J Anesth (1994) 8:55–59

Journal of
Anesthesia



# Sevoflurane reduced but isoflurane maintained hepatic blood flow during anesthesia in man

TAKASHI HONGO

Department of Anesthesiology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo, 113 Japan

**Abstract:** The indocyanine green (ICG) clearance rate (K) and estimated total hepatic blood flow (THBF) were studied by the single injection technique. The THBF was estimated from the calculated circulating blood volume and the fixed extraction rate. The blood concentration of ICG was determined by the finger piece technique. Twenty-seven patients were randomly divided into three groups of nine and received 67% nitrous oxide, 33% oxygen, and the following volatile anesthetics: 0.8% halothane, 1.2% isoflurane, or 1.7% sevoflurane. ICG (0.5 $mg \cdot kg^{-1}$) was administered intravenously and K was determined three times following the injection. The K value in the halothane and sevoflurane groups decreased significantly 1 h after induction of anesthesia: from $0.188 \pm 0.048$ to $0.142 \pm 0.029$ in the halothane group and from $0.178 \pm 0.027$ to $0.155 \pm 0.021$ in the sevoflurane group. There was no significant change in the K value in the isoflurane group throughout the study.

**Key words:** Indocyanine green, Halothane, Isoflurane, Sevoflurane, Hepatic blood flow

## Introduction

There are many methods to measure hepatic blood flow clinically. The conditions in the operating room require the method to be simple, noninvasive and time-saving without special instruments such as a radioisotope detector, fluoroscopy, and other equipment. Techniques which use a single injection of an indicator are simple and can be measured repeatedly. However, techniques which involve the continuous injection of an indicator [1] require insertion of a catheter into the hepatic vein and withdrawal of blood several times. Furthermore, steps to determine the concentration of the indicator in the blood take much time.

*Address correspondence to*: T. Hongo
Received for publication on November 2, 1992; accepted on May 19, 1993

Recently, an instrument has been developed to detect the blood concentration of the indicator indocyanine green (ICG). The use of an optical finger piece allows us to obtain clearance curves noninvasively [2]. The effects of two anesthetics, isoflurane and sevoflurane, on hepatic circulation have not been defined clinically [3–5]. In the present study, we applied this method to detect total hepatic blood flow (THBF) during inhalation anesthesia.

## Materials and methods

After detailed explanation of the study, informed consent was obtained from 27 patients, ASA class I or II, aged 18–64 years, who were scheduled for tympanoplasty, tonsillectomy, or radical maxillary and ethmoidal sinectomy. Patients with liver diseases were excluded from the study. The patients were randomly divided into three groups of nine to receive the following volatile anesthetics: halothane, isoflurane, or sevoflurane.

The patients received 0.5 mg atropine and 50 mg hydroxyzine pamoate intramuscularly 1 h before the induction of anesthesia. A finger piece for measuring blood concentration of the indicator was attached to the tip of the left index finger. A teflon-mantled needle was inserted into the right cephalic vein.

blood pressure was measured by the oscillometric method and printed out on a recorder (BX-2, Nihon Colin, Nagoya, Japan). ECG was also observed on a cathode-ray tube monitor and recorded on a polygraph (Life scope 08, Nihon Koden Kogyo, Tokyo, Japan). The blood concentration of the indicator, ICG, was determined by an ICG Clearance Meter (RK-1000, Daiichi Pharmaceutical, Tokyo, Japan). The principle whereby the blood concentration of ICG was measured involved the detection of 810 nm transmitted light absorbed by the indicator through the finger tip. The influ-

ence of finger tissue and blood was corrected by the absorbance of light at 940 nm. The central processor unit attached to the instrument calculated the half-decay time ($t_{1/2}$) of the ICG.

*Induction and maintenance of anesthesia*

Anesthesia was induced with 5 mg·kg$^{-1}$ thiamylal sodium, intravenously (i.v.), followed by 1 mg·Kg$^{-1}$ succinylcholine, i.v. After endotracheal intubation, anesthesia was maintained with volatile anesthetics carried with 67% nitrous oxide and 33% oxygen. Three anesthetics, halothane, isoflurane, and sevoflurane, were used for the experiment. The concentrations of the inhaled volatile anesthetics were 0.8% halothane (GOF group), 1.2% isoflurane (GOI group), and 1.7% sevoflurane (GOS group). When these concentrations were converted into minimum alveolar concentrations (MAC), they equaled 1.04 MAC halothane, 1.04 MAC isoflurane, and 1.05 MAC sevoflurane. The concentration of the inhaled anesthetics was measured by a gas analyzer, (type 1304, Brüel-Kjær, Copenhagen, Denmark). Each anesthetic at this concentration could maintain the depth of anesthesia necessary for the surgery.

*Determination of K*

ICG (0.5 mg·kg$^{-1}$) was administered by a bolus injection, and the clearance rate of ICG (K) was calculated from the half-decay time as follows, $K = 0.693/t_{1/2}$.

Namihisa et al. [2] reported that the K value obtained by the finger piece technique differed from the value obtained by the direct determination technique in the blood. The K value was corrected by Namihisa's formula [2]: corrected K = (Kf + 0.002)/0.816, where Kf is the K value obtained by the finger piece technique.

*Experimental protocol*

ICG (0.5 mg·kg$^{-1}$) was administered to all patients and K was determined three times: before induction of anesthesia, 1 h after induction of anesthesia, and 30 min after extubation in the recovery room. The hemodynamic changes in the three groups were recorded and analyzed. Liver functions were assessed for 7 days after anesthesia.

*Preliminary experiment*

Changes in the K value when ICG was administered two times were measured in the preliminary study. ICG (0.5 mg·kg$^{-1}$) was administered to six conscious volunteers two times at a 30-min interval. Then the K value was determined with the ICG Clearance Meter.

The mean and standard deviation of the K value was 0.188 ± 0.034 in the first injection of ICG and 0.187 ± 0.024 in the second injection. The mean difference was 0.001 ± 0.039 which was not statistically significant. There was also no significant difference between the two values of dye concentration which interpolated at zero time. These findings showed that there was no accumulation in the blood 30 min after injection.

*Estimation of hepatic blood flow*

THBF was estimated by the formula, THBF (ml/min) = BV·K/ER, where BV (ml) is the circulating blood volume, K is the clearance rate of ICG, and ER is the rate of extraction of ICG from the liver. The circulating blood volume was calculated by the formula of Ogawa et al. [6]: men, BV (ml) = $0.1682H^3 + 0.05048W + 0.444$; women, BV (ml) = $0.2502H^3 + 0.06253W - 0.662$, where BV is the circulating blood volume, H is body height in meters, and W is body weight in kilograms. The value of ER was fixed at 0.71 in this study according to the study of Kennedy et al. [7].

*Statistics*

The data obtained in this study were presented as the mathematical mean with standard deviation. Equality of paired or nonpaired data over the three groups was tested by Kruskal-Wallis's test or Friedman's test. Differences between two groups were assessed by the Wilcoxon U-test. A probability less than 0.05 was assumed to be significant.

## Results

Table 1 shows the distribution of sex, age, body weight, calculated circulating blood volume, body surface area, and operation time. There were no significant differences among the three groups in any items.

Table 2 shows the K values in the three groups. The K values decreased significantly at 1 h after induction of anesthesia in the GOF group ($P = 0.038$) and the GOS group ($P = 0.033$). In the the GOS group, K decreased from 0.178 ± 0.027 to 0.155 ± 0.021. Thirty min after extubation, the K values of the GOF and the GOS groups recovered to the control values. There were no significant changes in the K value of the GOI group throughout the study. In the values of the three groups at 1 h after induction of anesthesia, K of the GOI group was significantly higher than those of the other groups ($P = 0.049$). The K value of the GOF group at 1 h after induction of anesthesia was significantly lower than the values of the GOF group obtained before anesthesia and 30 min after extubation ($P = 0.045$).

**Table 1.** Patient data

| | GOF group | GOI group | GOS group |
|---|---|---|---|
| Sex (male/female) | 5/4 | 5/4 | 5/4 |
| Age (years) | 35.0 ± 16.2 | 43.2 ± 12.2 | 48.7 ± 12.5 |
| Body weight (kg) | 61.3 ± 10.3 | 57.8 ± 7.2 | 59.9 ± 7.2 |
| Circulating blood volume (ml)[a] | 4202 ± 610 | 4016 ± 536 | 4138 ± 453 |
| Body surface area ($m^2$) | 1.65 ± 0.17 | 1.60 ± 0.12 | 1.63 ± 0.12 |
| Duration of surgery (min) | 109 ± 45 | 120 ± 48 | 126 ± 31 |

GOF, 0.8% halothane; GOI, 1.2% isoflurane; GOS, 1.7% sevoflurane.
Values are expressed as mean ± SD.
[a] Calculated by the formula of Ogawa et al. [6].

**Table 2.** Indocyaning green clearance rate (*K*) and total hepatic blood flow and (*THBF*) values

| Group | Period | K[a] | THBF[a] (ml/min/$m^2$) |
|---|---|---|---|
| GOF | Before anesthesia | 0.188 ± 0.048 | 673 ± 177 |
| | 1 h after induction of anesthesia | 0.142 ± 0.029*† | 506 ± 104*† |
| | 30 min after extubation | 0.145 ± 0.047 | 521 ± 178 |
| GOI | Before anesthesia | 0.182 ± 0.040 | 636 ± 139 |
| | 1 h after induction of anesthesia | 0.174 ± 0.025‡ | 612 ± 98 |
| | 30 min after extubation | 0.157 ± 0.051 | 560 ± 194 |
| GOS | Before anesthesia | 0.178 ± 0.027 | 636 ± 96 |
| | 1 h after induction of anesthesia | 0.155 ± 0.021* | 553 ± 65* |
| | 30 min after extubation | 0.155 ± 0.048 | 557 ± 177 |

GOF, 0.8% halothane; GOI, 1.2% isoflurane; GOS, 1.7% sevoflurane.
* $P < 0.05$, compared with the value before anesthesia in each group.
† $P < 0.05$, compared with the values before anesthesia and 30 min after extubation in each group.
‡ $P < 0.05$, compared with the values of the other two groups at 1 h after induction of anesthesia.
[a] Mean ± SD.

THBF is shown in Table 2. The GOF and GOS groups showed significant decreases in THBF at 1 h after induction of anesthesia, but the GOI group maintained THBF. THBF of the GOF group decreased significantly ($P = 0.028$). THBF of the GOS group decreased from 636 ± 96 ml·min$^{-1}$·m$^{-2}$ to 553 ± 65 ml·min$^{-1}$·m$^{-2}$ ($P = 0.044$). Thirty min after extubation, THBF of the GOF and GOS groups recovered to the control values. There were no significant changes in the GOI group throughout the study.

The mean arterial blood pressure and heart rate are shown in Table 3. The mean arterial blood pressure decreased significantly at 1 h after induction of anesthesia in the GOI and GOS groups ($P = 0.025$ and 0.017, respectively). The heart rate increased significantly at 1 h after induction of anesthesia in the GOF group ($P = 0.021$). In each group, there was no correlation between the decreases of the THBF and the decrease of the mean arterial blood pressure at 1 h after induction of anesthesia.

Table 4 shows the blood chemistry data before and after anesthesia. The post-anesthesia value showed the largest value within 7 days after the surgery. Glutamic oxaloacetic transaminase (GOT) rose significantly after anesthesia in all groups (GOF group, $P = 0.012$; GOI group, $P = 0.008$; and GOS group, $P = 0.038$). There were no significant changes in glutamic pyruvic transaminase (GPT), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH). In each group, there was no correlation between the decrease in THBF at 1 h after induction of anesthesia and elevation of post-anesthesia value of GOT.

**Table 3.** Change of mBP and HR

| | Group | Before anesthesia[a] | 1 h after induction of anesthesia[a] |
|---|---|---|---|
| mBP (mmHg) | GOF | 90 ± 16 | 76 ± 6 |
| | GOI | 99 ± 10 | 80 ± 16* |
| | GOS | 99 ± 11 | 77 ± 12* |
| HR (beats · min$^{-1}$) | GOF | 67 ± 12 | 78 ± 9* |
| | GOI | 69 ± 10 | 79 ± 14 |
| | GOS | 70 ± 10 | 73 ± 11 |

mBP, mean arterial blood pressure; HR, heart rate; GOF, 0.8% halothane; GOI, 1.2% isoflurane; GOS, 1.7% sevoflurane.
* $P < 0.05$, compared with the value before anesthesia in each group.
[a] Mean ± SD.

**Table 4.** Blood chemistry data

| | Group | Before anesthesia[b] | After anesthesia[ab] |
|---|---|---|---|
| GPT (IU/l) | GOF | 16 ± 8 | 21 ± 13 |
| | GOI | 17 ± 6 | 16 ± 7 |
| | GOS | 16 ± 7 | 15 ± 6 |
| GOT (IU/l) | GOF | 18 ± 5 | 35 ± 15* |
| | GOI | 21 ± 6 | 28 ± 9** |
| | GOS | 18 ± 7 | 28 ± 6* |
| ALP (IU/l) | GOF | 130 ± 29 | 131 ± 34 |
| | GOI | 130 ± 35 | 143 ± 56 |
| | GOS | 142 ± 40 | 154 ± 42 |
| LDH (IU/l) | GOF | 307 ± 45 | 295 ± 39 |
| | GOI | 304 ± 51 | 299 ± 42 |
| | GOS | 270 ± 37 | 275 ± 37 |

GOF, 0.8% halothane; GOI, 1.2% isoflurane; GOS, 1.7% sevoflurane; GPT, glutamic pyruvic transaminase; GOT, glutamic oxaloacetic transaminase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase.
* $P < 0.05$; ** $P < 0.01$ compared with the value before anesthesia in each group.
[a] The data represent the largest values within 7 days following the surgery.
[b] Mean ± SD.

## Discussion

Currently, both direct and indirect methods are used to determine hepatic blood flow clinically. The indirect methods include the continuous indicator infusion method, the single indicator injection method, and the dilution method by injection of radioisotopes into the portal vein. Bradley et al. [1] developed the continuous indicator infusion method in 1945. His method requires inserting the catheter into the hepatic vein under fluoroscopy. The method of single injection of the indicator is simple and repeatable, with little invasion.

In the present study, we selected the technique of single injection of ICG. However, there are several problems related to this method that need to be solved. The first is selection of the best indicator. Because ICG combines immediately with plasma albumin, it remains in the circulation for a long time. The liver extracts 97% of the ICG and excretes it into the bile without degradation [8]. The second problem is to determine the blood concentration of the indicator. The concentration of ICG was measured continuously with an instrument developed to detect ICG in blood by means of a finger piece. The clearance rate (K) was calculated automatically by the half-life of ICG in blood ($t_{1/2}$). However, a difference was found between the K value determined with this instrument and direct measurement of the blood concentration. The K value was corrected by a formula proposed by Namihisa et al. [2] in this study. The third problem is estimating the circulating blood volume. The circulating blood volume could not be estimated by this technique, so it was estimated by the formula of Ogawa et al. [6]. It was considered that there was no marked change in blood volume during the study. Furthermore, all patients in the present study received operations involved in otorhinolaryngology with slight surgical invasion and bleeding. The fourth problem is the ER during first-pass elimination in the liver. Many investigators have reported rates between 62% and 77% [3,7,9,10]. There are some reports concerning ER during anesthesia. Goldfarb et al. [3] found no alterations in ER in patients with halothane-$N_2O$ anesthesia and a change from 75% to 58% with isoflurane-$N_2O$ anesthesia. The available information is very limited in patients with sevoflurane-$N_2O$ anesthesia. We set a fixed rate of 71% according to the report of Kennedy et al. [7].

The blood concentration of ICG decreased linearly on a semilogarithmic scale within 15 min after injection, but the tail of concentration curve appeared to deviate after that, suggesting the saturated liver cell by ICG or reverse flow of ICG from the liver cell to the blood. This phenomenon suggested the possibility of interference when ICG was administered repeatedly. The K value was determined two times over a 30-min interval in the preliminary experiments. The data showed no prolongation of the half-decay time. The amount of administered ICG also affected the K value. Gelman et al. [4] observed a marked prolongation of the half-life, when ICG, 5 $mg \cdot kg^{-1}$, was injected by a bolus into dogs. However, Cherrick et al. [11] found no alteration in the K value when they administered a bolus of ICG, 0.5 to 2.0 $mg \cdot kg^{-1}$, to patients with normal liver function. Therefore, the amount of 0.5 $mg \cdot kg^{-1}$ of ICG was administered and the K values were determined over a 1-h interval in the present study.

The K values represent THBF under the assumptions of calculated blood volume and fixed ER in patients with inhalational anesthesia and minor surgery. The THBF obtained before anesthesia in the present study was 649 ± 137 $ml \cdot min^{-1} \cdot m^{-2}$. It was lower than the value reported by Bradley et al. [1] who reported a mean THBF of 868 ± 117 $ml \cdot min^{-1} \cdot m^{-2}$ in healthy adult volunteers.

The effect of anesthetics or anesthetic techniques on hepatic blood flow has been widely investigated in animals. Thulin et al. [12] observed reductions of hepatic arterial blood flow to 54% of controls and portal venous blood flow to 60% of controls when 1% to 2% halothane was inhaled by dogs. Hughes et al. [13] reported a reduction of hepatic arterial blood flow to 35% of controls and portal venous blood flow to 45% of controls after inhalation of 2% halothane in dogs. Gelman et al. [4] reported that 1.4% isoflurane increased hepatic arterial blood flow to 197% of controls, but decreased portal venous flow to 74% of controls, showing no change in THBF. Kohno et al. [5] reported that 2.5% sevoflurane reduced hepatic arterial blood flow to 74% of controls and portal venous blood flow to 76% of controls in dogs.

There has been a small number of clinical investigations on liver hemodynamics. Price et al. [14] showed that inhalation of 1.3% to 1.9% halothane reduced THBF to 78% of controls, by continuous infusion of ICG. Goldfarb et al. [3] reported that 1.3% isoflurane anesthesia combined with $N_2O$ increased THBF to 140% of the value obtained after induction of anesthesia with thiopental and fentanyl. No clinical study on sevoflurane anesthesia has been reported. We found in the present study that halothane anesthesia, combined with $N_2O$, reduced THBF to 75% of controls, but isoflurane anesthesia combined with $N_2O$ maintained the THBF (96% of controls). Our data coincided with the reports of Price et al. [14]. and Goldfarb et al. [3]. We also observed that sevoflurane anesthesia combined with $N_2O$ reduced THBF to 87% of controls.

In summary, the K values in the three groups under inhalational anesthesia by the technique of single injection of ICG and THBF were investigated. The estimation of THBF was based on the calculated blood volume

and fixed ER. The blood concentration of ICG was determined by the finger piece technique and the K value was calculated with an ICG Clearance Meter. This technique allowed a rapid, noninvasive, and bedside estimate of THBF. It revealed a marked reduction in THBF by halothane-$N_2O$ and sevoflurane-$N_2O$ anesthesia, but no change by isoflurane-$N_2O$ anesthesia.

*Acknowledgments.* The author would like to express sincere thanks to Prof. R. Ogawa, M.D., for his guidance during this study, and also wishes to thank the other staff members of the Department of Anesthesiology, Nippon Medical School.

## References

1. Bradley SE, Ingelfinger FJ, Bradley GP, et al. (1945) The estimation of hepatic blood flow in man. J Clin Invest 24:890–897
2. Namihisa T, Awatsu K, Nanbu M, et al. (1990) Clinical evaluation of ICG test by using the optical finger-piece method (in Japanese). Kan Tan Sui 20:347–351
3. Goldfarb G, Debaene B, Ang ET, et al. (1990) Hepatic blood flow in humans during isoflurane-$N_2O$ and halothane-$N_2O$ anesthesia. Anesth Analg 71:349–353
4. Gelman S, Fowler KC, Smith LR (1984) Liver circulation and function during isoflurane and halothane anesthesia. Anesthesiology 61:726–730
5. Kohno Y, Abe Y, Hara S, et al. (1990) Effects of sevoflurane on liver blood flow and metabolism in dogs (in Japanese, with English abstract). Masui To Sosei (Hiroshima J Anesth) 26[Suppl]: 29–33
6. Ogawa R, Fujita T, Fukuda Y (1970) Blood volume studies in healthy Japanese (in Japanese, with English abstract). Kokyuu To Junkan (Respiration and Circulation) 18:833–837
7. Kennedy WF, Everett GB, Cobb LA, et al. (1970) Simultaneous systemic and hepatic hemodynamic measurements during high spinal anesthesia in normal man. Anesth Analg 49:1016–1024
8. Wheeler HO, Cranston WI, Meltzer JI (1958) Hepatic uptake and biliary excretion of indocyanine green in the dog. Proc Soc Exp Biol 99:11–14
9. Caesar J, Shaldon S, Chiandussi L, et al. (1961) The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. Clin Sci 21:43–57
10. Wiegand BD, Ketterer SG, Rapaport E (1960) The use of indocyanine green for the evaluation of hepatic function and blood flow in man. Am J Dig Dis 5:427–436
11. Cherrick GR, Stein SW, Leevy CM, et al. (1960) Indocyanine green: observation on the physical properties, plasma decay, and hepatic extraction. J Clin Invest 39:592–600
12. Thulin L, Andreen M, Irestedt L (1975) Effects of controlled halothane anesthesia on splanchnic blood flow and cardiac output in the dog. Acta Anaesthesiol Scand 19:146–153
13. Hughes RL, Campbell D, Fitch W (1980) Effects of enflurane and halothane on liver blood flow and oxygen consumption in the greyhound. Br J Anaesth 52:1079–1086
14. Price HL, Deutsch S, Davidson IA, et al. (1966) Can general anesthetics produce splanchnic visceral hypoxia by reducing regional blood flow? Anesthesiology 27:24–32