Effects of Sevoflurane and Isoflurane on Hepatic Circulation in the Chronically Instrumented Dog

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To compare the effects of sevoflurane and isoflurane on hepatic circulation, eighteen dogs were chronically instrumented for measurements of mean aortic blood pressure and cardiac output and for simultaneous measurements of hepatic and portal blood flows. Each animal was studied while awake and during 1.2 and 2 MAC of either isoflurane or sevoflurane. Both anesthetics induced tachycardia and a dose-dependent decrease in mean aortic blood pressure (isoflurane −27% and −39%; sevoflurane −22% and −37%). Cardiac output decreased only at the highest concentration (isoflurane −10%; sevoflurane −21%). During sevoflurane, portal blood flow decreased at both 1.2 and 2 MAC (−14 and −33%, respectively), whereas an increase in hepatic arterial blood flow was recorded at 2 MAC (+33%). During isoflurane, the only significant change was a decrease in portal blood flow (−16%) at 1.2 MAC. Neither anesthetic significantly changed renal blood flow. Therefore, both anesthetics led to similar systemic and hepatic vasodilation. (Key words: Anesthetics, volatile: isoflurane; sevoflurane. Liver: blood flow.)

DOCUMENTATION OF THE EFFECT of anesthetics on liver blood flow is important for several reasons. First, anesthetic depression of liver blood flow has been implicated in the hepatotoxicity seen with anesthesia, especially if the circulation or liver function is compromised.[1] Second, it has been postulated that the effect of inhalation anesthetics on drug pharmacokinetics during anesthesia may be related to their effect on liver blood flow.[2-4] We have previously studied the effects of enflurane, isoflurane, and desflurane on the hepatic circulations in our chronically instrumented dogs and, have shown that both isoflurane

and desflurane support the hepatic circulation even at high anesthetic concentrations that produce major cardiovascular depression (decreases in cardiac output and mean arterial pressure), whereas enflurane results in more depression in liver blood flow associated with greater cardiovascular depression.[5,6]

Recently, Fujita et al.[7] and Frink et al.[8] have reported on the effect of the new inhalation anesthetic sevoflurane on hepatic circulation and compared the effects with those of other inhalation anesthetics. The former reported that 1.5 MAC sevoflurane produced more depression of portal blood flow than an equipotent concentration of isoflurane,[7] whereas the latter investigators reported that the depression in portal blood flow was equivalent with isoflurane and sevoflurane.[8] Fujita et al.'s model is seriously flawed because the animals were studied immediately after a laparotomy with the hepatic arterial circulation ligated.[9] Although Frink et al. studied chronically instrumented animals, their model was the greyhound, an animal whose physiology has been bred for racing and whose heart rate and performance are much greater per unit of body weight than those of other dogs.[10] In addition, several aspects of Frink et al.'s preparation were not documented. Finally, the effects of isoflurane on cardiac output in both of these publications were considerably different than those previously reported by us[5,6,11,12] and others.[13-18]

Consequently, we believe that it is important to document the effect of sevoflurane on liver blood flow in our well-described chronically instrumented dog model compared with effects of isoflurane in the same model. In addition, we will compare the effects shown in this investigation with anesthetic effects that we have previously demonstrated on liver blood flow with enflurane[5] and desflurane.[6]

Materials and Methods

This study was approved by the Baylor Animal Protocol Committee. Our basic animal preparation has been published previously.[5,6] Briefly, 18 healthy mongrel dogs (weighing 16–27 kg) were surgically instrumented during halothane anesthesia as follows. After a left thoracotomy, an electromagnetic flow probe (Micron Inc., Los Angeles, CA) was placed around the pulmonary artery for measurement of cardiac output. Via a laparotomy, a Tygon catheter (Tygon, Norton Inc., Akron, OH) was inserted in the abdominal aorta to measure aortic blood pressure;

TABLE 1. Arterial Blood Gases at Various Anesthetic Concentrations

Blood Gases		Awake	1.2 MAC	2 MAC
Pa_{O_2} (mmHg)	Sevo.	95 ± 2	104 ± 4	101 ± 4
	Iso.	107 ± 6	129 ± 8	126 ± 8
Pa_{CO_2} (mmHg)	Sevo.	32.9 ± 0.4	32.6 ± 0.8	32.8 ± 0.7
	Iso.	31.4 ± 3.3	30.5 ± 1.5	30.6 ± 1.0
pH (unit)	Sevo.	7.40 ± 0.01	7.40 ± 0.01	7.38 ± 0.01
	Iso.	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01

Mean ± SEM.   Sevo. = sevoflurane; Iso = isoflurane.

pulsed Doppler flow probes (Baylor College of Medicine, Houston, TX) were placed around the hepatic artery, approximately 3 cm from its origin (sizes 3.0–3.5 mm) and portal vein (sizes 7.0–8.0 mm). The gastroduodenal branch of the hepatic artery was ligated to prevent the outflow from bypassing the liver.[19] Ishida *et al.*[20] have demonstrated that for vessels including the portal vein and the hepatic artery, the kilohertz output of the pulsed Doppler flow meters is linearly related to volume flow. We have repeatedly confirmed these findings.††

Dogs were carefully nursed through the first 24 postoperative hours with appropriate analgesics and antibiotics and on subsequent days were trained to lie quietly on the laboratory floor. No less than 10 days after surgery, when hematocrit was >30% and when body temperature, appetite, and general appearance were normal, the dogs were randomly assigned to two groups (n = 9), receiving 1.2 and 2 MAC of either sevoflurane or isoflurane.[21] Experiments were performed in fasted animals. Each animal was studied awake and during anesthesia. The order of anesthetic concentration was randomized.

After mask induction with N_2O and the appropriate anesthetic and tracheal intubation, the lungs were ventilated with a mixture of O_2, N_2, and the anesthetic agent, using a Harvard ventilator. Ventilation and FI_{O_2} were adjusted to maintain arterial blood gases and pH at awake levels. End-tidal anesthetic concentrations and CO_2 were continuously monitored *via* a catheter in the endotracheal tube positioned at the carina level, using infrared absorption technique (Datex Medical Instruments, Tewsbury, MA). Rectal temperature was maintained by external heating at awake levels throughout the experiment. Physiologic (0.9%) saline was infused at 3–5 $ml \cdot kg^{-1} \cdot h^{-1}$. Aortic blood pressure, cardiac output, hepatic arterial and portal blood flows, and arterial blood gases were measured before anesthesia and during a brief apneic period at least 15 min after a constant end-tidal anesthetic concentration was obtained.

Systemic and hepatic vascular resistances were calculated from the quotient of the mean arterial pressure and

the cardiac output or hepatic arterial blood flow. For each anesthetic, changes were analyzed using an analysis of variance for repeated-measure design. When significant, multiple comparisons within and between groups were performed by paired t tests after Bonferroni corrections.[22] α was set at a level of 0.05. Data are represented as mean ± SEM.

Results

There were no significant intergroup differences in the hemodynamic values prior to anesthesia. No changes in pH and Pa_{CO_2} were observed in either group (table 1).

Sevoflurane anesthesia and isoflurane anesthesia were associated with a similar and dose-dependent decrease in mean arterial pressure; a non–dose-dependent decrease in systemic vascular resistance; a non–dose-related increase in heart rate; and a decrease in cardiac output only at 2 MAC (table 2). The only significant difference between the two anesthetics was a greater decrease in cardiac output at 2 MAC by sevoflurane.

Both anesthetics maintained hepatic arterial blood flow, and a statistically significant increase was noted at 2 MAC sevoflurane. In contrast, both anesthetics induced a significant decrease in portal blood flow at 1.2 MAC, but only sevoflurane produced a significant decrease at 2 MAC. Consequently, total hepatic blood flow was not significantly decreased at either concentration of isoflurane but was significantly decreased by 2 MAC sevoflurane. Finally, both anesthetics produced significant hepatic arterial vasodilation that was not dose-related.

Discussion

The results of this study and the previously published studies of the effects of enflurane, isoflurane, and desflurane on the hepatic circulation from our and other laboratories support the concept that the effects of sevoflurane, desflurane, and isoflurane are essentially the same at the anesthetic concentrations likely to be used clinically (1.2–1.4 MAC).[5,6,16,17] Hepatic arterial, portal and total hepatic blood flow were well maintained and hepatic vascular resistance was significantly decreased. Enflurane did

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†† Unpublished data.

TABLE 2. Systemic and Hepatic Hemodynamics

		n	Awake	1.2 MAC	2 MAC
HR (beats per min)	Sevo.	9	85 ± 3	122 ± 9*	121 ± 7*
	Iso.	9	85 ± 3	121 ± 9*	126 ± 7
CO (l/min)	Sevo.	7	1.9 ± 0.6	2.1 ± 0.2	1.5 ± 0.1*·†
	Iso.	7	2.1 ± 0.3	2.1 ± 0.1	1.9 ± 0.1*·†·‡
MAP (mmHg)	Sevo.	9	98 ± 5	72 ± 2*	60 ± 2*·†
	Iso.	9	97 ± 6	76 ± 5*	62 ± 5*·†
HBF (ml/min)	Sevo.	9	132 ± 19	173 ± 18	176 ± 19*
	Iso.	9	141 ± 20	159 ± 20	170 ± 22
PBF (ml/min)	Sevo.	8	485 ± 43	419 ± 37*	326 ± 34*
	Iso.	9	430 ± 51	361 ± 36*	370 ± 37
Total HBF (ml/min)	Sevo.	8	610 ± 40	585 ± 46	506 ± 50*
	Iso.	9	571 ± 59	519 ± 38	540 ± 45
HVR (mmHg · ml^{-1} · min^{-1})	Sevo.	9	0.95 ± 0.20	0.48 ± 0.07*	0.40 ± 0.07*
	Iso.	9	0.88 ± 0.19	0.56 ± 0.09	0.43 ± 0.07*
SVR (mmHg · ml^{-1} · min^{-1})	Sevo.	7	50.7 ± 4.8	35.6 ± 2.8*	41.4 ± 2.9*
	Iso.	7	47.3 ± 3.1	36.8 ± 2.5*	34.7 ± 2.8*

Mean ± SEM.

HR = heart rate; CO = cardiac output; MAP = mean arterial pressure; HBF = hepatic blood flow; PBF = portal blood flow; total HBF = total hepatic blood flow; HVR = hepatic vascular resistance; SVR = systemic vascular resistance.

* $P < 0.05$ versus awake.
† $P < 0.05$ versus 1.2 MAC.
‡ $P < 0.05$ versus sevoflurane.

produce a decrease in portal and total hepatic blood flows at 1.2 MAC and further dose-related decreases in both flows.[5] At high doses, the other three anesthetics also decreased portal blood flow without dose dependence and, except for isoflurane, decreased total hepatic blood flow. However, hepatic arterial blood flow was well preserved with all three anesthetics even at high concentrations.

The study by Fujita et al.[7] could not be expected to show the effects of anesthetics on liver perfusion because of the following complicating factors: 1) basal anesthesia, 2) laparotomy, 3) hepatic artery ligation, and 4) administration of all anesthetics to the same animals on the same day. If the arterial supply to the liver is intact even during laparotomy, the portal vein, because of the low O_2 content, supplies a lesser proportion of perfusion and oxygenation to the liver than its total flow would imply. Therefore, we argue that the effect of anesthetics on hepatic arterial blood flow cannot be disregarded when a study is made of the effect of anesthetics on perfusion and oxygenation of the liver.

Although the investigation by Frink et al.[8] did use chronically instrumented animals, the greyhound is a distinctly abnormal cardiovascular model, as we have already mentioned.[10] The basal cardiac output in their greyhounds was 7–7.5 l/min versus 2–3 l/min our similar-size dogs. In addition, isoflurane produced a dose-dependent decrease in cardiac output at all concentrations, in contrast to previous work from our laboratory and others' with chronically instrumented animals[5,6,11,12,16-18] in which isoflurane did not decrease cardiac output at less than 2 times MAC anesthetic concentrations. In all of these previous studies with isoflurane, as well as with sevoflurane and desflurane, the decrease in cardiac output produced

by increasing doses of all three anesthetics was considerably less than that in mean arterial pressure, whereas isoflurane and sevoflurane in the greyhounds produced considerably more decrease in cardiac output than in mean arterial pressure at each anesthetic concentration.

In addition, at first glance, it would seem that enflurane depressed the circulation less in the study by Frink et al.[8] in that 1 MAC enflurane produced only a 16% decrease in mean arterial pressure, compared with a 46% decrease in our study at 1.2 MAC. However, Frink et al. used the human MAC value of 1.7% rather than the dog MAC of 2.3%,[23] so the comparison is misleading. Actually, at equi-MAC concentrations the effects were not greatly different, except again that the decrease in mean arterial pressure was considerably greater than the decrease in cardiac output produced by enflurane in our animal model. It must be recognized, however, that at the highest concentrations they studied, Frink et al.[8] delivered only about 1.6 MAC equivalents of enflurane. At 2 times MAC of enflurane in the dog, with a decrease in mean arterial pressure considerably greater than Frink et al. reported and equivalent decreases in cardiac output, we still saw no significant decrease in hepatic arterial blood flow and considerably less change in total hepatic blood flow. In addition, Frink et al.[8] provided no documentation of the accuracy of the measurement of hepatic arterial and portal blood flow by their electromagnetic flow meters. Electromagnetic flow meters are noted for "zero drift," which is more pronounced for the smaller magnet sizes used for Frink et al.'s instrumentation. Maintenance of body temperature was not mentioned, although especially with the vasodilating volatile anesthetics, animals become hypothermic if not actively heated. Finally, no mention of pHa or

Pa$_{O_2}$ was made, although the F$_{I_{O_2}}$ was 0.3 during anesthesia compared with 0.21 during the awake control.

In agreement with Gelman *et al.*,[16] we have noted increases in hepatic arterial blood flow and maintenance of total hepatic blood with all concentrations of isoflurane.[5,6] Frink *et al.*[8] saw significant decreases in total hepatic blood flow with all concentrations of isoflurane primarily as a consequence of the decrease in portal blood flow. Inasmuch as portal blood flow tends to follow cardiac output,[24] this difference between the studies may be related to the more pronounced depression of cardiac output by isoflurane reported by Frink *et al.*

Under physiologic conditions, portal blood flow changes modulate hepatic arterial tone to maintain total hepatic blood flow.[24] This "hepatic arterial buffer response" has been shown to be depressed by halothane and enflurane in the normal[5,15,17] and cirrhotic[25,26] animal models, whereas it is preserved by isoflurane.[5,6] Our results are in agreement with those previously reported and, furthermore, indicate that the same holds true for sevoflurane, particularly at relevant clinical concentrations (1.5 MAC and less). Frink *et al.*[8] confirmed these results for halothane and enflurane but also reported that sevoflurane depressed total hepatic blood flow at 1.5 MAC because the decrease in portal blood flow was not "buffered" by an increase in hepatic arterial flow.

Previous studies using microspheres in swine showed a marked decrease in portal blood flow at 1 MAC sevoflurane,[27] but the pig does not respond to isoflurane or sevoflurane with coronary vasodilation[28] as do dogs[6,12,18] and humans.[29] Therefore, it is possible that the effect of the vasodilatory volatile anesthetics on this circulation may be different as well.

In summary, our study shows that sevoflurane preserves hepatic arterial blood flow even at high concentrations that resulted in significant decreases in cardiac output and mean arterial blood pressure. Portal blood flow was depressed at 2 MAC concentrations. The results are similar to those recorded in this study for isoflurane and in previous studies for desflurane and isoflurane.[5,6] We suggest that the effect of sevoflurane on hepatic, coronary, and systemic circulations is similar to those of isoflurane and desflurane in the chronically instrumented dog. Except for the tachycardia caused by all volatile anesthetics in basally trained chronically instrumented dogs, the cardiovascular effects on the systemic and coronary circulations in the dog have mimicked those seen in humans.[30–32] We speculate that perhaps the same species relationship may be seen for the effects of the inhalation anesthetics on the hepatic circulation as well.

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