Anesthesiology
76:113–122, 1992

Dose–Response Relationship of Isoflurane and Halothane versus Coronary Perfusion Pressures

Effects on Flow Redistribution in a Collateralized Chronic Swine Model

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The authors studied the redistribution of myocardial blood flow in a collateral-dependent (CD) zone as a function of coronary perfusion pressure (CPP) during isoflurane and halothane anesthesia. A swine model with CD myocardium distal to a chronically occluded left anterior descending coronary artery was developed and studied. Sixteen piglets were allowed to grow for 8–10 weeks after banding of the left anterior descending coronary artery. They were randomly anesthetized with either isoflurane (n = 8) or halothane (n = 8) as the sole anesthetic, which was used to regulate specific CPP. The resultant regional myocardial blood flows were measured using radiolabeled microspheres. Four randomly allocated CPPs, of 30, 40, 45, and 55 mmHg, were studied in each animal. Four additional collateralized animals were anesthetized with α-chloralose, and the same CPPs were obtained using an intravenous adenosine infusion (1–5 μM kg^{-1}) to validate this model. There was a proportional decrease in heart rate and blood pressure in both the isoflurane and and the halothane group with CPP. Cardiac output was significantly decreased in the halothane group at 30 mmHg when compared to 55-mmHg CPP, but it was maintained in the isoflurane group. Systemic vascular resistance was significantly lower in the isoflurane group at 30 and 40 mmHg when compared to 55-mmHg CPP. Both the isoflurane and the halothane group showed a proportional and significant decrease in endo-, mid-, and epicardial blood flows at 30-mmHg CPP when compared to baseline. In both CD and normal perfusion zones, isoflurane consistently sustained a higher endocardial blood flow than halothane (5.7–41.1%). Although both anesthetics minimally affect coronary vascular resistance, isoflurane appears to be a relatively more potent coronary vasodilator than halothane over the CPPs studied. No significant intercoronary or transmural redistribution of blood flow was present with either anesthetic at any decrement of CPP. Intravenous adenosine was a definite positive control, causing significant intercoronary and transmural coronary steal from CD endocardial regions in a dose-response fashion. The authors conclude that neither isoflurane nor halothane as the sole anesthetic in clinical concentrations causes significant coronary vasodilation or coronary steal from 55 to 30 mmHg CPP in a swine model of chronic coronary occlusion with collateral development. (Key words: Anesthesia: cardiovascular. Anesthetics, volatile: isoflurane; halothane. Artery, coronary: steal; coronary perfusion pressure. Heart: blood flow; collateral; myocardial.)

THERE IS EVIDENCE that isoflurane is a direct-acting coronary vasodilator.[1–6] This coronary vasodilation has been contended to cause redistribution of myocardial blood flow away from collateral-dependent (CD) myocardial regions, toward areas for which no additional metabolic need exists, resulting in ischemia in the flow-limited areas.[1,2,4] Thus, it has been suggested that isoflurane should be avoided in patients with known coronary artery disease.[7] However, myocardial ischemia was recently shown not to be more commonly associated with isoflurane anesthesia, even in patients with steal-prone coronary anatomy.[8] Hemodynamically, it has been shown by Tarnow *et al.*[9] that with isoflurane anesthesia, heart rates could be paced to considerably higher levels before ischemic ECG patterns occurred in patients with coronary artery disease compared to the awake state. Metabolically, isoflurane has been shown to attenuate myocardial lactate production during sternotomy in patients undergoing coronary artery bypass graft surgery.[10]

Whether isoflurane causes coronary steal is still controversial, as examined by numerous experimental models.[4,11–15] The discrepancies in these studies may be attributable to differences in animal models of single-vessel[11,14] or multivessel coronary artery disease. However, studies of isoflurane in models of multivessel coronary artery disease also have produced conflicting results.[4,13,15] The inhalational anesthetics were studied in addition to a basal anesthetic in some experimental models.[4,11,14] Also, coronary perfusion pressure (CPP), which has a direct effect on the distribution of coronary blood flow, was considerably different when isoflurane and halothane groups were compared in one study.[4] A positive control study with adenosine was performed in only two of these studies.[4,15] In addition, differences in endogenous or enhanced collateral circulation in these models[4,13,15] may further complicate the issue of coronary steal by isoflurane.

This study was designed to test the hypothesis that redistribution of myocardial blood flow away from a CD

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Received from the Department of Anesthesia, University of Iowa College of Medicine, Iowa City, Iowa. Accepted for publication September 10, 1991. Supported in part by a grant from Anaquest. Presented in part at the 64th Congress, International Anesthesia Research Society annual meeting, Honolulu, Hawaii, March 1990.

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zone is more dependent on CPP than on the specific inhalational anesthetic being used. A chronic swine model, in which CD myocardial regions were induced[16] to mimic diseased collateral vessels in human, was used. After administering isoflurane or halothane as the sole anesthetic in question to produce the specific decrements in CPP (dose) in random order, measurements were made of resultant regional myocardial blood flow distribution (response). In other experiments, adenosine was administered as a "positive control" to validate this chronic swine model in producing coronary steal.

Materials and Methods

Preparation of Collateralized Coronary Circulation in The Swine Model

All experimental work conformed to NIH guidelines for the care and use of laboratory animals, and was approved by the Animal Care and Use Committee of the University of Iowa.

The induction of functional coronary collateral vessels in swine heart was describe in detail by Millard.[16] Approximately 3-week-old, farm-bred pigs weighing 6–8 kg were anesthetized *via* mask with halothane (0.5–1.5% end-tidal). After tracheal intubation (5–5.5-mm ID cuffed tube), the lungs were mechanically ventilated. Muscle relaxation was maintained by succinylcholine infusion. Through a left thoracotomy at the third intercostal space under sterile conditions, the pericardium was incised and the left atrial appendage reflected to expose the proximal left anterior descending coronary artery (LAD). Avoiding the anterior septal artery, a nonocclusive band of polyethylene tubing (PE-205, ID 1.57 mm, OD 2.08 mm) was secured with a 5-0 silk suture encircling the proximal one third of the LAD. A Doppler flow velocity probe (20 MHz) was used to assure continued distal flow, demonstrating that the band was not occlusive. The pericardium and chest were closed, and intercostal nerve blocks were performed using bupivacaine 0.25% (2–3 ml per nerve) for analgesia during recovery. Animals were given penicillin 100,000 units/kg twice daily for 7 days. The animals were allowed to grow for 8–10 weeks. After this time, a region of CD myocardium with limited mechanical reserve develops. The existence of collateral vessels was confirmed by angiography.[16] These are not previously existing collateral vessels and are therefore reasonable models of disease-related human collateral vessels.

During experiments, sixteen of these "collateralized" pigs (30–35 kg) were randomly allocated to either the halothane or isoflurane group. Anesthesia was induced with the selected inhalational agent and oxygen *via* mask. Succinylcholine was infused *via* an ear vein (20-G intravenous catheter) throughout the study. After tracheotomy, mechanical ventilation was employed *via* a 6.0-mm ID cuffed endotracheal tube to maintain normal Pa_{CO_2} and *p*H. Anesthesia for surgery and monitoring catheter insertion was maintained initially with 1 MAC of the inhalational agent. Continuous intraoperative monitors included ECG, end-tidal vapor concentration (Beckman LB-2 medical gas analyzer), right femoral arterial pressure (16-G catheter), and right internal jugular venous pulmonary artery catheter (5-Fr). A median sternotomy and pericardial cradle was established.

The constrictive band on the LAD was identified and was completely ligated to ensure total occlusion. The latter was validated by a Doppler flow velocity probe placed distal to the occlusion. If no or insufficient collateral coronary circulation had developed to supply myocardium distal to the LAD distribution, ventricular fibrillation ensued, and the animal died within 5–10 min. In the animals that did have a region of collateral-dependent (CD) myocardium, the experiment continued (n = 16). Further instrumentation included a left atrial catheter (PE-205) for microsphere injection; right internal carotid and left femoral arterial catheters (PE-190) for reference blood samples during coronary blood flow determination; and a transducer-tipped catheter (Millar Instruments) inserted and sutured into the left ventricle for left ventricular end-diastolic pressure (LVEDP) determination. All transducers were calibrated and checked for zero position drift before each measurement. CPP was calculated as diastolic arterial pressure minus LVEDP.

A total of 21 pigs were used in this investigation to provide 16 successful experiments. Two piglets died of myocardial infarction during the growth period after LAD banding. One collateralized pig died of ventricular fibrillation after LAD occlusion and during experimental instrumentation. Two experiments were excluded from analysis because of inadequate microsphere mixing for myocardial blood flow distribution.

Study Protocol

After the surgery and insertion of monitoring catheters, the animal's hemodynamic parameters were stabilized for at least 10 min, and arterial blood gases were adjusted to normal levels (*p*H = 7.38 to 7.45; Pa_{CO_2} = 35–45; Pa_{O_2} > 100 mmHg). Next, the end-tidal concentration of halothane or isoflurane was adjusted to obtain a predetermined, randomly selected CPP of 30, 40, 45, or 55 mmHg. Although 55 mmHg was considered the "baseline" CPP, all CPP levels were randomized for experimental measurements to offset the possible effects of preparation deterioration. Each CPP was maintained for 5 min before determination of regional blood flow. Approximately 2×10^6 radiolabeled microspheres (15 μm in diameter) were injected into the left atrium over a

15-s period. Four isotopes, ^{46}Sc, ^{95}Nb, ^{113}Sn and ^{141}Ce, were used, each for a specific CPP in every animal. Reference blood samples were simultaneously withdrawn into two heparinized glass syringes 15 s prior to microspheres injection at a rate of 1.96 ml · min^{-1} for 120 s to ensure thorough mixing of microspheres and calculation of blood flow.

At each CPP, end-tidal vapor concentration (percent), heart rate (HR), systolic and diastolic blood pressures, pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure, LVEDP, cardiac output (CO), arterial blood gas, hematocrit, and temperature measurements were recorded. Stroke volume, systemic vascular resistance, and pulmonary vascular resistance were calculated. At the end of all four CPP measurements, a lethal dose of potassium chloride (30 mEq) was injected into the left atrium. Because the CPPs chosen were decrements of the baseline pressure of 55 mmHg, the animals were relatively more deeply anesthetized at each of the other CPPs, and they were deeply anesthetized at the time they were killed.

Cardiac output (liters per minute) was measured in triplicate using 10 ml iced 5% dextrose–water by the thermodilution technique with a computer (model 9520A, Edwards Laboratories). Stroke volume (milliliters per beat) was calculated as the ratio CO/HR × 1,000. Systemic vascular resistance (dyn · s · cm^{-5}) was calculated as (mean blood pressure − central venous pressure) ÷ CO × 80, and pulmonary vascular resistance (dyn · s · cm^{-5}) was calculated as (mean pulmonary artery pressure − pulmonary capillary wedge pressure) ÷ CO × 80. Coronary vascular resistance (mmHg/ml · 100 g^{-1} · min^{-1}) was calculated as CPP ÷ regional blood flow.

Determination of Regional Myocardial Blood Flow

After removal of the heart, the CD zone was identified by infusing triphenyl tetrazolium chloride (1% solution in sodium phosphate buffer) into the LAD distal to the occlusion while simultaneously infusing Evans blue dye into the proximal left circumflex artery to identify the normally perfused zone. These infusions were made at equal nonpulsatile pressures controlled at 80 mmHg. The heart was then transversely sectioned. The LV area that stained red was considered the CD zone, and the area stained blue was considered the control zone of normal perfusion (CNT). After removal of epicardial fat, tissue samples (weighing 1.5–3 g) taken from each of the two zones were divided into epicardial, midcardial, and endocardial regions. Radioactivity for each isotope was counted in a γ scintillation counter (Packard Instrument). Reference blood samples were also counted and were corrected for emission from background and Compton crossover on-line. Experimental data were excluded if a discrepancy greater than 15% was found between the two simultaneously withdrawn reference blood samples from contralateral sites, because such discrepancy denoted incomplete mixing of microspheres for blood flow study. Actual blood flow (milliliters per 100 g per minute) was calculated for each myocardial region.[17] Intracoronary blood flow redistribution was expressed as the endocardial/epicardial blood flow ratio for each area and was compared by analyzing these ratios as functions of CPP, between anesthetic groups. Intercoronary blood flow redistribution was expressed by the CD/CNT blood flow ratio for each region and again comparing them at equivalent CPP between anesthetic groups.

Validation Protocol

In order to obtain a positive control, *i.e.*, to validate our model using conditions known to produce steal, we used α-chloralose as the basal anesthetic agent in a separate group of coronary collateralized animals and produced the same CPPs with an intravenous adenosine infusion (1–5 $\mu M \cdot kg^{-1}$). Six animals were studied using the same study protocol except that halothane was discontinued after induction and tracheotomy. Anesthesia was immediately substituted with an intravenous loading dose of α-chloralose 100 mg · kg^{-1} over 5 min, followed by a continuous infusion at 10 mg · kg^{-1} · h^{-1}.[4] Further experimental instrumentation continued over 60 min, during which end-tidal concentration of halothane returned to zero. Thereafter the same CPP levels as in the halothane and isoflurane were achieved by an infusion of adenosine at 1–5 $\mu M \cdot kg^{-1}$, and the same regional myocardial blood flow studies and analyses were performed. However, only four experiments were analyzed to validate this model because two were excluded due to inadequate microsphere mixing during blood flow study. The purpose of this validation protocol was to confirm that adenosine causes coronary steal in our model under the CPPs studied, so that the effects of isoflurane and halothane on coronary blood flows could be compared under the same CPPs.

Statistical Analysis

Comparison of data between isoflurane and halothane groups was done by two-way analysis of variance (ANOVA) with repeated measures to test for differences between groups over the effect of CPP (intergroup comparison). The effect of CPP for each group was analyzed using a repeated-measures ANOVA with 55-mmHg CPP as the baseline measurement in all contrasts when the null hypothesis was rejected (intragroup comparison). The adenosine group was analyzed by two-way ANOVA with repeated measures to test for differences between CD and

CNT zones over the effect of CPP and in contrast to baseline CPP (55 mmHg). A P value less than 0.05 was considered statistically significant. Mean values ± standard errors of the mean were presented for all parameters.

Results

Hemodynamics (table 1)

When isoflurane (n = 8) and halothane (n = 8) were used as the sole anesthetic agent, the dose–response decrease in CPP from 55 to 30 mmHg corresponded to a significant increase in end-tidal concentration of isoflurane, from 0.80 ± 0.24 to 2.08 ± 0.28%, and of halothane, from 0.62 ± 0.12 to 1.40 ± 0.14%. There were no significant differences between the two groups in Pa_{CO_2}, systolic blood pressure, diastolic blood pressure, central venous pressure, pulmonary capillary wedge pressure, LVEDP, CO, stroke volume, systemic vascular resistance, and pulmonary vascular resistance across any of the different CPPs. When compared with the 55-mmHg baseline CPP, there was a significant dose-dependent decrease in HR and BP at 30 mmHg CPP in both groups. Isoflurane was associated with a significant decrease (32.2%) in systemic vascular resistance in contrast to halothane (22.4%) from baseline CPP to 30 mmHg CPP. On the other hand, CO was maintained in the isoflurane group (3.9 ± 0.3 to 3.7 ± 0.3) but was significantly decreased in the halothane group (4.5 ± 0.4 to 3.3 ± 0.2) from baseline CPP to 30 mmHg CPP.

Regional Myocardial Blood Flow and Coronary Vascular Resistance

Endo-, mid-, and epicardial blood flows in both normal and CD zones all decreased in a dose-dependent fashion with decreasing CPP; they were significantly lower at 30-mmHg *versus* 55-mmHg CPP in both anesthetic groups. However, there was no significant difference in regional myocardial blood flow between the isoflurane and halothane groups in either CD or CNT zones over the range of CPP studied. In the adenosine group, the regional myocardial blood flow was significantly lower in CD than in CNT zones, particularly in endocardial regions, over the range of CPP studied. In addition, CD endocardial blood flow was significantly lower in 30-mmHg CPP when compared with baseline 55-mmHg CPP (86.7 ± 12.3 *vs.* 177.2 ± 44.8 $ml \cdot 100\ g^{-1} \cdot min^{-1}$) (table 2).

TABLE 1. Hemodynamic Effects of Isoflurane and Halothane in Relation to Coronary Perfusion Pressure

Parameters	Anesthetic	Coronary Perfusion Pressure (mmHg) 30	40	45	55
ET (%)	I	2.08 ± 0.28*	1.45 ± 0.28*	0.96 ± 0.17	0.80 ± 0.24
	H	1.40 ± 0.14*	1.05 ± 0.18*	0.81 ± 0.16	0.62 ± 0.12
Pa_{CO_2} (mmHg)	I	38.5 ± 2.0	37.1 ± 1.6	38.4 ± 2.3	36.8 ± 1.4
	H	37.3 ± 2.1	38.0 ± 1.8	36.5 ± 2.1	40.6 ± 2.1
HR (beats per min)	I	102 ± 6*	109 ± 8	116 ± 8	121 ± 9
	H	102 ± 4*	113 ± 7*	120 ± 7*	135 ± 7
SBP (mmHg)	I	84 ± 3*	100 ± 3*	110 ± 4	118 ± 4
	H	77 ± 4*	95 ± 6*	104 ± 6	119 ± 9
DBP (mmHg)	I	45 ± 3*	52 ± 3*	58 ± 3	66 ± 3
	H	42 ± 4*	53 ± 4*	58 ± 4	65 ± 4
MPAP (mmHg)	I	21 ± 2	21 ± 2	22 ± 3	25 ± 3
	H	18 ± 1	21 ± 2	21 ± 2	21 ± 2
CVP (mmHg)	I	7 ± 1	7 ± 1	7 ± 1	8 ± 1
	H	6 ± 1	6 ± 1	5 ± 1	5 ± 1
PCWP (mmHg)	I	12 ± 2	12 ± 1	13 ± 2	12 ± 1
	H	11 ± 1	11 ± 1	11 ± 1	12 ± 1
LVEDP (mmHg)	I	16 ± 2	15 ± 2	15 ± 2	14 ± 2
	H	16 ± 4	16 ± 4	16 ± 4	16 ± 5
CO ($l \cdot min^{-1}$)	I	3.7 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	3.9 ± 0.3
	H	3.3 ± 0.2*	3.8 ± 0.4	3.9 ± 0.3	4.5 ± 0.4
SV ($ml \cdot beat^{-1}$)	I	36.3 ± 2.9	34.9 ± 2.5	32.8 ± 2.6	32.2 ± 2.4
	H	32.4 ± 2.0	33.6 ± 3.1	32.5 ± 2.3	33.3 ± 3.0
PVR ($dyn \cdot s \cdot cm^{-5}$)	I	194 ± 32	193 ± 40	202 ± 50	294 ± 63
	H	172 ± 29	199 ± 28	205 ± 25	192 ± 26
SVR ($dyn \cdot s \cdot cm^{-5}$)	I	1145 ± 94*	1396 ± 126*	1527 ± 150	1688 ± 111
	H	1175 ± 70	1393 ± 110	1427 ± 94	1515 ± 156

Mean ± SEM; n = 8 in each group.

I = isoflurane; H = halothane; ET = end-tidal concentration; Pa_{CO_2} = arterial carbon dioxide tension; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MPAP = mean pulmonary arterial pressure; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; LVEDP = left ventricular end-diastolic pressure; CO = cardiac output; SV = stroke volume; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

* $P < 0.05$, intragroup comparison to baseline 55-mmHg CPP value. Intergroup comparison not significant.

TABLE 2. Effects of Coronary Perfusion Pressure by Isoflurane, Halothane, and Adenosine on Regional Myocardial Blood Flow

Regional Blood Flow (ml · 100 g^{-1} · min^{-1})	Anesthetic	Coronary Perfusion Pressure (mmHg) 30	40	45	55
CD.ENDO	I	95.2 ± 16.0*	144.2 ± 30.5	124.6 ± 21.8	144.2 ± 20.8
	H	90.0 ± 13.4*	102.2 ± 14.6	110.7 ± 19.2	134.8 ± 20.0
	A	86.7 ± 12.3*†	145.0 ± 28.3†	157.8 ± 37.6†	177.2 ± 44.8†
CD.MID	I	94.2 ± 15.1	137.3 ± 24.4	131.8 ± 19.4	128.3 ± 21.2
	H	95.8 ± 11.2*	114.3 ± 14.4	124.8 ± 16.5	152.9 ± 19.4
	A	214.2 ± 82.8†	346.9 ± 135.1†	340.4 ± 104.8	289.8 ± 123.4
CD.EPI	I	121.1 ± 16.6*	171.6 ± 23.3	144.5 ± 22.8	167.9 ± 19.7
	H	126.1 ± 18.1*	152.5 ± 31.0	154.5 ± 33.2	214.5 ± 44.9
	A	156.5 ± 18.9†	230.3 ± 29.5†	240.0 ± 40.6	208.0 ± 45.6
CNT.ENDO	I	109.6 ± 11.1*	139.0 ± 21.5*	160.9 ± 23.8	181.6 ± 23.3
	H	97.8 ± 14.5*	119.3 ± 17.2	127.0 ± 23.3	152.1 ± 21.1
	A	403.7 ± 42.7	534.1 ± 110.3	545.9 ± 171.2	524.0 ± 192.0
CNT.MID	I	120.4 ± 13.8*	152.5 ± 27.1	173.4 ± 24.7	197.4 ± 27.8
	H	104.0 ± 11.2*	120.0 ± 12.6	129.7 ± 20.6	156.0 ± 19.5
	A	542.7 ± 63.1	676.2 ± 192.1	641.4 ± 243.8	610.5 ± 255.1
CNT.EPI	I	129.1 ± 15.6*	167.1 ± 27.8	180.4 ± 24.1	206.7 ± 25.6
	H	112.4 ± 14.0*	126.9 ± 15.5	132.8 ± 19.3	166.9 ± 18.1
	A	424.5 ± 74.1	464.5 ± 102.4	475.5 ± 243.3	322.0 ± 99.2

Mean ± SEM, groups I and H (n = 8 each), group A (n = 4).
I = isoflurane; H = halothane; A = adenosine; CD = collateral-dependent zone; CNT = control zone; ENDO = endocardial region; MID = midcardial region; EPI = epicardial region.

* $P < 0.05$, intragroup comparison to baseline 55-mmHg CPP value.
† $P < 0.01$, zonal comparison of CD *versus* CNT.
No intergroup comparison between A and I or H, because of different n in groups.

Coronary vascular resistance (CVR) was independent of CPP or end-tidal concentration of isoflurane and halothane. Both anesthetics minimally affect CVR; isoflurane consistently showed a lower CVR in the CD endocardial zone and all CNT zones when compared to halothane. In contrast, adenosine caused a significant decrease in CVR in CNT *versus* CD zones (table 3).

REDISTRIBUTION OF REGIONAL BLOOD FLOW

Intercoronary redistribution expressed by the CD/CNT myocardial blood flow ratio showed no changes with the decrements in CPP from 55 to 30 mmHg in either the isoflurane or the halothane group. There was no significant difference between the isoflurane and halothane

TABLE 3. Effects of Coronary Perfusion Pressure by Isoflurane, Halothane, and Adenosine on Regional Coronary Vascular Resistance

CVR (mmHg/ml · 100 g^{-1} · min^{-1})	Anesthetic	Coronary Perfusion Pressure (mmHg) 30	40	45	55
CD.ENDO	I	0.32 ± 0.05	0.28 ± 0.06	0.36 ± 0.06	0.38 ± 0.05
	H	0.33 ± 0.05	0.39 ± 0.06	0.41 ± 0.07	0.41 ± 0.06
	A	0.35 ± 0.05	0.28 ± 0.05	0.29 ± 0.07	0.31 ± 0.08
CD.MID	I	0.32 ± 0.05	0.29 ± 0.05	0.34 ± 0.05	0.43 ± 0.07
	H	0.31 ± 0.04	0.35 ± 0.04	0.36 ± 0.05	0.36 ± 0.05
	A	0.14 ± 0.05	0.12 ± 0.05	0.13 ± 0.04	0.19 ± 0.08
CD.EPI	I	0.25 ± 0.03	0.23 ± 0.03	0.31 ± 0.05	0.33 ± 0.04
	H	0.24 ± 0.03	0.26 ± 0.05	0.29 ± 0.06	0.26 ± 0.05
	A	0.19 ± 0.02	0.17 ± 0.02	0.19 ± 0.03	0.26 ± 0.06
CNT.ENDO	I	0.27 ± 0.03	0.29 ± 0.04	0.28 ± 0.04	0.30 ± 0.04
	H	0.31 ± 0.04	0.34 ± 0.05	0.35 ± 0.06	0.36 ± 0.05
	A	0.07 ± 0.01†	0.07 ± 0.01†	0.08 ± 0.02†	0.10 ± 0.03†
CNT.MID	I	0.25 ± 0.03	0.26 ± 0.05	0.26 ± 0.04	0.28 ± 0.04
	H	0.29 ± 0.03	0.33 ± 0.03	0.35 ± 0.06	0.35 ± 0.04
	A	0.06 ± 0.01†	0.06 ± 0.02†	0.07 ± 0.02	0.09 ± 0.04
CNT.EPI	I	0.23 ± 0.03	0.24 ± 0.04	0.25 ± 0.03	0.27 ± 0.03
	H	0.27 ± 0.03	0.32 ± 0.04	0.34 ± 0.05	0.33 ± 0.04
	A	0.07 ± 0.01†	0.09 ± 0.02†	0.09 ± 0.05	0.17 ± 0.05

Mean ± SEM, groups I and H (n = 8 each), group A (n = 4).
I = isoflurane; H = halothane; A = adenosine; CD = collateral-dependent zone; CNT = control zone; ENDO = endocardial region; MID = midcardial region; EPI = epicardial region.

* $P < 0.01$, zonal comparison of CD *versus* CNT.
No intergroup comparison between A and I or H, because of different n in groups.

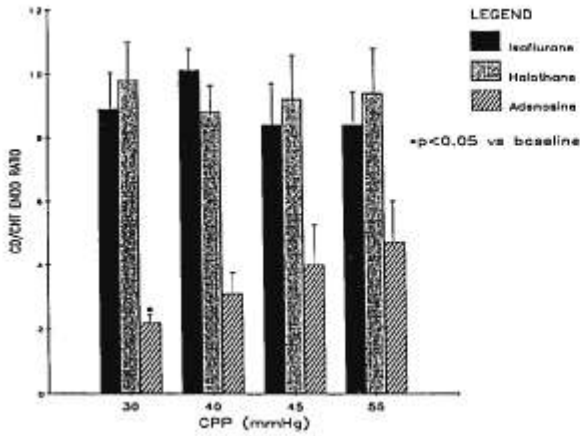

FIG. 1. The effects of coronary perfusion pressure (CPP) to the collateral-dependent (CD)/control (CNT) blood flow ratio in the endocardial (ENDO) region. Results are expressed as mean value of isoflurane (n = 8), halothane (n = 8), or adenosine (n = 4).

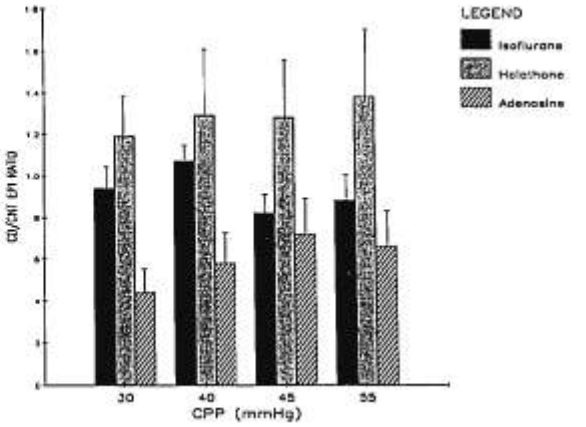

FIG. 3. The effects of coronary perfusion pressure (CPP) to the collateral-dependent (CD)/control (CNT) blood flow ratio in the epicardial (EPI) region. Results are expressed as mean value of isoflurane (n = 8), halothane (n = 8), or adenosine (n = 4).

groups in all regions (endocardial [fig. 1], midcardial [fig. 2], and epicardial [fig. 3]) over the range of CPP studied. In the adenosine group, there was a proportional relationship between regional intercoronary redistribution ratio and decreasing CPP (figs. 1–3), which was significantly lower in the CD/CNT endocardial ratio at 30 *versus* 55 mmHg CPP (0.219 ± 0.029 *vs.* 0.467 ± 0.146). This denoted significant intercoronary steal in the endocardial region at 30 mmHg CPP by adenosine, in relation to the significant decrease in absolute blood flow at the CD zone at the same CPP.

Transmural redistribution was expressed as the ratio of endocardial to epicardial regional blood flow. No differences were found between the isoflurane and halothane groups with any decrement in CPP within or between groups, in either the CD zones (fig. 4) or the CNT zones (fig. 5). Again, in the adenosine group, there was a proportional relationship between transmural redistribution ratio and decreasing CPP in the CD zone (fig. 4), which was significantly lower in the endocardial/epicardial CD ratio at 30-mmHg *versus* 55-mmHg CPP (0.585 ± 0.131 *vs.* 0.857 ± 0.094). In addition, there was significant transmural redistribution of blood flow in the CD zone when compared to the CNT zone at 30-mmHg CPP (0.585 ± 0.131 *vs.* 0.993 ± 0.207).

Discussion

For nearly a decade, the use of isoflurane in patients with coronary artery disease has remained controversial.

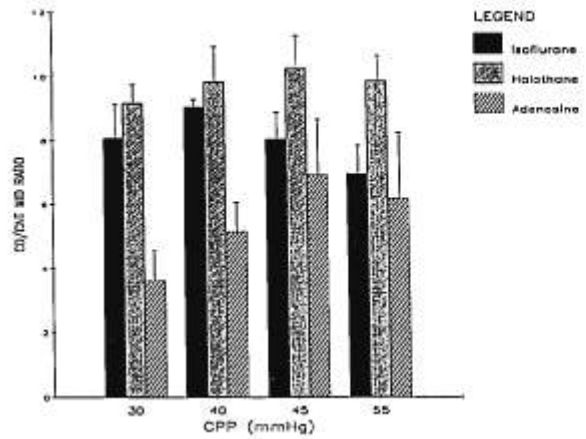

FIG. 2. The effects of coronary perfusion pressure (CPP) to the collateral-dependent (CD)/control (CNT) blood flow ratio in the midcardial (MID) region. Results are expressed as mean value of isoflurane (n = 8), halothane (n = 8), or adenosine (n = 4).

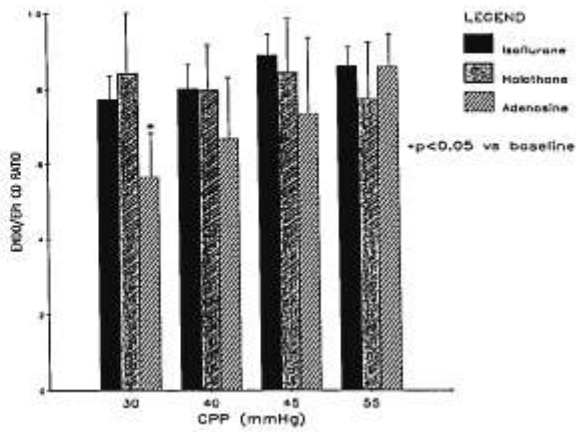

FIG. 4. The effects of coronary perfusion pressure (CPP) to the endocardial (ENDO)/epicardial (EPI) blood flow ratio in the collateral-dependent (CD) zone. Results are expressed as mean value of isoflurane (n = 8), halothane (n = 8), or adenosine (n = 4).

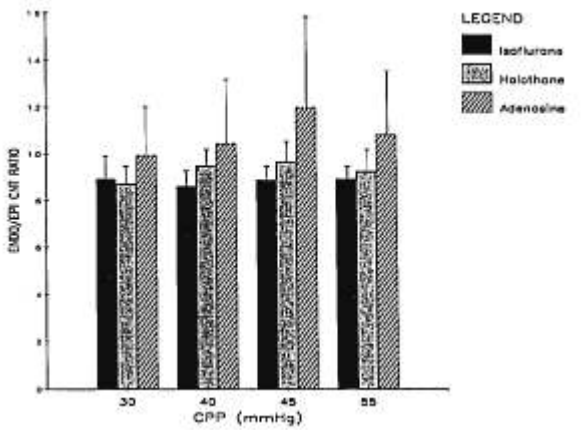

FIG. 5. The effects of coronary perfusion pressure (CPP) to the endocardial (ENDO)/epicardial (EPI) blood flow ratio in the control (CNT) zone. Results are expressed as mean value of isoflurane (n = 8), halothane (n = 8), or adenosine (n = 4).

Recently, it appears that this pendulum may have swung from danger to safety in the use of isoflurane in critical coronary stenosis in both clinical[8,18] and animal[15,19] studies.

Our study demonstrated that when either isoflurane or halothane was used as the sole anesthetic, there were proportional, dose–response decreases in regional myocardial blood flows related to the induced decrements in CPPs. In this swine model of chronic coronary artery occlusion, these decreases in absolute flow to the CD zones by the inhalational anesthetics were not the result of either intercoronary or transmural redistribution of coronary blood flow. Furthermore, coronary steal was confirmed to occur in a dose–response fashion with adenosine infusion in this chronic swine model.

Experimental Model

Swine are similar to humans in that their native coronary vessels have practically no anatomically demonstrable collateral circulation, whereas the normal canine collateral circulation consists of multiple epicardial interconnections.[20] In the human and porcine heart, collateral vessels develop predominantly in the subendocardium with a histologic structure of abnormally thin-walled arteries. In contrast, collateral vessels in canine hearts develop only in a narrow subepicardial zone at the lateral border of the potentially ischemic zone. By creating a fixed stenosis of the LAD when the pig is 3–4 weeks old, collateral vessels can be induced to supply the myocardium distal to the now occluded LAD over a 8–10-week period.[16]

Becker has contended that "coronary steal–prone anatomy" is often comprised of total occlusion of a major coronary branch with collateral flow distal to the occlusion, and proximal stenosis of a vessel supplying the collateral circulation.[21] However, the latter is not absolutely necessary for steal to occur. The stenosis does magnify the effect during pharmacologic coronary vasodilation.[22,23] It is the decrease in perfusion pressure distal to a stenosis, *i.e.*, at the origin of collateral vessels, that is responsible for the coronary steal phenomenon. Our model compared two agents, isoflurane and halothane, not at "equi-MAC" doses but at several equal reductions in CPP. The possibility of drug–drug interaction was eliminated, because no basal anesthetic, such as α-chloralose,[24] which is known to be sympathomimetic, was used with the studied anesthetics. The merit of our model is that the CPP was tightly regulated by the experimental inhalational agents as the independent variable. The decrease in CPP mimics the decrease in CPP distal to a proximal left circumflex stenosis and to the origin of collateral vessels that supply distal to an occluded LAD, and we believe, therefore, that it is a valid model of "steal-prone" anatomy and physiology. In addition, a separate set of experiments with adenosine as a positive control for coronary steal were performed.

Hemodynamic Effects

There were no significant hemodynamic differences between the two anesthetic groups across any of the different CPPs. When comparing 30-mmHg CPP to baseline 55-mmHg CPP, isoflurane was associated with a significant decrease (32.2%) in systemic vascular resistance, in contrast to halothane (22.4%), denoting a more potent peripheral vasodilator. In addition, CO was better maintained in the isoflurane group but was significantly decreased in the halothane group from baseline CPP to 30 mmHg CPP. Because stroke volume was similar in both groups, the significant decrease in CO with increasing halothane concentration was due mainly to a resultant decrease in HR. Usually inhalational anesthetic inhibits the baroreceptor reflex, but in swine, HR has been shown to relate inversely to end-tidal concentration of isoflurane.[25]

Regional Myocardial Blood Flow and Coronary Vascular Resistance

Our data indicated that the absolute regional myocardial blood flows in both normal and CD zones decreased in a dose-dependent fashion with decreasing CPP and were significantly lower at 30-mmHg *versus* 50-mmHg CPP in both anesthetic groups. Although not statistically significant, in CD endocardial and all CNT zones, isoflurane consistently sustained a higher myocardial blood flow than halothane in all CPPs studied. This is in agreement with the finding by Cason *et al.*[13] that isoflurane and halothane minimally affect coronary vascular resistance, and our results suggested that isoflurane is a relatively more

potent coronary vasodilator than halothane. In contrast, adenosine exerted significant vasodilation effects in CNT as compared to CD zones, resulting in intercoronary steal. In our model, CVR was independent of CPP or anesthetic concentration. The vascular tone appeared to be more reactive in the CNT zone as shown by the effect of adenosine.

In virtually all clinical and laboratory studies in which isoflurane has been associated with ischemic myocardial dysfunction or anaerobic metabolism, there have been concomitant decreases in aortic pressure and/or tachycardia.[1,2,4,6] Therefore, separating reflex from pharmacologic coronary vasodilation has not been easy. Whether the former itself could lead to a steal mechanism is not known.

When Gelman *et al.*[3] examined distribution of coronary blood flow in normal dogs, decreases in systemic blood pressure during isoflurane administration were associated with increases in myocardial blood flow. No change in the endocardial/epicardial blood flow ratio was found with either isoflurane or halothane. The authors concluded that isoflurane appeared to be a coronary vasodilator and that this increase in coronary flow might be beneficial as well as harmful.

Buffington *et al.*[4] demonstrated coronary steal in a CD zone produced by an ameroid constrictor in a canine model. In their study, heart rates and systemic pressure were kept constant, and coronary blood flow was maintained at a constant "mid-range" flow (35 ml·100 $g^{-1} \cdot min^{-1}$), which produced decreased systolic wall thickening in the CD zone. At 1 MAC of each agent, the CPP was 41 mmHg with isoflurane *versus* 51 mmHg with halothane. With the additional presence of the "basal" anesthetic α-chloralose, they reported significantly worsened CD/CNT flow ratios with isoflurane.[4] Interpretations of these data may vary because isoflurane was found to produce coronary steal only when superimposed upon a dysfunctional and presumably already ischemic heart. Also, CPP in the halothane *versus* the isoflurane groups was considerably different; that in the isoflurane group was about 20% less than that in the halothane group.[4] Our experiments used the dose–response effect of equal CPP on coronary blood flow. In contrast to others,[26,27] Buffington *et al.*[4] found that adenosine produced intercoronary steal but not transmural redistribution in the CD zone itself in their model. They used equi-MAC doses of each inhalational agent, which generated markedly different CPPs for the blood flow study. We believe that blood flow to the CD zone was likely underestimated in their model because microspheres were injected directly into the left main coronary vessel; therefore, inflow to the CD zone from the right coronary was not measured. Further, their canine model was anesthetized with a basal anesthetic to which either halothane or isoflurane were added. α-Chloralose is a well-known sympathomimetic agent.[24] If α-adrenergic–stimulated coronary vasoconstriction was present to any degree, especially in the CD zone, then isoflurane-induced vasodilation might be expected to produce a greater decrease in perfusion pressure than otherwise might occur.

Our data are in agreement with Cason *et al.*,[13] who studied the effects of isoflurane and halothane at two different MAC levels in addition to a basal anesthetic of fentanyl and pentobarbital in a chronically instrumented dog model. By controlling the coronary diastolic blood pressure and left atrial pressure, their CPPs were in the range of 40 mmHg. No coronary steal or ischemia was found, as measured by epicardial ECG ST segments. Our data show that even with CPP as low as 30 mmHg, no coronary redistribution was found between the two inhalational agents using accurate measurements of actual flow to the relevant myocardial regions.

Furthermore, in another chronically instrumented canine model, Hickey *et al.*[28] demonstrated that 1.0 MAC concentrations of halothane, enflurane, or isoflurane diminished but did not abolish autoregulation of coronary blood flow. Neither anesthetic is a "powerful coronary vasodilator" when compared to adenosine. Our results show that intercoronary redistribution of blood flow was not different as a function of CPP whether halothane or isoflurane was the anesthetic. This implies that at the same reduction in CPP (*not* equi-MAC levels), the two anesthetics had similar vasodilating properties but were not able to cause intercoronary steal despite decrements of CPP to low levels. In contrast, intravenous adenosine caused a dose-response decrease in each regional intercoronary redistribution ratio and significant intercoronary steal. Further, no transmural redistribution of blood flow was found in the normal zone or the CD zone between isoflurane and halothane, but intravenous adenosine caused significant transmural steal in the CD zone. Our data confirm that the two inhalational agents are much weaker coronary vasodilators than adenosine.[13,15,19] Isoflurane does cause some extra perfusion to the normal myocardium by vasodilation, but not coronary steal. Although not statistically significant, there was consistently higher coronary blood flow to the normal zone and subendocardial CD regions when compared to halothane.

Clinically, isoflurane has been found to be a safe and effective adjunct to control intraoperative hypertension in coronary artery bypass graft patients.[29] Sahlman *et al.*[10] reported that isoflurane at an end-tidal concentration of 1.5% used to control hypertensive response from sternotomy attenuated myocardial lactate production and may have had beneficial effects on stress-induced myocardial ischemia, as long as it was not associated with

tachycardia. Recently, prospective outcome studies specifically addressed the issue of anesthetic choice and found no deleterious effects when isoflurane was used as primary or secondary anesthetic in patients with coronary artery disease.[8,18,30]

Other studies have also shown a lack of deleterious effect of isoflurane in experimental models of myocardial ischemia. In a canine model of acute evolving myocardial infarction, isoflurane decreased the extent of myocardial necrosis.[31] In swine, isoflurane has been associated with greater coronary reserve and better preservation of cardiac function than halothane.[25] Our data indicate that isoflurane indeed was associated with a higher diastolic blood pressure at 30-mmHg CPP and greater CO when compared to halothane.

In summary, in a collateralized swine model of chronic coronary occlusion, clinical dosages of both isoflurane and halothane caused a proportional, CPP-related decrease in regional myocardial blood flow. Isoflurane was associated with higher endocardial blood flow in CD myocardium when compared to halothane. Both isoflurane and halothane minimally affect coronary vascular resistance. Intravenous adenosine caused a significant intercoronary and transmural coronary steal in the CD zone and acted as a positive control for our model. No intercoronary or transmural redistribution of regional myocardial blood flow was associated with either isoflurane or halothane, despite a wide range of anesthetic-induced decrements in CPP.

The authors would like to acknowledge the excellent technical assistance of Mr. P. Brown III and the secretarial assistance of Ms. C. Drane, who typed the manuscript.

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