Discrepant End-Tidal Concentrations of Sevoflurane at the Same A-Line Autoregressive Index Level During Induction of General Anaesthesia: An Observational Study

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Research

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Abstract

Background: The A-Line Autoregressive Index (AAI), which is derived from auditory evoked potentials, has been used for determining anaesthetic depth. This study verified the correlation between AAI values and the corresponding end-tidal concentrations of sevoflurane during general anaesthesia induction.

Methods: Thirty young male adults undergoing elective minor orthopaedic surgery were sequentially allocated to receive inspiratory 3%, 5%, or 6% sevoflurane for mask induction, followed by mechanical ventilation after tracheal intubation. The inspiratory, end-tidal, and estimated jugular bulb concentrations of sevoflurane were recorded at three target AAI values: below 20, below 10 and at the start of burst suppression.

Results: The mean time to loss of consciousness in the 6% sevoflurane group was shorter than that in the 5% and 3% groups; however, the groups had comparable AAI values (range: 16–45). The 6% group had a higher end-tidal concentration (4.5% ± 0.2% vs. 3.8% ± 0.2%, \( P < 0.05 \)) than did the 5% group, despite having the same target anaesthetic levels by AAI score \( \leq 10 \), whereas the estimated jugular bulb concentrations were comparable (1.9% vs. 1.9%) in both groups.

Conclusions: Following mechanical ventilation with inspiratory 3%, 5%, or 6% sevoflurane, the end-tidal concentrations were discrepant at the same end points of AAI levels, despite similar estimated jugular bulb concentrations of sevoflurane. Thus, conventional alveolar concentration may overestimate anaesthesia depth during rapid wash-in of sevoflurane.

Background

Use of the A-Line Autoregressive Index (AAI) by autoregressive modelling with exogenous input (ARX-model) enables quicker extraction of middle-latency auditory evoked potentials.(1) In the past two decades, the AAI has been applied to differentiate degrees of anaesthetic effects,(2) including the correlation with the end-tidal concentrations of sevoflurane(3) and desflurane.(4) The predictable and dose-dependent response in a graded, reversible manner to minimal alveolar concentrations of volatile anaesthetics provides a window to the brain for the assessment of matters such as potential awareness, burst suppression,(2) and adjustment of anaesthesia depth.(5)

For inhalational anaesthetics, however, a time lag between end-tidal and brain concentrations has been identified and physiologically modelled through measurement of the inspiratory, end-tidal, and jugular bulb concentrations.(6–8) Accordingly, the body's uptake and elimination(9) of anaesthetics across the alveolar membrane and blood–brain barrier depend on the partition coefficient,(10–12) ventilation,(13) and cardiac output.(7) Sevoflurane requires nearly 40 min to achieve a pharmacokinetic equilibrium between arterial and jugular bulb concentrations, indicating that no further brain uptake of inspiratory 3.5% sevoflurane occurs after general anaesthesia induction.(7)
Clinically, using a higher inspiratory concentration of anaesthesia could allow practitioners to adjust and achieve the target anaesthetic level more rapidly and obtain a higher end-tidal concentration. During the wash-in period of anaesthesia, data regarding the time delay between end-tidal concentrations and their electroencephalographic effects, as revealed by the modern AAI, are scarce. Therefore, this study examined the clinical correlations between AAI values following mechanical ventilation with different inspiratory concentrations of sevoflurane and their corresponding inspiratory and end-tidal (alveolar) concentrations during induction of general anaesthesia.

Methods

Participants

After obtaining approval from the relevant institutional review board (TSGHIRB-096-05-0082) and informed consent from each patient, the current study enrolled male patients classified as American Society of Anesthesiologists physical status I who were undergoing elective minor orthopaedic surgery. Those with coexisting obesity or hypertension were excluded.

Anaesthetic procedures

Thirty nonpremedicated young male patients were sequentially allocated to three groups: inspiratory 3%, 5%, or 6% sevoflurane. Before mask ventilation, the anaesthetic circuit was prewashed for 3 min with 3%, 5%, or 6% sevoflurane in 6 L/min oxygen. Under standard monitoring, the patients in each group were encouraged to take a deep breath of sevoflurane through an ordinary face mask, followed by normal spontaneous breathing or assisted mask ventilation for 5 min. After loss of consciousness (no response to verbal command), rocuronium (0.6 mg/kg) was administered for oral tracheal intubation. Next, mechanical normoventilation (end-tidal CO\textsubscript{2} 35–45 mmHg) was initiated with inspiratory 3%, 5%, or 6% sevoflurane for a maximum of 60 min or until the target sedation levels were achieved before initiating surgery. Hemodynamic variables, including heart rate, blood pressure, pulse oximetry, and capnography, were recorded at the start of induction and at 5, 10, 15, 20, 30, 40, 50, and 60 min, and inspiratory and end-tidal concentrations of sevoflurane were measured using side-stream gas sampling with a CardioCap 5 monitor (Datex, Helsinki, Finland). Intravenous bolus of nitroglycerin (50–100 mcg) for maintaining a systolic blood pressure below 160 mmHg during tracheal intubation and ephedrine (5–10 mg) for maintaining a subsequent mean blood pressure above 60 mmHg were incrementally administered, as required. No other intravenous medications were administered during the study period.

Data acquisition

An auditory evoked potential (AEP) monitor (AEP Monitor/2; version 1.6; Danmeter A/S, Odense, Denmark) was applied to the patients’ forehead with contact impedance < 5 K Ohm. Headphones connected to the device provided auditory stimulus, an intermittent click (6 Hz in frequency with automatically controlled volume according to the appropriate AEP extraction quality conditions). Processing time for the AAI was 30 seconds for the first detected signal, with a total update delay of 6
seconds. An AAI range of 0–60 is recommended to minimise oscillations while the patient is awake (high AAI values) and to provide higher-quality graphical resolutions when the patient is asleep or anaesthetised (low AAI values).\(^\text{(15)}\) The monitor included a burst suppression indicator to indicate periods when the electroencephalogram (EEG) was isoelectric. The AEP monitor indicated the percentage of burst suppression over the preceding 30 seconds of the EEG signal. After loss of consciousness, the aforementioned hemodynamic and inhalation parameters were also collected at three target AAI levels: below 20, below 10, and at the beginning of burst suppression. The estimated jugular bulb concentrations of sevoflurane were calculated using the end-tidal concentrations in this study and the calculated ratios of jugular bulb over end-tidal concentrations from a related pharmacokinetic study of sevoflurane brain uptake.\(^\text{(7)}\) The ratios were 0.378 at 5 min, 0.461 at 10 min, 0.503 at 20 min, 0.550 at 30 min, and 0.635 at 60 min following mechanical ventilation.

**Data analysis**

Statistical analysis was conducted using IBM SPSS version 21.0. Descriptive statistical analyses were performed to calculate the means and standard deviations of demographic and clinical variables. Because the data did not satisfy the assumptions of equality of variance and normal distribution, the Kruskal–Wallis test and Mann–Whitney U-test were employed to analyse the change in values for intergroup comparison. When a significant difference was observed between the groups, Dunn's test was performed to identify the deviating group. Differences with \(P < 0.05\) were considered statistically significant.

**Results**

The general data are presented in Table 1. The 6% sevoflurane group had a shorter time to loss of consciousness but similar AAI values relative to the 5% and 3% groups. The AAI scores in the 3% sevoflurane group did not fall below 10 during the 60-min period. Figure 1 illustrates the pharmacokinetics of inspiratory and end-tidal concentrations of sevoflurane in the three groups. The administration of sevoflurane in the 6% group was terminated at 30 min after burst suppression status had been achieved.
Table 1
Demographic data

|                          | Sevoflurane 3% | Sevoflurane 5% | Sevoflurane 6% | P value |
|--------------------------|----------------|----------------|----------------|---------|
| Patient Number           | 10 males       | 10 males       | 10 males       |         |
| Age, year                | 21.9 ± 1.2     | 21.7 ± 1.8     | 21.9 ± 1.4     | 0.956   |
| Height, cm               | 175.3 ± 8.4    | 169.9 ± 2.7    | 171.3 ± 4.7    | 0.293   |
| Weight, kg               | 71.2 ± 10.8    | 64.8 ± 12.1    | 62.8 ± 9.3     | 0.206   |
| Body mass index, kg/m²   | 23.2 ± 3.7     | 22.4 ± 4.1     | 21.3 ± 2.0     | 0.420   |
| Time to loss of consciousness, sec | 122.5 ± 35.0 (75–180) | 89.5 ± 22.5 (55–120) | 71.5 ± 12.5 (55–90) | 0.002   |
| AAI values at loss of consciousness | 31.7 ± 9.9 (16–45) | 26.2 ± 7.0 (20–36) | 28.6 ± 6.8 (20–41) | 0.355   |

Data are presented as the mean ± standard deviation (range).

AAI, A-Line Autoregressive Index.

Table 2 provides the comparable hemodynamic variables. Three patients in the 5% group and three patients in the 6% group received intermittent ephedrine (5 mg) to maintain their mean arterial blood pressure above 60 mmHg. None of the patients experienced adverse events.
|                              | Heart rate (beats per min) | Mean blood pressure (mmHg) | End-tidal CO₂ (mmHg) |
|------------------------------|-----------------------------|-----------------------------|----------------------|
| **Sevoflurane 3%**           |                             |                             |                      |
| Before induction             | 65.2 ± 8.7                  | 86.9 ± 7.0                  | –                    |
| Loss of consciousness, sec  | 64.7 ± 7.1                  | 82.6 ± 8.2                  | 40.4 ± 2.7           |
| 5 min                        | 67.3 ± 22.2                 | 89.1 ± 16.5                 | 41.7 ± 3.1           |
| 10 min                       | 71.4 ± 16.7                 | 73.4 ± 12.6                 | 42.3 ± 2.0           |
| 15 min                       | 69.1 ± 13.8                 | 71.6 ± 8.6                  | 42.7 ± 1.8           |
| 20 min                       | 66.1 ± 12.5*                | 69.5 ± 8.8                  | 43.0 ± 1.1           |
| 30 min                       | 66.6 ± 11.8                 | 68.9 ± 10.5                 | 43.2 ± 1.4           |
| 40 min                       | 66.6 ± 12.9                 | 67.7 ± 10.4                 | 43.4 ± 1.3           |
| 50 min                       | 65.1 ± 12.4                 | 66.4 ± 8.5                  | 43.9 ± 1.4           |
| 60 min                       | 63.2 ± 12.4                 | 65.9 ± 8.6                  | 44.1 ± 2.0           |
| **Sevoflurane 5%**           |                             |                             |                      |
| Before induction             | 72.9 ± 11.7                 | 86.3 ± 9.9                  | –                    |
| Loss of consciousness        | 69.1 ± 11.7                 | 81.0 ± 10.4                 | 35.0 ± 2.6           |
| 5 min                        | 92.0 ± 20.4                 | 79.7 ± 8.5                  | 35.2 ± 2.7           |
| 10 min                       | 82.7 ± 14.7                 | 74.4 ± 8.8                  | 35.6 ± 3.1           |
| 15 min                       | 82.0 ± 17.6                 | 70.6 ± 6.9                  | 36.1 ± 3.4           |
| 20 min                       | 79.0 ± 16.3                 | 69.4 ± 6.0                  | 37.6 ± 4.0           |
| 30 min                       | 83.4 ± 20.0                 | 69.6 ± 10.0                 | 38.7 ± 4.5           |
| 40 min                       | 83.7 ± 21.6                 | 65.2 ± 3.3                  | 39.4 ± 5.1           |
| 50 min                       | 78.0 ± 20.4                 | 63.0 ± 2.8                  | 40.0 ± 5.2           |
| 60 min                       | 73.4 ± 17.5                 | 61.1 ± 2.8                  | 41.5 ± 5.7           |
| **Sevoflurane 6%**           |                             |                             |                      |
| Before induction             | 72.7 ± 14.7                 | 86.8 ± 10.6                 | –                    |
| Loss of consciousness, sec  | 75.1 ± 22.4                 | 80.6 ± 9.4                  | 38.3 ± 3.4           |
| 5 min                        | 93.6 ± 22.7                 | 75.3 ± 13.9                 | 36.7 ± 2.9           |
|               | Heart rate (beats per min) | Mean blood pressure (mmHg) | End-tidal CO₂ (mmHg) |
|---------------|----------------------------|----------------------------|-----------------------|
| 10 min        | 80.6 ± 14.0                | 69.4 ± 13.1                | 35.9 ± 2.0            |
| 15 min        | 81.4 ± 9.4                 | 65.4 ± 5.0                 | 36.1 ± 1.4            |
| 20 min        | 80.3 ± 12.0                | 62.8 ± 4.1                 | 36.8 ± 2.3            |
| 30 min        | 79.4 ± 13.8                | 63.3 ± 6.5                 | 38.0 ± 2.2            |

The time required to reach the programmed AAI levels and their corresponding inspiratory, end-tidal, and estimated jugular bulb concentrations are summarised in Table 3. At the same AAI end points, including values ≤ 20, values ≤ 10, and at the start of burst suppression, the mean end-tidal concentrations in the 6% sevoflurane group were significantly higher than those in the 5% sevoflurane group, whereas the estimated jugular bulb concentrations were comparable between these two groups (Fig. 2). The estimated jugular bulb concentration at 30 min in the 6% group was twice that in the 3% group (2.8% ± 0.1% vs. 1.4% ± 0.1%, respectively).
Table 3
Time required to achieve the target A-Line Autoregressive Index (AAI) values and the corresponding inspiratory, end-tidal, and estimated jugular bulb concentrations of sevoflurane

|                      | Time (min) | Inspiratory concentration (%) | End-tidal concentration (%) | Estimated jugular bulb concentration (%) |
|----------------------|------------|-------------------------------|-----------------------------|------------------------------------------|
| **Loss of consciousness (sec)** |            |                               |                             |                                          |
| 3% sevoflurane       | 122.5 ± 35.0 | 2.6 ± 0.1                     | 2.2 ± 0.2                   |                                          |
| 5% sevoflurane       | 89.5 ± 22.5  | 4.1 ± 0.2                     | 3.2 ± 0.4                   |                                          |
| 6% sevoflurane       | 71.5 ± 12.5  | 4.2 ± 0.3                     | 3.9 ± 0.3                   |                                          |
| **AAI ≤ 20**         |            |                               |                             |                                          |
| 3% sevoflurane       | 5.9 ± 1.5   | 2.8 ± 0.1                     | 2.4 ± 0.1                   | 0.9 ± 0.0                                 |
| 5% sevoflurane       | 4.8 ± 3.0   | 4.3 ± 0.2                     | 3.4 ± 0.2                   | 1.3 ± 0.1                                 |
| 6% sevoflurane       | 2.6 ± 2.0   | 4.8 ± 0.6                     | 4.1 ± 0.2                   | 1.4 ± 0.1                                 |
| **AAI ≤ 10**         |            |                               |                             |                                          |
| 5% sevoflurane       | 21.4 ± 9.8  | 4.9 ± 0.1                     | 3.8 ± 0.2*                  | 1.9 ± 0.1                                 |
| 6% sevoflurane       | 8.3 ± 2.9   | 5.6 ± 0.2                     | 4.5 ± 0.2*                  | 1.9 ± 0.1                                 |
| **Start of burst suppression** |            |                               |                             |                                          |
| 5% sevoflurane       | 26.8 ± 11.1 | 4.9 ± 0.1                     | 3.9 ± 0.1#                  | 2.1 ± 0.1                                 |
| 6% sevoflurane       | 9.9 ± 2.6   | 5.7 ± 0.1                     | 4.7 ± 0.1#                  | 2.2 ± 0.1                                 |
| **30 min after induction** |          |                               |                             |                                          |
| 3% sevoflurane       | 30         | 3.0 ± 0.0                     | 2.6 ± 0.1                   | 1.4 ± 0.0                                 |
| 5% sevoflurane       | 30         | 5.0 ± 0.0                     | 3.8 ± 0.2                   | 2.1 ± 0.1                                 |
| 6% sevoflurane       | 30         | 6.0 ± 0.0                     | 5.1 ± 0.2                   | 2.8 ± 0.1                                 |
| Time after induction | Inspiratory concentration (%) | End-tidal concentration (%) | Estimated jugular bulb concentration (%) |
|----------------------|-------------------------------|-----------------------------|-----------------------------------------|
| 60 min after induction | 3% sevoflurane 60 3.0 ± 0.0 | 2.7 ± 0.1 | 1.7 ± 0.0 |
|                      | 5% sevoflurane 60 5.0 ± 0.0 | 4.2 ± 0.1 | 2.7 ± 0.1 |

Data are presented as the mean ± standard deviation.

Time is presented in minutes after induction was started and in seconds for time to loss of consciousness.

The estimated jugular bulb concentrations of sevoflurane were calculated using the ratios of jugular bulb over end-tidal concentrations in our previous pharmacokinetic study of sevoflurane uptake.(7)

* and #, P value < 0.001.

**Discussion**

By using AAI monitoring, we demonstrated that, relative to patients receiving inspiratory 5% or 3% sevoflurane, those receiving inspiratory 6% sevoflurane had a shorter time to loss of consciousness with comparable AAI values and a shorter time required to reach the target AAI values under mechanical ventilation but higher end-tidal concentrations at the same end-point AAI values. The estimated jugular bulb concentrations were similar between the 6% and 5% groups at the same AAI levels. These findings indicate that alveolar concentration may overestimate anaesthesia depth because of a notable gap between end-tidal and brain concentrations during rapid wash-in of a higher concentration of sevoflurane.

The minimum alveolar concentration (MAC) required to prevent movement in response to surgical incision in 50% of patients has been used as an indicator of anaesthesia depth of inhalational anaesthetics for decades.(16) This value is derived from a steady end-tidal concentration representing the arterial and brain concentrations of the anaesthesia. Lu et al.(7) demonstrated that the ratio of arterial/end-tidal concentration of sevoflurane remained at 0.63 after 30 min of mechanical ventilation with inspiratory 3.5% sevoflurane. They also revealed that a higher inspiratory concentration of isoflurane could accelerate its brain uptake.(8) Equilibrium between arterial and jugular bulb concentrations was achieved after 40 min for inspiratory 2% isoflurane and 50 min for 1% isoflurane.(8) The arterial and jugular bulb concentrations in the 2% isoflurane group were approximately double those of the 1% isoflurane group.(8) In the current study, a similar pharmacokinetic phenomenon was observed in estimated jugular bulb concentrations at 30 min (2.8% vs. 1.4%) between the 6% and 3% sevoflurane groups. As expected, the time to loss of consciousness and the time required to achieving the target AAI values were shorter in the 6% sevoflurane group. Theoretically, the clinical MAC values calculated using end-tidal concentrations should be similar at the same target AAI levels regardless of whether inspiratory 5% or 6% sevoflurane is used. However, the actual end-tidal concentrations were higher in the 6% group at
the same AAI values: ≤20, ≤10, and at the start of burst suppression. The estimated jugular bulb concentrations were similar at the same end points of AAI values between the 6% and 5% sevoflurane groups, which is consistent with our previous observations regarding the pharmacokinetics of sevoflurane uptake.(7) This finding indicates a lag in the time required to achieve transition of anaesthesia across the alveolar membrane and blood–brain barrier,(17) which is determined by various blood/gas and brain/blood partition coefficients of inhalational anaesthetics.(18) The MAC value might be overestimated as a result of higher end-tidal concentration during wash-in with a higher inspiratory concentration of anaesthetics, which may result in de facto inadequate anaesthesia depth under surgical stimulation.

A composite AEP index incorporating EEG has been used as an indicator for anaesthesia depth according to dose(2) and in relation to age,(3) which is a more discriminant predictor of different clinical states of general anaesthesia.(19) However, some studies have failed to observe a graded response with steady-state end-tidal concentrations of sevoflurane, neither decreasing from 2–1.5% and 1% in adults(20) nor increasing from 1.5–2% and 2.5% in infants and children.(21) The so-called steady-state is based on the constant administration of an end-tidal concentration of sevoflurane for 11 min(20) and was calculated using the Gas Man Anesthesia Simulator programme for equilibration of partial pressures between the brain and the lungs.(22) Our previous pharmacokinetic study, which employed blood sampling for sevoflurane concentration analysis, demonstrated that the time required to achieve equilibration between arterial and jugular bulb concentrations (no further brain uptake) was 38.5 min following mechanical ventilation with inspiratory 3.5% sevoflurane, and a near constant end-tidal concentration was achieved after 30 min of ventilation.(7) Therefore, the early change in end-tidal concentrations during wash-in or wash-out may not accurately reflect the true brain uptake and anaesthesia depth. The application of EEG processing could facilitate the adjustment of anaesthesia depth during the wash-in or wash-out periods.

The AAI values in the 3% sevoflurane group did not decrease to less than 10 during 60 min of ventilation despite the ultimate end-tidal concentration being 2.7%. Young male patients were recruited for this study to reduce the impact of interindividual comorbidities and age- or sex-related variability on MAC values. (23) One MAC of sevoflurane is 1.8% at the age of 40 years, with an approximate decrease of 6% every decade.(23) Women appear to have the same MAC as men.(24) However, AAI values were reported to be severely attenuated or reach a value of 0 under a 2% steady-state end-tidal concentration of sevoflurane in women aged 20–60 years.(25)

Two limitations of the current study should be addressed. First, all 30 patients were young male patients aged 20–25 years. The small sample size and the inclusion of only young men in this observational study may have limited the clinical application of the findings; future research could include a more diverse sample. Second, AAI values only indicated the sedation levels before surgery in our patients and not the clinical anaesthesia depth during surgery. Possible confounding factors that could interfere with EEG processing were excluded, such as surgical stimulation, noisy environment, hypoglycaemia, cerebral ischaemia, and neurological disorders,(1) and intravenous benzodiazepine and propofol.
In conclusion, we demonstrated that patients receiving a higher sevoflurane concentration had a shorter time to loss of consciousness with comparable AAI values and had higher end-tidal concentrations of sevoflurane at the same end-point AAI levels. Their estimated jugular bulb concentrations were also similar at the same AAI levels. Anaesthesia depth, calculated according to alveolar concentration, may be overestimated during the rapid wash-in of inhalation anaesthesia. This discrepancy between alveolar and brain concentrations at the same AAI values of anaesthesia should be considered by practitioners.

List Of Abbreviations

AAI, A-line Autoregressive Index
AEP, auditory evoked potential
EEG, electroencephalogram
MAC, minimum alveolar concentration

Declarations

Ethics approval and consent to participate
Yes, see “Methods” section.

Consent for publication
Yes, see “Methods” section

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interest.

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CRediT author statement
CHH: Methodology, investigation, and writing (original draft preparation)

STH: Conceptualisation, methodology, and writing (reviewing and editing)

CCL: Conceptualisation, investigation, and writing (reviewing and editing)

JOW: Formal analysis and writing (reviewing and editing)

TCY: Formal analysis and writing (original draft preparation)

TCL: Data curation, formal analysis, and writing (reviewing and editing)

All listed authors contributed to the planning of the study, analysis of the data, and drafting of the manuscript or critical revisions and have approved the final version of the manuscript.

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**Figures**

![Figure 1](image-url)

**Figure 1**

Inspiratory (Ci) and end-tidal (Ce) concentrations of inspiratory 3%, 5%, or 6% sevoflurane following loss of consciousness (LOC) during administration of general anesthesia.
Figure 2

At the same target A-Line Autoregressive Index (AAI) levels, the inspiratory (Ci) 6% sevoflurane group had a higher end-tidal concentration than did the 5% sevoflurane group, whereas the estimated jugular bulb concentrations were comparable in both groups.

Supplementary Files

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