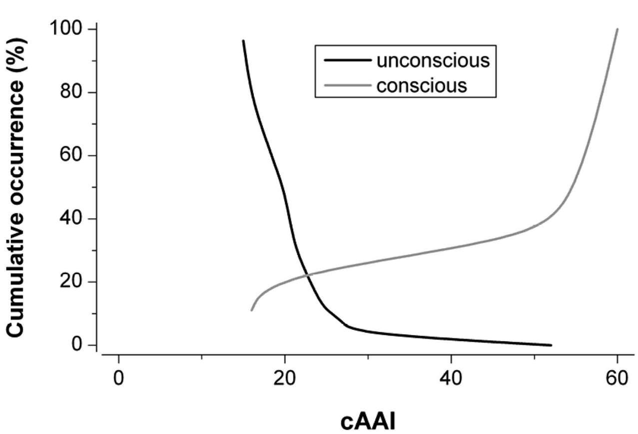

Fig. 3. Cumulative occurrences for consciousness and unconsciousness as a function of the University of Michigan Sedation Scale for the composite A-Line ARX Index (cAAI).

Table 3. Specific Sensitivity or Specificity of Different Cutoff BIS Levels to Describe Consciousness for Different Phases

Variable	Cutoff Value	Specificity	Sensitivity	Negative Predictive Value	Positive Predictive Value
BIS overall	90	100	37	99	100
	80	100	60	99	100
	78	100	62	99	100
	70	98	68	100	43
	60	89	69	99	10
	50	93	73	99	7
	40	55	94	100	3
	30	24	96	100	2
	20	3	98	99	2
	17	2	100	100	2
BIS induction	90	100	43	98	100
	80	100	63	99	100
	70	100	64	99	99
	60	92	64	99	24
	50	84	68	99	14
	40	59	93	100	8
	30	31	96	100	5
	20	8	98	99	4
	17	7	100	100	4
BIS emergence	90	100	12	99	94
	86	100	12	99	30
	80	96	22	99	10
	70	61	85	100	4
	60	26	93	100	2
	50	11	99	100	2
	48	9	100	100	2
	40	5	100	100	2
	30	2	100	100	2
	20	0	100	100	2

Data are presented as percentages.

BIS = Bispectral Index; BIS emergence = BIS during emergence phase; BIS induction = BIS during induction phase; BIS overall = BIS during overall study period.

aged 0–12 yr undergoing cardiac catheterization. In that study, during steady state concentrations of sevoflurane-based anesthesia, cAAI was a poor predictor of depth of anesthesia compared with BIS. In the 2- to 12-yr-old group, the P_K for BIS (0.89) was significantly higher than the P_K for cAAI (0.53). In contrast, in the 0- to 1-yr-old group, there was no evidence of a significant difference between P_K for BIS (0.74) and the P_K for cAAI (0.53). An explanation for the discrepancies between our findings and the results of Ironfield *et al.* may be differences in anesthesia technique. Our study was performed with non–steady state concentrations of isoflurane, because of the pharmacokinetic profile of isoflurane,[26] whereas Ironfield *et al.* used steady state concentrations of sevoflurane. In addition, Ironfield *et al.*[19] correlated electroencephalographic parameters with end-tidal sevoflurane concentrations, which will have a variable relation with arterial and effect site concentration depending on the amount of ventilation–perfusion mismatch, and a variable clinical effect depending on the pharmacodynamic susceptibility of the patient to the achieved effect site concentration. In our study, we correlated electroencephalographic parameters with clinical signs, thereby circum-

Table 4. Specific Sensitivity or Specificity of Different Cutoff cAAI Levels to Describe Consciousness for Different Phases

Variable	Cutoff Value	Specificity	Sensitivity	Negative Predictive Value	Positive Predictive Value
cAAI overall	60	100	56	98	95
	52	100	73	99	85
	50	99	76	99	85
	40	99	80	99	76
	30	94	84	99	36
	20	62	93	100	9
	12	3	100	100	4
	10	1	100	100	4
cAAI induction	60	100	54	96	94
	52	100	73	98	93
	50	99	75	98	93
	40	99	79	98	85
	30	92	83	98	48
	20	58	93	99	17
	12	4	400	100	9
	10	2	100	100	9
cAAI emergence	60	100	0	98	—
	50	75	89	100	7
	40	71	96	100	6
	30	62	97	100	5
	20	39	97	100	3
	14	9	100	100	2
	10	0	100	100	2

Data are presented as percentages.

cAAI = composite A-Line ARX Index; cAAI emergence = cAAI during emergence phase; cAAI induction = cAAI during induction phase; cAAI overall = cAAI during overall study period.

venting the problems caused by interindividual pharmacokinetic and pharmacodynamic differences.

The findings in our study show considerable overlap in both BIS and cAAI values for each level of the UMSS. The large interindividual variation we observed in cAAI values was also reported by Weber *et al.*[27] for the former A-Line monitor during sevoflurane anesthesia in children.

The ideal monitor of anesthetic depth should have 100% sensitivity (no false-negative results) and 100% specificity (no false-positive results) in distinguishing different levels of hypnotic depth. Not surprisingly, neither of the monitors in our study was found to be ideal, because no variable provided perfect sensitivity–specificity. To reach a 100% certainty of unconsciousness, a BIS value of less than 17 and a cAAI value of less than 12 were required. To undoubtedly ascertain consciousness, BIS values greater than 78 and cAAI values above 52 were required. Positive predictive values, or precision rates, were poor during emergence but comparable for both monitors (tables 3 and 4). One possible explanation for this observation might be that ROC after general anesthesia is much more difficult to determine than LOC during induction. Furthermore during emergence, only for cAAI was an on–off phenomenon observed in the majority of our patients. That means intraoperative cAAI values remained constant during emergence until the moment of ROC and then within seconds increased to 60. In addition, there is a theoretical chance that patients regained consciousness before being reassessed by the UMSS within a 2-min period.

The cumulative occurrence data in figures 2 and 3 show a remarkable overlap between "conscious" and "not conscious" data. This means BIS and cAAI data within the commonly accepted target ranges for general anesthesia do not always indicate an unconscious patient. This does also apply for the conscious patient, who may present with index values usually associated with deep levels of anesthesia. Our findings correspond with findings previously reported in adults, indicating some overlap of both monitors during propofol anesthesia.[16]

In our study, cAAI distinguished the transition from consciousness to unconsciousness faster than BIS. This may be explained by the faster signal processing of the AEP Monitor/2 compared with BIS. In daily practice, this time delay in processing is an important factor, because clinicians respond to the real-time indices observed on the monitor.

In this study, we observed frequent fluctuation between AEP-derived and electroencephalogram-derived cAAI values. Unfortunately, the AEP Monitor/2 only exports cAAI values without distinguishing between AEP or electroencephalogram derivation. Therefore, it is noteworthy to emphasize that cAAI data do not necessarily mean that the index is solely MLAEP derived.

We used the pediatric four-sensor BIS® probe, which, according to the manufacturer, removes electrical artifact that is interpreted as EMG by the BIS® monitor. The performance of the four-sensor probe may thus be somewhat different from the three-sensor probe, particularly in situations with significant EMG contamination such as emergence. To our knowledge, all previously published studies in children investigated the performance of BIS using the three-sensor probe; it may therefore be inappropriate to compare our results.

A shortcoming of this and the majority of other studies dealing with the evaluation of depth of anesthesia monitoring systems is the lack of an ideal tool for assessing the patient's hypnotic state. We selected the UMSS because it correlates well with clinical reflections of the hypnotic component of anesthesia and has been validated in children.[21] However, subjective clinical scoring systems, such as the UMSS, are only indicative for a specific moment and by their nature introduce potential error *via* individual implementation and interpretation. Furthermore, depending on the intensity of potentially distressing painful physical stimulation, they could be measuring spinal reflexes as well as cortical activity. Therefore, we cannot expect total agreement between the UMSS and BIS and cAAI scores. In addition, unconsciousness is likely to be associated with stage 2 of the UMSS, and assignment to this stage requires tactile stimulation. Because the transition from unconsciousness to consciousness after inhalational anesthesia is frequently accompanied by excitation phenomena, additional external stimuli could significantly increase the risk of developing laryngospasm.

Unfortunately, awake data were not obtainable in all children. Some children were agitated when sensors were applied, and in other children, parents did not allow the sensors to be applied before induction of anesthesia. The number of children who accepted sensor placement before anesthesia induction would have been higher had we chosen to premedicate with midazolam. Based on the fact that benzodiazepines have a known impact on the electroencephalogram,[28] we decided not to premedicate our patients.

In summary, we found that BIS and cAAI to perform equally in distinguishing different hypnotic conditions in the particular setting of isoflurane anesthesia in children. Because of faster signal processing, the cAAI seemed to be superior to the BIS in the prediction of LOC. However, both monitors showed notable interindividual variability and overlap between the different hypnotic states. It is important to note that these results should not be extrapolated to other anesthesia techniques in children.

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