

Awakening arterial blood and end-tidal concentrations of isoflurane in female surgical patients

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Abstract

Delayed extubation occurs after isoflurane anesthesia, especially following prolonged surgical duration. We aimed to determine the arterial blood concentrations of isoflurane and the correlation with end-tidal concentrations for predicting emergence from general anesthesia.

Thirty-four American Society of Anesthesiologists physical status class I–II gynecologic patients were included. General anesthesia was maintained with a fixed 2% inspiratory isoflurane in 6L/minute oxygen, which was discontinued after surgery. One milliliter of arterial blood was obtained for the determination of isoflurane concentration by gas chromatography at 20 and 10 minutes before and 0, 5, 10, 15, and 20 minutes after discontinuation, in addition to the time of eye opening to verbal command, defined as awakening. Inspiratory and end-tidal concentrations were simultaneously detected by an infrared analyzer.

The mean awakening arterial blood concentration of isoflurane was 0.20%, which was lower than the simultaneous end-tidal concentration 0.23%. The differences between arterial and end-tidal concentrations during emergence fell into an acceptable range (± 1.96 standard deviation). After receiving a mean time of 108-minute general anesthesia, the time to eye opening after discontinuing isoflurane was 18.5 minutes (range 11–30, median 18 minutes), without statistical significance with anesthesia duration ($P=0.078$) and body mass index ($P=0.170$).

We demonstrated the awakening arterial blood concentration of isoflurane in female patients as 0.20%. With well-assisted ventilation, the end-tidal concentration could be an indicator for the arterial blood concentration to predict emergence from shorter duration of isoflurane anesthesia.

Abbreviation: MAC = minimal alveolar concentration.

Keywords: arterial blood, awakening, concentration, inhalation anesthetics, isoflurane

1. Introduction

Isoflurane has been clinically used for 4 decades.^[1] Among the inhaled anesthetics, the cost of isoflurane is much lower than that

of sevoflurane (as 1/10) or desflurane (as 1/25).^[2] Low flow anesthesia with isoflurane provides an additional strategy to reduce costs.^[3] However, delayed extubation time has been a disadvantage of isoflurane in clinical practice,^[4] especially among neurosurgical patients needing a perioperative wake-up test or postoperative early recognition of any neurological deficits.^[5] Therefore, earlier discontinuation of isoflurane and close inspection of end-tidal concentrations are practical occurrences after isoflurane anesthesia.

The pharmacokinetics of isoflurane uptake into the arterial blood^[6] and brain^[7] reveals the inequality between arterial blood and end-tidal concentrations, due to its higher blood-gas partition coefficient (the ratio of dissolved amount in blood over the amount in contact alveolar gas) of 1.4.^[8] As a result, a certain time period is needed after initiation of isoflurane anesthesia to: cross the alveolar membrane, enter into the blood and brain, and achieve the minimal alveolar concentration (MAC), as 1.15% for isoflurane,^[9] to prevent movement in 50% patients in response to surgical stimulus. Similarly, elimination of isoflurane,^[10] sevoflurane,^[11] and desflurane^[12] from circulation blood into the lungs is known to be time-dependent.

The measurement of MAC by end-tidal concentrations provides real-time feedback and facilitates target controlled titration of inhaled anesthetics,^[9] assuming that the end-tidal concentration accurately reflects alveolar and arterial concentrations. The MAC-awake values of isoflurane are 0.32 to 0.36 MAC,^[13] at which 50% of patients remain unresponsive to verbal commands. Nevertheless, the reported eye-opening

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end-tidal concentrations of isoflurane fluctuates between 0.18%,^[14] 0.30%,^[15] and 0.41%.^[16] Ideally, detecting the actual brain or alternative arterial blood concentrations of an inhaled anesthetic is advantageous to ensure awakening in a smooth manner. However, these data are currently only available for desflurane^[17] and sevoflurane^[18] but not for isoflurane. The present study was designed to determine the arterial blood concentrations of isoflurane at awakening as well as to clarify the reliability of the end-tidal concentration for representing the arterial blood concentration during emergence from various durations of isoflurane anesthesia in gynecologic patients.

2. Methods

2.1. Patients

After obtaining the approval of Tri-Service General Hospital Institutional Review Board (TSGHIRB 097-05-189) and written informed consents, 34 American Society of Anesthesiologists physical status class I-II patients scheduled for elective gynecologic surgery under general anesthesia were enrolled from March 2010 to March 2011. Those with severe cardiopulmonary diseases, neuropathy, or receiving regular hypnotics or sedatives were excluded.

2.2. Anesthetic management and gas monitoring

In the operating room, a 20-gauge catheter was placed into the left radial artery for arterial blood sampling after premedication with intravenous fentanyl 100 µg and subcutaneous 2% lidocaine 0.5 mL. General anesthesia was induced with thiamylal 5 mg/kg, and succinylcholine 1.5 mg/kg for tracheal intubation. Anesthesia was maintained with cis-atracurium 0.1 mg/kg and a fixed inspiratory 2% isoflurane in 6 L/minute oxygen during the whole procedure. Nitrous oxide was not used. Fentanyl 25 or 50 µg was titrated to meet the patient's need for surgical stimulus beyond isoflurane administration. A Datex-Ohmeda Aestiva/5 anesthetic machine (Datex-Ohmeda, Madison, WI) was used with soda lime (the CO₂ absorber). We set the respiratory rate at 10 breaths/minute and adjusted the tidal volume to keep end-tidal CO₂ concentration between 38 and 42 mmHg. The sampled gases (approximately 210 mL/minute) were redirected into the circuit. Both inspiratory and end-tidal concentrations of isoflurane were detected by an infrared multigas analyzer (Datex-Ohmeda S/5 Anesthesia System; Datex-Ohmeda, Helsinki, Finland), calibrated according to the manufacturer's recommendations. A Jacket probe of the minimally invasive HemoSonic 100 monitor (Arrow International, Reading, PA) was inserted into each patient's esophagus after intubation to determine cardiac output by means of M-mode and pulsed Doppler ultrasound. Hypotension, defined as a decrease in blood pressure by 25% from baseline, was treated with intravenous fluid and/or ephedrine (5 mg bolus). After the operation was finished, the vaporizer was turned off, with 6 L/minute oxygen for fresh gas flow, and neostigmine 2 mg, as well as glycopyrrolate 0.4 mg, was administered intravenously to reverse the neuromuscular blockade. With manually assisted ventilation after reversal of spontaneous breathing, the end-tidal CO₂ was maintained between 38 and 42 mmHg during emergence in a quiet environment without any other stimulation. Awakening was defined as eye opening to verbal command and was tested every 30 seconds after discontinuing isoflurane until appropriate response. Extubation was accomplished after brief endotracheal

suction. The time from discontinuing isoflurane to awakening and duration of anesthesia was recorded. The data of inspiratory and end-tidal concentrations of isoflurane, end-tidal CO₂, heart rate, and blood pressure were recorded every 30 seconds by the commercial software (Datex-Ohmeda S/5 Collect; Datex-Ohmeda, Madison, WI) during the whole procedure.

2.3. Determination of arterial blood concentrations of isoflurane during elimination

At the end of surgery, each 1 mL arterial blood was obtained with a heparinized syringe at 20, 10 minutes and just prior to discontinuation of isoflurane administration (time zero), and then 5, 10, 15, and 20 minutes during emergence, and upon awakening (when the patient was able to obey the verbal command to open her eyes). Each blood sample was immediately injected into a tightly sealed 10-mL glass vial, stored at a 0 °C refrigerator, and measured within 24 hours. All blood samples were analyzed for isoflurane concentration using gas chromatography.

2.4. Determination of blood isoflurane concentration

Before induction, 10 mL arterial blood without isoflurane was collected to determine each patient's blood-gas partition coefficient (λ) of isoflurane.^[19] Isoflurane in each blood sample was converted to the corresponding concentration, based on gas chromatographic measurements and blood-gas partition coefficient of isoflurane (λ) measured in each patient.

2.5. Gas chromatography conditions

The HP 6890 series gas chromatography system (Hewlett-Packard, Wilmington, DE) consisted of a headspace sampler (Agilent G1888), an oven, a flame-ionization detector, and an integrator. The oven temperature was set at 40 °C, increased at a rate of 25 °C per minute to 200 °C, and kept at this level for 2.6 minutes. Both the injection and detection temperature were set at 250 °C. The inlet pressure was set at up to 349 kPa. Injection was performed in the direct injection mode. The carrier gas (helium) flow was 25.0 mL/minute. Separation was achieved via a capillary column (HP-5; 30.0 m*0.32 mm ID, 0.25 µm film thickness) (Restek, Bellefonte, PA). An integrator and a data acquisition system were provided by HP CHEMOSTATION software.

2.6. Calibration curve for measuring blood isoflurane concentration

A standard of liquid isoflurane was incubated in a water bath at 20 °C for 1 hour prior to use. Five known amounts of isoflurane liquid were taken up by using a microsyringe (Hamilton 0.5 µL syringe; No. 86259) and injected into 5 10-mL glass vials (containing 1 mL of blank blood from each patient) at 20 °C. Blood samples were analyzed with a gas chromatograph, a headspace sampler, and a flame-ionization detector. A linear relationship was observed between the signals for the peak height of isoflurane (y-axis) and the isoflurane concentration (x-axis), revealing an excellent correlation between the signal and isoflurane concentration, with a correlation range of 0.9991 to 0.9998. The analytical range of the isoflurane concentration was 0.01% to 3.28%. The concentration of isoflurane in the blood phase was calculated from the calibration curve of a known amount of isoflurane. The concentration of isoflurane in the gas

Table 1**Patient data (n=34).**

	Mean (SD)	Range	Median
Age, years	43.1 (9.3)	23–60	42.5
Weight, kg	58.9 (9.2)	50–87	57.5
Height, cm	159.0 (4.8)	150–166	159
Body mass index, kg/m ²	23.2 (3.2)	18.9–34.4	22.68
Fentanyl, µg/kg	2.3 (0.9)	1.4–4.8	1.923
Duration, minute	108.0 (43.1)	62–245	93.5
Time to eye opening, minute	18.5 (4.4)	11–30	18

SD=standard deviation.

phase was obtained by direct comparison to that in the blood phase. The coefficients of variation of the intraday accuracy and precision of isoflurane detection were 2.8% and 3.4%, respectively.

2.7. Statistics

Mean, range (minimum–maximum), and median (time to eye opening) were used to describe patients' characteristics. Clinical parameters were presented as mean (standard deviation [SD]) over time. Bivariate relationships between variables were analyzed by simple linear regressions and Pearson correlations. Moreover, the Bland–Altman agreement analysis was used to determine the degree of agreement between the awakening arterial blood and end-tidal concentrations by MedCalc[®] statistical software (Version 12.2.1.0). A *P* value < 0.05 was considered statistically significant.

3. Results

Demographic data of 34 patients and anesthetics are shown in Table 1. The time to eye opening was 18.5 (4.4) minutes (range 11–30, median 18 minutes), with 95% confidence interval (CI) 16.9 to 20.1 minutes.

Table 2 shows the arterial blood, inspiratory, and end-tidal concentrations of isoflurane during elimination phase. The

arterial concentration was 0.84 (0.08)%, with 95% CI 0.81% to 0.87%, at discontinuation of isoflurane and decreased to 0.20 (0.05)%, with 95% CI 0.18% to 0.21%, at awakening, which were lower than the end-tidal concentrations, 1.48 (0.09)% (as 1.29 MAC, with 95% CI [1.45%–1.51%]) at discontinuation and 0.23 (0.06)% (as 0.20 MAC, with 95% CI [0.21%–0.25%]) at awakening, respectively. The mean arterial and end-tidal concentrations were both 0.19% at 20 minutes after discontinuation. The hemodynamic and ventilatory variables were within 25% of baseline without significant differences during the period of study (Table 3).

As shown in Fig. 1, the arterial concentrations before discontinuing isoflurane and at awakening, as well as awakening end-tidal concentration, were not significantly correlated with duration of general anesthesia (62–245 minutes), *P*=0.354, 0.376, and 0.132, respectively. The contributing factors for prolonged emergence were further analyzed. There were increasing trends by anesthesia duration (from 62 to 245 minutes) and body mass index (range 18.9–34.4, with 95% CI [22.1, 24.3]), however, without statistical significance (*P*=0.078 and 0.170, respectively). Likewise, awakening time was not correlated with total fentanyl dose (*P*=0.487).

The Bland–Altman plot (Fig. 2) displayed the differences between the arterial concentrations and end-tidal concentrations at 15 minutes and at awakening. The differences between 2 awakening concentrations ranged from –0.05 to 0.07, with mean –0.04 (0.04)%, and fell into acceptable range (± 1.96 SD), regardless of the length of awakening time.

4. Discussion

This study first quantitatively measured the awakening arterial blood concentration of isoflurane as 0.20% and its simultaneous end-tidal concentration as 0.23% in gynecologic surgical patients. With well-assisted ventilation, the isoflurane end-tidal concentration could be an indicator of arterial concentration in order to predict emergence from mean 108-minute isoflurane anesthesia.

Table 2**The arterial blood, inspiratory, and end-tidal concentrations of isoflurane during emergence from general anesthesia in gynecologic patients (n=34).**

Time, minute	–20	–10	0	5	10	15	Eye opening	20
Arterial blood concentration	0.82 (0.08)	0.81 (0.09)	0.84 (0.08)	0.39 (0.06)	0.29 (0.06)	0.23 (0.05)	0.20 (0.05)	0.19 (0.05)
Inspiratory concentration	1.99 (0.02)	1.98 (0.06)	1.99 (0.05)	0.00	0.00			
End-tidal concentration	1.47 (0.08)	1.47 (0.10)	1.48 (0.09)	0.48 (0.08)	0.35 (0.06)	0.27 (0.06)	0.23 (0.06)	0.19 (0.10)

Values were presented as mean (standard deviation [SD]). The mean time to eye opening was 18.5 (4.4) minutes. 0 minute, just prior to discontinuation of 2% isoflurane.

Table 3**Hemodynamic and ventilatory variables during emergence (n=34).**

Time	–20	–10	0	5	10	15	Eye opening	20
HR	76 (13.9)	76 (13.7)	77 (12.4)	84 (13.6)	88 (20.3)	84 (18.8)	91 (19.4)	81 (14.7)
MAP	79.2 (12.1)	77.0 (10.4)	74.0 (10.0)	90.8 (14.9)	96.8 (14.8)	96.0 (15.3)	99.6 (17.1)	91.3 (27.7)
CO	6.1 (1.5)	6.0 (1.3)	5.8 (1.5)	6.1 (1.4)	5.5 (1.5)	5.8 (1.8)	6.0 (1.7)	6.0 (1.8)
CI	3.7 (1.1)	3.7 (0.8)	3.6 (0.9)	3.8 (0.8)	3.5 (0.9)	3.6 (1.1)	3.7 (1.1)	3.8 (1.2)
TPR	1112 (285)	1138 (249)	1131 (292)	1304 (330)	1570 (528)	1529 (545)	1578 (660)	1514 (557)
ETCO ₂	39.0 (1.8)	39.6 (1.8)	39.5 (1.8)	39.3 (2.3)	39.4 (2.8)	39.8 (4.2)	39.5 (5.9)	38.9 (9.1)

Values were presented as mean (SD). The mean time to eye opening was 18.5 (4.4) minutes. CI=cardiac index, CO=cardiac output, ETCO₂=end-tidal CO₂, HR=heart rate, MAP=mean arterial blood pressure, SD=standard deviation, TPR=total peripheral resistance.

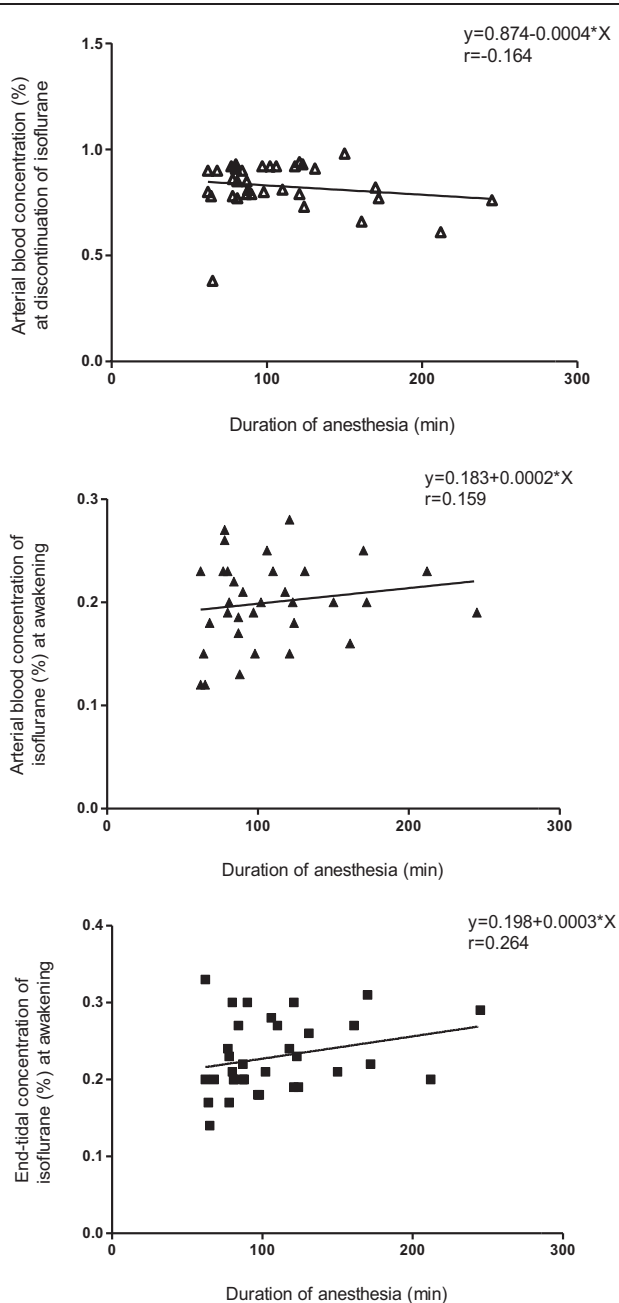


Figure 1. The arterial concentrations before discontinuing 2% isoflurane (upper) and at awakening (middle), as well as awakening end-tidal concentration (lower), were not correlated with duration of general anesthesia (62–245 minutes), $P=0.354$, 0.376 , and 0.132 , respectively, which indicated limited blood uptake of isoflurane within 4 hours and similar awakening concentrations.

The blood/gas and tissue/blood partition coefficients of inhalational anesthetics are important determinants of the rates of washin for induction, total body uptake, and washout for emergence from anesthesia.^[8] Isoflurane anesthesia tends to have a prolonged extubation time in comparison to sevoflurane at 13% and desflurane at 34%,^[4] in accordance with the blood/gas partition coefficient 1.4 for isoflurane,^[8] 0.69 for sevoflurane,^[20] and 0.42 for desflurane.^[8] The total body uptake and elimination period of isoflurane are supposed to be proportional to the administered concentrations and duration of general anesthesia according to computer simulation.^[21] In this study, the

awakening time was 18.5 minutes after discontinuing 1.29 MAC isoflurane, which was longer than 15.5 minutes in pediatric neurosurgical patients receiving maintained 0.9 to 1.0 MAC isoflurane.^[5] Furthermore, the actual arterial blood concentration of isoflurane was 1.18% at the end of mean 330-minute cardiac surgery in our previous 20-minute pharmacokinetic study,^[10] which was higher than 0.84% in this mean 108-minute study. Based on the awakening arterial concentration as 0.20% in this study, the estimated awakening time among the previous cardiac patients could be 35.6 minutes by using the extrapolated slopes of arterial concentrations from 0.57% at 15 minutes to 0.48% at 20 minutes.^[10] Beyond expectation, the awakening time among patients in the present study was not significantly correlated with anesthesia duration. The relatively shorter duration of anesthesia (mean of 108 minutes) and limited BMI ranges (95% confidence interval, 22.1–24.3) may have diminished the ranges of total body uptake. A population with more varied BMI ranges and prolonged anesthesia duration as seen in clinical practice might demonstrate a significant duration effect.

During elimination, isoflurane washout commences from the brain and periphery into the alveolar space via the circulating blood allowing the lungs to ventilate it into the air. Predicting awakening by the end-tidal concentrations depends on the rate-limiting equilibrium between cerebral-to-arterial and arterial-to-end-tidal anesthetic differences.^[22] Katoh et al^[22] demonstrated the MAC-awake value of isoflurane was 0.31 MAC following slow alveolar washout which was significantly higher than 0.22 MAC obtained by fast alveolar washout. Slow alveolar washout was conducted by decreasing anesthetic concentrations in predetermined steps of 15 minutes to allow equilibration between the brain, arterial, and alveolar partial pressures, while fast washout was obtained after directly discontinuing inhaled anesthetics.^[22] By examining the arterial concentrations before and after discontinuation in our previous studies,^[10–12] we could clarify the actual arterial-to-end-tidal differences during elimination. The rapid reduction of the end-tidal, but not arterial concentrations in the initial 5 minutes, reflects fast washout of anesthetics from functional residual capacity of lungs, while the later 15-minute slow component is dominated by the tangible manifestation of physiological membrane barriers, including the existence of alveoli-pulmonary capillary and blood-brain barriers.^[10–12] Consequently, the eye-opening end-tidal concentrations are 0.18%^[14] and 0.30%^[15] after fast alveolar washout, but 0.41% after slow alveolar washout. The decrement of inhaled concentrations and alveolar ventilation during elimination will alter the arterial-to-end-tidal difference which should be taken into consideration while using the end-tidal concentration to predict awakening after isoflurane anesthesia.

4.1. Limitations

There are 3 limitations in the current study. First, all of our patients are female. Women generally report greater sensitivity to pain than do men and healthy young women require 20% more anesthetic than healthy age-matched men to prevent movement in response to noxious electrical stimulation.^[23] Early extubation and eye-opening time are significantly shorter in male patients compared with female patients after receiving sevoflurane or desflurane.^[24] The impact of gender on recovery from isoflurane anesthesia, including awakening arterial concentration, needs further investigation. Second limitation is using excessive fresh gas. The fresh gas flow of 6L/minute 100% oxygen during maintenance in this study is usually excessive for clinical practice,

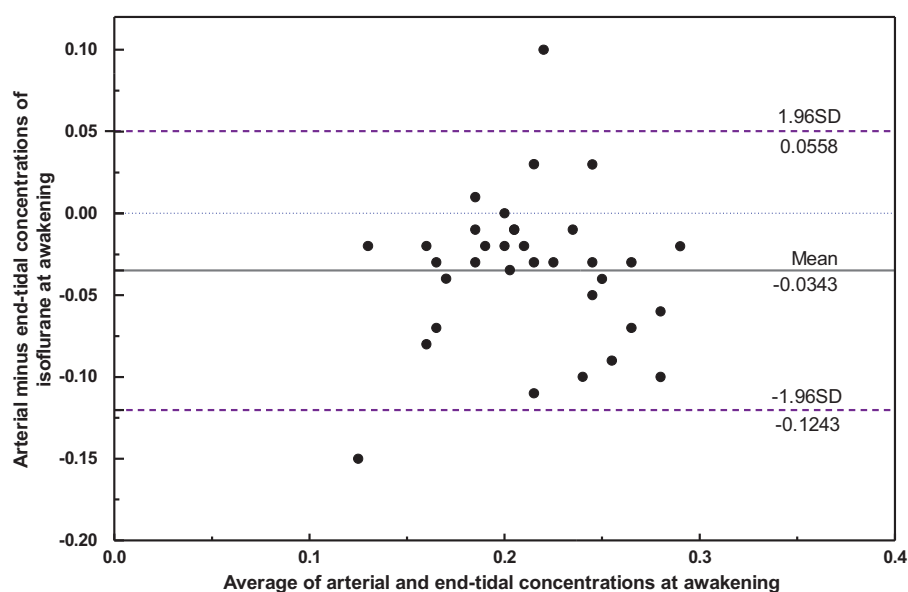


Figure 2. The Bland–Altman plot displayed the differences between awakening arterial blood and end-tidal concentrations of isoflurane plotted against the average of the 2 concentrations. The differences ranged mostly within ± 1.96 standard deviation (SD) range.

resulting in cost waste and air pollution.^[2] Reducing anesthetic fresh gas flows can diminish inhaled anesthetic consumption without affecting drug delivery to the patient.^[2,5] However, according to our clinical observation, the inspiratory and end-tidal concentrations detected by the analyzer are usually lower than the administrated vaporizer concentration if the fresh gas flow is lower than 4L/minute. To keep the administration of isoflurane constant and its accurate detection in this study, consistent higher fresh gas flow (6L/minute) was used to provide reliable body uptake and arterial blood concentrations during the entire procedure. Third limitation is that we manually assisted the ventilation after reversal of spontaneous breathing during emergence in order to keep the end-tidal CO₂ within 38 to 42 mmHg before extubation as possible for steady minute ventilation and cardiac index. The Bland–Altman plot demonstrated the awakening end-tidal concentration could be an indicator for the actual arterial concentration in this study, however, with more fluctuation in the end-tidal concentrations. By investigating both arterial blood and end-tidal concentrations, the clinical influence of minute ventilation and cardiac output could be further clarified during elimination of inhaled anesthetics.

In conclusion, this is the first demonstration of awakening arterial concentration of isoflurane in female surgical patients and the end-tidal concentrations during emergence were correlated with their simultaneous arterial concentrations after shorter duration of isoflurane anesthesia. The end-tidal concentrations could be an indicator for predicting awakening time during wake-up test or postoperative emergence in neurosurgical patients.

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