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Perfusion of Ischemic Myocardium during Anesthesia with Sevoflurane

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Background: **Sevoflurane produces direct vasodilation of coronary arteries *in vitro* and decreases coronary vascular resistance *in vivo*, pharmacologic properties that may contribute to the development of "coronary steal." This investigation examined the effects of sevoflurane on the distribution of regional myocardial perfusion in chronically instrumented dogs with steal-prone coronary artery anatomy.**

Methods: **Dogs were chronically instrumented for measurement of aortic and left ventricular pressure, diastolic coronary blood flow velocity and subendocardial segment length. After recovery from surgery, dogs underwent repetitive, brief, left anterior descending coronary artery (LAD) occlusions *via* an implanted hydraulic vascular occluder to enhance collateral development. A progressive left circumflex coronary artery (LCCA) stenosis was also obtained using an ameroid constrictor. After development of LCCA stenosis, the LAD was totally occluded to produce a model of multivessel coronary artery disease. Systemic hemodynamics, regional contractile function and myocardial perfusion measured with radioactive microspheres were assessed in the conscious state and during sevoflurane anesthesia at 1.0 and 1.5 MAC with and without restoration of arterial blood pressure and heart rate to conscious levels.**

Results: **Total LAD occlusion with simultaneous LCCA stenosis increased heart rate, mean arterial pressure, left ventricular systolic and end-diastolic pressures, end-diastolic segment length, and rate–pressure product in conscious dogs. Subsequent administration of sevoflurane caused dose-related decreases in arterial pressure, left ventricular systolic pressure, double product, and peak rate of increase of left ventricular pressure at 50 mmHg. Perfusion of normal myocardium was unchanged during sevoflurane anesthesia. In contrast, sevoflurane caused dose-dependent decreases in blood flow to myocardium supplied by the stenotic LCCA, which returned to control levels after restoration of heart rate and arterial pressure. No reduction in collaterally derived blood flow to the occluded region was produced by 1.0 or 1.5 MAC sevoflurane. No redistribution of blood flow away from the occluded LAD region to normal or stenotic myocardium occurred during sevoflurane anesthesia. In fact, increases in the ratio of blood flow between occluded and normal zones or occluded and stenotic zones were observed in the subepicardium during 1.5 MAC sevoflurane with maintenance of the heart rate and arterial pressure at conscious levels.**

Conclusions: **The results demonstrate that sevoflurane does not reduce or abnormally redistribute myocardial blood flow derived from coronary collateral vessels in a chronically instrumented canine model of multivessel coronary artery obstruction. (Key words: Anesthetics, volatile: sevoflurane. Arteries: coronary. Heart: coronary artery disease; coronary blood flow; coronary hemodynamics; coronary occlusion; coronary steal; myocardial ischemia.)**

THE ability of volatile anesthetics to produce potentially deleterious changes in the regional distribution of myocardial blood flow in patients with coronary artery disease has been the subject of intense investigation. Potent coronary vasodilators, including adenosine, chromonar and dipyridamole, have been shown to reduce collateral blood flow *via* a "coronary steal" mechanism in animal models of coronary artery obstruction.[1–4] Coronary steal is defined as an absolute decrease in perfusion to collateral-dependent ischemic myocardium despite an increase in flow to normal zones during constant coronary perfusion pressure and heart rate.[1] Since volatile anesthetics possess coronary vasodilating properties *in vitro*,[5–15] it has been suggested that these agents may cause coronary steal and lead to exacerbation of myocardial ischemia in patients with coronary artery disease undergoing inhalational anesthesia.[16]

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Sevoflurane reduces coronary vascular resistance[8,17,18] and decreases pharmacologic coronary vasodilator reserve,[8] suggesting that this volatile anesthetic may possess coronary vasodilator activity similar to that of isoflurane and desflurane. This investigation examined the effects of sevoflurane on regional myocardial perfusion to ascertain whether sevoflurane causes coronary steal in a chronically instrumented canine model of multivessel coronary artery obstruction. Myocardial blood flow was measured using the radioactive microsphere technique. Coronary collateral development was enhanced by multiple brief occlusions of the left anterior descending coronary artery (LAD), and a left circumflex coronary artery (LCCA) stenosis was produced by an ameroid constrictor. Subsequent total occlusion of the LAD was performed to create "steal-prone" coronary artery anatomy.

Previous investigations from this and other laboratories have demonstrated that adenosine and other potent coronary vasodilators induce marked redistribution of myocardial blood flow from ischemic to normal zones in this canine experimental preparation.[1,2,19,20] Thus, the present investigation used an extensively validated model to ascertain whether sevoflurane produces coronary steal.

Materials and Methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care and Use Committee of the Medical College of Wisconsin. Furthermore, all conform to the *Guiding Principles in the Care and Use of Animals* of the American Physiologic Society and were in accordance with the *Guide for the Care and Use of Laboratory Animals.*#

Animal Instrumentation

Conditioned mongrel dogs (n = 12) of either sex weighing 21 ± 1 kg (mean ± SEM) were fasted overnight. Anesthesia was induced with propofol (5 $mg \cdot kg^{-1}$ intravenously). After tracheal intubation, anesthesia was maintained with isoflurane (1.5–2.0%) in 100% oxygen (1 $l \cdot min^{-1}$) *via* positive-pressure ventilation. A left thoracotomy was performed under sterile conditions, and heparin-filled catheters were implanted in the thoracic aorta and the right atrial appendage for measurement of arterial pressure and fluid administration, respectively. A heparin-filled catheter was also positioned in the left atrial appendage for measurement of left atrial pressure, administration of radioactive microspheres and injection of adenosine for daily assessment of LAD and LCCA vascular reserve. A hydraulic vascular occluder was placed around the descending thoracic aorta distal to the arterial catheter. The proximal LAD (distal to the first diagonal branch) and LCCA (proximal to the first marginal branch) were isolated, and Doppler ultrasonic flow transducers (20 MHz) were placed around each vessel for measurement of phasic coronary blood flow velocity. A balloon-cuff vascular occluder was placed around the LAD to facilitate production of acute coronary artery occlusion. An ameroid constrictor was implanted around the LCCA distal to the flow probe to produce a slowly progressive vascular stenosis.

A precalibrated, miniature micromanometer (P7, Konigsberg Instruments, Pasadena, CA) was inserted in the left ventricular chamber through an incision in the apex and secured for continuous recording of left ventricular pressure. The peak rate of increase of left ventricular pressure at 50 mmHg (dP/dt_{50}), an index of global myocardial contractility, was determined by electronic differentiation of the left ventricular pressure waveform. Electrodes were sutured to the right atrial appendage for cardiac pacing. Pairs of miniature ultrasonic segment length transducers (5 MHz) were implanted in the subendocardium supplied by the LAD for measurement of regional contractile function.

All catheters and leads were secured, tunneled subcutaneously, and exteriorized between the scapulas through several small incisions. The chest wall was closed in layers and the pneumothorax evacuated by a chest tube. Each dog was treated with analgesic agents as needed in the perioperative period (fentanyl–droperidol, Innovar-Vet, Pitman Moore, Mundelein, IL). Antibiotic prophylaxis consisted of intramuscular cephalothin 40 $mg \cdot kg^{-1}$ and gentamicin 4.5 $mg \cdot kg^{-1}$. Each dog was permitted to recover for 2 days before initiation of repetitive, brief LAD occlusions and daily monitoring of systemic and coronary hemodynamics.

Regional Myocardial Contractile Function

Regional myocardial contractility in the LAD perfusion territory (percent segment shortening) was evaluated by pairs of cylindrical ultrasonic crystals. All signals were simultaneously monitored *via* ultrasonic am-

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plifiers (Crystal Biotech, Hopkinton, MA). By using the rate of change in left ventricular pressure, end-diastolic segment length was measured immediately before the onset of left ventricular isovolumic contraction. End-systolic length was determined at the time of maximum negative rate of change in left ventricular pressure. The lengths were normalized according to the method of Theroux *et al.*[21] Percent systolic shortening was calculated as ([EDL − ESL]/EDL) × 100, where EDL = end-diastolic segment length and ESL = end-systolic segment length.

Regional Myocardial Perfusion

Carbonized plastic microspheres (15 ± 2 μm in diameter, New England Nuclear, Boston, MA) labeled with ^{141}Ce, ^{103}Ru, ^{51}Cr, or ^{95}Nb were used to measure regional myocardial perfusion. Immediately before injection, the sphere suspension was ultrasonicated (model 450, E/MC) for 15 min. The injection consisted of 2–3 × 10^6 microspheres administered into the left atrium as a bolus over a 10-s period and flushed in with 10 ml of warm (37°C) sterile saline. A few seconds before the microsphere injection, a timed collection of reference arterial flow was initiated (precalibrated infusion–withdrawal pump, 1941, Harvard, Natick, MA) from the thoracic aortic catheter and withdrawn at a constant rate of 7 ml · min^{-1} for 3 min.

Transmural tissue samples were selected for mapping of tissue flow in the myocardium at the conclusion of each experiment. The samples were obtained from three regions of the left ventricle: (1) normal zone (myocardium proximal to both the hydraulic occluder and ameroid constrictor); (2) stenotic zone (distal to the LCCA stenosis produced by the ameroid constrictor); and (3) occluded zone (distal to the LAD occlusion produced by inflation of the hydraulic occluder). Two colored dyes (India ink and Patent Blue Dye) were injected simultaneously into the coronary circulation immediately distal to both the hydraulic occluder and ameroid constrictor at a pressure of 100 mmHg to accurately identify the occluded and stenotic zones, respectively. Normal myocardium remained unstained. Myocardial tissue samples were subdivided into subepicardial, midmyocardial, and subendocardial layers of approximately equal thickness. Samples were weighed, placed in scintillation vials and the activity of each isotope determined. Similarly, the activity of each isotope in the reference blood sample was assessed. Tissue blood flow (milliliters per minute per gram) was calculated as $Q_r \times C_m/C_r$, where Q_r = rate of withdrawal of the reference blood flow sample (milliliters per minute); C_m = activity (counts per minute per gram) of the myocardial tissue sample; and C_r = activity (counts per minute) of the reference blood flow sample.

Experimental Protocol

Starting on the 2nd postoperative day, dogs were monitored on a daily basis for systemic and coronary hemodynamic alterations during progressive stenosis of the LCCA induced by the ameroid constrictor. Coronary vascular reserve of the LAD and LCCA was evaluated each day by administration of 100 μg bolus injections of adenosine in saline *via* the left atrial catheter. Coronary collateral development was enhanced by repetitive, brief (2-min) occlusions of the LAD using the chronically implanted hydraulic vascular occluder. The brief occlusions were performed once every 0.5 h for 8 h, 5 days per week, during which systemic hemodynamics, resting coronary blood flow velocity, and regional segment shortening were continuously monitored.

Moderate stenosis was considered present when the LCCA hyperemic response to 100 μg adenosine was reduced by 50% of the response observed on the 2nd postoperative day. The LAD was totally occluded by inflation of the hydraulic cuff to simulate steal-prone coronary artery anatomy when the LCCA stenosis reached sufficient severity. This model of multivessel coronary artery obstruction was used to evaluate the actions of sevoflurane on systemic hemodynamics, regional myocardial blood flow, and segmental contractile function. All dogs received procainamide hydrochloride (300 mg intravenously) and lidocaine hydrochloride (60 mg intravenously) before LAD occlusion to prevent ventricular ectopy.

During a stable hemodynamic state 30 min after LAD occlusion, radioactive microspheres were injected and hemodynamic data recorded. Anesthesia was induced by inhalation of sevoflurane and oxygen at high flow rates (8 l · min^{-1}). After tracheal intubation, anesthesia was continued with sevoflurane in oxygen (100–250 ml · min^{-1}) and room air (2 l · min^{-1}) during positive-pressure ventilation using a semiclosed circle system. Tidal volume was set at 15 ml · kg^{-1}, and respiratory rate was adjusted to maintain arterial carbon dioxide tension in the normal range. The oxygen flow rate in each experiment was adjusted to maintain arterial oxygen tension near normal, conscious values. End-tidal anesthetic concentrations of sevoflurane were measured

at the tip of the endotracheal tube by an infrared anesthetic analyzer (Datex Capnomac, Helsinki, Finland) calibrated for detection of sevoflurane. The canine MAC value for sevoflurane used in this investigation was 2.36%.[22] The second and third microsphere injections were made and systemic and coronary hemodynamics recorded after 30-min periods of equilibration at 1.0 and 1.5 MAC sevoflurane (end-tidal concentration). Sevoflurane was then continued at 1.5 MAC, and arterial pressure and heart rate were returned to conscious levels by partial inflation of the thoracic aorta hydraulic vascular occluder and atrial pacing, respectively. A fourth injection of microspheres was performed at 1.5 MAC sevoflurane with the arterial pressure and heart rate corrected to conscious values.

At the conclusion of each experiment, dogs were killed with an overdose of sodium pentobarbital. The heart was rapidly excised, washed with saline, and fixed for 24–48 h in a 10% formaldehyde solution before specimens were obtained for myocardial blood flow analysis.

Statistical Analysis

Statistical analysis of the data was performed using analysis of variance with repeated measures followed by Duncan's modification of Student's *t* test. Changes from the conscious control state were considered statistically significant when $P < 0.05$. All data are reported as the mean ± SEM.

Results

Twelve dogs were used in the current investigation and provided seven successful experiments. Within the 1st 3 postoperative days, three dogs died of ventricular fibrillation during the brief, 2-min occlusions. On the final day of experimentation two other dogs died of ventricular fibrillation after permanent LAD occlusion.

Progression of Stenosis Development

Dogs were monitored daily for progression of ameroid constriction of the LCCA. Development of the LCCA stenosis was demonstrated by sequential reductions in the diastolic coronary blood flow velocity response to a 100-μg bolus of adenosine (fig. 1). A total of 10 ± 2 days (mean ± SEM) were required to obtain a LCCA stenosis. The LCCA diastolic coronary blood flow velocity increased in response to adenosine (47 ± 4 to 101 ± 17 Hz × 10^2) on postoperative day 2. This increase in LCCA diastolic coronary blood flow velocity was significantly ($P < 0.05$) attenuated on the final day (41 ± 9 to 65 ± 17 Hz × 10^2), indicating marked decrease in LCCA vascular reserve. In contrast, LAD vasodilator reserve elicited by adenosine was unchanged over time (62 ± 7 to 126 ± 15 Hz × 10^2 on day 2 *vs.* 59 ± 7 to 116 ± 15 Hz × 10^2 on the final day).

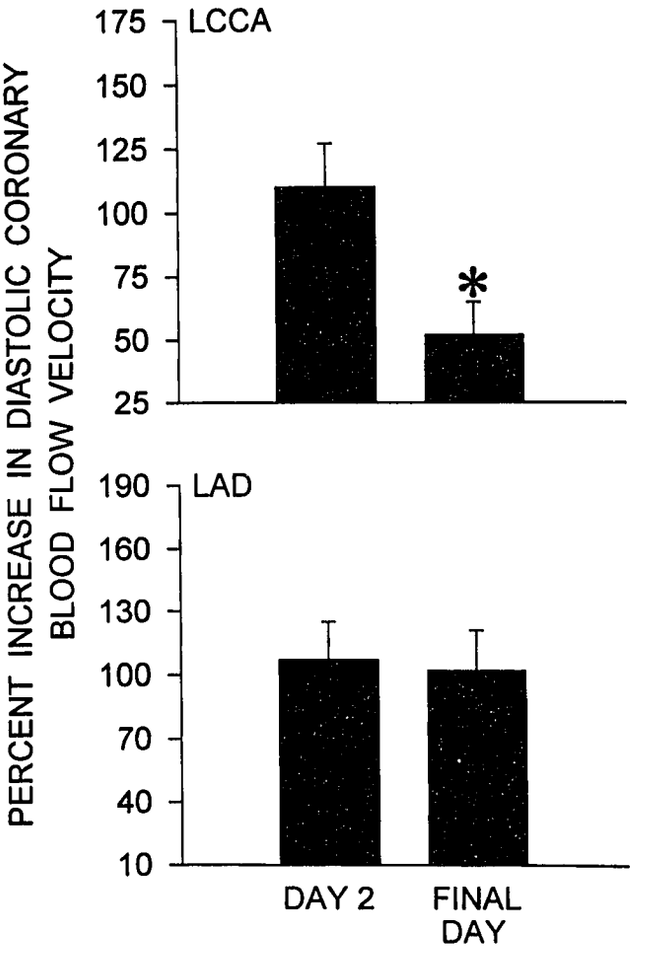

Fig. 1. Response of left circumflex and left anterior descending coronary arteries (LCCA and LAD, respectively) to intraarterial administration of adenosine on day 2 and on the final day, demonstrating the progression of LCCA stenosis. *Significantly ($P < 0.05$) different from day 2.

Hemodynamic Effects of Sevoflurane

Occlusion of the LAD in conscious dogs produced significant increases in heart rate, mean arterial pressure, left ventricular systolic and end-diastolic pressures, end-systolic and diastolic segment lengths, rate–

pressure product, and decreases in percent segment shortening in the occluded region (table 1). No changes in left ventricular dP/dt_{50} were observed. Sevoflurane caused dose-related decreases in mean arterial pressure, left ventricular systolic pressure, rate–pressure product, and dP/dt_{50}. No changes in heart rate, left ventricular end-diastolic pressure, LCCA diastolic coronary blood flow velocity or percent segment shortening were observed. Restoration of arterial pressure and heart rate to those levels present in the conscious state during 1.5 MAC sevoflurane resulted in a concomitant increase in left ventricular systolic pressure and rate–pressure product. Significant increases in left ventricular end-diastolic pressure compared to the conscious state were also observed. In addition, LCCA diastolic coronary blood flow velocity was significantly increased compared to 1.5 MAC sevoflurane alone before restoration of hemodynamics (table 1).

Regional Myocardial Perfusion during Sevoflurane

Perfusion of normal myocardium proximal to the LAD occlusion and LCCA stenosis was unchanged by sevoflurane (table 2). Sevoflurane caused significant decreases in midmyocardial (2.04 ± 0.33 during control to 1.18 ± 0.19 ml · min^{-1} · g^{-1} during 1.5 MAC) and transmural (1.74 ± 0.27 during control to 1.02 ± 0.16 ml · min^{-1} · g^{-1} during 1.5 MAC) blood flow to the LCCA stenotic region which were restored to conscious levels after correction of arterial pressure and heart rate. No reduction in coronary collateral blood flow in the occluded region was produced by sevoflurane. After restoration of arterial pressure and heart rate to conscious levels during 1.5 MAC sevoflurane, subepicardial, midmyocardial, and transmural collateral blood flow to the occluded region increased significantly (table 2). Subendocardial perfusion during sevoflurane administration was not significantly different from control and remained unchanged by blood pressure and heart rate modification. No maldistribution of myocardial blood flow away from the occluded LAD region to normal myocardium occurred during sevoflurane anesthesia as indicated by maintenance of the occluded- to normal-zone ratio (fig. 2). After restoration of arterial pressure and heart rate to conscious values during 1.5 MAC sevoflurane, the ratios of occluded- to normal-zone and occluded- to stenotic-zone myocardial perfusion increased significantly in subepicardium but did not change in the midmyocardium or subendocardium (figs. 2 and 3).

Table 1. Systemic and Coronary Hemodynamic Effects of Sevoflurane

	Conscious before LAD Occlusion	Conscious after LAD Occlusion	Sevoflurane (MAC)		
			1.0	1.5	1.5 (BP/HR)
HR (bpm)	106 ± 11*	142 ± 7	152 ± 11	132 ± 9	145 ± 15
MAP (mmHg)	97 ± 5*	115 ± 6	73 ± 6*	61 ± 4*	113 ± 6†‡
RPP (bpm · mmHg · 10^3)	12.2 ± 1.6*	19.8 ± 1.3	12.7 ± 1.7*	9.2 ± 1.2*	18.5 ± 2.2†‡
LVSP (mmHg)	116 ± 5*	131 ± 7	84 ± 6*	71 ± 6*	126 ± 8†‡
LVEDP (mmHg)	8 ± 2*	15 ± 3	13 ± 1	14 ± 2	25 ± 3*†‡
dP/dt_{50} (mmHg · s^{-1})	2,140 ± 100	2,160 ± 120	1,340 ± 140*	1,050 ± 140*†	1,160 ± 140*
LCCA DCBFV (Hz · 10^2)	41 ± 9*	67 ± 8	60 ± 14	58 ± 9	81 ± 16†‡
LAD EDL (mm)	13.9 ± 0.8*	15.7 ± 0.9	15.2 ± 1.0	15.4 ± 0.9	15.7 ± 1.1
LAD ESL (mm)	11.2 ± 0.8*	15.8 ± 0.9	15.7 ± 1.0	15.6 ± 0.9	15.9 ± 1.1
LAD SS (%)	19 ± 4*	−1 ± 2	−3 ± 1	−1 ± 1	−2 ± 1
*p*H (U)	—	7.43 ± 0.01	7.41 ± 0.03	7.37 ± 0.02*	—
P_{CO_2} (mmHg)	—	32 ± 1	30 ± 1	31 ± 1	—
P_{O_2} (mmHg)	—	83 ± 2	134 ± 12*	119 ± 5*	—

Data are mean ± SEM; n = 7.

HR = heart rate; MAP = mean arterial pressure; RPP = rate–pressure product; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; LCCA DCBFV = left circumflex coronary artery diastolic coronary blood flow velocity; LAD, EDL, and ESL = end-diastolic and end-systolic segment length, respectively; LAD SS = segment shortening in left anterior descending coronary artery perfusion territory; (BP/HR) = diastolic arterial pressure and heart rate corrected to conscious values after LAD occlusion.

* Significantly ($P < 0.05$) different from conscious after LAD occlusion.

† Significantly ($P < 0.05$) different from 1.0 MAC sevoflurane.

‡ Significantly ($P < 0.05$) different from 1.5 MAC sevoflurane.

Table 2. Effects of Sevoflurane on Regional Myocardial Perfusion ($ml \cdot min^{-1} \cdot g^{-1}$)

Region	Conscious LAD Occluded	Sevoflurane (MAC)		
		1.0	1.5	1.5 (BP/HR)
Normal				
Subepicardium	0.94 ± 0.16	0.83 ± 0.26	0.68 ± 0.14	0.93 ± 0.15
Midmyocardium	1.94 ± 0.30	1.38 ± 0.34	1.38 ± 0.34	2.14 ± 0.34
Subendocardium	1.75 ± 0.29	1.31 ± 0.25	1.09 ± 0.16	2.01 ± 0.33‡
Transmural	1.54 ± 0.24	1.17 ± 0.28	1.05 ± 0.20	1.69 ± 0.26
Stenotic				
Subepicardium	1.41 ± 0.22	1.10 ± 0.32	0.90 ± 0.16	1.39 ± 0.17
Midmyocardium	2.04 ± 0.33	1.30 ± 0.30	1.18 ± 0.19*	2.19 ± 0.29‡
Subendocardium	1.77 ± 0.28	1.04 ± 0.21	0.98 ± 0.16	1.89 ± 0.41†‡
Transmural	1.74 ± 0.27	1.15 ± 0.25	1.02 ± 0.16*	1.82 ± 0.25‡
Occluded				
Subepicardium	0.44 ± 0.11	0.35 ± 0.11	0.35 ± 0.07	0.88 ± 0.21*†‡
Midmyocardium	0.27 ± 0.07	0.21 ± 0.06	0.18 ± 0.05	0.44 ± 0.13*†‡
Subendocardium	0.16 ± 0.05	0.09 ± 0.05	0.11 ± 0.05	0.22 ± 0.14
Transmural	0.29 ± 0.06	0.22 ± 0.07	0.22 ± 0.05	0.51 ± 0.12*†‡

Data are mean ± SEM; n = 7.

(BP/HR) = diastolic arterial pressure and heart rate corrected to conscious values after LAD occlusion.

* Significantly ($P < 0.05$) different from conscious LAD occluded.

† Significantly ($P < 0.05$) different from 1.0 MAC sevoflurane.

‡ Significantly ($P < 0.05$) different from 1.5 MAC sevoflurane.

Discussion

The effects of sevoflurane on the distribution of regional myocardial blood flow were examined in a chronically instrumented canine model of multivessel coronary artery disease. Coronary collateral formation was enhanced by repetitive, brief occlusions of the LAD. Dogs were observed daily to determine the effects of progressive LCCA stenosis development on coronary vascular reserve. When a LCCA stenosis was attained (as assessed by a reduction in coronary vascular reserve of at least 50%), the LAD was completely occluded to produce a model of multivessel coronary obstruction resulting in varying degrees of regional ischemia (demonstrated by systolic aneurysmal bulging of myocardium during LAD occlusion) which simulates "steal prone" coronary artery anatomy in humans. A "steal prone" anatomy is characterized by a total occlusion of one major epicardial coronary artery but adequate collateralization distal to the occlusion and simultaneous stenosis of the artery of origin of the collateral vessels. Such an anatomic configuration is found in approximately 25% of patients undergoing coronary artery bypass graft surgery.[23] Sevoflurane caused reductions in myocardial blood flow to stenotic but not occluded regions when arterial pressure and heart rate were uncontrolled. Restoration of conscious systemic hemodynamic conditions normalized blood flow to areas distal to the stenosis and enhanced subepicardial occluded-zone perfusion to values above that observed in the conscious state.

Volatile anesthetics have been shown to dilate isolated coronary artery segments,[5–7,9–12] and cause vasodilation of resistance coronary arterioles in the isolated heart.[8,13–15] Despite this evidence *in vitro,* the hypothesis that inhalational agents have sufficient coronary vasodilator activity to cause coronary steal *in vivo* remains controversial. Isoflurane has been most often implicated in this process because the coronary vasodilating properties of this volatile anesthetic may be of sufficient magnitude to abnormally redistribute coronary blood flow away from ischemic zones.[24] Isoflurane, halothane, and desflurane have been shown to decrease subendocardial blood flow and produce regional contractile dysfunction in the presence of a coronary artery stenosis when coronary perfusion pressure is allowed to decrease.[19,20,25–28] Redistribution of coronary blood flow away from ischemic myocardium can also be demonstrated during isoflurane and desflurane anesthesia if diastolic arterial pressure is reduced.[19,28,29] However, such decreases in coronary collateral flow can be pre-

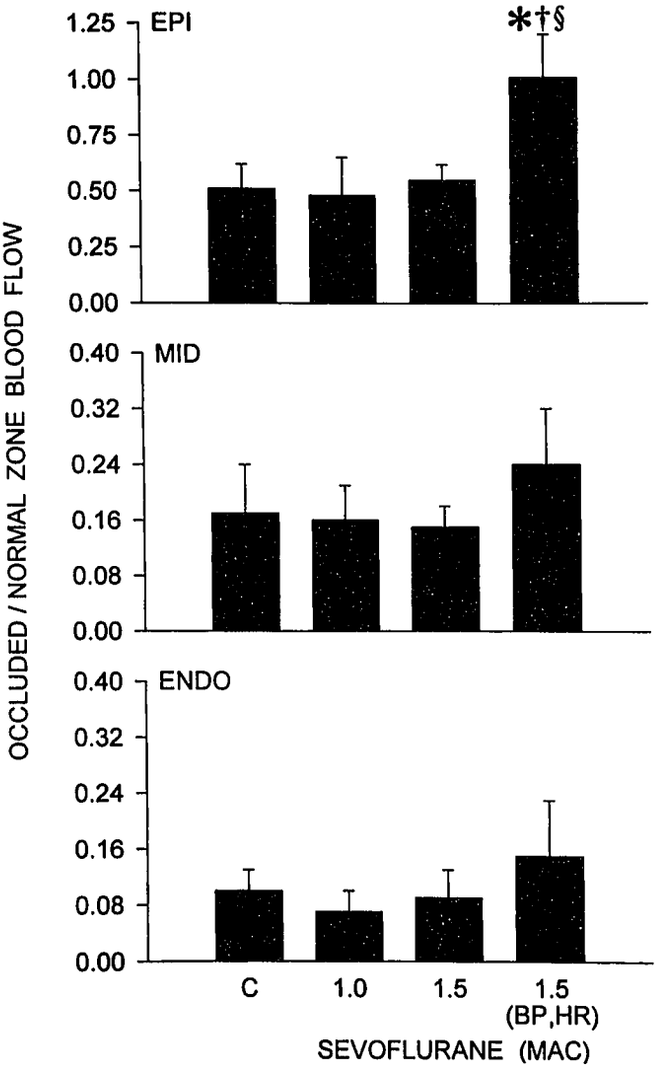

Fig. 2. Ratio of occluded to normal-zone myocardial blood flow in subepicardium (EPI), midmyocardium (MID), and subendocardium (ENDO), during the control state (C), with two concentrations of sevoflurane, and after blood pressure (BP) and heart rate (HR) were returned to control values during 1.5 MAC sevoflurane. *Significantly ($P < 0.05$) different from C; †significantly ($P < 0.05$) different from 1.0 MAC; §significantly ($P < 0.05$) different from 1.5 MAC.

vented by maintenance of normal coronary artery perfusion pressure.[19,20,28–30]

Sevoflurane has been shown to reduce pharmacologic coronary vasodilator reserve elicited by adenosine indicating that this volatile anesthetic causes coronary vasodilation. However, sevoflurane-induced reductions in coronary vasodilator reserve are less than those produced by halothane or isoflurane.[8] These results suggest that sevoflurane may be a less potent coronary vasodilator than halothane or isoflurane. This contention is supported by evidence that suggests that sevoflurane does not uniformly increase coronary blood flow. Myocardial perfusion (measured with radioactive microspheres) during sevoflurane anesthesia has been shown to decrease[18,31] or remain unchanged,[32] findings which

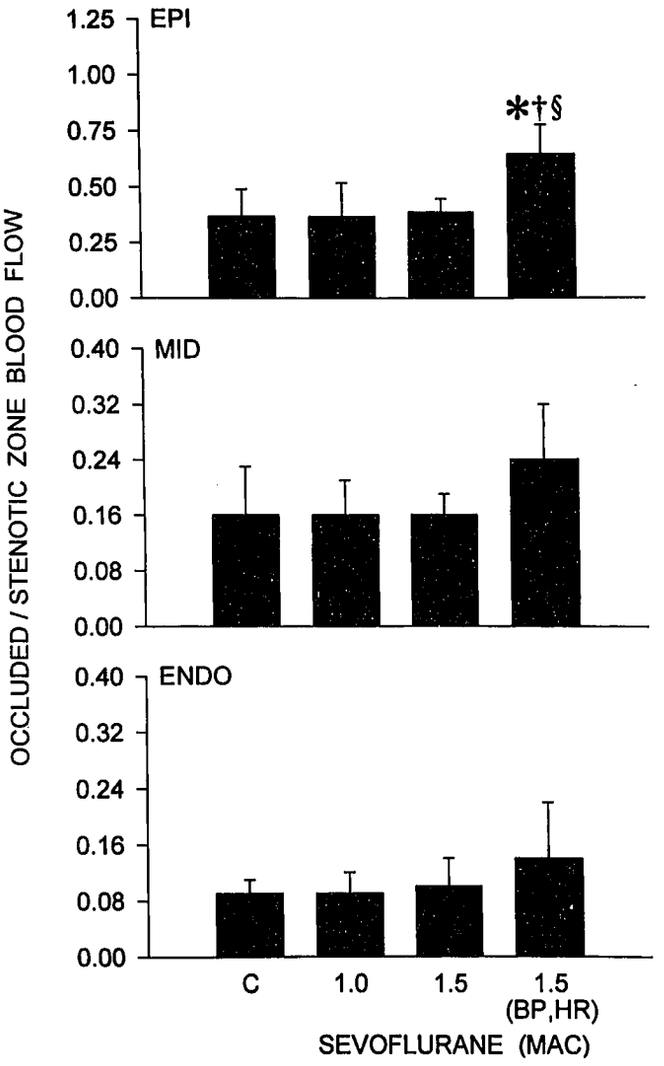

Fig. 3. Ratio of occluded to stenotic-zone myocardial blood flow in subepicardium (EPI), midmyocardium (MID), and subendocardium (ENDO), during the control state (C), with two concentrations of sevoflurane, and after blood pressure (BP) and heart rate (HR) were returned to control values during 1.5 MAC sevoflurane. *Significantly ($P < 0.05$) different from C; †significantly ($P < 0.05$) different from 1.0 MAC; §significantly ($P < 0.05$) different from 1.5 MAC.

occur in parallel with alterations in estimated myocardial oxygen consumption. Relative coronary vasodilation by sevoflurane has been suggested by reductions in myocardial oxygen extraction despite concomitant decreases in coronary blood flow in dogs.[33] Sevoflurane increased[17] Doppler-derived coronary blood flow velocity in chronically instrumented dogs. Concomitant decreases in coronary vascular resistance suggest that relative declines in coronary vascular tone may have occurred. Interpretation of the findings of these studies should be made with the recognition that the net effect of sevoflurane on coronary vasomotor tone is determined by not only direct coronary vasodilator actions but also indirect reductions of coronary blood flow associated with anesthetic-induced depression of myocardial contractility and oxygen consumption.

The results of the present investigation confirm and extend the findings of Bernard *et al.*[17] Myocardial contractility (as assessed with left ventricular dP/dt_{50}), and myocardial oxygen consumption (as estimated by the rate–pressure product) decreased with the administration of sevoflurane. Because no changes in diastolic blood flow velocity were produced by sevoflurane, these findings suggest that this anesthetic may cause relative coronary vasodilation. The magnitude of sevoflurane-induced decreases in coronary vasomotor tone was not, however, of sufficient magnitude to cause coronary steal.

Blood flow to normal myocardium did not change with the administration of 1.0 or 1.5 MAC sevoflurane. In contrast, blood flow to collateral-dependent myocardium increased during 1.5 MAC sevoflurane when arterial pressure and heart rate were maintained at conscious control values. The sevoflurane-induced increase in transmural collateral flow may have occurred because of preferential dilatation of coronary collateral vessels. Dilation of collateral vessels is also suggested by the observation that blood flow increased despite a relatively lower coronary perfusion pressure compared to conscious control values, since left ventricular end-diastolic pressure increased. Elevations in left ventricular end-diastolic pressure would be expected to limit collateral flow predominantly in subendocardium, since extravascular compressive forces in the loaded left ventricle play a dominant role in the transmural distribution of collateral flow.[34] However, while the coronary collateral circulation is subject to substantially different control mechanisms than normal coronary arteries,[35] the differential effects of volatile anesthetics on the coronary collateral vasculature have not been directly examined. Sevoflurane may also have different effects on mature *versus* immature collateral vessels. However, immature coronary collateral vessels retain the ability to vasodilate in response to nitroglycerin, despite impaired vasoconstrictor responses.[36] Alternatively, increases in transmural collateral blood flow during administration of sevoflurane may have occurred as an indirect response to regional increases in myocardial oxygen consumption rather than a direct response to the vasodilating effects of sevoflurane. Partial inflation of the thoracic aorta hydraulic vascular occluder caused increases in afterload (as indirectly indicated by mean arterial and left ventricular systolic pressures) and preload (left ventricular end-diastolic pressure). These artificially imposed alterations in ventricular loading conditions resulting in increases in estimated myocardial oxygen demand may have contributed to observed increases in transmural blood flow *via* flow–metabolism coupling.

Using the identical canine multivessel model, Hartman *et al.*[19,20] demonstrated that adenosine, a potent coronary vasodilator, caused marked increases in myocardial blood flow to both normal myocardium and that distal to a moderate LCCA stenosis. Adenosine-induced redistribution of collateral coronary blood flow from ischemic to normal zones occurred despite maintenance of coronary perfusion pressure and heart rate at control values. Thus, adenosine caused coronary steal as indicated by declines in collateral dependent myocardial blood flow despite restoration of systemic hemodynamics. These findings were in contrast to the results of the present investigation, which showed that sevoflurane did not reduce collateral myocardial blood flow or change the ratio of occluded- to normal-zone blood flow. While other models may be more sensitive in demonstrating the coronary vasodilating effects of volatile anesthetics, this contention is not supported by previous findings that coronary steal caused by adenosine is sensitively demonstrated in this model. A multivessel model of coronary artery obstruction using an occluded coronary artery with collateral vessels arising from an artery with a proximal stenosis most readily demonstrates the ability of pharmacologic agents to cause abnormal redistribution of myocardial blood flow.[2] In the present investigation, a stenosis of the LCCA was of comparable severity to that used in previous studies from this laboratory. Stenotic-zone myocardial blood flow and hyperemic response to adenosine administration were similar between the present and past studies.[19,20]

Isoflurane[19] and desflurane[28] have also been investigated in this canine multivessel model. Occlusion of the LAD in conscious animals produced similar increases in heart rate, mean arterial pressure and left ventricular end-diastolic pressure as observed in the current investigation. Isoflurane and desflurane administered after LAD occlusion produced declines in mean arterial pressure and dP/dt_{50}, while LCCA diastolic coronary blood flow velocity was unchanged, comparable to findings observed during sevoflurane administration. In contrast to the present results, 2.3% isoflurane and 12.7% desflurane reduced collateral perfusion to ischemic myocardium during systemic hypotension. However, blood flow to collateral-dependent myocardium was restored with correction of arterial pressure and heart rate to control values. In the presence of a severe LCCA stenosis, neither isoflurane nor desflurane possess sufficient coronary vasodilator potency to produce coronary steal.[19,28] In contrast to the findings with sevoflurane and other volatile anesthetics, adenosine causes coronary steal despite the presence of only a moderate degree of coronary artery stenosis.[19,20] Finally, isoflurane failed to cause coronary steal in dogs with poorly, moderately, or well developed coronary collateral vessels,[37] indicating that this volatile anesthetic with more potent coronary vasodilating properties did not redistribute blood flow from collateral-dependent myocardium independent of the degree of collateral development.

In conclusion, this investigation demonstrated that sevoflurane does not reduce collateral perfusion to ischemic myocardium in a chronically instrumented canine model of multivessel coronary artery disease. These results are consistent with the interpretation that sevoflurane lacks potent coronary vasodilating properties which are necessary to cause coronary steal. The present results also suggest, however, that sevoflurane unlike other volatile anesthetics may preferentially increase collateral blood flow in the presence of constant aortic pressure.

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