Neuromuscular block with vecuronium reduces the rapidly extracted auditory evoked potentials index during steady state anesthesia

[Un bloc neuromusculaire avec du vécuronium réduit l'index des potentiels évoqués auditifs d'extraction rapide pendant l'anesthésie en état d'équilibre]

Sheng-Jin Ge MD, Xin-Liang Zhuang MD, Ri-Hui He MSc, Ying-Tian Wang MSc, Xi Zhang MSc, Shi-Wei Huang MSc

Purpose: During clinical monitoring, vecuronium appeared to reduce the rapidly extracted auditory evoked potentials index (A-line ARX index or AAI) to some extent. A prospective and randomized study was designed to analyze this phenomenon.

Methods: Forty adult patients undergoing elective surgery were studied. After tracheal intubation, anesthesia was maintained with an end-tidal isoflurane concentration (F_{ET}ISO) of 1.0% for 20 min, then a 10-mL dose of either vecuronium 0.05 mg·kg^{-1}, 0.1 mg·kg^{-1}, 0.2 mg·kg^{-1} or saline was administered in a randomized, double-blind design. The AAI and bispectral index (BI^{hx}) were monitored throughout the study and analyzed off-line.

Results: BI^{hx} was unaltered after the administration of saline or vecuronium. The mean of the averaged (per patient) AAI values recorded from two minutes to ten minutes after the administration of saline or vecuronium 0.05 mg·kg^{-1} did not differ significantly from the corresponding mean recorded from 15 min to 20 min after F_{ET}ISO maintained 1.0% (P = 0.678, 0.169), however after the administration of vecuronium 0.1 mg·kg^{-1} or 0.2 mg·kg^{-1}, AAI was reduced from 18.3, 18.0 to 14.8, 13.4 (P = 0.016, 0.017).

Conclusions: Neuromuscular block with vecuronium reduces AAI in patients during steady state anesthesia without surgical stimuli, while BI^{hx} is unaltered. The cut-off values of AAI for events should be determined according to the level of neuromuscular blockade when monitoring the depth of anesthesia/sedation.

Objectif : *Pendant le monitorage clinique, le vécuronium a semblé réduire, jusqu'à un certain point, l'index des potentiels évoqués d'extraction rapide (A-line ARX index ou AAI). Nous avons voulu analyser ce phénomène par une étude prospective et randomisée.*

Méthode : *Quarante patients adultes devant subir une opération réglée ont participé à l'étude. Après l'intubation endotrachéale, l'anesthésie a été maintenue avec une concentration d'isoflurane téléexpiratoire (F_{ET}ISO) de 1,0 % pendant 20 min, puis une dose de10 mL de vécuronium, à 0,05 mg·kg^{-1}, 0,1 mg·kg^{-1} ou 0,2 mg·kg^{-1}, ou de soluté physiologique, a été administrée de façon randomisée et en double aveugle. L'AAI et l'index bispectral (BI^{hx}) ont été enregistrés tout au long de l'étude et analysé en différé.*

Résultats : *Le Bihx n'était pas modifié après l'administration de solution saline ou de vécuronium. La moyenne des valeurs centrales d'AAI (par patient), notée de deux à dix minutes après l'administration de solution salée ou de 0,05 mg·kg^{-1} de vécuronium, ne différait pas de façon significative de la moyenne correspondante notée de 15 à 20 min après le maintien de la F_{ET}ISO à 1,0 % (P = 0,678 ; 0,169), même si après l'administration de 0,1 mg·kg^{-1} ou de 0,2 mg·kg^{-1}, l'AAI a été réduit de 18,3, 18,0 à 14,8, 13,4 (P = 0,016, 0,017).*

Conclusion : *Le bloc neuromusculaire avec du vécuronium réduit l'AAI pendant l'anesthésie en état d'équilibre sans stimuli chirurgical, mais le Bihx n'est pas modifié. Les valeurs seuil de l'AAI des événements chirurgicaux doivent être déterminées selon le niveau de bloc neuromusculaire pendant le monitorage de la profondeur de l'anesthésie/sédation.*

From the Department of Anesthesiology, Shanghai Jiaotong University Affiliated Shanghai First People's Hospital, Shanghai, China.
Address correspondence to: Sheng-Jin Ge, Department of Anesthesiology, Shanghai First People's Hospital, Shanghai 200080, China.
E-mail: steeroncn@yahoo.com.cn
This work was attributed to the Department of Anesthesiology, Shanghai First People's Hospital.
Financial support was received from the Department of Anesthesiology, Shanghai First People's Hospital.
There are no commercial or non-commercial affiliations that are or may be perceived to be a conflict of interest with this work.
Accepted for publication May 12, 2003.
Revision accepted September 10, 2003.

RECENTLY, the autoregressive model with exogenous input (ARX model)[1,2] has been applied to achieve a faster extraction of the mid-latency auditory evoked potentials (MLAEP) waveform. This method enables extraction within 15 to 25 sweeps in less than six seconds.[2–4] The auditory evoked potentials (AEP) index calculated in this way is defined as the A-line ARX index (AAI). It has been tested as a prospective method to monitor the depth of anesthesia/sedation.[1–6] In a previous study from our group, AAI correlated well with the sedation induced by propofol or midazolam during epidural anesthesia, and even better than the bispectral index (BI^{hx}) (Huaxiang Technology Co. Ltd, Heilongjiang, China).[7]

Richmond *et al.*[8] reported that neuromuscular block with vecuronium 0.05 $mg \cdot kg^{-1}$ did not affect depth of anesthesia as measured by the AEP waveform (Pa and Nb), the primary components of MLAEP. Greif *et al.*[9] showed, in a recent study, that BIS® (Aspect Medical Systems, Newton, MA, USA) was unaltered by mivacurium administration during propofol anesthesia. However, during clinical monitoring, we observed that vecuronium administration appeared to reduce AAI. The present study aimed to verify this phenomenon.

Methods

After institutional Ethics Committee approval, informed consent was obtained from 40 patients, ASA physical status I and II, scheduled for elective surgery under general anesthesia. The exclusion criteria were psychiatric disorders, hearing difficulties or a history of diseases affecting neuromuscular function.

Patients were fasted for at least eight hours and were pre-medicated with atropine 0.5 mg and phenobarbital 0.1 g intramuscularly. In the operating room, electrocardiogram, heart rate, invasive arterial pressure, respiration, pulse oximetry and temperature with continuous recording were commenced via a Cardiocap/5 monitor (Datex-Ohmeda, Helsinki, Finland). In our preliminary observations, blood pressure cuff inflation seemed to increase AAI in one patient, so invasive arterial pressure was employed.

During the study, 500 mL Ringer's solution and 500 mL gelatin solution - Gelofusine® (Shengyang B. Braun, Heilongjiang, China) were infused in order to keep an appropriate circulating blood volume.

AAI was recorded using the A-line monitor (software version 1.5; Danmeter A/S, Odense, Denmark). The AEP were elicited with a bilateral click stimulus of 65dB intensity, 2 msec duration, and repetition rate of 9 Hz (one click each 110 msec) from three silver-silver chloride electrodes (Neuroline, Medicotest A/S, Oelstykke, Denmark) positioned at mid-forehead (+), left forehead (reference) and left mastoid (-). The AEP analysis window had an 80 msec duration and the pre-processing of the electroencephalogram (EEG) sweeps consisted of artifact rejection and 25 to 65 Hz finite impulse response 170th order band-pass filtering. The monitor was based on a short moving time average together with an ARX model. This technology facilitated fast extraction of the AEP. Figure 1 shows a flow chart of the signal processing.

BI^{hx} was monitored using the HXD-1 series block-type multifunctional monitor (software version 2002.5; Huaxiang Technology Co. Ltd., Heilongjiang, China). It was continuously calculated from two bipolar EEC channels using five silver-silver chloride electrodes (Medi-trace, Graphic Controls Corp., Gananoque, ON, Canada) applied to the scalp (Fp1–F7, Fp2–F8, international 10 to 20 system, with one placed at the midline near the mid-forehead as the reference). The pre-processing of the EEG sweeps consisted of artifact rejection and 0.5 to 60 Hz band-pass filtering. The total update delay was 30 sec.

All of the electrodes were positioned after the skin was cleaned with alcohol to remove surface oils and abraded with gauze to remove dead epidermal cells. Skin preparation was repeated if the impedance was greater than 5000 Ohms. In order to minimize artifacts, the patients were asked to close their eyes and relax after the electrodes were attached.

AAI and BI^{hx} values were generated every second and ten seconds, respectively, stored automatically and analyzed subsequently.

BI^{hx} and AAI have sophisticated artifact rejection algorithms and the auditory clicks generate signals 100 times smaller than the remainder of the EEG, so there is no interference between devices when used simultaneously.[2,7]

We induced general anesthesia with fentanyl 3 $\mu g \cdot kg^{-1}$, propofol 2 $mg \cdot kg^{-1}$ and succinylcholine 1.5 $mg \cdot kg^{-1}$ intravenously. After tracheal intubation, mechanical ventilation was commenced with 100% oxygen and the end-tidal carbon dioxide tension was adjusted to 34 to 38 mmHg. The end-tidal isoflurane concentration ($F_{ET}ISO$) was maintained at 1.0% for 20 min before a 10-mL dose of the study drug was administered in approximately 20 sec in a blinded fashion. The study ended ten minutes later.

The 10-mL study drug was prepared by a designated investigator, with sealed envelopes insuring randomization to vecuronium 0.05 $mg \cdot kg^{-1}$, vecuronium 0.1 $mg \cdot kg^{-1}$, vecuronium 0.2 $mg \cdot kg^{-1}$ or saline.

TABLE I Demographic data

	Group Saline	*Group V0.05*	*Group V0.1*	*Group V0.2*
Number of patients	9	10	11	10
Sex (female/male)	4/5	5/5	5/6	4/6
Age (yr) [mean (SD)]	49.4 (8.8)	48.2 (6.5)	43.4 (8.3)	44.7 (14.7)
Weight (kg) [mean (SD)]	65.0 (9.7)	58.6 (7.0)	63.6 (11.9)	57.1 (10.9)

No significant differences between groups. V0.05, V0.1 and V0.2 = vecuronium 0.05 mg·kg^{-1}, vecuronium 0.1 mg·kg^{-1} and vecuronium 0.2 mg·kg^{-1}, respectively.

TABLE II Absolute and percent changes in AAI and BI^{hx}

	AAI				*BI^{hx}*			
Group	Saline (n = 9)	V0.05) (n = 10	V0.1 (n = 11)	V0.2 (n = 10)	Saline (n = 9)	V0.05 (n = 10)	V0.1 (n = 11)	V0.2 (n = 10)
Awake	81.2 (73.3-89.1)	80.5 (68.7-92.3)	75.6 (69.0-82.2)	83.6 (74.2-93.0)	95.1 (93.5-96.7)	95.1 (93.4-96.7)	95.6 (94.0-97.2)	95.7 (94.4-97.0)
Iso15-20	16.1 (13.4-18.8)	15.2 (12.0-18.5)	18.3 (14.4-22.1)	18.0 (15.0-21.0)	47.9 (44.1-51.8)	48.0 (46.9-49.1)	47.4 (45.7-49.2)	47.3 (45.7-48.9)
S/V2-10	16.1 (13.1-19.0)	12.7 (10.9-14.5)	14.8* (12.4-17.3)	13.4* (11.9-15.0)	47.9 (46.6-49.2)	48.2 (46.7-49.6)	47.1 (45.2-48.9)	48.2 (46.6-49.8)
POD(%)	0.3 (-4.7-5.4)	10.1 (-10.9-31.0)	16.3† (4.9-27.7)	21.6† (6.7-36.6)	-0.7 (-7.6-6.2)	-0.4 (-3.2-2.5)	0.8 (-1.3-2.9)	-2.1 (-5.6-1.3)

Means and 95% confidence intervals of averaged (per patient) A-line autoregressive model with exogenous input (ARX) index (AAI) and bispectral index (BI^{hx}) during the periods 15 to 20 min after end-tidal isoflurane concentration was maintained at 1.0% (Iso 15–20) and two to ten minutes after the administration of saline or vecuronium (S/V 2–10), and the mean percentages of decrease (POD) of AAI and BI^{hx}, *$P < 0.05$, compared with Iso 15–20; †$P < 0.05$, compared with POD in the saline group.

Statistical analysis

AAI and BI^{hx} values were recorded from 15 min after $F_{ET}ISO$ stabilized at 1.0% to ten minutes after the injection of vecuronium or saline.

The means of averaged AAI or BI^{hx} values during five minutes before and from two minutes to ten minutes after the study drug injection were compared using Wilcoxon signed ranks test.

The mean percentages of decrease of AAI and BI^{hx} were calculated and compared using one-way analysis of variance.

Probability values below 0.05 were considered statistically significant.

Results

Demographic data of the four groups (Table I) were similar.

AAI and BI^{hx} decreased abruptly after the induction of anesthesia. Before the study drug injection, BI^{hx} remained constant. AAI fluctuated to some extent (Figure 2).

AAI and BI^{hx} were unaltered after the administration of saline. BI^{hx} remained stable after the administration of vecuronium (0.05 mg·kg^{-1}, 0.1 mg·kg^{-1} or 0.2 mg·kg^{-1}), whereas AAI tended to decrease within two minutes after the injection (Figure 2). The mean of averaged AAI values recorded during two to ten minutes after the administration of saline or vecuronium 0.05 mg·kg^{-1} did not differ from the corresponding mean prior to injection (P = 0.678, 0.169). Averaged AAI values decreased after the administration of vecuronium 0.1 mg·kg^{-1} or 0.2 mg·kg^{-1} (P = 0.016, 0.017; Table II). The mean percentages of decrease of AAI in the saline and vecuronium 0.05 mg·kg^{-1}, 0.1 mg·kg^{-1} and 0.2 mg·kg^{-1} groups were 0.3%, 10.1%, 16.3% and 21.6%, respectively. Decreases in the vecuronium 0.1 mg·kg^{-1} and 0.2 mg·kg^{-1} groups were greater (P = 0.016, 0.010) than in the saline group (Table II). The mean percentages of the decrease of AAI did not differ significantly (P = 0.533) in the vecuronium groups.

Discussion

With the introduction of neuromuscular blocking agents since 1942, physical signs, which were said to characterize the changing state of anesthesia, became more difficult to apply.[10] Recently, with the development of computer processing power, more efforts

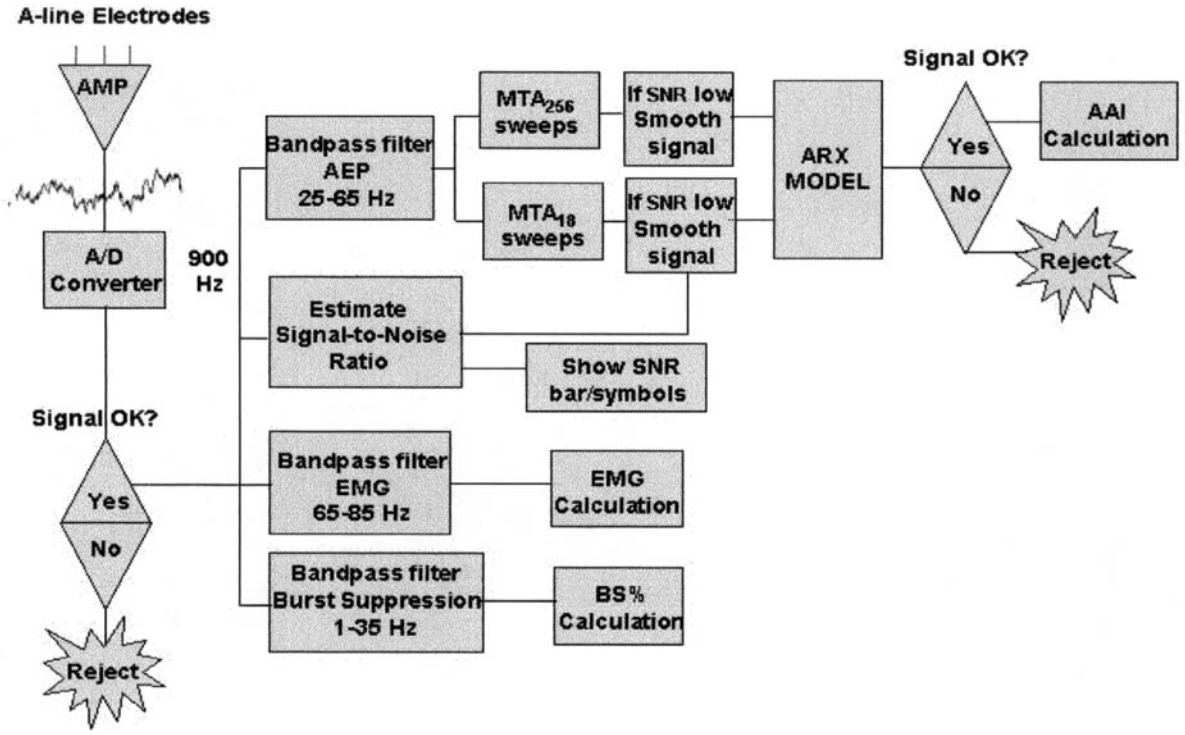

FIGURE 1 The A-line monitor (software version 1.5) signal processing flow chart. AMP = amplification; MTA = moving time average; ARX model = the autoregressive model with exogenous input; EMG = electromyography.

have concentrated on the bispectral index and MLAEP to monitor the depth of anesthesia.

The ARX model is a new model to evaluate the MLAEP index that can extract the information much faster than the classic model, the moving time average model.[1,3,6] Recently, the ARX model AEP index (AAI) has been proposed as a promising method to monitor the depth of anesthesia.[1–7] However, the effect of neuromuscular blocking agents on AAI remains unclear.

Similar to previous clinical observations, AAI fluctuated much more obviously than BI^{hx} in this study. The total update delay of BI^{hx} (30 sec) is longer than that of AAI (less than six seconds), and the BI^{hx} value generated much slower (per ten seconds) than the AAI value (per second), therefore rapid changes might not be detected by BI^{hx} with a result of less fluctuation. However, other differences in technologies might also contribute to this observed difference.

In the present study, we found that neuromuscular blockade with vecuronium did not alter BI^{hx}, as in the study by Greif *et al.*[9] However, vecuronium in doses of 0.1 and 0.2 $mg \cdot kg^{-1}$ reduced AAI significantly.

There are two reasons why neuromuscular blockade with vecuronium may affect AAI and BI^{hx} (BIS®):

1. The frequency composition of electromyographic (EMG) activity overlaps that of AAI and BI^{hx} and simple filtering will not completely remove EMG artifact from the recordings. Then the EMG signal from the frontalis, temporoparietalis, and mastoid muscles may interfere with the analysis and extraction of AAI and BI^{hx}. Moreover, EMG contamination can mimic the EEG and AEP of waking patients, thus falsely increasing BI^{hx} and AAI. Paralysis may therefore reduce BI^{hx} and AAI by alleviating artifact from muscles lying near the electrodes;
2. The "afferent muscle spindle theory" states that signals from muscle stretch receptors stimulate arousal centres in the brain.[9,11] Paralysis may also reduce signals from muscle stretch receptors that normally contribute to arousal.

But, why were BI^{hx} and BIS® not altered in this study and that of Greif *et al.*,[9] while AAI was reduced with neuromuscular blockade? Maybe this is because of the different algorithms and technologies used by BI^{hx} (BIS®) and

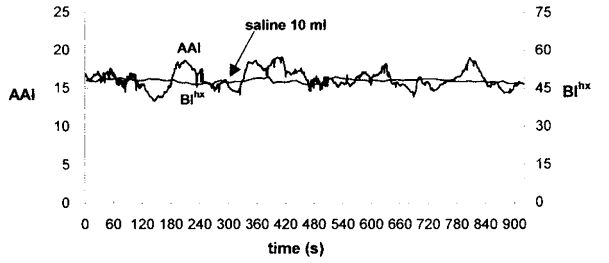

Fig. 2 A

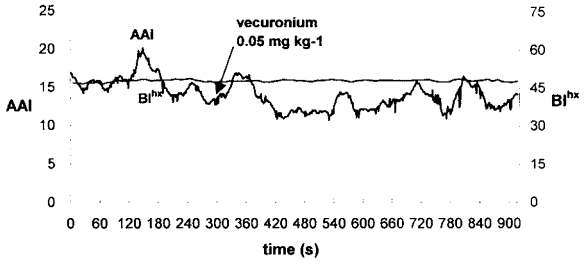

Fig. 2 B

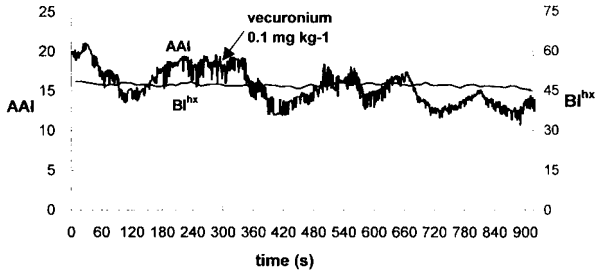

Fig. 2 C

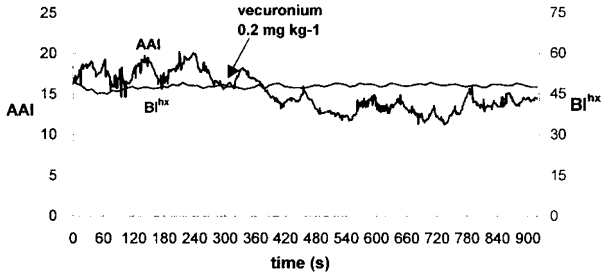

Fig. 2 D

FIGURE 2 The time-synchronized averages of A-line autoregressive model with exogenous input (ARX) index (AAI) every second and bispectral index (BI^{hx}) every ten seconds recorded five minutes before and ten minutes after the administration of saline or vecuronium.

AAI. BI^{hx} (BIS®) is largely derived from the spectrum of the spontaneous EEG, while AAI is calculated from the auditory evoked responses. Evoked responses have two advantages over the spontaneous EEG in the study of the depth of anesthesia: 1) evoked responses are an indication of the responsiveness of the central nervous system, whereas spontaneous EEG reflects the resting level;[3] 2) evoked responses have anatomical significance, each peak reflecting a specific anatomical structure.[3,12] BI^{hx} (BIS®) was developed based on a database of prior recordings and the expert opinion of anesthesiologists. It may more properly be regarded as an "expert system" rather than just a monitor. Thus, it is possible that EMG activity affected AAI greatly while it changed BI^{hx} (BIS®) little, or that neuromuscular blockade did effectively result in cortical depression, but BI^{hx} (BIS®) could not detect it while AAI could.

Since larger doses of vecuronium reduce AAI more, we hypothesize that AAI may be lower at deeper levels of neuromuscular block during steady state anesthesia. However, we could not monitor neuromuscular block (since it is a stimulus) simultaneously in this study. The EMG shown on the A-line device is the facial EMG. The way the EMG is calculated is by taking the energy in the 65 to 85 Hz range of the spectrum of the recorded data. It is only an estimation of the total energy of the EMG. AAI and BI^{hx} were calculated with 25 to 65 and 0.5 to 60 Hz band-pass filtering, respectively, so the EMG (65–85 Hz) activity may not represent the true information regarding interference with AAI and BI^{hx}. Consequently we did not use the EMG data shown on the A-line device.

EMG activity and the signal from muscle stretch receptors will be greater in patients under surgery, so it is possible that AAI will be reduced more after the administration of vecuronium. Nevertheless, we chose to perform this trial in anesthetized patients without surgical stimuli, which are highly variable in intensity.

Because AAI has been introduced into clinical monitoring, it will be important to take into consideration that AAI can be affected by neuromuscular blockade. If this is because of the EMG activity, which we think is likely, the technology to extract and calculate AAI needs to be improved. However, it is almost impossible to extract the AEP from the EMG background activity without any EMG interference. If, on the other hand, this is because of reduced signals from muscle stretch receptors, AAI can be assumed to be more sensitive than BI^{hx} for measuring the hypnotic level. Whatever the reason(s), the cut-off values of AAI for determining events should be determined according to the level of neuromuscular blockade when monitoring the depth of anesthesia/sedation.

We conclude that AAI is reduced by vecuronium during steady state anesthesia in patients without surgical stimuli, while BI^{hx} is unaltered.

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