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No Evidence for Blood Flow Redistribution with Isoflurane or Halothane during Acute Coronary Artery Occlusion in Fentanyl-anesthetized Dogs

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The present study examines the postulate that isoflurane, in contrast to halothane, causes redistribution of blood flow away from an ischemic myocardial region through vasodilation of adjacent normally perfused myocardium. The study was performed in open-chest dogs anesthetized with fentanyl; ischemia was induced by occlusion of the left anterior descending coronary artery. At 0.6% alveolar concentration, isoflurane increased transmural blood flow to 125% of control values ($P < 0.05$) in the normal region without concomitant changes in blood flow to the ischemic region or in the endocardial/epicardial flow ratio in the ischemic region. The evidence excludes either transmural steal or regional redistribution phenomena. Myocardial blood flow variables returned to control values at 1.8% isoflurane, and no blood flow redistribution effects were evident. In contrast, whereas halothane 0.4% caused no significant effect on myocardial blood flows, an alveolar concentration of 1.2% decreased transmural blood flow to normally perfused left ventricle to 70% of control ($P < 0.05$). Regional myocardial oxygen consumption in the normal and ischemic areas decreased at higher alveolar concentrations and was unchanged at the lower concentrations for both agents. Myocardial lactate production from the ischemic region was unchanged with either agent, suggesting that, in terms of metabolic changes, neither agent worsened ischemia during sustained occlusion of the left anterior descending coronary artery. The present data show no evidence for worsening of myocardial ischemia with either isoflurane or halothane. Isoflurane causes a relatively greater increase in perfusion compared to myocardial oxygen consumption of normally perfused myocardium; nevertheless, sufficient coronary vascular reserve remains in the native collateral circulation so that myocardial metabolic supply-and-demand relationships during ischemia are not further compromised. (Key words: Anesthetics, volatile: halothane; isoflurane. Heart, blood flow: coronary. Heart, ischemia: lactate production; oxygen consumption.)

IN RECENT YEARS, there has been debate[1–5] as to the propensity of isoflurane to evoke myocardial ischemia through the mechanism of coronary steal. Reiz and coworkers,[6,7] in studies of patients with severe coronary artery disease, postulated that, despite favorable decreases in global myocardial oxygen utilization, isoflurane induced coronary vasodilation in relatively normally perfused myocardium with a resultant redistribution of blood flow away from poorly perfused regions. Weight was added to the "steal" hypothesis by Buffington and colleagues,[8] who, using a canine model of coronary steal,[9] found evidence for both redistribution of blood flow away from an ischemic region and transmural redistribution away from endocardium to epicardium in response to isoflurane but *not* halothane. Additional studies[10,11] also describe more severe regional myocardial dysfunction and detrimental effects on coronary blood flow distribution with isoflurane in comparison to halothane. Moreover, there is evidence[12] that myocardial tolerance to total ischemia is improved in animals anesthetized with halothane compared to isoflurane.

In contrast, Cason *et al.*[13] found no evidence for coronary steal with either isoflurane or halothane and concluded that neither anesthetic, when used as an adjuvant to high-dose opioid anesthesia, is likely to cause myocardial ischemia through a mechanism of regional blood flow redistribution. Their model for evoking coronary steal was similar to that used by Buffington and co-workers[8] in that acute coronary artery occlusion was induced in a zone of collateral-dependent myocardium previously established by proximal vessel stenosis. However, there were major differences between study protocols[8,13] such that the coronary perfusion pressures at which measurements were made assume critical importance. Other differences that may have influenced the results included the nature of the background anesthetic (α-chloralose[8] *vs.* sodium pentobarbital–fentanyl[13]), the degree of vessel collateralization, and the control hemodynamic values at which the measurements of blood flow distribution were made.

Conzen and co-workers[14] provided evidence to support the role of coronary perfusion pressure on the interpretation of isoflurane effects when they found that norepinephrine infusions, used to correct the systemic hypotensive effects of isoflurane, improved blood supply to ischemic myocardium. Tatekawa *et al.*[15] also induced coronary steal with isoflurane, yet the decrease in myocardial flow was matched and exceeded by a concomitant decrease in myocardial oxygen demand, thereby negating any apparent deleterious effects mediated through blood flow redistribution.

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In view of the conflicting laboratory evidence,[8,10–15] the aim of the present study was to compare the effects of isoflurane and halothane in equianesthetic dosages on regional myocardial blood flow and metabolic function during established acute left anterior descending coronary artery (LAD) occlusion. Background anesthetic conditions were arranged to mimic techniques used in humans with coronary artery disease.

Materials and Methods

The study was approved by the Institutional Committee for Animal Use and Care of the University of California, Davis and was conducted in accordance with its guidelines for the care and use of laboratory animals.

Animal Preparation

Experiments were performed in 16 mixed-breed dogs of either sex and weighing 22.9 ± 0.7 kg (mean ± standard error of the mean). Two additional dogs were excluded from the analysis; in one, ventricular fibrillation occurred after ligation of the LAD, and in the second, ventricular fibrillation occurred immediately after the introduction of 0.4% halothane. Anesthesia was induced with thiamylal (15 $mg \cdot kg^{-1}$) and fentanyl (100 $\mu g \cdot kg^{-1}$); the trachea was intubated; and ventilation was controlled using a positive-pressure Harvard respirator. Anesthesia was maintained with nitrous oxide in oxygen and by a continuous infusion of fentanyl (1–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Ventilation and fractional inspired oxygen concentration were adjusted to maintain normoxia and normocapnia. Lidocaine (2 $mg \cdot kg^{-1}$) was given during surgical manipulation of the heart when ventricular ectopy was encountered; no lidocaine was used during the course of the experiment. Lactated Ringers solution was infused intravenously at a rate of 5 $ml \cdot kg^{-1} \cdot h^{-1}$ throughout the experiment. A semirigid catheter was inserted into the thoracic aorta *via* a femoral arteriotomy for reference blood sampling and aortic pressure measurements. Cardiac output was measured *via* a pulmonary arterial flow-directed catheter inserted through the right external jugular vein by the thermodilution technique, using iced saline and an Edwards computer (model 9520A, Santa Ana, CA); values were averaged from intermittent triplicate measurements.

A left thoracotomy at the fifth intercostal space was performed using aseptic surgical techniques; the pericardium was opened; and a flexible polyethylene catheter was inserted into the left atrium for pressure measurement and injection of radioactive microspheres. Left ventricular (LV) pressure was measured by a Konigsberg® micromanometer (model P7, Pasadena, CA) inserted through a stab wound in the apex of the ventricle and secured with a purse-string suture. The Konigsberg transducer was calibrated *in vitro* using a mercury manometer and *in vivo* using aortic systolic pressure and left atrial pressure; calibration was performed frequently to eliminate electrical drift. Blood pressures were measured using Statham® pressure transducers (model 23dB, Hato Rey, Puerto Rico). A pulsed Doppler flow transducer was placed around the LAD near its origin, and a ligature snare for future use was placed around the same artery just proximal to its first marginal branch.

Ventricular dimensions were monitored with a Triton® sonomicrometer (model 120, San Diego, CA). Ultrasonic dimension crystals were implanted in pairs to measure the transverse external diameter across the anterior–posterior minor axis and the wall thickness of the LV free wall 3 cm distant from the area of the LV supplied by the LAD. Proper alignment was confirmed with a Tektronix® oscilloscope (model RM647, Beaverton, OR). Percent of systolic shortening and percent of wall thickening were calculated as the percent of systolic dimension change divided by the end-diastolic dimension for paired anterior–posterior minor axis crystals and for paired wall thickness crystals, respectively.[16]

After anticoagulation with heparin, two small epicardial veins on the LV in the region of the LAD draining the region distal to the snare and a region outside the distribution of the LAD in an area supplied by the circumflex artery on the lateral LV were cannulated to allow blood measurements. Free drainage of each catheter was allowed, and blood was collected under vacuum for immediate analysis.

Body temperature was maintained above 37° C with a heating pad. Hemodynamic data were recorded on a direct writing polygraph (Gould®, model 2800S, Cleveland, OH) and on an analog frequency-modulation tape recorder (Kyowa Electronic Instruments, Tokyo, Japan) for subsequent analysis.

Physiologic Measurements

Variable parameters, including mean arterial pressure, stroke volume, systemic vascular resistance, and pulmonary vascular resistance were calculated using standard formulas. Coronary perfusion pressure was calculated from the difference between diastolic aortic pressure and the left ventricular end-diastolic pressure.

Regional blood flow was measured with radioactive microspheres as previously described.[16] In brief, approximately 2–3 × 10^6 microspheres (15 μm) labeled with ^{95}Nb, ^{46}Sc, ^{141}Ce, or ^{85}Sr were injected into the left atrium over 20 s. A reference blood sample was withdrawn from an arterial catheter starting 15 s before the microsphere injection and continuing for 2 min at a constant rate of 7.75 ml/min. The order of the isotopes was randomized. After the experiment was completed, the animal was killed with a halothane or isoflurane overdose and intravenous

injection of saturated potassium chloride. The sampled organs were then removed, sectioned, weighed, and counted for radioactivity. Regional blood flow was calculated from the ratio of radioactive count of measured sample over that of reference blood sample. The ischemic region of the LV produced during the experiment was identified by the intracoronary injection of 0.3 ml methylene blue through an arteriotomy at the site of arterial ligation. Tissue was sampled from the central core of stained tissue, leaving a margin of at least 1 cm of staining; one sample of ischemic tissue (average wet weight = 8.72 ± 0.57 g) was taken for analysis from each dog. Two samples were taken from unstained LV myocardium at least 3 cm distant from the stained area, and the blood flow values obtained for each sample were averaged for normal LV flow values.

Arterial and coronary venous samples were used for the measurement of oxygen contents (IL Co-oximeter 282, Lexington, MA) and blood lactate concentrations (YSI 2300 Stat, Yellow Springs Instruments, Yellow Springs, OH) and for the calculation of regional myocardial extraction ratios, production, and consumption for oxygen and lactate using standard formulas: regional myocardial oxygen consumption was determined as the arteriovenous oxygen content difference multiplied by the regional myocardial blood flow to the area; the regional oxygen extraction ratio was calculated as the arteriovenous oxygen content difference divided by the arterial oxygen content. Blood lactate concentrations were substituted in the above formulas to obtain regional myocardial lactate production or consumption. Complete data were obtained in six dogs in each group for venous oxygen content values and for five dogs for venous lactate values. In the remainder, catheter occlusion or inadequate sampling precluded further analysis.

Experimental Protocol

At the completion of instrumentation, nitrous oxide was discontinued, and an oxygen—air mixture was delivered by ventilation. The thoracotomy was loosely closed; lungs were hyperinflated for several breaths to reduce lung atelectasis; and ventilation was adjusted to provide normoxia and normocapnia. Sodium bicarbonate was given if the base deficit exceeded 5 $mEq \cdot l^{-1}$; no additional sodium bicarbonate was given for the duration of the experiment. After cessation of nitrous oxide, fentanyl was maintained at a rate of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 1 h was allowed to elapse before baseline measurements were obtained. End-tidal gases were measured throughout the experiment using a Medspect® mass spectrometer (Allegheny International Medical Technology, St. Louis, MO).

After baseline measurements were obtained, LAD occlusion was achieved by closure of the ligature snare. Postocclusion hemodynamic, blood-flow, and metabolic indices were obtained after 30 min. Occasional ventricular ectopic beats accompanied ligature of the LAD but were not treated. All measurements were performed during stable conditions with the animals in sinus rhythm. Dogs were randomized to receive either halothane or isoflurane, and anesthetic concentrations also were administered in randomized order to minimize time-based effects on the preparation. Measurements were repeated at each stage of the experiment under stable end-tidal anesthetic gas concentrations. When steady-state was achieved, comparisons were made at equianesthetic dosages (*i.e.*, MAC equivalents) at low (halothane 0.4% and isoflurane 0.6%) and high alveolar concentrations (halothane 1.2% and isoflurane 1.8%). In relation to anesthetic concentrations as mentioned, the order was randomized so that four dogs in each agent group received a low-to-high sequence and four received a high-to-low sequence.

Data Analysis

Data were compared within each group at each experimental stage and between anesthetic groups using a model III three-factor analysis of variance with repeated measures.[17] Newman-Keul's test[17] was used to determine significant differences between pairs of mean values within an agent and between agents, with a significance level set at 0.05. Values are expressed as means ± standard errors of the means.

Results

Values for arterial oxygen and carbon dioxide tension, *p*H, base deficit, hemoglobin, and blood temperature are shown in table 1. Hemoglobin content decreased to 84 ± 1.7% of control values ($P < 0.001$) in all dogs. Time-based effects were not significant for other values.

Systemic and Cardiac Hemodynamics

There were no significant differences in systemic and cardiac hemodynamic variables after LAD occlusion when compared to preocclusion control values (table 2).

After LAD occlusion, heart rate increased with isoflurane at 0.6 and 1.8% alveolar concentrations to 136% ($P < 0.05$) and 141% ($P < 0.05$), respectively, of postocclusion baseline (hereafter defined as control). Heart rate increases with halothane were smaller and were not significant. Cardiac output changes did not reach significance throughout the experimental protocol.

Dose-dependent decreases in mean arterial pressure occurred with both agents. Isoflurane caused a decrease to 75% ($P < 0.05$) and 52% ($P < 0.01$) of control at 0.6 and 1.8% alveolar concentrations, respectively. Halothane responses were similar: mean arterial pressure decreased

TABLE 1. Effects over Time on Pa_{O_2} and Pa_{CO_2}, *p*H, Base Deficit, Hemoglobin, and Blood Temperature in 16 Dogs

		Before Occlusion 0 MAC	LAD Occlusion		
			0 MAC	Low MAC	High MAC
Pa_{O_2} (mmHg)	Halothane (n=8)				
	Order 1	130 ± 22	122 ± 21	163 ± 40	133 ± 12
	Order 2	105 ± 10	106 ± 15	106 ± 18	99 ± 21
	Isoflurane (n = 8)				
	Order 1	116 ± 28	113 ± 26	117 ± 29	161 ± 29
	Order 2	122 ± 30	110 ± 28	97 ± 18	88 ± 15
Pa_{CO_2} (mmHg)	Halothane				
	Order 1	39 ± 2	40 ± 2	40 ± 2	39 ± 2
	Order 2	38 ± 3	37 ± 4	36 ± 4	35 ± 5
	Isoflurane				
	Order 1	41 ± 2	44 ± 2	45 ± 3	44 ± 3
	Order 2	41 ± 1	43 ± 1	45 ± 1	44 ± 2
*p*H	Halothane				
	Order 1	7.32 ± 0.01	7.30 ± 0.02	7.31 ± 0.02	7.33 ± 0.03
	Order 2	7.35 ± 0.03	7.35 ± 0.04	7.36 ± 0.05	7.36 ± 0.05
	Isoflurane				
	Order 1	7.36 ± 0.01	7.31 ± 0.02	7.29 ± 0.03	7.31 ± 0.03
	Order 2	7.34 ± 0.02	7.30 ± 0.01	7.26 ± 0.02	7.30 ± 0.01
Base deficit (mM)	Halothane				
	Order 1	4.9 ± 0.4	5.6 ± .7	5.9 ± 0.9	6.0 ± 0.6
	Order 2	3.6 ± 1.0	4.7 ± 1.0	4.5 ± 1.5	4.9 ± 1.2
	Isoflurane				
	Order 1	2.6 ± 1.0	3.6 ± 0.9	3.9 ± 0.8	3.6 ± 0.9
	Order 2	3.0 ± 0.7	4.9 ± 0.7	5.7 ± 0.7	4.8 ± 0.7
Hemoglobin* ($g \cdot dl^{-1}$)	Halothane				
	Order 1	12.5 ± 0.4	12.4 ± 0.7	10.8 ± 0.7	11.1 ± 0.7
	Order 2	13.5 ± 0.4	13.2 ± 0.7	12.6 ± 0.7	10.6 ± 0.3
	Isoflurane				
	Order 1	12.2 ± 0.2	12.4 ± 0.2	10.8 ± 0.3	11.3 ± 0.3
	Order 2	12.8 ± 0.4	12.7 ± 0.5	11.6 ± 0.4	10.7 ± 0.4
Temperature (° C)	Halothane				
	Order 1	38.1 ± 0.3	38.2 ± 0.4	38.0 ± 0.4	38.2 ± 0.4
	Order 2	38.6 ± 0.4	38.7 ± 0.4	38.6 ± 0.3	38.4 ± 0.3
	Isoflurane				
	Order 1	37.6 ± 0.4	37.7 ± 0.5	37.7 ± 0.3	37.7 ± 0.3
	Order 2	37.9 ± 0.1	38.1 ± 0.1	38.1 ± 0.2	38.1 ± 0.2

n = 4. Values expressed as means ± SEM.

LAD = left anterior descending artery; MAC = minimum alveolar concentration.

Order of measurements: order 1: 0 MAC (before occlusion); 0 MAC (LAD occlusion); high MAC (LAD occulsion); low MAC (LAD occlusion); order 2: 0 MAC (before occlusion); 0 MAC (LAD occlusion); low MAC (LAD occlusion); high MAC (LAD occlusion).

* $P < 0.001$ control *versus* values measured over time.

to 81% ($P < 0.05$) at 0.4% and decreased 61% ($P < 0.01$) at 1.2% alveolar concentration. Coronary perfusion pressure changes reached significance only at the high alveolar concentration stage for both agents, decreasing to 63% ($P < 0.01$) and 53% ($P < 0.01$) of control values, respectively, for halothane and isoflurane. Similarly, left ventricular end-diastolic pressure decreased at high alveolar concentration for halothane and isoflurane, to 58% ($P < 0.01$) and 36% ($P < 0.01$) of control, respectively. Systemic vascular resistance decreased to 59% ($P < 0.01$) of control at 1.8% isoflurane. Pulmonary vascular resistance was not significantly changed throughout the experiment.

Stroke volume decreased to 76% ($P < 0.05$) and 61% ($P < 0.01$) of control at 0.4 and 1.2% halothane and to 70% ($P < 0.05$) and 55% ($P < 0.01$) of control at 0.6 and 1.8% isoflurane (table 2). Although the percent of systolic shortening of LV wall thickness ($F = 4.788$, $P < 0.05$) and minor axis ($F = 3.526$, $P < 0.05$) decreased with both agents when examined among stages, comparison of paired means did not detect any significant differences within and between agents.

Effects on Myocardial Blood Flow, Oxygen Utilization, and Lactate Metabolism

Transmural blood flow responses to the volatile anesthetic in normal LV was significantly different for each agent (table 3 and fig. 1) at the corresponding low and high alveolar concentrations. With halothane, transmural flow in the normal region was not significantly changed at 0.4% alveolar concentration but decreased to 70% of control values ($P < 0.05$) at 1.2%, whereas with isoflurane

TABLE 2. Effects of Halothane (n=8) or Isoflurance (n=8) on Systemic Hemodynamic Variables during Acute LAD Occlusion

		Before Occlusion 0 MAC	LAD Occlusion		
			0 MAC	Low MAC	High MAC
Heart rate (beats per min)	Halothane	69.2 ± 4.4	83.0 ± 5.0	100.0 ± 4.9*	105.9 ± 9.0*
	Isoflurane	77.3 ± 7.8	85.8 ± 7.5	116.4 ± 9.3*†	121.1 ± 8.1*†
Cardiac output (l/min)	Halothane	2.52 ± 0.14	2.52 ± 0.19	2.30 ± 0.26	1.92 ± 0.21
	Isoflurane	2.57 ± 0.15	2.76 ± 0.16	2.69 ± 0.41	2.22 ± 0.22
Mean arterial pressure (mmHg)	Halothane	95.4 ± 4.0	89.8 ± 6.5	72.3 ± 5.1*†	55.0 ± 3.9*†‡
	Isoflurane	95.2 ± 3.4	94.6 ± 2.6	71.3 ± 4.3*†	49.8 ± 5.1*†‡
Mean pulmonary arterial pressure (mmHg)	Halothane	13.2 ± 0.8	15.0 ± 0.7	14.0 ± 0.8	13.4 ± 1.1
	Isoflurane	14.1 ± 1.0	13.8 ± 0.8	13.5 ± 1.2	11.8 ± 0.7
Left ventricular end-diastolic pressure (mmHg)	Halothane	7.9 ± 0.4	8.0 ± 0.8	4.5 ± 0.7*†	4.6 ± 0.5*†
	Isoflurane	5.6 ± 1.2	5.8 ± 0.6	2.9 ± 0.7	2.1 ± 0.4*†
Coronary perfusion pressure (mmHg)	Halothane	64.0 ± 4.5	61.8 ± 4.8	55.6 ± 5.3	39.1 ± 3.9*†‡
	Isoflurane	66.1 ± 2.3	68.1 ± 2.1	51.5 ± 4.4	36.3 ± 4.8*
Systemic vascular resistance ($dyne \cdot s^{-1} \cdot cm^{-5}$)	Halothane	3009 ± 207	2892 ± 314	2628 ± 259	2197 ± 146
	Isoflurane	2906 ± 188	2843 ± 204	2147 ± 221	1685 ± 113*†‡
Pulmonary vascular resistance ($dyne \cdot s^{-1} \cdot cm^{-5}$)	Halothane	211 ± 22	233 ± 28	308 ± 46	368 ± 79
	Isoflurane	290 ± 27	247 ± 29	312 ± 57	291 ± 39
Stroke volume (ml)	Halothane	37.3 ± 3.0	31.1 ± 2.4	23.6 ± 3.2*	19.1 ± 2.5*†
	Isoflurane	34.8 ± 2.3	33.4 ± 2.1	23.3 ± 2.7*†	18.5 ± 1.5*†
Minor axis§ (%SS)	Halothane	7.1 ± 1.3	7.3 ± 1.2	5.8 ± 1.0	5.3 ± 0.8
	Isoflurane	8.9 ± 1.0	7.7 ± 0.6	5.4 ± 0.5	5.5 ± 0.7
Wall thickness§ (%ST)	Halothane	15.6 ± 2.4	15.6 ± 2.4	11.9 ± 2.0	8.0 ± 1.7
	Isoflurane	13.8 ± 2.2	13.8 ± 2.1	9.4 ± 1.3	7.8 ± 1.4

All values expressed as means ± SEM.

LAD = left anterior descending artery; MAC = minimum alveolar concentration; %SS = percent of systolic shortening; %ST = percent of systolic thickening.

* $P < 0.05$ *versus* mean value before occlusion in corresponding anesthetic.

† $P < 0.05$ *versus* mean value after occlusion at 0 MAC in corresponding anesthetic.

‡ $P < 0.05$, low MAC *versus* high Mac in corresponding anesthetic.

§ $P < 0.05$ among columns (*i.e*, among dosage stages for both agents); multiple comparison test not significant between individual paired mean values.

it increased to 125% ($P < 0.05$) of control at 0.6% and returned to within control values at the 1.8% concentration level. Endocardial/epicardial flow ratios in the normal region were unaltered by either anesthetic agent.

Transmural flow in the ischemic zone decreased in seven of eight dogs in each anesthetic agent group at high alveolar concentrations; however, the trend did not reach statistical significance (table 3). Endocardial/epicardial blood flow ratios (table 3) in the LV ischemic region were not significantly altered by either agent. There were no systematic changes in blood flow to the LV septum, right ventricular septum, right ventricular wall (transmural), and right atrium.

Myocardial oxygen extraction ratio was unchanged in the normal region after LAD occlusion (table 4) and was not significantly different for either agent at low and high alveolar concentrations. Before occlusion, normal region and designated ischemic region myocardial oxygen extractions were not significantly different. After LAD occlusion, extraction ratios increased to similar levels in the ischemic region for both groups ($P < 0.001$). Coronary venous oxygen contents decreased significantly ($P < 0.001$) in the ischemic region after LAD occlusion and were unchanged in the venous blood from the normal region (table 4). No changes within or between agents were observed after LAD occlusion. Isoflurane or halothane had no effect on oxygen extraction ratios at either low or high concentration.

Myocardial oxygen consumption (fig. 2) in the LV normal region decreased to 68% ($P < 0.05$) and 64% ($P < 0.05$) of control for halothane and isoflurane, respectively, at the high alveolar concentration and was unaltered for either agent at the low end-tidal concentration (fig. 2). In the ischemic region, myocardial oxygen consumption was not significantly different for either agent at low alveolar concentrations but at high end-tidal concentrations decreased to 49% ($P < 0.01$) and 47% ($P < 0.01$) of control values for halothane and isoflurane, respectively.

In the normal region, net myocardial lactate consumption was unaltered by either anesthetic agent (fig. 3). In the ischemic region, lactate production was present and, although there was considerable within-animal variability in the baseline values, neither agent caused any systematic changes in lactate production (fig. 3).

There were no significant correlations between the net

TABLE 3. Effects of Halothane (n=8) of Isoflurane (n=8) on Regional Myocardial Blood Flow Distribution during Acute LAD Occlusion (15-μm microspheres)

	0 MAC		Low MAC		High MAC	
	Halothane	Isoflurane	Halothane	Isoflurane	Halothane	Isoflurane
LV blood flows						
Normal region						
Transmural	93.3 ± 7.5	97.1 ± 5.0	87.4 ± 6.2*	121.4 ± 4.0†	65.7 ± 6.0*,†,‡	89.7 ± 6.3‡
Endo/epi ratio	1.05 ± 0.09	0.97 ± 0.06	0.98 ± 0.09	0.91 ± 0.04	0.98 ± 0.11	0.87 ± 0.06
Ischemic region						
Transmural	35.4 ± 10.8	41.0 ± 6.8	29.0 ± 7.7	40.0 ± 7.1	17.7 ± 4.7	22.8 ± 4.3
Endo/epi ratio	0.53 ± 0.10	0.85 ± 0.08	0.60 ± 0.08	0.88 ± 0.10	0.53 ± 0.08	0.74 ± 0.12
Ischemic/normal ratio	0.34 ± 0.08	0.43 ± 0.07	0.33 ± 0.08	0.33 ± 0.06	0.25 ± 0.06	0.27 ± 0.06
LV septal	103.9 ± 11.0	96.3 ± 8.3	92.2 ± 8.3	118.9 ± 18.8	68.8 ± 5.9	87.5 ± 10.5
RV blood flows						
Transmural	80.1 ± 5.3	71.9 ± 6.1	69.8 ± 5.8	89.8 ± 6.5	54.7 ± 5.7	70.4 ± 6.6
RV septal	79.1 ± 5.6	84.4 ± 9.7	73.6 ± 6.3	100.2 ± 18.7	56.0 ± 4.6	80.0 ± 11.9
Right atrial flow	108.1 ± 16.2	104.3 ± 19.8	112.5 ± 15.7	117.9 ± 12.6	66.0 ± 10.7	75.8 ± 7.1

All values expressed as means ± SEM.
Blood flow units: milliliters per minute per 100 g tissue.
LAD = left anterior descending artery; MAC = minimum alveolar concentration; LV = left ventricle; RV = right ventricle.

* $P < 0.05$ Halothane *versus* isoflurance in corresponding stages.
† $P < 0.05$ *versus* control in corresponding anesthetic.
‡ $P < 0.05$ Low MAC *versus* high MAC in corresponding anesthetic.

lactate production values in the ischemic region in relation to 1) transmural ischemic region flow (r = 0.34), 2) endocardial-to-epicardial blood flow ratios (r = 0.21) in the ischemic region or 3) the ischemic normal blood flow ratios (r = 0.19).

Discussion

Clinical reports[6,7,18] of isoflurane-induced myocardial ischemia and conflicting animal studies[8,10–15] as to the effects of isoflurane on myocardial blood flow have led investigators to seek further information on the issue. The present study adds impetus to the argument that isoflurane, under background conditions and in dosages similar to those used clinically, while causing modest increases in blood flow to normally perfused LV, provides no additional mismatch of oxygen supply to demand to a poorly perfused region. Effects on total blood flow, its transmural distribution, myocardial oxygen consumption, and lactate production are similar in an ischemic region for both isoflurane and halothane, regardless of hemodynamic changes in adjacent normally perfused myocardium.

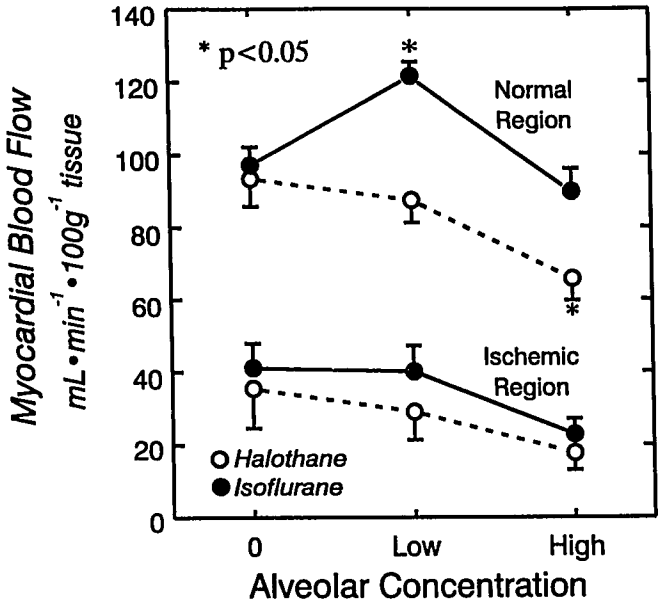

FIG. 1. Effects of halothane (n = 8) and isoflurane (n = 8) on regional myocardial blood flow in normally perfused region of left ventricle and in an area supplied by an occluded LAD artery, *i.e.*, an ischemic area. Values are expressed as means ± SEM.

CORONARY VASOMOTOR EFFECTS OF ISOFLURANE

In contrast to halothane, isoflurane evokes increases in myocardial blood flow at a low end-tidal concentration (0.6%) in the normal myocardium perfused by the circumflex coronary artery. Differences emerge at equianesthetic dosages despite similar background changes in coronary perfusion pressure. Because septal, right ventricular, and right atrial flows are not appreciably altered by either agent, the data suggest that differential effects may be evoked by isoflurane so that the LV is more susceptible to vasodilation. This reinforces the concept that factors regulating blood flow to the LV may differ from those regulating flow to the right ventricle.[19] This theory was not explored any further in the present analysis, but because myocardial oxygen consumption is unaltered by isoflurane in normally perfused LV, and because coronary perfusion is reasonably well maintained, we can conclude that isoflurane improves blood flow above myocardial tissue requirements in the normal LV myocardium.

TABLE 4. Effects of Halothane (n=6) or Isoflurance (n=6) on Coronary Venous Oxygen Contents and Regional Myocardial Oxygen Extraction Ratios after LAD Occlusion

		Before Occlusion 0 MAC	LAD occlusion 0 MAC	LAD occlusion Low MAC	LAD occlusion High MAC
Normal region					
O_2ER	Halothane	0.60 ± 0.04	0.63 ± 0.03	0.63 ± 0.03	0.67 ± 0.02
	Isoflurane	0.63 ± 0.04	0.66 ± 0.04	0.61 ± 0.04	0.57 ± 0.03
Ccv_{O_2} (ml · dl^{-1})	Halothane	6.6 ± 0.7	5.9 ± 0.5	5.3 ± 0.5	4.6 ± 0.3
	Isoflurane	6.3 ± 0.7	5.6 ± 0.6	5.6 ± 0.4	6.1 ± 0.3
Ischemic region					
O_2ER	Halothane	0.61 ± 0.04	0.73 ± 0.02*	0.71 ± 0.02*	0.73 ± 0.03*
	Isoflurane	0.59 ± 0.03	0.75 ± 0.02*	0.73 ± 0.03*	0.71 ± 0.02*
Ccv_{O_2} (ml · dl^{-1})	Halothane	6.6 ± 0.8	4.4 ± 0.2*	4.2 ± 0.2*	3.7 ± 0.4*
	Isoflurane	7.0 ± 0.5	4.0 ± 0.4*	4.0 ± 0.6*	4.0 ± 0.4*

All values expressed as means ± SEM.

O_2ER = oxygen extraction ratio; Ccv_{O_2} = coronary venous oxygen content.

* $P < 0.05$ *versus* mean value before occlusion in corresponding anesthetic.

The coronary vasodilator properties of isoflurane are now well established.[6–8,18,20–24] Nevertheless, in previous studies when background hemodynamic changes such as heart rate increases[20,24] and decreases in coronary perfusion pressure[6–8,11] were taken into account, the increases in myocardial blood flow were small. Indeed, Hickey *et al.*,[23] who examined the relative vasodilator properties of halothane, enflurane, and isoflurane in conscious dogs, reported that all three agents only mildly disrupted coronary blood flow autoregulation; *i.e.*, although the autoregulation slope was increased by isoflurane, similar values for coronary blood flow at coronary artery diastolic pressure of 40 and 60 mmHg were observed when compared to awake values. Moreover, although isoflurane was a more powerful vasodilator than enflurane or halothane, similar vasodilator reserve persisted in the coronary bed when compared to awake values. They concluded[23] that all three agents reduce autoregulation, both by increasing flow out of proportion to the reduced myocardial oxygen demand and by making flow more pressure-dependent.

In relation to its coronary vasodilator properties, Sill and colleagues,[21] in a study in fentanyl–pentobarbital–anesthetized dogs, demonstrated that epicardial vessel diameter was not affected by isoflurane. They concluded that coronary vasodilation was confined at higher concentrations of isoflurane to intramyocardial arterioles[21]; *in vitro* studies[22] confirmed a relative resistance to relaxation in epicardial vessels. At higher concentrations, iso-

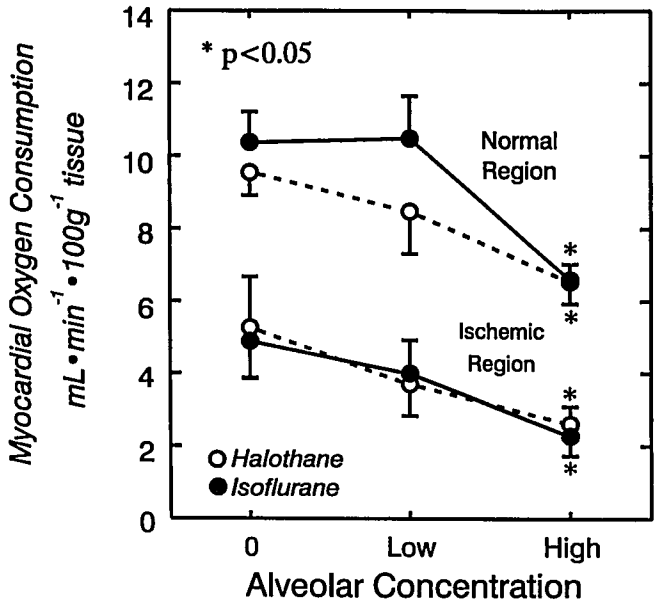

FIG. 2. Effects of halothane (n = 6) and isoflurane (n = 6) on regional myocardial oxygen consumption during acute LAD occlusion.

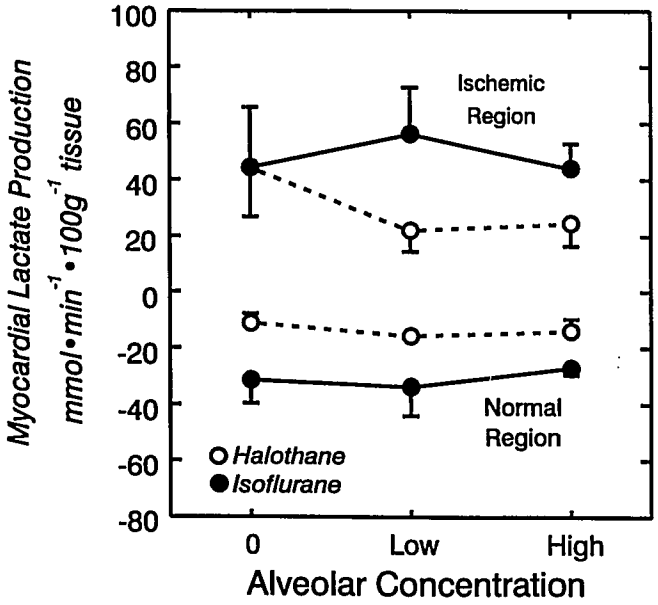

FIG. 3. Effects of halothane (n = 5) and isoflurane (n = 5) on regional myocardial lactate production or consumption (*i.e.*, negative values) during acute LAD occlusion.

flurane, for any given value of myocardial oxygen consumption, increased myocardial blood flow above control values.[21] These findings[21] and others[8,14,15] are compatible with our data showing that isoflurane provides a relative increase in perfusion under conditions of constant myocardial oxygen demand in normal myocardium.

Propensity for Isoflurane to Induce Myocardial Ischemia

Although isoflurane evokes an increase in myocardial blood flow in adjacent myocardium, no redistribution of blood flow away from an ischemic region is observed in our study. Moreover, transmural blood flow distribution is unaffected, ruling out any transmural steal effects. This contrasts strongly with previous evidence of both collateral and transmural steal[8,14,15] but is supported by the data obtained by Cason *et al.*[13] However, leaving aside considerations concerning unusually low[8,13] or abnormally high[15] baseline coronary flows[19] that might influence results, there are several other possibilities that may account for the contrasting findings. In particular, changes in coronary perfusion pressure evoked by isoflurane assume critical importance to the analysis.

For example, in dogs with experimentally induced steal-prone anatomy,[8,13] any evidence for coronary steal was evident only when a significant decline in coronary perfusion pressure in the collateral system[8] was allowed to develop and was not evident when collateral perfusion pressure was well maintained.[13] In another study, any reductions in myocardial blood flow and tissue oxygen pressure in collateral-dependent myocardium[14] could be reversed when systemic arterial pressure was normalized by concomitant infusion of norepinephrine.

Confirmation for the theory that perfusion pressure changes play the predominant role in the responses of the coronary circulation to isoflurane have been obtained recently in studies of chronically instrumented dogs with perfusion defects mimicking multivessel coronary artery disease.[24,25] Hartman *et al.*[24] found that reductions in blood flow to normal, stenotic, and occluded regions produced by isoflurane were reversed when systemic hypotension was corrected mechanically by aortic constriction. In contrast, a maximal vasodilating dose of adenosine administered into the LV produced a redistribution of blood flow away from collateral-dependent myocardium at similar perfusion pressures.[25]

Heart rate effects on coronary blood flow and myocardial metabolism must also be considered in any analysis of myocardial ischemia. For example, Hysing and coworkers,[26] in a well-controlled study in conscious chronically instrumented dogs, found that coronary blood flow was unchanged by isoflurane. By contrast, a decrease in systemic arterial pressure and an increase in heart rate (of 50–60%) were the predominant changes, suggesting that, provided that perfusion pressure remained in the autoregulatory range, coronary flow was well maintained despite concomitant tachycardia, and any direct effects of the agent on vascular tone were small.

To emphasize further the importance of heart rate effects, it is interesting to observe in an animal model of coronary occlusion[27] that tachycardia, *per se,* caused an increase in blood flow to nonischemic myocardium. In ischemic myocardium, however, although a redistribution from endocardium to epicardium occurred,[27] overall flow did not change. This finding points to the importance of controlling heart rate in patients with myocardial ischemia, but it is equally important to note that low concentrations of isoflurane improved tolerance to pacing-induced myocardial ischemia in patients with coronary artery disease and normal LV function.[28]

The data reinforce the theory that isoflurane provides a more favorable balance, compared to awake values, between myocardial oxygen supply and demand when LV myocardial metabolic demand is raised by heart rate increases.[28] This is supported in the present study by the lack of correlation between regional blood flow measurements and lactate production in the ischemic area. For example, if the imbalance already established by acute coronary occlusion were to be further aggravated by redistribution to normal myocardium, then further increases in lactate production would have ensued. Because this did not occur, the evidence suggests that a concomitant reduction in metabolism is evoked by isoflurane so that any mismatch is not enlarged. This also points to the difficulty of interpreting blood-flow ratio changes as evidence for adverse redistribution phenomena in the absence of a reliable quantification of ischemia, such as lactate production.

In the present study in fentanyl-anesthetized dogs, free expression of heart rate and blood pressure effects were allowed, and heart rate increases tended to be more pronounced during isoflurane; however, as previously mentioned, blood flow effects were similar for both agents in ischemic myocardium. Because myocardial blood flows increase in the adjacent normally perfused bed at a low concentration of isoflurane, regional metabolic effects become the key evidence for analyzing the propensity of either agent to exacerbate ischemia. According to those criteria, whereas isoflurane provides a relative increase in perfusion to normal myocardium at low MAC levels, lactate production as a quantitative index of ischemia is unchanged in the ischemic region, therefore excluding any evidence for a worsening of ischemia.

Studies in Other Species and in Humans

Effects of isoflurane on systemic hemodynamic variables in the pig[29–31] and in the human[6,7,18,32–34] for the most

part approximate results described in the dog. Nonetheless, in the pig, it has been postulated[35] that isoflurane compared to halothane may provide a greater index of safety, presumably due to better-preserved cardiac function and greater coronary vascular reserve in that species,[35] whereas in patients with coronary artery disease, isoflurane has been implicated as a potentiating factor for myocardial ischemia[1] through mechanisms previously discussed. In the pig, in addition to increasing coronary vascular reserve,[35] dose-related decreases in coronary blood flow, possibly gaited to concomitant decreases in myocardial oxygen demand, were observed[30,31] suggesting a negligible direct vasodilator action on coronary vasculature in that species.

Evidence for coronary steal in humans[6,7,18,34] places great import on measurements of great cardiac vein and coronary sinus flows. Since changes in great cardiac and coronary sinus venous flows with isoflurane are small, and because errors in the technique are large,[36] conclusions regarding myocardial blood flow distribution should be treated with great caution; errors arise because of uncontrollable factors such as catheter movement[37] and blood reflux into the coronary sinus.[38] Nevertheless, data concerning changes to lactate production and ST-segment effects evoked by isoflurane[6,18,34] provide presumptive evidence for ischemia, if not for steal. However, any conclusions regarding the propensity of isoflurane to cause ischemia[32] are confounded by the same questions raised in the animal studies. For example, concern about the indirect effects on coronary hemodynamics of profound decreases in coronary perfusion pressures[6,7] and concomitant increases in heart rate[18] raise doubts about the causation of myocardial ischemia. The use of higher doses of isoflurane,[34] concomitant nitrous oxide administration,[5] the use of historic controls for comparison,[39] and the apparent reversal of ischemia in some but not all patients by correction of coronary perfusion to normal values using phenylephrine infusion[6] compound the problems of analysis.

In contrast to previous evidence,[6,7,18,34] when isoflurane was used as an adjuvant to high-dose sufentanil anesthesia[33] and systemic hypotension was avoided and heart rate rigidly controlled, isoflurane provided safe anesthesia as evidenced by global and regional myocardial lactate flux. Moreover, stability of global and regional myocardial blood flows and regional oxygen consumptions was achieved[33] even during the stimulus of sternotomy and its associated pressor response.

Large-scale epidemiologic studies[40–42] of patients undergoing cardiac surgery, with the exception of one report,[43] have been unable to distinguish an anesthetic agent–specific factor in the causation of myocardial ischemia, a finding that may hold true even for patients with "steal-prone" coronary anatomy.[42]

Limitations of the Present Analysis

There are limitations to the present analysis that relate primarily to the model.[9,44] The study was performed as an acute experiment in open-chest dogs, and the ischemic region was established by acute occlusion of the LAD. Therefore, collateral flow to the ischemic region was dependent only on native collateral vessels, which in the dog are reasonably plentiful; *e.g.*, in the present study, ischemic region flow was approximately one third of normal flow, consistent with previous studies using acute LAD occlusion.[44,45] However, factors controlling blood flow through native collateral vessels may be different from those controlling flow through collateral vessels formed by relative underperfusion of a region of myocardium. For example, native collateral vessels are believed to have less vascular reactivity than collateral vessels formed through gradual coronary occlusion.[46–48] Moreover, the experimental design did not meet the optimal criteria for the steal model[8,9,13]; the latter uses techniques whereby occlusion is gradual and blood flow is supplied by an adjacent stenotic artery, thus allowing the development of new collateral vessels.

There was also considerable variability in the blood-flow responses to LAD occlusion in the ischemic area, both in the transmural and endocardial blood flow measurements, which were unlikely to be due to tissue-sampling errors, because wide margins between zones were allowed. This points to the possibility of between-dog variability with respect to the degree of native collateral communications and to the inherent problem of using a model that relies on epicardial collaterals to maintain blood flow to the ischemic area. Also, control measurements using adenosine to examine the degree to which redistribution phenomena might be expressed were not used and may have been useful in defining the limits of the analysis.

However, despite these limitations and in consideration of studies using similar models,[44,45,49–52] it seems that adequate collateral flow was present for the expression of blood-flow redistribution phenomena through vasodilator mechanisms, and yet redistribution did not occur despite the increased perfusion in normal LV myocardium. Myocardial blood flow responses in an ischemic area were not further compromised, and lactate production remained constant. It is possible, but unlikely, that a model with greater baseline collateral flow through ischemic collateral vessels might have yielded different results. However, such models with ischemic collateral vessels at early[8] and later[13] stages of maturity have been unable to demonstrate myocardial blood flow redistribution when coronary blood flow was held or maintained in the autoregulatory range.

The present study, as mentioned, used an acute open-chest preparation in order that more precise regional

metabolic data could be obtained. This approach places limitations on the analysis because the stability of the preparation is open to question. Arterial blood gas data, however, suggest that the model exhibited reasonable stability and that the comparisons between agent groups at each stage were valid. Time-based random effects cannot be excluded but were diminished to some extent by randomizing the order of dosages for each agent.

A legitimate concern is the depth of anesthesia during oxygen–air and fentanyl infusion ($2\ \mu g \cdot kg^{-1} \cdot min^{-1}$). The absence of movement and the indirect evidence of stable basal heart rates and blood pressures, resembling those observed in resting unstressed conscious dogs, and the absence of response to the noxious stimulus provided by acute LAD artery occlusion, though not complete confirmation, provide some proof that the dogs were unresponsive to surgical or noxious stimuli and satisfied the criteria usually applied to clinical practice.

An additional factor of importance in the present analysis is the extent to which the regional venous samples were representative of normal or ischemic myocardium. Values obtained from the normal region were directly comparable to values obtained in another study[19] from coronary sinus samples. Moreover, values were unchanged after LAD occlusion, reinforcing the conclusion that venous samples from the designated normal region were indeed representative of venous effluent from normally perfused myocardium. Venous samples from the ischemic region offer less certainty; however, some confidence can be gained from the observations that baseline values closely approximated control values from the normal region before occlusion and that LAD occlusion evoked a shift in oxygen extraction to extreme values, signaling a profound change in oxygen supply–demand relationship. Although unlikely, given the oxygen-extraction ratios obtained, there is the possibility that venous effluent samples from the ischemic region contained some blood from the surrounding myocardium. In both agent groups before the introduction of volatile agents, changes evoked by LAD occlusion were identical, and considering the experimental design, the possibility of a random factor does not diminish the validity of the comparison between agents.

The role of the background anesthetic, namely fentanyl, as an influencing factor in the results cannot be discounted, since the present results diverge from those reported by others[14,15] using similar acute animal models. The major difference lies in the observed background hemodynamic values, for which fentanyl provided conditions more closely resembling awake dogs in terms of both the myocardial blood flow measurements obtained and the systemic hemodynamic values, thus strengthening the validity of this approach for acute studies. In contrast, others,[14,15] using a variety of background anesthetics, including sodium pentobarbital infusion[15] and ketamine–flunitrazepam–piritramid–atropine,[14] induced baseline conditions of tachycardia and changes in blood pressure and contractility that were not comparable to values obtained in the present study and that may account for the divergent results.

During acute coronary artery occlusion in dogs, isoflurane induces an increase in blood flow in contiguous normal myocardium when used as a low-dose (approximately 0.5 MAC) supplement to fentanyl anesthesia. However, blood flow through collaterals to ischemic myocardium is well maintained, and the transmural steal established by occlusion is not increased. Moreover, lactate production from ischemic myocardium under the above conditions provides further confirmation that a low concentration of isoflurane does not lead to worsening of ischemia in this model. At higher isoflurane concentrations, approximating 1.5 MAC, regional myocardial oxygen supply–demand effects were similar to baseline measurements despite wide disparity in systemic hemodynamic values. In contrast to isoflurane, halothane caused a dose-dependent reduction in myocardial blood flow to normally perfused myocardium; the established imbalance in myocardial blood flow and oxygen demand in ischemic LV myocardium was not aggravated, and lactate production remained constant throughout the step-increases in end-tidal anesthetic concentrations.

Although background conditions and anesthesia in this study resembled techniques used with patients, the conclusions are not directly transferable to clinical practice: in humans, greater variability exists with respect to 1) the number, nature and physiologic responses of collateral vessels and 2) the pathology, anatomy, and time course of vessel narrowing and obstruction. However, these data highlight the importance of obtaining an objective measure of ischemia in addition to measures of regional blood flow before conclusions are made as to the propensity of isoflurane to worsen ischemia in animal and human studies.

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