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Effects of Isoflurane and Halothane on Coronary Vascular Resistance and Collateral Myocardial Blood Flow: Their Capacity to Induce Coronary Steal

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Some coronary vasodilators, paradoxically, may endanger patients with coronary artery disease by causing "coronary steal." To determine the capacity of isoflurane and halothane to cause coronary steal, the authors studied their effects on coronary vascular resistance (CVR), diastolic coronary artery pressure, and collateral myocardial blood flow. Using ameroid constrictors, chronic occlusions of the left anterior descending (LAD) coronary artery were created in ten dogs. Six to eight weeks after implantation, the dogs were anesthetized with fentanyl and pentobarbital, and a stenosis was created on the circumflex (Cx) coronary artery. Isoflurane and halothane were each administered in doses of 0.5 and 1.5 MAC. Diastolic aortic pressure was held constant. Using small catheters in the circumflex and LAD coronary arteries, the authors measured diastolic coronary artery pressures. Collateral myocardial blood flow was measured by the microsphere method. In this model, halothane and isoflurane minimally affect CVR. The maximum change in CVR, which was found during 1.5 MAC isoflurane, was −8% (not significant). Diastolic coronary pressures distal to the Cx stenosis (54.5 ± 11.5 mmHg) and distal to the LAD occlusion (44.5 ± 5.2 mmHg) did not change significantly with either isoflurane or halothane. Transmural collateral blood flow distal to the LAD occlusion (0.51 ± 0.11 cc · g^{-1} · min^{-1}) was unaltered by either drug. There was no evidence of coronary steal. Epicardial ECG S-T segments showed no evidence of ischemia. The finding of minimal direct effects of halothane and isoflurane on CVR, diastolic coronary pressure, and collateral myocardial blood flow suggest that, under the conditions of this study, neither agent, when used as an adjuvant to high-dose narcotic anesthesia, is likely to cause myocardial ischemia by a coronary "steal" mechanism. (Key words: Anesthetics, volatile: halothane; isoflurane. Artery, coronary: steal. Coronary steal. Heart: blood flow; collateral; myocardial.)

THE MOST COMMONLY used volatile anesthetic in the United States, isoflurane,[1] causes vasodilatation in the systemic circulation[2] and has been described as a powerful coronary vasodilator.[3] Systemic vasodilatation may benefit patients with coronary artery disease, since lowering preload or afterload decreases left ventricular wall stress and myocardial oxygen demand. Paradoxically, isoflurane-induced coronary vasodilatation may endanger patients with coronary artery disease, if it causes an intercoronary redistribution of blood flow or "coronary steal,"[4] increasing flow to normal myocardium by diverting it away from potentially ischemic areas. Coronary steal has been invoked as a cause of intraoperative myocardial ischemia in patients with coronary artery disease who undergo isoflurane anesthesia.[3,5]

Halothane also is a direct systemic and coronary vasodilator,[6,7] but is a much less potent vasodilator than isoflurane. Despite its direct coronary vasodilatation effect, halothane usually decreased total coronary blood flow,[6,8] because it reduces myocardial metabolic demand, resulting in reactive coronary vasoconstriction. Since net coronary blood flow does not increase with halothane, its potential for causing ischemia by inducing coronary steal should be minimal.

The comparative capacity of halothane and isoflurane to cause coronary steal has been directly tested in a recent study by Buffington *et al.*[9] This investigator used a canine model of chronic coronary occlusion with very poor collateral flow, and found in this model that halothane did not cause a coronary steal, whereas isoflurane did. Interpretation of this important study is controversial, however, because isoflurane was found to produce coronary steal only when superimposed upon an already ischemic and dysfunctional heart (see Discussion).

Coronary steal may be evaluated by measuring drug effects on coronary vascular resistance (CVR) and on the coronary collateral circulation.[10–13] Becker[10] suggested that vasodilators cause coronary steal by decreasing peripheral coronary pressure at the origin of the collateral circulation. Coronary steal is, therefore, most likely to occur when a zone of collateral-dependent myocardium is supplied by a vessel with a proximal stenosis[10] (fig. 1).

To confirm the effects of halothane and isoflurane on the coronary collateral circulation and to determine whether either drug is likely to cause a deleterious coronary steal, we created an animal model that accounts for the principles proposed by Becker. We then measured the effects of halothane and isoflurane on three measures of coronary function: CVR, diastolic coronary pressure, and collateral myocardial blood flow.

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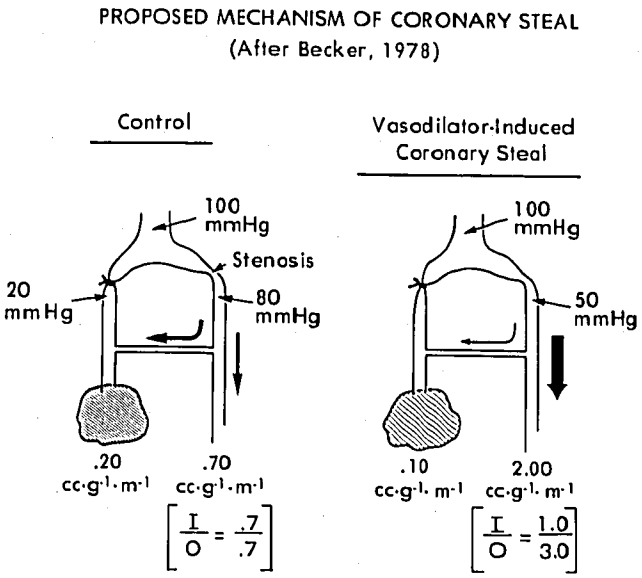

FIG. 1. "Schematic diagram of coronary circulation showing proposed mechanism of vasodilator-induced coronary steal. Coronary artery divides into two branches, one completely occluded, the other stenosed but providing collaterals to the first. In the control situation on the left, distal pressure is low in the occluded arterial bed and there is a small gradient in mean pressure across the stenosis. Flow in the ischemic region (shaded area) is 0.20 cc·g^{-1}·min^{-1} and is determined by the collateral driving pressure, or the difference between distal pressures in the bed supplying collaterals (80 mmHg) and the ischemic bed (20 mmHg). Flow in the distribution of the stenotic vessel is normal at 0.70 cc·g^{-1}·min^{-1} and is evenly distributed between subendocardium (lower value in bracket) and subepicardium (upper value). When a potent coronary vasodilator is applied (right) with blood pressure maintained constant, flow increases in the nonischemic bed to 2.00 cc·g^{-1}·min^{-1} but becomes maldistributed between subendocardium and subepicardium. In addition, pressure distal to the stenosis falls to 50 mmHg, causing a reduction in collateral driving pressure. As a result, flow to the ischemic region decreases to 0.10 cc·g^{-1}·min^{-1}, interpreted as coronary steal." (Modified, with permission, from figure 2, Becker L: Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation 57:1108, 1978.)

Materials and Methods

Preparatory Surgery: Implantation of Ameroid Coronary Constrictors

To produce collateral-dependent myocardium in ten large mongrel dogs (22–26 kg), we implanted ameroid coronary constrictors (Three Point Products, Montreal) causing gradual occlusion of the left anterior descending (LAD) coronary artery.[14,15] These hygroscopic devices slowly expand and constrict *in vivo*, eventually causing total occlusion in 1–2 weeks due to their compressive and inflammatory effects. The gradual occlusion stimulates development of the collateral circulation, usually resulting in complete occlusion without infarction.[16]

To implant the ameroid constrictor, dogs were anesthetized with halothane (1–2%), their tracheas intubated, and their lungs mechanically ventilated. A thoracotomy was performed at the fourth or fifth left intercostal space, the pericardium opened, and the LAD coronary artery dissected free just proximal to the first major diagonal branch. An ameroid coronary constrictor, 2.2–2.5 mm internal diameter (i.d.), was placed around the LAD, and the pericardium and chest wall were closed. Dogs were allowed to recover with postoperative antibiotics and analgesics. Over the next 6–8 weeks, the collateral circulation to the distal LAD-perfused myocardium was allowed to develop.

Acute Experimental Preparation

For study, each dog was anesthetized with a basal barbiturate/narcotic anesthetic consisting of pentobarbital (25 mg/kg) plus fentanyl (23 $\mu g \cdot kg^{-1} \cdot min^{-1}$ given for 10 min), followed by a continuous infusion of fentanyl for the duration of the experiment (0.8 $\mu \cdot kg^{-1} \cdot min^{-1}$). This anesthetic regimen was chosen to maintain a stable, normal heart rate and blood pressure. Tachycardia or hypertension, if permitted, may exhaust coronary vasodilator reserve and preclude the demonstration of the effects of experimental intervention.[17] The fentanyl infusion rates were calculated to maintain a fentanyl blood level of 25–30 ng/ml,[18-22] which is known to decrease anesthetic minimal alveolar concentration (MAC) by about 60% in dogs.[20] The trachea was intubated and the lungs mechanically ventilated to maintain normocapnia (Pa_{CO_2} = 36–44 mmHg).

The pericardium was opened through a left thoracotomy, and #8 French catheters were inserted into the aortic arch, left atrium, and coronary sinus. A calibrated electromagnetic flow probe (Zepeda Instruments, Seattle, WA) was positioned around the proximal circumflex (Cx) coronary artery. Distal to this, a hydraulic occluder (manufactured in our laboratory) and an adjustable arterial stenosis device (Selverstone Clamp, Codman Instruments, Pomona, CA) were positioned. A cinch made of umbilical tape was placed around the descending aorta to allow control of diastolic aortic pressure. Eight-millimeter Ag/AgCl epicardial ECG electrodes (IVM Company, Healdsburg, CA) were sutured to the epicardium overlying the distal LAD, and the left ventricular (LV) lateral wall supplied by the CX. Using a modified Herd-Barger technique,[23] silastic catheters (0.635 mm outer diameter, 0.304 mm i.d.) were inserted into the distal LAD and circumflex coronary arteries. Insertion of these catheters did not diminish resting circumflex coronary artery flow, suggesting that they caused no significant obstruction of the coronary arteries.

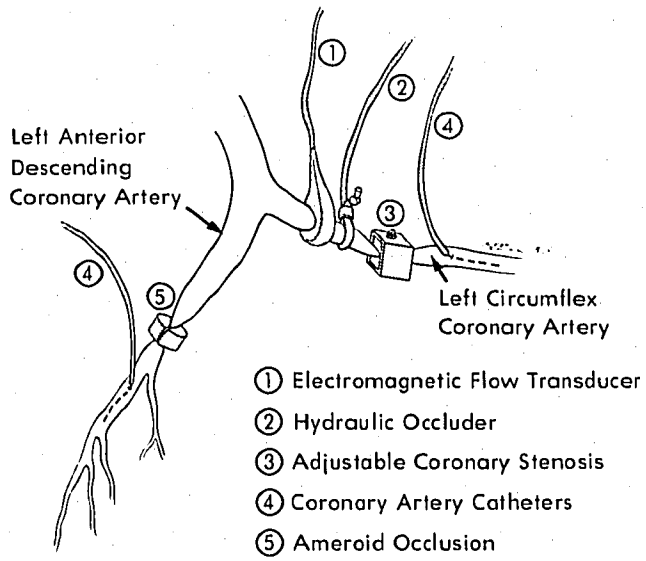

FIG. 2. Coronary instrumentation.

After application of all instrumentation, the Cx coronary artery was occluded for 10 s and peak reactive coronary flow was measured. Cx coronary flow typically increased by 200–300% after these transient occlusions, confirming that the coronary circulation retained the capacity to vasodilate and was not somehow "fixed" by the high doses of barbiturate and fentanyl used. The Cx stenosis device was then tightened to limit peak flow after subsequent 10-s occlusions to 50–60% of that found after the first measurement. This significant coronary stenosis did not decrease resting flow. This model, a single coronary occlusion with a stenotic vessel supplying collateral circulation (fig. 2), mimics a common finding in patients with multivessel coronary artery disease.[24]

STUDY PROTOCOL

Each study included a control period (pentobarbital/fentanyl anesthesia only) followed by four experimental periods: halothane (0.5 MAC and 1.5 MAC) and isoflurane (0.5 MAC and 1.5 MAC) (fig. 3). The values used for halothane MAC and isoflurane MAC in dogs were 0.87% and 1.5%, respectively.[25] The order of administration of halothane and isoflurane was alternated in successive experiments, to minimize the effects of any time-dependent deterioration of the preparation. Both high and low dosages of the first anesthetic were administered before proceeding to the second, but the order of dose change (high to low, *vs.* low to high) was alternated. End-tidal anesthetic concentrations were measured by mass spectrometry (Perkins-Elmer, Pomona, CA), and were held constant for 10 min prior to experimental measurements. A 30-min washout period followed halothane and isoflurane periods to ensure that the end-tidal concentration of the preceding vapor had fallen below 0.08%. We maintained diastolic pressure at the control value with the aortic cinch, to avoid changes in collateral blood flow due to decreased diastolic pressure.[26]

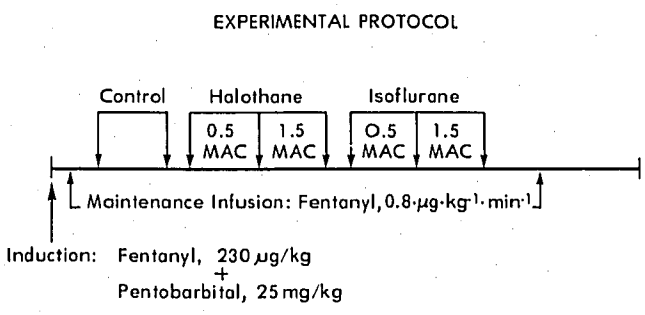

FIG. 3. Experimental protocol: anesthesia was induced with pentobarbital and fentanyl, maintained with fentanyl infusion. The order of administration of halothane and isoflurane was alternated.

MEASUREMENTS: HEMODYNAMICS AND MYOCARDIAL OXYGEN BALANCE

Aortic pressure, left atrial pressure, heart rate, and LAD and Cx coronary artery diastolic pressure were measured during each experimental period. Arterial and coronary sinus hemoglobin O_2 saturation were measured by hemoximeter (Radiometer, Copenhagen). P_{O_2} and P_{CO_2} were measured with an ABL-II blood gas analyser (Radiometer, Copenhagen).

Myocardial oxygen consumption (MVO_2) was calculated for each experimental period by multiplying microsphere-measured myocardial blood flow by the arterial-coronary sinus oxygen content differences ($C_{aO_2} - C_{csO_2}$). Myocardial oxygen extraction was calculated as:

$$O_2 \text{ Extraction } (\%) = \frac{C_{aO_2} - C_{csO_2}}{C_{aO_2}} \times 100$$

CORONARY ARTERY PRESSURES

Diastolic coronary pressures were recorded at end-diastole, which was defined as the time immediately before the pressure upstroke due to systolic compression of the coronary arteries.

Coronary vascular resistance (CVR) was calculated for each period using a hydraulic analogue of Ohm's law:

$$CVR = \frac{P_{ao} \text{ diastolic} - P_{la}}{LVBF},$$

where P_{ao} = diastolic aortic pressure; P_{la} = left atrial pressure; and LVBF = left ventricular blood flow.

Many different formulations for calculating CVR have been proposed, using different combinations of mean and instantaneous pressures and flows. These formulae are controversial, and the results can be misleading for reasons recently summarized by Marcus and Klocke.[27,28] The actual back pressure to coronary flow (P_{zf}) is higher than coronary venous pressure or left atrial pressure, and may be altered by anesthetic intervention.[29] Additionally, the driving pressure for coronary flow may be better estimated by mean aortic or mean coronary diastolic pressure than by end-diastolic pressures. Finally, coronary resistance varies inversely with pressure, as reflected by the nonlinearity of the diastolic pressure-flow relationship.[27] Therefore, whatever the method of calculation, modest changes in CVR must be interpreted cautiously. A given change in calculated CVR does not necessarily reflect a proportionate change in coronary vascular *geometry* or "tone."

Epicardial ECG

Monopolar epicardial ECGs were recorded over the collateral-dependent distal LAD zone and over the LV lateral wall, a one-tenth normal surface electrocardiographic sensitivity (1 mv/mm recording).[30,31] S-T segment height at each site was used as an index of the severity of local myocardial injury, and was measured relative to the Q-T baseline, in the midportion of the S-T segment.

Myocardial Blood Flow

During each experimental period, regional myocardial blood flow was measured using radionuclide-labeled microspheres.[32] Different species of microspheres (^{85}Sr, ^{95}Nb, ^{113}Sn, ^{57}Co, ^{54}Mn, ^{51}Cr, ^{153}Gd, ^{114}In, ^{65}Zn), 15 microns in diameter, were prepared in a dextran solution with a small amount of Tween-80® added. One to three million microspheres were suspended by vigorous agitation for 30 s, then injected into the left atrium over a 20-s period. Simultaneously, a 3-min reference sample was withdrawn from the aorta at a rate of 10 ml/min, and was collected in six sequential fractions, allowing us to define the end of the microsphere distribution. Reference flow (cc/min) was calculated by dividing the weight of the 3-min reference sample by 3, and by the specific gravity of blood, 1.05.

Methods of Myocardial Tissue Sampling

Dogs were killed by injection of KCl and the heart excised. We verified complete occlusion of the LAD coronary artery by filling the proximal LAD with saline solution under 150 mmHg pressure and confirming that no saline would flow past the ameroid constrictor site. The zone of collateral-dependent myocardium was then identified by dye perfusion.[33] Eighteen-gauge catheters were inserted into the right, the distal LAD, and the left main coronary arteries, which were then simultaneously perfused with different-colored dextran solutions delivered at the pre-mortem mean arterial pressure. The heart was fixed in formalin for 5–7 days before dissection for gamma counting. No specimens had gross evidence of myocardial infarction.

At dissection, each heart was cut into four slices perpendicular to the long axis of the left ventricle. Transmural samples from the center of the normal and collateral-dependent zones were taken and divided into three approximately equal portions representing endocardial, midmyocardial, and epicardial flow.

If a potent vasodilator increases myocardial blood flow in normal tissue but decreases flow in adjacent collateral-dependent tissue by a steal mechanism, the border zone between normal and collateral-dependent myocardium may show unchanged or increased flow, even though collateral blood flow has actually decreased.[34] To ensure that our myocardial tissue samples accurately represented the true collateral-dependent myocardium and not a border zone, samples were taken only from the center of the area identified by dye perfusion. In most cases, the apparent area of collateral-dependent myocardium weighed at least 25 grams, and tissue samples from the center of this zone weighed at least 3 to 5 grams. Samples of this size ensured a harvest of 400 or more microspheres per sample, and a precision of our microsphere blood flow measurements of about 10%.[35]

Myocardial blood flow (MBF) was calculated for each layer using the equation:

$$MBF = \frac{Counts_t \times Flow_{ref}}{Counts_{ref}},$$

where $Counts_t$ = counts in the tissue sample; $Counts_{ref}$ = counts in the reference sample; and $Flow_{ref}$ = reference sample flow.

Methods of Analysis

Repeated-measures analysis of variance was used to analyse measurements of collateral blood flow, coronary pressure, and all other hemodynamic variables. For multiple comparisons among groups which were indicated by ANOVA results, we used the Newman-Keuls test. Two-tailed *t* tests were also used where appropriate. Differences were considered statistically significant when $P < 0.05$.

TABLE 1. Hemodynamics

	Control	Halothane 0.5 MAC	Halothane 1.5 MAC	Isoflurane 0.5 MAC	Isoflurane 1.5 MAC
Heart rate (bpm)	68.8 ± 10.8	78.7 ± 18.9	84.9 ± 16.5*	80.2 ± 20.6	85.0 ± 23.6*
Systolic BP (mmHg)	98.3 ± 11.5	93.9 ± 10.2*	88.7 ± 10.0*	94.6 ± 11.4	91.4 ± 12.4*
Diastolic BP (mmHg)	57.8 ± 9.4	56.8 ± 9.6	55.6 ± 8.4	56.4 ± 9.8	58.7 ± 10.9
Mean BP (mmHg)	71.2 ± 8.9	69.1 ± 9.5	66.5 ± 8.1*	69.0 ± 9.3	69.5 ± 10.7
LA pressure (mmHg)	4.6 ± 1.6	5.3 ± 2.7	6.6 ± 3.0*	4.3 ± 1.9	6.7 ± 2.6*

All values are mean ± SD; n = 10.

* Significantly different from control, $P < 0.05$.

Results

Hemodynamics and Myocardial Oxygen Balance

We obtained normal mean values for control blood pressure and heart rate (table 1). Heart rate increased slightly (mean change 23%) at 1.5 MAC isoflurane and halothane, with greater variability during 1.5 MAC isoflurane. The reason for the slightly increased heart rate at deeper levels of anesthesia is not clear, but this finding is consistent with prior reports of increased heart rate in dogs given both halothane[36] and isoflurane.[37] Diastolic aortic pressure was controlled to a mean of 57 mmHg. Left atrial pressures were normal during the control period, but increased to similar values during 1.5 MAC isoflurane and halothane.

Coronary sinus O_2-hemoglobin saturation was 41% during the control period of barbiturate-fentanyl anesthesia (table 2). This relatively high saturation is presumably due to the slow heart rate and low oxygen consumption of the control state. Only the 1.5 MAC isoflurane group had a significant increase in coronary sinus O_2 saturation and a decrease in left ventricular O_2 extraction. Left ventricular oxygen consumption did not change significantly with anesthetic interventions ($P = 0.38$).

Diastolic Coronary Pressures

Neither isoflurane nor halothane, at either dose, changed LAD ($P = 0.08$) or Cx ($P = 0.15$) diastolic pressures (fig. 4). Diastolic pressures in the occluded, collateral-dependent LAD coronary artery were 8–10 mmHg lower than the corresponding CX pressures. This indicates good collateral supply to the LAD-dependent myocardium but substantial resistance in the collateral circulation between LAD and CX.

Neither isoflurane or halothane ($P = 0.61$) altered mean coronary vascular resistance (fig. 5).

Epicardial ECGs

Local injury caused by suturing the epicardial electrodes produced initial but transient S-T segment elevations that resolved in 10–20 min. ECG complexes were normal at the time the first control period measurements were made, and did not change throughout this study.

Myocardial Blood Flow

Neither isoflurane nor halothane ($P = 0.20$) altered total left ventricular blood flow (table 3).

Flow to the collateral-dependent LAD myocardium equalled that in the corresponding Cx zone and did not change with the administration of either isoflurane or halothane. Neither agent decreased flow in the vulnerable subendocardium. There was no "steal" of collateral blood flow from the LAD to the CX zone; there was no redistribution of flow from the endocardium to epicardium (*i.e.*, there was no subendocardial steal).

Inner:outer (I:O) zone myocardial blood flow ratios were normal in the circumflex zone (about 1.00) and did not change with anesthetic interventions. I:O flow ratios in the LAD zone were somewhat lower, ranging from 0.74–0.88. These lower LAD I:O ratios did not suggest ischemia, however, because they were not

TABLE 2. Myocardial Oxygen Balance

	Control	Halothane 0.5 MAC	Halothane 1.5 MAC	Isoflurane 0.5 MAC	Isoflurane 1.5 MAC
Arterial O_2-Hgb saturation (%)	99.8 ± 0.5	99.8 ± 0.4	99.8 ± 0.5	99.8 ± 0.5	99.5 ± 0.7
Coronary sinus O_2-Hgb saturation (%)	41.5 ± 6.5	42.9 ± 8.5	42.6 ± 9.6	47.6 ± 10.6	52.7* ± 10.9
LV O_2 consumption ($cc \cdot 100\ g^{-1} \cdot min^{-1}$)	4.87 ± 1.2	5.02 ± 1.5	4.43 ± 0.7	4.17 ± 0.5	4.05 ± 0.9
LV O_2 extraction (%)	65.5 ± 0.1	64.0 ± 0.1	64.0 ± 0.1	58.8 ± 0.11	53.1* ± 0.11

All values are mean ± SD.

* Significantly different from control, $P < 0.05$.

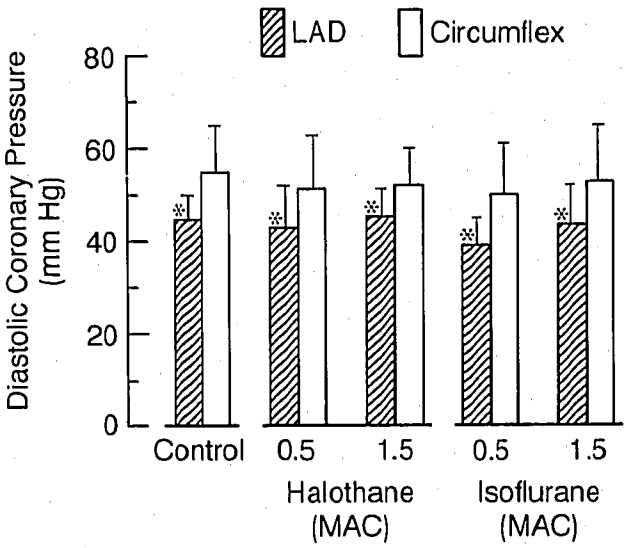

FIG. 4. Effects of halothane and isoflurane on diastolic coronary pressures.

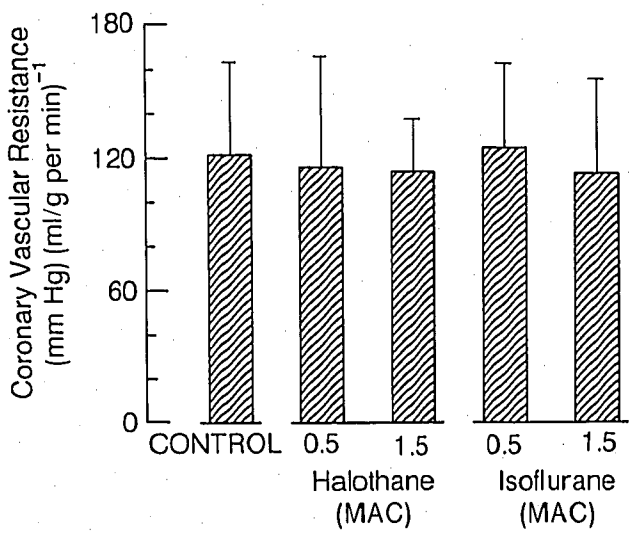

FIG. 5. Effects of halothane and isoflurane on coronary vascular resistance.

caused by decreased endocardial blood flow, but, rather, by a slightly increased epicardial blood flow in the collateral-dependent LAD zone. The high local concentration of predominantly epicardial collaterals may account for the slight increase in epicardial LAD flow under all experimental conditions.

Discussion

Our data indicate that, in dogs anesthetized with fentanyl and pentobarbital, the effects of halothane and isoflurane on diastolic coronary pressure (fig. 4), coronary vascular resistance (fig. 5), and collateral myocardial blood flow (table 3) are minimal. The smallness of these effects suggests that, under these conditions, neither halothane not isoflurane is likely to cause myocardial ischemia by a coronary steal mechanism.

Effects of Halothane

Our results for halothane are compatible with prior reports of the effects of halothane on coronary blood flow and CVR. The effects of halothane on diastolic coronary pressure have not been previously studied.

Most prior reports indicate decreased coronary blood flow with halothane, which is well-correlated with de-

TABLE 3. Total and Regional Left Ventricular Blood Flow

	Control	Halothane 0.5 MAC	Halothane 1.5 MAC	Isoflurane 0.5 MAC	Isoflurane 1.5 MAC
Total left ventricular blood flow ($cc \cdot g^{-1} \cdot min^{-1}$)	0.50 ± 0.10	0.49 ± 0.17	0.43 ± 0.05	0.44 ± 0.08	0.55 ± 0.19
Circumflex, transmural blood flow ($cc \cdot g^{-1} \cdot min^{-1}$)	0.48 ± 0.10	0.50 ± 0.15	0.46 ± 0.06	0.50 ± 0.10	0.52 ± 0.22
Circumflex, inner third blood flow ($cc \cdot g^{-1} \cdot min^{-1}$)	0.47 ± 0.15	0.51 ± 0.14	0.46 ± 0.09	0.47 ± 0.10	0.48 ± 0.20
Circumflex, outer third blood flow ($cc \cdot g^{-1} \cdot min^{-1}$)	0.48 ± 0.12	0.49 ± 0.17	0.49 ± 0.12	0.50 ± 0.10	0.56 ± 0.27
Circumflex, I:O ratio	1.02 ± 0.41	1.08 ± 0.27	0.97 ± 0.21	0.95 ± 0.24	0.94 ± 0.49
LAD, transmural blood flow ($cc \cdot g^{-1} \cdot min^{-1}$)	0.51 ± 0.11	0.58 ± 0.23	0.51 ± 0.09	0.47 ± 0.09	0.58 ± 0.17
LAD, inner third blood flow ($cc \cdot g^{-1} \cdot min^{-1}$)	0.45 ± 0.19	0.52 ± 0.27	0.42 ± 0.11	0.38 ± 0.11	0.46 ± 0.18
LAD, outer third blood flow ($cc \cdot g^{-1} \cdot min^{-1}$)	0.59 ± 0.15	0.62 ± 0.26	0.59 ± 0.17	0.56 ± 0.16	0.72 ± 0.29
LAD, I:O ratio	0.79 ± 0.32	0.88 ± 0.33	0.75 ± 0.25	0.74 ± 0.20	0.74 ± 0.36

No experimental values were significantly different from corresponding control values. No LAD values were significantly different from corresponding circumflex values by two-tailed *t* test. All values are mean ± SD.

creased metabolic demands.[7,36,38] CVR is reported to be unchanged[39] or slightly decreased.[7] In the current experiment, metabolic demands (LVO_2 consumption) did not decrease significantly with halothane, even at 1.5 MAC. This is a surprising finding, but can be explained by considering how the major determinants of myocardial oxygen demand were affected in this experiment. As halothane was added to the basal anesthetic, the aortic cinch was tightened to hold diastolic blood pressure constant. This increase in impedance to ejection probably increased left ventricular wall stress, one major determinant of myocardial oxygen consumption, although this factor was not measured. Heart rate, a second determinant of MVO_2, increased slightly (23%). Contractility, the third major determinant of MVO_2, was certainly decreased, although we did not quantitate this change. Thus, two of the major determinants of MVO_2 (wall stress, heart rate) increased, whereas contractility decreased, the net result being no significant change in left ventricular MVO_2.

Sivarajan *et al.*[40] and Buffington *et al.*[9] have also used ameroid occlusions of the LAD to test the effects of halothane on coronary collateral flow. Buffington *et al.*[9] studied dogs 3–5 weeks after ameroid occluder implantation, and found that 1 MAC halothane did not cause coronary steal. Sivarajan used awake controls, with consequently higher heart rates and arterial pressures than in our study, and found that 1% halothane decreased flow in both normal and collateralized myocardium, but had no disproportionate effect on the collateralized zone. Superimposition of pacing-induced tachycardia, not tested in our study, produced severe hemodynamic decompensation and decreased collateral flow in most cases. Our study confirms that halothane has no disproportionate effect on collateral-dependent myocardium in absence of tachycardia. The differences in results (equally decreased collateral and normal myocardial blood flow in Sivarajan's study *versus* no significant change in either variable in our study) are accounted for by significant differences in control state hemodynamic measurements due to the basal anesthetic in our experiment.

Effects of Isoflurane

We found that, under the conditions of this study, isoflurane does not significantly decrease coronary vascular resistance or diastolic coronary pressures, and is, therefore, not a potent coronary vasodilator when added to a basal barbiturate/narcotic anesthetic. Myocardial oxygen extraction did decrease with 1.5 MAC isoflurane, indicating that oxygen delivery was increased disproportionately to oxygen consumption, and confirming that the net effect of isoflurane is coronary vasodilatation. However, left ventricular blood flow did not increase significantly with isoflurane, at any dose. These data are most consistent with a moderate vasodilatory action of isoflurane, causing decreased myocardial oxygen extraction, which is counterbalanced by slightly decreased myocardial metabolic demands (measured left ventricular oxygen consumption decreased by a mean of 17%, although not statistically significant). This conclusion is at variance with several published reports of the effects of isoflurane on CVR, which is discussed below.

Merin *et al.*[41] found, as did we, that a high dose of isoflurane (3%) had no significant effects on coronary vascular resistance, when compared to a low dose (1.5%). Myocardial blood flow did not increase with the higher dose of isoflurane, but fell in proportion to the decrease in oxygen consumption. However, Merin's study measured only the comparative effects of two doses of isoflurane. The study included no other awake or anesthetized control group for comparison, and allowed significant changes in blood pressure, so is not directly comparable to our current study.

In contrast, other investigators have reported that isoflurane can decrease CVR by up to 40%,[9,42–44] and can increase coronary blood flow by up to 98%.[45] The differences between those results and ours may be explained by several factors.

First, decreasing aortic pressure *normally* caused decreased CVR, due to autoregulation of coronary blood flow. That is, over a wide range of aortic pressures (MAP = 50–130), coronary blood flow tends to remain relatively constant.[28] Even though coronary autoregulation may be significantly blunted by isoflurane, there is no evidence to date that it is totally eliminated. Some prior reports of decreased CVR due to isoflurane[42–44] must, therefore, be considered in this context, as the isoflurane-induced decrements in CVR have often been reported in association with significantly decreased systemic pressures. In such circumstances, the isoflurane-induced decrease in CVR could be due to either direct coronary vasodilatation or to an indirect effect of isoflurane: decreased blood pressure causing autoregulatory coronary vasodilatation. In fact, both effects may be significant, but the distinction between direct and indirect effects of isoflurane is important.

For example, Priebe found that mean CVR decreased 39% with 1.8% isoflurane, compared to a fentanyl/droperidol anesthesia control state.[44] CVR decreased because coronary blood flow fell only slightly (−15%), despite lower mean arterial pressure (−41%) and lower myocardial oxygen consumption. However, because diastolic hypotension was induced, it was impossible to quantify the relative contribution of indirect effects (hypotension-induced autoregulation) and direct coronary effects of isoflurane.

Similarly, Hysing anesthetized chronically instrumented dogs with isoflurane 1.6% and 3.0%, comparing hemodynamic measurements to the awake control state.[43] Isoflurane caused a 23% decrease in calculated CVR, compared to the awake controls, and no change in CBF. Again, because blood pressure decreased significantly (MAP, −23%), it was impossible to distinguish between the direct and indirect coronary effects of isoflurane or to quantify the direct coronary effects of this drug.

Gelman *et al.*[37] found, however, that isoflurane significantly increased myocardial blood flow over awake control values (+23% at 2 MAC isoflurane), despite decreased cardiac output and blood pressure. Thus, when administered as the sole anesthetic agent, isoflurane is indeed a significant coronary vasodilator in dogs. The discrepancy (increased myocardial blood flow with isoflurane in Gelman's study *vs.* no significant change in our study) is almost certainly related to differences in control conditions, including the absence of adjunctive anesthesia and the generally higher blood pressures in Gelman's experiment.

Sill *et al.*[45] used quantitative coronary angiography to determine the site of isoflurane-associated coronary vasodilatation, and found that isoflurane did not dilate epicardial coronary arteries. To quantify the effects of isoflurane on coronary blood flow at different levels of MVO_2, blood pressure was manipulated at different isoflurane dosages. An intraaortic balloon was inflated to raise blood pressure, and 10–20 cm H_2O positive end-expiratory pressure (PEEP) was added to decrease it. At comparable levels of MVO_2, coronary blood flow was found to be up to 98% greater with 2.25% isoflurane than during a control state of fentanyl/pentobarbital anesthesia. However, the largest changes in coronary blood flow in Sill's experiment were due to PEEP, not to isoflurane, thus making it difficult to isolate the isoflurane dosage as an independent variable and to quantify its potency as a coronary vasodilator. Nevertheless, Sill's study confirms that isoflurane is a coronary vasodilator, and furthermore documents that its primary site of action is on coronary arterioles, not on large epicardial arteries.

The effect of isoflurane on diastolic coronary pressure has not previously been studied, but Buffington *et al.*[9] has described a significant decrease (up to 38%) in mean coronary artery pressure when isoflurane is added in the presence of constant, non-pulsatile flow through a coronary perfusion cannula. Although non-pulsatile coronary perfusion is atypical of normal physiological conditions, this finding is additional evidence of the coronary vasodilatory properties of isoflurane. In our study, diastolic coronary pressure was measured during pulsatile coronary flow, and was not decreased significantly by isoflurane. The difference between our findings and those of Buffington is probably due to the much higher "control" coronary pressures in Buffington's experiment, permitting a greater downstream pressure drop with a given degree of isoflurane-induced vasodilatation.

Two recent studies suggest that isoflurane can redistribute coronary blood flow and induce myocardial ischemia in canine models of coronary artery disease. Priebe demonstrated that isoflurane-induced hypotension to a MAP of 70 mmHg can induce ischemic myocardial dysfunction in the area distal to a "critical" (resting CBF, −10%) coronary stenosis. Regional ischemic dysfunction worsened when isoflurane reduced the MAP to 50 mmHg.[46] This study confirms that addition of isoflurane in the setting of critical coronary stenosis can cause myocardial ischemia, either due to hypotension or to coronary steal, although it was not possible to determine which mechanism was operating. In our study, hypotension was prevented, and no myocardial ischemia was found.

Buffington[9] used, as we did, a canine model of ameroid-induced LAD coronary occlusion to study the potential of isoflurane to cause coronary steal. In that report, experiments were performed 3–5 weeks after ameroid implantation, so the coronary collateral circulation was substantially less mature than in our study, and should have been more susceptible to coronary steal. Even so, when isoflurane (0.94%) was added to a chloralose anesthesia control state, with coronary blood flow held at the autoregulated level (labelled "Full" flow in Buffington's paper), Buffington found no evidence of coronary steal. There was no significant redistribution of myocardial blood flow (microsphere method), and no evidence of ischemic contractile dysfunction as measured by sonomicrometry, a methodology which is more sensitive than the epicardial ECG measurements used in our experiment.

However, Buffington then eliminated any residual vasodilator reserve in the risk zone by decreasing coronary inflow until the risk zone became ischemic (systolic contraction, −27% of control value at this "Mid Range" flow). Under these conditions, when superimposed on pre-existing myocardial ischemia, 0.94% isoflurane decreased systolic contraction disproportionately in the risk zone, and caused a regional and transmural redistribution of blood flow typical of coronary steal. At this same "Mid Range" flow, an unspecified dose of the potent coronary vasodilator adenosine was also found to cause coronary steal, whereas 0.87% halothane did not.

Our study is in agreement with that of Buffington, in that we found no evidence of coronary steal when isoflurane is supplied to the canine heart with a recent

ameroid-induced LAD occlusion, in absence of major hemodynamic changes. We did not test the effects of the addition of isoflurane to a preexisting ischemic state, but agree with Buffington's finding that isoflurane (and, for that matter, any small-vessel coronary vasodilator) may cause a coronary steal in this circumstance.

Could the pentobarbital and fentanyl in our experiment have directly counteracted or masked the effects of halothane and isoflurane on coronary vessels? Barbiturates do cause vascular smooth muscle relaxation,[47] but fentanyl is not known to have potent direct actions on the coronary circulation.[48] However, it may be important that fentanyl reduces basal sympathetic activity during anesthesia with volatile agents,[49] and reduces sympathetic response to surgical incision in patients anesthetized with these agents.[49,50] By increasing sympathetic blockage, narcotic adjuvants might decrease the incidence of intraoperative ischemia associated with volatile anesthetics by minimizing increases in heart rate, blood pressure, myocardial contractility, or coronary artery tone. This possibility remains speculative, however, and is an area for future study.

The fact that myocardial oxygen consumption and extraction were low in the control state in our experiment indicates that there was an element of relative coronary vasodilation during the control measurements, even though control coronary flows were not high. However, the coronary circulation did remain responsive to vasodilating stimuli; repeated brief coronary occlusions during creation of the CX coronary stenosis reproducibly caused reactive hyperemic responses and increased coronary flow by 200–300%. Thus, with the addition of halothane or isoflurane, we should have found a significant increase in LV blood flow, were either of these agents powerful coronary vasodilators.

Methodological Remarks: Appropriateness of this Canine Model

The normal canine collateral circulation consists almost exclusively of epicardial interconnections, in contrast to normal human collaterals, which are primarily endocardial.[16] The pig, which was exclusively endocardial collaterals in the unstimulated state, probably better mimics *normal* human collateral physiology.[24] However, both epicardial and endocardial collaterals are present with human coronary artery disease.[51] Consequently, even though no animal model exactly mimics the human pathological condition, the dog with a chronic coronary occlusion can serve as a satisfactory model of human collateral function in disease. One limitation to the epicardial location of canine collaterals is that they are less sensitive to interventions affecting ventricular diastolic pressure, a factor which may significantly affect endocardial collaterals in humans. Another limitation of this model is unknown species differences in response to drugs; dogs may have coronary responses to isoflurane and halothane that are not typical of human responses. However, canine coronary responses to other vasodilators are known to be similar in direction and magnitude to human responses.[52]

Six weeks after ameroid occluder implantation, canine collaterals are relatively mature, can supply normal flow under resting conditions, and have some ability to vasodilate.[28] If these vessels are too mature, their vasodilator reserve will allow coronary vasodilators to increase collateral blood flow, thus avoiding coronary steal. On the other hand, if insufficient time is allowed after occluder implantation, coronary occlusion may not have occurred, or may be precariously near to completion. If the latter is true, small changes in blood pressure or heart rate will cause ischemia, thereby confounding the study of coronary steal. We chose to conduct these experiments at 6–8 weeks after ameroid implantation because prior reports predict a greater than 90% occlusion rate at this stage.[16] Postmortem examinations revealed a 100% occlusion rate in this experiment.

One limitation of our model is that we used no "positive control," *i.e.*, no drug known to cause coronary steal, such as adenosine, was given. This was because the number of different microspheres that could reliably be obtained for any one experiment was limited. We felt it more important to thoroughly test the effects of at least two different doses of both isoflurane and halothane in the same animals, than to add another experimental drug to the protocol. It should be noted that Buffington *et al.* did use a positive control (adenosine), but did not find isoflurane-induced coronary steal in a model with even worse collateral supply than ours, unless acute ischemia was also superimposed by a controlled decrease in coronary flow.[9]

In summary, in dogs anesthetized with pentobarbital and fentanyl, the additive effects of halothane and isoflurane on coronary vascular resistance are small, if diastolic hypotension is avoided. In this model with relatively mature collateral circulation, neither agent significantly decreased diastolic coronary pressure, which is probably a requirement for any drug to induce coronary steal.[10] Neither halothane or isoflurane, when superimposed on a basal barbiturate/narcotic anesthetic, decreased collateral myocardial blood flow or caused a measurable coronary steal.

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