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Comparative Effects of Halothane, Isoflurane, and Sevoflurane on the Liver with Hepatic Artery Ligation in the Beagle

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Recently, there has been increasing interest in the alterations in splanchnic and hepatic circulation and preservation of hepatic oxygenation and function during anesthesia and surgery. However, the effects of volatile anesthetics under a condition of marginal hepatic oxygen supply are not well understood. Using a crossover design, we therefore studied the effects of equianesthetic concentrations (1.5 MAC) of halothane, isoflurane, and sevoflurane on hepatic oxygenation and function in nine beagles in which the hepatic artery had been ligated. Portal blood flow was measured by an electromagnetic flow meter. Hepatic function was assessed by indocyanine green elimination kinetics. While cardiac output and mean arterial pressure were greater during halothane anesthesia than during isoflurane and sevoflurane anesthesia, portal blood flow and hepatic oxygen supply were significantly less during halothane and sevoflurane anesthesia than during isoflurane anesthesia. With regard to hepatic oxygen uptake, there was a significant difference between halothane (2.7 ± 1.2 ml · min^{-1} · 100 g^{-1}) and sevoflurane (3.7 ± 2.0 ml · min^{-1} · 100 g^{-1}; $P < 0.05$). Consequently, the hepatic oxygen supply/uptake ratio and the hemoglobin oxygen saturation and oxygen partial pressure in hepatic venous blood during sevoflurane anesthesia were significantly less than they were with the other anesthetics. Indocyanine green clearance was better preserved during sevoflurane anesthesia (39.7 ± 12.0 ml · min^{-1}) than during halothane anesthesia (30.9 ± 8.4 ml · min^{-1}; $P < 0.05$). We conclude that sevoflurane is accompanied by a smaller oxygen supply/uptake ratio than is halothane and isoflurane, while it preserves hepatic function. We speculate that the difference between sevoflurane and isoflurane may be attributed to sevoflurane's less potent vasodilatory effect on the splanchnic system, and that the difference between sevoflurane and halothane may be attributed to the sevoflurane's weak metabolic depressant effect on the liver. (Key words: Anesthetics, volatile: halothane; isoflurane; sevoflurane. Liver: blood flow; hypoxia; indocyanine green clearance.)

RECENTLY, THERE HAS BEEN increasing interest in the alterations in splanchnic and hepatic circulation and preservation of hepatic oxygenation and function during anesthesia and surgery.[1-4] Although the hepatic oxygen supply ($H\dot{D}_{O_2}$) depends on the hepatic arterial blood flow to a greater extent, it has been suggested that such flow is regulated not by the metabolic demand of the liver but by the changes in the portal blood flow itself so as to maintain a total hepatic flow constant.[5] This response is known as "hepatic arterial buffer response" (HABR). The HABR plays an important role in liver function and protection against hypoxia during anesthesia, when portal blood flow (PBF) is decreased substantially by hemorrhagic shock or major abdominal surgery.[1,3-5] In previous studies, halothane has been shown to depress the HABR,[6] whereas isoflurane or opioids have preserved it, resulting in better $H\dot{D}_{O_2}$ during isoflurane than during halothane anesthesia.[3,4] On the other hand, surgical stress, especially laparotomy, is known to induce considerable alteration in hepatic blood flow.[1] It may be possible that surgical stress also affects the HABR. In addition, in patients with advanced liver disease, hepatic arterial blood supply and the HABR may be compromised.[7] Furthermore, other factors, such as hypoxia, acidosis, and enzyme induction may combine to inactivate the HABR.[4] Therefore, it seemed worthwhile to study whether isoflurane preserves hepatic oxygenation better than does halothane in situations of complete HABR inactivation.

To inactivate the HABR, we ligated the hepatic artery in the beagle. This procedure also substantially reduces the $H\dot{D}_{O_2}$,[8] such that small changes in the hepatic oxygen balance will be reflected in changes in hepatic function. With this model the systemic hemodynamic effect of hypoxia can be excluded, which it cannot be when hypoxic hypoxia is caused by a decrease in fractional inspired oxygen (FI_{O_2}).

Using this model, we compared the effects of halothane, isoflurane, and sevoflurane on hepatic oxygenation and function. Although the effect of sevoflurane on hepatic circulation has not been studied quantitatively, it has potential advantages over other volatile anesthetics with regard to hepatotoxicity, since it is quickly eliminated after anesthesia due to low solubility in tissue.[9]

Materials and Methods

The study protocol was approved by the Kawasaki Medical School Animal Research Committee. Nine beagles of either gender (body weight 10.5 ± 1.1 kg, mean ± standard deviation [SD]) were anesthetized with intravenous pentobarbital 30 mg · kg^{-1} after overnight fasting. After tracheal intubation, mechanical ventilation was provided by a constant volume respirator (R-10, Aika, Tokyo, Japan) with a mixture of oxygen and nitrous oxide

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(FI_{O_2} = 0.4). Pancuronium (4 mg), pentazocine (15 mg), and diazepam (5 mg) were administered intravenously. At a rate of 14–16 breaths per min, tidal volume was adjusted to obtain arterial blood carbon dioxide partial pressure (Pa_{CO_2}) between 35 and 40 mmHg. The setting of the controlled ventilation was not changed after that.

The animals received lactated Ringer's solution (5–8 $mg \cdot kg^{-1} \cdot h^{-1}$) throughout the experiment. Metabolic acidosis was corrected only at the end of the surgical preparations by intravenous administration of sodium bicarbonate. Body temperature was maintained between 36.5 and 37.5° C with a warming blanket throughout the experiment.

Surgical Preparations

A polyethylene catheter was inserted into the abdominal aorta *via* the right femoral artery, and a 5-Fr thermodilution catheter (SP 5105, Gould) was inserted into the pulmonary artery *via* the right external jugular vein for determination of cardiac output (CO) and monitoring of the body temperature. A radioopaque catheter with a side pore was advanced into the main hepatic vein *via* the right femoral vein for pressure monitoring and blood sampling. The placement of the catheters was carried out under fluoroscopic guidance, and the correct position of the catheter tip was confirmed by injection of contrast material. Through a midline abdominal incision, a polyethylene catheter was inserted into the portal vein through a branch of the splenic veins for pressure monitoring and blood sampling. The gastroduodenal artery, the right gastric artery, and the gastroduodenal vein were ligated. A precalibrated cuff-type electromagnetic flow probe (6-mm internal diameter) was placed around the portal vein. The flow probe had been placed in a saline-filled glass for about 6 h and was kept connected to the flow meter for stabilization. Electronic zero was checked periodically throughout the experiment. The PBF wave was continuously monitored. The hepatic artery was completely occluded by the ligation.

Measurement

Mean arterial pressure (MAP) portal vein pressure, hepatic vein pressure, and PBF were recorded on a multichannel recorder. Arterial, portal venous, and hepatic venous blood samples were withdrawn for blood gas and *p*H analysis (IL 1304 *p*H and Blood Gas Analyzer, Instrumentation Laboratory), hemoglobin concentrations, and oxygen saturations (IL 482 CO-Oxymeter, Instrumentation Laboratory). The oxygen contents of the blood samples were calculated by an IL 482 CO-Oxymeter. We calculated $H\dot{D}_{O_2}$ as the product of PBF and the oxygen content of portal vein blood and calculated hepatic oxygen uptake ($H\dot{V}_{O_2}$) as the difference of oxygen contents between portal vein blood and hepatic vein blood.[8] These variables were corrected for liver weight.

Hepatic function was evaluated by indocyanine green (ICG) elimination kinetic analysis as previously described.[2,10] In brief, we injected 0.25 $mg \cdot kg^{-1}$ ICG into the inferior vena cava through the proximal portion of the thermodilution catheter. Arterial blood samples were withdrawn before and 2, 4, 6, and 8 min after injection for determination of ICG plasma concentrations. The plasma concentration of ICG was determined at 805 nm by a spectrophotometer (UV-160A, Shimazu, Kyoto, Japan). The plasma concentration at zero time was extrapolated from the assumed linear semilogarithmic concentration–time plot. The distribution volume (Vd) of ICG was calculated by dividing the injected dose by the plasma concentration at zero time. The elimination rate constant (k) was obtained from the slope of the plot. ICG clearance (ICG_{Cl}) and ICG half-time ($ICG_{t1/2}$) were calculated as $ICG_{Cl} = Vd \cdot k$ and $ICG_{t1/2} = 0.693/k$, respectively. The extrapolation and calculations were performed with a personal computer (PC-9800, NEC, Tokyo, Japan).

Experimental Protocol

The animals' vital signs were stabilized for 60 min after the completion of the experimental preparation, which took about 3 h. Oxygen and nitrous oxide then were discontinued, and three volatile anesthetics of 1.5 MAC (halothane 1.34%, isoflurane (Forane) 2.09%, and sevoflurane (Sevofrane) 3.54%, end-expiratory)[11] with air were administered in a randomized sequence. The concentrations of the anesthetics were measured continuously through a small-bore tube connected to the endotracheal tube by a calibrated gas analyzer (Anesthetic Agent Monitor, Datex Instrumentarium, Finland).[12] Each anesthetic gas was administered for 60 min; a period of 10–20 min of ventilation with air was interposed between each administration of volatile anesthetic. Hemodynamic measurements and blood sampling were carried out at 50 min after the beginning of each anesthetic administration. Subsequently, an ICG bolus was injected for evaluation of hepatic function.

Statistics

All data are expressed as means ± SD. The data were analyzed by a one-way analysis of variance for repeated measures followed by Fisher's least-significant-difference method to determine the significant difference among the three anesthetics. The relationship between ICG_{Cl} and $H\dot{V}_{O_2}$ was evaluated by linear regression analysis and cor-

relation analysis. A P value < 0.05 was considered statistically significant.

Results

The systemic hemodynamics and hepatic oxygenation data are summarized in tables 1 and 2, respectively. Both CO and MAP were significantly greater during halothane anesthesia than during isoflurane and sevoflurane anesthesia, whereas PBF was greater during isoflurane than during halothane and sevoflurane anesthesia. Corresponding to the difference in PBF, $H\dot{D}_{O_2}$ was the greatest during isoflurane anesthesia. $H\dot{V}_{O_2}$ was significantly less during halothane (2.7 ± 1.2 ml · min^{-1} · 100 g^{-1}) than during sevoflurane anesthesia (3.7 ± 2.0 ml · min^{-1} · 100 g^{-1}). The hepatic oxygen supply/uptake ratio ($H\dot{D}O_2/H\dot{V}_{O_2}$) was significantly less with sevoflurane than with halothane or isoflurane. Similarly, hemoglobin oxygen saturation and oxygen partial pressure in hepatic venous blood were significantly less during sevoflurane anesthesia than during anesthesia with the other anesthetics. Portal vein pressure and hepatic vein pressure were similar with all three anesthetics.

Table 3 summarizes the variables of ICG elimination kinetics. The semilogarithmic plot of the plasma concentration of ICG against time was consistently linear ($r > 0.973$). Although there were no statistical differences in $ICG_{t1/2}$ among anesthetics, ICG_{Cl} was significantly greater during sevoflurane (39.7 ± 12.0 ml · min^{-1}) than during halothane anesthesia (30.9 ± 8.4 ml · min^{-1}). Although the correlation between ICG_{Cl} and $H\dot{V}_{O_2}$ under the separate anesthesia did not reach statistical significance, there was a significant correlation between these variables during the entire experiment ($r = 0.501$, $P < 0.05$; fig. 1).

Discussion

CO and MAP were greater during halothane than during isoflurane or sevoflurane anesthesia. It is well known that isoflurane depresses cardiac function considerably at higher concentrations and that its effect is weak at lower concentrations. However, we have no explanation why in our study isoflurane depressed systemic hemodynamics more than did halothane.

The results of the current study delineate the effects of halothane, isoflurane, and sevoflurane on the liver without arterial oxygen supply. The principal findings were 1) that halothane and sevoflurane both are associated with a lower $H\dot{D}_{O_2}$ than is isoflurane; 2) that $H\dot{V}_{O_2}$ and hepatic function are more depressed by halothane than by sevoflurane; 3) sevoflurane has the lowest $H\dot{D}_{O_2}/H\dot{V}_{O_2}$ among the three anesthetics.

Some methodologic issues need to be addressed. First, the lungs were ventilated mechanically during the experiment. Mechanical ventilation, hypercapnia, and hypocapnia substantially affect hepatic circulation and function.[1,10] The effects of these factors on the comparison have been excluded, however, because the lungs were ventilated under the same conditions throughout the experiment and because the Pa_{CO_2} values were similar and within the normal range during anesthesia with each of the three anesthetics. Second, in the current study, anesthesia was induced with pentobarbital, and surgical preparations were performed under nitrous oxide–oxygen anesthesia supplemented with pentazocine, diazepam, and pancuronium. Among these drugs, pentazocine and diazepam are well known to reduce the MAC of inhalation anesthetics.[13] Therefore, even though the measurement was initiated about 4 h after administration, it is theoretically possible that these drugs, because they have a long elimination half-time,[14,15] may have slightly increased the anesthetic depth during the measurements. This situation mimics clinical practice, in which these drugs are given as premedications.

A third potential criticism may be that the carryover effect may exist in the crossover design. Although this experimental design has the advantage of reducing the sample size, it is essential for statistical accuracy to minimize the carryover effect, in which the first anesthetic effect persists during the study of the second anesthetic effect.[16] However, we believe that a 60-min period of anesthetic administration with a 20-min interval for recovery

TABLE 1. Systemic Hemodynamics and Arterial Blood Gas and pH Values during Halothane, Isoflurane, and Sevoflurane Anesthesia

	Halothane	Isoflurane	Sevoflurane
CO (l/min)	1.52 ± 0.38*†	1.34 ± 0.24§	1.22 ± 0.16§
MAP (mmHg)	88 ± 14*†	76 ± 15§	71 ± 11§
Pa_{O_2} (mmHg)	92.1 ± 8.7	88.2 ± 13.5	87.6 ± 11.6
Pa_{CO_2} (mmHg)	38.4 ± 4.8	38.3 ± 4.5	39.8 ± 4.9
pHa	7.364 ± 0.041	7.364 ± 0.043	7.348 ± 0.038

Values are mean ± SD.
CO = cardiac output; MAP = mean arterial pressure.
* Significant (*vs.* isoflurane anesthesia, $P < 0.05$).
† Significant (*vs.* sevoflurane anesthesia, $P < 0.05$).
§ Significant (*vs.* halothane anesthesia, $P < 0.05$).

TABLE 2. Splanchnic Hemodynamics and Hepatic Oxygen Supply and Uptake during Halothane, Isoflurane, and Sevoflurane Anesthesia

	Halothane	Isoflurane	Sevoflurane
PBF ($ml \cdot min^{-1}$)	146 ± 42*	172 ± 43†,§	149 ± 38*
PVP (mmHg)	9.1 ± 1.1	9.3 ± 1.6	8.6 ± 1.3
HVP (mmHg)	5.1 ± 1.0	5.4 ± 1.5	5.4 ± 1.5
Shv_{O_2} (%)	38.0 ± 8.5†	38.5 ± 10.2†	29.1 ± 7.7*,§
Phv_{O_2} (mmHg)	34 ± 7†	32 ± 7†	29 ± 6*,§
$H\dot{D}_{O_2}$ ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	6.6 ± 1.8*	7.9 ± 1.9†,§	6.6 ± 2.0§
$H\dot{V}_{O_2}$ ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	2.7 ± 1.2†	3.5 ± 1.4	3.7 ± 2.0*
$H\dot{D}_{O_2}/H\dot{V}_{O_2}$	2.6 ± 0.8†	2.5 ± 1.1†	1.9 ± 0.5*,§

Values are mean ± SD.
PBF = portal blood flow; PVP = portal vein pressure; HVP = hepatic vein pressure; $H\dot{D}_{O_2}$ = hepatic oxygen supply; $H\dot{V}_{O_2}$ = hepatic oxygen uptake; Shv_{O_2} = hemoglobin oxygen saturation in hepatic vein blood; Phv_{O_2} = oxygen partial pressure in hepatic vein blood.
* Significant (*vs.* isoflurane anesthesia, $P < 0.05$).
† Significant (*vs.* sevoflurane anesthesia, $P < 0.05$).
§ Significant (*vs.* halothane anesthesia, $P < 0.05$).

is sufficient to minimize this effect, since even after 60 min of administration of halothane, which has the largest blood–gas partition coefficient among the three anesthetics studied, the alveolar concentration declined to less than 10% of the initial value after 60 min.[17]

Fourth and finally, it may be argued that ligation of the hepatic artery may cause an additional effect on PBF—a compensatory increase in PBF and hepatic oxygenation. Although it has been long believed that the hepatic artery and portal vein act reciprocally to maintain a constant flow to the liver,[18] recent work indicates that there is no compensatory mechanism by the portal vascular bed for hepatic artery flow.[5,19] Therefore, ligation of the hepatic artery should result in a reduction in the $H\dot{D}_{O_2}$ without eliciting secondary changes in PBF. On the other hand, surgical preparations such as laparotomy and manipulations of the abdominal viscera have induced splanchnic circulatory disturbance.[1,20] Hence, data in the current study must be interpreted as the combined effects of anesthetics and surgical stress rather than the pure effects of anesthetics. Our study therefore may have clinical relevance to major abdominal surgery with restriction of hepatic arterial blood flow.

A number of studies in animals without restriction of the hepatic artery and portal vein flow shows that isoflurane preserves hepatic oxygenation whereas halothane reduces it.[3,21,22] Preservation of hepatic oxygenation during isoflurane has been reported in rats receiving a subMAC dose of anesthetics combined with hypoxia ($FI_{O_2} = 0.12$).[4] The difference has been ascribed mainly to the depressant effect of halothane on the HABR.[23] Our data show that isoflurane provides a better $H\dot{D}_{O_2}$ than does halothane, even if the HABR is inactivated. The beneficial effect of isoflurane in the current study was related to a greater PBF during isoflurane anesthesia than halothane anesthesia.

We assessed hepatic function by ICG elimination kinetics, *i.e.*, by $ICG_{t1/2}$ and ICG_{Cl}. Whereas $ICG_{t1/2}$ defines the rate at which ICG concentration decreases, ICG_{Cl} indicates the efficiency of removal.[24] ICG_{Cl} is thus a better index for overall performance of the liver than is $ICG_{t1/2}$. In fact, we found a close correlation between ICG_{Cl} and $H\dot{V}_{O_2}$.

Although there were no differences in PBF and $H\dot{D}_{O_2}$ between halothane and sevoflurane, there were statistical differences in ICG_{Cl} and $H\dot{V}_{O_2}$ between the two anesthetics, suggesting suppression of the hepatic function by halothane. The effect of anesthesia with volatile anesthetics on hepatic blood flow and $H\dot{D}_{O_2}$ has been demonstrated in nonlaparotomized dogs[23] and laparotomized pigs.[22] Gelman *et al.*[25] found that halothane anesthesia is associated with a significant decrease in both the hepatic blood flow and ICG_{Cl} but that $ICG_{t1/2}$ and ICG_{Cl} did not correlate with the hepatic blood flow. They inferred from the data that halothane affects liver function adversely at the cellular level. Our data is in accordance with their findings. Several reports have suggested that there is inhibition of hepatocyte activity by halothane.[26–28] Furthermore, recent work supports the hypothesis of calcium-ion-mediated depression of hepatocyte function by halothane, because it has been demonstrated that among volatile anesthetics halothane induces the greatest increase in intracellular calcium ion concentration due to release from the endoplasmic reticulum in the hepatocyte.[29] In the current study, the difference in the hepatic function

TABLE 3. Effects of Halothane, Isoflurane, and Sevoflurane Anesthesia on ICG Elimination Kinetics

	Halothane	Isoflurane	Sevoflurane
ICG_{Cl} ($ml \cdot min^{-1}$)	30.9 ± 8.4*	36.4 ± 10.2	39.7 ± 12.0†
$ICG_{t1/2}$ (min)	10.69 ± 2.73	9.72 ± 3.43	8.96 ± 1.92

Values are mean ± SD.
ICG_{Cl} = clearance; $ICG_{t1/2}$ = half-time.
* Significant (*vs.* sevoflurane anesthesia, $P < 0.05$).
† Significant (*vs.* halothane anesthesia, $P < 0.05$).

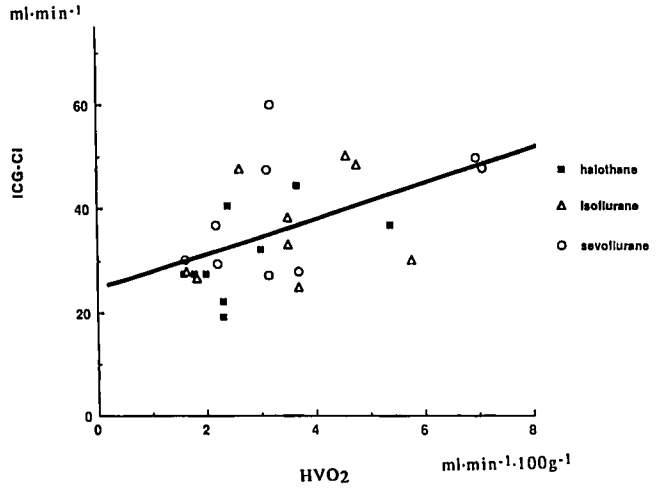

FIG. 1. Relationship between ICG clearance (ICG_{Cl}) and hepatic oxygen uptake ($H\dot{V}_{O_2}$) measured during 1.5 MAC halothane, isoflurane, or sevoflurane anesthesia. The ICG_{Cl} was significantly related with $H\dot{V}_{O_2}$ ($y = 3.41x + 24.3$, $r = 0.501$, $P < 0.05$).

between halothane and sevoflurane assessed by ICG_{Cl} was reflected in the $H\dot{V}_{O_2}$. Although precise mechanism for this difference is unknown, it at least suggests a difference in intensity of depression of hepatocellular activity by anesthetics.

Although an increasing number of reports has been published on the hemodynamic effects of sevoflurane,[30,¶] there have been relatively few quantitative studies concerning the effects of sevoflurane on hepatic circulation. Sevoflurane is reported to have a vasodilatory effect comparable to that of isoflurane on overall systemic and coronary circulation in equipotent concentrations.[31] Similarity of the effect of sevoflurane on the cerebral circulation to that of isoflurane also has been confirmed.[32] Sevoflurane may not, however, have a profound vasodilatory effect on the splanchnic vascular system, since in the current study PBF was lower during sevoflurane anesthesia than during isoflurane anesthesia, whereas there were no differences in systemic hemodynamics. Due to the lower $H\dot{D}_{O_2}$ compared to isoflurane and the greater $H\dot{V}_{O_2}$ compared to halothane, sevoflurane was associated with a lower $H\dot{D}_{O_2}/H\dot{V}_{O_2}$ and hemoglobin oxygen saturation than were halothane and isoflurane.

Clinically, our observations may imply that sevoflurane is not a good choice when the HABR is disabled and hepatic hypoxia is anticipated. Clearly, however, this implication should not be extrapolated to patients with intact hepatic arterial oxygen flow. Manohar and Parks[30] have shown that sevoflurane at both 1.0 and 1.5 MAC concentrations increases hepatic arterial blood flow in pigs, indicating the absence of a depressant effect on the HABR. Moreover, sevoflurane may be indicated, if the liver is not exposed to hypoxia, because it preserves hepatic function better than does halothane.

It must be kept in mind that in the current study we compared the effects of volatile anesthetics at equianesthetic concentrations; the dose-dependent effects of the anesthetics on the liver without a hepatic arterial blood supply remains to be clarified. Similar to our results, however, a study by Nagano *et al.*[8] showed in their study using a 1 MAC concentration in miniature pigs that halothane anesthesia is associated with a significantly lower $H\dot{V}_{O_2}$ and a lower but not statistically significant $H\dot{D}_{O_2}$ than is isoflurane anesthesia when the hepatic artery is occluded. It appears appropriate to assume that these effects are inherent to both anesthetics in clinical concentrations. Further studies comparing the effects of these volatile anesthetics focusing on the dose-dependent effects are desirable.

In conclusion, the current study in beagles indicates that isoflurane preserves the $H\dot{D}_{O_2}$ better than does either halothane or sevoflurane, even if the HABR does not occur. However, sevoflurane anesthesia preserves the hepatic function better than does halothane despite a hepatic blood flow and $H\dot{D}_{O_2}$ with sevoflurane similar to those with halothane. The $H\dot{D}_{O_2}/H\dot{V}_{O_2}$ during sevoflurane anesthesia was significantly less than was that of isoflurane or halothane, suggesting a smaller margin of safety against hypoxia than with halothane or isoflurane when the HABR is lost.

Isoflurane (Forane) and sevoflurane (Sevofrane) were kindly supplied by Dainabot, Osaka, Japan and Kodama Pharmaceutical, Tokyo, Japan, respectively.

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