Effect of Halothane and Enflurane on Hepatic Blood Flow and Oxygen Consumption in Dogs

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We investigated the relative effects of 0.5, 1.0, 1.5, 2.0 MAC halothane and enflurane, and concurrent noxious stimulus on hepatic blood flow and oxygen consumption in 14 mongrel dogs randomly divided into groups of seven each. Hepatic arterial and portal venous blood flow (HABF and PVBF, respectively) were measured continuously using ultrasonic transit time flow meter. Mean arterial blood pressure (MAP), cardiac index (CI), hepatic oxygen supply, and hepatic oxygen consumption ($H\dot{V}_{O_2}$) were measured. Halothane significantly deceased HABF, but not PVBF in a dose dependent manner. Enflurane did not affect HABF and PVBF significantly. MAP and CI decreased in both groups, with halothane producing more marked decreases than enflurane. $H\dot{V}_{O_2}$ did not change with enflurane, but did with halothane, producing significant differences, with halothane being greater at 1.5, 2.0 MAC. A noxious stimulus only caused minor change in blood flow. The results suggest that liver blood flow and oxygen consumption are affected differently by halothane and enflurane and that halothane has a stronger tendency to cause an imbalance between liver oxygen supply and consumption than dose enflurane. (Key words: halothane, enflurane, hepatic blood flow, hepatic oxygen consumption)

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Over the past few decades, there have been several reports on the hepatic damage associated with halothane anesthesia[1,2]. The mechanism of halothane hepatotoxicity is still in debate. It is suggested that there are two types of halothane-induced hepatic damage, severe and mild[2,3]. Immunologic and metabolic factors may govern the mechanism of the former type, whereas toxic or hypoxic factors may play a major role in the latter type[3]. Hypoxia *per se* may cause hepatic damage[4], and halothane is reported to change hepatic blood flow[5,6]. From these studies, it is predicted that halothane may produce hypoxia in the liver by causing imbalance between hepatic oxygen supply and hepatic oxygen consumption induced by the change of hepatic blood flow.

There are only a few reports of hepatic damage after enflurane anesthesia[7,8]. So it may be more safe to use enflurane than halothane when repeated inhalation anesthetics are to be used or when any suspicion of liver desease exists. The difference between halothane and enflurane may result from the reductive metabolism of halothane and/or from a more pronounced hypoxia during halothane anesthesia.

To examine the latter postulate, we in-

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Table 1. Effect of halothane and enflurane on MAP, CI and Chv_{O_2}

		Anesthetic concentration (MAC)			
		0.5	1.0	1.5	2.0
MAP (mmHg)	halothane	87.5 ± 5.5	75.1 ± 2.7	62.1 ± 5.5***	52.5 ± 4.1***
	enflurane	122.8 ± 7.9	99.8 ± 8.6	84.6 ± 6.3***	63.0 ± 6.6***
CI ($\ell min^{-1}m^{-2}$)	halothane	2.01 ± 0.16	1.74 ± 0.12	1.97 ± 0.23	1.35 ± 0.10***
	enflurane	2.94 ± 0.19	2.54 ± 0.18	2.29 ± 0.21*	1.76 ± 0.17***
Chv_{O_2} ($m\ell\ d\ell^{-1}$)	halothane	12.8 ± 1.3	12.4 ± 1.7	11.4 ± 1.4	9.3 ± 1.1
	enflurane	16.5 ± 1.1	16.1 ± 0.9$^+$	14.3 ± 0.8	13.2 ± 1.2$^+$

Values are mean ± SE n = 7
*$P < 0.05$, ***$P < 0.01$ vs 0.5MAC, $^+P < 0.05$ vs halothane

vestigated the effects of halothane and enflurane at equipotent anesthetic concentrations (MAC equivalent) on hepatic blood flow, oxygen supply and oxygen consumption.

Materials and Methods

Fourteen mongrel dogs weighing 12–20 kg were divided into two groups of 7 dogs. Anesthesia was induced with the designated agent (halothane or enflurane) and 100% oxygen. Pancuronium bromide 0.15 $mg \cdot kg^{-1}$ i.v. was administered for immobilization during laparotomy. After tracheal intubation, controlled ventilation with a constant Pa_{CO_2} (35–40 mmHg) was assured. Following laparotomy, the gastroduodenal artery was ligated and ultrasonic transit time flow meter probes were placed on the common hepatic artery and the portal vein. The femoral artery was cannulated to permit blood sampling and measurement of mean arterial pressure. Cardiac output was measured by thermal dilution using a Swan-Ganz catheter placed in the pulmonary artery. The hepatic and portal vein were cannulated via the external jugular and splenic vein respectively.

Halothane was administered from a Fluotec 3 (Cyprane) and enflurane was administered from a Enfluratec (Cyprane). One MAC is regarded to be 0.9% halothane[9] and 2% enflurane[10] in dogs. After maintaining end expiratory anesthetic (halothane and enflurane) concentration stable at 0.5, 1.0, 1.5 and 2.0 MAC (each for more than 15 min), a clamp was applied to the tail and the tail was twisted for one minute as a noxious stimulus. End tidal concentrations of anesthetics were monitored with a PERKIN-ELMER 1100 Medical Gas Analyzer.

Hepatic arterial blood flow (HABF), portal venous blood flow (PVBF) and mean arterial pressure (MAP) were recorded continuously on a polygraph. The following measurements were performed before and immediately after tail clamp; cardiac output (CO), and blood oxygen content of arterial (Ca_{O_2}), portal venous (Cpv_{O_2}), and hepatic venous (Chv_{O_2}) blood.

Hepatic oxygen consumption ($H\dot{V}_{O_2}$) and hepatic oxygen supply (O_2supp.) were calculated as:

$H\dot{V}_{O_2} = HABF\ (Ca_{O_2} - Chv_{O_2})/100 + PVBF\ (Cpv_{O_2} - Chv_{O_2})/100$

$O_2supp. = HABF \cdot Ca_{O_2}/100 + PVBF \cdot Cpv_{O_2}/100$

where $H\dot{V}_{O_2}$, O_2supp., HABF, and PVBF are in ml min^{-1}.

Blood gas tentions, and oxygen content were measured using a CORNING 178 pH/Blood Gas Analyzer and a LEX CONTL, respectively.

The data are presented by mean values ± standard errors of the mean. Statistical evaluation was performed using Multiple comparison after Analysis of Variance (ANOVA) test.

Results

The tail clamp did not affect any values. We therefore show only the data taken before stimulation. MAP and CI decreased in a linear fashion from the value of 0.5 MAC dose-dependently with both halothane and enflurane. There were small decreases in

Table 2. Effect of halothane and enflurane on HABF, PVBF and THBF

		Anesthetic concentration (MAC)			
		0.5	1.0	1.5	2.0
HABF	halothane	15.9 ± 1.7	13.4 ± 1.6	11.3 ± 1.9	8.2 ± 1.2*
($m\ell\ min^{-1}100g^{-1}$)	enflurane	12.3 ± 2.6	1.29 ± 3.1	15.7 ± 4.6	13.3 ± 3.5
PVBF	halothane	59.2 ± 4.2	59.4 ± 4.5	56.6 ± 6.0	53.8 ± 6.4
($m\ell\ min^{-1}100g^{-1}$)	enflurane	59.5 ± 11.3	52.6 ± 9.3	45.2 ± 8.3	34.9 ± 5.7
THBF	halothane	74.5 ± 3.7	72.0 ± 4.5	67.8 ± 6.1	60.8 ± 7.4
($m\ell\ min^{-1}100g^{-1}$)	enflurane	71.3 ± 11.2	65.0 ± 9.7	60.4 ± 8.8	47.0 ± 7.0

Values are mean ± SE n = 7, $^*P < 0.05$ vs 0.5MAC

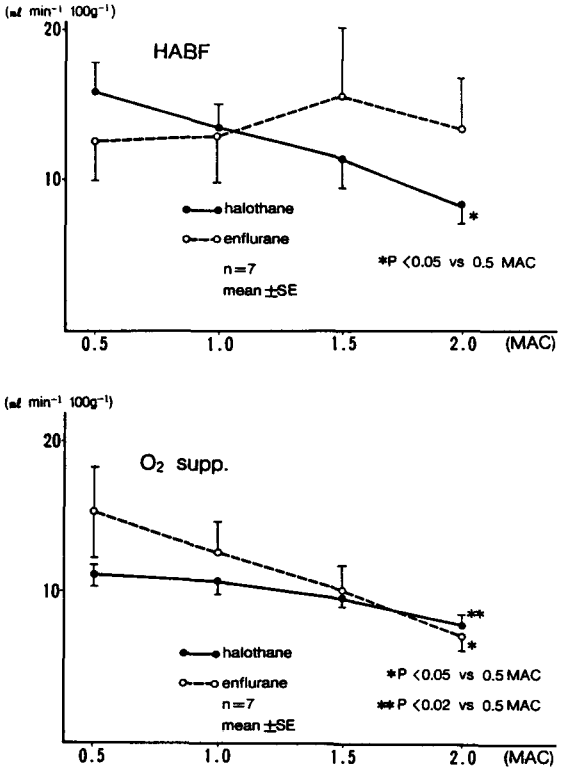

Fig. 1. Changes in hepatic arterial blood flow (HABF) and hepatic oxygen supply (O_2 supp.) by increasing of anesthetic concentrations.

Chv_{O_2} with increasing concentration of anesthetics which were not significant. Halothane and enflurane differed significantly in their effect on Chv_{O_2} at 1.0, 2.0 MAC. Halothane produced greater decreases than enflurane (table 1).

HABF decreased significantly under halothane at 2.0 MAC compared to 0.5 MAC but did not change during enflurane anesthesia. On the other hand, neither anesthetic altered PVBF. Total hepatic blood flow (THBF) decreased slightly which were not significant under both groups (table 2).

Hepatic oxygen consumption ($H\dot{V}_{O_2}$) tended to increase dose-dependently under halothane, but did not change under enflurane anesthesia and there were significant differences between the effect of halothane and enflurane at 1.5, 2.0 MAC (fig. 2). Hepatic oxygen supply (O_2supp.) decreased significantly in both groups in a similar manner dose-dependently (fig. 1).

Discussion

We found that increasing concentrations of halothane and enflurane significantly and

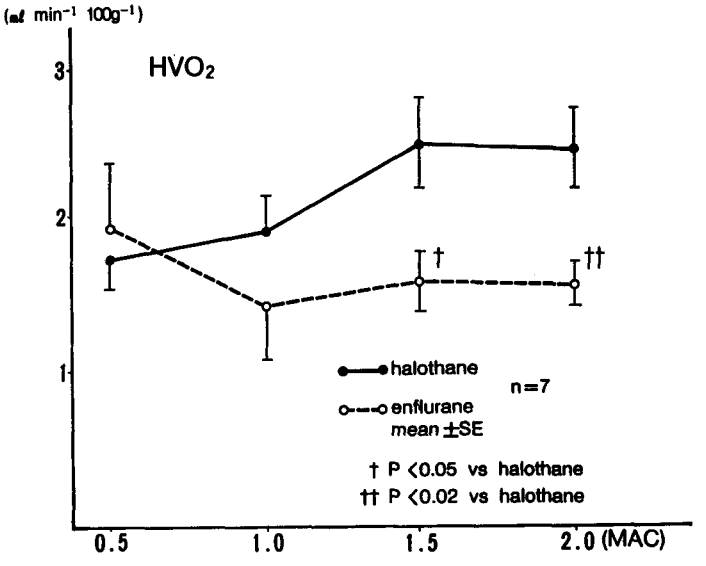

Fig. 2. Changes in hepatic oxygen consumption ($H\dot{V}_{O_2}$) by increasing of anesthetic concentration.

dose-dependently decreased circulatoly variables in the systemic (MAP, CO) but not hepatic (HABF, PVBF, THBF) circulations. Only halothane decreased HABF confirming the report by Thulin and Andreen[11]. PVBF and THBF did not change significantly with anesthetic dose.

In previous studies, halothane produced progressive decreases in PVBF and THBF with parallel decreases in CO[5,12]. PVBF, THBF and HABF have been found to be decreased during enflurane anesthesia[13,14]. The discrepancy between these studies and our study may be due to several differences in methods. First, we compared the values at each MAC (1.0, 1.5, 2.0 MAC) to the value at 0.5 MAC. In most previous studies, awake values were used as control. Possibly, our values for PVBF, THBF and HABF changed slightly with increasing concentration of anesthetics because they began at already decreased levels. Secondly, in many studies, barbiturate was used to induce anesthesia or control state. In contrast we used the inhalation agent and 100% oxygen. Several reports indicate that barbiturate anesthesia influences hepatic blood flow[15,16]. Lastly, HABF and PVBF in other studies were usually measured with electromagnetic flow meters or radioactive microspheres. Laparotomy was not performed in studies using the microsphere technique. Regarding electromagnetic flow probes, inaccuracies may result from misfitting between the probes and vessel walls[17]. The ultrasonic transit time flow meter overcomes this obsticle.

In the present study, changes in HABF were different during halothane and enflurane anesthesia. HABF decreased in a linear fashion from 0.5 MAC with increasing concentrations of halothane, but did not change during enflurane anesthesia. On the other hand, hepatic oxygen supply decreased dose-dependently in a similar fashion with both anesthetics (fig. 1). It is shown that there is a HABF-PVBF reciprocal relationship to maintain the oxygen supply to the liver[9,10]. Some studies have suggested that the hepatic oxygen requirement itself governs the reciprocity between HABF and PVBF[18,19]. It seems conceivable that the pattern of the HABF-PVBF reciprocal relationship may be affected differently among anesthetics and the loss of the HABF-PVBF reciprocal relationship may produce significant decreases in hepatic oxygen supply at 2.0 MAC with both anesthetics.

In our study, changes in hepatic oxygen consumption ($H\dot{V}_{O_2}$) were different between halothane and enflurane. These changes were dose-independent for both anesthetics. However, $H\dot{V}_{O_2}$ was noted to decrease signifi-

cantly with enflurane at 1.5, 2.0 MAC where with halothane $H\dot{V}_{O_2}$ did not decrease. Since oxygen supply decreased similarly with both anesthetics, the balance between $H\dot{V}_{O_2}$ and oxygen supply become marginal with increasing concentration of halothane, compared to enflurane. This was also represented by the change of hepatic venous content (Chv_{O_2}). Anything that produces imbalance between oxygen supply and uptake leading to a rise in hepatic oxygen extraction, causes a decrease in Chv_{O_2}[20] In our study, Chv_{O_2} was more reduced by halothane than enflurane.

In conclusion, halothane and enflurane affect hepatic blood flow and $H\dot{V}_{O_2}$ in different manners. $H\dot{V}_{O_2}$ is held at higher levels with halothane than enflurane, and imbalance between hepatic oxygen supply and $H\dot{V}_{O_2}$ is more likely to occur with halothane than enflurane. This may be one of the factors of halothane hepatotoxicity.

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