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Steal-prone Coronary Circulation in Chronically Instrumented Dogs: Isoflurane versus *Adenosine*

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The influence of isoflurane and adenosine on left ventricular myocardial blood flow was investigated in dogs chronically instrumented for measurement of systemic and coronary hemodynamics, regional myocardial contractile function (with ultrasonic sonomicrometers), and myocardial perfusion (by the radioactive microsphere method). An Ameroid constrictor was implanted on the left circumflex coronary artery to produce a progressive stenosis that gradually reduced vascular reserve of the distal perfusion territory. The depletion of reserve was evaluated by daily monitoring of the hyperemic response to adenosine. A stenosis of moderate severity was considered present when left circumflex reserve was attenuated by approximately 60–70%. During left circumflex stenosis development, the left anterior descending coronary artery was totally occluded for 2 min each hour eight times daily with a hydraulic occluder to stimulate coronary collateral development over a period of 9–13 days. Contractile dysfunction during and flow debt repayment after each brief occlusion were used to monitor coronary collateral development. After stenosis and collateral development had occurred, the left anterior descending coronary artery was permanently occluded to simulate a condition of multivessel coronary artery disease with enhanced collateral development. In separate groups of experiments, hemodynamics and myocardial perfusion were measured before and after administration of adenosine (0.54 and 1.08 mg/min) or isoflurane (1.1 and 1.9%, end-tidal) and in the presence of either agent during adjustment of diastolic aortic pressure and heart rate to control levels. Total left anterior descending coronary artery occlusion in the presence of a moderate left circumflex stenosis produced an increase in mean arterial and left ventricular end diastolic pressures. Isoflurane decreased arterial pressure, left ventricular systolic pressure, and positive rate of increase of left ventricular pressure (dP/dt_{50}) without altering heart rate. Administration of the high concentration of isoflurane reduced blood flow in normal areas and in regions distal to the partial (from 1.05 ± 0.10 to 0.76 ± 0.11 ml·min^{-1}·g^{-1}) or total coronary occlusion (from 0.64 ± 0.10 to 0.41 ± 0.11 ml·min^{-1}·g^{-1}). However, when arterial pressure and heart rate were restored to levels present in the conscious state, perfusion in all zones was maintained at control levels (1.06 ± 0.11 for the stenotic and 0.69 ± 0.12 ml·min^{-1}·g^{-1} for the occluded region). Ratios of transmural blood flow between occluded and normal or occluded and stenotic zones were not different from the conscious state during a constant aortic pressure and heart rate. In contrast, adenosine produced a dose-related reduction in collateral blood flow (from 0.47 ± 0.08 to 0.23 ± 0.08 ml·min^{-1}·g^{-1}) and an occluded-to-normal or occluded-to stenotic zone flow ratio that persisted during control of arterial pressure and heart rate. The current results demonstrate that adenosine but not isoflurane redistributes blood flow away from collateral-dependent myocardium in the presence of a coronary steal-prone anatomy in the chronically instrumented dog. Reductions in myocardial perfusion during isoflurane anesthesia depend on systemic arterial pressure, and isoflurane does not produce coronary steal in this model of multivessel coronary artery disease. (Key words: Anesthetics, volatile: isoflurane. Arteries: coronary. Heart: coronary artery disease; coronary blood flow; coronary hemodynamics; coronary occlusion; coronary steal; myocardial ischemia. Pharmacology: adenosine.)

ADMINISTRATION OF ISOFLURANE to animal models of and humans with coronary artery disease has been suggested to produce a redistribution, or "steal," of coronary blood flow away from collateral-dependent myocardium to other regions.[1–3] Certain vasodilator drugs have also been demonstrated to reduce collateral perfusion by coronary steal in several animal models of coronary artery disease.[4–6] Coronary steal has been defined as an absolute decrease in flow to a collateral-dependent region during an increase in flow to normal myocardium, independent of changes in systemic hemodynamics,[7,8] and has been shown to occur more readily under conditions of multi- rather than single-vessel obstruction.[4,5] Experimental and clinical investigations have documented the importance of the coronary collateral circulation. Myocardial ischemia or infarction may not occur distal to a total coronary artery occlusion if an adequate perfusion through collateral channels is present. Animal models of single or multivessel coronary artery disease have explored the influence of both physiologic stimuli (pacing[9,¶] or exercise[10,11]) and pharmacologic interventions (vasoactive agents[3,9,12–19] or anesthesia [3,19–21,¶,**]) on an augmented collateral vascular

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bed. Human investigations have confirmed that collateral perfusion limits myocardial ischemia,[22] preserves viability of myocardium peripheral to infarction,[23] and positively affects survival after acute coronary occlusion.[24] However, the action of anesthesia on the compromised coronary circulation with enhanced collateral function remains controversial.[3,19–21,¶,**]

The current investigation was designed to evaluate the influence of isoflurane on regional myocardial blood flow in a canine model of multivessel coronary artery disease. The sequential development of a progressive left circumflex coronary artery stenosis was observed by daily measurement of resting flow velocity and pharmacologic coronary vasodilator reserve. Simultaneous with stenosis development, multiple brief occlusions of the left anterior descending coronary artery were performed daily to stimulate coronary collateral development.[25] When the evolving stenosis arrived at a moderate level of constriction, the left anterior descending coronary artery was permanently occluded to create a "coronary steal-prone anatomy"[26] in the conscious state. Isoflurane was then administered as the sole anesthetic to determine the influence of this agent on regional myocardial perfusion. In a separate group of experiments, the coronary vasodilator adenosine was administered to document that coronary steal could occur in this preparation.

Materials and Methods

Surgical Preparation

All experimental procedures and protocols in this investigation were reviewed and approved by the Animal Care Committee of the Medical College of Wisconsin. All conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society and to the Guide for the Care and Use of Laboratory Animals.††

Conditioned mongrel dogs of either sex weighing between 20 and 30 kg were fasted overnight. Anesthesia was induced with sodium thiamylal (10 mg/kg, intravenously [iv]). After intubation of the trachea with a cuffed endotracheal tube, anesthesia was continued with halothane (1.0–1.8%) in 100% oxygen (1 l/min) *via* a ventilator. Under sterile conditions, a thoracotomy was performed in the left fifth intercostal space and the lungs retracted. Heparin-filled catheters were implanted in the thoracic aorta and the right atrial appendage for measurement of arterial pressure and drug administration, respectively. A catheter was positioned in the left atrial appendage and secured by a purse-string suture. This catheter was used for measurement of left atrial pressure, administration of radioactive microspheres for evaluation of regional myocardial blood flow, and injection of adenosine for determination of coronary flow reserve. Distal to the aortic catheter, a balloon-cuff occluder (In Vivo Metric Systems, Healdsburg, CA) was placed around the aorta to facilitate acute elevations in systemic arterial pressure. The heart was suspended in a pericardial cradle, and 1.5–2.0-cm sections of the proximal left anterior descending (distal to the first diagonal branch) and left circumflex coronary arteries (proximal to the first marginal branch) were isolated for instrumentation.

Doppler ultrasonic flow transducers (20-MHz) were placed on each vessel for measurement of phasic and mean coronary blood flow velocity. In addition, distal to the flow transducer, a balloon-cuff vascular occluder (In Vivo Metric Systems) was placed around the left anterior descending coronary artery to facilitate production of acute coronary artery occlusion. An Ameroid constrictor was implanted around the left circumflex coronary artery distal to the flow probe to produce a slowly progressive vascular stenosis. No arterial branches were present between flow transducer and vascular occluder or Ameroid constrictor.

A precalibrated, miniature micromanometer (model P7, Konigsberg Instruments, Pasadena, CA) was inserted in the left ventricular chamber through an incision in the apex and secured for recording of left ventricular pressure. A left ventricular catheter was implanted adjacent to the transducer for subsequent intraarterial infusions of adenosine. The left ventricular micromanometer was cross-calibrated against pressures measured *via* left ventricular, aortic and left atrial fluid-filled catheters (model P50, Statham, Oxnard, CA). The rate of increase of left ventricular pressure at 50 mmHg (positive dP/dt_{50}), an index of global left ventricular contractility, was determined by electronic differentiation of the ventricular pressure waveform. Electrodes were sutured to the right atrial appendage for cardiac pacing. Pairs of miniature ultrasonic length transducers were implanted in subendocardium supplied by the left anterior descending and left circumflex coronary arteries, respectively. All catheters and leads were secured, tunneled subcutaneously, and exteriorized between the scapulae through several small incisions. The chest wall was closed in layers and the pneumothorax evacuated by a chest tube. Each dog was fitted with a jacket (Alice King Chatham, Los Angeles, CA) to prevent damage to the instruments and catheters, which were enclosed in an aluminum box within the jacket pocket. After surgery, each dog was permitted to recover for at least 2 days prior to daily hemodynamic monitoring and was treated with intramuscular analgesics (buprenorphine, 0.02 mg/kg) as needed, procaine penicillin G (400,000 U), and dihydrostreptomycin (560 mg). For

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several days prior to surgery and during the postoperative recovery period, all dogs were trained to stand quietly in a sling to ensure a stable baseline hemodynamic state.

Regional Myocardial Contractile Function

Regional myocardial contractility (segment shortening) was evaluated in the perfusion territories of the left anterior descending and left circumflex coronary arteries by pairs of cylindrical ultrasonic crystals. All signals were simultaneously monitored *via* ultrasonic amplifiers (Crystal Biotech, Holliston, MA). Using left ventricular dP/dt, end-diastolic segment length (EDL) was measured immediately prior to the onset of left ventricular isovolumetric contraction. End-systolic length (ESL) was determined at the time of maximum negative dP/dt. The lengths were normalized according to the method of Theroux *et al.*[27] Percent systolic shortening (%SS) was calculated by the equation: $\%SS = ([EDL - ESL]/EDL) \times 100$.

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.[28] Immediately prior to injection, the sphere suspension was ultrasonicated (model 450, E/MC Corp.) for 15 min and subsequently agitated in a vortex mixer (model 4722, Cole-Parmer) for 5 min. The injection consisted of approximately 2–3 × 10^6 microspheres administered into the left atrium as a bolus over 10 s and flushed in with 10 ml warm (37 °C) sterile saline. A few seconds prior to the microsphere injection, a timed collection of reference arterial flow was initiated (model 1941 precalibrated Harvard infusion/withdrawal pump) from the thoracic aortic catheter and was withdrawn at a constant rate of 7 ml/min for 3 min.

At the conclusion of each experiment, transmural tissue samples were selected for mapping of tissue flow in the myocardium. The samples were extracted from three regions of the left ventricle: 1) the normal zone (myocardium proximal to both the hydraulic occluder and Ameroid constrictor); 2) the stenotic zone (distal to the left circumflex stenosis produced by the Ameroid constrictor); and 3) the occluded zone (distal to the left anterior descending occlusion produced by inflation of the hydraulic occluder). Two dyes (Monastral Blue B suspension; India ink) were injected into the coronary circulation immediately distal to both the hydraulic occluder and the Ameroid constrictor, simultaneously at a pressure of 100 mmHg, to 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 and placed in scintillation vials, and the activity of each isotope was determined. Similarly, the activity of each isotope in the reference blood sample was assessed. Tissue blood flow (Q_m, in milliliters per minute per gram) was calculated from the equation: $Q_m = Q_r/C_r \cdot C_m$, where Q_r = rate of withdrawal (in milliliters per minute) of the reference blood flow sample , C_r = activity (in counts per minute) of the reference blood flow sample, and C_m = activity (in counts per minute per gram) of the myocardial tissue sample.

Experimental Protocol

Starting on the second postoperative day, dogs were monitored daily for coronary hemodynamic changes (recorded by a Sensormedics Polygraph, Anaheim, CA) during the slowly advancing stenosis of the left circumflex coronary artery produced by the Ameroid constrictor. Left anterior descending and left circumflex coronary artery vascular reserves were evaluated by administration of 25-, 50-, and 100-μg bolus injections of adenosine in saline *via* the left atrial catheter. In addition, coronary collaterals were enhanced by multiple, brief (2-min) occlusions of the left anterior descending coronary artery using the previously implanted hydraulic occluder. The brief occlusions were performed once every hour for 8 h, 7 days per week. Systemic hemodynamics, resting coronary blood flow velocity, reactive hyperemia, and regional segment shortening were monitored at these times. Collateral enhancement was functionally indicated by a successive reduction in flow debt repayment as calculated from the postocclusive reactive hyperemic response (debt repayment (%) = 100 × excess reactive hyperemic flow velocity/[resting flow velocity × occlusion duration]) and by diminishing contractile dysfunction (systolic aneurysmal bulging progressively reduced so that systolic shortening was maintained) during coronary occlusion, as demonstrated in a prior investigation from this laboratory.¶ When the left circumflex hyperemic response to 100 μg of adenosine was reduced by more than half of that observed on the second postoperative day, a stenosis of moderate severity was considered to be present. At this time, the left anterior descending coronary artery was totally occluded by inflation of the hydraulic cuff to simulate a coronary steal-prone anatomy. Prior to cuff inflation, all dogs received procainamide hydrochloride (300 mg, iv) and lidocaine hydrochloride (60 mg, iv) to prevent ventricular arrhythmias after occlusion of the left anterior descending coronary artery.

Before experimentation, each dog was fasted, and fluid deficits were replaced with 0.9% normal saline (500 ml). Fluid supplementation was maintained at 3 $ml \cdot {}^{-1}kg \cdot h^{-1}$ for the duration of each experiment. During a stable he-

modynamic state 30 min after left anterior descending coronary occlusion, radioactive microspheres were injected, and conscious, control hemodynamic data were recorded. At this time dogs were randomly assigned to one of two groups and either isoflurane *via* a precision vaporizer (Cyprane, Keighley Yorkshire, UK) or adenosine *via* the left ventricular catheter was administered. Isoflurane anesthesia was induced by inhalation of isoflurane (5%) and oxygen at high flow rates (8 l/min). After tracheal intubation, anesthesia was continued with isoflurane in combination with oxygen (100–250 ml/min) and room air (2 l/min) during positive pressure ventilation using a semiclosed anesthesia circuit. Tidal volume was set at 15 ml/kg, and respiratory rate was adjusted to maintain arterial carbon dioxide tension within the conscious control range. The oxygen flow rate in each experiment was modified to maintain arterial oxygen tension at conscious levels. The effects of two concentrations of isoflurane producing a decrease in arterial pressure of 25–30 mmHg or 30–35 mmHg were studied. In each experiment, the end tidal concentration (range 0.8–1.6%) of isoflurane was altered to produce a decrease in diastolic arterial pressure of approximately 25–30 mmHg. End-tidal gas and anesthetic concentrations sampled from the tip of the endotracheal tube were continuously monitored by a precalibrated mass spectrometer (Marquette Gas Analysis, St. Louis, MO).

The first concentration of isoflurane equilibrated for a period of 30 min to provide a hemodynamic steady state before a second set of radioactive microspheres was administered and arterial blood gas tensions measured. The end-tidal concentration (range 1.5–2.3%) of isoflurane was then changed to produce a 30–35-mmHg decrease in diastolic arterial pressure from conscious levels. The new anesthetic level was allowed to equilibrate for an additional 30 min prior to injection of a third set of microspheres. Arterial blood pressure during the high concentration of isoflurane was then restored to the levels recorded earlier in the conscious state by inflation of the thoracic aorta balloon cuff constrictor. During this procedure, occasionally heart rate was reflexively reduced to levels below the control-state rate. In these instances, heart rate was then returned to control levels *via* atrial pacing with an electronic stimulator (model SD9, Grass, Quincy, MA). A final injection of radioactive microspheres was administered during the high inspired concentration of isoflurane with arterial pressure and heart rate adjusted to control levels.

In a separate group of experiments, the effect of adenosine on regional myocardial blood flow was studied. Adenosine was infused *via* the left ventricular catheter so that small doses could be used and systemic hemodynamic effects minimized. The doses of adenosine to be administered were determined for each dog prior to occlusion of the left anterior descending coronary artery and the initial administration of microspheres during the control state. For each experiment, a low dose (range 0.25–1.0 mg/min) of adenosine was selected, which increased left anterior descending coronary blood flow velocity by approximately 50% and was accompanied by a decrease in diastolic aortic pressure of no more than 10 mmHg. The high dose (range 1.0–2.5 mg/min) of adenosine was selected by increasing the infusion rate until left anterior descending flow velocity was additionally elevated (100% increase from resting levels) and diastolic aortic pressure reduced by 10–20 mmHg.

After the specific doses of adenosine were established for each dog, the left anterior descending coronary artery was totally occluded, and control measurements of hemodynamics and myocardial flow obtained as previously described. The two doses of adenosine were infused, and 15 min after the start of each dose during a hemodynamic steady state, radioactive microspheres were injected. A 15-min recovery period was allowed between the two doses of adenosine. Finally, the high concentration of adenosine was readministered, and heart rate and blood pressure were simultaneously adjusted to control conditions. Diastolic aortic pressure was elevated *via* inflation of the balloon-cuff occluder previously implanted around the thoracic aorta, and when required, heart rate was restored *via* atrial pacing. Radioactive microspheres were again injected during steady-state hemodynamic conditions 15 min after the final adenosine infusion was started.

At the conclusion of each experiment, dogs treated with either isoflurane or adenosine were killed with sodium pentobarbital. The heart was excised, washed with saline, and fixed for 24–48 h in a 10% formaldehyde solution before obtaining specimens for myocardial blood flow analysis.

Statistical Analysis

A total of 22 dogs were used in the current investigation to provide 14 successful experiments for data analysis. Two dogs died immediately after surgery of undetermined causes, and two dogs had ventricular fibrillation on the second postoperative day after the initial brief, 2-min occlusion was performed. Four dogs were excluded because of instrumentation failure.

Coronary flow velocity and segment shortening data collected during development of the left circumflex stenosis and collateral enhancement were analyzed with one-way analysis of variance with repeated measures.[29] Data shown to be different on all postoperative days were compared to postoperative day 2 using Duncan's multiple-range test and were considered significant when $P < 0.05$. Hemodynamic, myocardial blood flow, and contractile

TABLE 1. Coronary Hemodynamic and Regional Contractile Function during Coronary Collateral Development

	Isoflurane Experiments (n = 8)			Adenosine Experiments (n = 6)		
	Day 2	Median Day	Final Day	Day 2	Median Day	Final Day
Stenosis Region (LCCA)						
Resting DBFV (Hz × 10^2)	39 ± 11	46 ± 17	46 ± 14	27 ± 2	33 ± 4	33 ± 4
DBFV during LAD occlusion (Hz × 10^2)	43 ± 14	63 ± 22	62 ± 17	32 ± 2	36 ± 3	38 ± 5
SS during occlusion (%)†	97 ± 7	102 ± 5	121 ± 13*	95 ± 6	105 ± 7	124 ± 12*
Collateral-dependent region (LAD)						
Resting DBFV (Hz × 10^2)	32 ± 3	39 ± 6	41 ± 7	28 ± 3	30 ± 7	33 ± 8
Peak RH DBFV (%)†	227 ± 38	191 ± 27	148 ± 21*	232 ± 36	204 ± 16	163 ± 21*
Flow debt repayment (%)	127 ± 33	76 ± 25*	39 ± 19*	132 ± 30	86 ± 16*	51 ± 17*
RH duration (s)	194 ± 25	170 ± 42	79 ± 28*	141 ± 19	154 ± 21	98 ± 28*
SS during occlusion (%)†	−6 ± 19	30 ± 17	71 ± 12*	1 ± 8	14 ± 13	69 ± 18*

Values are mean ± SEM.
DBFV = diastolic blood flow velocity; RH = reactive hyperemic response after a 2-min LAD occlusion; SS = segment shortening; LAD and LCCA = left anterior descending and left circumflex coronary arteries, respectively.
* Significantly ($P < 0.05$) different from day 2.
† Reported as percent of resting value on that day.

function data collected during each experiment were analyzed in a similar fashion. All data are expressed as mean ± standard error of the mean (SEM).

Results

Augmentation of the Coronary Collateral Circulation

Results at various intervals, during which collateral development was stimulated by repeated 2-min total coronary artery occlusions, are summarized in table 1 and figure 1. Mean ± SEM data are listed for three postoperative intervals: day 2; the median day of monitoring (day 7 ± 1 for isoflurane experiments and day 5 ± 1 for adenosine experiments); and the final day of monitoring (day 13 ± 2 for isoflurane experiments and day 9 ± 1 for adenosine experiments). Few changes in systemic hemodynamics during these periods of coronary constriction were observed. Data acquired on day 2 demonstrate that left anterior descending reactive hyperemic flow and flow debt repayment were large in both experimental groups (table 1). Furthermore, active segment shortening was severely reduced in both groups during the 2-min left anterior descending occlusion, which indicated that coronary collateral blood supply to the ischemic zone was minimal on day 2. The duration of reactive hyperemia, flow debt repayment, and the decrement in segment shortening during a 2-min occlusion were significantly reduced by the final day of monitoring, documenting that

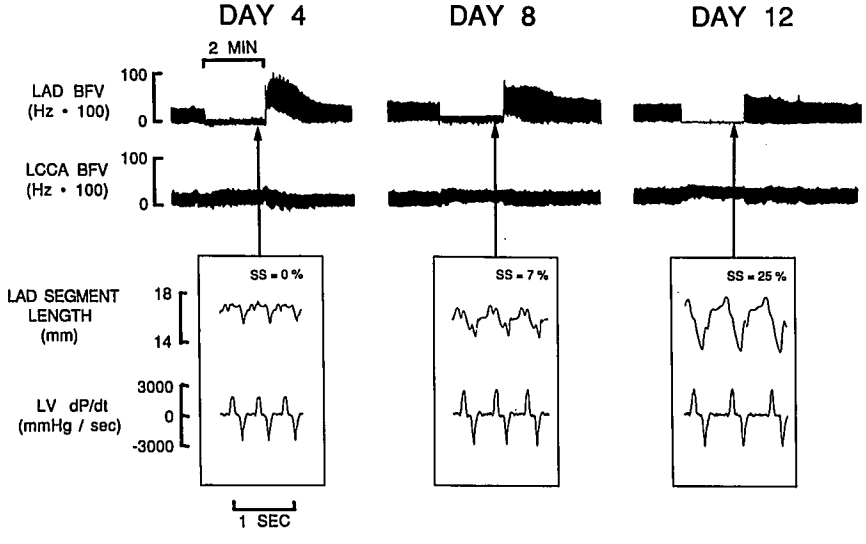

FIG. 1. Left anterior descending and left circumflex coronary artery blood flow velocity (LAD and LCCA BFV, respectively) at days 4, 8, and 12 during collateral development in a representative dog. Reactive hyperemic responses after brief (2-min) total occlusions of the LAD are depicted at each interval. Enclosed in boxes below each day are phasic LAD segment length and left ventricular (LV) dP/dt signals, which were recorded at an accelerated chart speed prior to LAD reperfusion (*arrow*). Reactive hyperemia was minimal by day 12, and LAD percent segment shortening (SS) calculated immediately prior to reperfusion was progressively increased during the 12-day period. Records shown are from the last coronary occlusion performed on the respective day.

TABLE 2. Resting and Adenosine-induced Changes in Diastolic Blood Flow Velocity (DBFV) during LCCA Stenosis Development

	Isoflurane Experiments (n = 8)			Adenosine Experiments (n = 6)		
	Day 2	Median Day	Final Day	Day 2	Median Day	Final Day
LAD DBFV resting (Hz × 10^2)	33 ± 3	41 ± 6	40 ± 5	32 ± 3	33 ± 6	35 ± 8
LCCA DBFV resting (Hz × 10^2)	41 ± 10	50 ± 13	47 ± 13	32 ± 1	34 ± 2	30 ± 3
Peak LAD DBFV after adenosine (100 μg) (% increase)	72 ± 18	60 ± 10	59 ± 12	100 ± 17	95 ± 14	99 ± 19
Peak LCCA DBFV after adenosine (100 μg) (% increase)	97 ± 10	76 ± 10	29 ± 4*	67 ± 13	55 ± 11	28 ± 9*

Values are mean ± SEM.
LAD and LCCA = left anterior descending and left circumflex coronary arteries, respectively.
* Significantly ($P < 0.05$) different from day 2.

collateral development within the left anterior descending perfusion territory had occurred.

Changes in coronary blood flow velocity and segment shortening in the stenosis region supplied by the left circumflex coronary artery are summarized in table 1. Resting left circumflex blood flow velocity was not significantly changed during left anterior descending occlusion over the time course of stenosis and collateral development. Contractile function within the left circumflex stenosis region was improved during the 2-min left anterior descending occlusion by the final day of collateral stimulation in both groups. These changes are further illustrated in figure 1, which in a representative dog depicts typical recordings of phasic coronary blood flow velocities, left anterior descending segment length, and left ventricular dP/dt at three intervals over 12 days during multiple brief left anterior descending coronary occlusions.

PROGRESSIVE STENOSIS DEVELOPMENT

Sequential changes in coronary hemodynamics in both experimental groups of dogs monitored during progressive constriction of the left circumflex coronary artery are summarized for the second, median, and final days of monitoring in table 2 and figure 2. Left atrial bolus injections of adenosine (100 μg), administered daily to establish the degree of reduction in coronary reserve during left circumflex stenosis development, produced minimal changes in arterial pressure and heart rate. During left circumflex stenosis development, no change in resting left circumflex or left anterior descending diastolic blood flow velocities were observed (table 2). Left anterior descending coronary flow reserve as measured by the hyperemic response following injection of adenosine remained unchanged over the time course of left circumflex stenosis development in all dogs. In contrast, left circumflex coronary flow reserve (fig. 2) was significantly ($P < 0.05$) attenuated by the final day of observation, demonstrating that coronary reserve in the Ameroid-constricted vessel was reduced in comparison to reserve of the normal left anterior descending coronary artery.

HEMODYNAMICS AND REGIONAL CONTRACTILE FUNCTION

Systemic and coronary hemodynamic actions of isoflurane (1.1 ± 0.1 and 1.9 ± 0.1%, end-tidal) are sum-

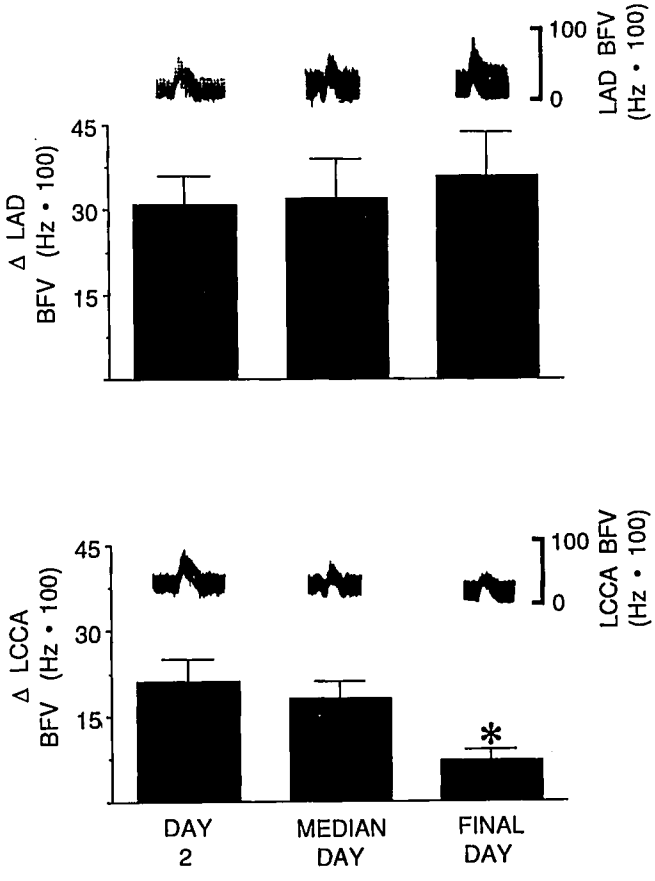

FIG. 2. Phasic blood flow velocity (BFV) during a bolus administration of adenosine (100 μg) in the left anterior descending (LAD) and left circumflex (LCCA) coronary arteries during progressive LCCA stenosis over the second, median, and final days of recording in a representative dog. Below each set of phasic tracings are bar graphs (mean ± SEM) summarizing the changes in LAD (ΔLAD) and LCCA (ΔLCCA) BFV following adenosine for all dogs studied (n = 14). *Significantly ($P < 0.05$) different from day 2.

marized in table 3. Mean arterial and left ventricular end diastolic pressures were elevated after left anterior descending coronary artery occlusion in all dogs, but heart rate, left ventricular systolic pressure, and positive dP/dt_{50} remained unchanged. After left anterior descending coronary occlusion, left circumflex diastolic and mean blood flow velocities and segment shortening in myocardium supplied by either the left circumflex or left anterior descending arteries were also unchanged. The lack of change in contractile function after permanent coronary occlusion documented enhancement of collateral development.

Isoflurane caused concentration-dependent reductions in mean arterial and left ventricular systolic pressures that were not associated with any alteration in heart rate (table 3). Positive dP/dt_{50} was decreased by isoflurane and remained depressed when arterial pressure and heart rate were restored to conscious control levels. Segment shortening in the left circumflex and left anterior descending zones were also significantly reduced during the high concentration of isoflurane and remained decreased upon restoration of systemic hemodynamic conditions (arterial pressure and heart rate). Isoflurane anesthesia did not alter diastolic and mean blood flow velocities in the constricted left circumflex artery. Left ventricular end-diastolic pressure was not changed by isoflurane, but it increased when arterial pressure and heart rate were restored to levels present in the conscious control state.

Systemic and coronary hemodynamic actions of adenosine (0.54 ± 0.10 and 1.08 ± 0.20 mg/min) in dogs having multivessel coronary obstructions and enhanced collaterals are summarized in table 4. As in dogs treated with isoflurane, coronary occlusion caused a significant increase in mean arterial and left ventricular end diastolic pressures during the control state. Heart rate, left ventricular systolic pressure, and positive dP/dt_{50} were unchanged by occlusion of the left anterior descending coronary artery. Subendocardial segment shortening in the left anterior descending and left circumflex zones was unchanged after left anterior descending occlusion. Left circumflex diastolic and mean coronary flow velocities remained unchanged after occlusion of the left anterior descending coronary artery.

Administration of adenosine decreased mean arterial and left ventricular systolic pressures and significantly increased heart rate (table 4). Positive dP/dt_{50}, diastolic and mean blood flow velocity in the stenotic left circumflex artery, and segment shortening in the left circumflex perfusion territory were unaltered by adenosine. In contrast, segment shortening in the left anterior descending collateral-dependent perfusion territory was significantly reduced by adenosine. Left ventricular end diastolic pressure was unchanged by adenosine but was increased when arterial pressure was elevated to control levels by balloon-cuff inflation during administration of the high dose.

Regional Myocardial Perfusion

The regional distribution of coronary blood flow to normal, stenotic, and occluded zones in chronically instrumented dogs is summarized in tables 5 and 6 and figures 3 and 4. In all experiments, myocardial perfusion

TABLE 3. Hemodynamic Effects of Isoflurane

			Isoflurane (%)		
	Preocclusion	Postocclusion	1.1	1.9	(BP) 1.9
Heart rate (beats per min)	106 ± 9	113 ± 9	119 ± 6	108 ± 6	116 ± 8
Mean arterial pressure (mmHg)	96 ± 2*	102 ± 4	75 ± 4*	66 ± 4*	100 ± 3
Left ventricular systolic pressure (mmHg)	123 ± 3	128 ± 5	99 ± 5*	89 ± 5*	117 ± 4
Left ventricular end-diastolic pressure (mmHg)	7 ± 1*	11 ± 1	12 ± 1	14 ± 2	22 ± 2*
$+dP/dt_{50}$ (mmHg/s)	1960 ± 130	1890 ± 170	1520 ± 150*	1170 ± 140*	1170 ± 120*
LCCA diastolic blood flow velocity (Hz × 10^2)	40 ± 9	46 ± 10	43 ± 10	38 ± 10	44 ± 11
LCCA mean blood flow velocity (Hz × 10^2)	26 ± 6	31 ± 6	30 ± 6	26 ± 6	32 ± 7
LCCA segment shortening (%)	14 ± 2	14 ± 2	13 ± 2	10 ± 1*	8 ± 1*
LAD segment shortening (%)	20 ± 2	15 ± 3	10 ± 3	9 ± 3*	6 ± 2*
Arterial *p*H	–	7.42 ± 0.01	7.38 ± 0.02	7.39 ± 0.01	–
Pa_{CO_2}	–	28 ± 2	29 ± 1	30 ± 1	–
Pa_{O_2}	–	82 ± 2	94 ± 4*	93 ± 3*	–

Values are mean ± SEM (n = 8).

LCCA = left circumflex coronary artery; LAD = left anterior descending coronary artery; Pa_{CO_2} = arterial CO_2 tension; Pa_{O_2} = arterial O_2 tension; (BP) = blood pressure and heart rate adjusted to postocclusion levels.

* Significantly ($P < 0.05$) different from postocclusion levels.

TABLE 4. Hemodynamic Effects of Adenosine

	Preocclusion	Postocclusion	Adenosine (mg/min) 0.54	1.08	(BP) 1.08
Heart rate (beats per min)	103 ± 16	129 ± 14	138 ± 8	151 ± 11*	133 ± 10
Mean arterial pressure (mmHg)	94 ± 5*	106 ± 4	96 ± 4*	89 ± 5*	106 ± 3
Left ventricular systolic pressure (mmHg)	122 ± 5	131 ± 5	123 ± 4	116 ± 5*	128 ± 6
Left ventricular end-diastolic pressure (mmHg)	8 ± 1*	13 ± 2	10 ± 2	12 ± 2	19 ± 3*
$+dP/dt_{50}$ (mmHg/s)	2180 ± 250	1960 ± 150	2020 ± 200	2020 ± 170	1850 ± 100
LCCA diastolic blood flow velocity (Hz × 10^2)	29 ± 2	33 ± 4	34 ± 5	33 ± 4	35 ± 5
LCCA mean blood flow velocity (Hz × 10^2)	18 ± 2	24 ± 4	25 ± 4	27 ± 4	28 ± 4
LCCA segment shortening (%)	19 ± 3	18 ± 2	18 ± 2	19 ± 2	16 ± 3
LAD segment shortening (%)	13 ± 5	10 ± 4	4 ± 4*	4 ± 4*	3 ± 3*

Values are mean ± SEM (n = 6).
LCCA = left circumflex coronary artery; LAD = left anterior descending coronary artery; (BP) = blood pressure and heart rate adjusted to postocclusion levels.
* Significantly ($P < 0.05$) different from postocclusion levels.

distal to the total left anterior descending coronary occlusion was reduced as compared to the normal zone (tables 5 and 6) during control conditions. Occluded zone perfusion was 54 ± 8% of that in the corresponding normal region in isoflurane experiments (table 5) and 48 ± 18% of that in the normal zone in adenosine experiments (table 6).

High concentrations (1.9% end-tidal) of isoflurane significantly decreased blood flow to normal, stenotic, and occluded myocardium (table 5). When blood pressure and heart rate were restored to conscious control levels during the high concentration of anesthetic, blood flow was returned to control levels in all regions. Ratios of blood flow between occluded and normal or stenotic zones were unchanged by isoflurane alone (fig. 3). Furthermore, the flow ratios remained unchanged when blood pressure and heart rate were restored to conscious control levels during isoflurane anesthesia.

The effects of adenosine on regional myocardial perfusion in dogs with a left circumflex coronary artery stenosis and total left anterior descending occlusion are summarized in table 6 and figure 4. Adenosine increased blood flow to normal myocardium. Myocardial blood flow increased further when blood pressure and heart rate were restored to control levels. In contrast, adenosine increased perfusion to only the subepicardium distal to the left circumflex stenosis. Adenosine decreased blood flow within subepicardial, midmyocardial, and subendo-

TABLE 5. Effects of Isoflurane on Regional Myocardial Perfusion ($ml \cdot min^{-1} \cdot g^{-1}$)

Region	Control	Isoflurane (%) 1.1	1.9	(BP) 1.9
Normal				
Subepicardium	0.79 ± 0.05	0.83 ± 0.09	0.64 ± 0.10*	0.87 ± 0.08
Midmyocardium	1.22 ± 0.10	1.17 ± 0.11	0.95 ± 0.17*	1.19 ± 0.13
Subendocardium	1.61 ± 0.20	1.32 ± 0.13	0.95 ± 0.19*	1.48 ± 0.14
Transmural	1.21 ± 0.11	1.07 ± 0.10	0.85 ± 0.15*	1.18 ± 0.10
Stenotic				
Subepicardium	0.78 ± 0.08	0.73 ± 0.09	0.58 ± 0.12*	0.84 ± 0.14
Midmyocardium	1.14 ± 0.11	1.11 ± 0.12	0.83 ± 0.11*	1.20 ± 0.13
Subendocardium	1.22 ± 0.12	1.10 ± 0.11	0.78 ± 0.10*	1.13 ± 0.11
Transmural	1.05 ± 0.10	1.01 ± 0.11	0.76 ± 0.11*	1.06 ± 0.11
Occluded				
Subepicardium	0.60 ± 0.09	0.51 ± 0.13	0.40 ± 0.10*	0.67 ± 0.11
Midmyocardium	0.68 ± 0.12	0.53 ± 0.16	0.42 ± 0.11*	0.69 ± 0.15
Subendocardium	0.64 ± 0.12	0.44 ± 0.12	0.32 ± 0.12*	0.70 ± 0.13
Transmural	0.64 ± 0.10	0.50 ± 0.13	0.41 ± 0.11*	0.69 ± 0.12

Values are mean ± SEM (n = 8).
(BP) = diastolic arterial pressure and heart rate returned to control levels.
* Significantly ($P < 0.05$) different from control.

TABLE 6. Effects of Adenosine on Regional Myocardinal Perfusion ($ml \cdot min^{-1} \cdot g^{-1}$)

Region	Control	Adenosine (mg/min)		
		0.54	1.08	(BP) 1.08
Normal				
Subepicardium	1.07 ± 0.23	1.67 ± 0.56	2.26 ± 0.61*	2.81 ± 0.90*
Midmyocardium	1.61 ± 0.31	2.60 ± 0.96	3.27 ± 0.72*	4.79 ± 1.00*
Subendocardium	1.60 ± 0.36	2.54 ± 0.87	2.88 ± 0.61*	4.32 ± 0.83*
Transmural	1.43 ± 0.29	2.27 ± 0.80	2.80 ± 0.64*	3.97 ± 0.87*
Stenotic				
Subepicardium	1.23 ± 0.22	1.45 ± 0.31	1.83 ± 0.38*	2.56 ± 0.55*
Midmyocardium	1.58 ± 0.29	1.67 ± 0.29	1.50 ± 0.11	1.85 ± 0.20
Subendocardium	1.57 ± 0.26	1.45 ± 0.20	1.30 ± 0.18	1.10 ± 0.25
Transmural	1.46 ± 0.25	1.52 ± 0.24	1.54 ± 0.15	1.83 ± 0.23
Occluded				
Subepicardium	0.49 ± 0.05	0.29 ± 0.08*	0.27 ± 0.09*	0.36 ± 0.10
Midmyocardium	0.42 ± 0.12	0.21 ± 0.11*	0.17 ± 0.10*	0.13 ± 0.07*
Subendocardium	0.53 ± 0.10	0.37 ± 0.11*	0.25 ± 0.08*	0.16 ± 0.06*
Transmural	0.47 ± 0.08	0.29 ± 0.09*	0.23 ± 0.08*	0.22 ± 0.07*

Values are mean ± SEM (n = 6).
(BP) = diastolic arterial pressure and heart rate returned to control levels.
* Significantly ($P < 0.05$) different from control.

cardial regions distal to the total occlusion. The reduction in coronary collateral blood flow to the midmyocardium and subendocardium remained present despite control of arterial pressure and heart rate. Ratios of transmural flow between occluded and normal zones or occluded and stenotic zones were reduced by both doses of adenosine, and these reductions were sustained during restoration of blood pressure and heart rate (fig. 4).

Discussion

The action of isoflurane and adenosine on systemic and coronary hemodynamics and regional myocardial perfusion were investigated in a chronically instrumented canine model of multivessel coronary artery disease with an enhanced collateral circulation. The left circumflex coronary artery was progressively narrowed with an Ameroid constrictor and stenosis severity measured by attenuation of coronary vasodilator reserve. Simultaneous with stenosis development, brief multiple occlusions of the left anterior descending coronary artery were performed daily to enhance development of the collateral circulation. When the left circumflex stenosis reached a moderate level of constriction, the left anterior descending coronary artery was permanently occluded to produce a coronary steal-prone anatomy. Isoflurane caused equivalent reductions in regional myocardial blood flow distal to the stenotic and occluded (collateral-dependent) regions during a decrease in aortic pressure. Perfusion of all areas was maintained at conscious levels when arterial pressure and heart rate were restored to control levels during isoflurane. In contrast, adenosine reduced collateral blood flow when systemic hemodynamic conditions were unregulated or adjusted to control levels.

Animals models of coronary artery disease with single[30,31,32,¶,**] or multiple coronary arterial obstructions in serial[32] or parallel[5,9,10,11,20,21,33] arrangements have been used to evaluate the influence of physiologic factors or pharmacologic agents on ischemic myocardium. Several of these studies have documented that as stenosis severity increases, regional coronary vascular reserve is reduced[30–32,¶]; however, contractile function of the respective zone may** or may not[33,¶] be depressed, depending on the adequacy of coronary collateral supply to the affected area. Clinical reports have demonstrated that an augmented coronary collateral circulation can maintain

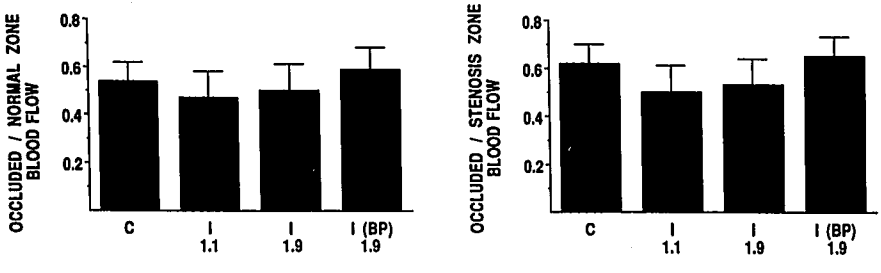

FIG. 3. Ratios of occluded to normal zone or occluded to stenosis zone transmural myocardial blood flow during the control state (C), with two concentrations of isoflurane (I; 1.1 and 1.9%, end tidal), and with blood pressure and heart rate returned to levels present in the conscious state (BP) during the high concentration of isoflurane. *Significantly ($P < 0.05$) different from the control state (mean ± SEM; n = 8).

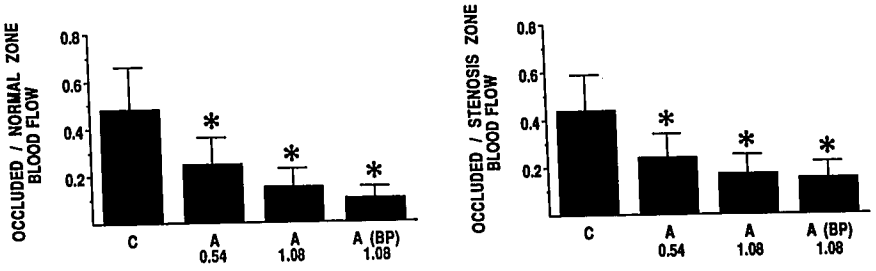

FIG. 4. Ratios of occluded to normal zone or occluded to stenosis zone transmural myocardial blood flow during the control state (C), with two concentrations of adenosine (A; 0.54 and 1.08 mg/min) and with blood pressure and heart rate returned to levels present in the conscious state (BP) during the high concentration of adenosine. *Significantly ($P < 0.05$) different from the control state (mean ± SEM; n = 6).

adequate perfusion of myocardium in the presence of vascular obstruction and may provide vascular reserve in the face of physiologic stress[34] or pharmacologic vasodilation.[35] Schmidt *et al.*[34] atrially paced humans with coronary artery disease and found that a well-developed collateral circulation was capable of increasing flow similar to that observed in normal myocardium. Wolf *et al.*[35] observed increases in collateral blood flow of up to 75% by dipyridamole in patients with a single total coronary artery occlusion. The functional benefits of enhanced coronary collateralization in humans have been correlated with a lower incidence of positive exercise stress tests,[36,37] as well as improved left ventricular function[38] and reductions of infarct size.[3]

Experimental studies have confirmed clinical investigations of the influence of well-developed coronary collaterals on myocardial blood flow and regional contractile function. Development of the collateral circulation has been induced by gradual Ameroid constriction,[3,9,10,12-21,33,39-41] multiple brief occlusions,[25,42-45] and chronic ligation[11] or stenosis[46] of an epicardial coronary artery. In some of these studies, Ameroid constrictors were chronically implanted on a coronary artery to induce collateral development, and an acute experiment requiring additional surgery was performed after a period of weeks to evaluate the action of various vasodilators or anesthetics on regional myocardial blood flow.[3,9,12-21] More recent investigations have periodically monitored systemic and coronary hemodynamics in chronically instrumented animal preparations while utilizing Ameroid[10,39-41] or brief occlusion methods in a single vessel disease model.[25,42-45] These studies were able to evaluate temporal relationships of coronary hemodynamics and contractile function throughout the collateralization process. In the current investigation, multiple brief occlusions of the left anterior descending coronary artery were performed daily to enhance coronary collateral development. Gradual improvement of regional contractile function during periods of brief occlusion and reduction in flow debt repayment during reperfusion provided a functional indication that an alternative vascular source supplied increasing levels of blood flow to collateral-dependent myocardium throughout the series of brief occlusions. Subsequent administration of radioactive microspheres verified that collateral blood flow was increased in this model of multivessel coronary artery disease.

The influence of several coronary vasodilators[13-18,41] and exercise[46,47] on myocardial blood flow has been evaluated in animal models of single-vessel coronary obstruction with well-developed collateral circulations. Administration of nitroglycerin,[13] diltiazem,[15,41] nifedipine,[15] nitrendipine,[16] nicorandil,[17] and atrial natriuretic peptide[18] all have been demonstrated to increase blood flow to collateral-dependent myocardium. In contrast, lidoflazine[14] produced reductions in collateral blood flow. In a chronically instrumented canine model, administration of the volatile anesthetic halothane or isoflurane were shown to maintain myocardial blood flow in collateral-dependent zones when arterial pressure and heart rate were adjusted to control levels.¶ Results of such investigations of the effects of vasodilation on the regional distribution of coronary flow require careful interpretation, since these studies often used models of single-vessel coronary artery disease although clinical data have revealed a high incidence of multivessel obstructions.[26,48] In the presence of multivessel disease, physiologic factors and pharmacologic agents may have different actions than those observed in a single-vessel disease model.

Flameng *et al.*[9] and Schaper *et al.*[12] used a multivessel disease model in which two Ameroid constrictors were implanted on the left circumflex and right coronary arteries. Acute experiments performed four weeks to six months after surgery demonstrated dipyridamole or chromonar to produce coronary steal. Recent studies using Ameroid stimulation of collateral development in a multivessel disease model evaluated the actions of halothane,[3,20,21] isoflurane,[3,21] or adenosine[3,11] on myocardial blood flow. One report suggested that isoflurane and adenosine caused coronary steal,[3] whereas results of another study indicated that isoflurane did not.[21] Halothane was not found to produce any maldistribution of myocardial blood flow.[3,20,21] Results of these reports must be interpreted with caution, since extensive acute surgery was performed[3,21] and basal anesthetics[3,20,21] were used. Anesthetics and thoracotomy have been demonstrated to alter systemic hemodynamics and myocardial blood flow

independent of a compromised coronary circulation.[49] Also, combination of intravenous and volatile anesthetic agents may modify global and regional circulatory control systems[50–52] to a greater extent than any agent alone.

The current investigation used a chronically instrumented canine model in which ongoing constriction of the artery of origin of the collateral vessels (left circumflex coronary artery) *via* an Ameroid constrictor was observed daily until a moderate level of stenosis was attained. Multiple, brief occlusions of the left anterior descending coronary artery were performed daily to augment collateral development simultaneous with stenosis progression. When appropriate left circumflex stenosis severity was present, the left anterior descending coronary artery was totally occluded to complete the model of multivessel coronary artery disease. Neither baseline anesthesia nor acute surgery was performed prior to administration of adenosine or isoflurane, although antiarrhythmic agents were used to prevent development of lethal ventricular arrhythmias after left anterior descending coronary occlusion. The results demonstrate that isoflurane did not redistribute flow from the collateral-dependent zone to either the normal region or to myocardium distal to a moderate coronary artery stenosis. In contrast, infusion of adenosine produced a steal of collateral perfusion and served as a "positive control" verifying the relevance of the preparation. Reductions in blood flow caused by isoflurane were shown to be pressure-dependent. Myocardial perfusion in all regions was restored to conscious control levels when arterial pressure and heart rate were maintained constant. In contrast, the decrease in collateral flow produced by adenosine remained depressed upon adjustment of systemic hemodynamics.

Thus, adenosine redistributed collateral blood to normal regions by a steal mechanism independent of systemic hemodynamic changes. A significant reduction in both the ratios of occluded-to-normal and occluded-to-stenosis zone perfusion during adenosine confirmed that blood flow to collateral-dependent myocardium was decreased at the expense of increased flow to other zones. Concomitant with administration of either isoflurane or adenosine, left ventricular end-diastolic pressure was increased during elevation of arterial pressure by inflation of the hydraulic occluder. This increase in left ventricular end diastolic pressure potentially could have limited subendocardial perfusion, particularly in the collateral-dependent zone; however, blood flow to subendocardium was preserved in all regions during hydraulic occluder inflation in the presence of isoflurane.

The current method of multiple brief occlusions of an epicardial artery to augment coronary collateral function has been described in prior studies using a single-vessel coronary artery disease model.[25,42–45] In none of these previous reports were radioactive microspheres administered to confirm absolute increases of blood flow to collateral-dependent myocardium. Rather, alterations in large epicardial coronary artery blood flow and regional contractile function[25,42–45] as well as electrocardiographic[44] and angiographic[45] changes were used to provide indirect evidence that collateral perfusion was enhanced. In the current investigation, development of the coronary collateral circulation as demonstrated by progressive reduction in flow debt repayment and improvement of regional contractile function during brief occlusion was subsequently verified by measurement of myocardial perfusion by the radioactive microsphere method.

The technique (multiple brief occlusions) used in this preparation to augment collateral development was different from the method (Ameroid constrictor) used by Buffington *et al.*[3] and Cason *et al.*[21] in studies of isoflurane on myocardial blood flow in models of multivessel coronary obstruction. Although the results of the current investigation agree with the conclusion of the latter report[21] in that isoflurane did not cause coronary steal, the results contrast with those of the former study.[3]

The influence of the alternate methods by which the coronary collateral circulation was enhanced on the obtained results is unknown. For example, the relative degree of collateralization to subepicardium *versus* subendocardium in dogs with Ameroid-induced *versus* multiple brief occlusions has not been determined. Investigations have not been conducted to determine whether such collaterals have different sizes, a varying content of vascular smooth muscle, or functional integrity of vascular endothelium, or provide different degrees of collateral reserve or capability of limiting myocardial infarct size during sustained coronary artery occlusion. The current method of induction of collateral growth has the primary limitation of being labor-intensive when compared to Ameroid-induced coronary occlusion. However, because an Ameroid constrictor was used in the current investigation to produce left circumflex coronary artery stenosis, a series of multiple brief occlusions was the only method available to induce collateral growth. Thus, this represents a major difference between the current study and the studies by Buffington *et al.*[3] and Cason *et al.*[21] Furthermore, the total Ameroid-induced occlusion used in these prior studies[3,21] provided a greater degree of collateralization than did multiple brief occlusions in the current investigation. Finally, an additional limitation of the current model in dogs is that isoflurane produced no coronary vasodilation. Coronary steal would not be expected to occur in the absence of coronary vasodilation.

An important factor that determines perfusion of collateral-dependent myocardium is the driving pressure at the origin of the collateral vessels. A stenosis of the artery

of origin of these vessels reduces collateral driving pressure.[30] The potential for coronary steal during isoflurane anesthesia has been suggested because of the coronary vasodilator property of this agent. Vasodilation of small coronary arteries by isoflurane may decrease collateral driving pressure by reducing vascular resistance of non-collateral-dependent myocardium distal to a stenosis.[1] Although pressure distal to the left circumflex stenosis was not measured in this investigation, only at the high concentration did isoflurane produce a moderate reduction in collateral blood flow, which was restored to conscious levels upon restoration of heart rate and systemic arterial pressure. Adenosine decreased collateral blood flow, and that effect was maintained in subendocardial and midmyocardial regions when systemic hemodynamics were adjusted. These results suggest that adenosine but not isoflurane possesses sufficient coronary vasodilator efficacy within the range of concentrations administered to reduce collateral driving pressure and cause coronary steal. This conclusion is in accord with the study of Cason *et al.*,[21] in which no alteration of distal coronary pressure was found during administration of isoflurane while systemic arterial pressure was maintained.

In summary, results of the current investigation indicate that in chronically instrumented dogs with a coronary steal-prone anatomy, isoflurane does not selectively redistribute blood flow away from collateral-dependent myocardium. Reduction of myocardial perfusion during isoflurane anesthesia depended on systemic arterial pressure, and any decrease in coronary collateral blood flow was abolished when pressure was controlled. In contrast, infusion of adenosine caused coronary steal by preferentially shunting blood flow away from the collateral-dependent region, even when arterial pressure was prevented from decreasing.

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