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Direct Coronary Vasomotor Effects of Sevoflurane and Desflurane in In Situ *Canine Hearts*

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Background: **An extracorporeal system was used to investigate the direct coronary vasomotor effects of sevoflurane and desflurane in vivo. The role of the adenosine triphosphate–sensitive potassium channels (K_{ATP} channels) in these effects was evaluated.**

Methods: **Twenty-one open-chest, anesthetized (fentanyl–midazolam) dogs were studied. The left anterior descending coronary artery was perfused at controlled pressure (80 mmHg) with normal arterial blood or arterial blood equilibrated with either sevoflurane or desflurane. Series 1 (n = 16) was divided into two groups of equal size on the basis of whether sevoflurane (1.2, 2.4, and 4.8%) or desflurane (3.6, 7.2, and 14.4%) was studied. The concentrations for the anesthetics corresponded to 0.5, 1.0, and 2.0 minimum alveolar concentration (MAC), respectively. Coronary blood flow (CBF) was measured with an ultrasonic, transit-time transducer. Local coronary venous samples were obtained and used to evaluate changes in myocardial oxygen extraction (EO_2). In series 2 (n = 5), changes in CBF by 1 MAC sevoflurane and desflurane were assessed before and during intracoronary infusion of the K_{ATP} channel inhibitor glibenclamide (100 μg/min).**

Results: **Intracoronary sevoflurane and desflurane caused concentration-dependent increases in CBF (and decreases in EO_2) that were comparable. Glibenclamide blunted significantly the anesthetic-induced increases in CBF.**

Conclusions: **Sevoflurane and desflurane have comparable coronary vasodilative effects in *in situ* canine hearts. The K_{ATP} channels play a prominent role in these effects. When compared with data obtained previously in the same model, the coronary vasodilative effects of sevoflurane and desflurane are similar to those of enflurane and halothane but considerably smaller than that of isoflurane. (Key words: ATP-sensitive potassium channels; coronary circulation; coronary vasodilators; volatile anesthetics.)**

SEVOFLURANE and desflurane are new volatile anesthetics that are being used increasingly in clinical practice.[1] A number of studies in experimental animals have attempted to assess the coronary vasomotor effects of these anesthetics.[2–8] However, these studies were inconclusive, because sevoflurane and desflurane were administered *via* the lungs; thus, the changes in coronary blood flow (CBF) and coronary vascular resistance were complicated by the systemic hemodynamic effects of the anesthetics, which included increases in heart rate and decreases in mean arterial pressure, cardiac output, and myocardial contractility. Furthermore, the studies lacked direct measurements of myocardial oxygen consumption (MV_{O_2}) or myocardial oxygen extraction (EO_2), which made it difficult to separate the direct vascular effects of the anesthetics from those secondary to anesthetic-related changes in cardiac metabolism. To avoid these potential pitfalls, the coronary vasomotor effects of sevoflurane and desflurane were investigated in crystalloid-perfused, isolated rodent hearts,[9,10] but the value of these investigations was limited by the artificial work conditions and reduced vasodilator reserves of these preparations.

Series 1 of the current study was performed to evaluate

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the direct coronary vasomotor effects of sevoflurane and desflurane *in vivo* under stable hemodynamic conditions. A portion of the left anterior descending coronary artery (LAD) in *in situ* canine hearts was perfused under constant pressure with arterial blood equilibrated extracorporeally with clinically relevant concentrations of the anesthetics. Because the remainder of dog, including most of the heart, was naturally supplied with arterial blood free of the volatile anesthetics, this approach avoided the hemodynamic instabilities that complicated interpretation of previous *in vivo* studies. The observed changes in CBF caused by sevoflurane and desflurane were assessed in the context of the accompanying changes in MV_{O_2}, EO_2, and segmental shortening (SS) obtained in the LAD-perfused myocardium. The new findings using sevoflurane and desflurane were compared with previous findings obtained in the same preparation during isoflurane, halothane, and enflurane.

The findings in series 1 indicated that sevoflurane and desflurane both had coronary vasodilative effects. Recent studies from this laboratory[11,12] and others[13,14] have suggested that an opening of the adenosine triphosphate-sensitive potassium channels (K_{ATP} channels) is involved in the coronary vasodilation caused by isoflurane, halothane, and enflurane. Thus, we carried out additional studies in the same canine model (series 2) to evaluate the ability of the K_{ATP} channel inhibitor glibenclamide to attenuate the coronary vasodilative effects of sevoflurane and desflurane.

Methods

Canine Preparation

This study was conducted with compliance of the institutional research committee. Experiments were performed on 21 mongrel dogs of either gender (weight range, 20.5–34.5 kg). Anesthesia was induced with an intravenous bolus injection of thiopental 20 mg/kg and maintained by continuous intravenous infusion of fentanyl and midazolam at rates of 12 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 0.6 $mg \cdot kg^{-1} \cdot h^{-1}$, respectively. Additional intravenous bolus injections of fentanyl were given as necessary to maintain heart rate at approximately 130 beats/min. After tracheal intubation, the lungs were mechanically ventilated (Air Shields, Inc., Hatboro, PA), with fraction of inspired oxygen ($F_{I_{O_2}}$) equal to 1.0. The volume and rate of the ventilation were established to maintain arterial partial pressure of carbon dioxide (P_{CO_2}) at a physiologic level (30–40 mmHg). Partial pressure of oxygen P_{O_2}, P_{CO_2}, and *p*H of coronary arterial and venous blood samples (discussed in Experimental Measurements) were measured electrometrically (Blood Gas Analyzer model 413; Instrumentation Laboratories, Lexington, MS). Muscle paralysis was obtained using an intravenous injection of vecuronium bromide 0.1 mg/kg with supplements at 0.05 $mg \cdot kg^{-1} \cdot h^{-1}$ to facilitate mechanical ventilation. Body temperature was maintained at 38°C with a heating pad. Lactated Ringer's solution was administered continuously intravenously at a rate of 5 $ml \cdot kg^{-1} \cdot h^{-1}$ to compensate for fluid losses. Heparin 400 U/kg with supplementation was used for anticoagulation.

After a left-sided thoracotomy in the fourth intercostal space, the LAD was cannulated just distal to its first major diagonal branch and perfused *via* an extracorporeal system, as described in detail previously.[15–17] In brief, this system consisted of two pressurized reservoirs that served as alternate sources of blood for the LAD. The volatile anesthetic-free blood reservoir was supplied with blood withdrawn directly from the left femoral artery, and the volatile anesthetic-equilibrated blood reservoir was supplied with blood from the right femoral artery that was first pumped into a hollow-fiber oxygenator (Capriox 300 series; Terumo Corp., Tokyo, Japan). The oxygenator was supplied with a 95% O_2–5% CO_2 gas mixture that passed through a calibrated vaporizer providing either sevoflurane or desflurane. Blood was recirculated for at least 15 min through the extracorporeal oxygenator to ensure complete equilibration at the desired anesthetic concentration.

The LAD perfusion line was equipped with a heat exchanger to maintain the temperature of coronary perfusate at 38°C, an ultrasonic transit-time flow transducer (Transonic System Inc., Ithaca, NY) to measure CBF, and a port for collecting samples of coronary perfusate. Coronary perfusion pressure (CPP) was measured through a small-diameter tube positioned at the orifice of the perfusion cannula. To avoid hypovolemia in the experimental animal, lactated Ringer's solution was infused intravenously during priming of the perfusion system.

Measurements of aortic, left atrial, and left ventricular pressures; left ventricular dP/dt max; and heart rate were obtained using standard methods.[15] A continuous record of these variables was obtained on a physiologic recorder (model 2800; Gould, Cleveland, OH).

Experimental Measurements

Myocardial Oxygen Consumption. Measurements of MV_{O_2} were obtained in the LAD bed by applying the

Fick principle. The anterior interventricular vein was cannulated in a retrograde direction to obtain blood samples. This vein has been shown to drain exclusively the LAD perfusion territory.[18] The venous cannula was allowed to drain freely into a beaker to prevent venous stagnation and interstitial edema. The coronary venous blood was returned intermittently to the dog to maintain isovolemic conditions. At specified times during the study, 1-ml coronary arterial and venous blood samples were obtained for determination of the local arteriovenous oxygen difference. CBF was constant during the period of blood sampling, which satisfied the requirement of the Fick principle for steady state conditions. Hemoglobin concentration and percent hemoglobin saturation of these samples were measured with a CO-Oximeter (model 482, Instrumentation Laboratories) and used to calculate oxygen bound to hemoglobin, assuming an oxygen-carrying capacity for hemoglobin of 1.39 ml O_2/g. The amount of oxygen dissolved in the blood was computed (oxygen dissolved = 0.003 ml $O_2 \cdot$ 100 ml blood$^{-1} \cdot$ mmHg^{-1}) and added to the bound component to calculate total oxygen content. MV_{O_2} (in ml $\cdot$ min$^{-1} \cdot$ 100 g^{-1}) was calculated as the product of the coronary arteriovenous oxygen difference and CBF at the time that blood samples were taken. EO_2 (in percentage) was calculated by dividing arteriovenous oxygen difference by arterial oxygen content.

Myocardial Segmental Shortening. Measurements of SS, an index of regional myocardial contractile function, were obtained by sonomicrometry.[19] A pair of ultrasonic crystals was implanted into the LAD-perfused myocardium to a depth approximating the subendocardium. Location and functionality of the crystals were verified by segmental lengthening during a brief (30-s) occlusion. The crystals were oriented so that they were parallel with the anticipated direction of myocardial fibers in the subendocardium. Changes in distance between the crystals were recorded from measurements of ultrasonic transit time between the crystals (Triton Technology, San Diego, CA). The end-diastolic and end-systolic lengths were identified by the beginning of a rapid increase in the left ventricular pressure just before isovolumetric contraction and the maximum rate of decrease of left ventricular systolic pressure (−dP/dt min), respectively. Percent SS was calculated using the following formula:

$$\%SS = [(EDL - ESL)/EDL] \times 100$$

where EDL = end-diastolic length; and ESL = end-systolic length.

Blood Anesthetic Concentration. The concentration of sevoflurane and desflurane in the coronary arterial blood was evaluated using a modification of the equilibration method described by Yamamura *et al.*[20] Briefly, a 2-ml sample of blood was obtained from the LAD perfusion tubing using a airtight glass syringe and introduced into a 5-ml glass vial. The vial was placed in a constant-temperature chamber at 38°C for 30 min. After equilibration, 100 μl of the gas in the vial was introduced into a gas chromatograph (model 5890; Hewlett Packard, Wilmington, DE) equipped with a flame ionization detector, and the area under the curve was measured. Anesthetic concentration in blood was determined by means of a calibration curve derived from appropriate standards. The data are presented in both units of mg/100 ml and mM to facilitate comparisons with previous studies.[9,12]

Experimental Protocols

Series 1 (n = 16).

Concentration-related Coronary Effects of Sevoflurane and Desflurane. The dogs in this series were divided randomly into two equal groups according to whether sevoflurane or desflurane was studied. After at least 45 min of recovery from surgical preparation, initial control measurements for CBF, MV_{O_2}, and SS were obtained during perfusion from the volatile anesthetic-free blood reservoir with CPP at 80 mmHg. This level of CPP was maintained throughout the study. The LAD was then switched to the volatile anesthetic-equilibrated blood reservoir, and at the peak increase in CBF (approximately 3–5 min after switching reservoirs), measurements were repeated. Perfusion was then returned to the volatile anesthetic-free blood reservoir, and at least 20 min was allowed for recovery. This protocol, with each exposure to a volatile anesthetic immediately preceded by a control period, was followed as the vaporizer setting for sevoflurane was varied from 1.2, 2.4, and 4.8% and that for desflurane was varied from 3.6, 7.2, and 14.4% (equivalent to 0.5, 1.0, and 2.0 minimum alveolar concentration [MAC] for dogs).[21,22] The order of exposure to the various volatile anesthetic concentrations was randomized. Adenosine was infused into the LAD perfusion tubing at 8 mg/min (1 ml/min) to assess the vasodilator reserve of each preparation.[19] We showed in preliminary studies that infusion of the saline vehicle at this rate had no effect on CBF.

Series 2 (n = 5).

Effect of Glibenclamide on Anesthetic-induced Coronary Blood Flow Changes. The changes in CBF

by 1.0 MAC sevoflurane and desflurane (administered as described under series 1) were evaluated in the same dogs before, during, and after (recovery) an intracoronary infusion of glibenclamide (Sigma Chemical Co., St. Louis, MO) 100 μg/min.[11] At least 30 min was allowed after discontinuation of glibenclamide administration before the recovery response to the anesthetic was assessed. Glibenclamide was dissolved with 10 mM NaOH under gentle heat and diluted to a concentration of 100 μg/ml in isotonic saline, which permitted intracoronary infusions at the rate of 1 ml/min. The protocol adopted for the glibenclamide infusions was based on our previous investigation,[11] which indicated that these infusions markedly inhibited the coronary vasodilator responses to the K_{ATP} channel-opening drug cromakalim while permitting a full recovery of these responses within 30 min of stopping glibenclamide, and that they had no effect on the coronary vasodilation by the K_{ATP} channel-independent drugs sodium nitroprusside and acetylcholine or on systemic hemodynamic parameters. We also showed that intracoronary infusions of the vehicle for glibenclamide alone had no effect on CBF or related parameters.[11]

After the multiple administrations of sevoflurane (before, during, and after glibenclamide), it was removed from the oxygenator-supplied circuit by recirculating the blood for at least 20 min with the oxygenator provided with anesthetic-free gas. After complete washout of sevoflurane was confirmed by gas chromatography, desflurane was added to the oxygenator-supplied circuit, and its coronary effects were also evaluated in the absence and presence of glibenclamide. The order of the sevoflurane and desflurane trials was randomized. The interval between the two glibenclamide infusions in each preparation was at least 90 min. Adenosine, as described in series 1, was used to evaluate coronary vasodilator reserve. Series 2 did not include measurements of MV_{O_2} or SS. Coronary arterial blood samples were obtained for measurements of sevoflurane and desflurane concentration during the administrations of these agents before and during (but not after) glibenclamide.

At the completion of each experiment, Evans blue dye was injected into the LAD perfusion tubing to delineate the LAD perfusion field. The heart was stopped with KCl and removed, and the dyed tissue was excised and weighed so that CBF could be expressed on a per-100-g basis. The average weight of the LAD perfusion field was 28 ± 8 g.

Statistical Analysis

The Student *t* test for paired samples was used to assess the difference of values during sevoflurane, desflurane, and adenosine administration relative to their respective control values.[23] Hemodynamic responses were normalized on the basis of percentage change from control to facilitate comparisons at equivalent MAC for sevoflurane and desflurane. A two-way analysis of variance (ANOVA) for repeated measurements was used to make these comparisons.[23] A one-way ANOVA was used to evaluate the effects of sevoflurane and desflurane before, during, and after administration of glibenclamide.[23] *Post hoc* comparisons were made using the Student *t* test with the Bonferroni correction.[23] Control values for systemic hemodynamic parameters for the sevoflurane and desflurane groups were compared using the Student *t* test for unpaired samples.[23] Data are expressed as mean ± SD. All comparisons were two-sided. $P < 0.05$ was considered significant throughout the study.

Results

Preanesthetic control values for systemic and cardiac parameters did not differ significantly. Therefore, for the sake of simplicity and brevity, the pooled means for all controls are presented in tables 1 and 2.

Series 1

Concentrated-related Coronary Effects of Sevoflurane and Desflurane. Figure 1 is a representative tracing showing the effect of 2.0 MAC desflurane on CBF, SS, and systemic hemodynamic parameters. At "A," perfusion of the LAD was switched to the desflurane-equilibrated reservoir, and at "B," perfusion was returned to desflurane-free reservoir. After a short delay (corresponding to the time necessary for the desflurane-equilibrated blood to reach the vascular bed), desflurane caused an approximately threefold increase in CBF reflecting a proportional decrease in coronary vascular resistance, and it converted SS to segmental lengthening and reduced left ventricular dP/dt max. Return to the desflurane-free reservoir reversed these effects. Intracoronary desflurane did not affect aortic pressure or heart rate. This was a consistent finding throughout the study (table 1). There were no significant differences between the control values for systemic hemodynamic parameters in the sevoflurane and desflurane groups, with the exception that mean aortic pressure and left

Table 1. Systemic Hemodynamic Variables and Coronary Arterial Values during Intracoronary Administrations of Sevoflurane or Desflurane

	Control (pooled)	Sevoflurane			Control (pooled)	Desflurane		
		0.5 MAC	1.0 MAC	2.0 MAC		0.5 MAC	1.0 MAC	2.0 MAC
Hemodynamic variables								
Mean aortic pressure (mmHg)	111 ± 11	108 ± 14	110 ± 11	109 ± 11	92 ± 15	99 ± 25	94 ± 14	84 ± 14
Mean left atrial pressure (mmHg)	5.0 ± 1.5	4.7 ± 1.4	4.6 ± 1.1	5.3 ± 2.8	5.3 ± 2.0	5.6 ± 2.3	6.0 ± 2.8	6.1 ± 2.3
Left-ventricular dP/dt max (mmHg/s)	1529 ± 372	1525 ± 376	1411 ± 334	1444 ± 325.2	1317 ± 176	1286 ± 328	1275 ± 127	1218 ± 93*
Heat rate (beats/min)	125 ± 29	131 ± 31	129 ± 25	129 ± 37	126 ± 15	128 ± 17	125 ± 11	130 ± 11
Coronary values								
Pa_{O_2} (mmHg)	378 ± 127	548 ± 130	469 ± 85	478 ± 78	404 ± 132	474 ± 129	532 ± 104	477 ± 122
Pa_{CO_2} (mmHg)	38 ± 5	33 ± 3	33 ± 3	34 ± 3	34 ± 5	33 ± 3	32 ± 3	30 ± 3
p_aH	7.37 ± 0.10	7.40 ± 0.03	7.40 ± 0.10	7.40 ± 0.06	7.37 ± 0.05	7.40 ± 0.03	7.40 ± 0.03	7.40 ± 0.06
Hematocrit (%)	35 ± 5	33 ± 6	34 ± 3	34 ± 3	35 ± 5	35 ± 3	34 ± 6	33 ± 6
Anesthetic concentration								
mg/100 ml	—	5.6 ± 2.3	9.2 ± 3.0	22.6 ± 6.1	—	19.1 ± 3.8	36.9 ± 8.3	67.9 ± 7.5
mM	—	0.28 ± 0.11	0.46 ± 0.15	1.13 ± 0.30	—	1.14 ± 0.22	2.20 ± 0.49	4.04 ± 0.45

Values are mean ± SD obtained from 24 observations during control conditions and eight observations during each anesthetic concentration.

*$P < 0.05$, from respective control.

MAC = minimum alveolar concentration.

ventricular dP/dt max were approximately 15% higher in the sevoflurane group.

Table 2 presents the concentration-related effects of sevoflurane and desflurane on CBF and related cardiac parameters. The control values for CBF, MV_{O_2}, and SS were moderately higher in the sevoflurane group *versus* the desflurane group; the control values for EO_2 in the two groups did not differ. Both anesthetics caused concentration-related increases in CBF. When viewed on the basis of percentage increase from the respective control value, the increases in CBF caused by equivalent MAC of sevoflurane and desflurane were comparable (fig. 2). Adenosine caused fivefold to sixfold increases in CBF in both groups (from 97 ± 31 to 509 ± 164 ml · min^{-1} · 100 g^{-1} in the sevoflurane group and 95 ± 23 to 711 ± 112 ml · min^{-1} · 100 g^{-1} in the desflurane group). The increases in CBF at the highest concentrations of sevoflurane (4.8%) and desflurane (14.4%) were 52 ± 24% and 57 ± 17% of the adenosine-induced responses, respectively.

Although 0.5 and 1.0 MAC sevoflurane did not affect MV_{O_2}, 2.0 MAC sevoflurane reduced MV_{O_2}. Desflurane did not alter MV_{O_2} at any concentration. The combination of an increased CBF and either unchanged or decreased MV_{O_2}-reduced EO_2 during administration of sevoflurane or desflurane caused concentration-depen-

Table 2. Effects of Intracoronary Sevoflurane and Desflurane on Coronary Blood Flow and Related Cardiac Parameters

	Control (pooled)	Sevoflurane			Control (pooled)	Desflurane		
		0.5 MAC	1.0 MAC	2.0 MAC		0.5 MAC	1.0 MAC	2.0 MAC
Coronary blood flow (ml · min^{-1} · 100 g^{-1})	119 ± 34	166 ± 51*	212 ± 70*	360 ± 93*	94 ± 24	130 ± 48*	161 ± 31*	298 ± 71*
Myocardial oxygen consumption (ml · min^{-1} · 100 g^{-1})	9.5 ± 1.9	9.8 ± 2.1	10.1 ± 1.7	6.1 ± 1.7*	7.0 ± 2.0	9.3 ± 2.6	7.5 ± 1.1	5.7 ± 2.0
Segmental shortening (%)	16.3 ± 7.3	15.3 ± 5.4*	12.3 ± 5.0*	1.8 ± 7.8*	12.9 ± 4.4	−0.9 ± 4.5	−8.7 ± 8.5*	−16.8 ± 7.9*
Oxygen extraction (%)	51 ± 9	38 ± 8*	28 ± 11*	12 ± 3*	53 ± 4	46 ± 8*	35 ± 14*	15 ± 6*

Values are mean ± SD obtained from 24 observations during control conditions and eight observations during each anesthetic concentration.

*$P < 0.05$, from respective control.

MAC = minimum alveolar concentration.

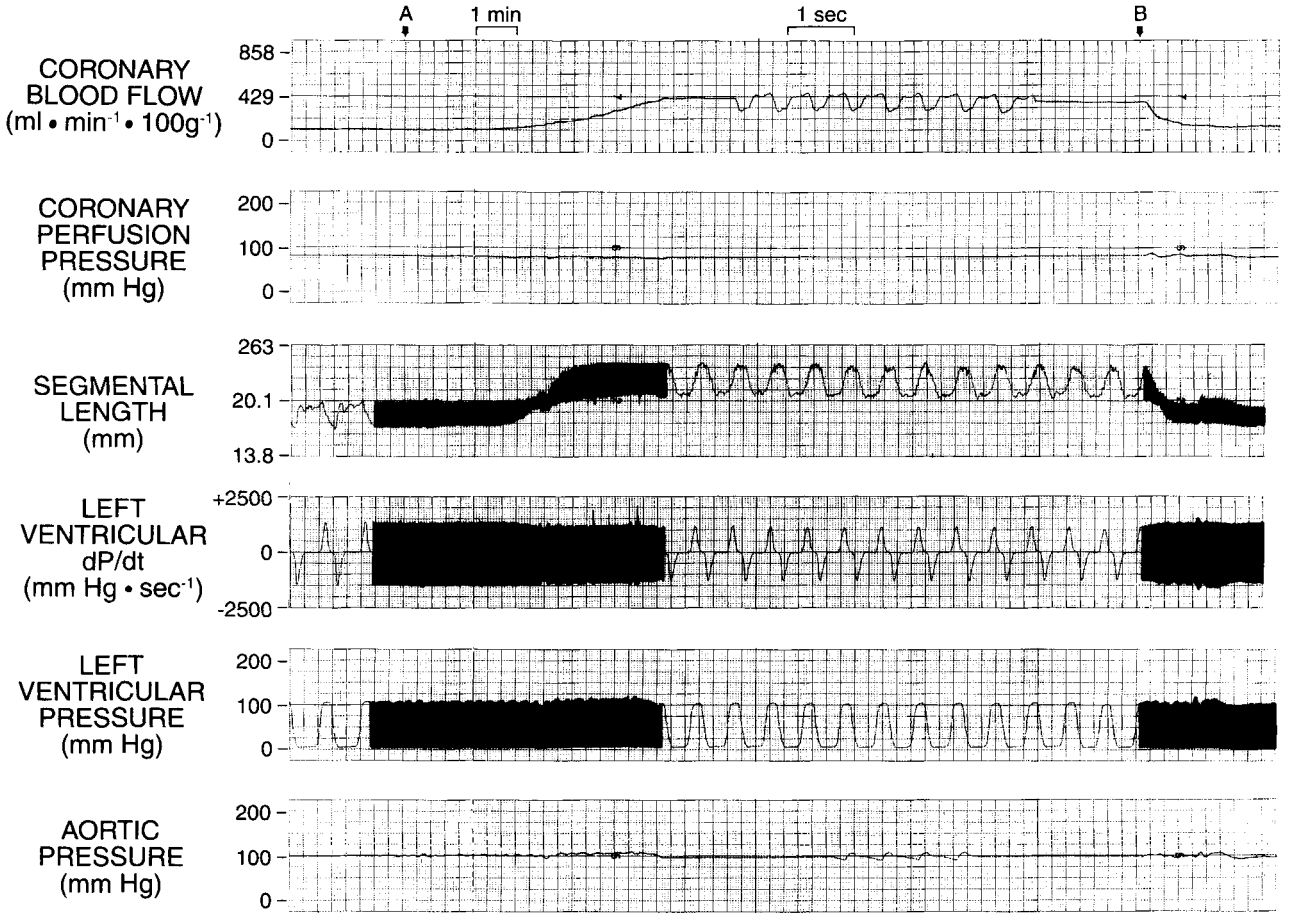

Fig. 1. Original tracing showing effect of selective exposure of the left anterior descending coronary artery (LAD) to blood equilibrated with 2.0 minimum alveolar concentration (MAC) desflurane. (*A*) Perfusion of the LAD was switched to the desflurane-equilibrated blood reservoir. (*B*) Perfusion was returned to the desflurane-free reservoir. Desflurane caused a marked increase in coronary blood flow and converted segmental shortening to segmental lengthening. These effects were reversible.

dent decreases in EO_2 (range equal to −20% to −75%). The decreases in EO_2 were similar for sevoflurane and desflurane at equivalent MAC.

Both sevoflurane and desflurane caused decreases in SS. At each MAC equivalent, the decreases in SS by sevoflurane were less than those by desflurane (0.5 MAC, −10 ± 11 *vs.* −106 ± 48%; 1.0 MAC, −28 ± 15% *vs.* −165 ± 57%; 2.0 MAC, −101 ± 62% *vs.* −250 ± 93%). The 0.5 and 1.0 MAC sevoflurane reduced SS, and 2.0 MAC sevoflurane completely abolished SS. Conversely, 0.5 MAC desflurane completely abolished SS, and 1.0 and 2.0 MAC desflurane converted SS to segmental lengthening.

Table 1 shows that the coronary arterial concentrations for sevoflurane and desflurane varied directly with the percentage provided by the vaporizer.

Series 2

Effect of Glibenclamide on Anesthetic-induced Coronary Blood Flow Changes. Glibenclamide infusion itself caused approximately 30% reversible decreases in CBF; the control (preanesthetic) values for CBF were 96 ± 17, 71 ± 12, and 88 ± 15 ml · min^{-1} · 100 g^{-1} before, during, and after glibenclamide administration, respectively. Figure 3 shows that glibenclamide blunted, in a reversible manner, the increases in CBF caused by 1.0 MAC sevoflurane and desflurane. The arterial blood concentrations for the anesthetics were similar before and during glibenclamide: Sevoflurane, 8.4 ± 1.2 and 8.1 ± 1.4 mg/100 ml (equivalent to 0.42 ± 0.06 and 0.40 ± 0.07 mM); desflurane, 31.1 ± 4.1 and 30.1 ± 5.7 mg/100 ml (equivalent to 1.85 ± 0.25 and

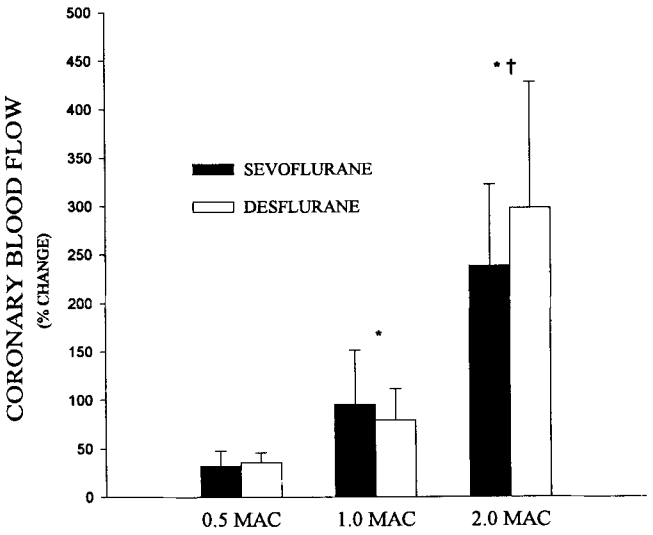

Fig. 2. Effects of intracoronary sevoflurane and desflurane on coronary blood flow (normalized on the basis of the percentage change from the respective control [preanesthetic] value). The volatile anesthetics caused concentration-dependent increases in coronary blood flow that did not differ. $P < 0.05$, * *versus* 0.5 minimum alveolar concentration (MAC); † *versus* 1.0 MAC. Values are mean ± SD.

1.79 ± 0.34 mM). Control values for systemic hemodynamic parameters in series 2 were comparable to those in series 1 (table 1); the intracoronary administrations of the volatile anesthetics (and of glibenclamide) did not alter these values. Adenosine caused fourfold increases in CBF (104 ± 20 to 440 ± 44 ml · min^{-1} · 100 g^{-1}) in the dogs in series 2.

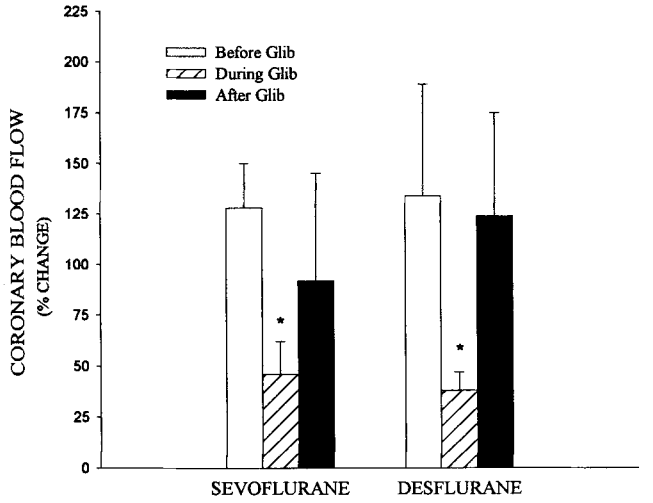

Fig. 3. Percentage changes in coronary blood flow during intracoronary administrations of 1 minimum alveolar concentration (MAC) sevoflurane and desflurane before, during, and after glibenclamide (Glib) infusion. Glibenclamide attenuated, in a reversible fashion, the sevoflurane- and desflurane-induced increases in coronary blood flow. *$P < 0.05$ *versus* before Glib. Values are mean ± SD.

Discussion

Critique of Methods

We have used this model of regional coronary perfusion in canine hearts to evaluate the direct coronary vascular effects of volatile anesthetics[15–17,24] and to clarify the role of mechanisms potentially responsible for these effects, such as nitric oxide[25] and the ATP-sensitive potassium channels.[11] The baseline values for EO_2 in the cannulated LAD bed were moderately lower than those usually found in anesthetized dogs with an intact coronary circulation.[26] This suggests modest vasodilation in the control preparation, probably as a result of dilators released from blood cells within the extracorporeal circuit.[27] Nevertheless, this model shows pronounced vascular responsiveness to endothelium-dependent vasodilators (acetylcholine), nitric oxide donors (sodium nitroprusside), and K_{ATP} channel openers (cromakalim). Moreover, vasodilator reserve is appreciable, as shown by the better than fourfold increases in CBF during adenosine infusion in the current study.

In previous studies using the regional coronary perfusion preparation, we demonstrated that the coronary vasodilative effects of volatile anesthetics were blunted when arterial blood concentration was increased gradually[24] or when exposure of the coronary circulation to the anesthetic was prolonged.[25] These findings implied a tendency for coronary vascular smooth muscle to adapt to the relaxing effects of these agents. Such vascular adaptation would, of course, complicate interpretation of studies in which multiple administrations of volatile anesthetics were compared in the same heart. To obviate this factor, we used only abrupt, relatively brief exposures of the LAD to blood previously equilibrated with various concentrations of sevoflurane and desflurane.

Infusion of crystalloid during priming of the extracorporeal perfusion system produced modest reductions in hematocrit. The animals were ventilated on 100% oxygen to increase arterial P_{O_2} and thus minimize the concomitant decreases in arterial oxygen content. Previous studies have shown increases in coronary vascular resistance during hyperoxia, and that this response may be related to K_{ATP} channel closure.[28] Although we cannot rule out that hyperoxia limited the vasodilative effects of sevoflurane and desflurane, it is highly unlikely that this factor would have altered our conclusions. First, the

values for coronary arterial P_{O_2} were similar under control conditions and during administration of the anesthetics. Second, our previous study,[11] conducted with arterial P_{O_2} at similarly elevated levels, showed marked concentration-related coronary vasodilation in response to the K_{ATP}-channel opener cromakalim.

General anesthesia was necessary in this open-chest canine preparation. A balanced anesthetic technique using fentanyl and midazolam was used for several reasons. First, such techniques have been shown by clinical investigators to be free of significant effects on cardiac function.[29] Second, Flacke *et al.*[30] reported that the combination of fentanyl and diazepam (another benzodiazepine) caused no additional cardiac depression in dogs anesthetized with enflurane after elimination of cardiac sympathetic drive with a spinal block. Finally, Reves *et al.*[31] found that excessive doses of fentanyl and diazepam together were necessary to depress isolated perfused rat hearts and that this effect occurred in a strictly additive fashion.

A CPP of 80 mmHg was used to perfuse the LAD bed throughout our study. Because the values for mean aortic pressure were, on average, modestly higher, the possibility of incoming collateral flow cannot be ruled out. However, our previous findings in the same canine model showed that collateral flow made only a negligible (approximately 3%) contribution to overall perfusion of LAD-dependent myocardium when an aorta-LAD pressure gradient of 40–50 mmHg was created,[32] which suggests that this factor was not important under the conditions of the current study.

In our preparation, only the volatile anesthetic-equilibrated blood reservoir was supplied *via* a circuit equipped with an oxygenator. Thus, it was necessary to rule out that the oxygenator itself and/or the recirculation protocol used to equilibrate the blood with the volatile anesthetics contributed to the observed increases in CBF and decreases in SS. This was accomplished in previous studies using two protocols. First, we demonstrated that blood, which was recirculated for 15 min through a membrane oxygenator not supplied with a volatile anesthetic, had no effects in the LAD bed.[33] Second, we showed that turning off the vaporizer while maintaining perfusion from the oxygenator-supplied reservoir caused return of CBF to baseline.[15,17]

The ability of SS measurements to reflect changes in myocardial contractility is limited by variations in heart rate and in loading conditions of the heart.[34] However, the constant values for heart rate and for indices of afterload (aortic pressure) and preload (left atrial pressure) during intracoronary administration of the anesthetic suggest that this methodologic limitation does not apply to the current study.

To facilitate clinically relevant comparisons, the coronary and myocardial effects of sevoflurane and desflurane were compared on the basis of corresponding MAC values. It should be kept in mind that the MAC value for sevoflurane (2.4%) is one third that of desflurane (7.2%); thus, these comparisons were not a reflection of the relative pharmacologic potency of these agents in the coronary circulation.

Effects of Volatile Anesthetics

Both sevoflurane and desflurane caused concentration-dependent coronary vasodilation. When viewed on a MAC basis, these effects were similar for the two anesthetics. The extent of coronary vasodilation caused by the highest concentration of the sevoflurane or desflurane (4.8% and 14.4%, respectively, corresponding to 2.0 MAC) was impressive, being equivalent to approximately 50% of that achievable with adenosine. Because these agents either did not change or caused decreases in local MV_{O_2} (reflecting a direct negative inotropic effect), EO_2 decreased markedly. These decreases in EO_2 indicated an uncoupling of coronary oxygen supply from myocardial oxygen demands, which is the hallmark of a coronary vasodilative drug.[35]

Mechanical forces in the left ventricular wall compress the coronary arteries during systole, causing a physical impediment to blood flow.[35] This effect shows transmural variation (*i.e.*, subendocardium > subepicardium). Under normal conditions (intact vasomotor tone), metabolic vasodilative mechanisms operate during diastole to compensate for the systolic limitation to subendocardial flow, thus preserving a uniform distribution of flow across the ventricular wall over the cardiac cycle. Some, but not all, studies have shown that when coronary vasomotor tone is fixed with a maximally dilating infusion of adenosine and peak systolic left ventricular pressure is held constant, CBF varies inversely with the level of myocardial contractility.[35] Thus, we cannot rule out the possibility that reduced extravascular compressive forces secondary to decreased or completely abolished regional contractile activity contributed to the increases in CBF caused by sevoflurane and desflurane. The role of this factor may be more prominent during desflurane administration because of its stronger negative inotropic effect.

We used the same canine model and experimental approaches to evaluate the effects of halothane, isoflurane, and enflurane in the coronary circulation.[15–17] The

lack of concurrence with the current study notwithstanding, these studies can provide insight into how the direct coronary vasodilative effects of sevoflurane and desflurane compare with those of the other widely used volatile anesthetics. The findings indicate that the coronary vasodilative effects of sevoflurane and desflurane are similar to those of halothane and enflurane but smaller than that of isoflurane. It is difficult to compare our findings to other *in vivo* studies assessing the relative coronary vasodilative effects of the volatile anesthetics,[2-8] because these studies administered the anesthetics in the inspired gas; thus, the resultant changes in CBF were the summation of several interacting factors, including the direct relaxing action of the anesthetics on the vascular smooth muscle tone, and the influence of indirect mechanisms, including metabolic mechanisms secondary to reduced cardiac work demand, pressure-flow autoregulation, and time-dependent vascular adaptation.

Glibenclamide inhibited profoundly the increases in CBF caused by sevoflurane and desflurane, implying a significant role for the K_{ATP} channels in the responses. These findings are consistent with those obtained previously in studies of the coronary dilating effects of other volatile anesthetics (*i.e.*, isoflurane, enflurane, and halothane) in open-chest dogs[11] and swine[13] and *in vitro* in porcine coronary arterioles[12] and crystalloid-perfused rat hearts arrested with tetrodotoxin.[14] Recent evidence suggests that K_{ATP} channels are present in vascular smooth muscle cells and in vascular endothelial cells.[36] Opening of K_{ATP} channels in the vascular smooth muscle cells shifts the membrane potential closer to the K^+ reversal potential. Hyperpolarization then inhibits calcium entry through voltage-dependent calcium channels, leading to reduced vasomotor tone. Opening of the endothelial K_{ATP} channels can reduce vascular smooth muscle tone either by production and release of second messengers (*e.g.*, nitric oxide) or by direct transduction of electrical potentials. The current findings do not distinguish between the contribution of the K_{ATP} channels in vascular smooth muscle and in the endothelial cells to the volatile anesthetic-induced coronary vascular relaxation.

Several potential mechanisms can be proposed to explain K_{ATP} channel-mediated coronary vasodilation by the volatile anesthetics.

1. The volatile anesthetics may interact directly with the K_{ATP} channels.
2. A reduction in ATP concentration within the vascular smooth muscle cell may cause an opening of the K_{ATP} channels.
3. Prostacyclin may be released (perhaps from the vascular endothelium), which in turns open the K_{ATP} channels, perhaps *via* a G protein-mediated pathway. This mechanism was suggested by studies indicating that glibenclamide inhibited coronary vasodilation caused by exogenous prostacyclin or iloprost (the stable analog of prostacyclin) in saline-perfused hearts.[37]
4. An adenosine receptor may be activated, leading to an opening of the K_{ATP} channel *via* a G protein.[38]
5. An interaction may occur with phosphorylating enzymes, such as protein kinase C, which in turn may regulate activity of the K_{ATP} channel.

Further investigations are necessary to determine which, if any, of the these mechanisms are involved in the opening of the K_{ATP} channels in the coronary circulation by the volatile anesthetics.

The ability of sevoflurane and desflurane (and of the volatile anesthetics in general) to cause cardiac depression is well established.[11,16,17,39-41] The effect seems to be due to the combination of reduced Ca^{2+} current through the sarcolemmal membrane and depletion of Ca^{2+} from the sarcoplasmic reticulum.[42,43] The current findings indicate that sevoflurane is a less potent negative inotrope than desflurane. Comparison of these results to those obtained previously in the same canine model shows that sevoflurane has a negative inotropic effect approximating that of halothane and isoflurane, whereas desflurane has negative inotropic effect approximating that of enflurane.[16,17]

The current findings contrast with results obtained in autonomically blocked, chronically instrumented dogs in which myocardial contractility was assessed using the slope of the regional preload recruitable stroke work relation (a relatively heart rate- and load-independent index), indicating that inspired sevoflurane and desflurane had equivalent negative intropic effects.[39-41] We have no definitive explanation for this apparent discrepancy, but it is likely attributable to methodological differences, including those related to the index of contractility, route of administration of the volatile anesthetics, and the absence or presence of a background anesthetic.

We observed that 1.0 and 2.0 MAC desflurane caused systolic segmental lengthening, reflecting passive myocardial stretch in response to the rise in intraventricular pressure (fig. 1). This phenomenon is usually associated with regional myocardial ischemia, but it can occur when a negative inotrope administered directly into a branch of the left main coronary artery is potent enough

to completely arrest segmental contractile function.[44] The surrounding normal zones "pull" on the noncontracting myocardium during systole, causing it to lengthen. The ability of intracoronary desflurane to cause systolic lengthening in our model should not be construed as evidence that this same dose administered systemically would stop the heart from contracting. Under the latter condition, the entire heart would be exposed to the negative inotropic effect of desflurane; thus, there would be no tethering influence of normally contracting myocardium on depressed myocardium. Furthermore, mechanisms activated during the systemic administration of desflurane (*e.g.*, reduction in cardiac afterload, baroreceptor-mediated arousal of the sympathoadrenal system[1]) would be expected to mitigate the direct negative inotropic effect of the anesthetic.

The major determinants of myocardial oxygen demand are myocardial contractility, wall tension, and heart rate. Because mean aortic pressure, mean left atrial pressure, and heart rate were constant, a decline in MV_{O_2} might be expected during volatile anesthetic-induced reductions in local contractility. Why this did not occur is uncertain, but it may reflect an ability of the volatile anesthetics to directly reduce the efficiency of ATP production by the mitochondria. Further studies using sophisticated *in vitro* techniques are needed to test this possibility. Another factor (especially during desflurane administration) may have been the paradoxically high level of MV_{O_2} in the pharmacologically arrested bulging myocardial segments.[44]

The current study showed that abrupt intracoronary administrations of sevoflurane and desflurane caused concentration-dependent coronary vasodilation accompanied by a negative inotropic effect in *in situ* canine hearts. An opening of the K_{ATP} channels played a prominent role in the coronary vasodilation. The net effect of inspired sevoflurane or desflurane on CBF depends on to what extent their direct coronary vasodilative effects are counteracted by moderating factors, including time-dependent vasculature adaptation and metabolic mechanisms secondary to a reduced cardiac workload.

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