Effect of sevoflurane on hemodynamic and cardiac energetic parameters in ferrets

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Objective—To determine the effect of sevoflurane on cardiac energetic and hemodynamic parameters in ferrets.

Animals—7 healthy domesticated ferrets.

Procedure—Sevoflurane was used as the sole anesthetic agent for general anesthesia in ferrets. Standard midline laparotomy and median sternotomy were performed to permit instrumentation. Myocardial blood flow was determined by use of colored microsphere technology. Measurements and blood samples were obtained at 1.25%, 2.5%, and 3.75% expired concentration of sevoflurane.

Results—A dose-dependent decrease in arterial blood pressure, left ventricular pressure, systemic vascular resistance, aortic flow, and dp/dt (an index of contractility) was detected as expired concentration of sevoflurane increased. Heart rate, central venous pressure, coronary vascular resistance, myocardial oxygen extraction ratio, and τ (the time constant of relaxation) were unchanged. Cardiac external work decreased, as did myocardial oxygen consumption, causing increased cardiac efficiency at higher concentrations of sevoflurane.

Conclusions and Clinical Relevance—Sevoflurane caused minimal and predictable cardiovascular effects in ferrets without increasing myocardial metabolic demands. Data obtained from this study have not been previously reported for a species that is being commonly used in cardiovascular research. These findings also support use of sevoflurane as a safe inhalant anesthetic in ferrets for clinical and research settings. (*Am J Vet Res* 2004:65:653–658)

The ferret (*Mustela putoris furo*) is a popular companion animal and, because of its specific anatomic features, it is an excellent cardiovascular animal model.[1,2] Volatile inhalant agents are commonly used to anesthetize ferrets in clinical and research settings. Use of sevoflurane[a] as an inhalant anesthetic is becoming more common because induction and recovery are quicker and smoother because of a lower blood-to-gas solubility coefficient and minimal respiratory irritation,[3-5] compared with isoflurane. The effect of sevoflurane on the heart in ferrets has only been assessed during in vitro studies of calcium transport and myocardial contractility.[6,7] Sevoflurane has been evaluated in Siberian polecats, which is a close relative of the domestic ferret.[8] That study found that sevoflurane permitted a more rapid induction and recovery, compared with isoflurane, and had less effect on heart rate and blood pressure. However, the cardiovascular effects of sevoflurane on the domestic ferret remain widely undetermined. Establishing the effect of sevoflurane on cardiac function may provide information to further validate the use of ferrets as models for cardiovascular research, as well as justifying the use of sevoflurane for clinical anesthesia in ferrets. The purpose of the study reported here was to determine the effect of sevoflurane on cardiac energetic and hemodynamic parameters in ferrets.

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Materials and Methods

This study was approved by the Animal Care and Use Committee of Colorado State University. The 7 adult domesticated ferrets used in this study were determined to be of good general health from complete physical examination. Ferrets were anesthetized with sevoflurane in an induction chamber. After the righting reflex was lost, ferrets were removed from the chamber and sevoflurane was administered through an anesthetic mask until intubation could be performed. Ferrets were mechanically ventilated with intermittent positive-pressure ventilation of 10 to 12 breaths/min and 8 to 12 cm H_2O of peak inspiratory pressure. A 22-gauge, over-the-needle IV catheter was placed in a cephalic vein for administration of crystalloid fluids (10 mL/kg/h). Baseline heart rate and respiratory rate were recorded. During instrumentation, systolic blood pressure was monitored by a Doppler ultrasonic flow detector. The crystal was placed over the coccygeal artery with an occlusive cuff placed proximal to the crystal; mechanical ventilation and sevoflurane concentration were adjusted as needed to maintain end-tidal carbon dioxide at 40 mm Hg.

A standard midline laparotomy and median sternotomy were performed. The pericardial sac was opened, and the edges of the sac were sutured to either side of the sternotomy incision to support the heart in the field. A 22-gauge, over-the-needle catheter was placed in the abdominal aorta for direct measurement of arterial blood pressure and to collect arterial blood samples. A 22-gauge, over-the-needle catheter was placed in the cranial vena cava for direct measurement of central venous pressure. A 4-F microtip pressure transducer catheter was placed through a stab incision into the left ventricle for measurement of **left ventricular pressure (LVP)** and secured with an interrupted horizontal mattress suture of 4-0 polypropylene with pledgets.[b] A 2-mm transonic flow probe[c] was placed around the ascending aorta. A 22-gauge, over-the-needle catheter was placed in the left atrium for injection of colored microspheres. A 24-gauge, over-the-needle catheter was placed into the coronary sinus for collection of blood samples. The flow probe and pressure transducers were connected to a data acquisition system, and calibration was performed. Blood samples were analyzed by use of a hemoximeter to determine oxygen saturation and oxygen content from the aorta and coronary sinus. The **minimum alveolar concentration (MAC)** for sevoflurane in the ferret is unknown. However, extrapolating from rats, measurements and samples were obtained at 0.5, 1.0, and 1.5 MAC, which corresponded

to 1.25%, 2.5%, and 3.75% end-expiratory concentrations of sevoflurane. The MAC values selected for this study represent a range of clinically useful anesthetic concentrations; similar MAC values have been used in comparable studies evaluating sevoflurane in other species.[9-11] Ferrets were stabilized at each sevoflurane concentration for an arbitrarily chosen period of 10 minutes before data and samples were collected.

At each data point, colored microspheres were used to determine myocardial blood flow. Determination of tissue perfusion with microspheres requires injection into the left atrium and simultaneous withdrawal from the descending aorta. To prevent agglomeration of microspheres, ferrets were pretreated with an IV injection of 0.02 mL of 0.05% Tween 80. To assure uniform dispersion, each vial of colored microspheres was vortexed for 1 minute before administration. Microspheres were then immediately drawn from the vial into a syringe and administered to the ferret. At 1.25% expired concentration of sevoflurane, 0.35 mL of violet microspheres were injected into the left atrium. At 2.5% and 3.75% expired concentrations of sevoflurane, 0.15 mL yellow microspheres and 0.20 mL white microspheres were injected, respectively. Microspheres were injected as a bolus followed by a 1 mL bolus of saline (0.9% NaCl) solution. The number of injected microspheres varied to account for the different absorbance characteristics of each color. Blood samples during each injection were collected from the descending aorta at a rate of 0.6 mL/min starting 10 seconds before injection and continuing for 100 seconds after injection for a total collected blood volume of 0.8 mL. After the last data and sample collection, ferrets were humanely euthanatized with an overdose of pentobarbital sodium and the left ventricle was harvested.

The entire left ventricle was separated, weighed, and digested with 4M **potassium hydroxide (KOH)** solution. After tissue digestion, the solution was passed through a 10-µm filter to retain the microspheres. Filters were placed in microcentrifuge tubes, and 100 µL of dimethylformamide was added to extract the dye bonded to the microspheres. Blood samples were treated similarly except that digestion was performed with 8M KOH solution. Microcentrifuge tubes were centrifuged at 3,000 × *g* for 5 minutes. The supernatant of each sample was transferred to a microcuvet and placed in a spectrophotometer. Wavelengths of 594 nm for the violet dye, 448 nm for the yellow dye, and 370 nm for the white dye were used to measure the absorption of each sample. A reference sample of 10^6 microspheres of each color was used to establish a reference for the absorption of 10^3 microspheres. Calculation of myocardial blood flow was determined by comparing the number of microspheres in each tissue sample to the number of microspheres in the blood sample with the following equation:

Myocardial blood flow (mL/min/g) =
Total tissue spheres/tissue weight (g) ×
1/total reference spheres (mL/min)

Collected data included heart rate; **systolic diastolic (DAP)** and **mean (MAP)** arterial blood pressure; **central venous pressure (CVP)**; aortic flow; LVP; arterial oxygen saturation and oxygen content, and coronary sinus oxygen saturation and oxygen content. Computer determined data included **left ventricular end-diastolic pressure (LVEDP)**, +dp/dt (an index of contractility), –dp/dt (an index of relaxation), and τ (the time constant of relaxation). τ Was determined from linear regression analysis of dp/dt versus LVP with τ being equal to the slope of the regression plot during diastole.[12] Calculated data included **systemic vascular resistance (SVR)**, **coronary vascular resistance (CVR)**, myocardial **oxygen extraction ratio (OER)**, **myocardial oxygen consumption (MvO_2)**, external cardiac work, and cardiac efficiency:

SVR (mm Hg × mL/min) =
(MAP [mm Hg]–CVP [mm Hg])/aortic flow (mL/min)

CVR (mm Hg × mL/min) =
(DAP [mm Hg]–LVEDP [mm Hg])/
mean left ventricular coronary blood flow (mL/min)

Myocardial OER =
(arterial O_2 content–coronary sinus O_2 content)/
arterial O_2 content × 100

MvO_2 (J) =
(arterial O_2 content–coronary sinus O_2 content) ×
(LVBF/100) × 20

Cardiac external work (J) =
(MAP–LVEDP) × aortic flow (mL/min) × 0.133

Cardiac efficiency (%) =
(cardiac external work [J]/MvO_2 [J]) × 100

Statistical analyses—Analyses were performed with a computer software package[d] by use of ANOVA for repeated measures with the *P* value set at < 0.05. Results are presented as mean ± SD. Because of the small sample size of this experiment, statistical power was calculated for nonsignificant variables to determine the likelihood of type II error. This was performed by use of a separate computer software program.[e]

Results

No adverse reactions to sevoflurane were observed in any ferret during the entire experiment. Ferrets were placed into the induction chamber at time zero; the righting reflex was lost in 1.83 ± 0.3 minutes. All ferrets were breathing spontaneously (40.5 ± 8.6 breaths/min) following removal from the chamber, and an anesthetic mask was used to continue sevoflurane administration. Intubation was performed 11.83 ± 4.2

Table 1—Mean ± SD values for hemodynamic parameters at various expired concentrations of sevoflurane in 7 ferrets

	Expired concentration of sevoflurane				
Variable	**1.25%**	**2.50%**	**3.75%**	***P* value**	**Power**
Heart rate (beats/min)	222.4 ± 35.3	229.1 ± 42.1	218.0 ± 36.6	0.432	0.46
SAP (mm Hg)	100.7 ± 14.3	83.4 ± 15.4	66.7 ± 8.9	< 0.001	NA
MAP (mm Hg)	91.2 ± 14.7	72.4 ± 15.9	54.0 ± 8.3	< 0.001	NA
DAP (mm Hg)	81.1 ± 15.1	45.0 ± 8.1	31.2 ± 4.8	< 0.001	NA
CVP (mm Hg)	2.4 ± 1.0	2.3 ± 1.1	2.7 ± 1.1	0.593	0.62
Aortic flow (mL/min)	83.7 ± 11.5	76.7 ± 19.0	72.4 ± 10.9	0.014	NA
LVP (mm Hg)	124.6 ± 7.7	98.4 ± 17.4	81.1 ± 6.8	< 0.001	NA

SAP = Systolic arterial pressure. MAP = Mean arterial pressure. DAP = Diastolic arterial pressure. CVP = Central venous pressure. LVP = Left ventricular pressure. NA = Not applicable.

Table 2—Mean ± SD values for calculated hemodynamic and energetic parameters at various expired concentrations of sevoflurane in 7 ferrets

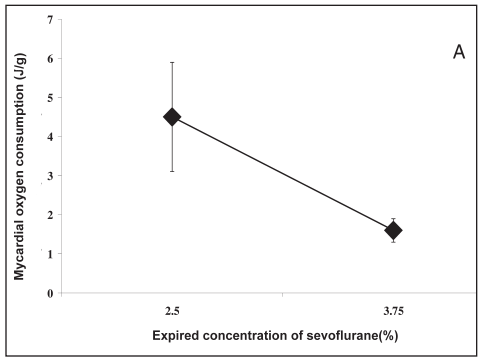
Variable	Expired concentration of sevoflurane 1.25%	2.5%	3.75%	*P* value	Power
LVEDP (mm Hg)	5.6 ± 2.74	5.6 ± 1.9	5.6 ± 2.73	> 0.999	1.0
+dp/dt	2,771.4 ± 407.1	2,071.4 ± 515.5	1,500.0 ± 216.0	< 0.001	NA
–dp/dt	–1,942.9 ± 386.7	–1,371.4 ± 508.9	–1,014.3 ± 186.4	< 0.001	NA
τ (sec)	0.022 ± 0.006	0.025 ± 0.008	0.023 ± 0.006	0.664	0.68
SVR (mm Hg×mL/min)	1.07 ± 0.2	0.9 ± 0.2	0.7 ± 0.1	< 0.001	NA
CVR (mm Hg×mL/min)	NA	14.3 ± 10.0	18.7 ± 2.8	0.192	0.21
Myocardial blood flow (mL/min/g)	NA	2.7 ± 1.1	1.1 ± 0.3	0.035	NA
MvO_2 (J/g)	NA	4.5 ± 3.1	1.6 ± 0.3	0.023	NA
Cardiac work (J)	0.96 ± 0.2	0.71 ± 0.3	0.47 ± 0.1	0.002	NA
Cardiac efficiency (%)	NA	4.0 ± 3.1	7.3 ± 2.5	0.017	NA

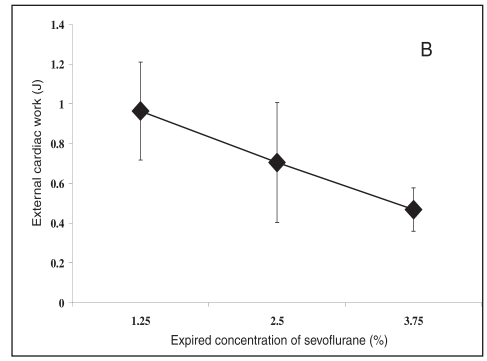
LVEDP = Left ventricular end-diastolic pressure. τ = Time constant of relaxation. SVR = Systemic vascular resistance. CVR = Coronary vascular resistance. MvO_2 = Myocardial oxygen consumption. +dp/dt = Index of contractility. –dp/dt = Index of relaxation. NA = Not applicable.

Table 3—Mean ± SD values for blood gas parameters at various expired concentrations of sevoflurane in 7 ferrets

Variable	Expired concentration of sevoflurane 1.25%	2.50%	3.75%	*P* value	Power
Arterial O_2 content	14.5 ± 2.6	13.7 ± 2.8	11.8 ± 3.5	0.003	NA
Coronary sinus O_2 content	6.3 ± 1.7	5.6 ± 1.5	4.8 ± 2.2	0.005	NA
Hemoglobin concentration (%)	10.8 ± 1.9	10.4 ± 2.5	9.0 ± 2.6	0.002	NA
Myocardial oxygen extraction ratio (%)	56.3 ± 7.0	59.5 ± 4.2	60.3 ± 7.4	0.286	0.31

NA = Not applicable.





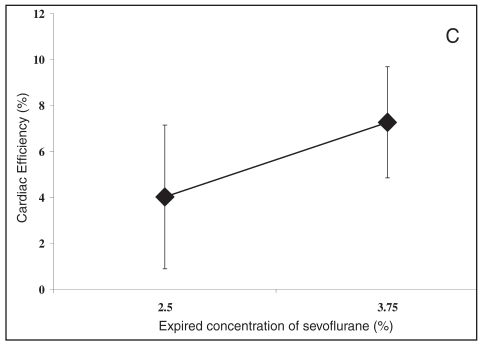


Figure 1—Effect of increasing expired concentrations of sevoflurane on myocardial oxygen consumption (A; $P = 0.04$), cardiac external work (B; $P = 0.002$), and cardiac efficiency (C; $P = 0.02$) in 7 ferrets.

minutes from time zero. Respiratory rate at that time was 38.8 ± 7.2 breaths/min. Baseline heart rate and systolic pressure were 247.4 ± 27.3 beats/min and 99.7 ± 25.3 mm Hg, respectively. Rectal temperature at the time of intubation was 38.4°C (101.1°F).

From 1.5% to 3.75% expired concentration of sevoflurane, there was a significant dose-dependent decrease in arterial pressure ($P < 0.001$), aortic flow ($P = 0.014$), and LVP ($P < 0.001$; **Table 1**). However, heart rate ($P = 0.43$), CVP ($P = 0.59$), and LVEDP ($P >$

0.99) remained stable. Heart rate did not differ from baseline values obtained at intubation. Systemic vascular resistance ($P < 0.001$), +dp/dt ($P < 0.001$), and the magnitude of –dp/dt ($P < 0.001$) significantly decreased, and τ was unaffected ($P = 0.664$) as expired concentration of sevoflurane increased (**Table 2**). Rectal temperature decreased significantly from baseline to when measurements were taken at 1.5% expired sevoflurane concentration (38.4 ± 1.0° to 35.0 ± 1.1°C; $P < 0.001$), but did not decrease further for the remainder of the experiment, which was approximately 1 to 1.5 hours.

Both arterial ($P = 0.003$) and coronary sinus ($P = 0.005$) oxygen content significantly decreased with increasing concentration of sevoflurane (**Table 3**). This was most likely caused by the corresponding significant ($P = 0.002$) decrease in hemoglobin concentration. A mild increase in myocardial oxygen extraction ratio was observed during this same time frame, but it was not significant ($P = 0.29$).

Myocardial blood flow could be correctly collected in 5 ferrets at 1.5% sevoflurane; microspheres could not be retrieved at this data point for 2 ferrets. Therefore, there were insufficient data points for myocardial blood flow at 1.5% sevoflurane to statistically compare with other concentrations. Consequently, data was also deficient for CVR, MvO_2, and cardiac efficiency at 1.5% sevoflurane because myocardial blood flow was a determinant in those calculations. However, myocardial blood flow did significantly decrease from 2.5% to 3.75% expired concentrations of sevoflurane (4.6 ± 4.1 to 1.9 ± 1.8 mL/min/g; $P = 0.04$) as did MvO_2 (11.5 ± 12.4 to 2.6 ± 1.7 J/g; $P = 0.17$; **Fig 1**). Coronary vascular resistance was unaffected as sevoflurane concentration increased from 2.5% to 3.75% ($P = 0.19$; Table 1). Cardiac external work also decreased significantly ($P = 0.002$) from 1.5% to 3.75% concentrations of sevoflurane (0.96 ± 0.2 to 0.46 ± 0.11 J). Cardiac efficiency significantly ($P = 0.02$) increased from 2.5% to 3.75% expired concentrations of sevoflurane (4.3 ± 3.1% to 7.0 ± 2.7%).

Discussion

In the study reported here, myocardial blood flow and MvO_2 decreased as expired sevoflurane concentration increased from 2.75% to 3.5%, resulting in a more efficient transfer of energy in the myocardium. Use of sevoflurane in ferrets caused a dose-dependent decrease in arterial blood pressure, aortic flow, LVP, SVR, dp/dt, and cardiac external work as previously described in other species.[11,13-19]

Cardiac efficiency is the ratio of cardiac work to the MvO_2 and is influenced by heart rate, preload, afterload, and contractility. In this study, increasing the concentration of sevoflurane did not affect preload because CVP and LVEDP remained unchanged. However, SVR and dp/dt decreased with increasing concentrations of sevoflurane. Myocardial oxygen consumption was reduced by 65%, whereas the external work was reduced by 33%. The reduction of MvO_2 represents a true myocardial sparing effect because the myocardial OER did not change significantly. If the reduction in MvO_2 was caused by a reduction in contractility, as suggested by dp/dt, myocardial oxygen extraction would be expected to decrease resulting from a myocardial oxygen wasting effect. Therefore, afterload reduction, as suggested by the decrease in SVR, was the most important parameter to improve cardiac efficiency.

Volatile inhalant anesthetics cause a certain degree of hypotension, as well as a reduction in myocardial contractility. Sevoflurane is similar to isoflurane in that it induces a stable heart rate and rhythm, has a high arrhythmogenic dose of epinephrine, and has less effect on myocardial contractility than halothane and enflurane.[9,20-21] Decreases in arterial blood pressure induced by sevoflurane are known to develop as a result of a reduction in afterload and reduction of contractility.[22] Sevoflurane is a less potent coronary vasodilator than isoflurane, which better preserves coronary blood flow reserve.[3] Conzem et al[14] found similar findings in rats anesthetized with varying concentrations of sevoflurane when compared with the ferrets in our study. In that study, they observed dose-dependent decreases in heart rate, cardiac output, aortic impedance, coronary blood flow, and CVR.

One particular concern about the use of sevoflurane to anesthetize patients with heart disease is that it may contribute to coronary steal (coronary vasodilation causing redistribution of collateral blood flow away from ischemic regions). Regulation of coronary circulation is known to be dependent on myocardial oxygen demand.[13,23] Bernard et al[13] found sevoflurane to be a potent coronary vasodilator in chronically instrumented dogs; however, myocardial oxygen demand was not evaluated in that study. However, it was speculated that sevoflurane may interfere with coronary autoregulation.[13] This concern was supported by results of a study by Hirano et al[23] who found that in dogs, although sevoflurane was a less potent coronary vasodilator than isoflurane, myocardial oxygen extraction decreased, suggesting luxury perfusion of the myocardium and decrease in efficiency. In contrast, Crawford et al[15] found no effect of sevoflurane on coronary blood flow or any other organ blood flow in rats. Kersten et al[21] studied chronically instrumented dogs with steal-prone coronary artery anatomy undergoing sevoflurane anesthesia and found that no redistribution of blood flow away from the ischemic regions occurred. In our study, CVR was unaffected from 2.5% to 3.75% expired concentration of sevoflurane, as was myocardial OER. The minimal influence of sevoflurane on CVR and myocardial OER in our study suggests that in ferrets, sevoflurane has a myocardial sparing effect, maintains coronary vascular autoregulation, and does not potentiate coronary steal. These properties may make sevoflurane a preferential choice over other inhalants for patients with heart disease undergoing anesthesia by optimizing myocardial oxygen balance and protecting ischemic myocardium.

The effect of sevoflurane on myocardial relaxation in normal and diseased hearts has only been partially examined. In 1994, Harkin et al[24] suggested that sevoflurane may have a greater lusitropic effect than other volatile anesthetics. This was determined by results from a study of dogs anesthetized with sevoflurane, which found a dose-related increase in τ and a

dose-related decrease in the magnitude of –dp/dt, which implies a delay in the isovolumic relaxation phase of diastole that is worsened with increasing concentrations of sevoflurane. The concern is that delay in left ventricular relaxation may impair coronary blood flow. This was found in dogs undergoing halothane anesthesia, which had a reduction in coronary blood flow during isovolumic relaxation and a strong inverse correlation of coronary blood flow with τ.[25] Although the magnitude of –dp/dt also significantly decreased in our study, τ was unaffected. τ, the time constant of relaxation, is believed to be a more accurate assessment of isovolumic relaxation, compared with –dp/dt. The –dp/dt has limited reliability when evaluating left ventricular relaxation because it is dependent on LVP induced during systole, specifically the LVP at the time of aortic valve closure.[26] τ Most closely reflects the rate of LVP decay even though it is heavily influenced by heart rate, ventricular loading conditions, and contractility.[27] Therefore, it is possible the lusitropic effect of sevoflurane and other volatile anesthetics in ferrets is not as significant as it is in dogs. Isoflurane, halothane, and enflurane have already been found to modestly enhance isotonic relaxation of isolated ferret myocardium in vitro.[28] Results of a study[29] in humans anesthetized with sevoflurane also found no change in myocardial relaxation before and after cardiopulmonary bypass. Therefore, because volatile anesthetics may have similar lusitropic effects on ferrets and humans, the ferret may be the preferable animal model for comparative cardiovascular research.

One limitation of the study reported here was that hemodynamic parameters may have been affected by the duration each ferret was anesthetized. Ferrets were normothermic at the time of intubation, but rectal temperature decreased rapidly during instrumentation, most likely because of loss of heat from open body cavities. Hypothermia can adversely affect hemodynamic parameters and anesthetic requirements. Reportedly, in anesthetized ferrets, rectal temperature can decrease as much as 10°C in 15 to 20 minutes.[30] Also, in the study reported here, data was obtained in an order of increasing expired concentrations of sevoflurane rather than randomization of the concentration, and expired sevoflurane concentration was not returned to a baseline of 1.5% between data collections. This may be more of a concern if other volatile anesthetics were being evaluated. Because of the low blood-to-gas partition coefficient of sevoflurane, accumulation in body tissues is less of an issue than with halothane or isoflurane.

The ferret is believed to be an excellent model for cardiovascular research for the following reasons. Because of its small size, the ferret permits for economic drug use, and it is simple and inexpensive to house and care for them, especially with the increasing cost and decreasing availability of larger species.[31] The ferret has been validated as an animal model in an acute in vivo model for evaluation of the inotropic effects of cardiovascular drugs and for study of in vivo model for myocardial ischemic injury and salvage assessments.[31,32] The favorable characteristics of the ferret heart include a well-differentiated conduction system, a dominant left coronary artery, good mechanical and electrical stability, large energy reserve, slower basal heart rate and higher arterial pressure than rats, and lack of an extensive coronary circulation.[1,33-35] Although the rat heart shares many of the anatomic and physiologic characteristics of the ferret heart, it has been suggested that the rat may be an inappropriate model for myocardial infarction research.[36] The ferret is particularly suited to nonterminal surgery as the heart has good mechanical and electrical stability in the recovery phase following injury.[2,31,34] Results of our study indicated that sevoflurane did not increase myocardial metabolic demands and did not interfere with isovolumic relaxation. There was also evidence of a myocardial sparing effect because coronary flow was maintained, oxygen extraction did not increase, and energy transfer was more efficient as concentration of sevoflurane increased. The sparing effect of sevoflurane observed in our study may also be beneficial to humans with heart failure or coronary disease undergoing anesthesia.

[a]Sevoflurane, SevoFlo, Abbott Laboratories, North Chicago, Ill.
[b]TFE polymer pledgets, Ethicon, Piscataway, NJ.
[c]S-series flow probes, Transonic Systems, Ithaca, NY.
[d]StatView, Abacus Concepts Inc, Berkely, Calif.
[e]Solo power analysis, BMDP Statistical Software, Los Angeles, Calif.

References

1. Truex RC, Belej R, Ginsberg LM, et al. Anatomy of the ferret heart: an animal model for cardiac research. *Anat Rec* 1974;179:411–422.
2. Gomoll AW. Cardioprotection associated with preconditioning in the anesthetized ferret. *Basic Res Cardiol* 1996;91:433–443.
3. Larach DR, Schuler HG. Direct vasodilation by sevoflurane, isoflurane, and halothane alters coronary flow reserve in the isolated rat heart. *Anesthesiology* 1991;75:268–278.
4. Yasuda N, Targ AG, Eger EI II. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. *Anesth Analg* 1985;64:640–643.
5. Doi M, Ikeda K. Airway irritation produced by volatile anesthetics during brief inhalation: comparison of halothane, enflurane, isoflurane, and sevoflurane. *Can J Anaesth* 1993;40:122–126.
6. Bartunek AE, Claes VA, Housmans PR. Effects of volatile anesthetics on elastic stiffness in isometrically contracting ferret ventricular myocardium. *J Appl Physiol* 2002;92:2491–2500.
7. Bartunek AE, Claes VA, Housmans PR. Effects of volatile anesthetics on stiffness of mammalian ventricular muscle. *J Appl Physiol* 2001;91:1563–1573.
8. Gaynor JS, Wimsatt J, Mallinckrodt C, et al. A comparison of sevoflurane and isoflurane for short-term anesthesia in polecats (*Mustela eversmanni*). *J Zoo Wildl Med* 1997;28:274–279.
9. Hikasa Y, Okabe C, Takase K, et al. Ventricular arrhythmogenic dose of adrenaline during sevoflurane, isoflurane, and halothane anaesthesia either with or without ketamine and thiopentone in cats. *Res Vet Sci* 1996;60:134–137.
10. Johnson RA, Striler E, Sawyer DC, et al. Comparison of isoflurane with sevoflurane for anesthesia induction and recovery in adult dogs. *Am J Vet Res* 1998;59:478–481.
11. Manohar M, Parks CM. Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anesthesia without and with 50% nitrous oxide. *J Pharmacol Exp Ther* 1984;231:640–648.
12. Kass DA. Assessment of diastolic dysfunction. Invasive modalities. *Cardiol Clin* 2000;18:571–586.
13. Bernard JM, Wouters PF, Doursout MF, et al. Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. *Anesthesiology* 1990;72:659–662.

14. Conzen PF, Vollmar B, Habazettl H, et al. Systemic and regional hemodynamics of isoflurane and sevoflurane in rats. *Anesth Analg* 1992;74:79–88.

15. Crawford MW, Lerman J, Saldivia V, et al. Hemodynamic and organ blood flow responses to halothane and sevoflurane anesthesia during spontaneous ventilation. *Anesth Analg* 1992;75: 1000–1006.

16. Ebert TJ, Harkin CP, Muzi M. Cardiovascular responses to sevoflurane: a review. *Anesth Analg* 1995;81:S11–S22.

17. Hikasa Y, Ohe N, Takase K, et al. Cardiopulmonary effects of sevoflurane in cats: comparison with isoflurane, halothane, and enflurane. *Res Vet Sci* 1997;63:205–210.

18. Hikasa Y, Okuyama K, Kakuta T, et al. Anesthetic potency and cardiopulmonary effects of sevoflurane in goats: comparison with isoflurane and halothane. *Can J Vet Res* 1998;62: 299–306.

19. Mutoh T, Nishimura R, Kim HY, et al. Cardiopulmonary effects of sevoflurane, compared with halothane, enflurane, and isoflurane, in dogs. *Am J Vet Res* 1997;58:885–890.

20. Hayashi Y, Sumikawa K, Tashiro C, et al. Arrhythmogenic threshold of epinephrine during sevoflurane, enflurane, and isoflurane anesthesia in dogs. *Anesthesiology* 1988;69:145–147.

21. Kersten JR, Brayer AP, Pagel PS, et al. Perfusion of ischemic myocardium during anesthesia with sevoflurane. *Anesthesiology* 1994;81:995–1004.

22. Pagel PS, Farber NE, Warltier DC. Volatile anesthetics and cardiovascular function. In: Miller RD, ed. *Anesthesia.* 5th ed. Philadelphia: Churchill Livingstone Inc, 2000;96–124.

23. Hirano M, Fujigaki T, Shibata O, et al. A comparison of coronary hemodynamics during isoflurane and sevoflurane in anesthesia in dogs. *Anesth Analg* 1995;80:651–656.

24. Harkin CP, Pagel PS, Kersten JR, et al. Direct negative inotropic and lusitropic effects of sevoflurane. *Anesthesiology* 1994;81:156–167.

25. Doyle RL, Foëx P, Ryder WA, et al. Effects of halothane on left ventricular relaxation and early diastolic coronary blood flow in the dog. *Anesthesiology* 1989;70:660–666.

26. Courtois M, Ludbrook PA, Kovacs SJ. Unsolved problems in diastole. *Cardiol Clin* 2000;18:653–657.

27. Little WC. Assessment of normal and abnormal cardiac function. In: Braunwald E, Zipes DP, Libby P, eds. *Heart disease: a textbook of cardiovascular medicine*. 6th ed. Philadelphia: WB Saunders Co, 2001;479–502.

28. Housmans PR, Murat I. Comparative effects of halothane, enflurane, and isoflurane at equipotent anesthetic concentrations on isolated ventricular myocardium of the ferret. II: Relaxation. *Anesthesiology* 1988;69:464–471.

29. De Hert SG, ten Broecke PW, Mertens E, et al. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. *Anesthesiology* 2002;97:42–49.

30. Flecknell PA. Anesthesia of small mammals. *Vet Clin North Am Exotic Anim Pract* 2001;4:47–56.

31. Gomoll AW, Lekich RF. Use of the ferret for a myocardial ischemia/salvage model. *J Pharmacol Methods* 1990;23:213–223.

32. Baryla UM, Fleming JS, Stanton HC. The anesthetized ferret, an in vivo model for evaluating inotropic activity: effects of milrinone and anagrelide. *J Pharmacol Methods* 1988;20:299–306.

33. Flores NA, Davies RL, Penny WJ, et al. Coronary microangiography in the guinea pig, rabbit and ferret. *Int J Cardiol* 1984;6:459–471.

34. Neubauer S, Ingwall JS. The isolated, buffer-perfused ferret heart: a new model for the study of cardiac physiology and metabolism. *Lab Anim* 1991;25:348–353.

35. Maxwell MP, Hearse DJ, Yellon DM. Species variation in the coronary collateral circulation during regional myocardial ischemia: a critical determinant of the rate of evolution and extent of myocardial infarction. *Cardiovasc Res* 1987;21:737–740.

36. Hearse DJ. Species variation in the coronary collateral circulation during regional myocardial ischaemia: a critical determinant of the rate of evolution and extent of myocardial infarction. *Cardiovasc Res* 2000;45:213–219.