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ORIGINAL ARTICLE

Hyperventilation accelerates rise in arterial blood concentrations of sevoflurane in gynecologic patients

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Abstract
Purpose We investigated whether ventilation volumes affected arterial blood sevoflurane concentration (A_{sev}) and its uptake into the body during general anesthesia.
Methods Thirty female patients undergoing elective gynecologic surgery were randomly allocated into three groups: hyperventilation, normal ventilation, and hypoventilation. Inspiratory (CI_{sev}) and end-tidal ($_{sev}$) sevoflurane concentrations were routinely measured by infrared analysis, and A_{sev} were analyzed by gas chromatography for 40 min after intubation. Cardiac index and total peripheral vascular resistance were measured with a Finometer.
Results During the first 10 min after sevoflurane administration, A_{sev} in the hyperventilation group was the highest and differed significantly from those in the normal ventilation group, followed by those in the hypoventilation group. In addition, hyperventilation significantly increased the slope of A_{sev} over time in the first 5 min, but there were no differences in slopes in the 5–10, 10–20, and 20–40 min periods, which indicates no difference in sevoflurane bodily uptake among the three groups after 5 min.
Conclusion Hyperventilation accelerated the rate of A_{sev} increase immediately after sevoflurane administration, which was time dependent with respect to different alveolar ventilation levels.

Keywords Sevoflurane · Pharmacokinetics · Ventilation · Arterial blood · End tidal

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Introduction

Theoretically, the passage of a volatile anesthetic from the alveolar space into the bloodstream depends on several factors, including concentration of the inspired anesthetic, its blood/gas partition coefficient, ventilation volume, and cardiac output [1–3]. Under a constant inspired concentration, the uptake of a volatile anesthetic into the arterial blood should mainly be governed by alveolar ventilation under the assumption that a patient's cardiac output remains stable during anesthesia.

In clinical anesthetic practice, end-expiratory concentration is conventionally used as a measure of inhaled anesthetic concentration in arterial blood and/or brain. Previous investigation has demonstrated that dissociation exists between the concentration in end-expiratory gas and in arterial blood and/or brain during the introduction of

inhaled anesthesia [4]. Compared with the routinely monitored end-tidal concentration, the arterial concentration of a volatile anesthetic is most likely to represent that in the brain and thus reflects its pharmacological effect [5].

In clinical practice, increase in minute alveolar ventilation (MAV) theoretically accelerates anesthetic gas transfer to arterial blood. Under isocapnia, ventilation with larger tidal volumes accelerates the rate of increase in arterial blood sevoflurane concentration (A_{sev}) than normal tidal volumes [6]. However, hyperventilation with lower end-tidal carbon dioxide (CO_2) theoretically decreases cardiac output to reduce the uptake of inhaled anesthetics. Thus, arterial concentration provides definite evidence to clarify the above inference. We therefore hypothesized that hyperventilation accelerates the uptake of sevoflurane into arterial blood. The aims of this study were to examine the increase of A_{sev} and to verify the impact on cardiac variables among gynecologic surgical patients with clinical hyperventilation (lower end-tidal CO_2), normal ventilation, and hypoventilation (higher end-tidal CO_2) after intubation.

Patients and methods

Patients

Our institutional ethics committee on human research approved the study protocol, and informed consent was obtained from each patient. Thirty female patients, of American Society of Anesthesiology (ASA) physical status I, scheduled to undergo elective gynecologic surgery under general anesthesia were recruited for the study. Patients were randomly assigned to three ventilation groups: hyperventilation, normal ventilation, and hypoventilation.

Anesthetic management

Anesthetic premedication consisted of intravenously administered fentanyl (2 μg kg^{-1}) and midazolam (40 μg kg^{-1}). Under local anesthesia with 2 % Xylocaine, a 20-gauge catheter was inserted into the left radial artery for blood sampling. Anesthesia was induced with thiopental (4–6 mg kg^{-1}), and intubation was facilitated by pretreatment with pancuronium (0.015 mg kg^{-1}) and succinylcholine (1.25 mg kg^{-1}). After tracheal intubation, fixed inspiration of 3.5 % sevoflurane with an oxygen flow of 6 L min^{-1} was administered. With a fixed respiratory rate of 10 min^{-1}, hyperventilation was achieved as an end-tidal CO_2 ($ETCO_2$) of around 30 mmHg by adjusting the tidal volume to 8–12 ml kg^{-1}. The goal of $ETCO_2$ was 40 mmHg in the normal ventilation group and 50 mmHg in the hypoventilation group by similar respiratory manipulations. In each patient, the surgical procedure began after the 40-min ventilation study was completed.

Anesthetic gas monitor

The anesthesia machine used in this study was an Aestiva/5 with a 7100 ventilator (Datex-Ohmeda, Louisville, CO, USA) and with soda lime as the CO_2 absorber. The leakage of each system was determined by measuring constant-pressure ventilation in a test lung. All results were corrected for any specific leak observed. Anesthetic gas concentrations inspiratory (CI_{sev}) and end-tidal (CE_{sev}) sevoflurane concentrations were monitored with a multigas analyzer (Aestiva/5 Anesthesia System; Datex, Helsinki, Finland) calibrated according to the manufacturer's recommendations. Ten milliliters of arterial blood was obtained before induction from each patient for individual blood/gas partition coefficient (λ) and calibration curve of sevoflurane. At time 0 (before intubation) and at 1, 3, 5, 10, 20, 30, and 40 min after intubation, arterial blood was drawn from the catheter into a heparinized syringe, which was precisely 1.0 ml, then placed immediately into a 10-ml glass vial and tightly sealed. Blood samples were stored in a refrigerator at 4 °C and analyzed within 24 h for sevoflurane concentration using gas chromatography (GC) according to the method described in our previously published study [3]. Additional analysis for arterial blood CO_2 using the Ultima Gas Analysis Machine (ABBOTT i-STAT, East Windsor, NJ) was performed 20 and 40 min after sevoflurane administration. A thermistor inserted into the nasal pharynx was used to measure body temperature, which was maintained at 35.0–37.5 °C during the study.

Determining hemodynamic and respiratory variables

Hemodynamic parameters were monitored by a Finometer (FMS, Finapres Measurement Systems, Arnhem, The Netherlands) [7], which provides continuous, noninvasive measurements of heart rate, stroke volume, cardiac output, cardiac index, and total peripheral vascular resistance. Baseline blood pressures were calibrated before data collection. Hypotension, defined as a decrease in blood pressure of 25 % or more from baseline, was treated with fluids and ephedrine (as a 5-mg bolus) intravenously. The minute ventilation was calculated as the expiratory tidal volume multiplied by the respiratory rate. The MAV was derived from the minute ventilation as described in previous publications [8, 9].

Determining arterial blood sevoflurane concentrations over time (A_{sev} slope vs. time)

Arterial blood sevoflurane concentration (A_{sev}) slopes over time were calculated at 0–5, 5–10, 10–20, and 20–40 min after sevoflurane administration, which represented the rate of sevoflurane uptake by the speed of sevoflurane vapor

passing from the alveolar space into the circulating arterial blood in each time interval.

Determining blood sevoflurane concentrations

Before determining sevoflurane blood concentration, 10 ml of a patient's blood without sevoflurane was collected to determine the blood/gas partitioning coefficient (λ) of sevoflurane for each patient (Appendix 1) [8, 9]. Sevoflurane in each blood sample was converted to the corresponding concentration based on GC measurements and the blood/gas partition coefficient of sevoflurane (λ) measured in each patient (Appendix 2).

GC conditions

The HP 6890 series GC system (Hewlett-Packard, Wilmington, DE, USA) consists of a headspace sampler (Agilent G1888), an oven, a flame-ionization detector, and an integrator. Oven temperature was set to 40 °C, increased at a rate of 25 °C min^{-1} to 200 °C, and maintained at this level for 2.60 min. Both injection and detection temperatures were set to 250 °C. Inlet pressure was set to 349 kPa. The injection was performed in the direct injection mode. 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-μm film thickness) (Restek, Bellefonte, PA, USA). An integrator and data acquisition system was provided by Agilent CHEMOSTATION software (Rev. B.03.02). The method used to create a calibration curve for measuring blood sevoflurane concentrations was modified according to our previous publication [3].

Statistical analysis

We used the sample size formula for longitudinal data [10] to assess continuous responses ($Y = A_{sev}$, %), including type I error ($\alpha = 0.05$), smallest meaningful difference ($d = 0.6$ %), power ($p = 0.8$), measurement variation ($\sigma^2 = 3$), number of repeated observations per person ($N = 7$), and correlation among the repeated observations ($\rho = 0.9$). The calculation result was nine study participants in each group, and we had ten in each. The power was >80 %. Generalized estimating equations (GEEs) were introduced as a method of dealing with correlated data in applied sciences [11]. Patient characteristics, mean arterial blood pressure, heart rate, end tidal CO_2, cardiac index, CE_{sev}, and A_{sev} are presented as mean ± standard deviation (SD). GEEs were used to assess group, time, and group-by-time effects, as well as to adjust correlations arising from repeated measurements (SAS, Cary, NC, USA). We also used analysis of variance (ANOVA) to assess the mean of the slopes of the A_{sev}-over- time curves in the three groups at different periods by GraphPad Prism version 5.00 for Window (GraphPad Software, San Diego, CA, USA). A p value <0.05 was considered indicative of a significant difference.

Results

Thirty female patients aged 21–54 (mean, 42) years undergoing elective gynecologic surgery were randomly allocated into three groups: hyperventilation, normal ventilation, and hypoventilation. Patients' characteristics are shown in Table 1. There were no statistic differences in total use of fluid administration and ephedrine between groups. There were no significant differences between groups at different times and within-group variations in hemodynamic parameters, including arterial pressure, heart rate, cardiac index, and total peripheral resistance (Table 2). Among the three groups, mean (SD; range) of $ETCO_2$ was the largest ($p < 0.001$) in the hypoventilation group [49.2 (1.1; 48–51) mmHg], followed by the normal ventilation group [39.4 (1.8; 38–42) mmHg] and then the hyperventilation group [30.6 (0.8; 29–32) mmHg]. Mean (SD; range) of the MAV was the largest ($p < 0.001$) in the hyperventilation group [3485 (164; 3,161–3,970) ml min^{-1}], followed by the normal ventilation [2,558 (220); 2,180–2,740) ml min^{-1}] and then the hypoventilation [1,717 (185; 1,462–1,970) ml min^{-1}] group. Mean (SD) of sevoflurane blood/gas partition coefficient (λ) for the 30 patients was 0.66 (0.02).

Figure 1 depicts A_{sev} values for the three groups during the 40-min study. A_{sev} in the hyperventilation group was the highest, followed by the normal ventilation group, and then the hypoventilation group. The patterns of CE_{sev}-over-time curves, shown in Fig. 2, were similar to those of A_{sev} in the three groups. CE_{sev} was highest in the hyperventilation group, followed by normal and then hypoventilation groups during the 40-min study.

Table 1 Patients' demographic characteristics in the three ventilation groups

Characteristic	Hyperventilation ($N = 10$)	Normal ventilation ($N = 10$)	Hypoventilation ($N = 10$)
Age (years)	39.0 (8.8)	42.3 (6.7)	42.7 (6.8)
Weight (kg)	58.0 (7.3)	60.5 (9.7)	56.6 (7. 8)
Height (cm)	159.0 (5.9)	160.2 (6.9)	157.2 (4.2)
BMI (kg m^{-2})	23.0 (2.3)	23.5 (2.9)	22. 9 (2. 9)
Fentanyl (μg)	110 (20)	125 (30)	115 (25)

Values are presented as mean (standard deviation)

BMI body-mass index

Table 2 Hemodynamic and respiratory variables, including mean arterial pressure (MAP), heart rate (HR), cardiac index (CI), total peripheral resistance (TPR), end-tidal carbon dioxide ($ETCO_2$), and arterial carbon dioxide ($PaCO_2$) in the three ventilation groups at 5, 10, 20, 30, and 40 min of the study

Time (min)	Hyperventilation ($N = 10$)	Normal ventilation ($N = 10$)	Hypoventilation ($N = 10$)
MAP (mmHg)			
5	71.6 (13.3)	68.8 (12.0)	77.4 (6.8)
10	71.5 (8.6)	68.5 (8.8)	76.9 (7.5)
20	74.70 (9.3)	86.0 (19.2)	80.3 (11.6)
30	83.07 (16.7)	85.23 (11.2)	90.3 (13.9)
40	79.60 (17.4)	83.10 (14.4)	89.3 (10.7)
HR (beats min^{-1})			
5	71.0 (13.0)	68.2 (12.0)	77.0 (6.8)
10	71.6 (13.0)	72.5 (11.0)	70.2 (11.1)
20	66.5 (12.6)	72.9 (12.5)	69.1 (9.1)
30	66.3 (12.6)	73.9 (11.6)	71.0 (12.3)
40	67.0 (10.6)	77.9 (9.9)	74.4 (13.3)
CI (L min^{-1} m^{-2})			
5	2.69 (0.42)	2.90 (0.66)	3.06 (0.67)
10	2.76 (0.33)	2.77 (0.63)	3.10 (0.68)
20	2.62 (0.56)	2.97 (0.41)	3.20 (0.86)
30	2.73 (0.61)	2.97 (0.75)	3.24 (0.95)
40	2.55 (0.65)	3.17 (0.73)	3.22 (0.85)
TPR (dyne s cm^{-5})			
5	1421 (222)	1457 (528)	1330 (241)
10	1529 (233)	1437 (498)	1394 (317)
20	1516 (340)	1546 (458)	1344 (546)
30	1668 (555)	1567 (362)	1324 (409)
40	1625 (277)	1439 (401)	1417 (494)
$ETCO_2$ (mmHg)			
20	30.3 (2.1)	39.6 (1.9)	50.2 (1.7)
40	30.4 (1.5)	41.0 (2.2)	49.3 (1.6)
$PaCO_2$ (mmHg)			
20	30.8 (1.4)	40.3 (1.9)	50.6 (3.0)
40	30.7 (1.4)	41.9 (2.2)	51.4 (2.0)

Values are presented as the mean (standard deviation)

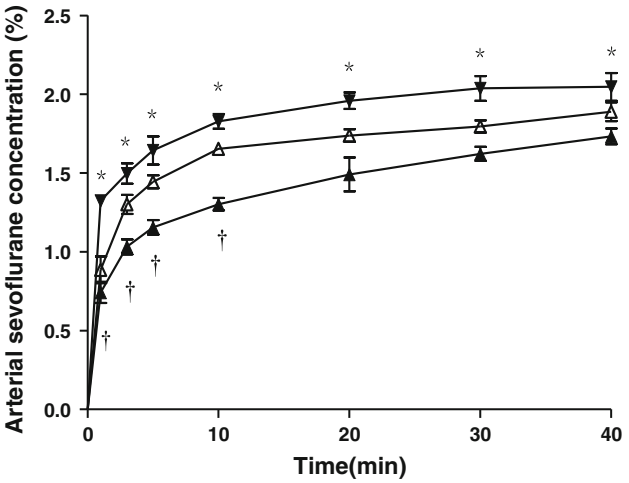

Fig. 1 Arterial blood sevoflurane concentration (A_{sev}) time curves under three different ventilatory states, including hyperventilation (*filled inverted triangles*), normal ventilation (*open triangles*), and hypoventilation (*filled upright triangles*) during 40 min of study. Data are presented as the mean ± standard deviation. Statistically significant differences are shown by $*p < 0.05$ for hyperventilation versus normal ventilation, and $^{\dagger}p < 0.05$ for hypoventilation versus normal ventilation

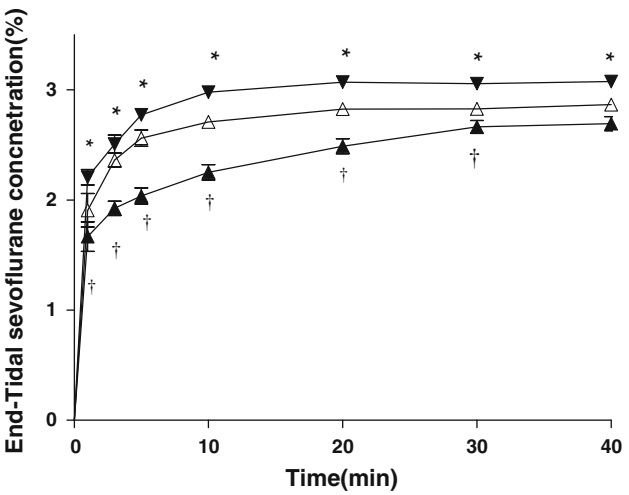

Fig. 2 End-tidal sevoflurane concentration (CE_{sev}) time curves under three different ventilatory states, including hyperventilation (*filled inverted triangles*), normal ventilation (*open triangles*), and hypoventilation (*filled upright triangles*), during 40 min of study. Data are presented as mean ± standard deviation. Statistically significant differences are shown by $*p < 0.05$ for hyperventilation versus normal ventilation and by $^{\dagger}p < 0.05$ for hypoventilation versus normal ventilation

There were significant differences in A_{sev} between the hyperventilation and normal ventilation groups ($p < 0.001$), as well as between the normal ventilation and hypoventilation groups ($p < 0.001$). In addition, there was an interaction effect on group by time (hypoventilation vs. normal ventilation, $p = 0.0022$), indicating significantly higher A_{sev} over time in normally ventilated compared with hypoventilated patients. Although there was no overall interaction effect on group by time (hyperventilation vs. normal ventilation; Table 3), there were significant differences in A_{sev} between the hyperventilation and normal groups and between the hypoventilation and normal groups. The significant between-group differences in A_{sev} between the hyperventilation and normal and the hypoventilation and normal groups are shown in Fig. 1. Within-group variance of A_{sev} (%) significantly increased in each respective group.

Table 3 Generalized estimating equation analysis for arterial blood sevoflurane concentrations (A_{sev}) comparing hyperventilation and hypoventilation groups to the normal group

Empirical standard error estimates						
Variable	Group	Estimate	Standard error	95 % confidence limits	*Z*	*P* value
Intercept		1.21	0.04	1.14/1.28	32.11	<0.0001
Group effect	Hyperventilation vs. normal ventilation	0.28	0.05	0.18/0.38	5.36	<0.0001
	Hypoventilation vs. normal ventilation	−0.26	0.05	−0.35/−0.17	−5.68	<0.0001
Time effect	Normal ventilation	0.02	0.00	0.01/0.02	9.23	<0.0001
Group × time effect	Hyperventilation vs. normal ventilation	0.00	0.00	0.00/0.01	0.13	0.8930
	Hypoventilation vs. normal ventilation	0.01	0.00	0.00/0.01	3.06	0.0022

Model adjusted for age and body mass index (BMI). Data assessed using PROC GENMOD (SAS 9.2 v.)

Table 4 Mean (standard deviation) of the slopes of the arterial blood sevoflurane concentration (A_{sev})-over-time curves in the three groups at different periods

Ventilation status	0–5 min	5–10 min	10–20 min	20–40 min
Hyperventilation	0.348 (0.022)*	0.004 (0.003)	0.013 (0.018)	0.004 (0.013)
Normal ventilation	0.289 (0.026)	0.008 (0.006)	0.006 (0.017)	0.000 (0.015)
Hypoventilation	0.231 (0.029**	0.007 (0.005)	0.019 (0.036)	0.012 (0.022)

Statistically significant differences are indicated by * $p < 0.05$ for hyperventilation versus normal ventilation, and ** $p < .05$ for hypoventilation versus normal ventilation. Data was assessed using analysis of variance (ANOVA) by GraphPad Prism version 5.00 for Window (GraphPad Software, San Diego, CA, USA)

Table 4 displayed A_{sev}-over-time curve slopes for the three ventilation groups. During the initial 5 min, there were significant differences between hyperventilation and normal ventilation groups ($p = 0.0004$) and between hypoventilation and normal ventilation groups ($p = 0.0023$).

Discussion

Our study demonstrated two main findings. First, hyperventilation significantly accelerated the rise in A_{sev}, especially during the first 10 min of administration. In the subsequent 30 min, the arterial concentration of sevoflurane in the hyperventilation group remained the highest. Second, the slope of the A_{sev}-over-time curve, indicating uptake into blood, was significantly higher in the hyperventilation group in the first 5 min only. With comparable hemodynamics and a fixed inspired concentration, changes in the slopes were mainly determined by alveolar ventilation and were time dependent. Increased alveolar ventilation resulted in faster changes in A_{sev} and CE_{sev}, but CE_{sev} was significantly higher than A_{sev}. Compared with CE_{sev}, A_{sev} is more likely to reflect concentration at its target site, the brain [3]. Our study demonstrated that hyperventilation produced higher A_{sev} than in the normal and hypoventilation groups during the first 10 min, which may provide a deeper anesthesia during the beginning of sevoflurane's effect. Inversely, hypoventilation led to a slower rise in A_{sev}, which provided a lighter level of anesthesia. There is no study to provide the relationship between A_{sev} and anesthetic depth. Thus, the clinical usefulness of this study focus on the effect of hyperventilation on the change of A_{sev}, which was thought to be more likely to reflect brain concentration and its pharmacological effect.

To understand how ventilation affected A_{sev}, it was necessary to look into the slope of A_{sev}-over-time curves as well as the time spent for sevoflurane to fill up the functional residual capacity (FRC). Changes in the slope of A_{sev}-over-time curves represent changes in rates of sevoflurane passage into arterial blood over time. CI_{sev} expresses inspiratory sevoflurane concentration at the mouth, and the inspiratory alveolar sevoflurane concentration indicates the inspiratory concentration of sevoflurane in alveoli. At the beginning of sevoflurane administration, there was no sevoflurane vapor in the existing space of the FRC at time 0. First, a breathing circuit (estimated as 6 L by the Datex AS/5 anesthetic machine) should be filled up in 1 min by 6 L min^{-1} of fresh gas flow with a fixed 3.5 % inspired sevoflurane concentration, and then the inspired sevoflurane immediately enters the existing space of the FRC, and its concentration is diluted by the existing air in the alveolar space. The inspiratory alveolar sevoflurane concentration decreased because the volume of the FRC was much larger

than the tidal volume. Thus, there was only a very small amount of sevoflurane delivered from alveoli to pulmonary capillary blood (a relatively small concentration gradient between pulmonary capillary circulating blood and alveolar sevoflurane) during initial sevoflurane administration. When ventilation has begun and is proceeding, alveolar concentration of sevoflurane rises rapidly, depending on the volume of alveolar ventilation to deliver sevoflurane from alveoli into the pulmonary capillary blood and subsequently arterial blood. The slope of the A_{sev}-over-time curve was the largest in the beginning of sevoflurane administration and then became smaller and smaller and approached zero in each group. Sevoflurane concentration gradient was greatest between alveoli and pulmonary capillary blood under hyperventilation than in the normal ventilation or hypoventilation groups, which hastened its passage into circulating blood during initial administration. Thus, hyperventilation accelerates the increase of A_{sev} and probably facilitates the rapid rise of brain sevoflurane to achieve the expected higher brain sevoflurane concentration at initial administration.

According to previous pharmacokinetic studies of isoflurane, hyperventilation accelerates the rise of arterial blood isoflurane concentration at the initial 20 min of isoflurane administration, but there was no change of isoflurane bodily uptake after the second 20 min [8]. Enekvist et al. [6] demonstrated that under isocapnia administration to achieve comparable cardiac output and cerebral blood flow, ventilation with larger tidal volumes accelerates the rate of increase in A_{sev} than normal tidal volumes. Our study demonstrates that hyperventilation with lower $ETCO_2$ accelerates the rate of A_{sev} rise during the initial 10 min of sevoflurane administration, but the effect disappears during following 30 min. As to why the change of alveolar ventilation affects A_{sev} during the first 10 min following sevoflurane administration, we believe that the partition coefficient of blood/gas in isoflurane (1.42) was greater than that of sevoflurane (0.66).

Increased ventilation causes a more rapid rise of CE_{sev} because FRC wash-in is faster, and the time constant (FRC/alveolar ventilation) becomes shorter, and vice versa [12]. One time constant is derived from the FRC value divided by MAV. Assuming that FRC is 2,400 ml in Taiwanese adult women in the supine position and the mean alveolar ventilation in the hypoventilation group was 1.717 ml min^{-1}, the time constant for the FRC wash-in should be 1.39 min (2,400 ml/1,717 ml min^{-1}) [1, 2, 13, 14]. The time needed to achieve 99 % FRC filling was thus 6.95 min (1.39 min × 5 time constants) in the hypoventilation group. For normal and hyperventilation groups, these values were 4.67 (0.94 min × 5 time constants) and 3.44 min (0.69 min × 5 time constants), respectively. Adding 1 min to fill up the breathing circuit at the initial administration of sevoflurane, the estimated differences in time needed to fill up the FRC could explain why the different levels of ventilation produced different effects on the slopes of the A_{sev}-over-time curves, especially in the initial 10 min of the study. During the last 30 min of the study, the impact of alveolar ventilation disappeared because the FRC had filled up; the effect of alveolar ventilation was time dependent during sevoflurane anesthesia.

This study has several limitations: First, only female patients were enrolled. Second, pharmacokinetic study of sevoflurane did not determine the cerebral hemodynamic, including cerebral blood flow and vascular resistance. Third, the study design was neither allowed determination of sevoflurane concentration in target-site brain tissue or analysis of the anesthetic effect of sevoflurane under different ventilation conditions.

In conclusion, hyperventilation accelerated sevoflurane uptake within 5 min by achieving higher arterial concentrations. Higher alveolar ventilation hastened FRC wash-in to provide faster target control of anesthetic depth, which was time dependent.

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Appendix 1: Determination of blood/gas partition coefficient (λ) of sevoflurane in each patient's blood

To obtain standard gas partial pressures, five 550-ml glass bottles, each with a turnable stopcock and Teflon septum were used [15]. After flushing each bottle with nitrogen for 6 min, each septum was pierced with the needle of a syringe, and 2, 5, 10, 20, or 50 μl of liquid sevoflurane at 20 °C was injected into the bottles. About 225 μl from each bottle of the calculated sevoflurane gas was then injected into a gas chromatograph using a 250-μl gas-tight Hamilton syringe (no. 81156). The calculated volume percent of sevoflurane was plotted against the measured gas chromatography counts. (Partial pressure was obtained by calculating the volume percent/100 × barometric pressure.)

We used a similar method to that described by Smith et al. [16] to determine blood/gas partition coefficient of sevoflurane (λ), as follows. Two milliliters of blood from each patient with an unknown sevoflurane partial pressure was added to the first 10-ml vial (with 2 ml of gas removed before injection), sealed with a Teflon septum in a 20 °C temperature room and then incubated at 37 °C for 30 min. The sevoflurane partial pressure in the headspace of the first vial ($C1$) was determined by GC. One milliliter of sample was immediately withdrawn from the first vial and

transferred to a second 10-ml vial (with 1 ml of gas removed before injection), sealed with a Teflon septum, and then incubated at 37 °C for another 30 min. The sevoflurane partial pressure in the headspace of the second vial ($C2$) was again determined by GC. Thus, λ was calculated by the following equation:

$$\lambda = \frac{9 \times C2}{C1 - C2}.$$

Appendix 2: Conversion of sevoflurane liquid to vapor by the known blood/gas partition coefficient (λ) of sevoflurane

The physical properties of sevoflurane were as follows: molecular weight/density (MW/D) was the volume of sevoflurane liquid; the blood/gas partition coefficient (sevoflurane) was 0.66 (0.63–0.69); MW of sevoflurane was 200.05; D at 20 °C was 1.5203.

According to the ideal gas law, 1 mole of sevoflurane (MW = 200.05 g) is equal to 22.4 L of sevoflurane vapor at 1 atm pressure and 0 °C. Therefore, 1 ml of sevoflurane vapor is 8.925 mg. As the temperature increases from 0 to 37 °C, 1 ml of sevoflurane vapor should be equal to 7.859 mg [(273 K/37 + 273 K) × 8.925 mg]. The patient's blood/gas partition coefficient was obtained as described in the above paragraph. If λ was assumed to be 0.66, a sample of 1 ml (1 % of 100 ml) of sevoflurane vapor equilibrated with 1 % 100 ml of blood contained 5.19 mg of sevoflurane. This means that 1 % of 100 ml of sevoflurane vapor (containing 7.859 mg) was equilibrated with 5.19 mg sevoflurane in 1 % of 100 ml of blood at 37 °C and 1 atm. Blood concentration (or partial pressure) of sevoflurane could be 1 %, which was comparable with the 1 % level of the gas phase. The 1 % blood concentration (or partial pressure) of sevoflurane indicated that there was 5.19 mg of sevoflurane liquid dissolved in the 100-ml blank blood sample of the patient, which was calculated according to the known blood/gas partition coefficient.

A standard of liquid sevoflurane was equilibrated in a cold bath at 20 °C for 1 h before use. Five known amounts of sevoflurane liquid were taken up into a Hamilton 0.5-μl microsyringe (PN: 86259) and then injected into five 10-ml glass vials (each containing 1 ml of a patient's blank blood). These vials were swirled in a cool bath at 20 °C for 30 min, and then transferred to a water bath at 37 °C for 30 min. The sevoflurane partial pressure in the blood was obtained and was comparable with the sevoflurane partial pressure in the gas phase. Blood samples were analyzed with a GC, a headspace sampler, and a flame-ionization detector. A linear relationship between signals for peak area of sevoflurane (y axis) and sevoflurane partial pressure (x axis) was obtained and revealed an excellent correlation, with a range of 0.9959–0.9999 between signal and sevoflurane partial pressure. The analytical range of sevoflurane partial pressure was 0.47–11.7 %. The partial pressure of sevoflurane in the blood phase was calculated from the calibration curve of a known amount of sevoflurane. The chromatographic area was proportional to the sevoflurane partial pressure over the entire range of partial pressures studied. The precision and accuracy were determined on spiked human samples at six partial pressures (0.47–11.7 %) with respect to the calibration graph prepared each day. The limit of detection (LOD) was 0.03 % ml^{-1} of gas based on a signal-to-noise ratio of 3. The limit of quantification (LOQ) of the method for standard samples was 0.1 % ml^{-1} of blood. The precision of the method was expressed as within-day and between-day coefficients of variation (%) of <7.9 %.

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