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Regional and Global Myocardial Circulatory and Metabolic Effects of Isoflurane and Halothane in Patients with Steal-prone Coronary Anatomy

Debra D. Pulley, M.D., George V. Kirvassilis, M.D.,* Nicholas Kelermenos, M.D.,† Kathy Kater, R.N., M.S.N., Benico Barzilai, M.D.,‡ Randall E. Genton, M.D.,‡ Constantinos Efstathiou, M.D.,† Demetrios G. Lappas, M.D.§*

The use of isoflurane in patients with coronary artery disease remains controversial because of the possibility of "coronary steal". In this study, the effects of isoflurane and halothane on global and regional myocardial blood flow and metabolism were compared, and the relationship between steal-induced myocardial ischemia and the administered volatile anesthetic was investigated in 40 patients with steal-prone coronary anatomy undergoing elective coronary artery bypass operations. The patients were randomly assigned to receive either isoflurane or halothane (0.5 MAC inspired concentration) immediately after induction with fentanyl (50 μg/kg). Hemodynamic measurements and blood samples were obtained at preinduction, postintubation, preincision, poststernotomy, at 60 min after beginning isoflurane or halothane, and precannulation (a total of 238 study events). Throughout the study, heart rate was kept constant by atrial pacing at approximately postintubation values while arterial pressure was maintained within 10% of postintubation values with fluid administration or phenylephrine infusion. Overall, systemic hemodynamic changes observed during the study were similar in the two groups. Myocardial ischemic episodes were defined as a new electrocardiographic ST-segment shift of ≥ 0.1 mV, new echocardiographic regional wall motion abnormalities (RWMA) and/or myocardial lactate production (MLP). A total of 18 new ischemic episodes were detected in 15 patients (7 episodes during isoflurane in 7 patients and 11 during halothane in 8 patients). Ten (56%) episodes were related to acute hemodynamic abnormalities, whereas 8 (44%) were random and unrelated to changes. Seven episodes were detected by echocardiography (38%), 6 by MLP (33%), and 1 by ECG (6%) only, whereas concomitant echocardiographic abnormalities and MLP were observed during 2 episodes (11%), echocardiographic and ECG during 1 (6%), and ECG and MLP during 1 other (6%). Ratios of regional to global coronary venous flow, coronary vascular resistance, myocardial oxygen content, and lactate extraction, along with hemodynamic data obtained during these episodes, do not support coronary steal for the development of myocardial ischemia. We conclude that in patients with steal-prone coronary anatomy anesthetized with fentanyl, neither isoflurane nor halothane administered at concentrations used in the current study is likely to cause myocardial ischemia by the coronary steal mechanism. (Key words: Anesthetics, volatile: halothane; isoflurane. Arteries, coronary: steal. Heart: coronary artery disease; coronary blood flow; myocardial metabolism; myocardial ischemia.)

* Resident in Anesthesiology.
† Research Fellow in Anesthesiology.
‡ Assistant Professor of Medicine.
§ Professor of Anesthesiology.

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Address reprint requests to Dr. Lappas: Division of Cardiothoracic Anesthesia, Washington University Medical Center, Box 8054, 660 South Euclid Avenue, St. Louis, Missouri 63110.

INHALATIONAL ANESTHETICS are commonly used as an adjunct to high-dose opioids in patients undergoing coronary artery bypass graft (CABG) operations to relieve adverse hemodynamic events.[1–3] The use of isoflurane, however, in patients with coronary artery disease remains controversial.[4–8]

First, Reiz *et al.*[4] demonstrated electrocardiographic (ECG) and metabolic evidence of myocardial oxygen imbalance during isoflurane administration in patients with coronary artery disease. These changes were attributed to decreased perfusion pressure and to redistribution of coronary blood flow, often termed "coronary steal", due to coronary vasodilation produced by the anesthetic. Subsequent clinical[9,10] and experimental[11] studies have suggested that isoflurane could produce or exacerbate myocardial ischemia by a coronary steal mechanism secondary to the coronary vasodilator property of this anesthetic.[12]

Buffington *et al.*[13] reported that 23% of 16,249 patients with coronary artery disease enrolled in the Coronary Artery Surgery Study had anatomy susceptible to coronary steal. It appears, therefore, that patients with steal-prone anatomy are likely to be susceptible to the development of regional myocardial ischemia induced by a coronary steal mechanism when isoflurane is given. A recent retrospective study, however, did find in patients with steal-prone anatomy undergoing CABG that the incidence of ischemic ECG changes was not greater during isoflurane anesthesia than during anesthesia with the other primary anesthetics evaluated.[14]

However, there are no prospective, randomized clinical studies that examine the direct effects of isoflurane on coronary circulation, independent of changes in heart rate or blood pressure in patients with steal-prone coronary anatomy. Such data seem essential for documentation of ischemia by isoflurane-induced coronary steal.[6] In view of this, the current study was designed to evaluate and compare the regional and global myocardial circulatory and metabolic effects of equipotent concentrations of isoflurane and halothane (0.5 MAC inspired), as an adjunct to high-dose fentanyl (50 μg/kg), on patients with steal-prone coronary anatomy undergoing CABG operations.

Materials and Methods

PATIENTS

The study protocol was approved by the institutional Human Studies Committee, and written consent was obtained from 73 patients scheduled for elective CABG surgery. Patients with associated significant valvular disease or receiving intravenous infusion of vasoactive or inotropic drugs were excluded from the study. Of the 73 consenting patients, 33 were eliminated from the study—6 patients because technical difficulties occurred and 27 because they did not meet the anatomic criteria for coronary steal, defined as an occluded coronary artery and ≥ 50% stenosis of the vessel supplying collaterals to the myocardial zone distal to the occlusion.[13] Forty patients with angiographically documented steal-prone coronary anatomy were included in the study. Ten of these patients (5 in each group) also had left main coronary artery disease (30–70% stenosis). Demographic data for these 40 patients are shown in table 1. All patients received their preoperative cardiac medication the morning of surgery. Patients were randomized (by random-numbers table) to receive either isoflurane or halothane (0.5 MAC inspired concentration).

MEASUREMENTS

In the holding area, radial arterial and peripheral intravenous catheters were inserted. In the operating room, during continuous ECG (lead II and V5) and blood-pressure monitoring, a thermodilution Baim coronary sinus (CS) catheter (EleCath, Rahway, NJ) and a triple-lumen atrioventricular pacing Swan-Ganz® thermodilution pulmonary artery catheter (Baxter, Santa Ana, CA) were inserted by the Seldinger technique *via* the right internal jugular vein using two venipunctures. Under fluoroscopic guidance, the tip of the CS catheter was positioned beyond the CS into the great cardiac vein (GCV), and the appropriate positioning of the catheter was confirmed by injection of 2–3 ml contrast medium and radiologic visualization.

Continuous monitoring and recording of systemic arterial, pulmonary arterial, pulmonary capillary wedge, and right atrial pressures (in millimeters mercury) were performed using Siemens SIRECUST 1281 8-channel monitor and a Siemens SIREDOC 220 thermal array recorder (Siemens Medical Electronics, Danvers, MA). The thermodilution technique for determining coronary venous flows (CVF) using the Baim catheter and the relative merits and liabilities of this technique have been discussed previously.[2] Cardiac output was measured by thermodilution as the average of two determinations. However, if the outputs were not within 10% of each other, a third was obtained.

Two-dimensional echocardiography was performed with a 5-MHz phased-array transesophageal imaging transducer (Hewlett-Packard model 21362A, Andover, MA) mounted on the distal tip of a gastroscope, and M-mode echocardiography was performed with an ultrasound imaging system (Hewlett-Packard model 77020AC). The transducer was inserted into the esophagus after tracheal intubation and was positioned and maintained at the midpapillary muscles to obtain a short-axis view of the left ventricle. This view was selected because it contains segments supplied by each of the three major coronary arteries. The transesophageal probe was left *in situ* with the monitor on between measurements, and echocardiographic recordings were performed for at least 2 min on videotape at prespecified study periods. A seven-lead ECG (leads I, II, III, aVR, aVL, aVF, and V5), hemodynamic measurements, and blood samples from the radial artery, CS and GCV, and pulmonary artery were obtained along with echocardiographic samples.

All blood samples were analyzed for *p*H, carbon dioxide and oxygen tensions, hemoglobin, and oxygen content using the IL System 1306™ *p*H/Blood Gas Analyzer and IL482 CO-Oximeter™ System (Instrument Laboratory, Lexington, MA). Blood samples were also analyzed for lactate using YSI Model 23L Lactate Analyzer (Yellow Springs Instruments Scientific, Yellow Springs, OH). The analyzer is a semiautomated stat system that measures L-lactate (millimolar) in whole blood or plasma using immobilized enzyme electrode technology. Inspired and end-

TABLE 1. Demographic Data

Group	Age* (yr)	Gender (M/F)	Previous MI	CABG*	Preoperative Medication		
					N	BB	CaCB
Halothane	63 (37–71)	17/3	14/20	3.6 (2–5)	14/20	6/20	16/20
Isoflurane	64 (46–74)	15/5	13/20	3.8 (2–5)	19/20	8/20	14/20

MI = myocardial infarction; CABG = number of coronary artery bypass grafts; N = nitrates; BB = β-blockers; CaCB = Ca^{2+}-channel blockers.
* Mean; value in parentheses is distribution.

tidal gas and anesthetic concentration sampled from the proximal end of the endotracheal tube were continuously monitored by a precalibrated mass spectrometer (6000 Multi Gas Monitor, Ohmeda, Madison, WI).

Cardiac index, stroke volume (milliliters per beat), systemic and pulmonary vascular resistance (dyne · s · cm^{-5}), left ventricular stroke work (g · m per beat) global and regional myocardial oxygen consumption (MV_{O_2}, milliliters per minute) and extraction ($M_{O_2}E$, percent), and myocardial lactate extraction (MLE, percent) were calculated by standard formulas. Coronary vascular resistance (CVR) was calculated as difference between the diastolic systemic arterial pressure and pulmonary capillary wedge pressure, divided by CVF (regional or global). The ECG and echocardiographic recordings were visually analyzed independently by two investigators blinded to hemodynamic data, myocardial metabolic values, and volatile anesthetic administered.

Study Protocol

Preanesthetic medication consisted of intramuscular morphine sulfate (0.1 mg/kg), scopolamine (0.4 mg), and oral lorazepam (1–2 mg). An additional 1–2 mg of lorazepam was given intravenously during catheter insertion. Approximately 10 min after insertion of all catheters, hemodynamic measurements and blood samples were obtained while the patient was awake. A seven-lead ECG was recorded and retained for comparison with the routine preoperative ECG (preinduction). Anesthesia was induced with fentanyl (50 μg/kg intravenously); vecuronium (10 mg intravenously) was administered to facilitate tracheal intubation. Ventilation was controlled (fractional inspired oxygen concentration 100%) and adjusted to maintain end-tidal carbon dioxide tension in the physiologic range. Two minutes after tracheal intubation measurements were repeated and blood samples were obtained (postintubation). Isoflurane or halothane then was administered, and the inspired concentration was maintained at 0.5 MAC. Additional hemodynamic measurements and blood samples were obtained at the following predetermined periods: preincision, poststernotomy, 60 min, and just prior to aortic cannulation (precannulation). Postintubation hemodynamic and metabolic values were considered control for the administration of the volatile anesthetic. Throughout this period and until the beginning of cardiopulmonary bypass, diastolic arterial blood pressure was maintained within 10% of postintubation levels with volume transfusion and phenylephrine infusion when required. During the study, heart rate was kept constant at postintubation levels by atrial pacing *via* the pacing Swan-Ganz catheter. Elevations in blood pressure (> 15%) occurring between measurement sampling events were treated by transiently increasing the inspired concentration of the volatile anesthetic. For the purpose of the study, changes in systemic arterial pressure or heart rate of 15% or more were defined as clinically significant. ECG and echocardiographic ischemic changes were treated with nitroglycerin.

ECG evidence of ischemia was defined as a horizontal or downsloping ST-segment depression of ≥ 0.1 mV or ST-segment elevation ≥ 0.1 mV, 0.08 s from the J-point. Ischemia on the echocardiogram was defined as a change

TABLE 2. Coronary Hemodynamic and Myocardial Metabolic Changes Observed during Ischemic Episodes in the Isoflurane Group

Study Patient		CVF (ml/min) r	CVF (ml/min) g	CVF (ml/min) Ratio	HR (beats per min)	SAP S/D (mmHg)	MLE (%) r	MLE (%) g	$M_{O_2}E$ (%) r	$M_{O_2}E$ (%) g	Ischemia: Time of Occurrence	Ischemia: Mode of Detection	Concentration (%): Inspired	Concentration (%): ET
1	B	71	105	0.68	63*	109/62	10	0	61	53			0.6	0.4
	I	72	115	0.63	78	125/78	8	−31	66	57	Poststernotomy	gLP	0.6	0.5
18	B	47	125	0.38	55*	114/28	47	38	65	57			0.6	0.5
	I	45	115	0.39	55*	138/75	29	18	60	54	Precannulation	ECHO	0.6	0.5
20	B	NA	NA	NA	65*	123/75	NA	NA	NA	NA			0.6	0.5
	I	NA	NA	NA	65*	132/82	NA	NA	NA	NA	Between poststernotomy and 60 min	ECHO	0.6	0.5
21	B	48	68	0.71	50*	121/70	28	26	62	55			0.7	0.6
	I	37	47	0.78	50*	125/69	26	14	58	56	Precannulation	ECHO, ECG	0.7	0.6
33	B	70	129	0.54	54*	123/76	46	33	62	63			0.6	0.5
	I	112	152	0.73	54*	113/61	−8	35	45	46	Precannulation	rLP	0.6	0.5
38	B	NA	193	NA	81	107/67	31	19	66	63			0.6	0.5
	I	NA	202	NA	81	114/67	16	18	60	59	60 min	ECHO	0.6	0.5
40	B	77	111	0.78	70*	113/65	12	11	66	57			0.6	0.5
	I	73	109	0.76	70*	116/63	−8	−7	68	64	Precannulation	ECHO, gLP, rLP	0.6	0.5

B = Before ischemic event; I = during ischemic event; r = regional; g = global; LP = lactate production; CVF = coronary venous flow; $M_{O_2}E$ = myocardial O_2 extraction; MLE = myocardial lactate extraction; SAP = systemic arterial pressure; s/d = systolic/diastolic; NA = value not available; HR = heart rate.

* Atrial pacing.

in wall motion from normal to hypokinesis or hypokinesis to akinesis or dyskinesia. A myocardial ischemic episode was diagnosed by new ECG change, new echocardiographic RWMA (from the preceding echocardiographic recordings), and/or myocardial lactate production (MLP). Appearance of new and persistent Q waves of > 0.04 s in duration and increase in cardiac-specific enzymes (total creatine kinase MB = 45 IU/l) were considered positive evidence of postoperative myocardial infarction.

One-way analysis of variance was used to analyze differences between the isoflurane and halothane groups at each study period. Multiple-comparison tests were used for comparing the differences between group means (by the Bonferroni and Scheffé methods). The incidence of ischemia between groups was determined by chi-squared analysis. A P value less than 0.05 was considered significant.

Results

The isoflurane and halothane groups were demographically similar (table 1). Hemodynamic measurements and blood samples were obtained at 238 study events (118 isoflurane and 120 halothane) in 40 patients. A total of 29 new myocardial ischemic episodes were documented in 21 patients during the study period. Ten of these ischemic episodes were detected prior to induction (10 patients = 25%). One episode was detected immediately after tracheal intubation. Eighteen episodes were detected in 15 patients (37%) during either isoflurane (7 episodes) or halothane (11 episodes) administration (tables 2 and 3). In 1 patient (patient 33) in the isoflurane group, nitroprusside was administered before cannulation of the aorta. Atrial pacing was initiated in all but 1 patient (patient 38), in whom tachycardia was present before and throughout the study period. In two patients atrial pacing was terminated poststernotomy (patient 1) and at precannulation (patient 11) because they developed intrinsic heart rates that exceeded the rate set for pacing. Phenylephrine infusion (10–15 μg/min) was administered in 5 patients during halothane and in 11 during isoflurane. Nitroglycerin (20–50 μg/min) was administered in 3 patients in each group.

Systemic Hemodynamic Data

Systemic hemodynamic data are summarized in tables 4 and 5. Systemic hemodynamic changes observed were similar in the two groups, except for stroke volume and left ventricular stroke work at 60 min. Right and left ventricular filling pressures remained unchanged throughout the study, while progressively, cardiac index, stroke volume, and left ventricular stroke work decreased ($P < 0.05$). Systolic blood pressure was lower than control at 60 min and precannulation ($P < 0.05$) in the halothane group. Diastolic blood pressure did not change.

TABLE 3. Coronary Hemodynamic and Myocardial Metabolic Changes Observed during Ischemic Episodes in the Halothane Group

Study Patient		CVF (ml/min)			HR (beats per min)	SAP s/d (mmHg)	MLE (%)		$M_{O_2}E$ (%)		Ischemia		Concentration (%)	
		r	g	Ratio			r	g	r	g	Time of Occurrence	Mode of Detection	Inspired	End-tidal
11	B	115	164	0.70	65*	155/82	6	0	74	69			0	0
	I	78	109	0.71	65*	131/74	8	−8	63	59	Preincision	gLP, rLP	0.5	0.4
	I	87	125	0.70	68*	146/84	10	7	67	69	60 min	ECHO	0.5	0.4
	I	86	134	0.64	77	122/71	−7	0	65	66	Precannulation	rLP, g0LE	0.5	0.4
12	B	NA	NA	NA	67*	122/75	NA	NA	NA	NA			0.5	0.4
	I	NA	NA	NA	67*	105/65	NA	NA	NA	NA	Between 60 min and precannulation	ECHO	0.5	0.4
16	B	48	115	0.42	70*	119/67	44	27	42	51			0.4	0.3
	I	39	110	0.35	70*	117/65	35	29	40	51	Precannulation	ECG	0.4	0.3
22	B	55	114	0.48	54*	127/72	7	6	61	52			0	0
	I	39	102	0.38	54*	124/67	−1	4	60	52	Preincision	rLP, g0LE	0.4	0.3
	I	44	117	0.38	54*	98/61	−3	0	58	51	60 min	rLP, g0LE	0.4	0.3
25	B	41	106	0.39	70*	154/71	62	65	66	57			0	0
	I	46	93	0.49	70*	113/61	50	−115	60	47	Preincision	gLP, ECG	0.4	0.3
30	B	73	186	0.39	68*	114/58	32	39	53	53			0.4	0.3
	I	91	188	0.48	68*	146/73	20	22	56	52	Poststernotomy	ECHO	0.4	0.3
37	B	81	117	0.69	60*	131/66	44	36	52	57			0.4	0.4
	I	72	102	0.70	60*	115/56	30	33	53	52	Precannulation	ECHO	0.4	0.4
39	B	42	128	0.33	58*	118/59	19	15	66	43			0.4	0.3
	I	43	136	0.32	58*	106/57	19	17	67	58	60 min	ECHO	0.5	0.4

B = Before ischemic event; I = during ischemic event; r = regional; g = global; LP = lactate production; CVF = coronary venous flow; $M_{O_2}E$ = myocardial O_2 extraction; MLE = myocardial lactate extraction; SAP = systemic arterial pressure; s/d = systolic/diastolic; 0LE = no lactate extraction; na = value not available; HR = heart rate.
* Atrial pacing.

TABLE 4. Effects of Isoflurane on Systemic Hemodynamics

Variable	Preinduction	Postintubation	Isoflurane			
			Preincision	Poststernotomy	60 min	Precannulation
Heart rate (beats per min)	66 ± 3	65 ± 3	60 ± 2	62 ± 2	62 ± 2	63 ± 2
Systemic arterial pressure (mmHg)						
Systolic	145 ± 5	128 ± 5	122 ± 3	126 ± 3	117 ± 2	116 ± 2
Diastolic	68 ± 2	62 ± 2	64 ± 2	68 ± 2	63 ± 2	62 ± 2
Mean	94 ± 3	84 ± 3	84 ± 2	88 ± 2	82 ± 2	82 ± 2
Right atrial pressure (mmHg)	9 ± 1	10 ± 1	10 ± 1	10 ± 1	9 ± 1	9 ± 1
Pulmonary capillary wedge pressure (mmHg)	14 ± 1	13 ± 1	14 ± 1	13 ± 1	13 ± 1	13 ± 1
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	2.7 ± 0.1	2.6 ± 0.2	2.3 ± 0.1	2.1 ± 0.1	2.0 ± 0.1*	2.1 ± 0.1
Stroke volume (ml/beat)	80 ± 4	75 ± 4	74 ± 3	66 ± 3	62 ± 2*†	64 ± 3
Systemic vascular resistance ($dyne \cdot s \cdot cm^{-5}$)	1379 ± 87	1311 ± 83	1383 ± 83	1586 ± 86	1589 ± 98	1539 ± 99
Left ventricular stroke work ($g \cdot m \cdot beat^{-1}$)	88 ± 6	73 ± 5	70 ± 3	67 ± 3	59 ± 2*†	61 ± 3

Values are mean ± SEM.
* $P < 0.05$ *versus* postintubation.
† $P < 0.05$ between isoflurane and halothane groups.

EFFECT OF INDUCTION OF ANESTHESIA

Before induction of anesthesia new myocardial ischemia was detected by ECG in eight patients (four patients in each study group). MLP was detected in two additional patients in the halothane group. There was no correlation between ECG changes and MLP.

After induction with fentanyl (50 μg/kg) and tracheal intubation, systemic hemodynamic, coronary circulatory, and myocardial metabolic changes were not significant (tables 4–9). In the isoflurane group, global CVF decreased and was significantly different from the halothane group after intubation (tables 6 and 8). During induction, ischemic ECG changes occurred in one patient and were unrelated to hemodynamic alterations. After induction and before the administration of the volatile anesthetic, RWMA were present in 18 of 40 patients (9 in each group). These RWMA were also present preoperatively.

EFFECTS OF ISOFLURANE

Coronary hemodynamic, myocardial metabolic data, and inspired and end-tidal concentrations of isoflurane are presented in tables 6 and 7. In 16 patients the inspired concentration of isoflurane was maintained at approximately 0.6% throughout the study (0.5–0.6% end-tidal), whereas in 4 patients the inspired concentration was transiently increased (0.7–0.9%) to control increases in blood pressure (0.6–0.7% end-tidal).

Regional and global $M\dot{V}_{O_2}$ decreased progressively. These changes were statistically significant at 60 min (regional $M\dot{V}_{O_2}$ only) and precannulation (table 7). Although

TABLE 5. Effects of Halothane on Systemic Hemodynamics

Variable	Preinduction	Postintubation	Halothane			
			Preincision	Poststernotomy	60 min	Precannulation
Heart rate (beats per min)	61 ± 3	63 ± 2	59 ± 2	59 ± 2	59 ± 2	61 ± 2
Systemic arterial pressure (mmHg)						
Systolic	148 ± 5	136 ± 6	124 ± 3	129 ± 3	117 ± 3*	119 ± 3*
Diastolic	69 ± 3	67 ± 2	66 ± 2	68 ± 2	66 ± 2	64 ± 2
Mean	96 ± 3	92 ± 4	86 ± 2	90 ± 2	84 ± 2	84 ± 2
Right atrial pressure (mmHg)	9 ± 1	10 ± 1	9 ± 1	9 ± 1	9 ± 1	9 ± 1
Pulmonary capillary wedge pressure (mmHg)	14 ± 1	14 ± 1	12 ± 1	12 ± 1	12 ± 1	12 ± 1
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	2.8 ± 0.1	2.6 ± 0.1	2.3 ± 0.1*	2.2 ± 0.1*	2.2 ± 0.1*	2.1 ± 0.1*
Stroke volume (ml/beat)	87 ± 3	82 ± 4	76 ± 5	72 ± 4	71 ± 3†	67 ± 3*
Systemic vascular resistance ($dyne \cdot s \cdot cm^{-5}$)	1350 ± 48	1321 ± 66	1465 ± 85	1594 ± 82	1483 ± 68	1546 ± 83
Left ventricular stroke work ($g \cdot m \cdot beat^{-1}$)	97 ± 5	88 ± 6	76 ± 5	77 ± 5	69 ± 4†	65 ± 3*

Values are mean ± SEM.
* $P < 0.05$ *versus* postintubation.
† $P < 0.05$ between isoflurane and halothane groups.

TABLE 6. Effects of Isoflurane on Coronary Hemodynamics

Variable	Preinduction	Postintubation	Isoflurane							
			Preincision		Posternotomy		60 min		Precannulation	
			INS	ET	INS	ET	INS	ET	INS	ET
			0.58 ± 0.05	0.48 ± 0.06	0.61 ± 0.08	0.52 ± 0.07	0.64 ± 0.09	0.54 ± 0.07	0.64 ± 0.09	0.54 ± 0.07
Diastolic arterial pressure (mmHg)	68 ± 3	62 ± 2	64 ± 2		68 ± 2		63 ± 2		62 ± 2	
Global coronary venous flow (ml/min)	133 ± 10	107 ± 7†	117 ± 9		116 ± 10		111 ± 8		111 ± 8	
Regional coronary venous flow (ml/min)	63 ± 6	55 ± 5	53 ± 4		51 ± 4		48 ± 3		52 ± 5	
Flow ratio	0.51 ± 0.05	0.55 ± 0.05	0.50 ± 0.05		0.50 ± 0.05		0.48 ± 0.04		0.52 ± 0.04	
Global coronary vascular resistance (mmHg · ml · min^{-1})	0.44 ± 0.04	0.49 ± 0.05	0.49 ± 0.06		0.54 ± 0.05		0.50 ± 0.05		0.51 ± 0.06	
Regional coronary vascular resistance (mmHg · ml · min^{-1})	1.02 ± 0.12	0.95 ± 0.09	1.05 ± 0.10		1.20 ± 0.12		1.12 ± 0.08		1.06 ± 0.09	

Values are mean ± SEM.
INS = Inspired concentration (%); ET = end-tidal concentration (%).
† $P < 0.05$ between isoflurane and halothane groups.

both regional and global MLE decreased progressively, these changes were significant at precannulation only. The MLE regional/global ratio remained unchanged. CVF, CVR, and $M_{O_2}E$ did not change. The regional/global ratio of myocardial oxygen content, CVF, and CVR did not change (tables 6 and 7).

Seven new ischemic episodes were detected by echocardiography, ECG, and/or MLP in 7 of 20 patients (table 2). One of these episodes was detected by echocardiography between two study points (patient 20). Four of the ischemic episodes (in patients 20, 21, 38, and 40) occurred in the absence of any systemic hemodynamic abnormalities, whereas three episodes (in patients 1, 18, and 33) occurred with hemodynamic changes. New RWMA were detected in 5 patients and MLP in 3 patients. One patient (patient 40) had both MLR (regional and global) and echocardiographic changes, and another (patient 21) had ECG and echocardiographic abnormalities. Regional MLP was detected in patient 33 as blood pressure decreased during nitroprusside administration before aortic cannulation. This patient suffered postoperative myocardial infarction. There were no adverse cardiac events in the other 6 patients who experienced intraoperative myocardial ischemia.

TABLE 7. Effects of Isoflurane on Myocardial Metabolism

Variable	Preinduction	Postintubation	Isoflurane							
			Preincision		Posternotomy		60 min		Precannulation	
			INS	ET	INS	ET	INS	ET	INS	ET
			0.58 ± 0.05	0.48 ± 0.06	0.61 ± 0.08	0.52 ± 0.07	0.64 ± 0.09	0.54 ± 0.07	0.64 ± 0.09	0.54 ± 0.07
Global myocardial O_2 consumption (ml/min)	11.5 ± 1.0	10.0 ± 1.0	9.5 ± 0.7		9.9 ± 1.0		9.5 ± 0.9		8.6 ± 0.8*	
Regional myocardial O_2 consumption (ml/min)	6.8 ± 0.8	5.6 ± 0.6	5.0 ± 0.4		5.0 ± 0.5		4.4 ± 0.4*		4.6 ± 0.5*	
Global myocardial lactate extraction (%)	41.1 ± 3.3	40.6 ± 3.2	34.8 ± 3.4		28.4 ± 4.2		26.1 ± 3.6		18.6 ± 2.6*	
Regional myocardial lactate extraction (%)	44.1 ± 3.5	44.4 ± 3.8	35.8 ± 3.7		32.2 ± 3.3		30.8 ± 3.8		21.5 ± 3.6*	
Global myocardial O_2 extraction (%)	52.7 ± 2.0	55.8 ± 1.8	50.7 ± 2.3		53.3 ± 1.8		52.6 ± 1.8		50.0 ± 2.3	
Regional myocardial O_2 extraction (%)	59.3 ± 1.8	59.9 ± 1.8	54.8 ± 2.6		57.9 ± 2.0		57.2 ± 1.7		55.3 ± 2.0	

Values are mean ± SEM.
INS = Inspired concentration (%); ET = end-tidal concentration (%).
* $P < 0.05$ *versus* postintubation.

TABLE 8. Effects of Halothane on Coronary Hemodynamics

Variable	Preinduction	Postintubation	Halothane							
			Preincision		Poststernotomy		60 min		Precannulation	
			INS	ET	INS	ET	INS	ET	INS	ET
			0.41 ± 0.06	0.35 ± 0.06	0.45 ± 0.07	0.36 ± 0.06	0.46 ± 0.08	0.37 ± 0.08	0.46 ± 0.09	0.36 ± 0.06
Diastolic arterial pressure (mmHg)	69 ± 3	67 ± 2	66 ± 2		68 ± 2		66 ± 2		64 ± 2	
Global coronary venous flow (ml/min)	134 ± 7	131 ± 8†	121 ± 9		118 ± 7		108 ± 7		110 ± 7	
Regional coronary venous flow (ml/min)	66 ± 5	62 ± 6	56 ± 5		54 ± 5		52 ± 5		56 ± 6	
Flow ratio	0.51 ± 0.03	0.49 ± 0.04	0.50 ± 0.04		0.47 ± 0.04		0.49 ± 0.04		0.53 ± 0.05	
Global coronary vascular resistance (mmHg · ml · min^{-1})	0.43 ± 0.02	0.43 ± 0.02	0.48 ± 0.04		0.50 ± 0.03		0.52 ± 0.03		0.50 ± 0.03	
Regional coronary vascular resistance (mmHg · ml · min^{-1})	0.92 ± 0.08	0.99 ± 0.11	1.07 ± 0.12		1.26 ± 0.13		1.21 ± 0.15		1.07 ± 0.11	

Values are mean ± SEM.
INS = Inspired concentration (%); ET = end-tidal concentration (%).
† $P < 0.05$ between isoflurane and halothane groups.

EFFECTS OF HALOTHANE

Coronary hemodynamic and myocardial metabolic data and the inspired and end-tidal concentration of halothane are presented in tables 8 and 9. Over time, global and regional $M\dot{V}_{O_2}$ and MLE decreased ($P < 0.05$), whereas $M_{O_2}E$ did not change. Global and regional CVF and CVR did not change. Diastolic arterial pressure did not change.

Eleven new myocardial ischemic episodes (echocardiographic, ECG, and/or metabolic) were observed in eight patients during halothane (table 3). Four of these episodes occurred in the absence of hemodynamic abnormalities; six episodes were related to a reduction in blood pressure; and one was related to elevation. MLP was detected during 6 ischemic episodes in three patients (patients 11, 22, and 25). During the course of the study, two of these patients (patients 11 and 22) with recent myocardial infarction and with abnormal MLE (10%) before induction of anesthesia developed more than 1 ischemic episode each, detected by MLP or RWMA or both. In another patient (patient 25) with 50% left main lesion and occluded left anterior descending coronary artery, marked MLP was detected regionally (GCV) while global CVF and $M_{O_2}E$ decreased as hypotension developed (28%). ECG ischemic changes were also present during this event and persisted throughout the study period. This patient suffered postoperative myocardial infarction. In two additional patients who developed new RWMA during halothane, myocardial infarction was diagnosed postoperatively (patients 12 and 39).

TABLE 9. Effects of Halothane on Myocardial Metabolism

Variable	Preinduction	Postintubation	Halothane							
			Preincision		Posternotomy		60 min		Precannulation	
			INS	ET	INS	ET	INS	ET	INS	ET
			0.41 ± 0.06	0.35 ± 0.06	0.45 ± 0.07	0.36 ± 0.06	0.46 ± 0.08	0.37 ± 0.08	0.46 ± 0.09	0.36 ± 0.06
Global myocardial O_2 consumption (ml/min)	13.2 ± 0.8	12.8 ± 1.1	11.2 ± 0.9		10.7 ± 0.7*		10.8 ± 0.7*		9.7 ± 0.7*	
Regional myocardial O_2 consumption (ml/min)	7.0 ± 0.6	6.9 ± 0.8	5.8 ± 0.5*		5.5 ± 0.5*		5.3 ± 0.6*		4.8 ± 0.4*	
Global myocardial lactate extraction (%)	27.5 ± 6.4	35 ± 4.6	28.4 ± 8.2		30.4 ± 3.3		23.3 ± 3.3		18.7 ± 4.4*	
Regional myocardial lactate extraction (%)	30.1 ± 6.0	37.4 ± 4.2	31.5 ± 4.1		34.6 ± 3.7		24.0 ± 3.6		19.1 ± 3.9*	
Global myocardial O_2 extraction (%)	55.4 ± 1.8	55.0 ± 2.4	54.3 ± 2.2		54.5 ± 2.3		58.1 ± 1.6		55.0 ± 1.8	
Regional myocardial O_2 extraction (%)	59.7 ± 1.5	60.9 ± 1.4	59.7 ± 1.2		61.1 ± 0.9		59.9 ± 1.8		58.1 ± 1.4	

INS = Inspired concentration (%); ET = end-tidal concentration (%). * $P < 0.05$ *versus* postintubation.

Discussion

These data demonstrate that in patients with steal-prone coronary anatomy, neither isoflurane nor halothane, administered at concentrations used in the study as an adjunct to high-dose fentanyl anesthesia, is likely to cause myocardial ischemia by the coronary steal mechanism, as judged by regional and global myocardial circulatory and metabolic findings and systemic hemodynamics. We also found that in this subset of patients with coronary artery disease, new myocardial ischemia occurs intraoperatively, and the incidence of these occurrences does not differ between the two inhalational anesthetics evaluated. To our knowledge this is the only prospectively designed study to examine the regional and global myocardial metabolic and circulatory effects of isoflurane on patients with steal-prone anatomy.

Changes in coronary blood flow that accompany administration of a pharmacologic agent need to be interpreted in relation to a variety of factors that are potentially altered by the drug and are themselves capable of affecting flow.[15] Both isoflurane[4,9,10] and halothane[16,17] can alter coronary flow, and thus myocardial perfusion, by their effects on heart rate, systemic and coronary vascular resistance, and myocardial contractile state. Theoretically, a vasodilator can decrease collateral perfusion by reducing aortic diastolic pressure through a decrease in peripheral vascular resistance and/or by selectively dilating resistance vessels in nonischemic areas distal to a coronary stenosis.[18] In the latter case, a decrease in arteriolar resistance within the region of origin of collateral circulation would divert blood flow away from the area distal to a coronary occlusion (coronary steal).[19,20] In the absence of a significant decline in arterial pressure or increase in myocardial oxygen demand, a small vessel–type coronary vasodilator could induce myocardial ischemia by the coronary steal mechanism.[18,21–23]

Several clinical studies[4,9,10] have demonstrated that in patients with coronary artery disease, isoflurane induces coronary vasodilation (decreased CVR) unrelated to normal autoregulation and that both decreased coronary perfusion pressure and redistribution of myocardial blood flow (coronary steal) may contribute to the development of regional myocardial ischemia. In the presence of hypotension, however, decrease in CVR *per se* is not necessarily evidence of a direct coronary vasodilatory effect because a simultaneous decrease in blood pressure will induce autoregulatory vasodilation.[24,25] Despite considerable differences in methodology, several studies[11,26–29] in animals point out the importance of perfusion pressure in assessing coronary steal during isoflurane administration. An important factor, therefore, in assessing the action of isoflurane is strict control of systemic arterial pressure to permit its effect on blood pressure to be distinguished from a selective dilation on nonischemic coronary vasculature.[19]

Reiz *et al.*[4] demonstrated ECG and myocardial metabolic evidence of ischemia during prolonged exposure to 1% isoflurane in patients with coronary artery disease undergoing vascular surgery. Decreased MLE and elevated coronary venous oxygenation were associated with marked systemic hypotension and decreased CVR. Upon restoration of coronary perfusion pressure with phenylephrine, the ECG and myocardial metabolic changes reverted in two of five patients. However, in the remaining three patients, ischemia persisted. Whether this implies that decreased perfusion pressure was not the major mechanism for regional myocardial ischemia or that α-adrenergic coronary vasoconstriction caused by phenylephrine contributed primarily to the persistent ischemia in these patients cannot be determined with certainty. The responsiveness of the coronary circulation to α-adrenergic stimulation may be variable. α-Adrenergic vasoconstriction is capable of competing with local myocardial metabolic control and thus opposing metabolically mediated vasodilation.[30] If coronary vasodilatory reserve is exhausted or the coronary vasculature pharmacologically vasodilated, sustained pharmacologic α-adrenergic stimulation can result in blood flow reduction.[31] Although coronary blood flow is regulated primarily by the metabolic demands of the myocardium, flow increases as long as further arteriolar dilation is possible.[32,33] In a state of near-maximal metabolic vasodilation, usually present in coronary arterial vasculature distal to critical stenosis or occlusion, flow is pressure-dependent. In these areas, despite an increase in aortic pressure, flow may continue to be limited in that it does not attain the same level as in a nonstenotic area.[25]

Moffitt *et al.*[9] found evidence of myocardial ischemia in patients undergoing CABG who experienced marked hemodynamic alterations and instability during isoflurane. Myocardial ischemia was attributed to isoflurane-induced flow redistribution (steal). It cannot be excluded, however, that hemodynamic instability[34,35] rather than isoflurane-induced coronary vasodilation was primarily responsible for the development of ischemia.

In a comparative study in CABG patients, Khambatta *et al.*[10] found ECG and metabolic evidence of myocardial ischemia during isoflurane anesthesia but not during halothane. Four of ten patients had global and regional lactate production and developed new ischemic ECG patterns. The authors attributed these ischemic changes to isoflurane-induced coronary vasodilation that caused coronary steal. However, on the basis of the presented data, this conclusion is not entirely justified. It seems that the differences between isoflurane and halothane can best be explained on the basis of their different effects on heart rate and blood pressure.[36,37] During halothane anesthesia,

heart rate did not change significantly (from 65 to 60 beats per min), and diastolic pressure decreased approximately 16% (from 69 to 58 mmHg). In contrast, during isoflurane anesthesia, heart rate increased by 20% (from 69 to 83 beats per min), and the decrease in diastolic pressure was more pronounced (from 77 to 55 mmHg = 29%). Clinical[36] and experimental[37] data suggest that in the presence of coronary stenosis, the absolute heart rate at which ischemia occurs depends on the existing level of arterial pressure. Therefore, the combination of hypotension and increase in heart rate appears to have contributed, primarily, to the development of myocardial ischemia observed during isoflurane in Khambatta *et al.*'s study. Although these prospective studies suggest a coronary steal mechanism as a cause of regional myocardial ischemia during isoflurane administration, the presence of steal-prone anatomy was not documented in any patient.

Intraoperative myocardial ischemia is not uncommon in patients undergoing CABG and appears to result from a complex interaction of numerous variables associated with oxygen supply and demand.[8,14,38,39] Most ischemic episodes observed before cardiopulmonary bypass were not preceded by or associated with marked changes in blood pressure or heart rate. It has been postulated[38] that these ischemic episodes represent the same phenomenon as silent ischemia detected in patients with coronary artery disease during their daily activities. In the current investigation, a total of 18 myocardial ischemic episodes (7 with isoflurane and 11 with halothane) were identified by ECG, echocardiography, and/or metabolic changes indicative of myocardial ischemia. Most episodes were detected by either echocardiography (7) or MLP (6). ECG changes were present in only two patients.

Transesophageal echocardiography has been found to be a more sensitive measure for detecting intraoperative myocardial ischemia than ECG.[40] Myocardial lactate production, a reliable marker of acute myocardial ischemia,[41-43] was detected in three patients in each group (tables 2 and 3). In one patient (patient 1) with MLE < 10% and ischemic ECG changes at preincision, MLP was detected in the CS while $M_{O_2}E$ increased, as acute increases in heart rate and arterial pressure occurred during sternotomy. Hemodynamic changes[34,35] rather than coronary steal appear to be responsible for worsening of preexisting borderline myocardial ischemia (abnormal MLE and ECG at control). In another patient (patient 33) with occluded left circumflex and right coronary arteries, ischemic cardiomyopathy (ejection fraction < 40%) and recent anteroseptal myocardial infarction (10 days old), MLP was detected in the GCV but not in the CS, as diastolic pressure decreased by 20% during nitroprusside infusion (table 2), just before aortic cannulation, approximately 90 min after isoflurane administration had begun. The decrease in global and regional $M_{O_2}E$ accompanied by and increase in CVF suggests coronary vasodilation.[25] Since nitroprusside may aggravate myocardial ischemia by causing hypotension and flow maldistribution,[44] coronary circulatory and myocardial metabolic changes observed in this patient cannot necessarily be attributed to isoflurane-induced coronary vasodilation.

Finally, a transient decrease in blood pressure (18%) that preceded precannulation measurements resulted in MLP (regional and global), as regional and global CVF and myocardial oxygen content decreased and $M_{O_2}E$ increased (patient 40). In this patient with proximal occlusion of the left anterior descending and right coronary artery, MLE was low throughout the study (<15%). These changes suggest that myocardial hypoperfusion rather than isoflurane-induced coronary steal was responsible for ischemia in this patient. During halothane, MLP was detected in 3 of 20 patients (table 3). In all three patients (patients 11, 22, and 25) myocardial hypoperfusion due to decrease in blood pressure appears to be the mechanism responsible for the MLP observed. Two of these patients (patients 11 and 22) had abnormal MLE throughout the study.

The parallel changes in regional and global CVF and CVR accompanying ECG, echocardiographic, and metabolic abnormalities suggest that coronary maldistribution was not responsible for the development of ischemia detected in our patients during isoflurane or halothane. Although the current investigation does not exclude the possibility that isoflurane may cause coronary vasodilation and redistribution of blood flow leading to ischemia during other clinical circumstances (*i.e.*, higher concentrations, tachycardia, or hypotension), it demonstrates that, under the conditions of our study, isoflurane did not affect regional myocardial oxygenation and metabolism in patients with steal-prone coronary anatomy. Furthermore, the incidence of intraoperative ischemia was not significantly greater during isoflurane than during halothane. These findings are supported by a recently published retrospective study by Slogoff *et al.*[14] Their data showed that intraoperative myocardial ischemic episodes can occur randomly as well as in response to hemodynamic abnormalities and are unrelated to the volatile anesthetic.

Several aspects of our study are different compared to other clinical investigations.[4,5,8-10,14] First, we studied prospectively patients with well-defined coronary artery stenosis, *i.e.*, with steal-prone coronary anatomy. Second, hemodynamics were controlled and marked alterations in blood pressure were prevented throughout the study period. Third, isoflurane was used as an adjunct to high-dose fentanyl and was administered at lower concentrations than those used in the other studies (1% end-tidal,[4] 0.7–3.8% inspired,[9] and 1 MAC[10]). Fourth, in the current study, administration of isoflurane started after induction

of anesthesia and continued throughout the prebypass period. In contrast, Reiz *et al.*[4] and Khambatta *et al.*[10] used isoflurane prior to surgical incision, whereas Moffitt *et al.*[9] maintained "controlled hemodynamic depression" (reduction of blood pressure by 30% from awake level) for the duration of the study. Finally, differences in preexisting cardiac function, effectiveness of preoperative cardiac medication, baseline anesthesia, intraoperative hemodynamic management, and methodology used to detect ischemia may explain contrasting findings. It is noteworthy, however, that myocardial ischemic episodes were detected both before induction of anesthesia and during surgery, in several clinical studies,[4,8–10,14,36,38,39,40] including ours, despite differences in investigational protocols.

Certain limitations of the current study should be mentioned. First, the relative advantages and disadvantages of the thermodilution method for measuring CVF have been discussed previously.[2] The reproducibility of coronary venous blood flow (CS and GCV) measurements may be affected by small position shifts of the catheter. Second, when coronary vascular resistance is measured in patients, the calculated value is less certain because computed resistance is usually based on measurements of CVF. Such calculations disregard the potential contributions of extravascular forces and coronary capacitance. In view of these limitations, little credence should be given to minor alterations ($\leq$ 15%) in coronary vascular resistance observed in clinical studies.[25] Third, in the current investigation, infusion of phenylephrine, an α-adrenergic agonist, was administered in 16 patients (5 during halothane and 11 during isoflurane). Adrenergic vasoconstriction mediated by α-receptors acts on both large epicardial arteries and small coronary vessels.[31,45,46] In patients with ischemic heart disease, vasoconstriction in the stenosis may worsen the stenotic pressure gradient and severely limit blood flow. Conversely, vasoconstriction of small coronary vessels may produce a beneficial antitransmural steal effect ("reverse coronary steal").[46] The net effect of adrenergic vasoconstriction depends on an interaction of severity of stenosis, myocardial oxygen demand, degree of ischemia, and large and small coronary vasoconstriction. Therefore, it cannot be determined with certainty whether or to what degree phenylephrine administration might have affected the incidence of myocardial ischemia detected in the current study. Finally, both anesthetics were administered as an adjunct to fentanyl. Although fentanyl is not known to have direct actions on coronary circulation,[47] a combination of volatile anesthetic and opioid may counteract or mask the effects on coronary vascular tone produced by the anesthetic alone. This possibility, however, remains speculative.

In summary, in patients with steal-prone coronary anatomy anesthetized with fentanyl, neither isoflurane nor halothane at concentrations used in the current study is likely to cause myocardial ischemia by coronary steal mechanism. Factors other than maldistribution of coronary blood flow are more likely to be responsible for the ischemic episodes observed. Despite the ability of isoflurane to cause coronary arteriolar vasodilation, our data indicate that under the conditions of the study, isoflurane did not affect regional myocardial oxygenation and metabolism in patients with steal-prone anatomy.

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