# Comparison of the Level of Free Hexafluoro-isopropanol in Adults' Blood and the Incidence of Emergence Agitation After Anesthesia With Different Concentrations of Sevoflurane in Laparoscopic Gastrointestinal Surgery: A Randomized Controlled Clinical Trial

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## ABSTRACT

**Purpose:** The aim of the study is to compare the free hexafluoro-isopropanol (HFIP) concentration in adults' blood and the incidence of emergence agitation (EA) after inhaled different concentrations of sevoflurane.

**Methods:** Sixty adult patients planning to undergo laparoscopic gastrointestinal surgery were randomly assigned to 3 groups. Each group received sevoflurane as the volatile anesthetic at different concentrations: 0.5 minimum alveolar concentration (MAC), 1.0 MAC, and 1.5 MAC. The use of sevoflurane was continued until the end of surgery. Venous blood samples were obtained at 30, 60, 120, and 180 minutes after starting the use of sevoflurane and subsequently at 60, 180, and 300 minutes after discontinuation of volatile anesthetic administration. Blood concentrations of sevoflurane and free HFIP were determined using gas chromatography. The recovery time and the incidence of EA at different time points were evaluated among the 3 groups.

**Findings:** Changes in the blood concentrations of sevoflurane and free HFIP during and after the use of sevoflurane were similar in all 3 groups. The peak blood concentration of free HFIP occurred 60 minutes after onset of sevoflurane anesthesia in all 3 groups ($P < 0.05$). The lowest level of free HFIP and the longest recovery time were found in the 1.5-MAC group ($P < 0.05$). No significant difference was found in the incidence of EA or moderate pain among the 3 groups during recovery.

**Implications:** The generation of HFIP would be inhibited when the inhaled sevoflurane concentration increased to 1.5 MAC. However, the incidence of EA during recovery had nothing to do with the inhaled different sevoflurane concentrations (within 1.5 MAC) in adults. ChicCTR.org identifier: ChiCTR-IPD-17011558. (*Clin Ther.* 2019;41:2263−2272) © 2019 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

**Key words:** emergence agitation, hexafluoro-isopropanol, laparoscopic gastrointestinal surgery, sevoflurane.

## INTRODUCTION

Sevoflurane has been widely used as part of the general anesthesia technique. Its low blood solubility and metabolism enable it to be a favorable anesthetic agent for fast-track anesthesia.[1] Approximately 5% of sevoflurane undergoes rapid biotransformation and metabolizes to hexafluoro-isopropanol (HFIP) and inorganic fluoride by liver cytochrome P450.[2,3] Approximately 85% of HFIP is conjugated with glucuronic acid and excreted in urine. Less than 15% of HFIP exists in the body in free form.[2] Studies have found that HFIP possesses very strong anesthesia potency. The minimum alveolar concentration (MAC) of HFIP in rats (0.0044%) is much smaller than that of sevoflurane (2.5%).[4,5] Because of a considerably high tissue solubility (263 for saline/gas partition coefficient),[5] HFIP is easy to accumulate in tissues and difficult to eliminate from the body and may affect patient's recovery from anesthesia. Postoperative behavioral disturbance known as emergence agitation (EA) has been recognized as a problem that may occur during recovery from sevoflurane anesthesia in children and adults,[6,7] and its mechanism is unknown. However, no evidence indicates that free HFIP affects human volunteers' recovery after inhaled sevoflurane for 10 MAC per hour.[8] Some studies had found a dose-dependent hepatic failure with sevoflurane anesthesia in isolated rat hepatocytes,[9] and the metabolism of sevoflurane in the liver was inhibited in adults when the inhaled sevoflurane concentration increased to a relatively high extent.[10] Therefore, we hypothesized that the level of free HFIP in the blood and the incidence of EA might not increase with the use of higher concentrations of sevoflurane. This study aimed to compare the free HFIP concentrations in adults' blood and the incidence of EA after inhalation of different concentrations of sevoflurane.

## METHODS

### Study Designs

This study was a double-blind randomized controlled trial conducted at the Affiliated Hospital of North Sichuan Medical College. Ethic approval was obtained from Ethic Committee for Human Research of Affiliated Hospital of North Sichuan Medical College, Nanchong, China (Ethical Committee No. 2017/002).
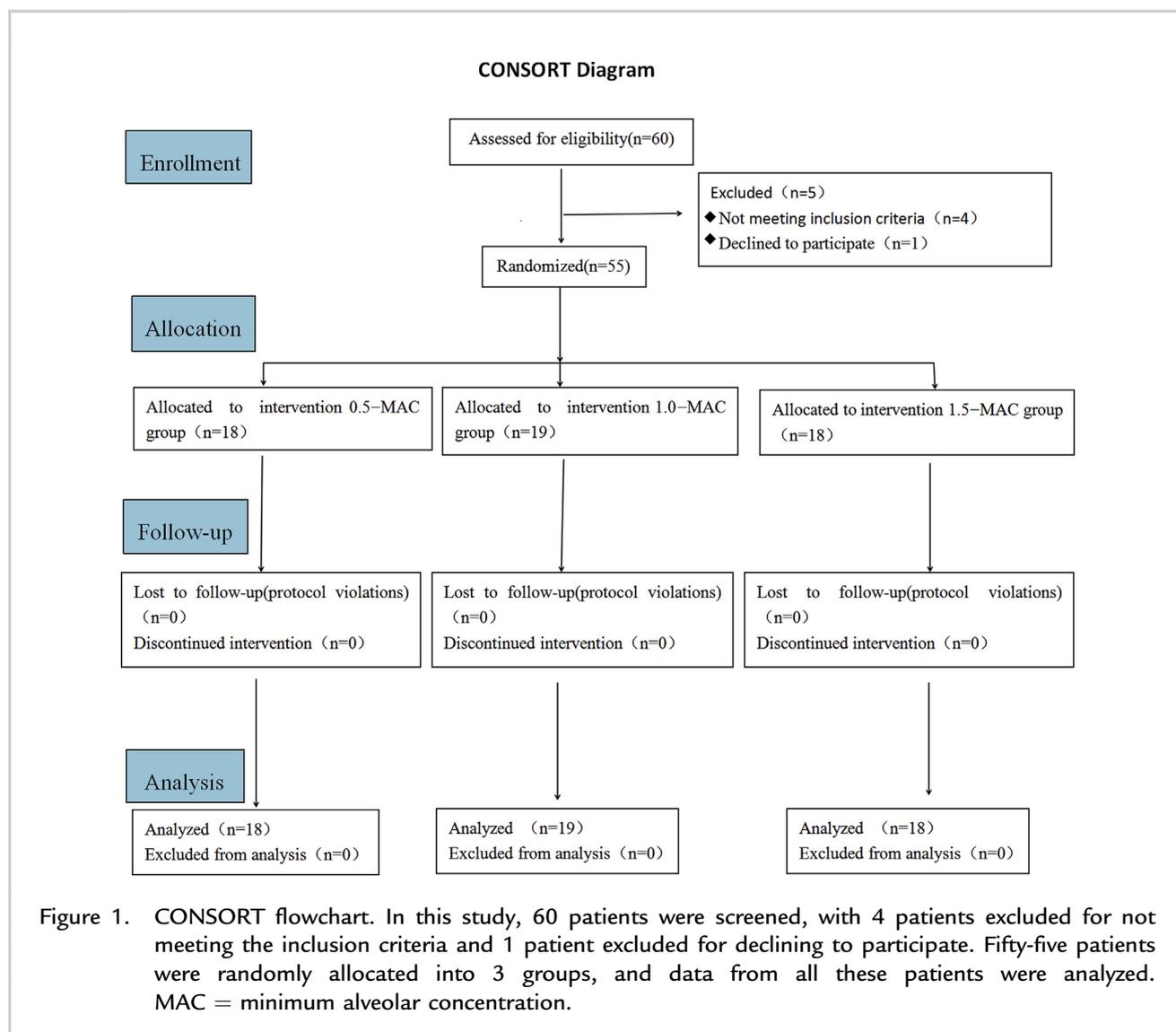
The study was registered with the Chinese Clinical Trials Registry (ChiCTRIPD identifier: 17011558) at http://www.chictr.org.cn and conducted from July 2017 to January 2018.

### Participants

After providing informed written consent, 60 patients with American Society of Anesthesiologists (ASA) physical status class I to II, who were 45 to 65 years old, and who were undergoing laparoscopic gastrointestinal surgery with an expected surgical duration of 2.5 to 3.5 hours were randomly (random number method) enrolled into 3 groups: the 0.5-MAC group, the 1.0-MAC group, and the 1.5-MAC group. All the patients and investigators were blinded to group allocation. Patients with hypertension, coronary artery disease, diabetes, chronic obstructive pulmonary disease, hematogenic and immune systemic disease, a history of central nervous system or mental disease, anemia (preoperative hematocrit <30%), contraindications for using sevoflurane or other intravenous anesthetics, smoking in the past 2 weeks, sevoflurane anesthesia treatment in the past 3 months,[11] and alcohol or drug abuse were excluded from this study. All eligible patients were analyzed. The flow of patients through the trial is shown in Figure 1.

### Study Protocol

Patients fasted for at least 8 hours before surgery and received no premedication. In the operating room, patient's pulse oxygen saturation, electrocardiograph, and invasive blood pressure were routinely monitored. One peripheral intravenous catheter was inserted in the left hand for administration of drugs and fluid, and one central intravenous catheter was inserted for blood sampling. In the 3 groups, anesthesia was induced with midazolam 0.1 mg kg$^{-1}$, remifentanil 2 µg kg$^{-1}$, and etomidate 0.3 mg kg$^{-1}$. Cisatracurium besilate 1.5 mg kg$^{-1}$ was intravenously given to facilitate tracheal intubation. Mechanical ventilatory support was administered using a mixture of oxygen in air (fraction of inspired oxygen of 0.5) and a tidal volume of 6 to 8 mL kg$^{-1}$ at a rate of 12 to 16 breaths min$^{-1}$ to maintain the end-tidal carbon dioxide tension at 35 to 45 mm Hg. The end-tidal concentration of sevoflurane was maintained at 0.5 MAC, 1.0 MAC, and 1.5 MAC (uncorrected for age, where MAC was 1.71%) and was monitored with a PM-9000 express multifunctional monitor (Mindray

**CONSORT Diagram**



Figure 1. CONSORT flowchart. In this study, 60 patients were screened, with 4 patients excluded for not meeting the inclusion criteria and 1 patient excluded for declining to participate. Fifty-five patients were randomly allocated into 3 groups, and data from all these patients were analyzed. MAC = minimum alveolar concentration.

Medical International Limited, Shenzhen, China). Patients' bispectral index[12] was maintained between 40 and 60 by adjusting the intravenous target-controlled infusion concentration of remifentanil ($4-7$ ng mL$^{-1}$) and the infusion rate of propofol ($4-12$ mg kg$^{-1}$ h$^{-1}$). Muscle relaxation was maintained by infusion of cisatracurium (0.1 mg kg$^{-1}$ h$^{-1}$). The administration of sevoflurane was continued to the end of surgery. Once sevoflurane administration was discontinued, the flow rate of oxygen was increased to more than minute ventilation volume to avoid rebreathing. The intraoperative fluid infusion rate was 10 mL kg$^{-1}$ h$^{-1}$ at a ratio of 2:1 for crystalloids versus colloids. The fluctuation of mean arterial pressure was controlled in a range of 20% within its base value using vasoactive drugs if necessary. The infusion of propofol, remifentanil, and cisatracurium was discontinued 10 minutes before the end of operation, and intravenous fentanyl 2 μg kg$^{-1}$ was given simultaneously.

After the surgical procedure had been finished, all patients were continuously supported by mechanical ventilation in the postanesthesia care unit. Each patient's name was called every 2 minutes after the operation, and the endotracheal tube was removed

when the patient could maintain adequate spontaneous respiration and open eyes or nod as required.

## Primary and Secondary Outcomes

The primary outcome was the concentrations of free HFIP and sevoflurane in the blood at different time points. Blood samples (each for 7 mL) were collected from the central venous catheter at 30, 60, 120, and 180 minutes after starting use of sevoflurane and again at 60, 180, and 300 minutes after discontinuation of volatile anesthetic use by a series of 20-mL gas-tight heparinized glass syringes capped with 3-way stopcocks. All blood samples in glass syringes were stored at –4°C in a refrigerator until analysis (maximum of a week). After a 2-hour water bath at 37°C 2 times, the blood samples were analyzed using a method of 2-stage headspace equilibration[13,14] by a gas chromatograph (GC) (model 7890A, Agient, Beijing, China), which was equipped with a 30-m stainless steel capillary column (320 × 0.25-μm film thickness) maintained at 325°C. A 20-mL/min nitrogen carrier stream flow was delivered through the column to a flame ionization detector (at 200°C) supplied by hydrogen at 30 mL/min and air at 150 mL/min. The GC oven temperature was set at 45°C. In these conditions, the output from the GC was collected by the integrator software. The peaks of sevoflurane and free HFIP were separated completely, and peak areas were calculated automatically. Standard curves of sevoflurane and free HFIP were built by half dilution of standard gases. All $R^2$ values for the linear regression between concentrations of anesthetics and peak area of GC output exceeded 0.9995, and the coefficient of variation (intraday, intermeasurement) was <2%. The concentrations of free HFIP and sevoflurane in the blood at different time points were calculated by standard curves.

The secondary outcome was the incidence of EA during recovery. The sedation agitation scale (SAS) score[15] ranges from failing to arouse (SAS score, 1) to dangerous agitation (SAS score, 7). Agitation is defined as a SAS score of 5 to 7. Once the patient appeared agitated, propofol 0.5 mg kg$^{-1}$ was immediately given intravenously. The visual analog scale (VAS) score[16] is labeled from 0 (no pain) to 10 (pain as bad as you can imagine): score of 1 to 3, mild pain; score of 4 to 6, moderate pain; and score of 7 to 10, severe pain. Once the patient experienced moderate or severe pain, fentanyl 2 μg kg$^{-1}$ was intravenously given immediately. The SAS and VAS scores were evaluated by blinded investigators. The incidence of EA at the time points of 0, 5, 10, and 30 minutes and 1, 2, and 4 hours after extubation was recorded.

## Sample Size and Statistical Analysis

In this study, the concentrations of free HFIP in the blood were the primary outcome. Our pilot study found that the mean SD values of HFIP were 0.043% (0.010%) in the 0.5-MAC group, 0.055% (0.008%) in the 1.0-MAC group, and 0.035% (0.007%) in the 1.5-MAC group. Achieving a power of 0.9 at an α level of 0.05, there would be at least 17 patients in each group to detect a significant difference. Considering a 20% sample exfoliate rate, a sample size of 60 cases for 20 cases per group was needed.

All data were analyzed with SPSS software, version 19.0 (SPSS Inc, Chicago, Illinois). Results are presented as mean (SD) for continuous variables and number (percentage) for categorical variables. Normal distribution was confirmed using the Kolmogorov–Smirnov test. The concentrations of sevoflurane and free HFIP in the blood at each time point were compared using repeated-measures analysis of variance among the 3 groups and one-way analysis of variance in each group, respectively. The incidence of EA during recovery was compared by the $\chi^2$ test among the 3 groups. Patient characteristics and recovery time from anesthesia were compared by one-way analysis of variance and Fisher exact test where appropriate among the 3 groups. Statistical significance was accepted as $P < 0.05$.

## RESULTS

This study included 55 patients undergoing laparoscopic gastrointestinal surgery with an expected surgical duration of 2.5 to 3.5 hours, and 5 patients were excluded from this study. The patients' preoperative characteristics and types of surgery were similar among the 3 groups (Table I). Compared with the 0.5-MAC group and the 1.0-MAC group, the 1.5-MAC group had a less propofol consumption and a longer recovery time (Table I). The blood/gas partition coefficients of sevoflurane and HFIP measured at 37°C were 0.66 (0.05) and 452.25

Table I. Patient characteristics.

| Characteristic | 0.5-MAC Group (n = 18) | 1.0-MAC Group (n = 19) | 1.5-MAC Group (n = 18) |
|---|---|---|---|
| Preoperative data | | | |
|   Age, mean (SD), y | 56.6 (8.0) | 57.1 (9.8) | 61.9 (5.5) |
|   M/F sex, No. | 9/9 | 10/9 | 8/10 |
|   BMI, mean (SD), kg/m$^2$ | 22.9 (1.9) | 22.8 (1.2) | 21.9 (1.5) |
|   ASA class I/II, No. | 10/8 | 10/9 | 11/7 |
|   Hemoglobin, mean (SD), g/L | 131.6 (10.5) | 130.8 (8.7) | 128.3 (16.2) |
|   Hematocrit, mean (SD) | 0.4 (0.2) | 0.4 (0.1) | 0.4 (0.1) |
|   Albumin, mean (SD), g/L | 44.7 (4.1) | 43.3 (1.9) | 44.4 (3.1) |
|   Triglyceride, mean (SD), mmol/L | 1.1 (0.5) | 1.4 (0.8) | 1.0 (0.7) |
|   Total cholesterol, mean (SD), mmol/L | 4.3 (0.9) | 4.1 (0.7) | 4.2 (0.4) |
|   Globulin, mean (SD), g/L | 30.4 (4.5) | 27.6 (4.1) | 30.1 (3.1) |
| Types of surgery, No. (%) | | | |
|   Radical correction of gastric cancer under laparoscope | 6 (33) | 7 (37) | 7 (39) |
|   Radical correction of colorectal cancer under laparoscope | 12 (67) | 12 (63) | 11 (61) |
| Intraoperative data, mean (SD) | | | |
|   Operation time, h | 2.9 (0.3) | 2.9 (0.2) | 2.9 (0.1) |
|   Midazolam, mg | 3.1 (0.3) | 3.3 (0.5) | 3.0 (0.5) |
|   Etomidate, mg | 18.4 (1.8) | 18.9 (1.5) | 19.3 (1.3) |
|   Remifentanil, μg | 1030.5 (96.5) | 1058.5 (109.4) | 998.9 (94.6) |
|   Rocuronium, mg | 66.5 (6.3) | 68.0 (5.8) | 66.8 (3.9) |
|   Fentanyl, μg | 115.0 (26.9) | 122.0 (27.5) | 112.5 (17.7) |
|   Propofol, mg | 899.0 (82.8) | 834.0 (195.2) | 233.0 (75.7)* |
|     Amount of bleeding, (mL | 79 (29) | 81 (51) | 60 (25) |
|     Total infusion liquid volume, mL | 2660 (446) | 2805 (545) | 2715 (513) |
| Postoperative data, mean (SD) | | | |
|   Spontaneous breathing recovery time, min | 4.2 (1.9) | 3.1 (2.6) | 11.1 (5.0)* |
|   Eye opening time, min | 7.90 (3.0) | 8.1 (3.5) | 9.9 (3.9)* |
|   Extubation time, min | 10.8 (3.2) | 9.9 (3.9) | 19.3 (7.1)* |

ASA = American Society of Anesthesiologists; BMI = body mass index; MAC = minimum alveolar concentration.
*$P < 0.05$ versus the value of the 0.5-MAC group and 1.0-MAC group.

(16.48), respectively. A similar increase and decrease of sevoflurane concentrations in the blood during and after anesthesia in the 3 groups was found, but the increase or decrease rate in the 1.5-MAC group was the fastest (Figure 2).

A similar increase and decrease of free HFIP concentrations in the blood during and after anesthesia was also found in the 3 groups (Figure 3). The level of free HFIP in the blood increased with the increase of inhaled sevoflurane concentration within 1.0 MAC. However, it no longer increased when the inhaled sevoflurane concentration increased to 1.5 MAC. On the contrary, it decreased to lower than that in the other 2 groups at each corresponding time point ($P < 0.05$). Both the SAS score and VAS score in the 1.5-MAC group were lower than those in the other 2 groups immediately at extubation and 5 minutes after extubation (Table II). However, no significant difference was found in the incidence of EA or moderate pain among the 3 groups during recovery (Table III).
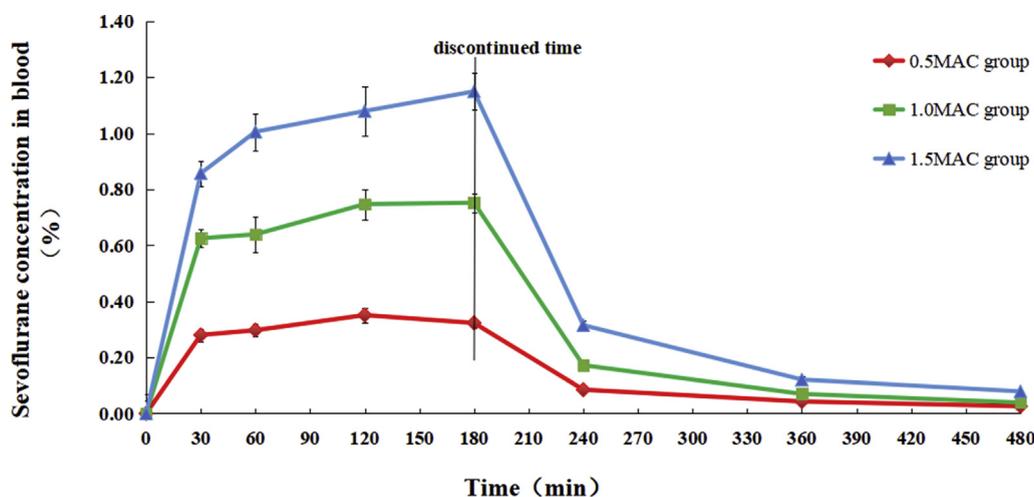
Figure 2. The changes of sevoflurane concentrations in the blood. The sevoflurane concentrations in the blood in all 3 groups were gradually increased, and the increased speed in the 1.5−minimum alveolar concentration (MAC) group was the fastest during inhalation for 180 minutes. On the contrary, the sevoflurane concentrations in the blood in all 3 groups were rapidly deceased, and the decreased speed in the 1.5-MAC group was the fastest after discontinuation of the given of sevoflurane.
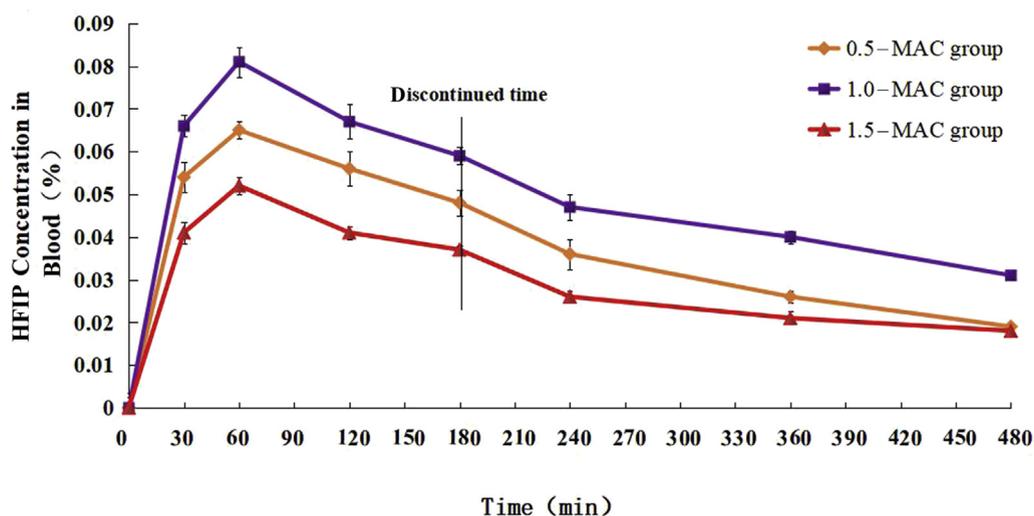


Figure 3. The changes of hexafluoro-isopropanol (HFIP) in the blood. Similar increases and decreases of free HFIP concentrations in the blood during and after anesthesia were found in the 3 groups. The peak blood concentration of free HFIP occurred 60 minutes after onset of sevoflurane anesthesia in all 3 groups. The level of free HFIP in the 1.5−minimum alveolar concentration (MAC) group was the lowest at each corresponding time point among the 3 groups.

Table II.   Patient SAS and VAS scores.

| Group | Immediately After Extubation | After Extubation | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 5 min | 10 min | 30 min | 1 h | 2 h | 4 h |
| SAS | | | | | | | | |
| 0.5 MAC | 4.2 (0.6) | 4.2 (0.0) | 4.0 (0.0) | 4.0 (0.0) | 4.0 (0.0) | 4.0 (0.0) | 4.0 (0.0) |
| 1.0 MAC | 4.3 (0.6) | 4.4 (0.5) | 4.3 (0.4) | 4.0 (0.0) | 4.0 (0.0) | 4.0 (0.0) | 4.0 (0.0) |
| 1.5 MAC | 3.5 (0.7)[*,†] | 4.0 (0.0)[†] | 4.0 (0.4) | 4.0 (0.0) | 4.1 (0.3) | 4.2 (0.4) | 4.0 (0.0) |
| VAS | | | | | | | | |
| 0.5 MAC | 2.3 (0.6) | 1.9(0.7) | 2.1 (0.5) | 2.4 (0.5) | 2.5 (0.5) | 2.1 (0.3) | 2.1 (0.3) |
| 1.0 MAC | 2.5 (1.5) | 2.6(1.4) | 2.7 (0.9) | 2.2 (0.6) | 2.3 (0.4) | 2.3 (0.4) | 2.2 (0.4) |
| 1.5 MAC | 0.8 (0.7)[*,†] | 1.3(0.9)[†] | 1.4 (1.0)[†] | 2.2 (0.6) | 2.3 (0.8) | 2.5 (0.9) | 1.9 (0.3) |

MAC = minimum alveolar concentration; SAS = Sedation Agitation Scale; VAS = visual analog scale.
*$P < 0.05$ versus values of the 0.5-MAC group.
†$P < 0.05$ versus values of 1.0-MAC group.

## DISCUSSION

Sevoflurane is an inhalational anesthetic used widely because of its excellent hemodynamic stability and low blood solubility, which allows rapid induction and emergence from general anesthesia and easy control of the depth of anesthesia. The rapid removal of residual anesthetics of sevoflurane has been suggested to cause EA in some patients,[17] but the exact mechanisms of EA remains unknown.

HFIP is one of the main metabolites of sevoflurane. Its subsequent metabolism (glucuronidation) is extensive but incomplete, leaving a small fraction unconjugated, which appears in the blood 5 minutes after inhaled sevoflurane.[2] In light of its considerable anesthetic potency and big blood/gas partition coefficient (452.25 at 37°C), HFIP will easily accumulate in the blood and may contribute to a residual anesthetic effect and affect patient's recovery from anesthesia. However, in this study, the lowest level of free HFIP was found in the highest inhaled sevoflurane concentration group, and no significant difference was found in the incidence of EA or

Table III.   Incidence of EA and moderate pain.*

| Group | No. of Cases | Incidence, No. (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | EA Immediately After Extubation | EA After Extubation | | | | | | Total EA | Moderate Pain |
| | | | 5 min | 10 min | 30 min | 1 h | 2 h | 4 h | | |
| 0.5 MAC | 18 | 2 (11.1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (11.1) | 2 (11.1) |
| 1.0 MAC | 19 | 4 (21.1) | 3 (15.8) | 2 (10.5) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 4 (21.1) | 6 (31.6) |
| 1.5 MAC | 18 | 2 (11.1) | 2 (11.1) | 2 (11.1) | 1 (5.6) | 0 (0) | 0 (0) | 0 (0) | 3 (16.7) | 3 (16.7) |

EA = emergency agitation; MAC = minimum alveolar concentration.
*No significant difference was found in the incidence of EA or moderate pain among the 3 groups during recovery.

moderate pain among the 3 groups during recovery (Table II). The study found that the incidence of EA was not affected by free HFIP after anesthesia with different concentrations of sevoflurane in adults. A delayed recovery in the highest inhaled sevoflurane concentration group (Table I) may mainly relate to the effect of more accumulation of sevoflurane in the body[18] (Figure 2) and relate less to the residual anesthetic efficacy of free HFIP. In other words, the clinical indexes of recovery will not be influenced by a small rate or extend of sevoflurane metabolism.[2,3]

In addition, we found that the peak free HFIP concentration in the blood among the 3 groups was <0.1% in this study. Kharasch et al[2] also found that the mean peak free HFIP concentration was <1% of the mean peak sevoflurane concentration in the blood after inhaled 2.7% of sevoflurane in adults. This finding implied that the level of free HFIP was too low to produce an anesthetic effect. Even if free HFIP existed in adults, it did so at trivial partial pressures. Whether the anesthetic efficacy of free HFIP will appear in children or in patients with hepatosis after anesthesia with the same concentrations of sevoflurane needs further study.

When the free HFIP concentration curves were compared among the 3 groups (Figure 3), the concentrations of free HFIP did not always increase with the increase of inhaled sevoflurane concentration. The level of free HFIP decreased when the inhaled sevoflurane concentration increased to 1.5 MAC. This finding might be related to the fact that a higher concentration of sevoflurane would inhibit the activity of cytochrome P450 2E1[10] and even induce hepatocyte damage. Several mechanisms exist for direct damage to hepatocytes, including immune reaction,[19–23] calcium overload in hepatocyte,[20–22] and inflammation.[20] In addition, hepatic artery buffer response might also be inhibited when the inhaled sevoflurane concentration increased to 1.5 MAC.[24] In addition, the decreased effective hepatic blood flow would result in a decrease of the metabolic rate of sevoflurane so that the produced free HFIP content decreased.

There were several limitations to our study. First, the time of monitoring free HFIP concentration of 8 hours was relatively short and may not fully reflect the trend of free HFIP concentration. Second, the changes of free HFIP in the blood were not studied with an inhaled sevoflurane concentration >1.5 MAC. Third, several studies in both adults and children found that propofol may decrease the incidence of EA.[25–27] Therefore, the use of propofol in this trial might be a confounding factor for the incidence of EA.

## CONCLUSION

In conclusion, the generation of HFIP in adults may be inhibited when the inhaled sevoflurane concentration reaches 1.5 MAC, and recovery time could be delayed. However, the incidence of EA may have nothing to do with the inhaled different sevoflurane concentrations (within 1.5 MAC).

## DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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