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Hepatic Oxygen Supply and Consumption in Rats Exposed to Thiopental, Halothane, Enflurane, and Isoflurane in the Presence of Hypoxia

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ABBREVIATIONS

Pb = phenobarbital
FI_{O_2} = inspired oxygen concentration
A = systemic arterial
HV = hepatic venous
PV = portal venous
BF = blood flow
IP = intraperitoneal
Hb = hemoglobin
CO = cardiac output
HABF = hepatic arterial blood flow
PVBF = portal venous blood flow
$\dot{V}hep_{O_2}$ = oxygen consumption in the liver
Ca_{O_2} = oxygen content in arterial blood
Cpv_{O_2} = oxygen content in portal venous blood
Chv_{O_2} = oxygen content in hepatic venous blood
THBF = total hepatic blood flow
Sa_{O_2} = arterial oxygen saturation
Pa_{O_2} = arterial oxygen tension
Pa_{CO_2} = arterial carbon dioxide tension

Hepatic oxygen supply and uptake were assessed in phenobarbital-pretreated male Sprague-Dawley rats receiving subanesthetic doses of thiopental, halothane, enflurane, or isoflurane combined with hypoxia (approximately 0.5 MAC and 12% oxygen) for the purpose of evaluating the role of these combinations in hepatic blood flow alterations and the concomitant hepatic oxygen supply and uptake. Hepatic blood flow was measured using microspheres; hepatic oxygen supply and consumption was calculated from measured hepatic blood flow and oxygen content in hepatic arterial, portal venous, and hepatic venous blood. In all anesthetic groups, total hepatic blood flow did not change from the control value. Oxygen supply to the liver was decreased from air control values in all anesthetic groups, but there were no significant differences among anesthetic groups. Hepatic oxygen consumption was significantly lower in animals exposed to halothane and isoflurane *versus* air controls, whereas it was not significantly decreased in animals receiving thiopental or enflurane. The hepatic oxygen supply/consumption ratio was higher in the air control and the isoflurane groups than in other groups; however, no significant differences in this ratio were observed among the thiopental, halothane, and enflurane groups. Oxygen content in hepatic venous blood correlated well with hepatic oxygen supply/consumption ratio in all five groups. These results show that, during exposure to mild hypoxia, a sub-MAC dose of isoflurane maintains the relationship of hepatic oxygen supply to uptake better than thiopental, halothane, or enflurane. However, a subanesthetic dose of halothane did not aggravate liver hypoxia specifically, compared with thiopental or enflurane. (Key words: Anesthetics, intravenous: thiopental. Anesthetics, volatile: enflurane; halothane; isoflurane. Liver: blood flow; hepatotoxicity; oxygen consumption. Measurement techniques: blood flow; microspheres. Metabolism: hepatic oxygen consumption; hypoxia.)

THE MECHANISM OF halothane-induced hepatotoxicity is not known. Toxic intermediate metabolites of halothane have been suspected of producing hepatotoxicity when rats are exposed to halothane and hypoxia simultaneously.[1,2] However, the relative contribution of halothane and hypoxia to liver damage is difficult to quantitate; *i.e.*, because hypoxia *per se* can produce hepatotoxicity,[3,4] it is difficult to define whether halothane or hypoxia is the main cause of the hepatic damage. For example, hypoxic conditions caused by less than 10% inspired oxygen upset the balance between liver oxygen supply and uptake resulting in hepatic venous oxygen tension below 5 mmHg in cats[5] and 14 mmHg in dogs,[6] at which time hepatic damage occurs even without any anesthetic agent.[5,6] In spontaneously breathing rats given 1% halothane, carbon dioxide accumulated,[7] suggesting that respiratory depression and the consequent hypoxia might be responsible for the liver damage observed. On the other hand, a subanesthetic dose of halothane (0.5%) with mild hypoxia (14% oxygen)—in which case respiratory depression seemed minimal—produced hepatotoxicity,[2] although mild hypoxia alone or a subanesthetic dose of other anesthetic agents with mild hypoxia did not produce hepatotoxicity in rats.[2,8] If a decrease in hepatic oxygen availability *per se* does not produce hepatotoxicity, there must be a difference in hepatic oxygen supply and uptake during exposure to halothane and the other anesthetic agents, even at subanesthetic doses of each agent with mild hy-

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TABLE 1. Distribution of Rats in each Anesthetic Group and Subgroup

	Groups Studied				
	Control in Air	Thiopental	Halothane	Enflurane	Isoflurane
A and HV	12	9	9	9	7
PV	9	8	8	9	8
BF	12	8	10	7	9
Total	33	25	27	25	24

A = arterial blood samples obtained; HV = hepatic venous blood sample obtained; PV = portal venous blood sample obtained; BF = hepatic blood flow determination performed.

poxia. If halothane produces the effect through disturbance of hepatic blood flow, a decrease of hepatic venous oxygen content (Chv_{O_2})[9] should be present.

This study examined the balance between oxygen supply and uptake in the rat liver in control animals breathing air and (1) in animals during mild hypoxia combined with subanesthetic dose of each of three volatile anesthetic agents (halothane, enflurane, or isoflurane), and (2) in a separate group of animals receiving only thiopental.

Materials and Methods

Male Sprague-Dawley rats, 240–280 g, were studied. All rats were given phenobarbital (Pb) in their drinking water (0.2%) for 4 days, and then given food and untreated water ad libitum for 24 h. Food was removed in the next 24 h while the experiment was conducted.

Animals were divided into five groups (table 1). Group 1 consisted of 33 rats that served as controls and were exposed only to the room air (control group). In group 2, 25 rats received a subcutaneous injection of thiopental (50 $mg \cdot kg^{-1}$, thiopental group); in group 3, 27 rats received 0.5% halothane (halothane group); in group 4, 25 rats received 1.0% enflurane (enflurane group); and in group 5, 24 rats received 0.75% isoflurane (isoflurane group). Each group of rats, except group 1, was given a hypoxic gas mixture ($F_{I_{O_2}}$, 0.12), achieved by mixing air and nitrogen through a calibrated flowmeter ($4\ l \cdot min^{-1}$) during administration of each anesthetic agent. The animals in all groups were further divided randomly into three subgroups: A and HV, for systemic arterial and hepatic venous blood gas analysis; PV, for portal venous blood gas analysis; and BF, for blood flow determination (table 1).

Subgroups A (systemic arterial) and HV (hepatic vein) were used for measurements of arterial and hepatic venous blood gas tension and calculation of oxygen content. A polyethylene catheter (PE-10) was placed into the tail artery for withdrawal of the arterial blood sample. The hepatic vein was cannulated as described by Yokota *et al.*[10] and Bredfeldt *et al.*[11] Briefly, a 3-cm midline abdominal incision was made to the xiphoid process under thiopental anesthesia (40 $mg \cdot kg^{-1}$ administered intraperitoneally [IP]) before exposure to hypoxia and the anesthetic agent. The central lobe of the liver was reflected to the upper left, and the hepatic junction of the left and the central lobe was identified. A venous injection needle (25-gauge) bent at a right angle from the top with a cannula attached was inserted downward into the junction in the hepatic vein and fixed by a surgical binding agent (AronAlpha, Toagosei Chemical Co. Ltd., Tokyo, Japan). The central lobe was replaced in its normal position and the abdomen was sutured.

Subgroup PV (portal vein) was used for determination of portal venous blood gas tension and oxygen content. As preparation for this measurement, the same surgical procedure was done as in subgroups A and HV. The abdominal cannula was placed into the portal vein instead of the hepatic vein and fixed by a surgical binding agent before the abdomen was closed.

Subgroup BF (blood flow) was used for blood pressure measurements and determination of splanchnic blood flow. Under thiopental anesthesia (40 $mg \cdot kg^{-1}$ IP), a PE-10 connected to PE-50 cannula was passed through the right carotid artery and placed in the left ventricle. The femoral artery was cannulated with a tapered PE-50 cannula which was advanced up into the distal aorta. In all animals of this subgroup, a 3-cm midline abdominal incision was made to the xiphoid process as a sham operation to simulate the intra-abdominal condition of subgroups A, HV, and PV. All incisions were closed at the end of the operation.

Animals were placed in a Plexiglas restraining tube immediately after placement of cannula and allowed to recover in room air for 2 h. After this time, all animals were awake and showed gross voluntary purposeful muscular movement, such as head jerking or twisting and extremities running or clawing.[12] At this time, a control arterial blood sample was withdrawn from the tail artery of animals of subgroups A and HV for analysis of blood gas tension, in order to standardize recovery from the anesthetic in each animal. Before the blood withdrawal, heparinized saline solution was injected through each cannula.

Thereafter, the rat in the restraining tube was exposed to hypoxia and received one of the anesthetic agents in a Plexiglas chamber (50 l). The dose of the volatile anesthetic agents ranged from 0.45–0.54 MAC. The air control group was neither exposed to hypoxia nor received anesthetic agent. The oxygen concentration in the chamber was monitored by a Beckman oxygen analyzer; and the $F_{I_{O_2}}$ adjusted to 0.12 approximately every 10 min if needed. The body temperature of the rat was maintained by a water blanket set at 37° C during exposure. After a 1.5-h exposure to these conditions, arterial and hepatic venous blood samples were withdrawn from the tail artery and the hepatic vein of subgroups A and HV for deter-

TABLE 2. Arterial Hemoglobin and Blood Gas Values in Room Air Before Exposure to Each Anesthetic Agent

	Control in Air	Thiopental	Halothane	Enflurane	Isoflurane
Hb ($g \cdot dl^{-1}$)	15.7 ± 0.37	16.8 ± 0.25	16.2 ± 0.44	15.5 ± 0.19	15.1 ± 0.14
Sa_{O_2} (%)	90.6 ± 1.0	89.8 ± 1.2	89.5 ± 1.0	90.0 ± 1.0	91.9 ± 0.9
Pa_{O_2} (mmHg)	90.4 ± 2.2	94.1 ± 3.9	87.5 ± 2.5	89.9 ± 1.9	90.1 ± 2.1
Pa_{CO_2} (mmHg)	40.8 ± 1.0	41.4 ± 1.2	40.8 ± 0.9	42.1 ± 1.2	39.4 ± 0.8
*p*H	7.39 ± 0.011	7.39 ± 0.015	7.39 ± 0.021	7.39 ± 0.013	7.38 ± 0.008

Values are means ± SEM. Hb = hemoglobin; Sa_{O_2} = arterial oxygen; Pa_{O_2} = arterial oxygen tension; Pa_{CO_2} = arterial carbon dioxide tension. There was no significant differences among the groups.

mination of blood gas tension and oxygen saturation. A blood sample was withdrawn through the cannula in the portal vein of rats in subgroup PV. Those blood samples were analyzed by an Instrumentation Laboratory (IL) 1303 blood gas analyzer to determine blood gas tension and *p*H values. Blood oxygen saturation and hemoglobin (Hb) concentration were analyzed by an IL 282 co-oximeter. Oxygen content of each blood sample was calculated from Hb, oxygen saturation, and oxygen tension values.

Using 15-μ spheres (3M Co., Medical Products Division, St. Paul, MN) labeled with ^{85}Sr or ^{141}Ce, splanchnic blood flow was determined of subgroup BF according to the technique described by Rudolph and Heymann[13] and Heymann *et al.*[14] The microspheres had been suspended in dextran (5%) containing polysorbate (Tween 80). After the agitation, 0.2–0.3 ml (80,000–120,000) suspension of microspheres was injected into the left ventricular cannula over 30 s and flushed with 0.5 ml saline solution. Fifteen seconds prior to and 60 s after the microsphere injection, blood was withdrawn from the femoral artery at a constant rate of 0.6–0.8 $ml \cdot min^{-1}$ for determination of cardiac output (CO) and regional blood flow. After the injection of isotopes, the animal was killed by injection of potassium chloride through the ventricular cannula. The organs of the body were removed, weighed, and placed in counting vials. Radioactivity in the tissues and reference blood samples were analyzed with the Tm Analytic 1193 Gammatrac (Radio Analytic Inc., Tampa, FL). Activity in the liver was used to calculate hepatic arterial blood flow (HABF) and activity in spleen, stomach, and large and small intestines was used to calculate portal venous blood flow (PVBF). Activity in the reference blood sample was used for CO calculation. If there was more than a 15% difference between blood flow in the right and left kidney, the data were not included in the study. Only three animals were excluded.

Oxygen consumption in the liver was calculated by the following formula:

$$\dot{V}hep_{O_2} = (Ca_{O_2} - Chv_{O_2}) \times HABF + (Cpv_{O_2} - Chv_{O_2}) \times PVBF = Ca_{O_2} \times HABF + Cpv_{O_2} \times PVBF - Chv_{O_2} \times THBF$$

In this formula, $\dot{V}hep_{O_2}$ is hepatic oxygen consumption in $ml \cdot g^{-1} \cdot min^{-1}$; Ca_{O_2} is oxygen content in arterial blood; Cpv_{O_2} is oxygen content in portal venous blood; and Chv_{O_2} is oxygen content in hepatic venous blood in ml O_2/ml blood; HABF is hepatic arterial blood flow; PVBF is portal venous blood flow; and THBF is total hepatic blood flow in $mg \cdot g^{-1} \cdot min^{-1}$.[15,16] Respiration was spontaneous through the entire course of experiment in all groups.

The data presented are the mean values ± standard errors of the means. The data among groups were compared using an analysis of variance. Pairwise comparisons between means were done by Fisher's protected least-significant difference test.[17]

Results

Hb, arterial oxygen saturation (Sa_{O_2}), arterial oxygen tension (Pa_{O_2}), arterial carbon dioxide tension (Pa_{CO_2}) and *p*H values were similar in each group of animals before exposure to anesthetic agent with hypoxia and were not significantly different from the control group or from each other (table 2). Administration of the anesthetic agents with hypoxia decreased the Sa_{O_2}, Pa_{O_2}, and Pa_{CO_2}, and increased the *p*H when compared to the control group (table 3). The anesthetic agents individually had similar effects on these blood gas values, except that Pa_{O_2} was significantly lower in the rats receiving enflurane than in the rats receiving thiopental, and the Pa_{CO_2} of the rats receiving halothane was significantly higher than measured in the group of rats receiving enflurane or isoflurane.

Systemic hemodynamic changes and changes in regional blood flow to the liver produced by anesthetic agents and hypoxia included a significant decrease in arterial blood pressure in all groups of animals studied (table 4) and a lower cardiac output (CO) (except in the group of rats exposed to enflurane). The distribution of CO to HABF was significantly higher in the rats receiving enflurane than either the controls or the rats receiving thiopental. The distribution of CO to total hepatic blood flow (THBF) in the groups of rats receiving thiopental, enflurane, or isoflurane exceeded that of controls.

The oxygen content in arterial, portal venous, and he-

TABLE 3. Arterial Hemoglobin and Blood Gas Values in Room Air and During Exposure to Each Anesthetic Agent With Hypoxia

	Control in Air	Thiopental	Halothane	Enflurane	Isoflurane
Hb ($g \cdot dl^{-1}$)	15.7 ± 0.37	15.7 ± 0.38	15.5 ± 0.39	15.6 ± 0.29	15.0 ± 0.26
Sa_{O_2} (%)	90.6 ± 1.0	57.9 ± 4.1*	50.5 ± 3.6*	52.5 ± 3.4*	53.7 ± 4.2*
Pa_{O_2} (mmHg)	90.4 ± 2.2	41.6 ± 2.4*	36.7 ± 1.5*	35.3 ± 1.3*†	40.6 ± 1.1*
Pa_{CO_2} (mmHg)	40.8 ± 1.0	34.1 ± 0.8*	36.1 ± 2.0*	32.1 ± 1.1*‡	30.9 ± 0.4*‡
*p*H	7.39 ± 0.011	7.45 ± 0.023*	7.46 ± 0.022*	7.49 ± 0.012*	7.48 ± 0.008*

Values are means ± SEM. Numbers of animals in each group are as shown in table 1. Hb = hemoglobin; Sa_{O_2} = arterial oxygen; Pa_{O_2} = arterial oxygen tension; Pa_{CO_2} = arterial carbon dioxide tension.

* $P < 0.05$ *versus* air control.
† $P < 0.05$ *versus* thiopental.
‡ $P < 0.05$ *versus* halothane.

patic venous blood was significantly lower in rats of all of the anesthetic groups than in the control group, but no differences existed among animals of the different anesthetic groups (table 5). Chv_{O_2} was significantly higher in the group of rats receiving isoflurane than in animals receiving any of the other anesthetics.

Oxygen supply to the liver contributed by the hepatic artery was not affected significantly by anesthetic agents with hypoxia (table 6). Total oxygen supply to the liver and oxygen supply to the liver contributed by the portal vein were reduced significantly by all anesthetics; halothane caused the greatest reduction in portal venous oxygen supply; however, the reduction caused by halothane was significantly lower only when compared to animals receiving thiopental. As expected, the oxygen remaining in the hepatic venous blood was significantly lower in animals of all of the anesthetic groups than in those of the control group; the lowest value measured was in the rats receiving halothane. The rats receiving isoflurane had the greatest oxygen remaining in the hepatic venous blood; thus, it is not surprising that hepatic oxygen consumption was significantly reduced in the rats who received isoflurane. Hepatic oxygen supply/oxygen consumption was decreased significantly in all anesthetic groups compared with the control group, but was maintained relatively and significantly higher in the group of rats receiving isoflurane than in each group of rats receiving thiopental, halothane, or enflurane.

A relatively high correlation was established between Chv_{O_2} and hepatic oxygen supply/oxygen consumption for five groups ($y = 11.3x + 1.12$, $r = 0.975$, $P < 0.01$).

Discussion

These studies provide evidence that a subanesthetic dose of halothane does not result in decreased hepatic blood flow. Similarly, isoflurane and enflurane, while also producing significant changes within the cardiovascular system, do not decrease hepatic perfusion.

Liver dysfunction occasionally seen following general anesthesia with halothane has been postulated to relate to hepatic ischemia caused by anesthetic-induced decreases in portal venous and/or hepatic arterial blood flow. Co-existing systemic hypoxia accentuates the liver dysfunction. Since blood flow from both the hepatic artery and portal vein contribute to the oxygenation of the liver, any attempt to relate anesthetic-induced liver dysfunction to anesthetic-induced alterations in hepatic blood flow

TABLE 4. Hemodynamic Variables and Regional Blood Flow to the Liver during Exposure to Each Anesthetic Agent with Hypoxia

	Control in Air	Thiopental	Halothane	Enflurane	Isoflurane
ABP (mmHg)	135/110	102/78*	84/62*†	86/56*†	88/62*†
CO ($ml \cdot min^{-1}$)	97 ± 3.2	79 ± 6.4*	76 ± 5.4*	85 ± 4.7	78 ± 4.4*
Distribution of CO (%)					
HABF	3.0 ± 0.57	3.0 ± 0.74	4.5 ± 0.56	5.9 ± 0.35*†	4.3 ± 0.67
PVBF	15.5 ± 0.95	19.4 ± 1.45	17.1 ± 1.29	17.7 ± 0.87	19.8 ± 1.36
THBF	18.5 ± 1.07	22.4 ± 1.45*	21.1 ± 1.66	23.6 ± 0.81*	24.0 ± 1.43*
Absolute Blood Flow ($ml \cdot g^{-1} \cdot min^{-1}$)					
HABF	0.22 ± 0.043	0.19 ± 0.042	0.27 ± 0.035	0.36 ± 0.033	0.25 ± 0.039
PVBF	1.18 ± 0.097	1.31 ± 0.095	1.04 ± 0.102	1.10 ± 0.087	1.18 ± 0.077
THBF	1.41 ± 0.108	1.50 ± 0.069	1.29 ± 0.129	1.46 ± 0.102	1.43 ± 0.081

Values are means ± SEM. ABP = arterial blood pressure (systolic/diastolic); CO = cardiac output; HABF = hepatic arterial blood flow; PVBF = portal venous blood flow; THBF = total hepatic blood flow.

* $P < 0.05$ *versus* air control.
† $P < 0.05$ *versus* thiopental.

TABLE 5. Oxygen Content in Arterial, Portal Venous, and Hepatic Venous Blood During Exposure to Each Anesthetic Agent With Hypoxia

	Control in Air	Thiopental	Halothane	Enflurane	Isoflurane
(ml $O_2 \cdot ml^{-1}$ blood)					
Ca_{O_2}	0.20 ± 0.004	0.13 ± 0.008*	0.11 ± 0.008*	0.12 ± 0.007*	0.11 ± 0.010*
Cpv_{O_2}	0.17 ± 0.006	0.09 ± 0.010*	0.08 ± 0.005*	0.08 ± 0.008*	0.10 ± 0.005*
Chv_{O_2}	0.09 ± 0.003	0.02 ± 0.005*	0.02 ± 0.002*	0.02 ± 0.002*	0.04 ± 0.005*†‡§

Values are means ± SEM. Ca_{O_2} = arterial oxygen; Cpv_{O_2} = portal venous oxygen; Chv_{O_2} = hepatic venous oxygen.
* $P < 0.05$ *versus* air control.
† $P < 0.05$ *versus* thiopental.
‡ $P < 0.05$ *versus* halothane.
§ $P < 0.05$ *versus* enflurane.

must consider both the hepatic arterial system and the portal venous system.

Several studies examining these components of total hepatic blood flow have suggested that there exists a physiologic principle of "reciprocity of total hepatic blood flow" between the hepatic artery and portal vein. Supposedly, this mechanism acts to maintain a relatively constant total hepatic blood flow. A decrease in portal venous blood flow would increase hepatic arterial blood flow and vice versa. Anesthetics might induce liver dysfunction by the uncoupling of this reciprocity. Andreen *et al.*[18] and Hughes *et al.*[19] have reported that halothane inactivates the mechanism in dogs. Longnecker also reported alteration of reciprocity of hepatic blood flow in rats anesthetized with halothane.[20] The principle of reciprocity of total hepatic blood flow appeared to have been maintained in our study in the presence of each of the anesthetic agents used, since increases and decreases in hepatic arterial and portal blood flow, while not always statistically significant, were always in appropriate directions to support the principle. However, this principle has not been supported by all studies.[21,22] A number of factors may combine to inactivate the mechanism, *e.g.*, co-existing hypoxia, acidosis, enzyme induction, or differences in anesthetic concentration, and it is possible that differences in studies may relate to species differences as well.

Recent studies by Segstro and Greenway[23] suggest that both α_1- and α_2-adrenoreceptors are involved in the control of vasoactivity in the blood vessels supplying the liver. Since the vasoreactivity of liver vasculature is under the influence of α-adrenoreceptors, and the anesthetic agents halothane, enflurane, and isoflurane appear to be devoid of agonist activities, the regulation of contractile activity is more logically by circulating epinephrine and NE than by neuronally released NE.

Hypoxia has been shown to increase the NE released from sympathetic nerve endings and to elevate blood levels of NE.[24,25] A marked increase in blood NE levels caused by hypoxia resulting from inadequate ventilation in spontaneously breathing animals could be one way by which halothane (and other volatile anesthetic agents) might produce hepatic vascular vasoconstriction. Liver dysfunction can be caused by hypoxia *per se* if the levels of hypoxia are severe; if the inspired oxygen tension is less than 10%, hepatic venous oxygen tensions were decreased to below 5 mmHg (cats),[5] and 14 mmHg (dogs),[6] producing hepatic dysfunction.[5,6] Therefore, greater than 10% oxygen should be used in studies of anesthetic-induced alterations in liver blood flow in order to eliminate the effect of hypoxia *per se* on hepatocytes. In our studies, 12% oxygen was used. A control group of hypoxic animals was not possible, because the cannulated hypoxic rats could not be maintained quiet for more than 1 h needed to do the experiment. Therefore, the animals received thiopental (0.35 MAC) and were designated as the thiopental-hypoxia group.

TABLE 6. Oxygen Supply and Demand in the Liver During Exposure to Each Anesthetic Agent With Hypoxia

	Control in Air	Thiopental	Halothane	Enflurane	Isoflurane
(ml $O_2 \cdot g^{-1} \cdot min^{-1}$)					
O_2 supply from HA	0.05 ± 0.009	0.02 ± 0.005	0.03 ± 0.004	0.04 ± 0.004	0.03 ± 0.005
O_2 supply from PV	0.20 ± 0.016	0.12 ± 0.008*	0.08 ± 0.008*†	0.09 ± 0.007*	0.11 ± 0.007*
Total O_2 supply	0.24 ± 0.019	0.14 ± 0.006*	0.11 ± 0.011*	0.13 ± 0.009*	0.14 ± 0.008*
Remaining O_2 in HV	0.12 ± 0.009	0.04 ± 0.002*	0.02 ± 0.002*	0.03 ± 0.002*	0.06 ± 0.003*‡
Hepatic O_2 consumption	0.12 ± 0.010	0.10 ± 0.004	0.09 ± 0.009*	0.10 ± 0.007	0.08 ± 0.005*
O_2 supply/O_2 consumption	2.06 ± 0.035	1.35 ± 0.005*	1.30 ± 0.022*	1.33 ± 0.009*	1.69 ± 0.007*†‡§

Values are means ± SEM. HA = hepatic artery; PV = portal vein; HV = hepatic vein. Calculated by multiplying hepatic blood flow and oxygen content in the blood.
* $P < 0.05$ *versus* air control.
† $P < 0.05$ *versus* thiopental.
‡ $P < 0.05$ *versus* halothane.
§ $P < 0.05$ *versus* enflurane.

The respiratory condition of the animals was not changed throughout the study. Steady state conditions are important, because increased Pa_{CO_2} itself increases systemic flow in man and in dogs,[26] although contradictory results have been reported.[27] In the report by Gelman *et al.*[7] Pa_{CO_2} was much higher in the halothane anesthesia group than in the other groups. This suggests that halothane-induced depression of ventilation had occurred and could reflect an altered experimental condition of the rat, in which case respiratory or metabolic acidosis might affect hepatic oxygen availability by increasing splanchnic blood flow. In our study, the Pa_{CO_2} value was lower in the rats receiving halothane than in the control group. This implies that the respiratory response to hypoxia was not abolished by the halothane. Therefore, we could eliminate the possibility that a subanesthetic dose of halothane could decrease hepatic oxygen availability through respiratory depression.

CO in normoxic unanesthetized rats (97 ± 3.2 $ml \cdot min^{-1}$) is less than that in control rats (122 ± 7.9 $ml \cdot min^{-1}$) reported by Ross and Daggy,[28] but closer to 106 ± 6 $ml \cdot min^{-1}$ reported by Tsuchiya *et al.*[29] both measured by a microsphere technique. This inconsistency is probably because of the smaller body weight of the animals used in our study. Our finding agrees closely with the value of 379 $ml \cdot min^{-1} \cdot kg^{-1}$ (approximately 94.8 $ml \cdot min^{-1}$ for 250 g) reported by Goldman and Sapirstein.[30] In this study, no anesthetic agent at a subanesthetic dose significantly changed absolute hepatic blood flow (HABF, PVBF, or THBF) from the control values, most likely because hepatic distribution of CO increased. Because mild hypoxia did not change HABF, PVBF, or THBF in dogs at a steady state,[31] our observations would mean that the effect of 12% oxygen on the hepatic blood flow was minimal, and a subanesthetic dose of halothane does not affect hepatic blood flow seriously as long as the concommitant hypoxia was not severe. In the report by Ross and Daggy,[28] PVBF was decreased significantly by hypoxia alone (8% oxygen), but halothane (0.6%) with hypoxia did not change PVBF. This suggests that the impairment of release of NE from nerve endings by halothane exceeds the potency of hypoxia to cause release of NE from these endings. The difference between their finding and our results may also relate to differences in degree of hypoxia, *i.e.*, 8% *versus* 12%. One more reason for the decreased PVBF might be that they injected microspheres twice, and PVBF tends to decrease and HABF to increase in rats after second and third microsphere injections.[29] In the report by Gelman *et al.*[7] PBVF was decreased by halothane with hypoxia compared with hypoxia alone.

Laparotomy has been said to disturb systemic blood flow[32] and to exacerbate halothane-induced hepatic dysfunction.[33] Therefore, the same operation was done in all groups studied. No significant decrease of systemic blood flow in the control animals was observed compared with the blood flow of the control group of Ross and Daggy[28] that were not subjected to operation; however, a higher portal venous distribution of CO was observed in our study. Rotating the duodenal loop to expose the portal vein was not found to produce changes in intestinal blood flow.[11]

Because there were no significant differences in arterial blood gas values among all five groups, it appeared that preanesthetic wakefulness of rats was similar in all five groups after the recovery period. The blood gas values shown in table 2 (represented by the air control group) were also consistent with those in awake, unrestrained rats reported by Olson *et al.*[34] despite the fact that our animals were given thiopental.

Oxygen supply from the hepatic artery was not significantly different among groups, whereas supply from the portal vein was significantly lower in all anesthetic groups than the air control group. This is attributed to the low oxygen content in the portal vein during hypoxia. A significant difference in oxygen supply from the portal vein was found only between the halothane and thiopental groups. Although, in every group, oxygen supplied from the portal vein was more than twice that supplied by the hepatic artery, the difference between oxygen supply from the portal vein in the halothane group and the thiopental group was so small that it was well compensated for by the increase of HABF.

In this study, hepatic oxygen consumption was decreased significantly to 72% of the control value by halothane and to 68% by isoflurane; similar decreases have been reported in dogs anesthetized with these drugs.[35] Despite a similar decrease in hepatic oxygen consumption in the halothane and the isoflurane groups, the remaining oxygen in the hepatic vein was significantly higher in the rats receiving isoflurane than in those receiving halothane, presumably because total hepatic oxygen supply tended to be higher in the isoflurane group than in the halothane group. Hepatic oxygen supply/oxygen consumption was highest in those receiving isoflurane and about equal in the three other anesthetic groups. A subanesthetic dose of isoflurane maintained oxygen supply to the liver relative to oxygen consumption better than thiopental, halothane, and enflurane, perhaps suggesting less depression of ventilation by isoflurane. Halothane did not decrease the ratio of hepatic oxygen supply to oxygen consumption specifically compared with thiopental and enflurane. This tendency was also represented by the change of Chv_{O_2}. Chv_{O_2} reflects the oxygen content of the blood at the venous end of all sinusoids, with homogenous perfusion and equal transit time of blood in different sinusoids.[5] Therefore, anything which produces an imbalance between hepatic oxygen supply and uptake leading to a rise in hepatic oxygen extraction, causes a decrease in Chv_{O_2}.[9] Low Chv_{O_2} implies that there are areas with very low oxygen tension distributed within the liver.[9] Because it is relatively difficult to measure Chv_{O_2} and intracellular

oxygen availability simultaneously *in vivo* and in a small animal, no studies of this nature have been reported.

In conclusion, the imbalance of hepatic oxygen supply and uptake during exposure to hypoxia was greater in the rats receiving thiopental, halothane, and enflurane than in those receiving isoflurane. Hypoxia in the liver brought on by low concentrations of inspired oxygen or decreased hepatic blood flow would not produce hepatic toxicity by itself, although a subanesthetic dose of halothane alone has been shown to cause hepatotoxicity with this extent of hypoxia.[2] However, experimental conditions were sufficiently different in that study such that comparison with our study may not be entirely valid. The main cause of halothane-induced hepatotoxicity might not be hypoxia *per se*, even though hypoxia contributes to the halothane-induced hepatotoxicity.

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