Isoflurane Induces Coronary Steal in a Canine Model of Chronic Coronary Occlusion

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The hypothesis that isoflurane causes coronary steal was investigated in a canine model of chronic coronary occlusion. An aortic constrictor was implanted in dogs to stimulate the development of intercoronary collateral vessels. During an acute experiment 3–4 weeks following implantation, heart rate, mean arterial pressure, and total coronary flow were held constant, and flow distribution was measured with microspheres in the presence and absence of isoflurane. Contractile function of the collateral-dependent zone and myocardial lactate extraction were also measured. Isoflurane produced a decrease in collateral flow and a decrement in collateral zone contraction, while, at the same time, enhancing flow in the normally perfused zone. In a second series of animals, isoflurane was found to have effects similar to those of adenosine, an arteriolar dilator known to produce coronary steal. In contrast, neither halothane nor nitrous oxide caused flow alterations or dysfunction of the collateral-dependent zone. (Key words: Anesthetics, volatile; isoflurane. Complication: coronary steal. Heart: collateral circulation; myocardial ischemia; myocardial function. Heart, blood flow: myocardial.)

THE VOLATILE ANESTHETIC agent isoflurane causes direct coronary vasodilation in humans with coronary artery disease. Myocardial oxygen extraction falls during isoflurane administration, indicating an excess of coronary flow and oxygen delivery over coexisting oxygen demand.1,2 It has been suggested that this direct vasodilation may produce coronary steal in patients with coronary artery disease.1

Coronary steal is defined as an increase in blood flow to an adequately perfused zone of myocardium that occurs at the expense of flow into another (usually ischemic) zone.3 Diversion from the bed of one coronary artery branch to another has been described (intercoronary steal), as well as diversion from the vulnerable subendocardium to the less-vulnerable subepicardium (transmural steal).4,5

Pharmacologic agents that have been shown to produce coronary steal include adenosine,6 diprydamole,7 lidoflazine,8 chromonar,4 and sodium nitroprusside.9 All of these agents reduce arteriolar tone in the artery supplying collateral flow, but have no direct effect on collateral vessel tone. As a result, the pressure at the head of the collateral vessels falls, and collateral flow decreases. In contrast, nitroglycerin dilates collateral vessels without a major effect on arteriolar resistance, and has been shown to increase collateral flow.10 Isoflurane decreases arteriolar resistance,11 but the effect on collateral resistance has not been determined. Depending on the balance of collateral versus arteriolar resistance effects, isoflurane may or may not cause coronary steal.

Unfortunately, current techniques do not permit accurate measurement of regional coronary blood flow in humans, and so an animal model must be used. Dogs develop collateral vessels during chronic coronary occlusion with atherosclerotic constrictors that, at 3–4 weeks, approximate the functional capacity of collaterals found in humans with long-standing coronary disease.12

This report concerns two studies that determined the effects of isoflurane on collateral blood flow and the mechanical and metabolic state of collateral-dependent myocardium in a canine model of chronic coronary occlusion. In the first study, isoflurane was shown, under carefully controlled hemodynamic conditions, to decrease both collateral blood flow and the contraction of the collateral-dependent zone, while, at the same time, increasing flow into normally perfused myocardium. Because this study could not separate a primary effect of isoflurane on flow distribution from a primary effect on function, a second study was performed. Isoflurane was compared, during identical hemodynamic conditions of blood pressure, heart rate, and total coronary flow, with halothane and adenosine. It was reasoned that halothane, an anesthetic with little direct effect on coronary resistance, should produce results similar to isoflurane if myocardial depression secondary to the negative inotropic properties of isoflurane was the primary event. On the other hand, if flow redistribution was responsible, then the results with iso-


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flurane should be comparable to those obtained with adenosine, a coronary arteriolar vasodilator that does not impair mechanical function.

The results suggest that isoflurane more closely resembles adenosine than halothane. Both isoflurane and adenosine produced an increase in flow to normally perfused areas at the expense of flow to the collateral-dependent zone. Significant decreases in the mechanical function of the collateral-dependent zone were also observed. This alteration in function appears to be an indication of worsening myocardial ischemia, because halothane produced neither a flow redistribution nor a decrement in function, despite its negative inotropic effects.

Methods

Surgical Preparation

Mongrel dogs of either sex were anesthetized with amobarbital and halothane and prepared for sterile surgery. The chest was entered through the fifth left intercostal space, and the heart suspended in a pericardial cradle. Formalin was injected into the region of the A-V node to produce a complete block of A-V conduction. A pacemaker lead was sutured to the right ventricle, and the heart was paced with a demand pacemaker during recovery. A leased, 5 mHz piezo-electric crystal was tunneled tangentially down to the subendocardium, and a second crystal was sutured to the epicardium at the location that minimized the distance between crystals (11 dogs). The location of the inner crystal and perpendicular orientation of each set was confirmed at autopsy. In five animals (all in Protocol 1), the second crystal was tunneled to the endocardium for measurement of segment length. Proper orientation of these sets relative to the circumferential fibers was verified at autopsy.

Following crystal placement, the proximal anterior descending artery was dissected free and encased in an atheroid constrictor. The atheroid was 3 mm in diameter and surrounded by a steel band. The lumen size ranged from 1.7–2.3 mm, and was chosen to provide a snug fit. Radioactive microspheres labeled with were injected into the anterior descending artery at the site of the atheroid to mark the area supplied by the vessel.

The pericardium was closed. Wires were tunneled to a subcutaneous pouch on the flank and the chest was closed in layers. The animal received 15 mg of morphine sulfate for postoperative pain relief, and then aspirin (325 mg po) each day during a 3-week recovery. Experimental work conformed to the standards of A.A.A.L.A.C. and the American Physiological Society, and was approved by the Animal Care and Use Committee of the University of Washington.

Experimental Preparation

Sixteen closed-chest dogs were studied 3–5 weeks following surgery when they were afebrile and active. Approximately 1 h after sedation with morphine sulfate (2.5 mg/kg, sc), each dog was anesthetized with an initial injection of a-chloralose (100 mg/kg, iv). Anesthesia was maintained with a continuous infusion of a-chloralose (10 mg·kg⁻¹·h⁻¹, iv) during the experiment. The animals were ventilated with a positive-pressure pump (Harvard®) operating with a 10 cmH₂O end-expiratory pressure (Boehringer®). Oxygen was delivered to a semiclosed circuit containing a soda lime cannister, and arterial blood oxygen tension was between 300 and 450 mmHg throughout the experiment. End-expiratory carbon dioxide was monitored continuously with an infrared device (Beckman® LB-1) and was held between 4.5% and 5% by adjustment of rate of ventilation and tidal volume. Metabolic acidosis caused by chloralose anesthesia was prevented by infusion of 150 mM sodium bicarbonate, 5 mL·kg⁻¹·h⁻¹, iv. Arterial blood was sampled periodically, and pH, PCO₂, and PO₂ were determined (Instrumentation Laboratories, 813). Arterial hemoglobin concentration was determined by use of a CO-oximeter® (Instrumentation Laboratories, 282). Rectal temperature was held at 37°C with a heating pad and temperature controller (Yellow Springs, 73A). Blood coagulation in the extracorporeal circuit was prevented by infusion of sodium heparin (750 U/kg, iv bolus plus 250 U·kg⁻¹·h⁻¹, iv).

Arterial blood pressure was measured with a catheter introduced into the arch of aorta via the right brachial artery. A solid state, catheter-tip transducer (Millar®) introduced via the left carotid artery was used to measure left ventricular pressure. The first derivative of left ventricular pressure with respect to time was derived with an analog circuit (Honeywell Accudata®, 132).

Coronary Perfusion

Blood was supplied to the left coronary artery through a special stainless steel cannula. The cannula was inserted into the ascending aorta via the right carotid artery (fig. 1). A circumferential balloon at the cannula tip was inflated, and the cannula was wedged into the ostium of the left coronary artery. The seal at the tip was tested by two maneuvers. First, flow through the cannula was temporarily stopped. Pressure at the cannula tip fell below 25 mmHg if the seal was complete. Second, coronary perfusion pressure was increased until it was 25 mmHg greater than aortic pressure. A leak was indicated by a large increase in flow measured by the electromagnetic flowmeter.

Blood from a femoral artery was supplied to the cannula by a servo-controlled roller pump (Sarns) that could be operated in constant pressure or a constant flow mode. Coronary pressure was measured at the tip of the cannula.
through a small internal tube. Total flow was measured with an electromagnetic flow meter (Zepeda SWF3rd) that was calibrated by a timed collection of blood following each experiment. The perfusion circuit contained a small mixing chamber and a site for withdrawal of reference samples of microspheres.

**Experimental Protocol 1: Graded Flow Reduction, Isoflurane Only**

Eight animals were studied 3–4 weeks following surgery. This 3–4 week period between ameroid implantation and the experiment allowed complete ameroid closure, so that flow into the region supplied by the constricted artery was completely dependent on collateral circulation from other coronary arteries. Flow into the left main coronary artery was supplied by the cannula and servo-controlled pump, so that total flow could be precisely controlled. Mean arterial pressure was reduced to 60 mmHg by blood withdrawal and held at this level during all measurements by use of a pressurized blood reservoir. Heart rate was held precisely at 100 beats/min by ventricular pacing (Medtronic). Blood pressure and heart rate were precisely controlled and matched during control and isoflurane measurements, so that these major determinants of myocardial oxygen consumption, a primary determinant of coronary resistance, would not influence the results. This hemodynamic control was also used because heart rate has direct effects on collateral perfusion pressure. The level of coronary flow that occurred under these conditions at a constant coronary pressure of 90 mmHg was noted and designated Full flow. The perfusion pump was then switched to a constant flow mode and set to deliver precisely this flow. The regional distribution of coronary flow was measured by injection of a set of radioactive microspheres, and samples of arterial and coronary sinus blood were withdrawn for lactate, hemoglobin, and blood gas measurements.

Total coronary flow was then decreased in a step-wise fashion until contraction of the collateral-dependent zone decreased slightly. Total flow was reduced in order to eliminate vasodilator reserve in the collateral-dependent zone, because pressure dependence is a necessary condition to test the hypothesis that isoflurane causes coronary steal. Flow was held at this Mid flow level for 6–10 min, while a second set of microspheres was injected and arterial and coronary sinus blood samples were drawn. Then total coronary flow was reduced a further 10–20%. Following equilibration period at this Low flow, a third set of measurement was made.

The perfusion system was set to constant pressure at 90 mmHg to insure sufficient coronary flow, and isoflurane 1.2–1.5% was added to the inspired oxygen supply. Following a 20–25 min equilibration period, mean arterial pressure was again set to 60 mmHg. Total coronary flow was sequentially adjusted to Full, Mid, and Low flow, and flow distribution and lactate measurements made at each flow level following a 6–10 min equilibration period.

This sequence was used in four animals. In four others, isoflurane was administered following determination of Full flow level. Equilibration with isoflurane was done at constant pressure, and then flow was fixed at the Full level. Mid and Low flow levels were determined during isoflurane anesthesia in the same manner as when control measurements were made first. Following a 20–25 min period of oxygen breathing through a non-rebreathing system, control measurements were made at identical flow levels. The sequence—isodeflurane first or control first—was randomized.
At the end of the experiment, each animal was killed with an injection of KCl, and the heart was removed. The right ventricle, great vessels, and atria were excised. The remainder was weighed, and this weight was used to normalize the electromagnetic flow measurements. Occlusion of the LAD was confirmed by inspection and by attempting to pass a 0.5 mm probe through the am eroid constrictor.

**Experimental Protocol 2: Agent Comparison**

Eight additional animals were studied to compare the effects of isoflurane with those of halothane, adenosine, and nitrous oxide. Animals were prepared in an identical fashion to those in Protocol 1. Mean arterial pressure was held constant at 60 mmHg, and heart rate at 100 beats/ min, during all measurements.

The strategy of Protocol 2 was to compare the effects of these agents at the critical Mid flow range. This range was chosen because flow into the collateral-dependent zone was pressure-dependent (as reflected by a slight decrement in regional contraction), yet the normal zone was capable of further vasodilation. In addition, marked alterations in flow distribution and regional function resulted from isoflurane at this flow level in Protocol 1 (see "Results").

Measurements were made with each agent in each animal during both constant coronary pressure (90 mmHg) and constant coronary flow (Mid range). The constant pressure measurement was designed to show the effects of the agent on total myocardial flow, regional contraction, and myocardial oxygen and lactate metabolism in the absence of flow restriction. Regional flow distribution was not measured at constant coronary pressure because of the limited number of isotopes available. Adenosine, a powerful coronary dilator that has little direct effect on contractility, was titrated to achieve a degree of vasodilation similar to that produced by isoflurane. Halothane, an anesthetic agent that reduces contractility but does not cause significant vasodilation, was administered to reduce contractility to a degree similar to that produced by isoflurane. The effect of nitrous oxide was also studied.

The constant flow measurements were made during an initial control period, and then following equilibration with isoflurane (average 1.46%, end tidal), halothane (average 0.87%, end tidal), adenosine (0.1 mM solution, intracorony infusion), and nitrous oxide (70% in oxygen). Total coronary flow was identical during all conditions in each dog. The order of agents was varied from animal to animal on a predetermined, random basis. Time was allowed for recovery and uptake-elimination of anesthetic agents between measurements. Following these agents, a second set of control measurements was made.

**Microsphere Measurements**

Regional myocardial blood flow was measured with radioactive microspheres. At defined points in the experiment, microspheres (9 ± 1 μm) labeled with 48Sc, 99mTc, 108Ru, 113Sn, 51Cr, and 141Ce were injected into the tubing that supplied blood to the left coronary artery. Approximately 6 × 10⁵ microspheres were injected over a 30–45 s period. The injection site was upstream of a mixing chamber and reference-sample withdrawal port. The mixing chamber was cylindrical in shape, and 1–2 mm larger in all dimensions than the 8-mm fluted magnetic stir bar that was rapidly rotated inside it. The reference sample withdrawal rate was 2.29 ml · min⁻¹. Withdrawal was started 15 s prior to microsphere injection and continued for 1 min after the injection ended. Following the experiment, the left ventricle was placed in a 4% solution of formaldehyde for at least 48 h. The perfusion territory of the anterior descending coronary artery was subdivided into four transmural sections that were, in turn, divided into inner, middle, and outer layers. Epicardial fat and vessels and endocardium were trimmed from the sections before the final division. Similar division of the region in the posterior wall of the heart near the posterior papillary muscle was performed. Each piece was weighed and counted in a well-type NaI Packard scintillation counter. The spectrum from 0.01 to 1.0 Mev was divided into seven regions corresponding to the major peaks of the isotope used. After correction for background counts and Compton scatter from higher energy isotopes, the counts were divided by tissue weight that had been corrected for dehydration in formalin.

Tissue samples containing a uniformly high concentration of 125I (injected as the marker microsphere at surgery) were considered to be in the collateral-dependent zone. Tissue samples in the posterior wall of the heart containing no 125I were considered the normally perfused zone. For each zone, total counts for each isotope was calculated and divided by the total weight of tissue to give regional counts per gram. A collateral: normal flow ratio was computed as the ratio of counts per gram in the collateral-dependent zone divided by counts per gram in the normally perfused zone. The inner: outer blood flow ratio in each region was calculated by dividing the counts per gram in the inner layer by the counts per gram in the outer layer. Blood flow to individual regions was calculated for the results of Protocol 1 using reference sample counts and flow. No reference samples were withdrawn during microsphere injections in Protocol 2.

**Coronary Sinus Blood Lactate**

A Sones catheter (USCI 007538) was advanced into the coronary sinus via the right jugular vein and right atrium with the aid of a fluoroscope. The location of the
catheter tip, measured post-mortem, ranged from 25–60 mm inside the ostium of the coronary sinus. Blood was withdrawn from the coronary sinus catheter slowly to prevent contamination of the coronary sinus sample with blood from the right atrium. Plasma lactate extraction or production across the coronary circulation was determined by measurements of simultaneously drawn arterial and coronary venous samples. Samples were quickly chilled, precipitated with 8% perchloric acid, and centrifuged at 3°C. Lactate concentration was determined photometrically by an enzymatic method. Myocardial lactate extraction was calculated as the arterial-coronary venous concentration difference divided by the arterial concentration, expressed as a percent.

**ANESTHETIC DELIVERY AND ANALYSIS**

Isoflurane was administered from a calibrated Fortec vaporizer. In Protocol 1, an inspired concentration of 1.2–1.5% isoflurane in oxygen was administered for 1 h. In Protocol 2, isoflurane and halothane were administered from calibrated Vermitrol vaporizers. End-tidal gas was sampled from the trachea via a small tube. Duplicate samples were withdrawn at the time of microsphere injection. Anesthetic concentrations were measured using a gas chromatograph. Known concentrations of the agents in oxygen were used to calibrate the chromatograph prior to each determination. End-tidal halothane concentration averaged 0.87 ± 0.12% (SEM), and isoflurane, 1.46 ± 0.07% during Protocol 2. End-tidal isoflurane concentration averaged 0.94 ± 0.08% during Protocol 1. Because of the limited time available for inhaled anesthetic washout, a small amount of the first agent was frequently present during subsequent measurement periods. The end-tidal concentrations ranged from 0.08–0.09% for this contaminant.

Nitrous oxide (71·min⁻¹) and oxygen (31·min⁻¹) were delivered with calibrated flowmeters into the semiclosed circuit for 15 min prior to measurement. Arterial oxygen tension during nitrous oxide administration was always greater than 115 mmHg. No direct measurement of nitrous oxide concentration in the end-tidal gas was made.

**MYOCARDIAL INFARCT STAINING**

Ameroid closure results in myocardial infarction if closure occurs rapidly or collateral vessels are inadequate. The presence of infarction was sought at autopsy by visual inspection of the myocardium perfused by the constricted artery. In addition, thin transmural slices of fresh myocardium were incubated for 10 min in warm triphenyltetrazolium chloride (1.5% solution in 20 mM potassium phosphate buffer). A region of infarction was identified by absence of the brick-red color produced when TTC reacts with vital tissue. None of the animals reported in this study displayed evidence of myocardial infarction. Three animals were excluded on this basis.

**DATA ANALYSIS**

Sonomicrometer and hemodynamic data were recorded on an oscillograph (Gould Brush® 260) at paper speeds of 125 mm/min and 25 mm/sec. The end-diastolic thickness or length was taken just prior to the onset of isovolumic contraction, as indicated by the first derivative of left ventricular pressure. The end-systolic dimension was taken 25 ms prior to peak negative dP/dt. Values for 4–6 contractions were averaged, and systolic contraction was calculated as the difference between end-systolic and end-diastolic dimensions divided by the end-diastolic value, converted to percent. Systolic and diastolic arterial pressures were taken as the average of 6–10 beats. Mean arterial pressure was obtained by electronic averaging. Heart rate was obtained by a cardiotachometer triggered from the arterial pressure signal. Coronary vascular resistance was calculated as the quotient of mean coronary pressure to total coronary flow.

**STATISTICAL ANALYSIS**

The null hypothesis in Protocol 1 that isoflurane causes no intercoronary redistribution of coronary flow was tested by comparing the collateral zone: normal flow ratio during control conditions with the ratio found during isoflurane at each flow level. A paired t test was used, since both measurements were made in the same animal. A probability of less than 0.05 was considered statistically significant. Similarly, paired t tests were used to compare the inner:outer flow ratios, regional contraction, and lactate extraction during control and isoflurane conditions.

The use of both initial and final control measurements in Protocol 2 was designed to take into account the effects of time on the experimental preparation. All dependent and independent variables were compared (initial vs. final control) by paired t tests, and no significant differences were found (P > 0.05). Because of the similarity, initial and final control values were averaged. Pre-planned comparisons between the averaged control values and values obtained with each agent (isoflurane, halothane, adenosine, and nitrous oxide) were carried out using paired t tests. A Bonferroni correction was used. A probability of less than 0.05 was considered significant.

**Results**

**PROTOCOL 1: CONSTANT CORONARY FLOW; GRADED REDUCTIONS**

The autoregulated level of coronary flow, measured at a mean arterial pressure of 60 mmHg and heart rate
### Table 1. Isoflurane only—Constant Coronary Flow—Graded Flow Decreases

<table>
<thead>
<tr>
<th>Flow Range</th>
<th>Coronary Flow (ml \cdot 100g^{-1}) min^{-1}</th>
<th>Full 58 ± 5</th>
<th>Mid 52 ± 5</th>
<th>Low 26 ± 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Isoflurane 0.94%</td>
<td>Control</td>
<td>Isoflurane 0.94%</td>
</tr>
<tr>
<td>Coronary pressure (mmHg)</td>
<td>102 ± 8</td>
<td>66 ± 4†</td>
<td>81 ± 10</td>
<td>55 ± 5</td>
</tr>
<tr>
<td>Coronary resistance mmHg (ml \cdot 100g^{-1}) min^{-1}</td>
<td>2.70 ± 0.17</td>
<td>1.86 ± 0.21†</td>
<td>2.57 ± 0.16</td>
<td>1.84 ± 0.25*</td>
</tr>
<tr>
<td>Coronary sinus Po_{2} (mmHg)</td>
<td>26 ± 1</td>
<td>32 ± 2†</td>
<td>23 ± 1</td>
<td>50 ± 2†</td>
</tr>
<tr>
<td>Systolic contraction, collateral zone (%)</td>
<td>18 ± 6</td>
<td>12 ± 6</td>
<td>12 ± 6</td>
<td>5 ± 6*</td>
</tr>
<tr>
<td>End-diastolic length, collateral zone (mm)</td>
<td>11.1 ± 1.5</td>
<td>12.0 ± 1.6</td>
<td>11.1 ± 1.3</td>
<td>12.7 ± 1.5†</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>59 ± 1</td>
<td>50 ± 1</td>
<td>58 ± 1</td>
<td>58 ± 1</td>
</tr>
<tr>
<td>Collateral:nominal flow ratio</td>
<td>0.75 ± 0.04</td>
<td>0.66 ± 0.07</td>
<td>0.71 ± 0.08</td>
<td>0.48 ± 0.07†</td>
</tr>
<tr>
<td>Inner:outer ratio, collateral zone</td>
<td>1.26 ± 0.09</td>
<td>1.08 ± 0.12</td>
<td>1.24 ± 0.13</td>
<td>0.95 ± 0.13*</td>
</tr>
<tr>
<td>Inner:outer ratio, normal zone</td>
<td>1.31 ± 0.10</td>
<td>1.13 ± 0.13</td>
<td>1.21 ± 0.09</td>
<td>0.92 ± 0.09*</td>
</tr>
<tr>
<td>Left ventricular dp/dt (mmHg \cdot s^{-1})</td>
<td>1107 ± 77</td>
<td>963 ± 72*</td>
<td>1025 ± 58</td>
<td>892 ± 81*</td>
</tr>
<tr>
<td>Arterial lactate concentration (mM \cdot L^{-1})</td>
<td>2.43 ± 0.27</td>
<td>2.12 ± 0.14</td>
<td>2.73 ± 0.30</td>
<td>2.00 ± 0.13</td>
</tr>
<tr>
<td>Myocardial lactate extraction (%)</td>
<td>39 ± 4</td>
<td>40 ± 4</td>
<td>37 ± 4</td>
<td>35 ± 6</td>
</tr>
<tr>
<td>Hemoglobin (g \cdot dl^{-1})</td>
<td>13.5 ± 0.4</td>
<td>14.0 ± 0.4*</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are mean ± 1 SEM; n = 8 unless otherwise noted.  
* P < 0.05, compared with control at same flow level.
† P < 0.01, compared with control at same flow level.

of 100 beats/min, and coronary pressure of 90 mmHg averaged 36 ± 4 ml \cdot min^{-1} \cdot 100 g^{-1} (mean ± 1 SEM). This value was taken as Full flow. The Mid flow range was 30 ± 3 ml/min per 100 g, or 82 ± 2% of Full flow. The Low range flow averaged 24 ± 3 ml/min per 100 g, or 67 ± 2% of Full flow.

Isoflurane (0.94% end tidal) decreased coronary resistance, calculated as the quotient of mean coronary pressure to total coronary flow, at Full and Mid flow range but not at the Low flow range (table 1). Mean arterial blood pressure was not allowed to change during isoflurane, and LV dp/dt, a measure of global ventricular contractile force, was reduced about 15%. These values suggest that myocardial oxygen consumption was similar during control and isoflurane. If anything, oxygen demand and vasodilator influence of metabolism was likely lessened during isoflurane, and cannot account for the observed vasodilation. A net vasodilation with isoflurane was also indicated by increased values for coronary sinus oxygen tension. These increases would likely have been larger if total coronary flow had not been constrained.

Total coronary flow was distributed between the collateral-dependent zone and the normal zone. The collateral:nominal flow ratio was 0.75 under Full flow conditions, indicating that flow to the collateral zone was less than that to the normal zone (fig. 2). The ratio was not significantly changed by isoflurane at Full flow, despite a fall in coronary resistance. This finding suggests that some vasodilator reserve was present in the collateral-dependent zone at Full flow. Elimination of this reserve by lowering total coronary flow to the Mid flow range resulted in uniform vasodilation in both collateral-dependent and normal zones, and the collateral:nominal flow ratio was unchanged from Full flow in the absence of isoflurane. However, the addition of isoflurane at the Mid flow resulted in a fall in collateral:nominal flow ratio from 0.71 ± 0.08 (mean ± SEM) to 0.48 ± 0.07 (P < 0.01) (fig. 2). No intercoronary redistribution with isoflurane was found at the Low flow range, probably because both beds were near maximally vasodilated by the metabolic signal resulting from reduced oxygen delivery.

Isoflurane also caused a shift in the transmural distribution of coronary flow (fig. 3). The inner:outer flow ratio was reduced from 1.24 to 0.93 (P < 0.05) in the collateral-dependent zone, and from 1.21 to 0.92 (P < 0.05) in the normal zone at the Mid flow range by isoflurane. In addition, the inner:outer flow ratio was decreased from 0.95 to 0.77 (P < 0.05) in the normally perfused zone at the

![Isoflurane Graph](https://via.placeholder.com/150)

**Fig. 2.** In Protocol 1, at constant coronary flow, isoflurane decreased flow to the collateral-dependent myocardium and increased flow to the normally perfused myocardium at the Mid flow range. As a result, the collateral:nominal flow ratio was significantly reduced. No effect was seen at the Full flow range, probably because the collateral-dependent circulation had a modest degree of vasodilator reserve. No effect was seen at the Low flow range, probably because vasodilator reserve in both beds was eliminated by the metabolic signal resulting from underperfusion. Mid flow averaged 82 ± 2%, and Low flow, 67 ± 2% of autoregulated flow (Full flow). Total flow was held constant at each range and was identical during control conditions and in the presence of isoflurane. These data demonstrate that isoflurane alters the intercoronary distribution of blood flow under conditions when oxygen supply is reduced relative to oxygen demand.
ISOFLURANE

Fig. 3. Isoflurane significantly decreased the inner:outer flow ratio in both the collateral-dependent and normally perfused zone at the Mid flow range. The ratio was also reduced in the normal zone at the Low flow. These data indicate that isoflurane alters the transmural distribution of flow when total flow is restricted. The data are from eight dogs in Protocol 1.

Low flow by isoflurane. The changes in regional blood flow are shown in figure 4. No tests for statistical significance were applied to these flow data, since ratios were used to test the intercoronary and transmural redistribution hypotheses.

The second purpose of Protocol 1 was to determine if an isoflurane-induced redistribution of coronary flow could cause or worsen myocardial ischemia. Regional contraction during systole was used to test this hypothesis. Significant changes caused by isoflurane were observed only at the Mid flow range (table 1); systolic contraction decreased to about 50% of the value observed without isoflurane in the collateral-dependent zone (P < 0.05). An increase in end-diastolic length occurred during isoflurane at the Mid flow range. However this increase in length cannot account for the decrease in systolic contraction observed. Metabolic evidence of myocardial ischemia was not found; myocardial lactate extraction was virtually identical during control and isoflurane at the Mid flow range (table 1).

Protocol 2: Agent Comparison, Constant Coronary Pressure

The aim of Protocol 2 was to compare isoflurane with halothane, adenosine, and nitrous oxide at constant coronary flow (Mid range). The strategy of the experiment was to match the negative inotropic effect of isoflurane with that of halothane, and the vasodilatory effect of isoflurane with that of adenosine. Prior to flow reduction, a set of measurements was made at constant coronary pressure to determine the effects of the agents independent of ischemia.

At a constant coronary pressure (90 mmHg; table 2), administration of halothane (0.87%, end-tidal) did not change coronary flow or calculated coronary resistance significantly. With halothane, there was a significant increase in coronary sinus blood oxygen tension, indicating that flow was in excess of metabolic requirements. The 20% fall in left ventricular dP/dt at constant heart rate and mean arterial pressure suggests that myocardial oxygen consumption was probably lower during halothane than during control.

Isoflurane (1.47%, end-tidal) significantly increased coronary flow, reduced coronary resistance (average 37% decrease), and resulted in a large increase in coronary sinus blood oxygen tension. Left ventricular dP/dt decreased 14% to a level that was not statistically different from halothane. Since blood pressure, heart rate, and dP/dt were virtually identical during the administration of these two anesthetics, myocardial oxygen demand was probably similar as well.

Intracoronary adenosine infusion resulted in a doubling of coronary flow and an average 52% decrease in coronary resistance from control. Despite the relatively greater increase in coronary flow produced by adenosine, the coronary sinus blood oxygen tension was similar during isoflurane and adenosine. A possible explanation for this result is that myocardial oxygen consumption was greater during adenosine infusion than during isoflurane. Differences in regional systolic contraction and left ventricular dP/dt support this contention. The relatively higher LV
dP/dt and systolic contraction during adenosine may also result from an unloading effect secondary to an action of adenosine on the systemic circulation. While isoflurane also decreases systemic resistance, the effect on contraction may have been balanced by the negative inotropic effect of this agent. Myocardial lactate extraction, expressed as a percent of delivery, was decreased by adenosine. Rather than reflecting myocardial ischemia, this finding probably results from increased coronary blood flow and relatively constant myocardial lactate uptake.

Nitrous oxide (70% inspired in oxygen) did not change coronary flow, coronary sinus blood oxygen tension, myocardial lactate extraction, or myocardial contraction.

**Protocol 2: Agent Comparison, Constant Coronary Flow**

Total coronary flow was reduced from 47 ± 3 to 35 ± 3 ml·100 g⁻¹·min⁻¹ (a 28% decrease), and held constant during all measurements. This flow reduction, by design, reduced systolic thickening in the collateral-dependent zone from 28 ± 4 to 16 ± 5%. The collateral: normal flow ratio was 0.77 under these conditions, a value remarkably similar to that obtained in Protocol 1 (Table 1).

Halothane administration was associated with a small increase in coronary sinus blood oxygen tension. This change indicates a direct effect on coronary vessels that was likely balanced by a reduction in oxygen demand, because coronary pressure and calculated coronary resistance did not change. Halothane was not, however, associated with a significant alteration in either the inter-

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**Table 2. Agent Comparison—Constant Coronary Pressure = 90 mmHg**

<table>
<thead>
<tr>
<th></th>
<th>Control, n = 8</th>
<th>Halothane 0.87%, n = 8</th>
<th>Isoflurane 1.65%, n = 8</th>
<th>Adenosine, n = 8</th>
<th>Nitrous oxide 70%, n = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary flow (ml·100 g⁻¹·min⁻¹)</td>
<td>47 ± 3</td>
<td>55 ± 5</td>
<td>84 ± 10†</td>
<td>104 ± 12‡</td>
<td>52 ± 5</td>
</tr>
<tr>
<td>Coronary resistance mmHg(·100 g⁻¹·min⁻¹)</td>
<td>1.97 ± 0.13</td>
<td>1.75 ± 0.15</td>
<td>1.24 ± 0.22†</td>
<td>0.95 ± 0.12‡</td>
<td>1.85 ± 0.17</td>
</tr>
<tr>
<td>Coronary sinus blood P₅₀ (mmHg) (n = 6 for all conditions)</td>
<td>26 ± 2</td>
<td>37 ± 2*</td>
<td>49 ± 6‡</td>
<td>44 ± 4‡</td>
<td>26 ± 3</td>
</tr>
<tr>
<td><strong>Systolic thickening collateral zone (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>End-diastolic thickness collateral zone (mm)</td>
<td>28 ± 4</td>
<td>25 ± 4</td>
<td>23 ± 4</td>
<td>35 ± 5*</td>
<td>25 ± 4</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>10.6 ± 1.0</td>
<td>10.4 ± 0.9</td>
<td>10.6 ± 1.0</td>
<td>11.1 ± 0.9*</td>
<td>11.0 ± 1.0</td>
</tr>
<tr>
<td>Left ventricular dP/dt (mmHg·S⁻¹)</td>
<td>60 ± 1</td>
<td>59 ± 1</td>
<td>58 ± 1</td>
<td>59 ± 1</td>
<td>60 ± 1</td>
</tr>
<tr>
<td>Arterial lactate concentration (mM·L⁻¹)</td>
<td>1193 ± 103</td>
<td>953 ± 94‡</td>
<td>1025 ± 74‡</td>
<td>1314 ± 96</td>
<td>1183 ± 74</td>
</tr>
<tr>
<td>Myocardial lactate extraction (%)</td>
<td>3.0 ± 0.4</td>
<td>3.0 ± 0.4</td>
<td>3.0 ± 0.3</td>
<td>3.0 ± 0.5</td>
<td>3.8 ± 0.4</td>
</tr>
<tr>
<td><strong>Values are mean ± 1 SEM.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† P < 0.01, compared to control.  
‡ P < 0.002, compared to control.
TABLE 3. Agent Comparison—Constant Coronary Flow—Mid Range (55 ± 3 [ml·100g⁻¹]·min⁻¹)

<table>
<thead>
<tr>
<th></th>
<th>Control, n = 8</th>
<th>Halothane 0.87%, n = 8</th>
<th>Isoflurane 1.46%, n = 8</th>
<th>Adenosine n = 8</th>
<th>Nitrous Oxide 70%, n = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary pressure (mmHg)</td>
<td>55 ± 6</td>
<td>51 ± 6</td>
<td>41 ± 3*</td>
<td>39 ± 3*</td>
<td>55 ± 8</td>
</tr>
<tr>
<td>Coronary resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmHg([ml·100g⁻¹]·min⁻¹)⁻¹</td>
<td>1.56 ± 0.12</td>
<td>1.45 ± 0.10</td>
<td>1.20 ± 0.10†</td>
<td>1.14 ± 0.12†</td>
<td>1.52 ± 0.21</td>
</tr>
<tr>
<td>Coronary sinus Blood P0₂ (mmHg)</td>
<td>23 ± 2</td>
<td>29 ± 2‡</td>
<td>51 ± 3‡</td>
<td>52 ± 1†</td>
<td>23 ± 1</td>
</tr>
<tr>
<td>Systolic thickening collateral zone (%)</td>
<td>16 ± 5</td>
<td>12 ± 6</td>
<td>9.2 ± 1.0*</td>
<td>10.0 ± 1.0</td>
<td>10.6 ± 1.2</td>
</tr>
<tr>
<td>End-diastolic thickness collateral zone (%)</td>
<td>10.6 ± 1.0</td>
<td>9.9 ± 1.0*</td>
<td>9.2 ± 1.0†</td>
<td>10.0 ± 1.0</td>
<td>10.6 ± 1.2</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>59 ± 1</td>
<td>57 ± 1</td>
<td>56 ± 1</td>
<td>60 ± 1</td>
<td>57 ± 1</td>
</tr>
<tr>
<td>Collatera: normal flow ratio</td>
<td>0.77 ± 0.10</td>
<td>0.71 ± 0.11</td>
<td>0.41 ± 0.09‡</td>
<td>0.48 ± 0.10‡</td>
<td>0.60 ± 0.12</td>
</tr>
<tr>
<td>Inner: outer ratio collateral zone</td>
<td>1.16 ± 0.09</td>
<td>1.15 ± 0.14</td>
<td>0.82 ± 0.08‡</td>
<td>1.39 ± 0.24</td>
<td>1.19 ± 0.12</td>
</tr>
<tr>
<td>Inner: outer ratio normal zone</td>
<td>1.15 ± 0.09</td>
<td>1.10 ± 0.07</td>
<td>0.73 ± 0.05‡</td>
<td>1.08 ± 0.14</td>
<td>0.97 ± 0.13</td>
</tr>
<tr>
<td>Left ventricular DP/ dt (mmHg·S⁻¹)</td>
<td>1174 ± 91</td>
<td>933 ± 93‡</td>
<td>918 ± 94‡</td>
<td>1045 ± 104</td>
<td>1183 ± 116</td>
</tr>
<tr>
<td>Arterial lactate concentration (mM·L⁻¹)</td>
<td>3.0 ± 0.4</td>
<td>2.8 ± 0.4</td>
<td>3.0 ± 0.3</td>
<td>3.2 ± 0.6</td>
<td>4.0 ± 0.4*</td>
</tr>
<tr>
<td>Myocardial lactate extraction (%)</td>
<td>21 ± 6</td>
<td>25 ± 5</td>
<td>18 ± 6</td>
<td>11.6 ± 8*</td>
<td>20 ± 7</td>
</tr>
<tr>
<td>Hemoglobin (g·dl⁻¹)</td>
<td>12.3 ± 1.0</td>
<td>11.9 ± 0.8</td>
<td>12.1 ± 0.8</td>
<td>11.6 ± 0.8</td>
<td>11.4 ± 0.7</td>
</tr>
</tbody>
</table>

Values are mean ± 1 SEM.  
* P < 0.05, compared to control.  
† P < 0.01, compared to control.  
‡ P < 0.002, compared to control.

The hypothesis that vasodilation alone accounts for alterations in collateral: normal flow ratio was examined by plotting the ratio (expressed as the change from control) versus the change in calculated resistance for each condition in each animal. Multiple regression analysis was used (SPSS, version M, Release 9.1) to define the strength of the relationship and to find out if the identity of the individual agents allowed more precise prediction of the results. Analysis demonstrated a significant, positive relationship between change in ratio and change in resistance (r = 0.70, fig. 5). The identity of the agents was not a significant factor, suggesting that the degree of flow redistribution was independent of anesthetic depression.

**Discussion**

The results demonstrate that isoflurane caused both intercoronary and transmural redistribution of coronary blood flow in a canine model of coronary artery occlusion. Regional flow was decreased in the collateral-dependent zone and rose in the normally perfused zone in response to inhalation of isoflurane in oxygen. Furthermore, this redistribution of coronary flow was associated with a decrease in systolic contraction in the collateral-dependent zone. However, the flow redistribution did not result in anerobic metabolism, as assessed by myocardial lactate extraction. The effects of isoflurane in this model were similar to low doses of adenosine, a coronary vasodilator that does not depress the heart. In contrast, neither halothane nor nitrous oxide was associated with flow redistribution or impairment of systolic contraction.

**CRITIQUE OF METHODS**

One methodologic consideration pertinent to interpretation of these results concerns the possibility that blood samples drawn from the coronary sinus may not
have accurately reflected metabolic activity in the collateral-dependent zone. The Sones catheter could be inserted 30–50 mm deep in the coronary sinus, but could not be threaded reliably into the great cardiac vein. The samples drawn through the catheter thus contained a variable mixture of blood from the collateral-dependent zone and from the normal zone. Lactate extraction may be a relatively insensitive indicator of regional myocardial ischemia under these conditions.

A second methodologic concern results from the interdigitation of tissue supplied by the aneurysm-occluded artery and by the surrounding non-occluded vessels. Pieces of tissue considered "collateral-dependent" may, in fact, have contained regions of normally perfused tissue. Thus, flow measurements would represent an averaged value susceptible to bias. Such inclusion is difficult to avoid, even with the technique used in the present experiment of direct injection of a marker microsphere at surgery. However, this effect results in an overestimation of collateral-dependent flow and would bias away from significant findings. In addition, the same pieces of tissue were used for all flow measurements, and so the comparison of agents should not be effected.

A third concern is that slow occlusion of the anterior descending artery (LAD) may have resulted in the development of collateral vessels from the right coronary artery (RCA), as well as from the septal and circumflex branches of the left coronary artery. Since microspheres were injected only into the cannula providing blood to the left main coronary artery, collateral flow from the RCA was not measured. Thus, the measured value probably underestimated true collateral flow. The magnitude of this underestimation is difficult to determine. Scheel et al. have demonstrated that the border between the perfusion territory of the RCA and the LAD is relatively small compared to the border between the LAD and the septal and circumflex branches of the left coronary artery. This finding suggests that collateral development connecting the RCA and LAD is likely to be limited. In addition, Downey estimated that collateral flow from the RCA was less than 8% of the total retrograde flow measured distal to an acute occlusion of the LAD in dogs. However, despite the small border of perfusion territories and the low flow through unstimulated collateral vessels, it is possible that the flow contribution from the RCA may have been substantial following aneurysm closure. This unmeasured flow would help support the functional integrity of the collateral-dependent zone, and may explain why regional contraction was normal, even though the measured collateral-to-normal flow ratio was only 0.70–0.80.

How would such an unmeasured contribution from the RCA affect the results? The unmeasured flow would not likely affect the results demonstrating a redistribution of flow from the left coronary artery during isoflurane administration and adenosine infusion. This unmeasured flow was probably reasonably constant during the measurement periods because mean arterial pressure and heart rate, the dominant determinants of collateral flow, were held constant. In addition, this flow would tend to support metabolism and function in the collateral-dependent zone, and thus cannot account for the observed dysfunction or for the differences between agents.

A fourth concern is that the use of blood withdrawal to adjust arterial pressure may have influenced the results. Mean arterial blood pressure in the absence of isoflurane or halothane ranged from 75–90 mmHg, and 500–800 ml of blood was withdrawn to lower pressure to 60 mmHg for approximately 15 min while measurements were made. Much smaller volumes were withdrawn during isoflurane and halothane. Reflex sympathetic activation probably occurred during these periods. Such activation may have caused coronary vasoconstriction and possibly contributed to a reverse steal phenomenon. Evidence for intense vasoconstriction is lacking, however, since coronary sinus oxygen tensions do not indicate excessive sympathetic tone.

A final methodologic consideration concerns the fact that some residual inhaled anesthetic may have influenced subsequent measurements. Measured values of halothane during isoflurane administration ranged from 0.01–0.05%, and of isoflurane during halothane administration from 0.02–0.09%. Note that this contamination affected only subsequent measurements, and that the order of agent administration was randomized, in part to account for this effect.

**CRITIQUE OF THE MODEL**

Extrapolation of these results to the human condition depends on the validity of an aneurysm-stimulated coronary collateral network as a model of chronic human coronary artery disease. The aneurysms were left in place for 3–4 weeks in the present study. This duration resulted in complete occlusion of the enclosed artery without myocardial infarction in approximately 2/3 of the dogs. Animals in whom closure resulted in infarction were excluded from the study. Gradual occlusion resulted in development of a collateral network from the septal and circumflex coronary arteries that was capable of delivering about 75% of the flow demanded by the normal zone. This finding is similar to the results reported by Schaper in a longitudinal study of collateral vessel development in dogs. In comparison, acute coronary ligation in dogs results in a collateral-to-normal zone flow ratio more on the order of 0.20. Oxygen delivery to the collateral-dependent zone was probably adequate, because the region contracted during systole, and contraction could not be enhanced by elevation of coronary perfusion pressure. In
addition, vasodilation without an alteration in flow distribution at Full flow in Protocol 1 suggests a modest vasodilator reserve in the collateral-dependent zone. This degree of collateral perfusion is common in patients with long-standing coronary artery disease. Normal or slightly impaired contraction of the collateral-dependent zone has been found at rest in these patients, but modest exercise stress produces ischemic dysfunction.27,28

The anatomic arrangement of occluder and coronary perfusion cannula was carefully constructed in this study. Perfusion of the left main coronary artery was used to include collateral flow into the LAD bed from septal branches, as well as from the circumflex artery. The use of constant flow was designed to mimic a situation in which there is a critical stenosis of the supplying artery proximal to the origin of the collaterals. By definition, flow through a critical stenosis does not increase in response to vasodilation. Instead, distal pressure falls. It is this decrease in distal coronary pressure that is responsible for the decrease in flow into the pressure-dependent collateral-supplied zone.4,5 A steal phenomenon, although of lesser magnitude, is possible even with a non-stenosed supply vessel.25 Although the results of the present study indicate an alteration in the transmural distribution of flow with isoflurane, the study did not directly address the possibility of a transmural steal distal to a single coronary stenosis.50,51

In the present experiments, mean arterial pressure and heart rate were carefully controlled. In clinical practice, isoflurane administration frequently leads to a decrease in arterial pressure, and either no change or an increase in heart rate. These effects alone are likely to reduce collateral blood flow.18,25 On the other hand, the concomitant decrease in myocardial oxygen consumption with isoflurane would serve to protect the collateral-dependent zone from ischemia.

INTERPRETATION

Coronary steal was demonstrated only when total flow was reduced 16–26% below the autoregulated value. Under these conditions, flow to the collateral-dependent zone was pressure-dependent because of the extra hydraulic resistance imposed by the collateral vessels. Vasodilator reserve remained in the normal zone, and vascular resistance in this zone decreased in response to isoflurane, decreasing coronary pressure, and, thus, collateral zone flow. In Protocol 1, intercoronary steal with isoflurane was not found at full flow, since both beds had vasodilator reserve, nor was it demonstrated at Low total flow, likely because both beds were vasodilated by the metabolic signal resulting from under-perfusion. Thus Protocol 1 establishes the conditions for isoflurane-induced coronary steal and the magnitude of the effect.

In Protocol 2, isoflurane, halothane, adenosine, and nitrous oxide were compared at identical heart rate, mean arterial pressure, hemoglobin concentration, and total coronary flow. The Mid flow range (see "Methods" for definition) was used. Each agent altered the intercoronary distribution of flow in proportion to its effect on coronary vascular resistance (fig. 5). This finding suggests that the direct effects of these agents on coronary tone was the major factor producing flow redistribution.

This finding is strong evidence against the hypothesis that a decrease in contractile function in the collateral-dependent zone was the initial event, and that a metabolism-related flow alteration followed. A clear separation between agents with negative inotropic effects and those without should have been evident if a decrease in metabolism was primary. Instead, these results are more consistent with the concept that direct vasodilation produced a steal that resulted in ischemic dysfunction of the collateral-dependent region.

The data from the present study suggest that isoflurane has a strong vasodilating effect on coronary arterioles. This effect is likely responsible for the flow redistribution observed under hemodynamic conditions that caused the collateral-dependent circulation to be pressure-dependent. Isoflurane may have dilated collateral vessels also because resistance through the collateral circulation decreased in response to isoflurane at Full flow conditions during Protocol 1. Whether the effect was on collateral vessels or on the collateral-supplied bed cannot be determined from the present experiment. A careful experiment of the type conducted by Ertl10 would be necessary to answer this question.

Adenosine dilates coronary arterioles without an effect on collateral vessel conductance,10 and produces an intercoronary steal in the presence of acute occlusion.10,29 In the present study, adenosine produced intercoronary steal, but did not affect transmural distribution of flow even in the collateral-dependent zone. This lack of effect is puzzling in light of previous studies demonstrating a transmural steal in the presence of a flow-limiting coronary stenosis.50,51 These differences may be the result of the relatively low dose of adenosine used in the present study. Sufficient adenosine was used to cause a doubling of coronary flow under constant coronary pressure conditions, whereas maximal doses of adenosine would likely have elicited a 4- to 5-fold increase in flow.

Isoflurane reduced coronary resistance approximately 25% in both protocols in the present study, despite the fact that the end-tidal isoflurane concentration was higher in the second protocol (1.46% of 0.94% in Protocol 1). This finding suggests a ceiling to the coronary vasodilation from isoflurane. In support of this concept, Merin reported no change in myocardial oxygen extraction when
inhaled isoflurane concentration was increased from 1.5 to 3.0%. 52

Isoflurane produces a similar degree of direct coronary vasodilation in humans as that found in this study. In Riez's study of humans, myocardial oxygen extraction decreased from 68% to 48%, indicating that coronary flow exceeded metabolic demand during isoflurane administration. 1 Mofitt et al. documented a 56% increase in coronary sinus blood oxygen content during isoflurane (1.7%, inspired) in patients with coronary artery disease. 2 Since myocardial oxygen extraction is normally quite constant over a wide range of hemodynamic states, 35,34 these changes suggest that isoflurane interferes with the mechanism responsible for the close coupling of coronary flow and myocardial oxygen demand. A direct effect on arteriolar smooth muscle seems probable.

A major finding of this study is that halothane does not produce intercoronary or transmural steal in this model of chronic coronary occlusion. Previous studies are consistent with this result. Smith et al. reported a proportional decrease in flow to both collateral-dependent and normally perfused myocardium during halothane in a greyhound model of acute occlusion. 55 While total flow decreased during halothane, the distribution of flow was unaltered. Sivanarjan obtained similar results in a canine model of chronic amiodarone occlusion. 56

The human response to halothane is similar to that observed in the present study. Halothane causes either no change 57 or a small increase 58 in coronary sinus oxygen tension in patients with coronary artery disease. The negative inotropic effects of halothane may mitigate potential flow redistribution caused by this small direct dilation. In the present study, calculated coronary resistance was unchanged by halothane, although coronary sinus blood oxygen tension increased. A modest vasoconstriction resulting from decreased myocardial oxygen demand may have offset the small direct dilation leading to no change in calculated resistance, and, thus, no change in flow distribution. A similar mechanism has been demonstrated for nifedipine in pigs. 59 Although isoflurane may have also increased resistance because of lower oxygen demand, this effect seems to have been overwhelmed by direct vasodilation, and steal resulted.

Nitrous oxide has been shown to increase myocardial oxygen extraction in patients with coronary artery disease, 40,41 perhaps because of its sympathomimetic properties. 42 The present results demonstrate no increase in coronary resistance with nitrous oxide, nor do they indicate vasodilation. Nitrous oxide did not affect flow distribution or lactate extraction in the present study. These findings of "no difference" are somewhat suspect, because technical problems limited the number of animals in which data during nitrous oxide was obtained to five. A small

and not statistically significant decrease in systolic contraction in the collateral-dependent zone occurred during nitrous oxide administration. This finding is similar to the effect reported by Philbin in a model of acute coronary stenosis. 45 The pathophysiologic significance of this finding is uncertain.

Isoflurane increased blood flow to normally perfused myocardium at the expense of flow into collateral-dependent zones. Isoflurane also decreased the inner:outer flow ratios in both zones, indicating an alteration in the transmural distribution of flow. Mechanical contraction of the collateral-dependent zone was impaired as a result of the flow redistribution, rather than as a result of the negative inotropic effects of isoflurane. Lactate production was not observed. These results with isoflurane are similar to results obtained with low-dose intracoronary infusion of adenosine. Neither halothane nor nitrous oxide altered flow distribution or mechanical function. The study demonstrates that isoflurane causes coronary steal in a carefully controlled animal model of chronic coronary occlusion.

The authors are indebted to Anaquest for a grant supporting this study. Excellent technical assistance was provided for the experiments by Rod Gronka and Cris Poulson. Marilou Gronka, Lisa Embry, and Martha Hutson assisted with animal surgery and postoperative care. The coronary cannula was expertly constructed by Fellner Smith, Stephanie Lathrop and Linda Artman produced the figures. Katrina Stampe, Julie Baker, and Mary Lee typed the manuscript.

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