Noninvasive ICG clearance test for estimating hepatic blood flow during halothane and isoflurane anaesthesia

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The purpose of this study was to estimate hepatic blood flow during halothane (HAL) or isoflurane (ISO) anaesthesia with the noninvasive indocyanine green (ICG) clearance test. Twenty-four ASA status I adult patients, scheduled for elective surgery without liver disease, were allocated into four groups. Before surgery, ICG clearance was measured twice in patients before and after 1, 2 MAC HAL-N₂O, 1 and 2 MAC ISO-N₂O anaesthesia by ICG clearance meter (Sumitomo Electronics®, Japan). This method eliminates the blood sampling and delay of the conventional ICG test. The ICG clearance is displayed in two indices: K (ICG disappearance rate) and R₁₅ (ICG retention rate 15 min after 0.5 mg · kg⁻¹ ICG injection). Indirect blood pressure and heart rate were measured simultaneously. Mean arterial pressure (MAP) decreased by 27, 22 and 29% with 2 MAC HAL-N₂O, and with 1 and 2 MAC ISO-N₂O groups, respectively ($P < 0.05$). The ICG clearance was less ($P < 0.05$) in the 2 MAC HAL-N₂O group ($K, 0.087 \text{ min}^{-1}$) than with either awake ($K, 0.131 \text{ min}^{-1}$) or other groups ($K, 0.114$ and 0.144 min^{-1} , in the 1 MAC HAL and ISO-N₂O groups, respectively) in spite of a similar degree of the depletion of MAP in 2 MAC ISO-N₂O group ($K, 0.124 \text{ min}^{-1}$). We conclude that isoflurane has a more favourable effect on liver circulation than does halothane.

Ce travail vise à évaluer le débit sanguin hépatique pendant l'anesthésie à l'halothane (HAL) ou à l'isoflurane (ISO) par

Key words

ANAESTHETICS, VOLATILE: halothane, isoflurane;
LIVER: blood flow – indocyanine green test.

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Accepted for publication 4th November, 1994.

l'épreuve de clairance non invasif du vert d'indocyanine (ICG). Vingt-quatre adultes ASA I exempts de toute affection hépatique, programmés pour une chirurgie non urgente sont répartis en quatre groupes. Avant l'intervention, la clairance de l'ICG est mesurée à deux reprises avant et après une anesthésie HAL-N₂O MAC 1 et 2, et ISO-N₂O MAC 1 et 2, avec un appareil de mesure d'ICG (Sumitomo Electronics®, Japon). Cette méthode élimine l'échantillonnage sanguin et le délai propre à l'épreuve d'ICG conventionnelle. La clairance de l'ICG est affichée sous deux index: K (la vitesse de disparition de l'ICG) et R₁₅ (le taux de rétention de l'ICG 15 min après l'injection de 0,5 mg · kg⁻¹ d'ICG). La pression artérielle indirecte et la fréquence cardiaque sont mesurées simultanément. La pression artérielle moyenne (PAM) diminue de 27, 22 et 29% respectivement dans le groupe HAL-N₂O MAC 2, et dans les groupes ISO-N₂O MAC 1 et 2 ($P < 0,05$). La clairance de l'ICG est moins élevée ($P < 0,05$) dans le groupe HAL-N₂O MAC 2 ($K, 0,087 \text{ min}^{-1}$) que soit dans les groupes éveillés ($K, 0,131 \text{ min}^{-1}$) ou les autres groupes ($K, 0,114$ et $0,144 \text{ min}^{-1}$, respectivement, dans les groupes HAL-N₂O MAC 1 et ISO-N₂O) malgré un niveau de diminution de la PAM identique dans le groupe ISO-N₂O MAC 2 ($K, 0,124 \text{ min}^{-1}$). Nous concluons que l'isoflurane a un effet plus favorable sur la circulation hépatique que l'halothane.

Inhalational anaesthetics that decrease cardiac output will lead to at least proportional decrements in total hepatic blood flow. Halothane has been reported to reduce hepatic blood flow and hepatic oxygen supply in animal experiments.^{1,2} Isoflurane increases hepatic arterial blood flow and maintains total hepatic blood flow, in contrast to halothane.¹⁻⁴ There have been only a few studies addressing the effects of anaesthetics on hepatic blood flow in humans:^{5,6} no dose-related clinical studies have compared the effects of halothane and isoflurane on indocyanine green (ICG) clearance.

A new method of measuring the disappearance rate

TABLE I Details of patients studied

	<i>n</i>	<i>Age (yr)</i>	<i>BW (kg)</i>	<i>Body mass index (BMI)</i>
H-1 (halothane 1 MAC)	6	40.4 ± 1.9	55.1 ± 1.4	22.2 ± 0.1
H-2 (halothane 2 MAC)	6	45.7 ± 1.9	60.0 ± 1.9	22.0 ± 0.1
I-1 (isoflurane 1 MAC)	6	43.0 ± 2.4	54.2 ± 1.7	22.1 ± 0.1
I-2 (isoflurane 2 MAC)	6	38.9 ± 2.8	60.7 ± 1.2	22.2 ± 0.1

(Mean ± SEM).

of ICG from the plasma through a photopiece⁷ eliminates the blood sampling and delay of the original ICG test while providing an estimation of hepatic blood flow. With this instrument, the optical sensor utilizes two light-emitting diodes operating at 810 and 940 nm wavelength, and one photodiode to sample the transmittance of light through the tip of the index finger. Thus, the plasma disappearance rate of ICG is measured and expressed as K. The 15 min retention rate of ICG (R_{15}) is calculated from K. The aim of this study was to evaluate the effects of halothane and isoflurane on ICG clearance using the finger piece method.

Methods

We studied 24 adult patients undergoing elective minor oral or otolaryngeal surgery. Ethics Committee approval and informed consent were obtained. The patients were allocated randomly to four groups: Group H-1, H-2, I-1 and I-2 were given 1 MAC halothane ($n = 6$), 2 MAC halothane ($n = 6$), 1 MAC isoflurane ($n = 6$) and 2 MAC isoflurane ($n = 6$), respectively. Concentrations of 0.8% for halothane and 1.3% for isoflurane were considered as 1 MAC. Patients with evidence of liver disease, either clinical or biochemical, or who had received an inhalation anaesthetic within three months, were excluded.

All patients were premedicated with midazolam (2.5 mg *im*) and atropine sulphate (0.5 mg *im*) at least one hour before entering the operating theatre. Anaesthesia was induced with thiamylal (5 mg · kg⁻¹) followed by succinylcholine (1 mg · kg⁻¹) to facilitate tracheal intubation. The patients' lungs were ventilated mechanically with 67% nitrous oxide (N₂O) in oxygen and the respective inhalational anaesthetic. End-tidal carbon dioxide concentrations (PETCO₂) were monitored (Capnomac™, Datex™, Helsinki, Finland) to maintain normocapnia and end-expired concentration of the inhalational anaesthetics were measured (Normac™, Datex™, Helsinki, Finland) throughout the experiment. The ICG clearance was read from an ICG clearance meter RK-1000™ (Sumitomo Electric™), following the intravenous injection of 0.5 mg · kg⁻¹ of ICG within 30 sec.

The data are shown as the ICG disappearance rate (K) and the ICG retention rate 15 min after ICG injection

(R_{15}). Before the surgical procedure, the measurements were performed prior to and 15 min after induction of each anaesthetic. Heart rate and blood pressure were monitored simultaneously.

The data were analyzed to compare values obtained for each anaesthetic agent at various MAC values and for comparison between anaesthetic agents at comparable MAC values. Two-way analysis of variance and Duncan multiple-range testing were used, with significance defined as $P < 0.05$. All data are represented as mean ± SEM.

Results

There were no differences among the groups in either age, body weight or body mass index (Table I).

Haemodynamic changes, PETCO₂ and ICG clearance before and after induction of anaesthesia in each group are shown in Table II. There were no differences among the groups in PETCO₂; mean arterial pressure (MAP) was decreased in the H-2 (−26.5%), I-1 (−22.0%) and I-2 (−28.9%) groups after induction of anaesthesia. Only in the H-1 group did MAP remain close to the pre-induction level during the study. The 2 MAC isoflurane group was the only group in which the heart rate increased 54.3% ($P < 0.05$) compared with the pre-anaesthesia value. The ICG disappearance rate (K) was reduced from $0.131 \pm 0.001 \text{ min}^{-1}$ in awake to $0.087 \pm 0.001 \text{ min}^{-1}$ during 2 MAC halothane anaesthesia ($P < 0.05$). The ICG retention rate 15 min after the ICG injection showed an increase from $14.3 \pm 0.5\%$ in awake to $27.2 \pm 0.9\%$ in the H-2 group ($P < 0.05$). The differences between the results with 2 MAC halothane and those in other groups were statistically significant ($P < 0.05$).

Discussion

Indocyanine green clearance techniques can be used to estimate hepatic blood flow (HBF) and hepatic function.⁸ Because the conventional ICG clearance test requires multiple blood sampling and several hours for processing before receiving the results, it is unsuitable for practical and non-invasive clinical measurement. Our previous study found that the ICG clearance meter test can be performed quickly and non-invasively.⁹

Knowledge of the hepatic extraction ratio for ICG is

TABLE II Haemodynamics, PETCO₂ and ICG clearance during halothane and isoflurane anaesthesia

	Halothane				Isoflurane			
	Awake	1 MAC	Awake	2 MAC	Awake	1 MAC	Awake	2 MAC
HR (bpm)	70.2 ± 3.5	76.0 ± 1.6	77.0 ± 2.2	72.7 ± 1.6	73.8 ± 1.3	75.8 ± 2.8	60.5 ± 1.4	93.3 ± 4.8 ^{*b}
sBP (mmHg)	123.0 ± 4.0	113.4 ± 4.3	120.0 ± 3.0	87.7 ± 2.0 ^{*a}	130.0 ± 2.1	98.0 ± 2.5 ^{*a}	120.8 ± 2.2	91.3 ± 2.5 ^{*a}
dBp (mmHg)	76.0 ± 1.6	72.2 ± 2.7	73.0 ± 3.2	53.3 ± 2.6 ^{*a}	78.0 ± 2.3	54.3 ± 0.9 ^a	67.8 ± 2.7	43.5 ± 1.2 ^{*a}
MAP (mmHg)	91.4 ± 2.3	85.8 ± 3.2	88.7 ± 3.1	64.7 ± 2.4 ^{*a}	76.2 ± 8.7	69.3 ± 0.8 ^{*a}	86.8 ± 2.4	61.5 ± 1.4 ^{*a}
PETCO ₂ (mmHg)		38.1 ± 0.1		39.0 ± 0.2		38.5 ± 0.1		38.4 ± 0.2
K	0.120 ± 0.003	0.114 ± 0.004	0.131 ± 0.001	0.087 ± 0.001 ^{*†}	0.135 ± 0.004	0.144 ± 0.003	0.124 ± 0.006	0.124 ± 0.007
R ₁₅ (%)	17.1 ± 0.9	19.6 ± 1.2	14.3 ± 0.5	27.2 ± 0.9 ^{*†}	14.2 ± 1.2	11.9 ± 0.6	18.4 ± 2.3	18.7 ± 2.8

(Mean ± SEM)

K = ICG disappearance rate; R₁₅ = ICG retention rate 15 min after the injection of ICG.^{*}P < 0.05 vs control in corresponding anaesthetic[†]P < 0.05 vs 1 or 2 MAC isoflurane in corresponding stages.^aP < 0.05 vs 1 MAC halothane in corresponding stages.^bP < 0.05 vs other three groups in corresponding stages.

necessary to measure liver blood flow quantitatively, because such a dye removal test reflects the blood flow, uptake, intracellular binding, metabolic transformation, and biliary excretion. If any of these physiological functions is impaired, systemic retention of the dye will occur. Although it is impossible to determine the accurate HBF changes by ICG clearance without knowing the hepatic extraction rate, fluoroscopic hepatic catheterization is not performed so that traumatic insertion and irradiation are avoided. However, the ICG clearance technique has been used as a reliable method to estimate HBF in humans^{5,6,10} and animals.¹¹ Thus, non-invasive ICG clearance test can provide valuable information concerning intraoperative hepatic blood flow.

Our present study shows that during 1 MAC halothane-N₂O, 1 and 2 MAC isoflurane-N₂O in humans ICG clearance is maintained. Only the use of 2 MAC halothane-N₂O caused reduced ICG clearance despite a similar degree of MAP depression in the 2 MAC isoflurane-N₂O group. Because halothane and isoflurane show a different degree of myocardial depression even at the same MAC, the possibility that halothane reduces the ICG clearance by decreasing cardiac output may exist. Therefore, it is difficult to determine whether halothane causes the delayed ICG clearance directly or indirectly because we did not measure cardiac output in the present study. Cousins *et al.*⁶ reported that 0.5% halothane-N₂O did not cause any changes in ICG clearance in humans. Their results are in agreement with our data of 1 MAC halothane-N₂O but they did not perform a dose-response study and their measurements were performed following laparotomy.

The effects of anaesthetics on hepatic blood flow (HBF) have not been studied extensively in humans without surgical stimulation. It has been reported that laparotomy per se caused a greater decrease in hepatic blood

flow than anaesthetics.¹² Controlled ventilation¹³ and application of PEEP¹⁴ reduce portal venous blood flow or HBF, respectively. In humans, it has been reported that anaesthetic induction using either thiopentone-succinylcholine¹² or thiopentone-fentanyl-pancuronium⁵ decreases HBF by 20%. It remains difficult to distinguish the effects caused by either ventilation or induction of anaesthesia from other factors, but the present study was designed to minimize the effects of other factors. Thus, the differences between the groups seems to be attributable to the differential effects of the anaesthetic agents and dosages.

Hepatic arterial blood flow shows pressure-flow autoregulation in the normal animals but not during severe fasting.¹⁵ Under physiological conditions, portal blood flow (PBF) changes modulate hepatic arterial tone to maintain total hepatic blood flow.¹⁶ This phenomenon is called the "hepatic arterial buffer response," and its sensitivity to inhalational anaesthetics is currently under investigation. Halothane impairs this response and decreases HBF secondary to reductions in both portal blood flow and hepatic arterial blood flow in animal studies.^{1-3,17-19}

In dogs, Gelman *et al.*³ reported that the hepatic arterial buffer response was maintained during isoflurane anaesthesia; the decrease in PBF was compensated by the increase of hepatic arterial blood flow. Although ICG clearance did not correlate with changes in liver blood flow in their experiment, they observed that ICG clearance decreased during halothane anaesthesia and did not change during isoflurane anaesthesia. Their findings agree with the present study. However, the effect of isoflurane on hepatic blood flow has been debated. Bernard *et al.*²⁰ observed no change in HBF during isoflurane anaesthesia in the chronically instrumented dogs. Frink *et al.*¹⁷ observed a decrease in PBF and total hepatic

blood flow in greyhounds, though the effect of isoflurane was less than that of halothane. These conflicting results may be due to the differences of breeds (mongrel dog vs greyhound) or techniques for estimating HBF (electromagnetic flow probe vs pulsed Doppler flow probe vs labeled microspheres).

In humans, Goldfarb *et al.*⁵ observed a non-significant 20% decrease in HBF during 1 MAC halothane anaesthesia, and an increase (+40%) during 1 MAC isoflurane anaesthesia with nitrous oxide, using conventional ICG and fluoroscopic hepatic catheterization. However, some methodological difficulties may have existed in their study because they changed the position of the Swan-Ganz catheter from the pulmonary artery into a hepatic vein at each measurement and the timing of blood samplings for measuring ICG clearance was not mentioned. Moreover, only a single dose of each anaesthetic was studied. They reported that ICG clearance decreased during 1 MAC halothane anaesthesia and postulated that the effects of halogenated agents stem from direct effects on the splanchnic circulation. In the present study, only 2 MAC halothane induced delay of ICG clearance; neither 1 MAC or 2 MAC isoflurane resulted in any deterioration. The difference between our results and Goldfarb *et al.* may have been due to the different techniques for measuring ICG clearance.

In conclusion, it appears that isoflurane and halothane cause different types and degrees of liver circulatory disturbance. We suggest that isoflurane at 2 MAC has a less deteriorative effect on liver circulation than does halothane in humans. The finger piece ICG test is useful to evaluate a liver circulation in operating room because it is non-invasive and convenient.

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