General Anesthesia

The A-line ARX index may be a more sensitive detector of arousal than the bispectral index during propofol-fentanyl-nitrous oxide anesthesia: a preliminary investigation

[L'index «A-line ARX» peut être un détecteur plus sensible du réveil que l'index bispectral pendant l'anesthésie avec propofol-fentanyl-protoxyde d'azote : une recherche préliminaire]

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Purpose: To compare changes in the A-line ARX index (AAI) by the Alaris AEP monitor™ with those of the bispectral index (BIS) during propofol-fentanyl-nitrous oxide anesthesia.

Methods: Eighty female patients undergoing partial mastectomy were randomly allocated to AAI or BIS (40 per group). Anesthesia was induced with propofol 2 mg·kg⁻¹ and fentanyl 3 µg·kg⁻¹ during the inhalation of oxygen. A laryngeal mask airway (LMA) #3 was inserted. Anesthesia was maintained with propofol 4 mg·kg⁻¹·hr⁻¹, fentanyl 1 µg·kg⁻¹ given at the start of surgery, and nitrous oxide 4 L·min⁻¹ in oxygen 2 L·min⁻¹. Blood pressure, heart rate, and AAI or BIS were monitored, including recovery time of the index after disturbance by electrocautery.

Results: The AAI but not the BIS increased significantly with LMA insertion and skin incision, while blood pressure and heart rate did not change. The BIS decreased from 87 ± 7 to 30–60 while the AAI decreased from 75 ± 8 to 10–25 during anesthesia. The increase of the AAI was larger than that of the BIS at recovery from anesthesia. The variation of the index was smaller in the AAI than in the BIS. Recovery time of the index after electrocautery was significantly longer in the BIS group (21 ± 9 sec) than that in the AAI group (5 ± 3 sec).

Conclusions: During propofol-fentanyl-nitrous oxide anesthesia, the AAI responded to LMA insertion or surgical incision, but not the BIS, and the AAI had smaller variations. The AAI recovered faster from the disturbance by electrocautery than the BIS. Thus, the AAI may be a more sensitive and useful detector of arousal than the BIS.

Objectif : Comparer les changements de l'index «A-line ARX» (AAI) par le Alaris AEP monitor™ avec ceux de l'index bispectral (BIS) pendant l'anesthésie avec propofol-fentanyl-protoxyde d'azote.

Méthode : Quarante-femmes devant subir une mastectomie partielle ont été réparties également en deux groupes (AAI ou BIS). L'anesthésie a été induite avec 2 mg·kg⁻¹ de propofol et 3 µg·kg⁻¹ de fentanyl pendant l'inhalation d'oxygène. Un masque laryngé (ML) n° 3 a été inséré. L'anesthésie a été maintenue avec 4 mg·kg⁻¹·h⁻¹ de propofol, 1 µg·kg⁻¹ de fentanyl au début de l'opération et 4 L·min⁻¹ de protoxyde d'azote dans 2 L·min⁻¹ d'oxygène. La tension artérielle, la fréquence cardiaque, et l'AAI ou le BIS ont été enregistrés, y compris le temps de récupération de l'index après la perturbation causée par l'électrocautérisation.

Résultats : L'AAI, mais non le BIS, s'est élevé de façon significative avec l'insertion du ML et l'incision cutanée, tandis que la tension artérielle et la fréquence cardiaque n'ont pas changé. Le BIS est passé de 87 ± 7 à 30–60 pendant que l'AAI a baissé de 75 ± 8 à 10–25 pendant l'anesthésie. La hausse de l'AAI a été plus importante que celle du BIS lors du réveil. La variation de l'index a été plus petite dans l'AAI que dans le BIS. Le temps de récupération de l'index après l'électrocautérisation a été significativement plus long avec le BIS (21 ± 9 sec) qu'avec l'AAI (5 ± 3 sec).

Conclusion : Pendant l'anesthésie avec propofol-fentanyl-protoxyde d'azote, l'AAI a été sensible à l'insertion du ML ou à l'incision chirurgicale, mais non le BIS, et l'AAI n'a eu que de faibles variations. L'AAI a été récupéré plus rapidement que le BIS après la perturbation causée par l'électrocautérisation. L'AAI peut donc être un détecteur plus efficace et sensible du réveil que le BIS.

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No grant and support were used for this study.

Accepted for publication October 28, 2003.

Revision accepted February 18, 2004.

RECENTLY, changes in the electroencephalogram (EEG) during anesthesia have been the subject of several studies. Indexes that indicate the level of sedation as a number, such as the bispectral index (BIS), spectral edge frequency, median frequency, A-Line ARX index (AAI), etc., have been developed. The BIS is derived from the bifrontal EEG recordings¹ and is expressed as a number from 0 to 100. Glass *et al.*² reported a good correlation between BIS and sedation levels during propofol anesthesia. The middle latency auditory evoked potentials (MLAEP), which are small changes of the EEG caused by auditory stimuli, can detect the level of sedation in a patient during anesthesia.^{3,4} Autoregressive modelling with exogenous input of MLAEP has been proposed to monitor sedation using an AAI,⁵ also expressed as a number from 0 to 100. Even though both BIS and AAI are designed to produce a number in the range between 0 and 100, they are not identical. The BIS reflects spontaneous EEG whereas AAI evaluates the electrical response of the brain to auditory stimuli. The purpose of this study was to observe changes of the AAI and of the BIS during propofol-fentanyl-nitrous oxide anesthesia to see the differences between the two indexes as a preliminary investigation.

Methods

After obtaining approval of the Review Board of the hospital and informed consent from the patients, 80 female patients aged 30 to 60 yr scheduled for partial mastectomy were divided into two groups of 40 patients: BIS and AAI groups. Patients were randomized by opening an envelope in which BIS or AAI was mentioned. Patients with neurologic disorders, deafness, liver disease, mental impairment, or taking medications affecting brain function such as hypnotics, antidepressants, etc., were excluded.

Midazolam 5 mg and atropine 0.5 mg were administered intramuscularly 30 min before anesthesia. Anesthesia was induced with propofol 2 mg·kg⁻¹ and fentanyl 3 µg·kg⁻¹ while patients breathed oxygen. After loss of response to verbal command and eyelash reflex, a laryngeal mask airway (LMA) #3 was inserted. Anesthesia was maintained with propofol 4 mg·kg⁻¹·hr⁻¹, fentanyl 1 µg·kg⁻¹ given at the start of surgery (total 4 µg·kg⁻¹), and nitrous oxide 4 L·min⁻¹ in oxygen 2 L·min⁻¹. Ventilation was adjusted to keep the end-tidal carbon dioxide tension between 30 and 35 mmHg during surgery. No muscle relaxants were used. The propofol infusion was stopped when skin suture started. Inhalation of nitrous oxide was stopped at the end of skin suture. After stopping nitrous oxide,

awakening was evaluated every minute. When patients responded to verbal command "open your eyes" and "grip my hand" and breathed spontaneously, the LMA was removed. All patients were anesthetized by a single senior anesthesiologist and operated by the same surgeons.

Non-invasive blood pressure, heart rate, AAI or BIS, and the recovery time of the index after each signal disturbance by electrocautery (measured from the end of electrocautery to the recovery of good signals shown by the disappearance of alarm at each randomly selected five cauteries, mean recovery time calculated) were measured to observe the differences between the two devices. The AAI was measured by the Alaris AEP monitorTM (A-AEPTM, version 1.5, Alaris Medical Systems, Hampshire, UK) and the BIS was measured by the A-2000 BISTM monitor (BISTM, version 3.1, Aspect Medical Systems, Newtown, MA, USA). The BISTM uses special electrodes, is calculated on the basis of two second epochs and its mean value is updated every second. The A-AEPTM uses a headphone and three separate electrodes, is elicited with a binaural click stimulus of 65-dB intensity, 2 msec duration, and repetition rate of 9 Hz (one click each 110 msec). The AEP is extracted over 15 sweeps, producing an update delay of six seconds. The AAI is calculated every two seconds.

Data are expressed as mean ± standard deviation. Statistical analysis was performed with Student's *t* test for demographic data and the recovery time of the index after electrocautery, and repeated measures analysis of variance followed by the Student-Newman-Keuls method as a post-hoc test for blood pressure, heart rate, and both indexes. A *P* < 0.05 was considered statistically significant. Sample size was analyzed by post hoc power analysis (G PowerTM, v 2.1.2, Trieter University, Trieter, Germany).

Results

Demographic data were not different between the two groups (Table). No patient moved during induction and maintenance of anesthesia. Blood pressure and heart rate decreased significantly with anesthesia induction, did not change significantly after LMA insertion and surgical incision, and returned to baseline at the end of surgery in both groups. Blood pressure and heart rate were not different between groups (Figure 1).

The BIS decreased to the 30 to 60 range while the AAI decreased to the 10 to 25 range during surgery (*P* < 0.05 between the groups, Figure 2). The AAI, but not the BIS, increased significantly with LMA insertion and skin incision. When patients responded to verbal command at recovery from anesthesia, both

TABLE Demographic data

	AAI group	BIS group
Number	40	40
Age (yr)	45 ± 9	46 ± 10
Body weight (kg)	56 ± 9	53 ± 8
Height (cm)	152 ± 9	156 ± 7
Duration of surgery (min)	98 ± 18	102 ± 20

AAI = A-line ARX index; BIS = bispectral index. Mean ± SD.

FIGURE 1 Systolic blood pressure (upper) and heart rate (lower) are shown as mean ± standard deviation. LMA = laryngeal mask airway. **P* < 0.05 *vs* the value before anesthesia.

BIS and AAI were still lower than control values (*P* = 0.04 and 0.014 in BIS and AAI groups, respectively), while the increase of the index during recovery from anesthesia was larger with the AAI than with the BIS. Both returned to control values at extubation. The BIS showed larger variations than the AAI. The BIS at the end of propofol infusion was significantly larger

FIGURE 2 The A-line ARX index (AAI) and bispectral index (BIS) values are shown as mean ± standard deviation. LMA = laryngeal mask airway. **P* < 0.05 *vs* the value before anesthesia, a: *P* = 0.041 *vs* the value before LMA insertion, b: *P* = 0.043 *vs* the value at three minutes after LMA insertion, c: *P* = 0.042 *vs* the value before LMA insertion, d: *P* = 0.044 *vs* the value at end of propofol, e: *P* < 0.01 *vs* the value at end of propofol. †*P* < 0.05 *vs* the AAI group.

than that before LMA insertion but the AAI was not.

The recovery time of the index after signal disturbance by electrocautery was 21 ± 9 sec in the BIS group, which was significantly longer than 5 ± 3 sec in the AAI group (*P* < 0.01).

Discussion

During propofol-fentanyl-nitrous oxide anesthesia, the BIS ranged between 30 and 60 and the AAI between 10 and 25. The AAI increased significantly with LMA insertion and skin incision but the BIS did not. The BIS showed larger variations compared to the AAI. Recovery of the index after signal disturbance by electrocautery was significantly faster with the AAI than with the BIS.

We tested each monitor on different patients. To compare these two monitors more precisely, both should have been tested simultaneously in the same patients. However, the effects of auditory stimuli on the BIS remain unclear. Therefore, only one monitor was used in each patient.

During propofol anesthesia, the BIS at which 50 and 95% of the population lose consciousness is reported to be 63 (62–65) and 51 (48–55), respectively.⁶ In the

study by Litvan *et al.*,⁷ the AAI is 30.7 ± 9.5 when patients respond only after mild prodding or shaking (modified observer's assessment of alertness/sedation scale (MOAAS 2), and 21.1 ± 9.5 when patients respond only after painful trapezius squeeze (MOAAS 1) during propofol induction. In the present study, BIS and AAI in awake patients were 87 ± 7 and 75 ± 8 and decreased to 38 ± 9 and 15 ± 3 , respectively, before LMA insertion when patients ceased to respond to verbal command and lost their eyelash reflex. These variations of the indexes are almost identical to those reported in other studies.^{6,7} We did not measure the depth of sedation precisely during anesthesia, but the absence of movements during surgery without any muscle relaxants suggests patients were adequately anesthetized. The preoperative values were slightly lower than the usual awake values, which might reflect the effects of premedication.

During recovery from an induction dose of propofol, concentration related effects on the AEP were found.⁸ Doi *et al.*⁹ reported no difference between the awake index and the index when patients open their eyes on command. However, in our study, when patients responded to verbal command during the recovery phase, both BIS (67 ± 8) and AAI (46 ± 11) were still significantly lower than before anesthesia (BIS; 87 ± 7 , $P = 0.04$, AAI; 75 ± 8 , $P = 0.014$). The difference between our results and the report by Doi *et al.*⁹ might be due to the difference in time when the response was examined and the different monitors used.

BIS is reported to respond to laryngoscopy and intubation,¹⁰ to movement with LMA insertion,¹¹ to intubation,¹² or to skin incision.¹³ However, in this study, the AAI increased significantly in response to LMA insertion and skin incision, while the BIS did not. Blood pressure and heart rate increased after these stimuli in both groups but not significantly. Even when blood pressure does not change significantly or no movements occur, intubation or skin incision can still be stressful to the patient, send an impulse to the spinal cord and then to the brain to induce changes in the EEG. Therefore, the AAI might be more sensitive to fine changes than the BIS, while further studies are necessary to confirm this.

The AAI was reported to be able to follow rapid changes from wakefulness to sleep and detect short-term periods of consciousness.¹⁴ The more rapid response of the AAI to LMA insertion or skin incision, and faster recovery from signal disturbance by electrocautery compared to BIS might be simply due to the faster response time of the A-AEP. Extraction of the MLAEP is usually done by moving time averaging over many sweeps (usually 250 to 1,000), which can

produce a delay of more than one minute.¹⁵ However, this problem was addressed by applying autoregressive modelling with exogenous input that enables extraction of the AEP within 15 sweeps by the A-AEP.¹⁶ The BIS value represents the mean of at least 15 but sometimes 60 sec of data, and a delay of one minute can be expected. However, in Nieuwenhuijs's study,¹⁷ the delay was two minutes or longer with the BIS.

Surgical stimulation is reported to increase the amplitude of MLAEP, which indicates that the amplitude does not simply reflect graded concentrations of the anesthetic agent but, more importantly, depicts the balance between surgical stimulation and anesthetic depression.¹⁴ Therefore, the AAI would indicate both sedation and response to stimuli, i.e., level of anesthesia. The evoked response is an indication of the responsiveness of the central nervous system whereas the EEG reflects the resting level. This difference might be the reason for the different response to stimuli between the AAI and the BIS. However, the BIS at the end of propofol infusion was significantly larger than that before LMA insertion but the AAI was not and the BIS had larger variations than the AAI. These might suggest again that the AAI was more sensitive to the changes of stimulation with smaller variations between subjects. In the study by Kreuer *et al.*,¹⁸ the AAI had larger variations than the BIS, which is inconsistent with our results. However, their study controlled the BIS to achieve target values, therefore there is no doubt that the BIS had to be in a more narrow range than the AAI.

Further studies are necessary to elucidate whether the different response between BIS and AAI is due only to different response times or not.

In the present study, we administered midazolam 5 mg with atropine 0.5 mg as a premedication in all patients. In the study using volunteers, *im* atropine dose dependently increased delta power, decreased alpha power, and tended to increase theta power and reduce beta and theta frequency in EEG.¹⁹ No data are available for the effects of atropine on the BIS and AAI. In the study by Liu *et al.*,²⁰ the BIS exhibited a good correlation with sedation levels during midazolam induced sedation, while Barr *et al.*²¹ reported a large variation of BIS during clinically adequate anesthesia with midazolam and fentanyl. Our anesthesia protocol included fentanyl and nitrous oxide. The MLAEP has been reported to be an insensitive marker of opioid and nitrous oxide effect.^{22,23} BIS was reported to decrease from 47.7 to 39.8 by increasing nitrous oxide concentration from 0 to 60% during sevoflurane anesthesia,²⁴ while it did not change with the addition of nitrous oxide to isoflurane anesthe-

sia.²⁵ The addition or withdrawal of nitrous oxide during constant sevoflurane anesthesia was found to cause only minor changes in the AAI.²³ With fentanyl or nitrous oxide, MLAEP have been reported to remain nearly unchanged.²⁶ In the present study, we could not differentiate the effects of each anesthetic on the BIS and the AAI.

In conclusion, during propofol-fentanyl-nitrous oxide anesthesia, the AAI responded to the stimuli of LMA insertion and skin incision but the BIS did not. The AAI recovered faster from the disturbance by electric cautery than the BIS. The variation of the index was smaller in the AAI than in the BIS. Thus, the AAI might be a more useful monitor than the BIS during propofol-fentanyl-nitrous oxide anesthesia.

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