Anesthesiology
1999; 90:246–56

Sevoflurane Selectively Increases Coronary Collateral Blood Flow Independent of K_{ATP} Channels In Vivo

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Background: **Volatile anesthetic agents produce coronary vasodilation *via* activation of adenosine triphosphate–sensitive potassium (K_{ATP}) channels. The authors tested the hypothesis that sevoflurane selectively increases coronary collateral blood flow and assessed the role of K_{ATP} channel activation in this process.**

Methods: **Experiments were conducted in dogs 8 weeks after long-term implantation of a left anterior descending coronary artery (LAD) ameroid constrictor to stimulate coronary collateral growth. Dogs were instrumented for measurement of retrograde LAD blood flow (an index of large coronary collateral blood flow) and LAD tissue flow (*via* radioactive microspheres; an index of small collateral blood flow). Coronary collateral perfusion and normal (left circumflex coronary artery [LCCA]) zone tissue blood flow were determined in four groups of dogs pretreated with intracoronary glyburide (50 μg/kg) or vehicle in the presence or absence of sevoflurane (1 minimum alveolar concentration). Dose–response relationships to the K_{ATP} channel agonist nicorandil were established in each dog using doses (25, 50, and 100 μg/min) previously shown to increase coronary collateral blood flow.**

Results: **Sevoflurane increased blood flow through large and small collaterals and increased collateral vascular conductance in the presence of glyburide but did not affect LCCA blood flow or conductance. In contrast, nicorandil increased blood flow through small but not large collaterals. Nicorandil also increased LCCA blood flow and conductance, actions that were attenuated by glyburide.**

Conclusions: **The results demonstrate that sevoflurane selectively increases large and small coronary collateral blood flow *via* mechanism(s) independent of K_{ATP} channel activation. (Key words: Coronary collateral circulation; myocardial ischemia.)**

SEVOFLURANE reduces coronary vascular resistance[1–4] and decreases coronary vasodilator reserve, suggesting that this volatile anesthetic agent is a coronary vasodilator.[1] Despite these actions, we have shown previously that sevoflurane does not abnormally redistribute coronary collateral blood flow away from ischemic myocardium in an experimental model of multivessel coronary artery disease.[5] To the contrary, sevoflurane actually increased blood flow to collateral-dependent myocardium when arterial pressure and heart rate were maintained at conscious values.[5] Our previous findings[5] suggested that sevoflurane, in contrast to other volatile anesthetic agents, may selectively increase coronary collateral blood flow. Previous investigations have demonstrated that adenosine triphosphate–sensitive potassium (K_{ATP}) channels play an important role in the coronary vascular effects of halothane, isoflurane, and enflurane *in vivo*.[6–8] Coronary collateral blood flow was differentiated on the basis of collateral size because coronary vascular responses to pharmacologic stimuli are heterogenous in different-sized vessels.[9] Further, the coronary circulation has been shown to respond heterogeneously to volatile anesthetic agents.[10] Isoflurane causes dilation of predominately small coronary arteries, whereas halothane dilates large coronary arteries.[11] The differential effects of sevoflurane on small and large coronary arteries or coronary collaterals are unknown. Therefore, we tested the hypothesis that sevoflurane selectively increases coronary collateral blood flow *via* K_{ATP} channel activation in a canine model of enhanced coronary collateral development produced by a chronic coronary artery occlusion. The effects of sevoflurane on large and

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Received from the Departments of Anesthesiology, Pharmacology and Toxicology, and Medicine, the Division of Cardiovascular Diseases, the Medical College of Wisconsin, the Zablocki VA Medical Center, and the Department of Biomedical Engineering, Marquette University, Milwaukee, Wisconsin. Submitted for publication January 29, 1998. Accepted for publication September 17, 1998. Supported in part by American Heart Association/Wisconsin Affiliate grant 95-GB-49 (to Dr. Kersten), US Public Health Service grants HL 03690 (to Dr. Kersten) and HL 54280 (to Dr. Warltier), and Anesthesia Research Training grant GM 08377 (to Dr. Warltier). Dr. Warltier is a recipient of funding from Abbott Laboratories.

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small coronary collateral perfusion were compared directly to those of the K_{ATP} channel agonist nicorandil, a drug that has been shown previously to increase coronary collateral blood flow.[12]

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. All procedures conformed to the *Guiding Principles in the Care and Use of Animals* of the American Physiological Society and were performed in accordance with the *Guide for the Care and Use of Laboratory Animals* of the National Institutes of Health (revised, 1996).

Implantation of Ameroid Constrictors

Conditioned mongrel dogs were fasted overnight. Anesthesia was induced with intravenous propofol (5 mg/kg). After tracheal intubation, anesthesia was maintained with isoflurane (1.5–2.0%) in 100% oxygen *via* positive pressure ventilation. A left thoracotomy was performed during sterile conditions, and a segment (1.0–1.5 cm) of the left anterior descending coronary artery (LAD) immediately distal to the first diagonal branch was isolated. An ameroid constrictor (Research Instruments and MFG, Corvallis, OR) was placed around the vessel. The diameter of the internal lumen of the constrictor was 2.0–3.0 mm, and its size was chosen for a snug fit around the vessel without producing a stenosis. The chest was closed in layers and pneumothorax evacuated with a chest tube. Each dog received antibiotic (cefazolin, 40 mg/kg; and gentamicin, 4.5 mg/kg) and analgesic (buprenorphine, 0.01 mg/kg) agents in the postoperative period.

General Preparation

Eight weeks after implantation of ameroid constrictors (moderately well developed collaterals), dogs were anesthetized with sodium pentobarbital (15 mg/kg) and sodium barbital (200 mg/kg) and ventilated *via* positive pressure with oxygen-enriched air (fractional inspired oxygen tension = 0.25) after tracheal intubation. A dual, micromanometer-tipped catheter (Millar Instruments, Houston, TX) was inserted into the aorta and left ventricle *via* the left carotid artery to measure arterial and left ventricular (LV) pressures, respectively. Heparin-filled catheters were inserted into the right femoral vein and artery for administration of intravenous fluids and withdrawal of reference arterial blood samples, respectively. The arterial catheter was advanced to the level of the descending thoracic aorta.

A thoracotomy was performed in the left fifth intercostal space, the lung gently retracted, and the heart suspended in a pericardial cradle. A heparin-filled catheter was positioned in the left atrium for injection of radioactive microspheres. A descending thoracic aortic snare was placed to facilitate control of arterial pressure. Segments of the left circumflex coronary artery (LCCA; proximal to the first marginal branch) and LAD (distal to the ameroid constrictor) were dissected free from the surrounding myocardium. A transit time flow probe (Transonic, Ithaca, NY) was positioned around the LCCA to determine coronary blood flow (ml/min), and a fluid-filled catheter was inserted into this vessel for drug infusion. Each dog was anticoagulated with heparin (500 U/kg). A large-bore polyethylene cannula attached to Silastic tubing was inserted in the right carotid artery. The proximal LAD was ligated, a large-bore metal cannula was positioned and secured in the distal arterial segment, and a carotid artery to LAD shunt was established (to ensure patency of the distal LAD perfusion cannula between measurements of retrograde blood flow). Left anterior descending coronary artery perfusion was restored within 3 min after ligation. A segment of tubing perpendicular to the metal cannula was used to measure retrograde coronary flow during interruption of antegrade flow through the carotid artery to LAD shunt (fig. 1). Hemodynamics were monitored continuously on a polygraph and digitized *via* a computer interfaced with an analog-to-digital converter.

Measurement of Regional Myocardial Perfusion

Carbonized plastic microspheres labeled with ^{141}Ce, ^{103}Ru, ^{51}Cr, or ^{95}Nb were used to measure regional myocardial perfusion as previously described.[13] Microspheres were administered into the left atrium as a bolus injection over 10 s. A timed (2-min) collection of reference arterial flow was started from the femoral arterial catheter a few seconds before the microsphere injection. At the conclusion of each experiment, 10 ml Patent blue dye was injected into the LCCA simultaneously with saline infused intracoronary into the LAD perfusion tubing at equal pressure to delineate the normal and collateral-dependent regions, respectively. Transmural tissue samples were selected from the collateral-dependent

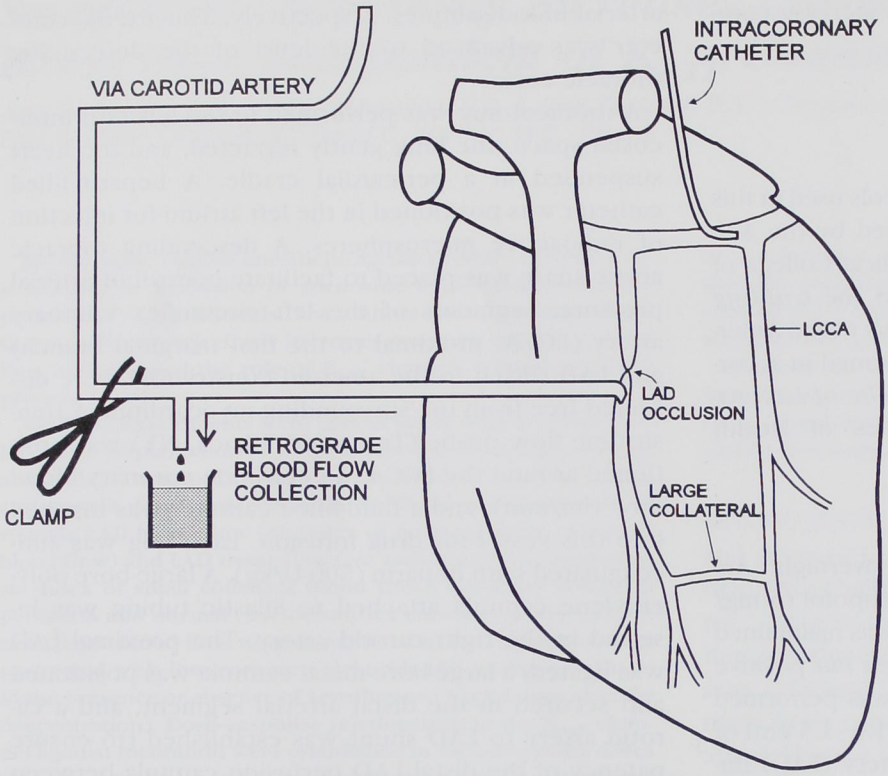

Fig. 1. Experimental design used to measure coronary collateral blood flow. After carotid to left anterior descending coronary artery (LAD) shunt was established, large collateral flow was measured by collecting retrograde LAD flow with the cannula tip held at the level of the right atrium during cessation of antegrade flow through the carotid shunt. LCCA = left circumflex coronary artery.

(distal to the LAD ameroid constrictor) and normal (LCCA) zones. Tissue samples with a significant degree of overlap flow usually present in the peripheral, lateral, superior, and inferior margins of the ischemic region[14] were not used. Samples were subdivided into subepicardial, midmyocardial, and subendocardial layers of approximately equal thickness and weight. Tissue blood flow ($ml \cdot min^{-1} \cdot g^{-1}$) was calculated as $Q_r \cdot C_m \cdot C_r^{-1}$, where Q_r is the rate of withdrawal of the reference blood flow sample (ml/min); C_m is the activity (cpm/g) of the myocardial tissue sample; and C_r is the activity (cpm) of the reference blood flow sample. Transmural blood flow was considered as the average of subepicardial, midmyocardial, and subendocardial blood flows. Coronary perfusion pressure was determined as the difference between end-diastolic arterial pressure and LV end-diastolic pressure. Large and small LAD collateral conductance and LCCA conductance were calculated as the ratio of LAD retrograde, LAD transmural, and LCCA transmural blood flow, respectively, to coronary perfusion pressure.

Experimental Protocol

Hemodynamics were recorded, radioactive microspheres injected, and LAD retrograde blood flow measured 30 min after completion of the acute surgical preparation. Retrograde blood flow was measured by collecting blood from the LAD cannula into a graduated cylinder for 90 s while the cannula tip was maintained at the level of the left atrium. The initial baseline measurements of retrograde blood flow were repeated (usually three to four times) until consistent volumes were obtained. Thereafter, all measurements were performed in triplicate and the results averaged. Microsphere injections were performed with the retrograde flow cannula open so that retrograde and LAD transmural blood flow were measured simultaneously.[15] This procedure differentiates collateral blood flow into two components. Large vessel coronary collateral blood flow is estimated by retrograde flow measurements, and microvascular collateral flow is determined by measurement of tissue blood flow with radioactive microspheres.[15,16]

The actions of sevoflurane to increase coronary collat-

eral blood flow were compared with those of the K_{ATP} channel agonist, nicorandil, in four groups of dogs. Nicorandil previously has been shown to increase coronary collateral blood flow[12]; however, it is unknown whether nicorandil increases blood flow primarily through large or small collaterals. Experiments were performed in one group of dogs, as a positive control, to characterize the response of the coronary collateral circulation to a known K_{ATP} channel agonist that dilates coronary collaterals. In a second group of experiments, nicorandil was administered after blockade of K_{ATP} channels with glyburide. These experiments were performed to characterize the specific role of K_{ATP} channel activation as a mechanism through which nicorandil increases coronary collateral blood flow. Although nicorandil also has been shown to possess nitrate-like properties,[17] this K_{ATP} agonist was chosen as a positive control because the effects of other K_{ATP} channel agonists, such as aprikalim, bimakalim, and cromakalim on collateral blood flow, are unknown. The actions of the anesthetic agent sevoflurane on coronary collateral blood flow were evaluated and compared with the findings during K_{ATP} channel activation with nicorandil. To determine if K_{ATP} channel activation by sevoflurane was responsible for the coronary collateral circulatory effects of this agent, sevoflurane was administered after pretreatment with glyburide in a fourth group of dogs. Finally, nicorandil was administered during sevoflurane to determine if additional coronary collateral vasodilator reserve could be elicited *via* K_{ATP} channel activation. Nicorandil was administered in a cumulative manner *via* intracoronary infusions (25, 50, and 100 μg/min, 10 min each dose) in four groups of dogs pretreated with intracoronary glyburide (50 μg/kg over 10 min) or vehicle (50% polyethylene glycol and 50% ethyl alcohol) in the presence or absence of 1 minimum alveolar concentration (MAC) sevoflurane (2.36% end-tidal). End-tidal concentrations of sevoflurane were measured at the tip of the endotracheal tube using an infrared gas analyzer calibrated with known standards before and during experimentation. After administration of glyburide or vehicle, hemodynamics, retrograde flow, LAD small collateral blood flow (microspheres), LCCA tissue blood flow (microspheres), and LCCA blood flow (flow probe) were evaluated and measurements repeated in the presence or absence of sevoflurane (30 min of equilibration) and during a cumulative dose–response to nicorandil. Arterial pressure was maintained at control values by partial thoracic aortic constriction throughout experimentation. Arterial blood gases were maintained within a physiologic range throughout experimentation (*p*H 7.35–7.41; pCO_2, 27–35 mmHg; pO_2, 80–250 mmHg).

Statistical Analysis

Statistical analysis of data within and between groups during baseline conditions and during administration of vehicle, glyburide, sevoflurane, or nicorandil was performed with multiple analysis of variance for repeated measures followed by application of Student's *t* test with Duncan's correction for multiplicity. Changes within and between groups were considered statistically significant when the probability value was <0.05. All data are expressed as mean ± SEM.

Results

Fifty-three dogs were instrumented with ameroid constrictors to obtain 36 successful experiments. Six dogs died after implantation of the ameroid constrictors during coronary collateral development. The LAD cannulation was unsuccessful in 11 dogs that survived placement of the ameroid constrictor.

Effects of Nicorandil in Vehicle-pretreated Dogs

Drug vehicle caused no systemic or coronary hemodynamic effects (fig. 2 and table 1). Administration of nicorandil in vehicle-pretreated dogs (table 1) significantly ($P < 0.05$) decreased heart rate during maintenance of constant arterial pressure (aortic snare). Large coronary collateral (retrograde) blood flow and conductance were unchanged (fig. 3). In contrast to findings in large collaterals, nicorandil caused dose-dependent increases in small coronary collateral blood flow (LAD tissue flow measured during diversion of retrograde flow) and conductance (fig. 4). In addition, nicorandil profoundly increased LCCA tissue flow and conductance in a dose-dependent fashion (fig. 5). There were no changes in endo/epi blood flow within or between any experimental groups.

Effects of Nicorandil in Glyburide-pretreated Dogs

Glyburide caused no systemic or coronary hemodynamic effects (fig. 2 and table 2). In contrast to vehicle-pretreated dogs, administration of nicorandil to glyburide-pretreated dogs (table 2) did not alter heart rate. Increases in small collateral and LCCA blood flow and conductance (figs. 4 and 5) produced by nicorandil were significantly attenuated by glyburide.

Table 1. Hemodynamic Effects of Drug Vehicle and Nicorandil

			Nicorandil ($\mu g \cdot min^{-1}$)		
	Baseline	Vehicle	25	50	100
HR (bpm)	156 ± 7	147 ± 7	151 ± 7	140 ± 7*	140 ± 6*,‡
MAP (mmHg)	89 ± 3	88 ± 4	90 ± 4	88 ± 4	91 ± 4
LVSP (mmHg)	97 ± 4	98 ± 5	101 ± 6	101 ± 5	104 ± 5*,†
LVEDP (mmHg)	5 ± 1	6 ± 1	7 ± 1	7 ± 2	7 ± 1
RF ($ml \cdot min^{-1}$)	40 ± 9	41 ± 9	43 ± 9	42 ± 8	41 ± 8
LCCA CBF ($ml \cdot min^{-1}$)	42 ± 9	46 ± 10	55 ± 9*,†	58 ± 9*,†	61 ± 9*,†
LAD tissue flow ($ml \cdot min^{-1} \cdot g^{-1}$)	0.53 ± 0.11	0.47 ± 0.04	0.79 ± 0.28	—	1.00 ± 0.22*,†
LCCA tissue flow ($ml \cdot min^{-1} \cdot g^{-1}$)	0.79 ± 0.04	0.97 ± 0.08	1.21 ± 0.16*	—	1.96 ± 0.24*,†,‡

Data are mean ± SEM; n = 10.

HR = heart rate; MAP = mean aortic pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; RF = retrograde coronary collateral blood flow; LAD and LCCA = left anterior descending and left circumflex coronary artery, respectively; CBF = coronary blood flow.

* Significantly ($P < 0.05$) different from baseline.

† Significantly ($P < 0.05$) different from vehicle alone.

‡ Significantly ($P < 0.05$) different from nicorandil 25 $\mu g \cdot min^{-1}$.

Effects of Sevoflurane in the Absence or Presence of Glyburide

Sevoflurane decreased heart rate and increased LV end-diastolic pressure (table 3) during maintenance of constant arterial pressure in the absence or presence of glyburide (table 4). Large coronary collateral blood flow (fig. 2) was increased by sevoflurane, but small collateral and LCCA blood flows (table 3) and conductances (figs. 4 and 5) remained unchanged in vehicle-pretreated dogs. After pretreatment with glyburide, sevoflurane increased blood flow through large (fig. 2) and small coronary collaterals and increased large (fig. 3) and small (fig. 4) collateral conductance. Despite K_{ATP} channel blockade, increases in collateral blood flow during sevoflurane also were accompanied by unchanged LCCA tissue flow and conductance (fig. 5), demonstrating the selective effect of sevoflurane on coronary collateral blood flow.

Effects of Nicorandil in Sevoflurane-anesthetized Dogs in the Absence or Presence of Glyburide

In the presence of sevoflurane, nicorandil caused dose-dependent increases in LCCA blood flow and conductance (fig. 5). The highest dose of nicorandil (100 μg/min) increased large collateral conductance in the presence but not in the absence of sevoflurane (fig. 3). In addition, low doses of nicorandil increased small collateral blood flow and conductance (fig. 4), but high doses decreased small collateral flow. In the presence of glyburide and sevoflurane, administration of nicorandil caused no further increases in collateral blood flow beyond that caused by sevoflurane alone.

Discussion

Vasomotor responses remain intact in preexisting[18] or newly developed[19] coronary collateral vessels. Study of the vascular reactivity of coronary collaterals is facilitated by division of collateral blood flow into two separate components. Blood flow through large collaterals is typically measured with retrograde blood flow diverted from the distal segment of an occluded coronary artery. In contrast, blood flow through small coronary collaterals is quantified with radioactive microspheres during diversion of retrograde flow.[18,20] These techniques were used in the current investigation to examine the effects of sevoflurane on the components of coronary collateral blood flow and to determine whether K_{ATP} channel activation by this volatile anesthetic agent mediates coronary collateral vasodilation *in vivo*. The current results demonstrate that sevoflurane selectively increases large and small coronary collateral blood flow independent of K_{ATP} channel activation. Sevoflurane had no effect on blood flow to the normal LCCA zone but significantly increased retrograde blood flow (+38%) and small coronary collateral conductance (+70%) in the presence of the K_{ATP} channel antagonist, glyburide. Sevoflurane also increased retrograde blood flow in vehicle-pretreated dogs. Because of the variability of collateral flow present at baseline among individual dogs, however, this increase in collateral blood flow was statistically significant only after the data were normalized to baseline flow. Increases in LAD retrograde flow observed during administration of sevoflurane were similar to those previously described during intracoronary administration of nitro-

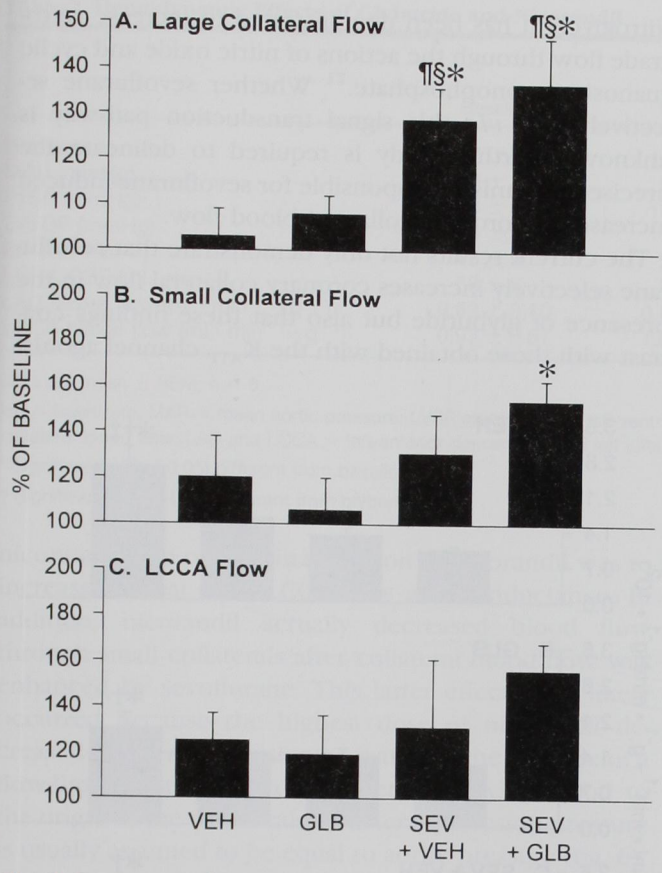

Fig. 2. Coronary collateral and left circumflex coronary artery (LCCA) blood flow (expressed as percent of baseline) in dogs receiving vehicle (VEH) or glyburide (GLB) in the presence or absence of sevoflurane (SEV). Sevoflurane increased large collateral (retrograde) (*A*) and small collateral (tissue) blood flow (*B*) in the presence of glyburide. (*C*) Sevoflurane did not alter LCCA blood flow. These findings demonstrate that sevoflurane selectively dilates coronary collaterals independent of K_{ATP} channel activation. * Significantly ($P < 0.05$) different from baseline; § significantly ($P < 0.05$) different from vehicle alone; ¶significantly ($P < 0.05$) different from glyburide alone.

glycerin (+28–38%).[18,21] In contrast, the K_{ATP} channel agonist nicorandil alone had no effect on large collateral retrograde flow but caused pronounced increases (+148%) in LCCA normal zone perfusion concomitant with increases (+89%) in small collateral blood flow to the LAD zone.

The current results confirm and extend our previous findings of increased coronary collateral blood flow during sevoflurane-induced anesthesia in a canine model of multivessel coronary artery disease.[5] In contrast to sevoflurane, isoflurane[22] or desflurane[23] did not alter collateral blood flow when arterial pressure was held constant. In another experimental model, desflurane, but not isoflurane or halothane, decreased retrograde coronary collateral blood flow after antegrade embolization of the LAD bed.[24] Therefore, sevoflurane-induced increases in coronary collateral blood flow distinguish this agent from other volatile anesthetic agents. The mechanism by which sevoflurane selectively increases coronary collateral flow is unclear. Activation of K_{ATP} channels has been strongly implicated as a major mechanism responsible for coronary vasodilation during isoflurane-,[7,8] halothane-,[6,7] and enflurane-induced[7] anesthesia. The current investigation, however, demonstrates that increases in coronary collateral blood flow by sevoflurane occur independently of K_{ATP} channels. Ni-

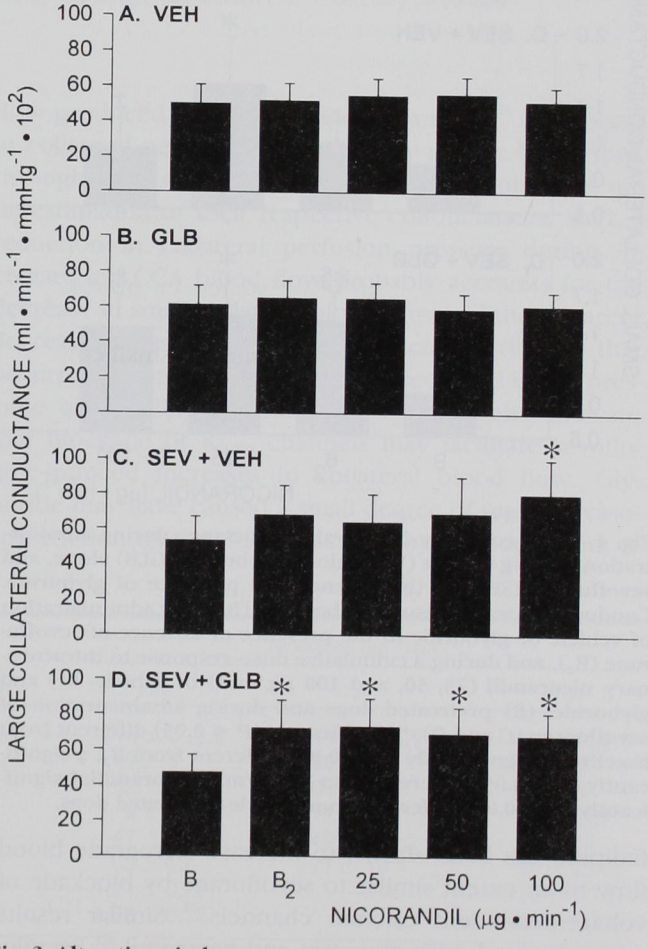

Fig. 3. Alterations in large coronary collateral conductance during administration of vehicle (VEH) alone, glyburide (GLB) alone, and sevoflurane (SEV) in the absence and presence of glyburide. Conductance was measured at baseline (B), after administration of vehicle or glyburide in the presence or absence of sevoflurane (B_2), and during a cumulative dose–response to nicorandil (25, 50, and 100 µg/min) in vehicle- (*A*) and glyburide- (*B*) pretreated dogs and during administration of sevoflurane (*C* and *D*). * Significantly ($P < 0.05$) different from baseline.

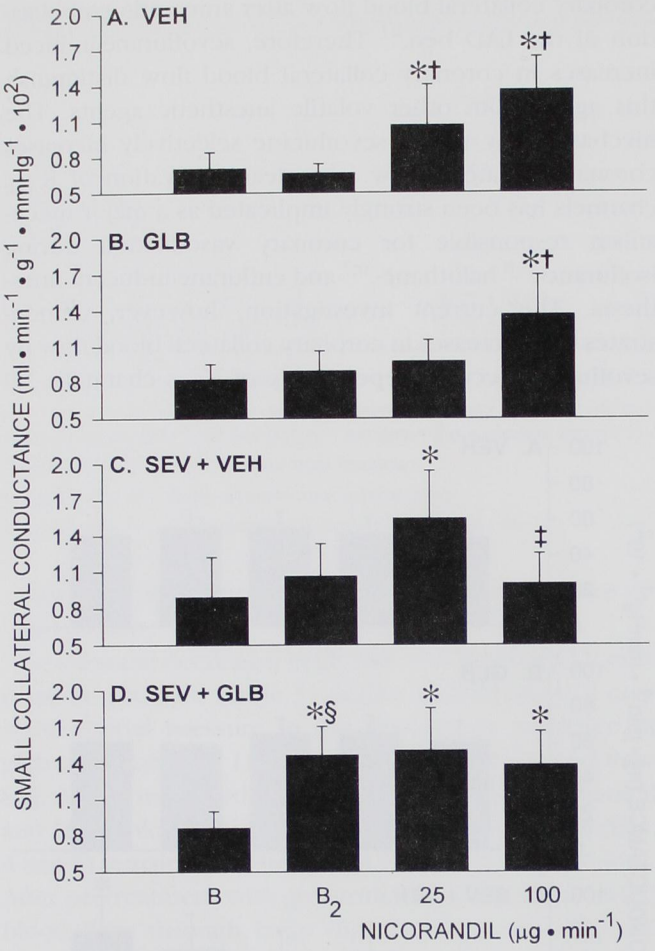

Fig. 4. Small coronary collateral conductance during administration of drug vehicle (VEH) alone, glyburide (GLB) alone, and sevoflurane (SEV) in the absence and presence of glyburide. Conductance was measured at baseline (B), after administration of vehicle or glyburide in the presence or absence of sevoflurane (B_2), and during a cumulative dose–response to intracoronary nicorandil (25, 50, and 100 μg/min) in vehicle- (*A*) and glyburide- (*B*) pretreated dogs and during administration of sevoflurane (*C* and *D*). * Significantly ($P < 0.05$) different from baseline; † significantly ($P < 0.05$) different from B_2; ‡ significantly ($P < 0.05$) different from 25 μg/min nicorandil; § significantly ($P < 0.05$) different from vehicle-pretreated dogs.

fedipine has been shown to increase retrograde blood flow to an extent similar to sevoflurane by blockade of voltage-dependent calcium channels.[21] Similar results were obtained with diltiazem and verapamil.[25] Sevoflurane also decreases calcium current in guinea pig myocytes,[26] suggesting that this agent may cause coronary collateral vasodilation by a calcium antagonist–like mechanism. Conversely, other volatile anesthetic agents also inhibit myocardial L-type calcium channels to varying degrees,[27] yet these agents do not increase retrograde blood flow in a similar experimental preparation. Nitroglycerin has been demonstrated to increase retrograde flow through the actions of nitric oxide and cyclic guanosine monophosphate.[21] Whether sevoflurane selectively acts *via* this signal transduction pathway is unknown. Further study is required to delineate the precise mechanisms responsible for sevoflurane-induced increases in coronary collateral blood flow.

The current results not only demonstrate that sevoflurane selectively increases coronary collateral flow in the presence of glyburide but also that these findings contrast with those obtained with the K_{ATP} channel agonist

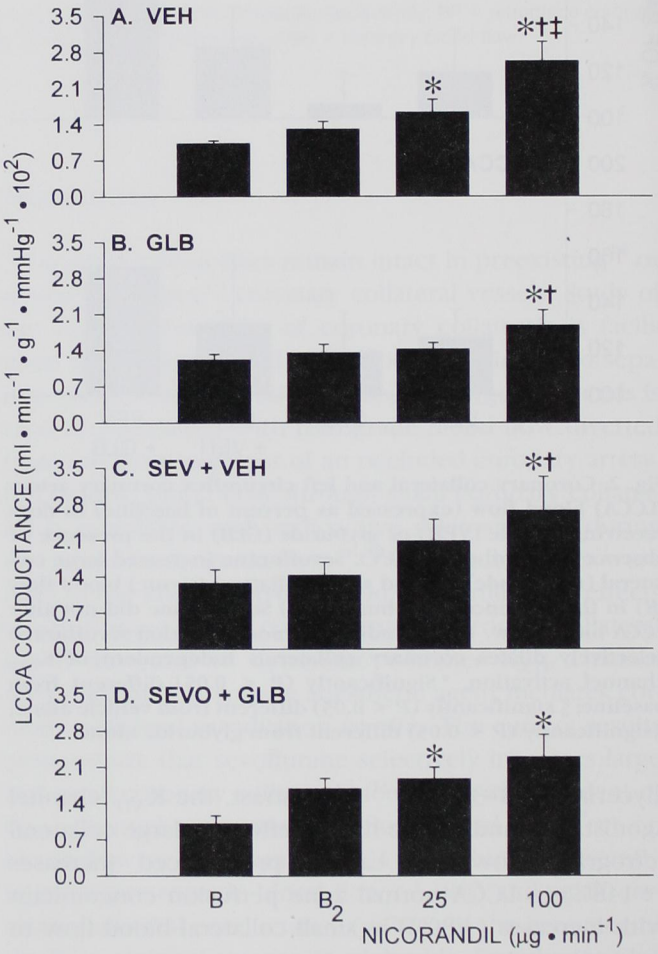

Fig. 5. Left circumflex (LCCA) normal zone conductance during administration of vehicle (VEH) alone, glyburide (GLB) alone, and sevoflurane (SEV) in the absence and presence of glyburide. Conductance was measured at baseline (B), after administration of vehicle or glyburide in the presence or absence of sevoflurane (B_2), and during a cumulative dose–response to nicorandil (25, 50, and 100 μg/min) in vehicle- (*A*) and glyburide- (*B*) pretreated dogs and during administration of sevoflurane (*C* and *D*). * Significantly ($P < 0.05$) different from baseline; † significantly ($P < 0.05$) different from B_2; ‡ significantly ($P < 0.05$) different from 25 μg/min nicorandil.

Table 2. Hemodynamic Effects of Glyburide and Nicorandil

	Baseline	Glyburide	Nicorandil ($\mu g \cdot min^{-1}$)		
			25	50	100
HR (bpm)	157 ± 6	156 ± 5	156 ± 6	153 ± 6	149 ± 7
MAP (mmHg)	89 ± 3	92 ± 3	93 ± 3*	91 ± 3	93 ± 3*
LVSP (mmHg)	98 ± 4	103 ± 4	103 ± 3	99 ± 4	103 ± 3
LVEDP (mmHg)	4 ± 1	4 ± 1	6 ± 1*,†	5 ± 1*,†	6 ± 1*,†
RF ($ml \cdot min^{-1}$)	48 ± 9	51 ± 9	52 ± 8	47 ± 8	47 ± 7
LCCA CBF ($ml \cdot min^{-1}$)	58 ± 5	61 ± 5	67 ± 5	67 ± 6	75 ± 8*,†
LAD tissue flow ($ml \cdot min^{-1} \cdot g^{-1}$)	0.63 ± 0.10	0.69 ± 0.14	0.77 ± 0.13	—	1.01 ± 0.23*,†
LCCA tissue flow ($ml \cdot min^{-1} \cdot g^{-1}$)	0.93 ± 0.07	1.09 ± 0.16	1.14 ± 0.13	—	1.45 ± 0.22*,†

Data are mean ± SEM; n = 8.

HR = heart rate; MAP = mean aortic pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; RF = retrograde coronary collateral blood flow; LAD and LCCA = left anterior descending and left circumflex coronary artery, respectively; CBF = coronary blood flow.

* Significantly ($P < 0.05$) different from baseline.

† Significantly ($P < 0.05$) different from glyburide.

nicorandil. The predominant action of nicorandil was to increase normal zone LCCA flow and conductance. In addition, nicorandil actually decreased blood flow through small collaterals after collateral blood flow was enhanced by sevoflurane. This latter effect most likely occurred because the highest dose of nicorandil decreased collateral perfusion pressure. In the absence of a flow-limiting stenosis in the artery supplying blood to the origin of the collaterals, collateral perfusion pressure is usually assumed to be equal to aortic pressure (fig. 6). A significant reduction in pressure may occur across the proximal LCCA, however, causing a subsequent decrease in perfusion pressure at the origin of the collaterals (fig. 6) during large increases in coronary blood flow produced by K_{ATP} channel activation.[28] A decrease in collateral perfusion pressure may reduce blood flow through large and small collaterals and result in an underestimation of their respective conductances. Such a reduction in collateral perfusion pressure during increases in LCCA blood flow probably accounts for the decrease in small collateral blood flow and the apparent decrease in small collateral conductance (fig. 4) that occurred during administration of nicorandil in the presence of sevoflurane. The current results also indicate that blockade of K_{ATP} channels may facilitate sevoflurane-induced increases in collateral blood flow. Glyburide may have caused a small degree of regional vasoconstriction that was undetectable by measurements of

Table 3. Hemodynamic Effects of Sevoflurane and Nicorandil

	Baseline	Vehicle + Sevoflurane	Nicorandil ($\mu g \cdot min^{-1}$)		
			25	50	100
HR (bpm)	143 ± 9	121 ± 7*,§,¶	116 ± 6*,§,¶	114 ± 7*,§,¶	114 ± 6*,§,¶
MAP (mmHg)	89 ± 4	91 ± 3	89 ± 5	90 ± 3	89 ± 3
LVSP (mmHg)	100 ± 4	103 ± 3	102 ± 6	104 ± 5	103 ± 5
LVEDP (mmHg)	5 ± 1	8 ± 2*	9 ± 2*	11 ± 2*	13 ± 2*,†
RF ($ml \cdot min^{-1}$)	42 ± 11	51 ± 14	47 ± 12	49 ± 15	51 ± 14
LCCA CBF ($ml \cdot min^{-1}$)	48 ± 13	56 ± 10	63 ± 13	71 ± 18	87 ± 25*,†
LAD tissue flow ($ml \cdot min^{-1} \cdot g^{-1}$)	0.64 ± 0.18	0.79 ± 0.19	1.21 ± 0.28*	—	0.72 ± 0.18‡
LCCA tissue flow ($ml \cdot min^{-1} \cdot g^{-1}$)	0.96 ± 0.16	1.08 ± 0.19	1.53 ± 0.32	—	1.63 ± 0.32

Data are mean ± SEM; n = 9.

HR = heart rate; MAP = mean aortic pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; RF = retrograde coronary collateral blood flow; LAD and LCCA = left anterior descending and left circumflex coronary artery, respectively; CBF = coronary blood flow.

* Significantly ($P < 0.05$) different from baseline.

† Significantly ($P < 0.05$) different from vehicle + sevoflurane.

‡ Significantly ($P < 0.05$) different from 25 $\mu g \cdot min^{-1}$ nicorandil.

§ Significantly ($P < 0.05$) different from dogs receiving vehicle and nicorandil (table 1).

¶ Significantly ($P < 0.05$) different from dogs receiving glyburide and nicorandil (table 2).

Table 4. Hemodynamic Effects of Glyburide, Sevoflurane, and Nicorandil

	Baseline	Glyburide + Sevoflurane	Nicorandil ($\mu g \cdot min^{-1}$)		
			25	50	100
HR (bpm)	146 ± 6	111 ± 5*,§,¶	105 ± 3*,§,¶	107 ± 3*,§,¶	104 ± 3*,†,§,¶
MAP (mmHg)	88 ± 4	87 ± 4	89 ± 5	88 ± 5	89 ± 5
LVSP (mmHg)	94 ± 3	97 ± 4	100 ± 5*	99 ± 5	99 ± 4
LVEDP (mmHg)	2 ± 1	8 ± 1*	10 ± 1*,†	9 ± 1*	10 ± 2*,†
RF ($ml \cdot min^{-1}$)	37 ± 8	51 ± 12*	52 ± 11*	50 ± 11*	49 ± 10*
LCCA CBF ($ml \cdot min^{-1}$)	47 ± 7	56 ± 9*	61 ± 10*	64 ± 10*	71 ± 10*
LAD tissue flow ($ml \cdot min^{-1} \cdot g^{-1}$)	0.67 ± 0.11	1.05 ± 0.22§	1.12 ± 0.33*	—	1.06 ± 0.29
LCCA tissue flow ($ml \cdot min^{-1} \cdot g^{-1}$)	0.76 ± 0.11	1.16 ± 0.17	1.32 ± 0.20	—	1.64 ± 0.32*

Data are mean ± SEM; n = 9.

HR = heart rate; MAP = mean aortic pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; RF = retrograde coronary collateral blood flow; LAD and LCCA = left anterior descending and left circumflex coronary artery, respectively; CBF = coronary blood flow.

* Significantly ($P < 0.05$) different from baseline.

† Significantly ($P < 0.05$) different from glyburide + sevoflurane.

‡ Significantly ($P < 0.05$) different from 25 $\mu g \cdot min^{-1}$ nicorandil.

§ Significantly ($P < 0.05$) different from dogs receiving vehicle and nicorandil (table 1).

¶ Significantly ($P < 0.05$) different from dogs receiving glyburide and nicorandil (table 2).

flow or vascular conductance. A small degree of LCCA arteriolar vasoconstriction could unmask the vasodilator actions of sevoflurane on upstream vascular segments such as large coronary collaterals.

The current findings must be interpreted within the constraints of several possible limitations. The effects of sevoflurane on coronary collateral blood flow may not be solely attributable to direct effects on vascular smooth muscle tone. Decreases in inotropic state and heart rate during sevoflurane may have decreased coronary collateral blood flow through effects to decrease myocardial oxygen consumption. Sevoflurane-induced increases in LV end-diastolic pressure also may have altered phasic intramyocardial collateral blood flow.[29]

Changes in retrograde flow are thought primarily to reflect vasomotor changes of the epicardial collateral vessels[18]; however, intramural collateral vessels also may contribute a minor component to retrograde flow.[18,30] Although the precise contribution of each component of collateral flow cannot be determined with certainty, and although collateral blood flow derived from the right coronary artery was not measured specifically, the methods used in this investigation allowed quantification of total collateral flow.[18] Increases in retrograde flow and LAD tissue flow may have occurred not only because of changes in collateral conductance but also in response to increases in proximal LCCA conductance. Increases in proximal LCCA conductance would increase collateral perfusion pressure and therefore be expected to increase LCCA tissue flow. Sevoflurane, however, did not increase LCCA blood flow measured with either microspheres or with a transonic blood flow probe. Therefore, it is unlikely that significant proximal LCCA dilation occurred in response to sevoflurane, findings consistent with a previous investigation.[4] Increases in blood flow to collateral-dependent myocardium (LAD tissue flow) could occur because of increases in small collateral conductance or increases in arteriolar conductance in the collateral-dependent bed. It has been suggested, however, that collateral-dependent vasculature is near maximally dilated during retrograde flow diversion,[18] and therefore, increases in LAD tissue flow during sevoflurane-induced anesthesia were more likely mediated by increases in small collateral conductance.

A single intracoronary dose (50 $\mu g/kg$ over 10 min) of glyburide was used in the current experiments. This dose of glyburide alone had no effect on retrograde flow but substantially attenuated the coronary vasodilator effects of the K_{ATP} channel agonist nicorandil. Profound decreases in retrograde flow were observed in response to higher doses of glyburide (100–200 $\mu g/kg$ over 10 min) during pilot experiments, confirming previous results indicating that glyburide decreases coronary blood flow in a dose-dependent manner.[8,31] Therefore, the dose of glyburide was chosen specifically to block K_{ATP} channels effectively without causing direct coronary vasoconstriction. Additional experiments were performed that confirmed the adequacy of K_{ATP} channel blockade with glyburide during nicorandil administration over the time course of these experiments. Nicorandil increased

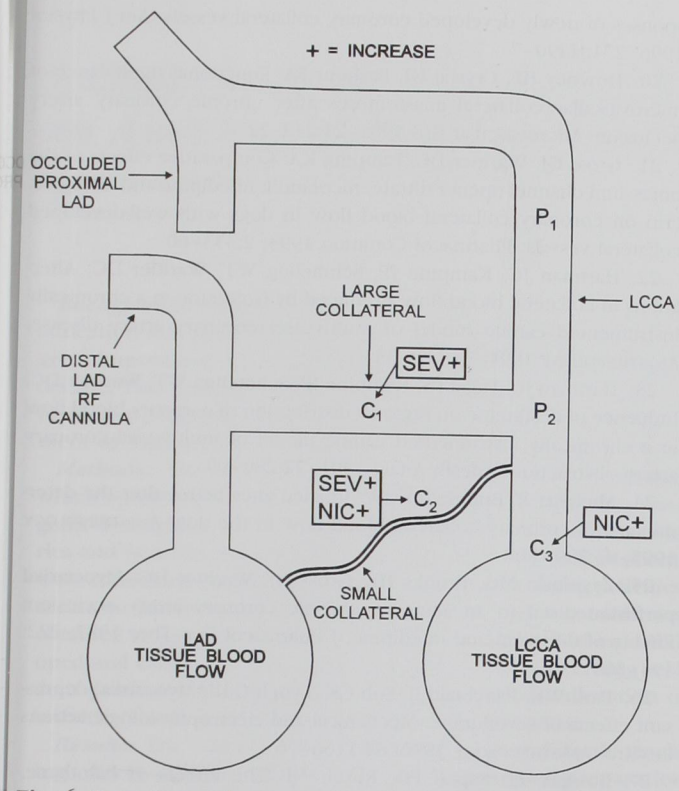

Fig. 6. Experimental preparation illustrating the left anterior descending coronary artery (LAD) occlusion produced with an ameroid constrictor and the position of the LAD retrograde flow (RF) cannula used to measure large coronary collateral blood flow. Coronary collateral conductance was calculated assuming that proximal left circumflex coronary artery (LCCA) perfusion pressure (P_1) was equivalent to aortic pressure and that the proximal LCCA offered no resistance to flow such that P_1 was equal to collateral perfusion pressure (P_2). Increases in large collateral conductance (C_1) occurred in response to sevoflurane (SEV) but not nicorandil (NIC). Sevoflurane and nicorandil increased the conductance of small collaterals (schematically illustrated) or the collateral-dependent bed, denoted collectively as C_2. Nicorandil primarily caused increases in normal zone LCCA conductance (C_3), whereas sevoflurane had no effect. Blood flow through collaterals was limited during high doses of nicorandil because increases in LCCA blood flow caused a pressure drop across the proximal LCCA and decreased collateral perfusion pressure (P_2).

coronary blood flow to 161 ± 5% of baseline in vehicle-pretreated dogs, whereas glyburide blocked these increases, and coronary blood flow increased to only 117 ± 11% of baseline. A single end-tidal concentration (1 MAC) of sevoflurane was chosen because lower anesthetic concentrations were not expected to cause detectable changes in collateral blood flow. Higher concentrations of sevoflurane were not examined because maintenance of arterial pressure at baseline values using partial aortic constriction would have been technically difficult and also may have precipitated excessive increases in LV end-diastolic pressure leading to reductions in coronary perfusion pressure. Nicorandil was used as a positive control because this K_{ATP} channel agonist previously has been shown to increase coronary collateral blood flow.[12] Nicorandil, however, also may dilate large coronary arteries through nitrate effects independent of the K_{ATP} channel.[17] Nonetheless, the doses of nicorandil used in the current investigation produced minimal effects on large coronary collaterals. In contrast, nicorandil dilated the normal arterial vasculature in the LCCA region and small LAD coronary collaterals, actions that were inhibited by glyburide. These findings are consistent with those previously reported,[32] suggesting that nicorandil dilates coronary resistance vessels in normal regions. Finally, coronary conductance was calculated using aortic pressure as an estimate of collateral perfusion pressure. Large and small collateral conductance, however, may have been underestimated during administration of high doses of nicorandil if a reduction in pressure occurred at the origin of the collateral vessels during these experimental conditions.

The current results demonstrate that sevoflurane selectively increases large and small coronary collateral blood flow in the presence of the K_{ATP} channel antagonist, glyburide. In contrast, the K_{ATP} channel agonist, nicorandil, caused vasodilation of the normal LCCA perfusion territory that was attenuated by glyburide. The findings suggest that sevoflurane produces coronary collateral vasodilation independent of K_{ATP} channels.

The authors thank David Schwabe for technical assistance and Angela Barnes for assistance in preparation of this manuscript.

References

1. Larach DR, Schuler HG: Direct vasodilation by sevoflurane, isoflurane, and halothane alters coronary flow reserve in the isolated rat heart. ANESTHESIOLOGY 1991; 75:268–78

2. Conzen PF, Vollmar B, Habazettl H, Frink EJ, Peter K, Messmer K: Systemic and regional hemodynamics of isoflurane and sevoflurane in rats. Anesth Analg 1992; 74:79–88

3. Bernard JM, Wouters PF, Doursout MF, Florence B, Chelly JE, Merin RG: Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. ANESTHESIOLOGY 1990; 72:659–62

4. Hirano M, Fujigaki T, Shibata O, Sumikawa K: A comparison of coronary hemodynamics during isoflurane and sevoflurane anesthesia in dogs. Anesth Analg 1995; 80:651–6

5. Kersten JR, Brayer AP, Pagel PS, Tessmer JP, Warltier DC: Perfusion of ischemic myocardium during anesthesia with sevoflurane. ANESTHESIOLOGY 1994; 81:995–1004

6. Larach DR, Schuler HG: Potassium channel blockade and halo-

thane vasodilation in conducting and resistance coronary arteries. J Pharmacol Exp Ther 1993; 267:72–81

7. Crystal GJ, Gurevicius J, Salem MR, Zhou X: Role of adenosine triphosphate-sensitive potassium channels in coronary vasodilation by halothane, isoflurane, and enflurane. ANESTHESIOLOGY 1997; 86:448–58

8. Cason BA, Shubayev I, Hickey RF: Blockade of adenosine triphosphate-sensitive potassium channels eliminates isoflurane-induced coronary artery vasodilation. ANESTHESIOLOGY 1994; 81:1245–55

9. Sellke FW, Myers PR, Bates JN, Harrison DG: Influence of vessel size on the sensitivity of porcine coronary microvessels to nitroglycerin. Am J Physiol 1990; 258:H515–20

10. Conzen PF, Habazettl H, Vollmar B, Christ M, Baier H, Peter K: Coronary microcirculation during halothane, enflurane, isoflurane, and adenosine in dogs. ANESTHESIOLOGY 1992; 76:261–70

11. Hatano Y, Nakamura K, Yakushiji T, Nishiwada M, Mori K, Anaes FC: Comparison of the direct effects of halothane and isoflurane on large and small coronary arteries isolated from dogs. ANESTHESIOLOGY 1990; 73:513–7

12. Lamping KA, Warltier DC, Hardman HF, Gross GJ: Effects of nicorandil, a new antianginal agent, and nifedipine on collateral blood flow in a chronic coronary occlusion model. J Pharmacol Exp Ther 1984; 229:359–63

13. Kersten JR, Schmeling TJ, Hettrick DA, Pagel PS, Gross GJ, Warltier DC: Mechanism of myocardial protection by isoflurane: Role of adenosine triphosphate-regulated potassium (K_{ATP}) channels. ANESTHESIOLOGY 1996; 85:794–807

14. Gross GJ, Buck JD, Warltier DC, Hardman HF: Separation of overlap and collateral perfusion of ischemic canine myocardium: Important considerations in the analysis of vasodilator-induced coronary steal. J Cardiovasc Pharmacol 1982; 4:254–63

15. Hautamaa PV, Dai XZ, Homans DC, Bache RJ: Vasomotor activity of moderately well-developed canine coronary collateral circulation. Am J Physiol 1989; 256:H890–7

16. Foreman B, Dai XZ, Homans DC, Laxson DD, Bache RJ: Effect of atrial natriuretic peptide on coronary collateral blood flow. Circ Res 1989; 65:1671–8

17. Satoh K, Yamada H, Taira N: Differential antagonism by glibenclamide of the relaxant effects of cromakalim, pinacidil and nicorandil on canine large coronary arteries. Naunyn-Schmiedebergs Arch Pharmacol 1991; 343:76–82

18. Altman J, Dulas D, Pavek T, Laxson DD, Homans DC, Bache RJ: Endothelial function in well-developed canine coronary collateral vessels. Am J Physiol 1993; 264:H567–72

19. Kinn JW, Altman JD, Chang MW, Bache RJ: Vasomotor responses of newly developed coronary collateral vessels. Am J Physiol 1996; 271:H490–7

20. Downey HF, Crystal GJ, Bashour FA: Functional significance of microvascular collateral anastomoses after chronic coronary artery occlusion. Microvascular Res 1981; 21:212–22

21. Gross GJ, Warltier DC, Lamping KA: Comparative effects of the potassium channel opener-nitrate, nicorandil, nifedipine and nitroglycerin on coronary collateral blood flow in dogs with well-developed collateral vessels. Pharmacol Commun 1993; 2:353–60

22. Hartman JC, Kampine JP, Schmeling WT, Warltier DC: Alterations in collateral blood flow produced by isoflurane in a chronically instrumented canine model of multivessel coronary artery disease. ANESTHESIOLOGY 1991; 74:120–33

23. Hartman JC, Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Influence of desflurane on regional distribution of coronary blood flow in a chronically instrumented canine model of multivessel coronary artery obstruction. Anesth Analg 1991; 72:289–99

24. Mignella R, Buffington CW: Inhaled anesthetics alter the determinants of coronary collateral blood flow in the dog. ANESTHESIOLOGY 1995; 83:799–808

25. Zyvoloski MG, Brooks HL, Gross GJ, Warltier DC: Myocardial perfusion distal to an acute or chronic coronary artery occlusion: Effects of diltiazem and nifedipine. J Pharmacol Exp Ther 1982; 222: 494–500

26. Park WK, Pancrazio JJ, Suh CK, Lynch C III: Myocardial depressant effects of sevoflurane: Mechanical and electrophysiologic actions in vitro. ANESTHESIOLOGY 1996; 84:1166–76

27. Bosnjak ZJ, Supan FD, Rusch NJ: The effects of halothane, enflurane, and isoflurane on calcium current in isolated canine ventricular cells. ANESTHESIOLOGY 1991; 74:340–5

28. Gross GJ, Warltier DC: Coronary steal in four models of single or multiple vessel obstruction in dogs. Am J Cardiol 1981; 48:84–92

29. Doyle RL, Foex P, Ryder WA, Jones LA: Effects of halothane on left ventricular relaxation and early diastolic coronary blood flow in the dog. ANESTHESIOLOGY 1989; 70:660–6

30. Scheel KW, Daulat G, Williams SE: Functional anatomical site of intramural collaterals in dogs. Am J Physiol 1990; 259:H706–11

31. Samaha FF, Heineman FW, Ince C, Fleming J, Balaban RS: ATP-sensitive potassium channel is essential to maintain basal coronary vascular tone in vivo. Am J Physiol 1992; 262:C1220–7

32. Yoneyama F, Satoh K, Taira N: Nicorandil increases coronary blood flow predominantly by K-channel opening mechanism. Cardiovasc Drugs Ther 1990; 4:1119–26