

Duration effect of desflurane anesthesia and its awakening time and arterial concentration in gynecologic patients

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OBJECTIVES: To determine the awakening arterial blood concentration of desflurane and its relationship with the end-tidal concentration during emergence from various durations of general anesthesia.

METHOD: In total, 42 American Society of Anesthesiologists physical status class I-II female patients undergoing elective gynecologic surgery were enrolled. General anesthesia was maintained with fixed 6% inspiratory desflurane in 6 l min⁻¹ oxygen until shutoff of the vaporizer at the end of surgery. One milliliter of arterial blood was obtained for desflurane concentration determination by gas chromatography at 20 and 10 minutes before and 0, 5, 10, 15, and 20 minutes after the discontinuation of desflurane and at the time of eye opening upon verbal command, defined as awakening. Concentrations of inspiratory and end-tidal desflurane were simultaneously detected by an infrared analyzer.

RESULTS: The mean arterial blood concentration of desflurane was 1.20% at awakening, which correlated with the awakening end-tidal concentration of 0.96%. The mean time from the discontinuation of desflurane to eye opening was 5.2 minutes (SD = 1.6, range 3-10), which was not associated with the duration of anesthesia (60-256 minutes), total fentanyl dose, or body mass index (BMI).

CONCLUSIONS: The mean awakening arterial blood concentration of desflurane was 1.20%. The time to awakening was independent of anesthetic duration within four hours. Using well-assisted ventilation, the end-tidal concentration of desflurane was proven to represent the arterial blood concentration during elimination and could be a clinically feasible predictor of emergence from general anesthesia.

KEYWORDS: Desflurane; Arterial Blood; End-Tidal; Awakening.

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■ INTRODUCTION

Desflurane has been clinically used in anesthesia for two decades (1). The major advantages include rapid induction and recovery (2,3), lower cost (4), and myocardial protection during cardiac surgery (5). Due to its lower blood-gas partition coefficient (0.42), the ratio of the dissolved amount in the blood to the amount in the alveolar gas in contact with the blood, desflurane has been clearly proven to provide a shorter time to extubation compared with sevoflurane (20% reduction) (2)

and isoflurane (34% reduction) (3), especially in those individuals undergoing prolonged surgical procedures (4,6).

Growing evidence (7-12) indicates that a certain time period is needed for inhaled anesthetics to cross the alveolar membrane and enter the body and brain in the beginning of general anesthesia in order to achieve the minimal alveolar concentration (MAC), the point at which no movement is observed in 50% of patients in response to a surgical stimulus. Similarly, elimination of the inhaled anesthetics from the blood to the lungs during emergence is time-dependent (13). Clinically, the end-tidal concentration has been a feasible predictor of awakening from general anesthesia (14). However, irregular respiration during emergence usually results in the fluctuation of end-tidal concentrations of inhaled anesthetics (15). The arterial blood concentration provides a steadier, more reliable representation of the anesthetic concentration in the brain. Thus, we hypothesized that desflurane, with its low coefficient, would not accumulate in

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**Table 1 - Characteristics of patients (N=42).**

Characteristics	Mean (SD)	Range	Median
Age, years	40.8 (9.7)	24-57	41.0
Weight, kg	61.0 (10.1)	45-85	59.5
Height, cm	161.0 (6.0)	148-174	161.0
Body mass index, kg m ⁻²	23.5 (3.6)	17.6-32.0	23.0
Fentanyl, mcg kg ⁻¹	2.5 (0.8)	1.4-4.6	2.4
Duration of anesthesia, min	127.9 (44.0)	60-256	122
Time to eye opening, min	5.2 (1.6)	3-10	5

the blood and delay emergence after a prolonged duration of general anesthesia. In addition, due to the rapid elimination of desflurane, the end-tidal concentration could reflect the arterial blood concentration during well-assisted ventilation and be used to predict awakening during emergence.

The primary aim of this study was to examine the arterial blood concentration of desflurane during emergence and the time to awakening after various durations of general anesthesia. The secondary aim was to examine the validity of the noninvasively determined end-tidal concentration of desflurane as a reliable indicator of the arterial blood concentration.

MATERIALS AND METHODS

Patients

After obtaining approval of Institutional Review Board (TSGHIRB-097-05-189) and written informed consent, 42 ASA I or II 20- to 60-year-old gynecologic patients scheduled for elective surgery under general anesthesia were included. Patients with severe cardiopulmonary diseases, irritable airways, such as ongoing asthma or acute upper respiratory infection, hepatic diseases (16), neuropathy, or regular hypnotic or sedative use were excluded.

Anesthetic management and gas monitoring

In the operating room, after premedication with 100 mcg intravenous fentanyl and 0.5 ml subcutaneous 2% lidocaine,

a 20-gauge catheter was placed into the left radial artery for blood sampling. General anesthesia was induced with 1.5 mg kg⁻¹ propofol, and 1.5 mg kg⁻¹ succinylcholine was administered for endotracheal intubation. We maintained anesthesia with 0.1 mg kg⁻¹ cis-atracurium and 6% fixed inspiratory desflurane in 6 l min⁻¹ oxygen during the entire procedure. Nitrous oxide was not used. Fentanyl, 25 or 50 mcg, was titrated to meet the patients' pain responses beyond desflurane administration. A Datex-Ohmeda Aestiva/5 anesthetic machine (Datex-Ohmeda, Madison, WI) was used with soda lime (CO₂ absorbent), and the minute ventilation was adjusted to keep the end-tidal CO₂ between 38 and 42 mmHg. The leakage of each system was determined using constant-pressure ventilation with a test lung. The sampled gases (approximately 210 ml min⁻¹) were redirected into the circuit. Both the inspiratory and the end-tidal concentrations of desflurane were detected by an infrared multi-gas analyzer (Datex-Ohmeda S/5 Anesthesia System; Datex-Ohmeda, Helsinki, Finland) that was calibrated according to the manufacturer's recommendations. A Finometer (FMS, Finapres Measurement Systems, Arnhem, Netherlands) was used to determine cardiac output. Hypotension, defined as a 25% decrease in blood pressure from baseline, was treated with intravenous fluid and ephedrine (5 mg bolus). A nasopharyngeal thermometer was used to measure and maintain the body temperature in the range of 36.5-37.5°C. After the operation was completely finished, the vaporizer was turned off, with 6 l min⁻¹ oxygen for fresh gas flow. Next, 2 mg Neostigmine and 0.4 mg glycopyrrolate were administered intravenously to reverse the neuromuscular blockade. The end-tidal CO₂ was maintained between 38 and 42 mmHg with manually assisted ventilation under quiet circumstances, without additional stimulation. Awakening was defined as eye opening upon verbal command and was tested every 30 seconds after the discontinuation of desflurane until the appropriate response. Extubation was accomplished after brief endotracheal suction. The time from the discontinuation of desflurane to awakening and the duration of surgery and

Table 2 - The arterial blood, inspiratory, and end-tidal concentrations of desflurane during emergence from general anesthesia in gynecologic patients (N=42).

Time (min)	-20	-10	0	5	Eye Opening	10	15	20
Arterial concentration	3.91 (0.37)	3.87 (0.35)	3.82 (0.45)	1.17 (0.29)	1.20 (0.30)	0.73 (0.16)	0.57 (0.18)	0.48 (0.17)
Inspiratory concentration	6.01 (0.14)	6.01 (0.12)	5.99 (0.11)	0.01 (0.04)	0.08 (0.13)			
End-tidal concentration	5.62 (0.19)	5.61 (0.18)	5.62 (0.15)	1.02 (0.31)	0.96 (0.32)	0.54 (0.17)	0.43 (0.14)	0.33 (0.15)

The values are presented as means (SD). The mean time to eye opening was 5.2 (1.6) minutes.
0 min: Immediately prior to the discontinuation of 6% desflurane.

Table 3 - Hemodynamic and ventilatory variables during emergence (N=42).

Time	-20	-10	0	5	Eye Opening	10	15	20
HR	71 (14.8)	74 (19.9)	75 (15.5)	110 (21.2)	114 (17.7)	91 (15.0)	82 (14.5)	78 (13.5)
MAP	94.8 (17.1)	97.1 (15.5)	95.5 (16.1)	117.4 (16.2)	119.8 (21.7)	104.2 (16.5)	98.3 (16.3)	102.2 (14.6)
CO	5.4 (1.7)	5.9 (1.6)	5.3 (1.3)	6.0 (1.8)	5.8 (1.9)	5.9 (1.5)	5.6 (1.7)	5.4 (1.6)
CI	2.7 (1.0)	3.1 (0.9)	2.8 (0.7)	3.1 (1.0)	3.1 (1.1)	3.1 (1.0)	3.0 (0.8)	2.7 (0.8)
TPR	1576 (446)	1483 (456)	1518 (448)	1803 (633)	1795 (616)	1619 (546)	1668 (547)	1738 (761)
ETCO ₂	39.1 (3.8)	39.8 (2.7)	39.8 (1.8)	41.2 (6.2)	41.3 (6.7)	40.4 (5.7)	40.1 (6.5)	39.9 (6.9)

The values are presented as means (SD). The mean time to eye opening was 5.2 (1.6) minutes.

HR, heart rate; MAP, mean arterial blood pressure; CO, cardiac output; CI, cardiac index; TPR, total physical response; ETCO₂, end-tidal CO₂.

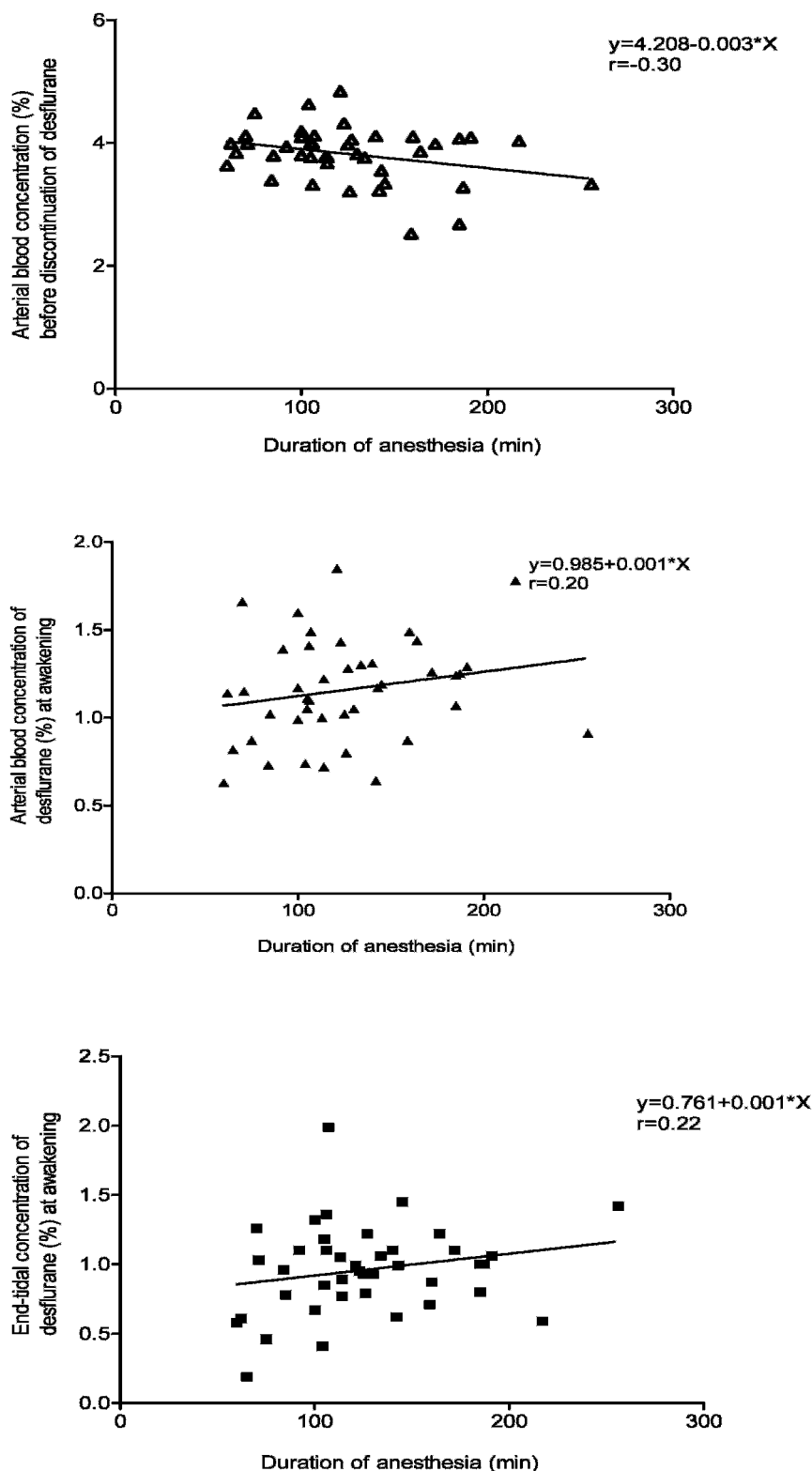


Figure 1 - The correlation between the duration of anesthesia and the arterial concentration of desflurane before discontinuation and at awakening. The arterial concentrations immediately prior to discontinuing 6% desflurane (upper) and at awakening (middle) and the awakening end-tidal concentration (lower) were not correlated with the duration of general anesthesia (60-256 minutes).

anesthesia were recorded. Inspiratory concentration, expired concentration, end-tidal CO_2 , blood pressure, heart rate, and body temperature data were recorded every 30

seconds by commercial software (Datex-Ohmeda S/5 Collect; Datex-Ohmeda, Madison, WI) until 20 minutes after the discontinuation of desflurane.

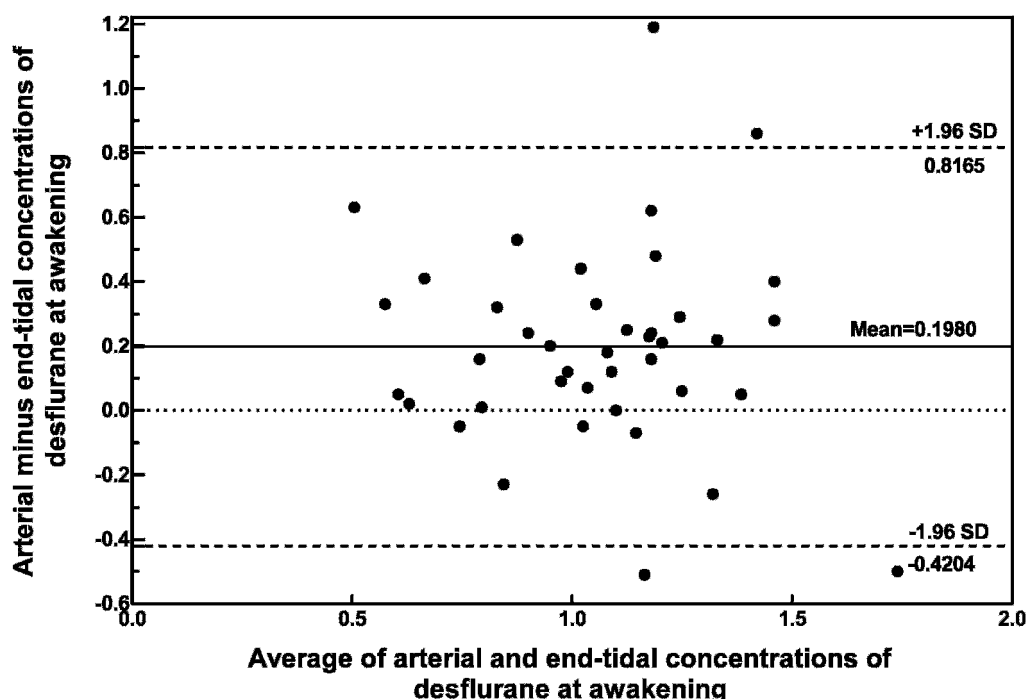


Figure 2 - Bland-Altman plot displaying the difference between the awakening arterial blood and end-tidal concentrations plotted against the average of the two concentrations. The differences were mostly within the ± 1.96 SD range.

Determination of the arterial blood concentration of desflurane during elimination

Prior to induction, 10 ml of blood was collected from each patient to determine the blood-gas partition coefficient (λ) of desflurane (8). In each blood sample, Desflurane was converted to the corresponding concentration, based on gas chromatographic measurements, and the blood-gas partition coefficient of desflurane (λ) was measured.

Gas chromatography conditions

The HP 6890 series GC system (Hewlett-Packard, Wilmington, DE) consists of a headspace sampler (Agilent G1888), an oven, a flame ionization detector, and an integrator. The carrier gas (helium) flow was 25.0 ml min⁻¹. Separation was achieved with a capillary column (HP-5; 30.0 m·0.32 mm ID, 0.25 μ m film thickness) (Restek, Bellefonte, PA). An integrator and a data acquisition system were provided by HP CHEMOSTATION software. The method used to create a calibration curve for measuring the blood desflurane concentration was modified according to a previous publication (8).

Statistical analysis

Means (SD), ranges, and medians (for the time to eye opening) were used to describe the patients' characteristics. Clinical parameters were presented as mean (SD) over time. Bivariate relationships between variables were analyzed by simple linear regressions and Pearson correlations. Moreover, a Bland-Altman agreement analysis was used to determine the degree of agreement between the awakening arterial blood and end-tidal desflurane concentrations at three times to awakening with the aid of MedCalc version 12.2.1.0 (MedCalc Software, Marikereke, Belgium). A p -value < 0.05 was considered statistically significant.

RESULTS

Demographic data and anesthetics are summarized in Table 1. The mean time from the discontinuation of desflurane to eye opening upon verbal command was 5.2 (1.6) minutes (range 3-10, median 5 minutes). In total, 10 mg Ephedrine was administered to each of four patients to lower blood pressure after induction and before surgical incision.

Table 2 lists the arterial blood, inspiratory, and end-tidal concentrations of desflurane before and during emergence. Before the discontinuation of desflurane, the arterial concentration was 3.82 (0.45) %, and the end-tidal concentration was 5.62 (0.15) %. These values decreased to 1.20 (0.30) % and 0.96 (0.32) %, respectively, at awakening. The decrease in the end-tidal concentration was more prominent than the decrease in the arterial concentration in the initial five minutes after discontinuation. The hemodynamic and ventilatory variables during emergence were within 20% of the preoperative baseline, without apparent differences (Table 3).

As shown in Figure 1, the arterial concentrations before discontinuing desflurane and at awakening and the awakening end-tidal concentration were not significantly correlated with the duration of general anesthesia, with p =0.056, 0.197, and 0.177, respectively. Despite a larger scale of variation, the awakening end-tidal concentration (range 0.19-1.99%, with a 95% confidence interval of 0.33-1.59%) significantly represented the arterial concentration at awakening (range 0.63-1.85%, with a 95% confidence interval of 0.58-1.74%) (p =0.001).

The Bland-Altman plot (Figure 2) displays the difference between the arterial and the end-tidal concentrations at awakening plotted against the average of the two concentrations. The difference ranged from -0.51 to 1.19% and fell into an acceptable range (± 1.96 SD), regardless of the length

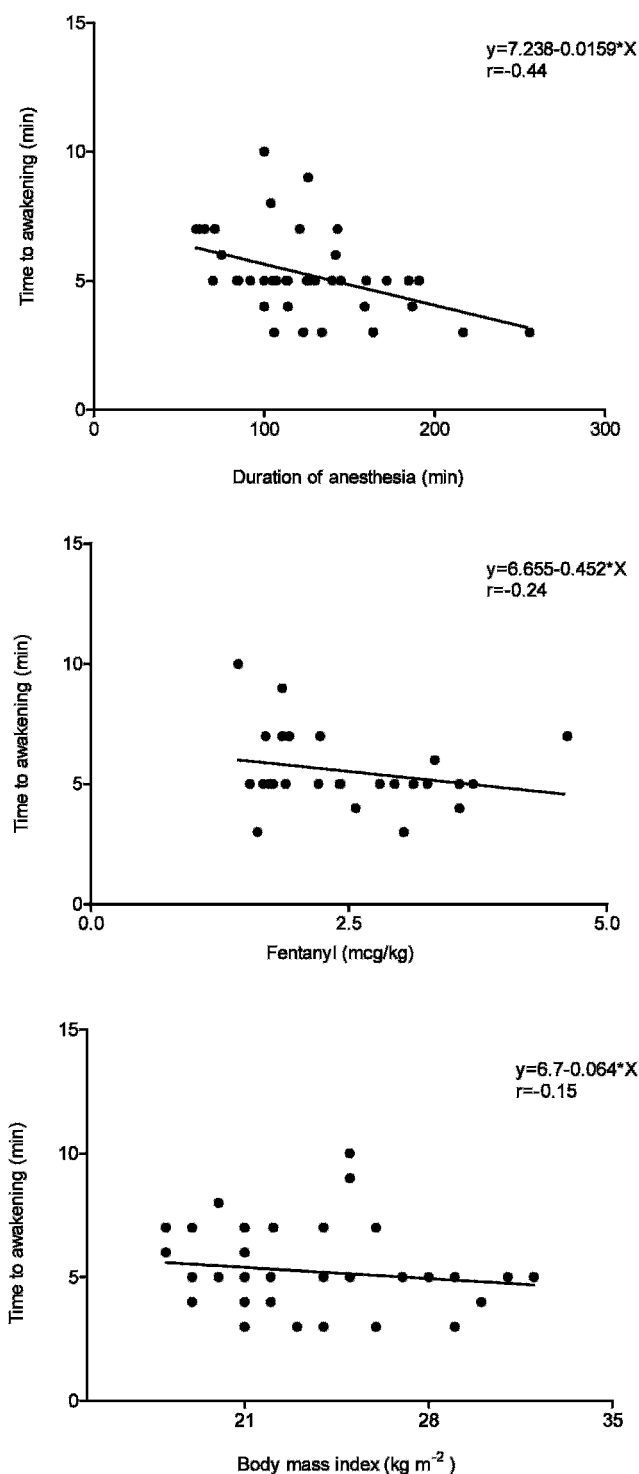


Figure 3 - The time to awakening after discontinuation of 6% desflurane was not prolonged by the duration of anesthesia and was not correlated with the total fentanyl dose or body mass index.

of awakening time. The arterial concentration at awakening was systematically higher than the end-tidal concentration, with a median of 0.2%.

The possible contributing factors upon awakening are also analyzed in Figure 3. The time to awakening was within 3-10 minutes, with a 95% confidence interval of 2.2-8.3 minutes. In

total, 50% of awakening occurred within five minutes, and 90% occurred within seven minutes, which was not prolonged by the duration of anesthesia, ranging from 60-256 minutes, and was not correlated with the total fentanyl dose ($p = 0.232$) or body mass index (BMI) ($p = 0.356$).

DISCUSSION

This is the first study to quantitatively demonstrate an awakening arterial blood concentration of desflurane of 1.20 (0.30) % in gynecologic surgery patients. Increasing the duration of desflurane anesthesia to a maximum of four hours did not elevate the arterial concentration before the discontinuation of desflurane and did not prolong the awakening time. During well-assisted ventilation, the end-tidal concentration of desflurane represents the higher arterial concentration at awakening and provides a feasible predictor of eye opening after a surgical procedure completed within 60-256 minutes.

The total body uptake and elimination of inhaled anesthetics are supposed to be proportional to the duration of general anesthesia (17,18). However, the lower blood-gas and blood-tissue partition coefficients of desflurane theoretically limit total body uptake, facilitating elimination in patients with longer-duration anesthetics and a higher BMI (19,20). Rohm et al. (4) demonstrated that patients undergoing prolonged surgical procedures (>150 min) showed faster recovery and required lower expenditure after a desflurane/fentanyl regimen than a propofol/remifentanyl regimen. Faster recovery following desflurane, compared with isoflurane, may be desirable after long surgical procedures (>5 hours) (6), enabling the patient's full cooperation and facilitating the early diagnosis of any potential neurological deficit. Nordmann et al. (21) also demonstrated that increasing the duration of inhalation anesthesia is associated with slower emergence and recovery in children, but this effect was less evident with desflurane compared with isoflurane. In this study, the arterial blood concentration of desflurane provided convincing evidence for the above findings. The arterial concentration before the discontinuation of desflurane was not correlated with the duration of anesthesia (60-256 min). In addition, the time to awakening mostly ranged between three and seven minutes in 39 of 42 patients and was not proportionally prolonged by the duration of anesthesia, further indicating limited total uptake and rapid alveolar washout during elimination.

The rate of uptake of inhaled anesthetics is dependent on the alveolar concentration and ventilation, blood solubility, and cardiac output (22). During the elimination phase, desflurane washout progresses from the brain and body to the alveolar space via the circulating blood, allowing the lungs to ventilate the anesthetic into the air. The end-tidal CO₂ may depict the status of the minute ventilation and cardiac output. Hypoventilation delays the alveolar washout of inhaled anesthetics. However, higher blood CO₂ levels elevate cardiac output and cerebral blood flow, which reversely accelerate the elimination of desflurane from the brain. Currently, no direct markers are available to adjust the above impact of alveolar washout and cerebral blood flow in clinical practice. Eventually, when the brain or arterial concentration decreases to a certain level, the patient awakens enough to respond to the verbal command for eye opening. By determining arterial blood concentrations, the clinical influence of the minute ventilation and cardiac output on the elimination of inhaled anesthetics can be clarified. In this



study, the minute ventilation and cardiac index of all patients were kept steady before extubation, which revealed a correlation between the awakening arterial blood and end-tidal desflurane concentrations. The end-tidal concentration of desflurane decreased more prominently during the initial five minutes after discontinuation and became persistently lower than the arterial concentration, indicating rapid alveolar washout. Compared with the simultaneous arterial blood level, the end-tidal concentration of desflurane was identified as a feasible predictor of emergence from general anesthesia.

There are certain limitations of the current study. First, the minute ventilation could hardly be controlled by a ventilator after the reversal of spontaneous breathing during emergence. We, therefore, manually assisted the ventilation to maintain the end-tidal CO₂ level between 38 and 42 mmHg before extubation. Despite greater fluctuation, the awakening end-tidal concentration represented the actual arterial concentration in this study. Second, all of our patients were female. Women are generally reported to have greater sensitivity to pain than men, and healthy young women require 20% more anesthetics than do healthy age-matched men to prevent movement in response to noxious electrical stimulation (23). A higher MAC has been reported for desflurane-6.2% for women compared to 6.0% for men-although the difference is insignificant (24). Additionally, a longer eye-opening time after general anesthesia with desflurane has been reported-6.0 (1.3) minutes in female patients and 4.9 (0.9) minutes in male patients ($p<0.001$) (25). Further investigation is needed to verify the gender effect on the awakening arterial blood concentration. Third, the patients received up to four hours of anesthesia, and the maximal BMI was close to 32 kg m⁻². The clinical inferences should be adjusted based on a patient's outlying factors, such as morbid obesity and a more prolonged duration of anesthesia.

In conclusion, we are the first to demonstrate the awakening arterial concentration of desflurane in gynecologic patients. The arterial concentrations before discontinuation and at awakening were not significantly elevated by the increasing duration of desflurane anesthesia (1-4 hours), which was consistent with the rapid awakening time, indicating suitability for a prolonged duration of anesthesia. Using well-assisted ventilation during emergence, the end-tidal concentration of desflurane can be a feasible predictor of awakening from general anesthesia.

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■ AUTHOR CONTRIBUTIONS

Lin TC, Lu CC, and Hsu HC performed this clinical study and drafted the manuscript. Lee MS performed the statistical analysis. Ho ST conceived the study and provided laboratory support to measure the blood desflurane concentration. Wu GJ participated in the study design and coordination. All authors read and approved the final version of the manuscript.

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