# Effects of Enflurane and Isoflurane on Hepatic and Renal Circulations in Chronically Instrumented Dogs

Jean-Marc Bernard, M.D.,* Marie-Françoise Doursout, Ph.D.,† Patrick Wouters, M.D.,‡ Craig J. Hartley, Ph.D.,§ Marvin Cohen, M.D.,¶ Robert G. Merin, M.D.,** Jacques E. Chelly, M.D., Ph.D.††

Seven dogs were chronically instrumented for measurements of mean aortic blood pressure and cardiac output and for simultaneous measurements of hepatic, portal, and renal blood flows. Each animal was studied on two separate occasions, awake and during 1.2, 1.4, 1.75, and 2.0 MAC isoflurane and enflurane. Both anesthetics induced tachycardia; to a greater degree than isoflurane, enflurane lowered mean aortic blood pressure in a dose-dependent manner (−37, −45, −48, and −62% vs. −19, −25, −41, and −44%, respectively) and cardiac output (−20, −26, −41, and −48% vs. −3, −5, −11, and −15%, respectively). With isoflurane, cardiac output decreased only at 1.75 and 2.0 MAC, and portal blood flow did not change significantly, whereas hepatic arterial blood flow increased at 1.75 and 2 MAC (by 28 and 33%, respectively). With enflurane, no significant changes were recorded in hepatic arterial blood flow, whereas portal blood flow decreased in a dose-dependent manner. Except at 2 MAC, hepatic circulation did not differ between anesthetics. Likewise, neither anesthetic significantly changed renal blood flow, except for enflurane at 2.0 MAC, which was associated with a 35% reduction. Both anesthetics led to similar systemic, hepatic, and renal vasodilations. Our data suggest that high concentrations of enflurane are associated with decreases in portal, total hepatic, and renal blood flows, most likely as a result of an anesthetic-induced cardiac depression. (Key words: Anesthetics, volatile: enflurane; isoflurane. Kidney: blood flow. Liver: blood flow.)

IT IS ESTABLISHED that inhalational anesthetic effects on hepatic circulation play an important dose-dependent role in drug elimination during anesthesia.[1-3] For example, in the presence of halothane, verapamil and propranolol

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* Postdoctoral Research Fellow, Department of Anesthesiology, Baylor College of Medicine.

† Research Assistant Professor, University of Texas Medical School at Houston.

‡ Research Fellow, Department of Anesthesiology, University of Texas Medical School at Houston.

§ Professor, Department of Medicine, Baylor College of Medicine.

** Professor, Department of Anesthesiology, University of Texas Medical School at Houston.

¶ Assistant Professor, Department of Anesthesiology, University of Texas Medical School at Houston.

†† Professor, Department of Anesthesiology; Director, Division of Clinical Pharmacology, Department of Pharmacology, University of Texas Medical School at Houston.

Received from the Department of Anesthesiology, Baylor College of Medicine, Houston, and the Department of Anesthesiology, University of Texas Medical School at Houston, Houston, Texas. Accepted for publication September 28, 1990. Dr. Bernard's current address: Département d'Anesthésiologie, CHU, Hôpital St. Jacques, 44035 Nantes Cedex 01, France. Dr. Wouter's current address: Department of Anesthesia, Katholieke Universiteit Gasthuisberg, Belgium.

Address reprint requests to Dr. Chelly: Department of Anesthesiology, University of Texas Medical School at Houston, 6431 Fannin, MSB 5.020, Houston, Texas 77030.

plasma concentrations increase as the result of a decrease in clearance. Gelman et al.,[4] using injection of radioactive microspheres, have studied the effects of 1 and 2.0 MAC halothane and isoflurane. Other reports of anesthetic effects on hepatic and/or portal blood flow are questionable because of 1) the excessive weight of the electromagnetic flow probes used for measurement of portal blood flow; 2) the deleterious consequences of basal anesthesia and surgical stress[5]; and 3) the lack of appropriate awake controls for studies conducted in chronically instrumented swine[6,7] and rats.[8,9] In these studies, radiolabeled microspheres were used to measure regional blood flows. Although this method is more appropriate than electromagnetic flowmetry, radiolabeled microspheres allow only discontinuous measurements of blood flow—a methodologic limitation since the time course and nature of changes have not yet been established.

In the past few years, we have developed a method for continuous recording of portal and hepatic arterial blood flows based on the use of Silastic® pulsed Doppler flow probes in chronically instrumented dogs. This method has been validated in vitro and in vivo[10,11] and has been validated against injection of radioactive microspheres and electromagnetic flowmetry.[12] It therefore represents an appropriate experimental approach for assessing the effects of anesthetics on hepatic circulation.

Even though renal and hepatic circulations are important in drug elimination, the effects of enflurane and isoflurane—which are used commonly—on hepatic and renal blood flow have been documented only incompletely.

This study was designed to document the effects of four concentrations of isoflurane and enflurane on hepatic arterial and portal blood flow in chronically instrumented, conditioned dogs. Isoflurane, an isomer of enflurane, was used as a reference for enflurane because in the United States today it is the most commonly administered inhalational anesthetic. Since renal circulation may be important in drug elimination, we decided to document concomitantly the effects of anesthetics on renal blood flow in chronically instrumented dogs. Finally, our design documented the effects of four concentrations to determine the dose–effect relationship.

## Materials and Methods

This study was approved by the Baylor Animal Protocol Committee. Seven dogs (weight range 16–24 kg) were

surgically instrumented as follows. After a left thoracotomy, an electromagnetic flow probe (Micron, Los Angeles, CA) was placed around the pulmonary artery for measurement of cardiac output. A catheter (Tygon, Norton, Akron, OH) was inserted *via* laparotomy in the abdominal aorta to measure aortic blood pressure; 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 around the 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.[13] Finally, after the appropriate incision, a Doppler flow probe was placed around the renal artery. Ishida *et al.*[11] have demonstrated that for vessels including the portal vein and hepatic and renal arteries, 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 and on subsequent days were trained to lie quietly on the laboratory floor. The dogs were studied no less than 10 days after surgery, when hematocrit was >30% and when body temperature, appetite, and general appearance were normal.

The effects of enflurane and isoflurane were studied in each dog; each experiment was separated by at least 5 days and was performed in fasted animals. End-tidal anesthetic concentrations of 2.6, 3.2, 4.0, and 4.6 vol% for enflurane and of 1.6, 1.8, 2.3, and 2.6 vol% for isoflurane, equivalent to 1.2, 1.4, 1.75, and 2.0 MAC, were studied.[14,15] The order and the concentrations of anesthetic administration were randomized. Each animal was studied awake and during anesthesia, which was induced *via* mask. Tracheal intubation was performed with the appropriate anesthetic. With an Ohmeda ventilator (Ohmeda, Madison, WI), the lungs were ventilated with a mixture of $O_2$, $N_2$, and the anesthetic agent. Ventilation was adjusted to maintain $Pa_{CO_2}$ and $pH$ at awake levels (Instrumentation Laboratory, Inc., Lexington, MA). Inspired and expired concentrations of anesthetic and $CO_2$ were continuously monitored *via* a catheter in the endotracheal tube at the carina level by means of an infrared Datex analyzer (Datex Medical Instruments, Tewksbury, MA) calibrated with known standards (2.0 and 4.1% for enflurane and 1.57 and 3.02% for isoflurane, balanced with $N_2$). Lactated Ringer's solution (3–5 ml $\cdot$ kg$^{-1}$ $\cdot$ h$^{-1}$) was infused *via* a foreleg vein. Rectal temperature, measured with a thermocouple probe (Yellow Springs Instruments, Yellow Springs, OH), was maintained at awake levels throughout the experiment.

Prior to anesthesia and during a brief apneic period 20 min after reaching constant end-tidal anesthetic con-

centration, measurements were made of: heart rate; aortic blood pressure; cardiac output; renal, hepatic and portal blood flows; and arterial blood gases. Systemic and regional resistances were calculated as the ratio between mean arterial blood pressure and cardiac output or the appropriate regional (renal and hepatic) blood flow. Changes in hepatic and portal blood flows were also expressed as a fraction of cardiac output (ratio between regional blood flow and cardiac output).

For each anesthetic, changes were analyzed by analysis of variance for repeated-measure design. When significant, multiple comparisons within and between groups were performed after Bonferroni corrections.[16] In addition, to assess the relationship between hemodynamic changes and anesthetic concentrations, data were fitted to a linear model. Alpha was set at a level of 0.05. Data are represented as means ± SEM.

## Results

The systemic effects of isoflurane and enflurane anesthesia are summarized in table 1. Their hepatic and renal vascular effects are shown in figures 1 and 2, respectively. In awake animals, $Pa_{CO_2}$ and $pH$ were 30.8 ± 1 mmHg and 7.38 ± 0.01, respectively, in the isoflurane group and 29 ± 1.7 mmHg and 7.38 ± 0.02, respectively, in the enflurane group. $Pa_{CO_2}$ and $pH$ did not change significantly during the study.

Isoflurane administration was associated with tachycardia, a systemic vasodilation (except at 1.2 MAC), and a dose-dependent decrease in mean aortic pressure. High concentrations of isoflurane led to a decrease in cardiac output, whereas no significant changes were observed at 1.2 and 1.4 MAC. Enflurane administration was associated with tachycardia, systemic vasodilation, and dose-dependent decreases in mean aortic pressure and cardiac output. Mean aortic pressure at each anesthetic concentration and cardiac output at 1.75 and 2.0 MAC were lower during enflurane than during equipotent isoflurane anesthesia.

With isoflurane, no significant changes in portal and total hepatic blood flows were observed. At 1.75 and 2.0 MAC, hepatic arterial blood flow and its cardiac output fraction increased significantly (9.9 ± 1.4% at 1.75 MAC and 11.3 ± 1.9% at 2.0 MAC *vs.* 6.8 ± 0.9% awake). With enflurane, portal and total hepatic blood flows decreased in a dose-dependent manner. No significant changes were recorded in hepatic arterial blood flow. However, the hepatic fraction of cardiac output increased significantly (9.2 ± 1.3% at 1.4 MAC, 10.9 ± 1.5% at 1.75 MAC, and 10.2 ± 1.2% at 2.0 MAC) in comparison to this fraction in awake animals (6.6 ± 0.9%).

Isoflurane and enflurane administration resulted in a similar dose-dependent hepatic vasodilation. Differences between the anesthetics for lower hepatic arterial, portal, and total hepatic blood flows were significant at 2.0 MAC

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‡‡ Unpublished data.

TABLE 1. Effects of Enflurane and Isoflurane on Cardiac Function

| Parameter | Anesthetic | Awake | MAC | | | |
|---|---|---|---|---|---|---|
| | | | 1.2 | 1.4 | 1.75 | 2.0 |
| MAP (mmHg) | E | 104 ± 2 | 66 ± 2* | 57 ± 3*·† | 45 ± 3*·†·¶ | 40 ± 2*·†·‡·§·¶ |
| | I | 97 ± 7 | 79 ± 4* | 72 ± 3* | 67 ± 3* | 64 ± 6*·† |
| HR (beats per min) | E | 87 ± 7 | 109 ± 4* | 108 ± 3* | 111 ± 5* | 110 ± 4* |
| | I | 82 ± 5 | 119 ± 11* | 123 ± 12* | 127 ± 8* | 127 ± 9* |
| CO (l/min) | E | 2.2 ± 0.2 | 1.8 ± 0.1* | 1.7 ± 0.1* | 1.3 ± 0.1*·†·‡·¶ | 1.2 ± 0.1*·†·‡·¶ |
| | I | 2.1 ± 0.1 | 2.0 ± 0.1 | 2.0 ± 0.1 | 1.9 ± 0.1*·†·‡ | 1.8 ± 0.1*·†·‡ |
| SVR (mmHg · l⁻¹ · min⁻¹) | E | 48 ±4 | 37 ± 2* | 35 ± 2* | 33 ± 2* | 34 ± 1* |
| | I | 47 ± 4 | 39 ± 2 | 36 ± 1* | 34 ± 1* | 36 ± 3* |

Mean ± SEM.
$P < 0.05$: *versus awake; †versus 1.2 MAC; ‡versus 1.4 MAC; §versus 1.75 MAC. ¶$P < 0.05$: versus isoflurane at each concentration.

E = enflurane; I = isoflurane; MAP = mean aortic pressure; HR = heart rate; CO = cardiac output; SVR = systemic vascular resistances.

enflurane. However, when expressed as fractions of cardiac output, both anesthetics produced similar effects.

Isoflurane and enflurane anesthesia resulted in a similar degree of renal vasodilation. With isoflurane, no significant changes were observed in renal blood flow. Renal blood flow decreased at 2 MAC enflurane, but did not differ from that recorded at an equipotent MAC of isoflurane.

## Discussion

Our study provides original findings on the effects of isoflurane and enflurane (at four concentrations) on hepatic and renal circulations in chronically instrumented dogs. We intentionally precluded concentrations above 2.0 MAC since these are of limited clinical value. The effects of inhalational anesthetics on hepatic and renal circulations have been described previously on the basis of data generated by separate studies with no more than two concentrations.[4,17,18] In addition, except for the work of Gelman et al.,[4] models used were either acutely and surgically stressed or in the presence of basal anesthesia.
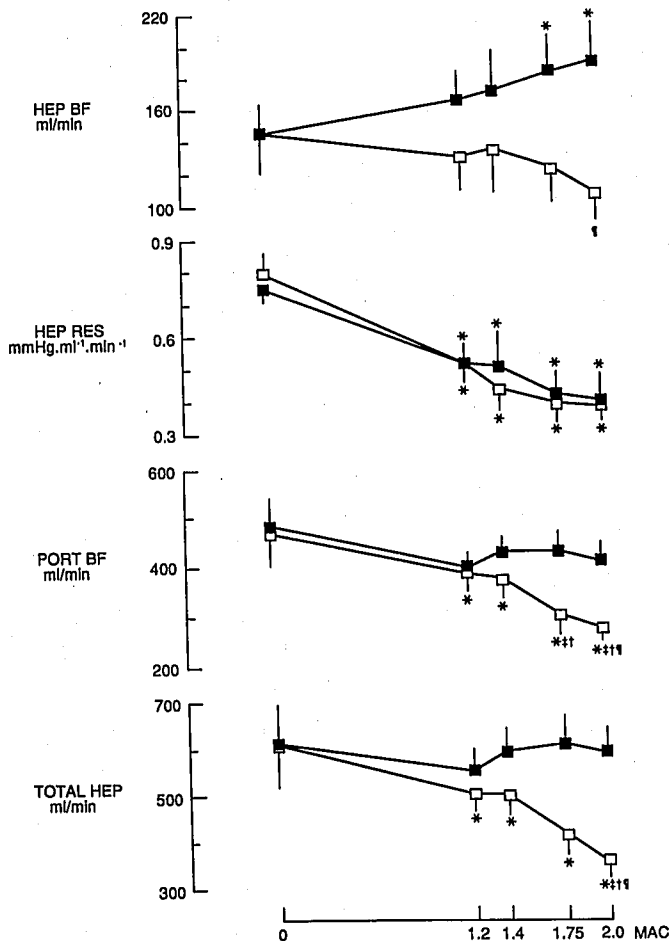


FIG. 1. Effects of enflurane (open squares) and isoflurane (filled squares) on hepatic blood flow (HEP BF) and resistance (HEP RES), portal blood flow (PORT BF), and total hepatic blood flow (TOTAL HEP). Mean ± SEM; *$P < 0.05$ versus awake; †$P < 0.05$ versus 1.2 MAC; ‡$P < 0.05$ versus 1.4 MAC; §$P < 0.05$ versus 1.75 MAC; ¶$P < 0.05$ versus isoflurane.
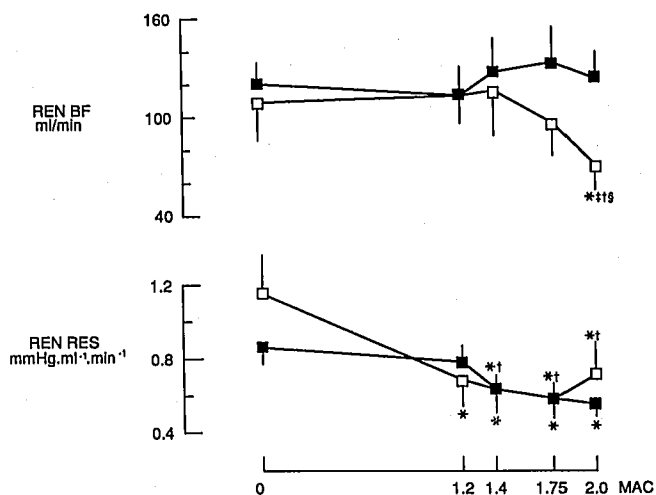


FIG. 2. Effects of enflurane (open squares) and isoflurane (filled squares) on renal blood flow (REN BF) and resistance (REN RES). Mean ± SEM; *$P$ versus awake; †$P < 0.05$ versus 1.2 MAC; ‡$P < 0.05$ versus 1.4 MAC; §$P < 0.05$ versus 1.75 MAC; ¶$P < 0.05$ versus isoflurane.

Furthermore, in a number of cases rats and swine were the species of choice. Unfortunately, these animals' responses to inhalational anesthetics has been demonstrated to differ from those of humans. Thus, it is established that isoflurane produces a coronary vasodilation that is not observed in swine[7] and rats.[8] Our design included exposure to four levels of either isoflurane or enflurane, which allowed more appropriate assessments of the dose–effect relationship in chronically instrumented dogs. In addition, the two anesthetics were investigated within the same group of animals. In these conditions, both anesthetics were found to produce similar degrees of dose-independent tachycardia and decreases in blood pressure. At low concentrations of isoflurane, cardiac output was unchanged and at high concentrations was better maintained than with enflurane. Since no significant differences in peripheral resistances were found between anesthetics, the lower mean aortic blood pressure at each concentration and at the same level of heart rate documented the more depressant effect of enflurane on cardiac pump function.

A pulsed Doppler method was used to assess the effects of isoflurane and enflurane on hepatic and renal circulations. With this method, isoflurane was found to increase hepatic arterial blood flow, whereas no change in total hepatic blood flow was recorded. Our findings on hepatic circulation agree with those of Gelman et al.,[4] who have used radionuclide-labeled microspheres for similar purposes. Prior to the current study, the effects of enflurane were controversial. Using microspheres in rats, Miller et al.,[9] found an increase in hepatic blood flow and in most splanchnic organs at 1.0 MAC enflurane, whereas in a similar study at similar concentrations of enflurane, Seyde and Longnecker reported a 43% decrease in hepatic arterial and no change in portal vein flow.[8] Again, the use of rats—a species known to respond differently to inhalational anesthetics than humans—and the presence of surgical stress as indicated by high heart rate and mean arterial blood pressure limited the value of the latter investigators' findings.[8]

Our results provide original evidence that enflurane induces a dose-dependent decrease in portal and total hepatic blood flow in the absence of significant changes in hepatic arterial blood flow. Our data contrast with those obtained in acutely instrumented and pentobarbital-anesthetized dogs, in which Irestedt and Andreen[17] and Hughes et al.[18] demonstrated with electromagnetic flowmetry that 1.0 MAC enflurane was associated with a 50–65% decrease in hepatic blood flow. Again, the discrepancies between the findings of these two studies and the current study are due most likely to the role of basal anesthesia and surgical stress.[19] Furthermore, portal blood flow is also impeded by the bulkiness and weight of electromagnetic flow probes. Thus, the portal vein is a high-compliance vessel that is acutely affected by the surgical trauma necessary for implantation of an electromagnetic flow probe. The weight of electromagnetic flow probes, and consequently, its effect on portal compliance is of importance when considering the thinness of the vessel wall.

Although increases in hepatic arterial blood flow changes may be related to decreases in portal blood flow,[20] it is unlikely that this was the mechanism of the effects of isoflurane on hepatic circulation. In fact, exposure to isoflurane resulted in an increase in hepatic arterial blood flow, whereas portal blood flow remained essentially unchanged. Blood pressure also has been recognized as a modulator of local vascular tone. However, it is established that this type of autoregulation plays a minor role in the control of hepatic circulation, and in contrast, Chauvin et al.[21] demonstrated that during nitroprusside-induced hypotension, changes in hepatic plasma flow were linearly correlated to changes in cardiac index but not to changes in mean arterial blood pressure.

In our study, hepatic blood flow increases paralleled decreases in mean arterial pressure in the presence of isoflurane. Since hepatic blood flow was maintained despite a slight but significant reduction in cardiac output in the presence of 1.75 and 2.0 MAC isoflurane, it appears that other factors also contributed to the control of hepatic circulation during inhalational anesthesia. Thus our results concur with those of Gelman et al.[4] in that isoflurane provided a specific effect on the hepatic vasculature by directly dilating the hepatic artery—an effect that is independent of a decrease in portal blood flow.

Our study showed that with 1.75 and 2.0 MAC isoflurane hepatic arterial blood flow significantly increased, whereas with 2.0 MAC enflurane it decreased. In addition, there were no significant differences in hepatic arterial resistance between enflurane and isoflurane. With both anesthetics, the hepatic fraction of cardiac output increased similarly. Since enflurane produced a more pronounced decrease in cardiac output than did isoflurane, our findings suggest that the differences between anesthetics in effects on hepatic artery blood flow were due not to differences in potency, but to the respective effects of isoflurane and enflurane on cardiac function.

Both isoflurane and enflurane, except for 2.0 MAC enflurane, affected renal autoregulation only minimally, since renal blood flow was maintained despite a significant decrease in mean aortic blood pressure. It is most likely that the decrease in renal blood flow recorded at 2.0 MAC enflurane was due to hypotension beyond the range of autoregulation. Therefore, some consideration should be given to the deleterious consequences of high-concentration enflurane on the renal elimination of drugs.

In conclusion, both enflurane and isoflurane administration resulted in potent and similar renal and hepatic vasodilations in chronically instrumented dogs. However, contrasting with isoflurane, the highest concentration of

enflurane resulted in a marked reduction in cardiac output and mean arterial blood pressure—effects most likely responsible for decreases in total hepatic and renal blood flows.

## References

1. Reilly CS, Wood AJ, Koshakji R, Wood M: Effects of halothane on drug disposition: Contributions of intrinsic drug metabolizing capacity and hepatic blood flow. ANESTHESIOLOGY 63:70–76, 1985

2. Chelly JE, Hysing ES, Abernethy DR, Doursout MF, Merin RG: Effects of inhalational anesthetics on verapamil pharmacokinetics in dogs. ANESTHESIOLOGY 65:266–271, 1986

3. Wood M, Wood AJJ: Contrasting effects of halothane, isoflurane, and enflurane on in vivo drug metabolism in the rat. Anesth Analg 63:709–714, 1984

4. Gelman S, Fowler KC, Smith LR: Liver circulation and function during isoflurane and halothane anesthesia. ANESTHESIOLOGY 61:726–730, 1984

5. Doursout M-F, Chelly JE: Effects of basal anaesthesia on cardiac function. Br J Anaesth 60:119S–122S, 1988

6. Tranquilli WJ, Manohar M, Parks CM, Thurmon JC, Theodorakis MC, Benson GJ: Systemic and regional blood flow distribution in unanesthetized swine and swine anesthetized with halothane + nitrous oxide, halothane, or enflurane. ANESTHESIOLOGY 56:369–379, 1982

7. Lundeen G, Manohar M, Parks C: Systemic distribution of blood flow in swine while awake and during 1.0 and 1.5 MAC isoflurane anesthesia with or without 50% nitrous oxide. Anesth Analg 62:499–512, 1983

8. Seyde WC, Longnecker DE: Anesthetic influences on regional hemodynamics in normal and hemorrhaged rats. ANESTHESIOLOGY 61:686–698, 1984

9. Miller ED, Kistner JR, Epstein RM: Whole-body distribution of radioactively labelled microspheres in the rat during anesthesia

10. Hartley CJ, Hanley HG, Lewis RM, Cole JS: Synchronized pulsed Doppler blood flow and ultrasonic dimension measurement in conscious dogs. Ultrasound Med Biol 4:99–110, 1978

11. Ishida T, Lewis R, Hartley CJ, Entman ML, Field JB: Comparison of hepatic extraction of insulin and glucagon in conscious and anesthetized dogs. Endocrinology 112:1098–1109, 1983

12. Vatner SF, Franklin D, Van Citters RL: Simultaneous comparison and calibration of the Doppler and electromagnetic flowmeters. J Appl Physiol 29:907–910, 1970

13. Miller ME: The heart and arteries, Miller's The Anatomy of the Dog. Edited by Evans HE, Christensen GC. Philadelphia, WB Saunders, 1979, pp 632–756

14. Eger EL, II, Lundgren C, Miller SL, Stevens WC: Anesthetic potencies of sulfur hexafluoride, carbon tetrafluoride, chloroform and enthrane in dogs. ANESTHESIOLOGY 30:129–135, 1969

15. Maze M, Vickery RG, Merlone S, Gaba DM: Anesthetic and hemodynamic effects of the alpha₂-adrenergic agonist, azepexole, in isoflurane-anesthetized dogs. ANESTHESIOLOGY 68:689–694, 1988

16. Keppel G: Correction for multiple comparisons, Design and Analysis. Edited by Keppel G. Englewood Cliffs, Prentice-Hall, 1982, pp 144–166

17. Irestedt L, Andreen M: Effects of enflurane on haemodynamics and oxygen consumption in the dog with special reference to the liver and preportal tissues. Acta Anaesthesiol Scand 23:13–26, 1979

18. Hughes RL, Campbell D, Fitch W: Effects of enflurane and halothane on liver blood flow and oxygen consumption in the greyhound. Br J Anaesth 52:1079–1086, 1980

19. Gelman S, Dillard E, Bradley E: Hepatic circulation during surgical stress and anesthesia with halothane, isoflurane or fentanyl. Anesth Analg 66:936–943, 1987

20. Richardson PDI, Withrington PG: Liver blood flow. Gastroenterology 81:159–173, 1981

21. Chauvin M, Bonnet F, Montembault C, Lafay M, Curet P, Viars P: Hepatic plasma flow during sodium nitroprusside-induced hypotension in humans. ANESTHESIOLOGY 63:287–293, 1985