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Effects of sevoflurane and halothane anesthesia on liver circulation and oxygen metabolism in the dog during hepatolobectomy

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Abstract

Purpose. Effects of sevoflurane and halothane anesthesia on liver circulation and oxygen metabolism during hepatolobectomy were investigated in the dog, with the aim of choosing a better anesthetic for hepatic resection.

Methods. Sixteen mongrel dogs were randomly divided into two groups with eight in each. Electromagnetic flowmeters were used to measure hepatic arterial and portal venous blood flows (1) before the inhalation of each anesthetic (base line); (2) 1 h after the start of inhalation of 1.5 minimum alveolar concentration (MAC) anesthetic; (3) 1 h after hepatolobectomy with the same MAC of anesthesia; and (4) 2 h after the discontinuation of anesthesia. Measurements of systemic hemodynamics, blood gas tensions, plasma enzyme leaks and arterial ketone body ratio were made at the same time.

Results. Sevoflurane maintained hepatic arterial blood flow better than halothane anesthesia, both before and after hepatolobectomy. Hepatic arterial vascular resistance increased in the halothane group but did not change in the sevoflurane group after hepatolobectomy. No significant difference was found in oxygen metabolism and arterial ketone body ratio between two groups. Serum enzyme leakage was less in the sevoflurane group.

Conclusion. Sevoflurane has less adverse effects on liver circulation, especially hepatic arterial blood flow, and hepatic function than halothane in the case of hepatolobectomy.

Key words: Inhalation anesthetic, Sevoflurane, Halothane, Hepatic circulation, Hepatolobectomy

Introduction

Many studies have confirmed that halothane anesthesia significantly decreases hepatic blood flow [1–3]. This is thought to be one of the reasons by which "halothane hepatitis" is induced as decreased hepatic blood flow, especially that affecting hepatic arterial blood flow, may reduce the oxygen supply to, and/or create an imbalance in the oxygen supply-demand ratio in the liver, which may subsequently damage hepatocytes if combined with hypotension, bleeding, or hypoxia [4]. Surgical stress per se can cause decreases in hepatic blood flow mediated in part by endogenous factors including catecholamines, renin-angiotensin, and vasopressin. Also, hepatic resection could elevate vascular resistance against intrahepatic circulation.

As the above factors are often seen during hepatic surgery and the postoperative period, selecting anesthetics with less adverse effects on liver circulation and oxygen metabolism therefore becomes desirable. Sevoflurane has the advantages of rapid, smooth induction and emergence, and less effects on circulation than halothane [5]. However, few papers have studied the hepatic effects of sevoflurane, and evaluated the effects of sevoflurane on hepatic hemodynamics and oxygen metabolism, on the occasion of liver surgery.

In this study, we compared the effects of 1.5 minimum alveolar concentration (MAC) sevoflurane anesthesia on liver circulation and oxygen metabolism with 1.5 MAC halothane anesthesia in the dog during hepatolobectomy.

Materials and methods

Sixteen mongrel dogs (9–13 kg) were randomly divided into sevoflurane (n = 8) and halothane (n = 8) groups. Anesthetized with thiamylal 10–20 mg·kg^{-1}, the dogs were intubated with the aid of pancuronium 0.2 mg·kg^{-1}. Respiration was controlled by an animal ventilator (Respirator R-60, Aika, Matsudo, Japan) at FiO_2 0.5 (oxygen and nitrogen). Anesthesia was maintained with a supplemental dose (4–5 mg·kg^{-1}) of thiamylal i.v.

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when required later in the preparation. End-expiratory CO_2 concentration was monitored continuously (CO_2 analyzer, RAS-41, Aika) to ensure normocapnia. An arterial catheter was inserted into the aorta through the femoral artery for measuring MAP and to obtain blood samples for measurement of blood gas tensions (blood gas analyzer 213 and Co-oximeter 282, IL, Barcelona, Spain). An intravenous catheter was used for infusing lactated Ringer's solution at a constant rate (15 ml·kg^{-1}·h^{-1}) throughout the experiment. Laparotomy was performed and a portal venous catheter was inserted into a branch of the superior mesenteric vein for measurement of portal venous pressure (PVP) and for sampling of portal venous blood. The probes of electromagnetic flowmeters (MFV-1200, Nihon Kohden, Tokyo, Japan) were applied on the common hepatic artery (diameter 4 mm) and the portal vein (diameter 7 mm). The gastroduodenal and right gastric arteries were ligated to ensure that all blood passing through the common hepatic artery supplied the liver. A triple lumen pulmonary arterial catheter was introduced for measuring cardiac output (CO) (thermodilution technique, AH and EQ-611V, Nihon Kohden) and central venous pressure (CVP). A hepatic venous catheter was introduced into the right hepatic vein through the right external juglar vein for monitoring hepatic venous blood gas tension. After these procedures, the abdominal cavity was closed. Then, an interval of 1 h was used for the animals to recover from surgical stress and to establish a steady splanchnic circulatory state as hepatic arterial blood flow (HABF) approaching 25%–30% of total hepatic blood flow (THBF), at which time baseline measurements were made. During this period, it was necessary to administer 5 mg·kg^{-1} of thiamylal and 0.1 mg·kg^{-1} of pancuronium two or three times.

After baseline values were obtained, anesthesia was commenced and maintained with 1.5 MAC of each test anesthetic for 1 h to assure equilibration of anesthetic concentrations in arterial blood and alveolar gas. The end-tidal concentrations of halothane and sevoflurane were monitored continuously using a calibrated anesthetic gas monitor (POET II. 602-3, CSI, Waukesha, WI, USA). Measurements ("anesthesia" values) were repeated, after which hepatic lobectomy (left external lobectomy) was performed and the abdominal cavity was again closed. Hepatic lobes are well separated in dogs, and we had no serious bleeding using this preparation and resection. However, because of the unstable condition immediately after the lobectomy, 1 h passed before all measurements were repeated ("hepatolobectomy" values). The test anesthetic was then discontinued and the animals were allowed to recover with several supplemental doses of 5 mg·kg^{-1} of thiamylal, which were administered when mean arterial pressure (MAP) exceeded 150 mmHg. Two hours later, the last set of measurements were made ("recovery" values) while respiration was still controlled. The animals were then killed by i.v. injection of potassium chloride (KCL) and the remaining liver was removed and weighed.

Hepatic blood flow was expressed as ml^{-1}·min^{-1}·100 g^{-1}. Hepatic arterial vascular resistance (HAVR) was calculated as the MAP to CVP gradient divided by HABF. Preportal vascular resistance (PPVR) was calculated as the difference between MAP and PVP divided by portal venous blood flow (PVBF). Portal vascular resistance (PVR) was calculated as the difference between PVP and CVP divided PVBF. Hepatic oxygen delivery (DO_2) and hepatic oxygen consumption (VO_2) were calculated by the following formulae:

$$DO_2 = CaO_2 \times HABF + CpvO_2 \times PVBF$$

$$VO_2 = (CaO_2 - ChvO_2) \times HABF + (CpvO_2 - ChvO_2) \times PVBF$$

Where CaO_2 is arterial oxygen content, $CpvO_2$ is portal venous oxygen content, and $ChvO_2$ is hepatic venous oxygen content. Glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT), lactate dehydrogenase (LDH), and arterial ketone body ratio (acetoacetate/β-hydroxybutyrate) (AKBR) were also measured at each stage of experiment for indices of hepatic cell damage and energy charge in the liver mitochondria.

Data were summarized as the mean ± standard error of the mean (SEM). Statistical analysis was performed by ANOVA and Fisher's protected least-significant difference test for pairwise comparisons. $P < 0.05$ was considered statistically significant.

The study was approved by the Animal Investigation Committee of Saitama Medical School.

Results

Tables 1–4 show the data of the halothane group and the sevoflurane group, respectively. There were no significant differences in baseline values between the two groups.

With 1.5 MAC inhaled concentrations, both anesthetics significantly depressed systemic hemodynamics. Although there were no statistically significant differences between the two anesthetics, sevoflurane anesthesia was associated with slower heart rate (HR) ($P < 0.01$ *vs* baseline) than halothane anesthesia.

During anesthesia, HABF and THBF decreased sharply in the halothane group ($P < 0.01$ and $P < 0.05$ *vs* baseline, respectively), but were well maintained in the sevoflurane group (not significant (n.s.) *vs* baseline). HABF as a percentage of THBF significantly

Table 1. Variables of systemic and hepatic hemodynamics throughout the experiment in the halothane group (mean ± SEM)

	A	B	C	D
MAP (mmHg)	147 ± 6	88 ± 6**	83 ± 3**	141 ± 3
CO ($l \cdot min^{-1}$)	1.80 ± 0.08	1.14 ± 0.09**	1.21 ± 0.10**	1.61 ± 0.14
HR (min^{-1})	133 ± 12	106 ± 7	100 ± 8	141 ± 7
CVP (mmHg)	2.3 ± 0.5	4.2 ± 0.8	4.5 ± 0.8	2.3 ± 0.4
PVP (mmHg)	8.6 ± 0.8	9.1 ± 0.7	9.9 ± 1.1	11.7 ± 0.8*
HABF ($ml \cdot min^{-1} \cdot 100 g^{-1}$)	32.8 ± 3.4	14.4 ± 2.0**	9.5 ± 2.0**	13.2 ± 3.6**
PVBF ($ml \cdot min^{-1} \cdot 100 g^{-1}$)	86.6 ± 10.5	61.7 ± 7.0	80.8 ± 7.6	98.4 ± 6.1
THBF ($ml \cdot min^{-1} \cdot 100 g^{-1}$)	119 ± 10.7	76.1 ± 8.7*	90.3 ± 8.9	112 ± 6.9
% of HABF to THBF	28.5 ± 3.6	19.0 ± 1.4*	10.5 ± 1.9**	11.5 ± 2.9**
HAVR ($mmHg \cdot min^{-1} \cdot ml^{-1}$)	1.36 ± 0.30	1.75 ± 0.30	4.07 ± 1.04*	6.40 ± 1.98**
PPVR ($mmHg \cdot min^{-1} \cdot ml^{-1}$)	0.46 ± 0.06	0.36 ± 0.05	0.33 ± 0.04	0.46 ± 0.04
PVR ($mmHg \cdot min^{-1} \cdot ml^{-1}$)	0.019 ± 0.003	0.022 ± 0.005	0.026 ± 0.007	0.034 ± 0.004*

A, baseline; B, anesthesia; C, hepatolobectomy; D, recovery; MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; CVP, central venous pressure; PVP, portal venous pressure; HABF, hepatic arterial blood flow; PVBF, portal venous blood flow; THBF, total hepatic blood flow; HAVR, hepatic arterial vascular resistance; PPVR, preportal vascular resistance; PVR, portal vascular resistance.
* $P < 0.05$, ** $P < 0.01$ *vs* baseline values.

Table 2. Variables of systemic and hepatic hemodynamics throughout the experiment in the sevoflurane group (mean ± SEM)

	A	B	C	D
MAP (mmHg)	142 ± 4	74 ± 2**	75 ± 3**	134 ± 4
CO ($l \cdot min^{-1}$)	1.93 ± 0.14	1.22 ± 0.10**	1.21 ± 0.11**	1.74 ± 0.18
HR (min^{-1})	141 ± 8	97 ± 8**	93 ± 7**	129 ± 7
CVP (mmHg)	2.7 ± 0.5	4.4 ± 0.5*	4.4 ± 0.5*	2.3 ± 0.4
PVP (mmHg)	8.5 ± 0.4	7.4 ± 0.4	8.1 ± 0.4	9.3 ± 1.0
HABF ($ml \cdot min^{-1} \cdot 100 g^{-1}$)	31.8 ± 3.8	23.9 ± 2.8§	18.4 ± 3.1*§	16.5 ± 1.8**
PVBF ($ml \cdot min^{-1} \cdot 100 g^{-1}$)	86.0 ± 9.0	62.5 ± 7.3	94.5 ± 14.1	104 ± 13.7
THBF ($ml \cdot min^{-1} \cdot 100 g^{-1}$)	118 ± 10.5	86.4 ± 8.0	113 ± 12.1	121 ± 13.9
% of HABF to THBF	27.6 ± 2.8	28.3 ± 3.1§	18.8 ± 4.3	15.4 ± 2.5*
HAVR ($mmHg \cdot min^{-1} \cdot ml^{-1}$)	1.42 ± 0.21	0.91 ± 0.08§	2.07 ± 0.61	3.43 ± 0.64*
PPVR ($mmHg \cdot min^{-1} \cdot ml^{-1}$)	0.49 ± 0.05	0.34 ± 0.05	0.31 ± 0.05*	0.51 ± 0.07
PVR ($mmHg \cdot min^{-1} \cdot ml^{-1}$)	0.020 ± 0.004	0.018 ± 0.005	0.019 ± 0.004	0.030 ± 0.019

A, baseline; B, anesthesia; C, hepatolobectomy; D, recovery.
* $P < 0.05$, ** $P < 0.01$ *vs* baseline values; § $P < 0.05$ *vs* the halothane group.

decreased during halothane anesthesia ($P < 0.05$ *vs* baseline), but did not show any changes in the sevoflurane group (n.s. *vs* baseline and $P < 0.05$ *vs* halothane). Halothane increased, while sevoflurane anesthesia decreased HAVR ($P < 0.05$ *vs* halothane).

Both halothane and sevoflurane induced sharp reductions in DO_2 ($P < 0.01$ and $P < 0.05$ *vs* baseline, respectively). No significant difference was found in VO_2 or DO_2/VO_2 between the two groups. The AKBR, an index reflecting oxygen metabolism in hepatic mitochondria, did not change significantly in both anesthesia groups.

The HABF in the remaining liver was further decreased by hepatolobectomy in both groups, especially in the halothane group ($P < 0.01$ *vs* baseline, $P < 0.05$ *vs* sevoflurane). As PVBF was not influenced by the surgery, and recovered to the baseline level at this stage, the percentage of HABF to THBF reduced to an extremely low level in the halothane group ($P < 0.01$ *vs* baseline). The decrease in HABF was smaller in the sevoflurane group than the halothane group ($P < 0.05$), and the percentage of HABF to THBF was also maintained in the sevoflurane group (n.s. *vs* baseline). The surgery resulted in a significant rise of HAVR in the halothane group ($P < 0.05$ *vs* baseline). The PPVR was reduced to the statistically significant level in the sevoflurane group ($P < 0.05$ *vs* baseline). The mean values of PVR were unchanged in both groups. A significant difference was found in GPT between the two anesthesia groups ($P < 0.05$).

All indices recovered to, or nearly to, the baseline levels in both groups by 2 h after discontinuation of the anesthetic except for the HABF, the percentage of HABF to THBF, HAVR, PVR, and plasma enzyme

Table 3. Variables of hepatic oxygen metabolism and function throughout the experiment in the halothane group (mean ± SEM)

	A	B	C	D
DO_2 ($ml \cdot min^{-1} \cdot 100 g^{-1}$)	21.6 ± 2.5	10.7 ± 1.5**	11.8 ± 1.2*	19.4 ± 1.7
VO_2 ($ml \cdot min^{-1} \cdot 100 g^{-1}$)	4.96 ± 1.34	3.17 ± 0.62	3.19 ± 0.37	5.30 ± 0.65
DO_2/VO_2	6.59 ± 1.61	4.33 ± 1.10	4.40 ± 1.00	3.97 ± 0.51
GPT ($IU \cdot l^{-1}$)	118 ± 18	112 ± 16	138 ± 14	180 ± 18*
GOT ($IU \cdot l^{-1}$)	87 ± 12	86 ± 14	110 ± 21	134 ± 27
LDH ($IU \cdot l^{-1}$)	281 ± 45	299 ± 67	355 ± 77	388 ± 55
AKBR	1.18 ± 0.13	0.99 ± 0.08	0.97 ± 0.09	1.08 ± 0.19

A, baseline; B, anesthesia; C, hepatolobectomy; D, recovery, DO_2, hepatic oxygen delivery; VO_2, hepatic oxygen consumption; GPT, glutamic-pyruvic transaminase; GOT, glutamic-oxaloacetic transaminase; LDH, Lactate dehydrogenase; AKBR, arterial ketone body ratio (acetoacetate/β-hydroxybutyrate).
* $P < 0.05$, ** $P < 0.01$ *vs* baseline values.

Table 4. Variables of hepatic oxygen metabolism and function throughout the experiment in the sevoflurane group (mean ± SEM)

	A	B	C	D
DO_2 ($ml \cdot min^{-1} \cdot 100 g^{-1}$)	20.5 ± 2.6	10.8 ± 1.2*	12.4 ± 1.4*	18.2 ± 2.6
VO_2 ($ml \cdot min^{-1} \cdot 100 g^{-1}$)	5.20 ± 0.92	3.66 ± 0.76	4.34 ± 0.97	5.87 ± 1.42
DO_2/VO_2	4.46 ± 0.57	3.94 ± 0.87	3.63 ± 0.65	3.84 ± 0.73
GPT ($IU \cdot l^{-1}$)	80 ± 9	73 ± 9	85 ± 10§	101 ± 14§
GOT ($IU \cdot l^{-1}$)	60 ± 8	57 ± 5	73 ± 7	94 ± 16
LDH ($IU \cdot l^{-1}$)	288 ± 32	207 ± 17	204 ± 19	265 ± 28
AKBR	1.25 ± 0.16	1.19 ± 0.20	1.46 ± 0.24	1.01 ± 0.11

A, baseline; B, anesthesia; C, hepatolobectomy; D, recovery.
* $P < 0.05$ *vs* baseline values; § $P < 0.05$ *vs* the halothane group.

leaks. The HABFs were still at low levels in both groups ($P < 0.01$ *vs* baseline). The percentage of HABF to THBF at the recovery period was significantly lower than the baseline value in the halothane group ($P < 0.01$) and in the sevoflurane group ($P < 0.05$). The PVR significantly increased in the halothane group ($P < 0.05$ *vs* baseline). Serum enzyme leaks revealed a significant elevation of GPT in the halothane group ($P < 0.05$ *vs* baseline), and was also significantly higher than that of the sevoflurane group ($P < 0.05$).

Discussion

Most of the studies concerning the effects of inhalation anesthetics on liver circulation and oxygen metabolism have been performed in dogs [3,6–10]. This made the comparison of the results of different studies possible. In addition, a well accepted normal range of the index of liver circulation has been established in the dog [11]. In this study, the baseline values were comparable with results from other studies except for the serum enzyme leaks which, unfortunately, exceeded the normal range.

1.5 MAC of inhaled anesthetic concentration were used in this study. The reason for the selection of 1.5 MAC was that the identical anesthesia depth could not be ensured if 1 MAC of anesthetic was inhaled according to the definition of MAC [12]. Only a concentration which was higher than 1 MAC could ensure that almost all the dogs were anesthetized well and made the results comparable.

We used thiamylal and pancuronium for induction and maintenance of anesthesia. The effects of these drugs should be considered when interpreting the present results. To our knowledge, however, pancuronium has a minimal effect on hepatic circulation, and barbiturates might affect hepatic circulation immediately after a bolus injection but the effect is assumed to be short-lasting [4]. A low rate of infusion with thiopentone did not affect hepatic circulation in the study of Thomson et al. [13]. Speculating from these reports, thiamylal would not disturb hepatic circulation 2h after a bolus injection and with the administration of small additional doses in the present study.

Before we discuss the effects of anesthesia on liver circulation and oxygen metabolism, the fact should be kept in mind that the liver circulation is one part of the systemic circulation, and therefore it is worthwhile to notice the changes in systemic hemodynamics in this study. The data indicate that changes in MAP and

CO were identically suppressed in both anesthesia groups. These results imply that sevoflurane, in general, produces a similar cardiovascular effect to halothane at the eqipotent concentration.

There are reports in the literature dealing with the effects of sevoflurane anesthesia on hepatic circulation in the dogs [9,10]. Frink et al. [9] reported that with 1, 1.5 and 2 MAC inhaled concentrations, there were dose-dependent reductions in MAP, CO, and PVBF, but the HABF was maintained well in chronically instrumented dogs. Bernard et al. [10] performed a similar study but added another group of 1.2 and 2 MAC inhaled concentration. Their results showed similar dose-dependent reduction in MAP, CO, PVBF, and THBF. However, the changes in the HABF were quite particular. In both the 1.2 and 2 MAC inhaled concentration group, the HABF increased about 30% as compared with the baseline value. These results seem to suggest that the auto-regulation mechanism, so-called "hepatic arterial buffer response" [14], by which the THBF is kept constant, was conserved during sevoflurane anesthesia in chronically instrumented animals. In the present study, we compared the effects of sevoflurane on liver circulation and oxygen metabolism with those of halothane in the acute surgical phase. Our results showed that sevoflurane anesthesia maintained HABF better than halothane anesthesia, and this finding is partially consistent with those of Frink et al. [9] and Bernard et al. [10] even in the case of hepatic resection. The percentage of HABF to THBF, an important index which determines oxygen delivery to the liver and possibly implies the driving force of the blood stream in the liver, was well maintained in the sevoflurane group, but decreased seriously in the halothane group. These results suggest that sevoflurane anesthesia could induce less disturbance on liver circulation compared with halothane anesthesia.

An interesting phenomenon, that intrahepatic vascular resistance (HAVR and PVR) tended to increase during halothane anesthesia but did not increase during sevoflurane anesthesia, was found in this study. The mechanism of this phenomenon is unclear. Is it possible that it is due to the depression of the cardiovascular system? The answer is clearly negative because the hemodynamic indices indicate that the depression of the cardiovascular system in the halothane group is almost equivalent to that in the sevoflurane group. We speculate that halothane anesthesia could inhibit endothelium-derived nitric oxide-mediated regulation of splanchnic circulation, and this same possibility has been suggested by Sigmon et al. [15]. Another possibility is that the tendency of the increase in HAVR and PVR during halothane anesthesia might reflect the swelling of hepatocytes caused by some unconfirmed mechanisms such as the direct effect of halothane on the permeability of hepatocytes' membrane, or on the intracellular Ca^{2+} reserves through a stimulation of the α-adrenergic receptors [16]. The rise in GPT in the halothane group seems to partially support this speculation.

Hepatolobectomy significantly decreased the HABF in both anesthesia groups. This result agrees with Gelman's work [17] that surgical operations, especially a procedure on the upper abdomen, produced a stronger disturbance on liver circulation than the effect of anesthesia alone. However, the percentage of HABF to THBF significantly decreased from the baseline value only in the halothane group, and HABF in the sevoflurane group was significantly higher than that in the halothane group. These facts indicate that sevoflurane anesthesia causes less adverse effects on hepatic circulation than halothane anesthesia, even after hepatolobectomy.

Indices of hepatic oxygen metabolism (DO_2, VO_2, DO_2/VO_2 or AKBR) in this study did not reveal significant difference between sevoflurane and halothane, although sevoflurane maintained HABF better than halothane. This might be due to the fact that we used a high FiO_2 without hypoxia. If hypoxic hypoxemia had combined with hepatolobectomy, different results on those indices might have been produced between the two anesthesia groups, because the relatively oxygen-rich blood supply from the hepatic artery would have been kept better by sevoflurane anesthesia.

The HABF could not recover to the baseline values even 2 h after the discontinuation of anesthesia. Intrahepatic vascular resistance increased significantly at this stage, especially in the halothane group. This might be due mainly to the effect of hepatolobectomy. These results, if they can be extrapolated to clinical situations, may imply that the recovery period is also dangerous when considering the effects of anesthesia and surgery on the liver circulation and oxygen metabolism, because the respiratory and circulatory depressions are often seen during this period. Hepatic dysfunction may easily be induced if hypotension or hypoxia occurs in the postoperative period in patients undergoing hepatolobectomy.

In conclusion, this study demonstrates that sevoflurane anesthesia has less adverse effects on liver circulation and function than halothane anesthesia. Hepatolobectomy strongly decreases HABF, but the decrease of HABF was smaller under sevoflurane anesthesia. HAVR and PVR were maintained relatively constant by sevoflurane anesthesia. GPT leakage from hepatocytes was less in sevoflurane anesthesia.

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