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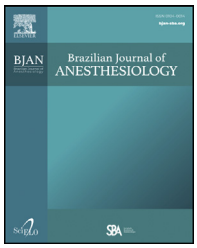

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ORIGINAL INVESTIGATION

Using the Perfusion Index to predict changes in the depth of anesthesia in children compared with the A-line Autoregression Index: an observational study☆

Hala Saad Abdel-Ghaffar *, Amani Hassan Abdel-Wahab, Mohammed Mahmoud Roushdy

Assiut University, Faculty of Medicine, Anesthesia and Intensive Care Department, Assiut, Egypt

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KEYWORDS
Children;
Sevoflurane;
Consciousness;
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Perfusion index;
Auditory evoked potentials

Abstract
Background: We investigated the performance of the Perfusion Index (PI) derived from pulse oximetry waveform as a tool for assessment of anesthetic depth in comparison with A-line Autoregression Index (AAI) derived from analysis of Middle-Latency Auditory Evoked Potentials (MLAEP) waveform integrated by aepEXplus monitor in children receiving sevoflurane anesthesia for tonsillectomy.
Methods: Forty-one patients (4–12 years old) were included in this study. The PI and AAI were recorded simultaneously every minute during different stages of anesthesia delivery. The statistical tests included descriptive analysis, significance tests, correlation tests, and Receiver Operating Characteristic (ROC) curve. The AAI served as a reference.
Results: The PI significantly decreased during light anesthesia and recovery, and significantly increased during deeper planes of anesthesia, with an inverse mirror-image relationship with the AAI. A negative correlation of low to moderate degree was detected between PI and AAI during the study ($p > 0.05$), that reached a statistical significance at the 5th minute during sevoflurane mask induction ($r = -0.457$, $p = 0.008$). ROC analysis at an AAI < 25 extracted the best cut-off value for PI before intubation as 1.48 (AUC = 0.698 [0.537–0.859], 94.4% sensitivity, 44.5% specificity) and at 10-minute intraoperatively as 2.4 (AUC = 0.537 [0.354–0.721], 91.7% sensitivity, 31% specificity). During recovery, at an AAI $\geq$ 50, the best cutoff was 1.82 (AUC = 0.661 [0.46–0.863], 100% sensitivity and 50% specificity) 2 minutes before spontaneous eye opening.
Conclusions: Compared with the AAI, the PI can track changes in depth of anesthesia in pediatric patients undergoing tonsillectomy under sevoflurane anesthesia.
Trial registration: Clinical Trials. Gov. Identifier: NCT03412214.

☆ Reprints: Hala S. Abdel-Ghaffar, Anesthesia and intensive care department, Assiut university hospital, Assiut, Egypt. Study Affliation: Assiut university main hospital, Assiut University, Assiut, Egypt. Setting: Assiut university main hospital.

* Corresponding author.
E-mails: hala_abdelghaffar@med.aun.edu.eg, hallasaad@yahoo.com (H.S. Abdel-Ghaffar).

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Introduction

Can the perfusion index (PI) derived from the pulse oximetry wave form reported to track the depth of anesthesia in children under sevoflurane anesthesia? Using the receiver operating characteristic curve (ROC), we determined the best cutoff values of PI during different stages of anesthesia delivery taking the AAI as a reference monitor. The PI can consistently differentiate between different planes of anesthesia in pediatric patients receiving sevoflurane anesthesia.

Monitoring the depth of anesthesia in anesthetized children is important. It enables the anesthesiologists to adjust the doses of anesthetic agents, helps avoiding intraoperative awareness, and facilitates a faster recovery.[1–3] The depth of anesthesia correlates with the changes in the partial pressure of administered anesthetic drugs in the brain.[1] Monitoring the depth of anesthesia using raw Electroencephalograph (EEG) − based monitoring devices such as the Bispectral Index (BIS) has been linked to improved patient outcomes after anesthesia.[4] Mid-Latency Auditory Evoked Potentials (MLAEP) have also been utilized to monitor the depth of anesthesia. The developmental time of MLAEP extends through the first decade of life, while the raw EEG is not mature before early adulthood.[5,6] Therefore, MLAEP is a potentially more useful parameter to assess the depth of anesthesia than EEG in children.[7] The A-line Autoregression Index (AAI) is calculated from the fast extracted MLAEP waveform analysis.[8]

However, monitors of the depth of anesthesia are expensive and not available in every operating room.[9] Instead, physicians utilize clinical variables denoting sympathetic stimulation such as blood pressure, heart rate, and respiratory rate to assess the depth of anesthesia.[10] The sympathetic nervous system output is increased with lighter planes of anesthesia and surgical stimulation and is depressed by anesthetic drugs. Increased sympathetic tone leads to peripheral vasoconstriction, while its decrease is associated with peripheral vasodilatation.[10]

The Perfusion Index (PI) is the ratio of the pulsatile to the non-pulsatile signal obtained from the pulse oximetry waveform that is incorporated in several modern pulse oximeter monitors available in operating theatres.[11] It decreases with vasoconstriction and increases with vasodilatation, and several studies have suggested that the PI may be a sensitive estimate of the level of sympathetic activity.[12–14] Though working by different principles, both the AAI and the PI can be used to monitor the depth of anesthesia.[13–18]

We conducted this study to investigate the use of PI to predict changes in the depth of anesthesia and recovery in children anesthetized with sevoflurane in direct association with the AAI.

Methods

Ethics

This prospective observational cohort was carried out at the main teaching hospital of the Faculty of Medicine, Assiut University, Assiut, Egypt, after approval from its medical ethics committee (protocol ID: 17300155, date: 14-12-2017, head of ethical committee: Prof. Hamdy N. EL-Talawy). This approval was followed by registration in Clinical Trials (gov. identifier: NCT03412214) before patient enrollment. The study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies. Written informed consent was taken from the parents or legal guardians of the children.

Study population

Forty-one children aged 4 to 12 years, American Society of Anesthesiologists (ASA) physical status I and II and scheduled for elective tonsillectomy with and without adenoidectomy were enrolled in this study. Patients with significant neurological, cardiac, respiratory, renal, and neuromuscular diseases or hearing impairment were excluded from the study.

Conduct of anesthesia

No sedative premedication was administered to any of our patients. Standard monitoring included electrocardiography, noninvasive blood pressure, end-tidal capnography, and a pulse oximeter (Shenzhen Mindray Bio-Medical Electronics Co. Ltd., China). The pulse oximeter was placed on the index finger of the child, shielded to prevent outside light from interfering with the signal, and kept in place for the whole procedure. In the meantime, the noninvasive blood pressure cuff was put on the other arm. The pulse oximeter continuously displayed the peripheral arterial oxygen saturation and the PI. The skin of the forehead was prepared according to the manufacturer's guidelines. Then the electrodes of the AEP Monitor/2 (Danmeter A/S, Odense, Denmark) were placed on the child's forehead to continuously display the AAI throughout the procedure. The anesthetic protocol was standardized. Anesthesia induction started with sevoflurane inhalation followed by venous cannulation and the administration of 1 $\mu g.kg^{-1}$ fentanyl, 1−1.5 $mg.kg^{-1}$ lidocaine, and 0.5 $mg.kg^{-1}$ atracurium for muscle relaxation. Older children also received 2−3 $mg.kg^{-1}$ intravenous (IV) propofol during the induction of anesthesia, if needed. The size of the cuffed endotracheal tube was selected according to the patient's age. Anesthesia and muscle relaxation were maintained with sevoflurane in a 50% oxygen/air mixture and 0.15 $mg.kg^{-1}$ atracurium at fixed intervals. All the patients received 15 $mg.kg^{-1}$ IV paracetamol and 0.2 $mg.kg^{-1}$ dexamethasone. At the end of the surgery, sevoflurane was turned off, and the patients were extubated awake after the reversal of muscle relaxation with neostigmine and atropine. The monitoring of the children continued in the OR until extubation so as not to interrupt the AAI recordings. After extubation, the patients were transferred to the Postanesthesia Care Unit (PACU) to be discharged to the ward afterward.

Study protocol

To certify an equal condition when comparing the performance of the two investigated indices, the AAI and the PI were recorded simultaneously in the same patient during the

whole procedure of anesthesia delivery and during recovery from anesthesia. The AAI recordings range from 0–100 and are interpreted as follows: 0–15 = deep anesthesia; 15–25 = surgical anesthesia with a peak at 20; 25–40 = light anesthesia, denoting intraoperative awareness; and above 50 = awake level.[3] The clinical stages of anesthesia and recovery were classified into four stations:

Stage I: From mask induction to endotracheal intubation. The pre-induction values of the AAI and the PI were recorded (baseline). Then the two indices were recorded simultaneously for every minute from the start of mask induction of the anesthesia until endotracheal intubation.

Stage II: From endotracheal intubation to surgical incision. Both the AAI and the PI were recorded 1, 2, 3, 4, and 5-minutes after intubation.

Stage III: During the surgical procedure. Both the indices were recorded 1, 2, 3, 4, 5, 10, 20, and 30 minutes intraoperatively.

Stage IV: During recovery from anesthesia. The AAI and the PI were recorded every minute from the discontinuation of sevoflurane until spontaneous eye opening.

Statistics

Power of the study

Changes in the PI during different stages of anesthesia delivery and recovery in direct association with the AAI served as the primary outcome parameter in this study. The secondary outcomes were descriptive analysis, significance tests, correlation testing between the PI and the AAI at different stages of anesthesia delivery, and Receiver Operating Characteristic (ROC) analysis, with the determination of the best cut-off value of the PI at an AAI < 25 and ≥ 50. Based on a previous study,[13] using the G-Power calculator 3.1.9.7 for sample size determination, a minimum of 34 patients for this cohort would be sufficient for our statistical testing based on a priori analysis with the *t*-test family: the difference between two dependent means (matched pairs) for one sample at a two-tailed type I error of 0.05 and a power of 0.8 and effect size of 0.5. Forty-two patients were enrolled to compensate for the dropouts.

Statistical tests

Statistical analysis was done via the Statistical Package for the Social Sciences (SPSS), software version 20, for Microsoft Windows (SPSS Inc., Chicago, IL, USA). The data was checked for normality using the Shapiro-Wilk test. The continuous data was presented as the mean (±SD) with a 95% Confidence Interval for normally distributed data and as the median (range) for not normally distributed data. The categorical data was expressed as numbers and frequencies (%). Data analysis was performed using paired *t*-tests for normally distributed data and the Wilcoxon rank test for abnormally distributed data. A *p*-value of < 0.05 was considered statistically significant.

The correlation between the variables was carried out by applying the Pearson correlation equation for linear relations and the Spearman correlation equation for nonlinear correlation. The degree of correlation was determined based on the coefficient correlation (r) into perfect positive (r = +1), perfect negative (r = -1), no correlation (r = 0), high-degree positive (r = +0.75 to +1), high-degree negative (r = -0.75 to -1), moderate-degree positive (r = +0.25 to +0.75), moderate-degree negative (r = -0.25 to -0.75), low-degree positive (r = 0 to +0.25), and low-degree negative (r = 0 to -0.25).

The ROC curve and its corresponding Area Under the Curve (AUC) was constructed to evaluate the ability of the PI to detect the depth of anesthesia and to distinguish between consciousness and unconsciousness compared with the AAI. The best cut-off value for the PI was the value at which both the specificity and the sensitivity were the highest. For analysis, we defined consciousness as an AAI ≥ 50 and unconsciousness (adequate hypnosis) as an AAI < 25. ROC analysis was conducted using MedCalc for Windows, version 5.6.1 (MedCalc Software, Mariakerke, Belgium).

Table 1 Patients' demographic and clinical characteristics.

Study cohort (n = 41)	
Age (years)	6 (4–12)
Weight (Kg)	23.7 ± 6.5 (21.6–25.7)
Sex: Male/Female	31/10
Induction agent	
Sevoflurane/Sevoflurane and propofol	29/12
Anesthesia time (min)	46.4 ± 13.3 (42.2–50.6)
Induction time (min)	6.2 ± 1.72 (5.7–6.7)
Surgery time (min)	36.1 ± 13.3 (31.9–40.3)
Time to spontaneous eye opening (min)	11.95 ± 2.6 (range: 7–17 min)

Data presented as median (range), mean (±SD) with 95% Confidence Interval, range, and number.

Results

Forty-two patients were enrolled in this study. One patient was dropped because of incomplete data, and 41 patients successfully completed the statistical analysis. Their clinical variables such as the heart rate, blood pressure, temperature, and peripheral arterial oxygen saturation were within the normal limits throughout the procedure. The patients' demographic and baseline characteristics are listed in Table 1.

The trend of PI and AAI through the anesthetic procedure

The baseline median PI was 0.7 (range: 0.2–2.7), which gradually increased during the induction of general anesthesia ($p < 0.0001$). The baseline mean AAI was 62.1±9.1 (95% CI: 59.2–64.9), which gradually decreased during the induction of anesthesia until endotracheal intubation ($p < 0.001$) (Fig. 1A). After endotracheal intubation, a small increase in the PI ($p < 0.021$) was recorded, with no change in the AAI ($p = 0.341$) (Fig. 1B). Intraoperatively, the PI increased further ($p < 0.0001$), and the AAI decreased further ($p < 0.0001$) throughout the anesthetic procedure (Fig. 1C). During recovery from anesthesia, the PI gradu-

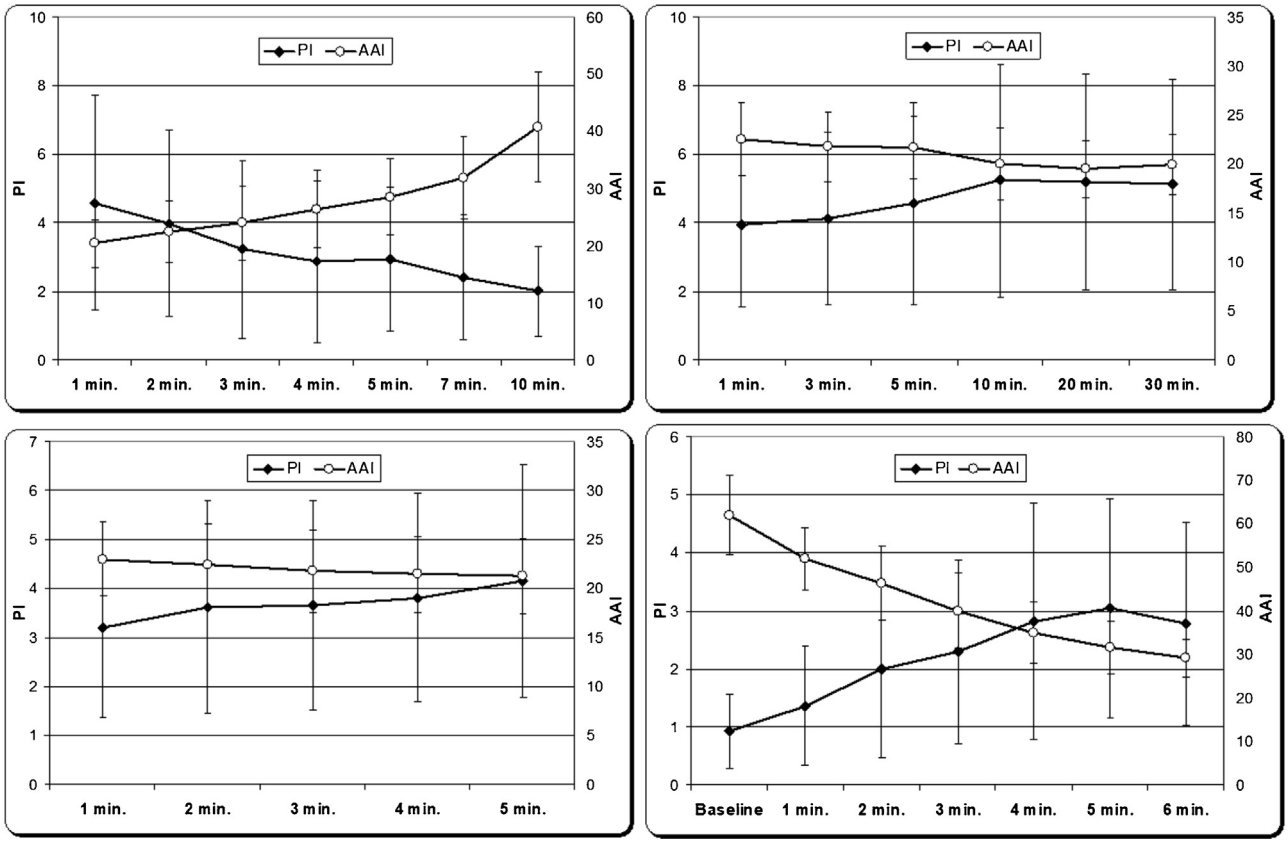

Figure 1 (A) Trend of AAI and PI from induction of anesthesia to endotracheal intubation. (B) Trend of AAI and PI from endotracheal intubation till start of surgery. (C) Trend of AAI and PI during the surgical procedure. (D) Trend of AAI and PI from discontinuation of sevoflurane till spontaneous eye opening. PI, Perfusion Index; AAI, A-line Autoregression Index. Values are presented as mean ± SD.

ally decreased ($p < 0.0001$), and the AAI gradually increased ($p < 0.0001$) (Fig. 1D). At spontaneous eye opening, the median PI, 1.5 (range: 0.5–5.2), was higher ($p < 0.0001$) and the mean AAI (53.2 ± 6.1, 95% CI: 51.2–55.3) was lower ($p < 0.0001$) than their respective baseline values before the delivery of anesthesia. The inverse relationship between the AAI and the PI through the anesthetic procedure is presented as a trend Figure (1A–D) in which the PI and AAI were presented as mean ± SD.

Correlation between the PI and the AAI

Correlation analysis showed a negative correlation between the PI and the AAI of a low to moderate degree at the studied time points, with the p-value > 0.05 (data not represented) except at the 5thminute during the mask induction of sevoflurane, which showed a moderate significant negative correlation (r = -0.457, p = 0.008) (Fig. 2).

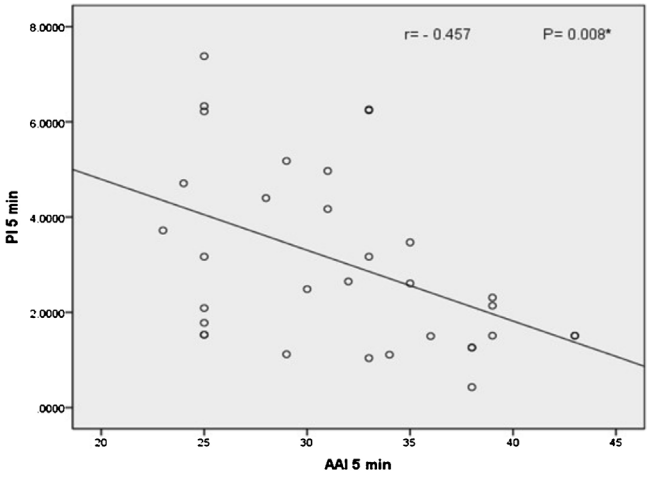

Figure 2 Correlation between PI and AAI at 5th minute before intubation. PI, Perfusion Index; AAI, A-line Autoregression Index.

Receiver operator characteristics analysis of the PI and the AAI

During anesthesia delivery (At an AAI < 25 denoting hypnosis), the best cut off value for the PI before intubation was 1.48, (AUC = 0.698 [95% CI: 0.537–0.859], 94.4% sensitivity and 44.5% specificity), and the best cut off value for the PI at 10 minutes intraoperatively was 2.4, (AUC = 0.537 [0.354–0.721], 91.7% sensitivity and 31% specificity] (Fig. 3A and B).

During recovery from anesthesia (at an AAI ≥ 50 denoting consciousness), the best cut off value for the PI was 1.82, (AUC = 0.661 [0.46–0.863], 100% sensitivity and 50% specificity) 2 -minutes before spontaneous eye opening, 0.78

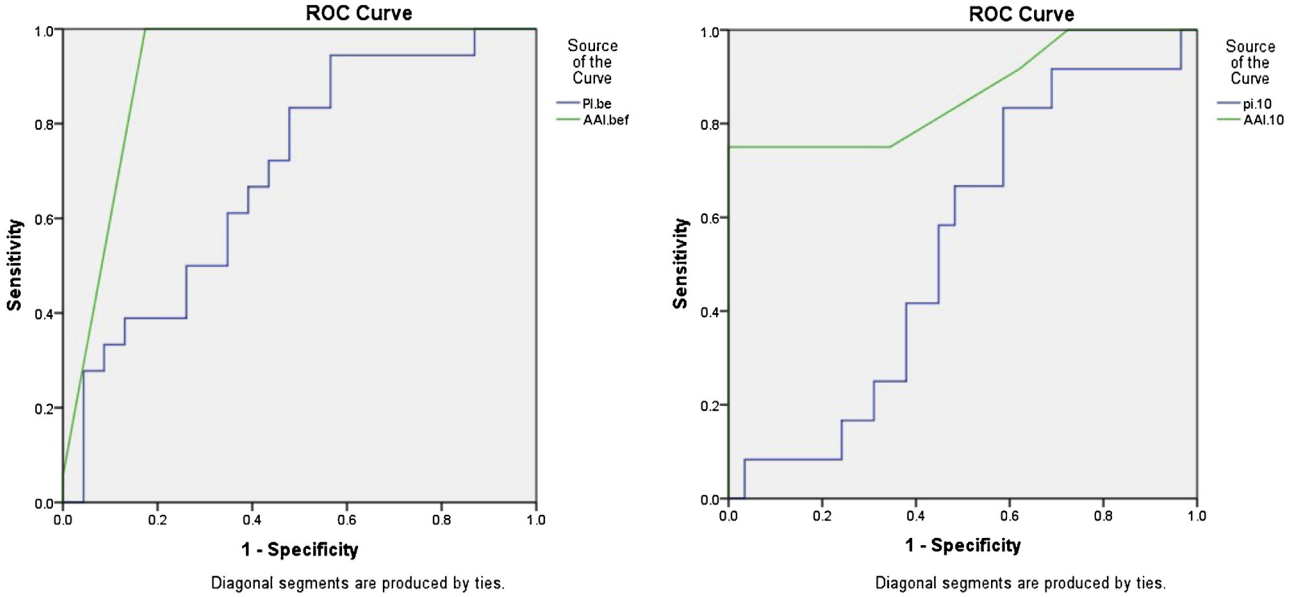

Figure 3 (A) Receiver Operator Characteristics (ROC) analysis of the PI and AAI before intubation. At an AAI < 25, The AUC for PI was 0.698 (0.537–0.859), 94.4% sensitivity and 44.5% specificity. The AUC for AAI was 0.918 (0.826–1.0), 100% sensitivity and 83.6% specificity. (B) Receiver Operator Characteristics (ROC) analysis of the PI and AAI at 10thmin. intraoperative. At an AAI < 25, The AUC for PI was 0.537 (0.354–0.721), 91.7% sensitivity and 31% specificity. The AUC for AAI was 0.918 (0.826–1.0), 75% sensitivity and 100% specificity.

(AUC = 0.545 [0.282–0.803], 100% sensitivity and 15% specificity) 1 minute before spontaneous eye opening, and 1.12 (AUC = 0.543 [0.356–0.730], 73.7% sensitivity and 40.9% specificity) at the event of spontaneous eye opening (Fig. 4 A–C).

Discussion

In this study, we investigated the performance of the PI as a tool to assess the depth of anesthesia during different stages of anesthesia delivery in direct comparison with the AAI. Our results demonstrated that the PI significantly decreased during light anesthesia and recovery and significantly increased during deeper planes of anesthesia, with an inverse relationship with AAI. At whatever time the AAI decreases, the PI increases and vice versa. While the correlation testing between these two indices was insignificant in most of the time points investigated, the ROC analysis was informative, showing clear cut off values with their corresponding sensitivity and specificity.

The physical principles of the PI and the AAI are completely different. Auditory-Evoked Potentials (AEPs) measure time-locked EEG responses to repetitive auditory clicks, testing the neural pathways carrying information from the periphery to the cerebral cortex reflecting the changes in the cortical area.[19] Meanwhile, the PI acts as an indicator of the plethysmographic pulse wave amplitude, reflecting changes in the peripheral vasomotor tone in response to changes in the sympathetic output (i.e., ''subcortical zone'').[12–14] The PI increases with peripheral vasodilatation in response to decreased sympathetic output and decreases with peripheral vasoconstriction in response to increased sympathetic output.[12–14,17]

Light anesthesia and inadequate analgesia both stimulate the sympathetic nervous system and decrease the PI.[12] Ezri et al., in their study on adult females undergoing D&C procedures, reported that the PI decreased with cervical dilatation and during light anesthesia.[10] Korhonen and Yli-Hankala, in their study, also confirmed the relationship between nociception and the PI. They concluded that the quality of analgesia delivered, the type of surgery, and its perceived level of nociception would all affect the PI.[12] This could have confounded the results when we investigated the PI as a tool to assess the depth of anesthesia. However, many clinicians found that these observations make the PI a useful, non-expensive, available continuous tool forecasting the patients' needs for additional analgesia and for deeper planes of anesthesia in busy operating rooms with rapid turnover, thus increasing the patients' safety and reducing perioperative risks.[17] Also, this will financially reserve the specific depth of anesthesia monitors to special patients' categories and types of operations that are commonly associated with intraoperative awareness.[19]

Correlation analysis showed a negative correlation between the PI and the AAI of a low to moderate degree at the studied time points, with the *p*-value > 0.05 except at the 5thminute during the mask induction of sevoflurane, which showed a moderate significant negative correlation (r = -0.489, *p* = 0.004). Indeed, this is the mean time needed to induce deep anesthesia through sevoflurane inhalational mask induction, and this observation is consistent with those of other studies on such a topic.[1,13]

In this study, we conducted an ROC analysis as an approach to quantify the PI performance in comparison to that of the AAI (as a specific monitor for the depth of anesthesia) for analysis at two different states: an adequate level of anesthesia (AAI < 25) and at recovery (AAI ≥ 50),

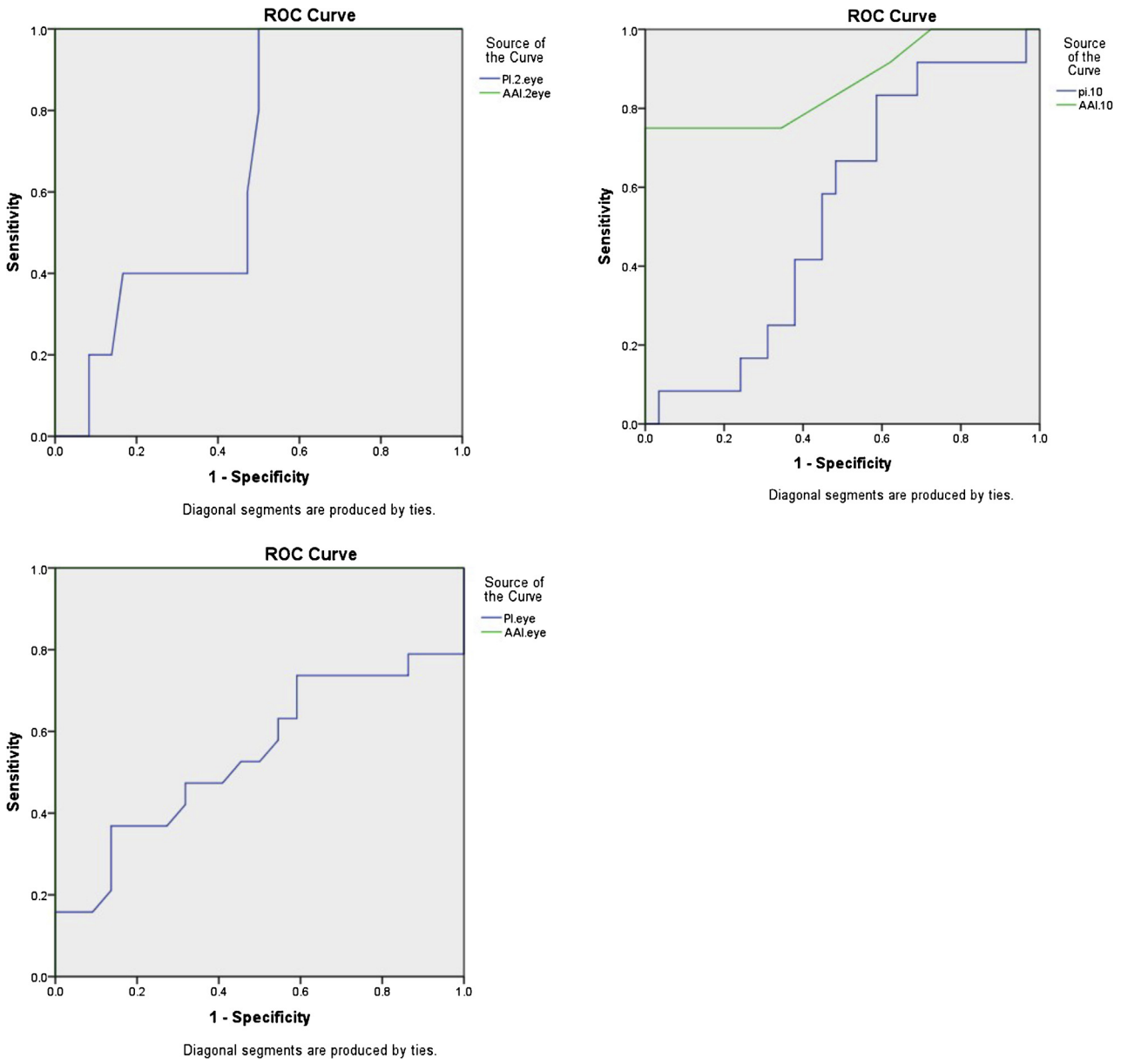

Figure 4 (A) Receiver Operator Characteristics (ROC) analysis of the PI and AAI two minutes before spontaneous eye opening. At an AAI $\geq$ 50, The AUC for PI was 0.661 (0.46–0.863), 100% sensitivity and 50% specificity. The AUC for AAI was 1.0 (1.0–1.0), 100% sensitivity and 100% specificity. (B) Receiver Operator Characteristics (ROC) analysis of the PI and AAI one minutes before spontaneous eye opening. At an AAI $\geq$ 50, The AUC for PI was 0.545 (0.282–0.803), 100% sensitivity and 15% specificity. The AUC for AAI was 1.0 (1.0–1.0), 100% sensitivity and 94.3% specificity. (C) Receiver Operator Characteristics (ROC) analysis of the PI and AAI at spontaneous eye opening. At an AAI $\geq$ 50, The AUC for PI was 0.543 (0.356–0.730), 73.7% sensitivity and 40.9% specificity. The AUC for AAI was 1.0 (1.0–1.0), 100% sensitivity and 100% specificity.

extracting a clear cut-off value with its corresponding sensitivity and specificity. In this study, the baseline preoperative median PI was 0.7 (range: 0.2–2.7). At an AAI < 25, the best cut-off value for the PI before intubation was 1.48 (94.4% sensitivity and 44.5% specificity), and the best cut-off value for the PI at 10 minutes was 2.4 (91.7% sensitivity and 31% specificity). During recovery from anesthesia at an AAI $\geq$ 50, the best cut off value for the PI was 0.78 (100% sensitivity and 15% specificity) 1 minute before spontaneous eye opening. Despite it not being specific, we found that the PI was sensitive in detecting the depth of anesthesia. Compared with its preoperative value, it doubled before intubation, tripled intraoperatively during adequate anesthesia and analgesia, and returned nearly to its baseline value at recovery. These results are in accordance with those of studies that confirmed the sensitivity of PI for detecting changes in the depth of anesthesia.[10,13,15,17] An added advantage of this study was that we defined clear cut off values for the PI at different stages of anesthesia delivery and during recovery. Considering that the AUC was < 0.7 at all the studied time points, the accuracy of the PI to differentiate the depth of anesthesia might be

defined as low. Further studies are needed to support these findings.

At spontaneous eye opening, the AAI was 53.2 ± 6.1 compared with 62.1 ± 9.1 ($p < 0.001$) before anesthesia induction. This finding is in accordance with those of previous studies that concluded that cortical activity does not fully recover during emergence from anesthesia.[17,18]

In this study, we reported large inter-individual variations in the PI, ranging from 0.18 preoperatively and up to 14.1 at 10 minutes intraoperatively. Similarly, Granelli and Ostman-Smith found a large inter-individual variation of the PI that ranged from 0.02 to 20 in 10,000 healthy newborns recruited in their case-control study.[20] Despite these large inter-individual variations, we think that the PI is a useful tool when comparing the trend of changes in the value of PI in comparison to its baseline value. We conclude that the surges and drops in the PI compared with its respective baseline are highly informative regardless of whatever this value was.

A limitation of this study was that changes in the PI reflect both anesthetic and analgesic needs. In this study, we assumed that the changes in the PI are mainly due to changes in the depth of anesthesia because our patients received an adequate analgesic protocol that is suitable for such operations. In addition, we studied a homogenous sample as regards operative procedure and patient category. So, we can assume that this bias has been controlled. Possible effects of iv propofol on AAI should be considered and a second limitation to this study is that we used IV propofol as a supplementation to sevoflurane inhalational induction in older children in this study. Twelve patients of this cohort (n = 41) received iv propofol supplementation to sevoflurane mask induction. Indeed, this is a common practice in pediatric anesthesia protocols. The minimum propofol dose required for loss of consciousness was used and we did not use any anesthetic adjuvants afterward. We assume that this technique did not affect our results.

In conclusion, compared with the AAI, the PI can track changes in the depth of anesthesia in pediatric patients undergoing tonsillectomy under sevoflurane anesthesia.

Author contribution

Hala S. Abdel-Ghaffar: This author helped study design, data analysis, writing and editing the manuscript.

Amani H. Abdel-Wahab: This author helped conduct of study, data collection and data entry.

Mohammed M Roushdy: This author helped conduct of study.

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Departmental resources were used for the conduct of this study.

Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no conflicts of interest.

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