

Effects of grade B liver dysfunction on the level of free hexafluoroisopropanol of sevoflurane metabolites in patients with abdominal surgery

Xiao-lin Yang (✉ 879921874@qq.com)

Affiliated Hospital of north sichuan medical college <https://orcid.org/0000-0003-0986-8001>

Ming Li

Department of Anesthesia Affiliated Hospital of North Sichuan Medical College(Current unit: Department of Anesthesia,Guang yuan Central Hospital)

Yan Feng

Department of Anesthesia,Nanchong Central Hospital,The Second Clinical Medical College of North Sichuan Medical College

Guo-Yuan Zhang

Department of Clinical Laboratory,Affiliated Hospital of North Sichuan Medical College

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Abstract

Background: Study shows the metabolite, hexafluoroisopropanol (HFIP) from sevoflurane, has a strong inhibition on the central nervous system. This study aims to compare the level of free HFIP in the blood after inhaled a same concentration of sevoflurane in patients with normal liver function versus grade B liver dysfunction and observe its effect on patients' recovery quality.

Methods: Twenty four patients with normal liver function and twenty four patients with grade B liver dysfunction undergoing elective abdominal surgery were selected and assigned to group A and group B, respectively. All patients were inhaled sevoflurane (1.5MAC) for anesthesia about 3 h. The free HFIP concentration was determined at the time points of 0.5 h, 1 h, 2 h, 3 h after inhaled sevoflurane and 0.5 h, 1 h, 2 h, 4 h after discontinuation of sevoflurane, respectively. Patients' eyes opening time, orientation recovery time, command response time and extubation time were observed after operation. The visual analogue scale (VAS) and Ramsay sedation score (RSS) were also evaluated at different time points after extubation.

Results: Although the peak time of free HFIP in group B was 1 h later than that in group A, no significant differences were found in the peak concentration and other corresponding time points' free HFIP concentrations between the two groups ($P<0.05$). All the eyes opening time, orientation recovery time, command response time and extubation time in group B were longer than those in group A ($P<0.05$). Compared to group A, a lower VAS score and a higher RSS score were found in group B at 0 min, 15 min, 30 min, 1 h, 2 h and 3 h after extubation, respectively ($P<0.05$).

Conclusion: The status of patients with grade B liver dysfunction does not affect the degree of sevoflurane metabolism. However, it can significantly prolong the peak time of free HFIP when compared with normal liver function.

Trial registry number: Identified as ChiCTR 2000028901 at <http://www.chictr.org.cn/>

Background

Sevoflurane is widely used in the clinic due to its low blood/gas partition coefficient, one of the main physical properties^[1]. Like other fluorinated anesthetics, sevoflurane is mostly excreted from the body by archetype, only approximately 3 to 5 percent undergoes rapid biotransformation and metabolizes to inorganic fluoride and organic hexafluoro-isopropanol (HFIP) by the liver cytochrome P450 system^[3]. About 85% of HFIP circulates in the blood as a form of glucuronide conjugate and is excreted in the urine. The rest part of HFIP (15%) in a free form remains in the blood and tissues. Study indicates that free HFIP has a strong depressant effect on the central nervous system^[1], and its minimum alveolar concentration (MAC, 0.0044%)^[1] in rats is about 530 times less than that of sevoflurane (2.32%). A very high blood/gas partition coefficient (452.25, at 37°C) was found in our previous study^[1], which means HFIP is easy to accumulate in the body and may affect patient's recovery quality after anesthesia with sevoflurane.

Patients with liver dysfunction and need surgery are prevalent in the clinic. Anesthesiologists are often prudent to choose anesthetics in this kind of patients [1]. We speculate that the pathophysiological changes in patients with liver dysfunction may lead to the change of sevoflurane's metabolism. This study aims to observe the changes of free HFIP concentrations in the blood and the recovery quality from anesthesia in patients with normal liver function vs. grade B liver dysfunction after inhaled a same concentration of sevoflurane for the same time.

Materials And Methods

Patients' selection and clinical protocol

This study was approved by the Ethic Committee for Human Research of Affiliated Hospital of North Sichuan Medical College, Nanchong, China (Ethical committee No.2019/001), and conducted at Affiliated Hospital of North Sichuan Medical College. The study was registered at <http://www.chictr.org.cn> (No. ChiCTR2000028901) and conducted from March 2020 to December 2020.

According to the Child-Turcotte-Pugh liver function grade, 24 patients with normal liver function were allocated to group A, and 24 patients with grade B liver dysfunction were allocated to group B. All the informed written consents were obtained from each patient. Both the two groups were scheduled for elective laparoscopic non-hepatic surgery with an anticipated surgical duration of 2.5–3.5 h. All patients were American Society of Anesthesiologists (ASA) physical status I-II, aged between 45–65 year, within 30% of ideal body weight and had normal indexes of renal function. The following patients were excluded from this study: Patients with hypertension, coronary artery disease, hematogenic disease, diabetes, chronic obstructive pulmonary disease, a history of central nervous system or mental disease, anemia (preoperative hematocrit < 30%), current use of medications known to change hepatic drug metabolism, and sevoflurane anesthesia in the past two months. Patients with blood loss more than 200 ml during operation or the operative approach changed from laparoscopy to open surgery were also excluded from this study. All eligible patients were analyzed.

All patients fasted for at least 8 hours before surgery and without premedication. The patients' pulse oxygen saturation, electrocardiograph, and invasive blood pressure were routinely monitored in the operating room. Anesthesia was induced intravenously with midazolam 0.05 mg kg^{-1} , propofol $1-2 \text{ mg kg}^{-1}$ and remifentanyl $1-2 \text{ } \mu\text{g kg}^{-1}$. Benzene sulfonic acid atracurium 0.15 mg kg^{-1} was administered intravenously to facilitate tracheal intubation. A right internal jugular vein catheter was inserted for blood sampling and administration of fluid after intubation. In the two groups, anesthesia was maintained by the intravenous infusion of remifentanyl ($0.1-0.3 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$) and inhalation of sevoflurane with 1.5 MAC. Muscle relaxation was maintained by the infusion of benzene sulfonic acid atracurium ($2 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$). The inhaled and end-tidal sevoflurane concentrations and the end-tidal carbon dioxide partial pressure were continuously monitored by a PM-9000 express multifunctional monitor (Mindray Medical International Limited, Shenzhen, China). The depth of anesthesia was monitored by an auditory evoked potential index (AEPi) monitor (BS5M284591, Denmark Danmeter), and the level of neuromuscular block

(T_4/T_1 less than 15%) was monitored by a muscle relaxation monitor using train-of-four stimulation (TOF Watch SX, Irish Organon). The intraoperative liquid infusion rate was controlled at about $10 \text{ ml kg}^{-1} \text{ h}^{-1}$ 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 baseline value using vasoactive drugs if necessary. The infusion of atracurium was discontinued 20 min before the end of operation. The administration of sevoflurane and remifentanyl was discontinued at the end of operation. Atropine 0.5 mg and neostigmine 1.0 mg were injected intravenously to antagonize the effect of residual muscle relaxant, and fentanyl $2 \mu\text{g kg}^{-1}$ was intravenously used for postoperative analgesia. Patients were transferred to the postanesthesia care unit (PACU) rapidly after operation and continuously supported by mechanical ventilation. The oxygen flow rate was increased to more than the minute ventilation to avoid the rebreathing of sevoflurane.

Determination of free HFIP

The primary outcome was the concentrations of free HFIP in the blood at different time points. Blood samples (each for 7 ml) were obtained from the internal jugular vein before induction and 0.5, 1, 2 and 3 h after the starting use of sevoflurane, and also obtained at 0.5, 1, 2, and 4 h after discontinuation of inhaled sevoflurane by a series of 20-ml gas-tight heparinized glass syringes. All blood samples were stored in a refrigerator at 4°C for later analysis.

Free HFIP in the blood was determined by a gas chromatograph (GC) (Agilent7890A, Beijing, China) using a two-stage headspace equilibration method^[5,]. The GC equipped with a 30-m steel column (Agilent1909J-413, -60 - 325°C , $320 \mu\text{m} \times 0.25 \mu\text{m}$ film thickness) maintained at 45°C . The GC injection port temperature was 100°C , and the detector temperature was 200°C . The nitrogen carrier flow was 20 ml min^{-1} , and the flame ionization detector supplied with hydrogen at 30 ml min^{-1} and air at 150 ml min^{-1} . In these conditions, the peaks of sevoflurane and HFIP were separated completely, and the typical retention time of HFIP was 1.827 min. The integrator software collected the output from the GC, and peak areas were calculated automatically. The standard curve of HFIP was built by multiple proportion dilution of standard gas with known concentration. All the R^2 values for the linear regression between concentrations of HFIP and peak areas of gas chromatography output were higher than 0.9995 throughout the study. The concentrations of free HFIP in the blood at different time points were calculated by standard curves.

Postoperative clinical evaluations

The secondary outcome was the postoperative clinical evaluation, including the recovery indexes, visual analogue scale (VAS) score[□] and Ramsay sedation scale (RSS)[□]. Each patient was called at an interval with every 5 minutes in PACU. The recovery indexes included four perspectives: the eyes opening time (from the end of surgery to the time when patients can open their eyes in response to observer's verbal command), the command response time (from the end of surgery to the time when patients can squeeze the observer's hands in response to the command for purposeful movement), the extubation time (from the end of surgery to the time when the tracheal catheter is removed), and the orientation recovery time (from the end of surgery to the time when patients can state their name, age or birth date). The tracheal

catheter was removed when patient's consciousness and spontaneous respiration were recovered and a minimal oxygen support was required. The VAS pain score is labeled from 0 (no pain) to 10 (pain as bad as you can imagine): a score of 1 to 3, mild pain; a score of 4 to 6, moderate pain; and a score of 7 to 10, severe pain. Once the patient experienced moderate or severe pain, fentanyl $2 \mu\text{g kg}^{-1}$ was intravenously given immediately. The RSS was labeled from anxiety and agitation (RSS score, 1) to drowsy and had no response (RSS score, 6). The VAS and RSS score were evaluated immediately after extubation (0 min) and at every 15 min interval within 4 hours after extubation. Blinded investigators judged the clinical recovery indexes and post-anesthesia recovery score.

Statistical analysis

All data were analyzed with the statistical package SPSS 21.0 (SPSS Inc., Chicago, Illinois, USA) and presented as mean (standard deviation) for continuous variables. The inhaled sevoflurane dose was calculated as the product of inhaled sevoflurane concentration times its exposure time (MAC \times hours). Patients' demographic data, recovery indexes and consumed anesthetic dosage were analyzed by student's unpaired *t*-test between the two groups. A repeated-measures analysis of variance was used to compare the concentrations of free HFIP in the blood at different time points in each group, and multivariate analysis of variance was used to compare the concentrations of free HFIP at corresponding time points between the two groups. Both the VAS score and RSS score between the two groups were analyzed using the Wilcoxon signed rank test. The difference had statistical significance when *P*-value was less than 0.05.

Results

A total of 48 patients participated in the experiment, 24 cases in each group. In group A, 1 case was excluded from the test due to the operation approach changed. In group B, 1 case with the operation mode changed, and 1 case with the blood loss volume > 200 ml were excluded from the test. Finally, all the data of 23 patients in group A and 22 patients in group B were analyzed (Fig. 1).

All the patients' preoperative characteristics are presented in Table 1. Excepted for the types of surgery, the contents of hemoglobin and platelet and the liver function indexes, patients' characteristics in terms of age, gender, weight, BMI, ASA class and renal function indexes were similar between the two groups. The blood/gas partition coefficient of HFIP measured at 37°C was 452.4 ± 36.7 . The consumed dose of sevoflurane in group A [(4.7 ± 0.3) MAC-h] vs. in group B [(4.7 ± 0.2) MAC-h] had no significant difference ($P > 0.05$). No difference was found in the peak concentration of free HFIP between the two groups after inhaled sevoflurane ($P > 0.05$), but the time to reach the peak value in group B was 1 h later than that in group A (Table 2, Fig. 2). The decreased trend of the level of free HFIP was similar, and no difference was found between the two groups at each corresponding time point after discontinuation of sevoflurane ($P > 0.05$). All the four recovery indexes in group B were significantly longer than those in group A (Table 3) ($P < 0.05$). Compared with group A, a lower VAS score and a higher RSS score were found in group B at 0 min, 15 min, 30 min, 1 h, 2 h and 3 h after extubation ($P < 0.05$). However, no significant differences were found both in the VAS and RSS score between the two groups at 4 h after extubation (Table 4). The

dose of propofol for anesthesia induction in group B was slightly lower than that in group A ($P < 0.05$). The consumed fentanyl in group B during the anesthesia recovery period was significantly lower than that in group A ($P < 0.05$). There was no significant difference in other consumed anesthetic drugs between the two groups (Table 5).

Table 1
Preoperative characteristics and types of surgery of patients

| Characteristics | Group A | Group B |
|---|------------|--------------|
| Number (n) | 24 | 23 |
| Gender (M/F) | 12/12 | 10/13 |
| Age (yr) | 51 ± 8 | 55 ± 10 |
| BMI(Kg m ⁻²) | 22.7 ± 2.5 | 20.9 ± 2.5 |
| ASA class (♢/♢) | 13/11 | 12/11 |
| Operation type (n) | | |
| Hysterectomy | 9 | 3 |
| Resection of gastric tumor | 7 | 2 |
| Resection of colon neoplasms | 8 | 2 |
| Splenectomy | 0 | 16 |
| Routine analysis of blood | | |
| Hemoglobin (gL ⁻¹) | 132 ± 23 | 94 ± 20* |
| Platelet (L ⁻¹) | 194 ± 70 | 65 ± 11* |
| Liver function | | |
| Albumin (gL ⁻¹) | 44.7 ± 6.4 | 39.7 ± 4.4* |
| Total bilirubin (umolL ⁻¹) | 12.9 ± 6.4 | 46.3 ± 24.5* |
| Prothrombin time (s) | 15.4 ± 2.1 | 19.0 ± 1.9* |
| ALT (UL ⁻¹) | 30 ± 7 | 53 ± 24* |
| AST (UL ⁻¹) | 23 ± 11 | 81 ± 21* |
| Renal function | | |
| Creatinine (umol L ⁻¹) | 63.3 ± 5.6 | 65.5 ± 8.1 |
| Urea nitrogen (mmol L ⁻¹) | 4.3 ± 0.8 | 4.5 ± 0.5 |
| Values are displayed as mean (SD).M = male, F = female, ASA class = American Society of Anesthesiologists physical status class, BMI = body mass index, ALT = alanine aminotransferase, AST = aspartate aminotransferase. * P < 0.05 versus the value of group A. | | |

Table 2
Free HFIP concentrations in the blood at different time points in the two groups.

| Group | During sevoflurane anesthesia (h) | | | | After discontinuation of sevoflurane(h) | | | |
|-------|-----------------------------------|------------------------|-----------------------|-----------------------|---|-----------------------|-----------------------|-----------------------|
| | 0.5 | 1 | 2 | 3 | 0.5 | 1 | 2 | 4 |
| A | 0.0414 ± 0.0109 | 0.0648 ± 0.0169 | 0.0549 ± 0.0095 | 0.0454 ± 0.0095 | 0.0432 ± 0.0083 | 0.0350 ± 0.0034 | 0.0331 ± 0.0050 | 0.0285 ± 0.0065 |
| B | 0.0356 ± 0.0072 | 0.0483 ± 0.0082* | 0.0571 ± 0.0046 | 0.0436 ± 0.0031 | 0.0395 ± 0.0034 | 0.0344 ± 0.0034 | 0.0305 ± 0.0030 | 0.0264 ± 0.0060 |

Free HFIP concentrations are expressed as percentage concentration (%). Values are displayed as mean (SD). * $P < 0.05$ versus the value of group A.

Table 3
Recovery indexes testing in the two groups.

| Recovery index | Group A | Group B |
|-----------------------------|---------|---------|
| Eyes opening time (min) | 30 ± 4 | 39 ± 7* |
| Orientation time (min) | 36 ± 4 | 47 ± 9* |
| Command response time (min) | 34 ± 3 | 44 ± 9* |
| Extubation time (min) | 38 ± 3 | 49 ± 8* |

Values are displayed as mean (SD). Clinical recovery indexes were judged by an independent observer who was not an investigator. * $P < 0.05$ versus the value of group A.

Table 4
VAS and RSS score in the two groups.

| | Group | 0 min | 15 min | 30 min | 1 h | 2 h | 3 h | 4 h |
|-----|-------|---------|---------|---------|-----------|-----------|----------|----------|
| VAS | A | 4(3-4) | 5(4-5) | 4(2-4) | 3(2-3) | 3(2-3) | 3(2-3.5) | 2(1-3) |
| | B | 2(0-2)* | 2(2-3)* | 2(1-3)* | 2(2-3.5)* | 2(1.5-3)* | 2(2-3)* | 2(2-3.5) |
| RSS | A | 3(3-4) | 3(3-4) | 2(2-3) | 2(2-3) | 2(2-2) | 2(2-2) | 2(2-2) |
| | B | 4(4-5)* | 4(4-4)* | 4(3-4)* | 4(3-4)* | 3(3-4)* | 3(2-3)* | 2(2-2) |

Values were displayed as median and quartile range (IQR). VAS = Visual analogue scale pain score, RSS = Ramsay sedation score. * $P < 0.05$ versus the value of group A.

Table 5
Comparison of anesthetic drugs in two groups.

| Drugs | Group A | Group B |
|--|--------------|---------------|
| Midazolam (mg) | 3.1 ± 0.5 | 2.1 ± 0.4 |
| Propofol (mg) | 97.3 ± 13.5 | 84.4 ± 11.3* |
| Atracurium (mg) | 18.4 ± 4.1 | 17.8 ± 5.2 |
| Remifentanil (µg) | 1.5 ± 0.0 | 1.4 ± 0.0 |
| Sevoflurane (MAC h) | 4.6 ± 0.3 | 4.7 ± 0.2 |
| Fentanyl (µg) | 163.6 ± 57.0 | 118.9 ± 25.7* |
| Values are displayed as mean (SD). MAC h = minimum alveolar concentration × hour. * <i>P</i> < 0.05 versus the value of group A. | | |

Discussion

In this study, both the patients with grade B liver dysfunction and normal liver function inhaled sevoflurane with 1.5 MAC during the maintenance of anesthesia. Free HFIP could be detected in the two groups at 0.5 hour after inhalation of sevoflurane. It indicates that sevoflurane can be rapidly metabolized by the liver, which has been confirmed in some related studies^[1]. The increase of free HFIP content in the initial phase should be due to the increase of its generation from sevoflurane in the liver. The subsequent reduction of free HFIP content in the blood may mainly relate to its excretion from the kidney with a conjugated form. It implied that the level of free HFIP in the blood did not continuously increase with the prolongation of anesthesia time. Although no significant difference was found in the peak concentration of free HFIP between the two groups, the time to reach the peak concentration in the group with grade B liver dysfunction was delayed for 1 h when compared with that in the group with normal liver function. It indicates that the liver function of grade B still has some influence on the metabolism of sevoflurane, which may be associated with some changes in the biological enzyme about sevoflurane metabolism. Studies have shown that the activity of enzyme CYP 2E1 related to sevoflurane metabolism is normal in cirrhotic patients with liver dysfunction^[2], and the expression of CYP 2E1 decreased significantly only in patients with severe cirrhosis^[3]. However, the content of uridine diphosphoglucuronyl transferase (UDPGT) involved in phase II reaction of sevoflurane metabolism increased significantly in patients with liver cirrhosis^[4]. Therefore, we speculate that the delayed peak time of free HFIP in patients with grade B liver dysfunction may result from the up-regulation of UDPGT. Glucuronidation is beneficial to the excretion of sevoflurane metabolites, which may be a compensatory response after liver injury. The concentrations of free HFIP in the group with grade B liver dysfunction were slightly lower than those in the group with normal liver function in the initial stage of inhalation. However, they had no significant difference after discontinuation of inhalation anesthesia. It indicates

that grade B liver dysfunction has no significant effect on the total metabolic level of sevoflurane. The blood/gas partition coefficient of HFIP (452) measured in this study is about 680 times of sevoflurane (0.66)¹. It means the elimination of HFIP from the body will become very slow. Some studies have shown that HFIP can still be detected in the blood at 24 hours after sevoflurane anesthesia ^[4]. However, the complete elimination time of HFIP needs further study.

HFIP may affect the recovery from anesthesia due to its central nervous system inhibitory action. It may delay the anesthesia recovery time, even result in the occurrence of emergence agitation during recovery. In this study, longer recovery time and deeper sedation and analgesia were found in the patients with grade B liver dysfunction than the patients with normal liver function during the period of anesthesia recovery (Table 4–5). Is this phenomenon caused by the retained free HFIP in the body? Our results indicate that the concentrations of free HFIP both in the two groups are deficient, and have no statistically significant difference in the period of recovery. Therefore, even if the free HFIP content influences the recovery of anesthesia, it should be consistent and slight in the two groups. The relatively deep sedation and analgesia in patients with grade B liver dysfunction may be mainly related to slow metabolism of intravenous anesthetics and the accumulation of sevoflurane in the body. Studies have shown that the metabolism of intravenous anesthetics is often affected by poor liver function, impaired hepatic perfusion, increased extrahepatic shunt and decreased plasma protein synthesis, etc.^[11]

As all know, the metabolism of drugs is mainly mediated by the cytochrome P450 (CYPs) in the liver¹. The contents and activities of enzymes, such as CYP 1A,2C19 and 3A mainly involved in the metabolism of propofol, midazolam and opioids, are easily affected by liver diseases^[19,20]. Intravenous anesthesia with propofol is easy to cause hemodynamic fluctuation, which has a significant individual difference. Studies have confirmed that the pharmacokinetics of propofol is not affected by a single intravenous injection in cirrhotic patients^[11]. However, the elimination half-life of fentanyl prolonged 4–5 times and the blood free concentration of diazepam increased obviously in patients with liver cirrhosis¹. Patients with liver dysfunction may delay drugs' metabolism and affect patient's recovery quality from anesthesia. Therefore, the dosage of these intravenous anesthetic drugs should be reduced appropriately, especially in the period of postoperative analgesia for those patients with liver dysfunction. The result of this study shows that almost no difference exists in the degree of sevoflurane metabolism in the two groups, except the delay of HFIP's peak time in the group with grade B liver dysfunction. Therefore, patients with liver dysfunction are recommended to use inhalation anesthesia with sevoflurane and reduce the amount of intravenous anesthetics, especially fentanyl.

This study only observed one trend of free HFIP in the blood for one inhaled sevoflurane concentration, and did not study the effects of more severe liver dysfunction, such as grade C, on the metabolism of sevoflurane. Therefore, the effects of different inhaled sevoflurane concentrations and different liver function status on the level of HFIP and anesthesia recovery quality needs further study.

In summary, the status of grade B liver dysfunction can significantly delay the peak time of HFIP, but not affect the degree of sevoflurane metabolism when compared with normal liver function.

Abbreviations

HFIP: hexafluoroisopropanol; **MAC:** minimum alveolar concentration; **BMI:** body mass index; **ASA:** American Society of Anesthesiologists; **AEPI:** auditory evoked potential index; **PACU:** post- anaesthesia care unit; **VAS:** visual analogue scale; **RSS:** Ramsay sedation scale; **CYP:** Cytochrome Oxidase; **UDPGT:** uridine diphosphoglucuronyl transferase

Declarations

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Availability of data and materials

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

Authors' contributions

Xiao-Lin Yang helped the study design and revised the paper. Ming Li helped clinical anesthesia management, data collecting and analysis and writing up the paper. Yan Feng helped clinical anesthesia and data collecting. Guo-Yuan Zhang helped the collection and determination of blood samples.

Consent for publication

None.

Conflicts of interest

None.

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Figures

CONSORT diagram

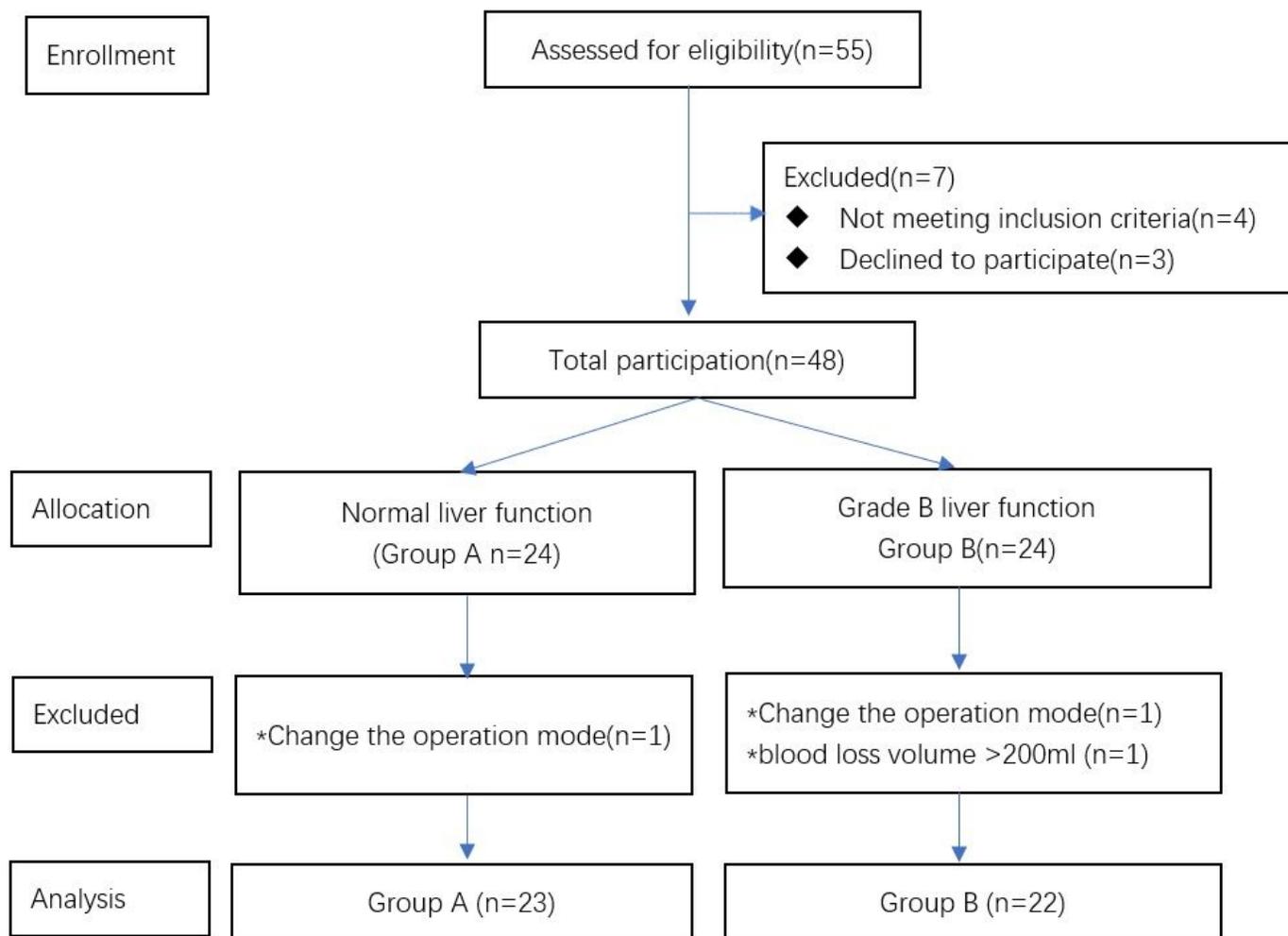


Figure 1

CONSORT flowchart. In this study, 55 patients were screened with 4 patients were exclude for not meeting the needs of inclusion criteria and 3 patients were exclude for declining to participate. Forty-eight patients participated in the experiment, 24 in each group. One case with the operation mode changed was excluded from group A, and two cases were excluded from group B for the operation mode changed and the blood loss volume > 200 ml, respectively. Therefore, all the data of 23 patients in the group A and 22 patients in the group B were analyzed.

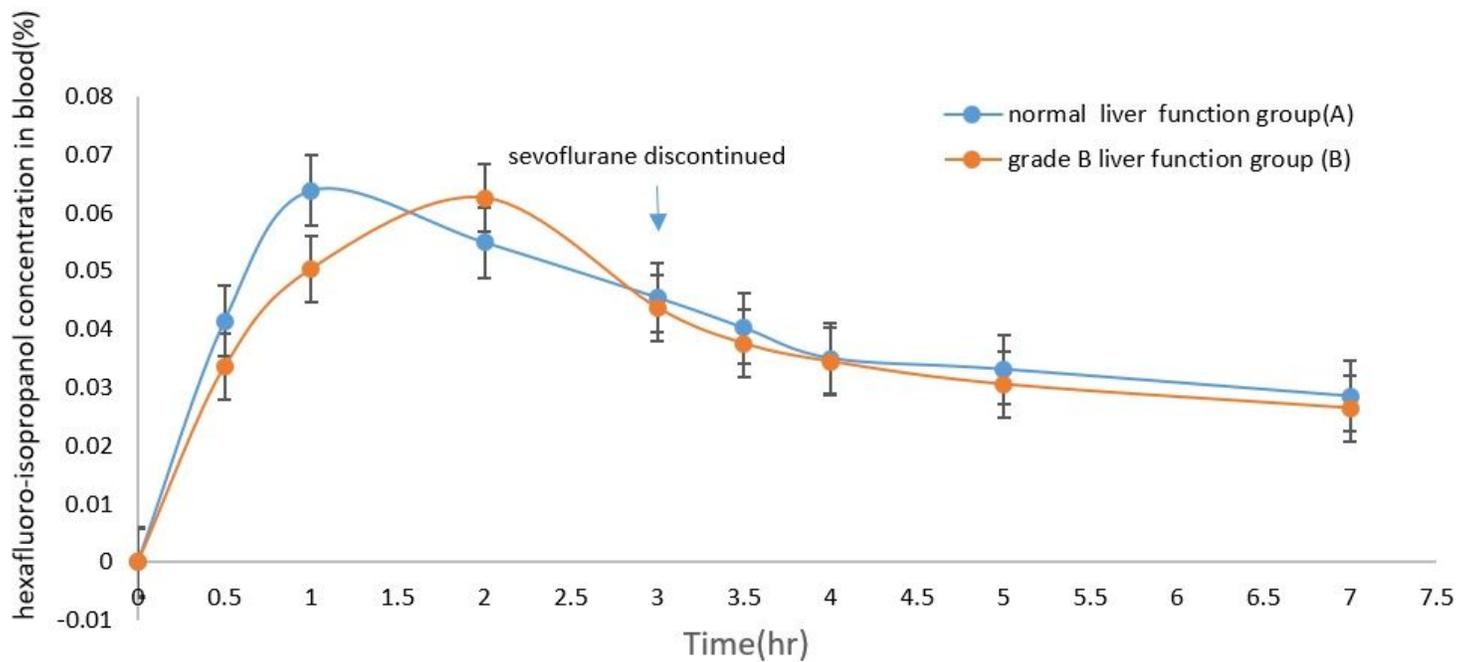


Figure 2

Trend of free HFIP concentration in the blood. The concentration of free HFIP increased and reached its peak value at 1 h in the group A and at 2 h in the group B after inhaled sevoflurane, then both decreased gradually. Free HFIP could still be detected in the blood after the discontinuation of sevoflurane for 4 h in the two groups.