Anesthesiology
75:640–649, 1991

Isoflurane Causes Only Minimal Increases in Coronary Blood Flow Independent of Oxygen Demand

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Studies on the coronary circulation during halothane or isoflurane anesthesia are conflicting. Also, little attention has been paid to the time course of the effect of these agents on the coronary circulation. Therefore, we investigated the direct and temporal effects of halothane and isoflurane on coronary hemodynamics in chronically instrumented dogs, in the presence and absence of autonomic nervous system blockade. On different days anesthesia was induced *via* inhalation with 5% halothane or isoflurane in 100% oxygen. After tracheal intubation, anesthesia was maintained at 1.0 MAC for 30 min. Hemodynamics were recorded continuously. Myocardial oxygen consumption was estimated from the pressure–work index. A total of 36 experiments (four sets of experiments) were completed using nine chronically instrumented dogs. Induction of anesthesia with halothane caused a significant ($P < 0.05$) increase in coronary blood flow (from 40 ± 6 to 68 ± 11 ml/min), which reached a peak at 1.4 ± 0.3 min. These changes were secondary to increases in heart rate, arterial pressure, and pressure–work index (10.2 ± 1.4 to 15.9 ± 0.8 ml $O_2 \cdot min^{-1} \cdot 100\ g^{-1}$). With autonomic nervous reflexes eliminated, halothane caused no change in coronary blood flow. Inhalation of isoflurane caused a greater ($P < 0.05$) increase in coronary blood flow (from 39 ± 6 to 85 ± 14 ml/min) than did halothane; flow reached a peak at 1.8 ± 0.6 min. With autonomic reflexes eliminated, isoflurane continued to produce an increase ($P < 0.05$) in coronary blood flow (from 39 ± 4 to 53 ± 5 ml/min), which reached a peak at 2.1 ± 0.4 min. Thereafter, coronary blood flow rapidly decreased and returned to control levels within 6 min despite continued administration of isoflurane. Thus, the increase in coronary blood flow during inhalation induction with halothane is related only to an increase in estimated myocardial oxygen demand. In contrast, isoflurane produces only small and transient increases in absolute coronary blood flow when increased myocardial oxygen demand is prevented. (Key words: Anesthetics, volatile: isoflurane; halothane. Heart: oxygen consumption; coronary blood flow; coronary circulation; coronary hemodynamics; coronary vasodilation. Hemodynamics. Vasodilation.)

THE EFFECTS of halothane and isoflurane on the coronary circulation remain controversial. In general, isoflurane[1,2] but not halothane has been considered a potent coronary vasodilator.[3,4] Despite this, recent *in vitro* investigations have indicated that halothane also may be a direct coronary vasodilator.[5] Other *in vivo* investigations have not demonstrated isoflurane to have the efficacy in increasing coronary flow that other well known coronary vasodilator drugs have.[6] *In vivo* studies of the coronary circulation, however, have been complicated by the actions of halothane and isoflurane on cardiac function,[7] systemic hemodynamics,[8,9] and myocardial oxygen consumption.[10] The effects of the volatile anesthetics on coronary flow *in vivo* are due to a combination of direct actions on coronary vascular smooth[11] muscle and/or endothelium[12] and indirect actions mediated by metabolic[13] and pressure autoregulation.[14] For example, any direct vasodilator action of volatile anesthetics on coronary vessels may be opposed *in vivo* by a tendency to vasoconstriction secondary to an anesthetic-induced decrease in metabolic demand of the heart.[15,16] Thus, the action of these agents on the coronary circulation is complex and composed of direct and multiple indirect effects. In addition, little attention has been paid to the time course of the effect of these agents on the coronary circulation. A variable time course of the action volatile anesthetics might be predicted because of the potential mulifactorial basis for change in coronary blood flow *in vivo* and because direct and indirect actions of volatile anesthetics may occur in different temporal sequences.

In the present investigation, the effects of halothane and isoflurane on the coronary circulation were studied in chronically instrumented dogs. To control for confounding variables involved in the regulation of coronary blood flow, the actions of halothane and isoflurane were compared in dogs with blocked and intact autonomic nervous system reflexes. Coronary vasodilator responses to adenosine before and during anesthesia in the presence and absence of autonomic nervous system blockade also were ascertained to document ability for vasodilation to occur. Furthermore, continuous recordings were made of coronary blood flow to determine the time course of the vasodilator action of the volatile anesthetics.

Materials and Methods

All experiments received prior approval of the Animal Care Committee of the Medical College of Wisconsin and

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Received from the Departments of Anesthesiology, Pharmacology, and Medicine, Medical College of Wisconsin, and the Zablocki Veterans Administration Medical Center, Milwaukee, Wisconsin. Accepted for publication June 3, 1991. Supported by United States Public Health Service grants HL 36144 and HL 32911, Anesthesiology Research Training Grant GM 08377, and Veterans Administration Medical Research Funds.

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were conducted in accordance with the Guide for the Care and Use of Laboratory Animals.¶

Animal Instrumentation

Nine conditioned mongrel dogs of either sex weighing 26 ± 3 kg were instrumented under sterile conditions as previously described.[17] Briefly, heparin-filled catheters were implanted in the thoracic aorta, right atrial appendage, and left atrium for measurement of arterial pressure, for drug administration, and for withdrawal of arterial blood gases, respectively. An ultrasonic flow transducer (Transonic Systems, Ithaca, NY) was fitted securely around the aortic root for measurement of cardiac output. The proximal left anterior descending coronary artery was fitted with a 2–3-mm ultrasonic flow probe (Transonic Systems) for measurement of coronary blood flow. For measurement of systolic shortening, pairs of transducers (5-mHz) were inserted parallel to muscle fiber orientation and perpendicular to the long axis of the left ventricle supplied by the left anterior descending coronary artery. A miniature solid-state pressure gauge (Konigsberg Instruments, Pasadena, CA) was implanted in the left ventricle for measurement of pressure and rate of change of pressure (dP/dt) at 50 mmHg (dP/dt_{50}). All dogs were treated with analgesics as necessary in the immediate postoperative period.

After surgery, each dog was treated with procaine penicillin G (25,000 U/kg) and gentamicin (4.5 mg/kg) and allowed to recover for a minimum of 7 days and trained to stand quietly in a sling while hemodynamics were monitored. Segment length signals were driven and monitored by ultrasonic amplifiers (Hartley, Houston, TX). With the use of left ventricular dP/dt, end-systolic segment length was determined at maximum negative dP/dt, and end-diastolic segment length was determined immediately before the onset of left ventricular isovolumic contraction. The lengths were normalized according to the method of Theroux *et al.*[18] Percent segment shortening (%SS) was calculated by use of the equation: %SS = ([EDL − ESL]/EDL) × 100, where ESL = end-systolic segment length and EDL = end-diastolic segment length. Cardiac output (minus coronary blood flow) was measured in liters per minute. Systemic vascular resistance was calculated as the quotient of mean arterial pressure and cardiac output. Coronary vascular resistance was calculated as the quotient of diastolic arterial pressure and diastolic coronary blood flow. The pressure–work index, an estimate of myocardial oxygen consumption,[19] was calculated with the formula:

$$PWI = K_1(SBP \times HR) + K_2 \times \left(\frac{[0.8\ SBP + 0.2\ DBP] \times HR \times SV}{BW}\right) + 1.43$$

where $M\dot{V}O_2$ = left ventricular myocardial oxygen consumption (ml $O_2 \cdot min^{-1} \cdot 100\ g^{-1}$); SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); HR = heart rate (beats per min); SV = stroke volume (ml); BW = body weight (kg); $K_1 = 4.08 \times 10^{-4}$; and $K_2 = 3.25 \times 10^{-4}$.

The balance between myocardial oxygen supply and demand was expressed as the ratio of diastolic coronary blood flow and pressure–work index. All hemodynamic data were recorded continuously on a Beckman polygraph (Sensormedics, Anaheim, CA) and digitized *via* a computer interfaced with an analog-to-digital converter.

Experimental Protocol

A total of nine dogs underwent experimentation. Experiments comparing the effects of halothane and isoflurane anesthesia were conducted in four sets (N = 9 in each set). Each dog underwent all parts of the experimental protocol (fig. 1). All dogs were fasted overnight, and maintenance fluids (0.9% normal saline) were continued at 3 $ml \cdot kg^{-1} \cdot h^{-1}$ for the duration of each experiment. In groups 1 and 2 (halothane in the absence and presence of autonomic nervous system blockade groups, respectively), hemodynamics were recorded in the conscious state for 30 min in dogs without (group 1) or with (group 2) ganglionic (hexamethonium 20 mg/kg intravenously), cholinergic (atropine methylnitrate 3 mg/kg intravenously), and β-adrenergic (propranolol 2 mg/kg intravenously) blockade. Then, bolus doses of adenosine (25, 50, and 100 μg/kg) were administered *via* the left atrial catheter, and coronary flow responses were recorded to document capacity for vasodilation. The order of adenosine administration was randomized and coronary blood flow allowed to return to baseline between injections of adenosine. Anesthesia was induced *via* inhalation with a mask using 5% halothane in 100% oxygen. Hemodynamics were recorded every 30 s for the first 3 min and every 1 min thereafter until tracheal intubation. After intubation, anesthesia was maintained at 1.0 MAC end-tidal halothane in a nitrogen (79%) and oxygen (21%) mixture. End-tidal anesthetic concentrations were measured with a mass spectrometer (Advantage 2000, Marquette Electronics, St. Louis, MO). Hemodynamics were recorded every 1 min after intubation for 30 min. Bolus doses of adenosine were administered again as in the conscious state after 30 min of steady-state anesthesia. Each dog then was allowed to emerge from anesthesia and was housed for at least 3 days before further experimentation.

Experiments in groups 3 and 4 (isoflurane in the ab-

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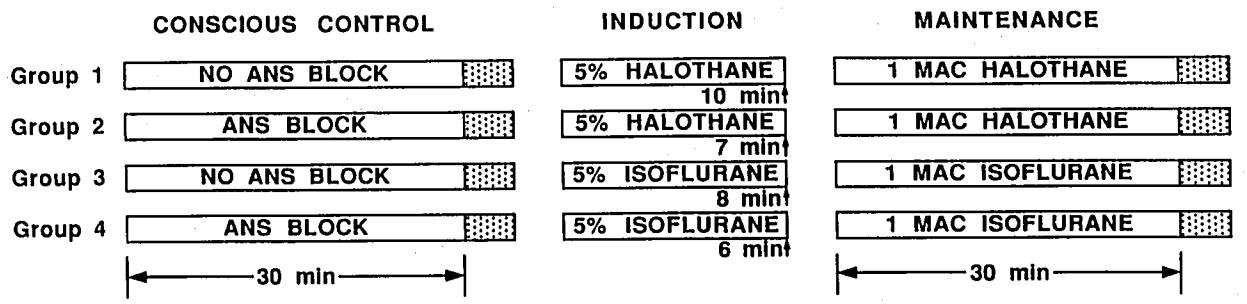

FIG. 1. Experimental protocols followed in groups 1–4 describing temporal relationships of control, induction, and maintenance anesthesia. Conscious control hemodynamic data was monitored for 30 min in dogs with and without autonomic nervous system blockade (ANS block). Shaded areas indicate approximate times during which adenosine was administered. Small arrows indicate mean times to intubation after induction of anesthesia.

sence and presence of autonomic nervous system blockade, respectively) were conducted as above, except that isoflurane was used instead of halothane. Experiments in groups 1–4 were completed in the same dogs (n = 9) on separate days in a random fashion.

STATISTICAL ANALYSIS

Data are presented as means ± standard errors. Hemodynamic responses were compared with control by use of analysis of variance with repeated measures followed by Duncan's multiple-range test. Changes between the conscious state, pharmacologic blockade of the autonomic nervous system, and volatile anesthesia or following administration of adenosine were considered significant when P was less than 0.05.

Results

The hemodynamic effects of halothane in the absence (group 1) or presence (group 2) of autonomic nervous system blockade are summarized in tables 1 and 2, respectively. During inhalation induction, high-concentration halothane caused a significant ($P < 0.05$) decrease in coronary vascular resistance and increase in diastolic coronary blood flow; flow reached a peak at 1.4 ± 0.3 min and then quickly decreased to conscious-state levels (table 1 and fig. 2). The peak increase in coronary blood flow produced by halothane occurred during a significant increase in heart rate, mean arterial pressure, left ventricular systolic and end-diastolic pressures, and cardiac output. These systemic hemodynamic changes were associated with large increases in the pressure–work index. The increase in coronary blood flow was directly related to the estimated increase in oxygen consumption. Thus, the balance between myocardial oxygen supply and demand as indicated by the ratio between coronary flow and pressure–work index remained unchanged from the conscious state (table 1). The increases in heart rate, mean arterial pressure, left ventricular pressure, and cardiac

TABLE 1. Effects of Halothane on Hemodynamics (Group 1)

		Induction		Postintubation	
	Conscious	Peak 1.4 ± 0.3 min	Intubation 10 ± 1 min	10 min	30 min
HR (beats per min)	88 ± 8	151 ± 10*	131 ± 9*	106 ± 10	108 ± 9
MAP (mmHg)	100 ± 5	118 ± 7*	75 ± 8*	67 ± 2*	72 ± 4*
LVSP (mmHg)	130 ± 9	149 ± 9*	100 ± 8*	91 ± 5*	98 ± 5*
LVEDP (mmHg)	9 ± 1	12 ± 3*	8 ± 2	9 ± 2	10 ± 2
dP/dt_{50} (mmHg/s)	1991 ± 83	1883 ± 105	1333 ± 107*	1169 ± 79*	1223 ± 82*
DCBF (ml/min)	40 ± 6	68 ± 11*	38 ± 7	33 ± 5	34 ± 5
DCVR (ru)	2.54 ± 0.39	1.73 ± 0.28*	1.91 ± 0.38*	2.46 ± 0.63	2.25 ± 0.44
CO (l/min)	2.69 ± 0.32	3.80 ± 0.40*	2.26 ± 0.20	1.76 ± 0.16*	1.94 ± 0.16*
CVR ($dyn \cdot s \cdot cm^{-5}$)	3091 ± 302	2791 ± 340	2595 ± 238	3077 ± 316	2977 ± 258
SS (%)	14.4 ± 2.3	10.9 ± 2.1*	10.9 ± 1.9*	10.4 ± 1.8*	11.4 ± 1.9*
PWI ($ml\ O_2 \cdot min^{-1} \cdot 100\ g^{-1}$)	10.2 ± 1.4	15.9 ± 0.8*	8.4 ± 0.7	6.3 ± 0.3*	7.2 ± 0.5*
DCBF/PWI	4.5 ± 0.8	4.5 ± 0.9	4.9 ± 0.9	5.3 ± 0.9	4.8 ± 0.8

Mean ± SEM data (n = 9)
Peak = time to peak increase in coronary blood flow.
HR = heart rate; MAP =mean arterial pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressures, respectively; dP/dt_{50} = rate of change of pressure at 50 mmHg; DCBF = diastolic coronary blood flow; DCVR = diastolic coronary vascular resistance; CO = cardiac output; SVR = systemic vascular resistance; SS = systolic shortening; PWI = pressure–work index.
* Significantly ($P < 0.05$) different from conscious.

TABLE 2. Effects of Halothane on Hemodynamics during Autonomic Nervous System Blockade (Group 2)

	Conscious	ANS Block	Induction		Postintubation	
			Peak 1.6 ± 0.4 min	Intubation 7 ± 1 min	10 min	30 min
HR (beats per min)	78 ± 5*	112 ± 5	115 ± 7	99 ± 4*	97 ± 4*	95 ± 4*
MAP (mmHg)	97 ± 5*	66 ± 6	58 ± 4	50 ± 3*	49 ± 4*	52 ± 5*
LVSP (mmHg)	124 ± 6*	97 ± 4	91 ± 4	82 ± 3*	83 ± 4*	86 ± 4*
LVEDP (mmHg)	9 ± 2	8 ± 2	9 ± 1	10 ± 2	10 ± 2	11 ± 1
dP/dt_{50} (mmHg/s)	1836 ± 114*	1538 ± 91	1313 ± 101*	1045 ± 71*	1021 ± 92*	1038 ± 81*
DCBF (ml/min)	34 ± 4	35 ± 4	42 ± 6	34 ± 6	33 ± 5	31 ± 5
DCVR (ru)	2.54 ± 0.41*	1.58 ± 0.42	1.34 ± 0.31	1.33 ± 0.27	1.30 ± 0.26	1.52 ± 0.33
CO (l/min)	2.36 ± 0.18*	3.16 ± 0.44	2.58 ± 0.27	2.23 ± 0.35*	2.15 ± 0.36*	1.90 ± 0.25*
SVR (dyne·s·cm^{-5})	3256 ± 175*	1571 ± 249	1817 ± 175	2030 ± 254	1936 ± 275	2147 ± 185*
SS (%)	16.0 ± 2.3	16.7 ± 1.7	14.9 ± 1.7	13.7 ± 1.4*	12.0 ± 1.6*	12.1 ± 1.5*
PWI (ml O_2·min^{-1}·100 g^{-1})	8.7 ± 0.6	8.5 ± 0.8	7.5 ± 0.6	6.3 ± 0.6*	6.1 ± 0.6*	6.0 ± 0.5*
DCBF/PWI	3.8 ± 0.6	4.3 ± 0.8	6.0 ± 1.2	5.5 ± 1.0	5.5 ± 0.9	5.2 ± 0.9

Mean ± SEM data (n = 9). Peak = time to peak increase in coronary blood flow.

ANS block = autonomic nervous system blockade; HR = heart rate; MAP = mean arterial pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressures, respectively; dP/dt_{50} = rate of change of pressure at 50 mmHg; DCBF = diastolic coronary blood flow; DCVR = diastolic coronary vascular resistance; CO = cardiac output; SVR = systemic vascular resistance; SS = systolic shortening; PWI = pressure–work index.

* Significantly ($P < 0.05$) different from ANS block.

output were prevented in dogs with autonomic nervous system blockade (group 2), and no increase in diastolic coronary blood flow during induction of anesthesia with halothane was observed (table 2 and fig. 2). Similar to experiments in group 1, the myocardial oxygen supply–demand relationship (diastolic coronary blood flow ÷ pressure–work index ratio) remained unchanged by halothane.

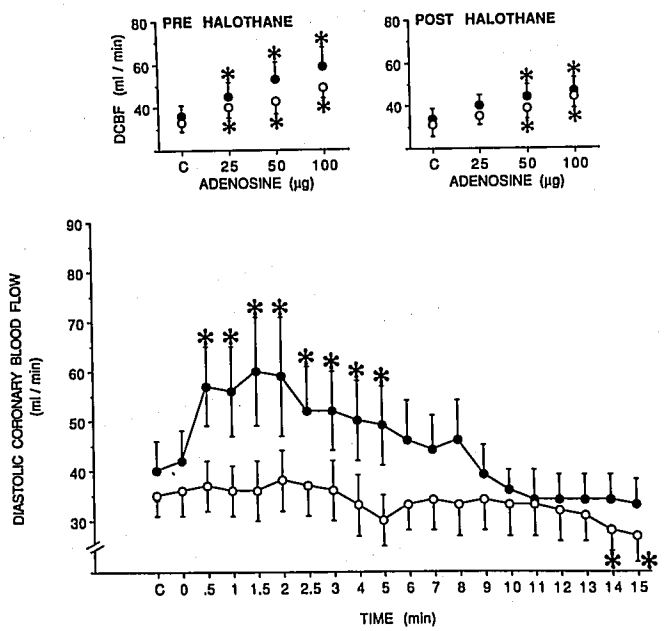

FIG. 2. Diastolic coronary blood flow during the conscious (C) state and induction of anesthesia with 5% halothane over a period of 15 min in dogs in groups 1 and 2. *Insets:* Changes in diastolic coronary blood flow produced by adenosine (25–100 µg) before and during halothane anesthesia. Open circles = intact autonomic reflexes; solid circles = autonomic nervous system blockade. *Significantly ($P < 0.05$) different from conscious state.

In dogs without autonomic nervous system blockade (group 1), the increase in coronary blood flow produced by high concentration of halothane rapidly decreased to conscious levels before intubation (fig. 2), despite continued administration of high (5%) inspired concentrations of anesthetic. Although heart rate was still increased from the conscious state at this time, mean arterial pressure, left ventricular systolic pressure, dP/dt_{50}, and segment shortening were significantly reduced from the conscious state (table 1). These systemic hemodynamic alterations were reflected in an absence of change in the pressure–work index as compared to the conscious state. Thus, the balance of myocardial oxygen supply and demand (diastolic coronary flow ÷ pressure–work index ratio) also remained unchanged from control. After intubation, continued administration of halothane (1 MAC) was associated with no further systemic or coronary hemodynamic changes in the absence (table 1) or presence of autonomic nervous system blockade (table 2). In both groups 1 and 2, small decreases in the pressure–work index remained present but the ratio of myocardial oxygen supply to demand was unchanged from the conscious state. Administration of adenosine during 1 MAC halothane in dogs with or without autonomic nervous system blockade caused an increase in coronary blood flow, demonstrating the ability of the coronary vasculature to dilate (fig. 2).

The systemic and coronary hemodynamic effects of isoflurane in the absence (group 3) and presence (group 4) of autonomic nervous system blockade are summarized in tables 3 and 4, respectively. During inhalation induction, high-concentration isoflurane caused a significant

TABLE 3. Effects of Isoflurane on Hemodynamics (Group 3)

		Induction		Postintubation	
	Conscious	Peak 1.8 ± 0.6 min	Intubation 8 ± 1 min	10 min	30 min
HR (beats per min)	88 ± 8	149 ± 11*	137 ± 9*	125 ± 8*	121 ± 8*
MAP (mmHg)	105 ± 8	118 ± 12	88 ± 7*	73 ± 6*	68 ± 6*
LVSP (mmHg)	131 ± 6	150 ± 12*	109 ± 5*	97 ± 5*	95 ± 6*
LVEDP (mmHg)	8 ± 1	10 ± 2	6 ± 1*	6 ± 1*	7 ± 1
dP/dt_{50} (mmHg/s)	1954 ± 103	2364 ± 223*	1886 ± 138	1506 ± 153*	1414 ± 144*
DCBF (ml/min)	39 ± 6	85 ± 14*	57 ± 10*	41 ± 6	38 ± 6
DCVR (ru)	2.77 ± 0.69	1.80 ± 0.66*	1.95 ± 0.78*	1.86 ± 0.48*	2.33 ± 0.96
CO (l/min)	2.55 ± 0.36	4.46 ± 0.70*	2.56 ± 0.31	1.88 ± 0.24	1.71 ± 0.26*
SVR (dyne·s·cm^{-5})	4362 ± 969	2910 ± 581*	3479 ± 689*	3633 ± 621*	3903 ± 782
SS (%)	17.6 ± 2.9	15.7 ± 2.9	9.1 ± 1.8*	14.0 ± 1.0*	13.3 ± 1.2*
PWI (ml O_2·min^{-1}·100 g^{-1})	10.0 ± 0.9	19.6 ± 2.7*	10.7 ± 1.1	7.8 ± 0.8	7.2 ± 0.9
DCBF/PWI	4.7 ± 1.3	5.5 ± 1.6	6.3 ± 1.8*	6.2 ± 1.4*	6.3 ± 1.4*

Mean ± SEM data (n = 9).
Peak = time to peak increase in coronary blood flow.
HR = heart rate; MAP = mean arterial pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressures, respectively; dP/dt_{50} = rate of change of pressure at 50 mmHg; DCBF = diastolic coronary blood flow; DCVR = diastolic coronary vascular resistance; CO = cardiac output; SVR = systemic vascular resistance; SS = systolic shortening; PWI = pressure–work index.
* Significantly ($P < 0.05$) different from conscious.

decrease in coronary vascular resistance and increase in diastolic coronary blood flow; the effect reached a peak at 1.8 ± 0.6 min. The peak increase in coronary blood flow during administration of isoflurane occurred simultaneously with significant increases in heart rate, left ventricular systolic pressure, left ventricular dP/dt_{50}, cardiac output, and pressure–work index. The majority of the early increase in coronary blood flow was related to estimated myocardial oxygen demand, and thus, no change in the ratio of diastolic coronary blood flow to pressure–work index was observed. With continued administration of high (5%) inspired concentrations of isoflurane by mask, mean arterial pressure, left ventricular systolic and end-diastolic pressures, and systolic shortening significantly decreased from conscious levels. These hemodynamic changes were associated with no change in the pressure–work index as compared to conscious levels, but diastolic coronary blood flow remained elevated. Thus, coronary vasodilation in excess of myocardial oxygen demand (*i.e.*, an increase in the ratio of diastolic coronary blood flow to pressure–work index) was observed before intubation (table 3 and fig. 3). An increase in heart rate and decreases in arterial, left ventricular systolic pressure, dP/dt_{50}, and systolic shortening persisted after intubation and after continued administration of 1 MAC isoflurane. Coronary blood flow, however, decreased to conscious-state levels

TABLE 4. Effects of Isoflurane on Hemodynamics during Autonomic Nervous System Blockade (Group 4)

			Induction		Postintubation	
	Conscious	ANS Block	Peak 2.1 ± 0.4 min	Intubation 6 ± 1 min	10 min	30 min
HR (beats per min)	87 ± 7*	111 ± 3	103 ± 3	99 ± 3*	97 ± 3*	95 ± 3*
MAP (mmHg)	101 ± 4*	75 ± 6	60 ± 6*	63 ± 6*	57 ± 4*	61 ± 3*
LVSP (mmHg)	123 ± 6*	95 ± 5	81 ± 5*	87 ± 7	82 ± 5*	82 ± 5*
LVEDP (mmHg)	9 ± 1*	6 ± 1	7 ± 1	8 ± 1*	8 ± 2*	9 ± 2*
dP/dt_{50} (mmHg/s)	1877 ± 57*	1473 ± 77	1232 ± 119*	1199 ± 117*	1108 ± 99*	1031 ± 105*
DCBF (ml/min)	40 ± 4	39 ± 4	53 ± 5*	43 ± 5	40 ± 4	39 ± 5
DCVR (ru)	2.39 ± 0.31*	1.84 ± 0.28	1.01 ± 0.15*	1.44 ± 0.30	1.38 ± 0.31*	1.50 ± 0.26
CO (l/min)	2.30 ± 0.38	2.55 ± 0.28	1.95 ± 0.21*	1.95 ± 0.17*	1.80 ± 0.17*	1.75 ± 0.13*
SVR (dyne·s·cm^{-5})	4330 ± 533*	2615 ± 299	2633 ± 269	2706 ± 285	2757 ± 304	2851 ± 238
SS (%)	15.5 ± 1.0	15.4 ± 1.1	13.6 ± 0.7	13.2 ± 1.3*	13.7 ± 1.5	12.2 ± 1.3*
PWI (ml O_2·min^{-1}·100 g^{-1})	9.0 ± 0.9	8.3 ± 0.6	6.6 ± 0.5*	6.7 ± 0.6*	6.0 ± 0.4*	6.0 ± 0.3*
DCBF/PWI	5.0 ± 1.0	5.2 ± 0.9	8.8 ± 1.4*	7.0 ± 1.2*	7.3 ± 1.0*	6.8 ± 0.9*

Mean ± SEM data (n = 9).
Peak = time to peak increase in coronary blood flow.
ANS block = autonomic nervous system blockade; HR = heart rate; MAP = mean arterial pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressures, respectively; dP/dt_{50} = rate of change of pressure at 50 mmHg; DCBF = diastolic energy blood flow; DCVR = diastolic coronary vascular resistance; CO = cardiac output; SVR = systemic vascular resistance; SS = systolic shortening; PWI = pressure–work index.
* Significantly ($P < 0.05$) different from ANS block.

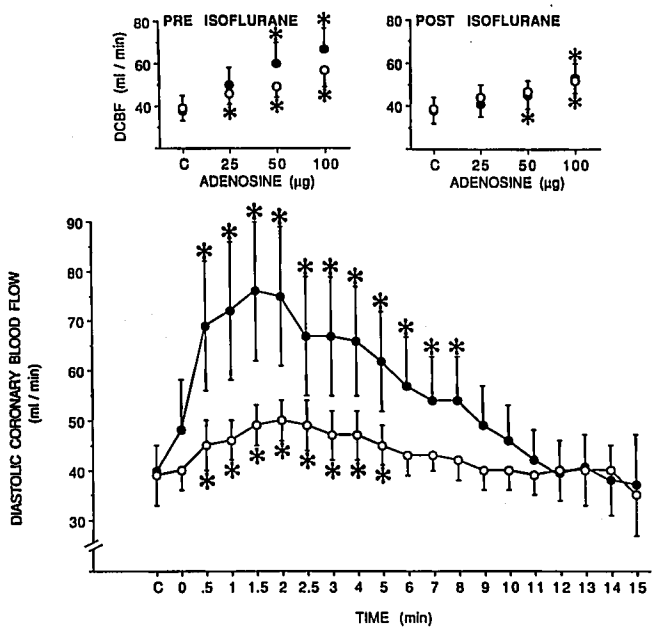

FIG. 3. Diastolic coronary blood flow during the conscious (C) state and induction of anesthesia with 5% isoflurane over a period of 15 min in dogs in groups 3 and 4. *Insets:* Changes in diastolic coronary blood flow produced by adenosine (25–100 μg) before and during halothane anesthesia. Open circles = intact autonomic reflexes; solid circles = autonomic nervous system blockade. *Significantly ($P < 0.05$) different from conscious state.

within a few minutes after intubation (table 3 and fig. 3). The myocardial oxygen supply–demand relationship remained elevated, indicating a relative excess of oxygen supply *via* coronary blood flow as compared to oxygen demand estimated by the pressure–work index.

In dogs with autonomic nervous system blockade (group 4), isoflurane caused an increase in diastolic coronary blood flow (fig. 3) in the presence of a reduction in the pressure–work index (table 4). Systemic hemodynamic changes occurring at the peak increase in coronary blood flow at 2.1 ± 0.4 min after initiation of induction included decreases in mean arterial pressure, left ventricular systolic pressure, left ventricular dP/dt_{50}, and cardiac output. Thus, the increase in diastolic coronary blood flow produced by isoflurane in dogs with autonomic blockade was not associated with elevations in estimated myocardial oxygen demand, and the ratio of diastolic coronary blood flow to pressure–work index was significantly increased (table 4). After this early increase in coronary blood flow, flow rapidly decreased to conscious-state levels before the time of intubation. The pressure–work index after intubation during 1 MAC isoflurane remained significantly reduced compared to the conscious state, secondary to decreases in heart rate, arterial pressure, left ventricular systolic pressure, dP/dt_{50}, cardiac output, and systolic shortening (table 4). The level of diastolic coronary blood flow, however, exceeded that of myocardial oxygen demand (as estimated from the ratio of diastolic coronary blood flow to pressure–work index). Despite a reduction in coronary blood flow to control levels, further coronary vasodilation during administration of 1 MAC isoflurane in dogs in groups 3 and 4 could be elicited by left atrial administration of adenosine (fig. 3).

Discussion

The results of this investigation demonstrate that high concentrations of the volatile anesthetics halothane and isoflurane transiently increase coronary blood flow. The increase in coronary blood flow was proportional to an increase in myocardial oxygen consumption as estimated by the pressure–work index in the dog with intact autonomic reflexes. This increase in myocardial oxygen demand was secondary to increases in heart rate and arterial pressure during the induction with high concentrations of anesthetics. When cardiovascular reflexes were eliminated with autonomic nervous system blockade, only isoflurane increased coronary blood flow relative to control values and estimated myocardial oxygen consumption. The increase in coronary flow, however, was short-lived and quickly returned to conscious levels during anesthetic-induced decreases in heart rate, contractility, and arterial pressure. Nevertheless, coronary blood flow remained relatively increased with isoflurane as compared to the reduction in the pressure–work index.

In this study, high (5%) inspired concentrations of both halothane and isoflurane were used to induce anesthesia. High concentrations of volatile agents were used to facilitate rapid induction and maximize relative hemodynamic effects. While it is possible that these results may not be applicable at lower concentrations, mask induction at lower anesthetic concentrations would produce a more prolonged excitement in conscious animals. The peak increase in coronary blood flow produced by halothane and isoflurane in dogs without autonomic blockade was transient and began to resolve while the animals continued to inspire high (5%) concentrations of either anesthetic before intubation. The pharmacokinetics of inhalational anesthetics are such that constantly increasing alveolar and blood concentrations of these agents would occur over this relatively short period of time.[20] Nevertheless, the present results document a decrease in coronary blood flow to conscious levels after the peak effect was reached at 1–2 min until endotracheal intubation was performed at 6–10 min. After intubation and adjustment of anesthetic concentration to 1 MAC (end-tidal), coronary blood flow remained at resting levels. This implies a very rapid adjustment of absolute coronary blood flow to halothane or isoflurane. However, because metabolic demand is reduced and the oxygen supply–demand index (flow

÷ pressure–work index) is increased, relative coronary dilation may remain. This may explain why other investigations of the influence of volatile anesthetics on coronary flow during steady-state conditions at 30–60 min after anesthetic administration have been unable to show coronary vasodilation.[21–23]

Results from this** and other laboratories[3,24] have demonstrated that while both halothane and isoflurane reduce major hemodynamic determinants of myocardial oxygen consumption, these agents do not unfavorably alter the regional distribution of coronary blood flow or produce coronary "steal."[25] Although efficacious arteriolar vasodilators may cause steal,[25] the brevity of vasodilation produced by the volatile anesthetics also may explain why a number of studies have not been able to demonstrate an unfavorable alteration in the regional distribution of coronary blood flow or production of coronary steal.[26,27] However, one study suggested that isoflurane causes a redistribution of flow from a collateral-dependent zone to a region with reduced perfusion.[28]

Larach *et al.*[5] demonstrated that halothane and isoflurane were equipotent for inducing direct vasodilation of coronary resistance vessels in isolated, perfused, and arrested rat hearts. However, previous studies of the effects of volatile anesthetics on hemodynamics in the dog have contradicted results obtained from the rat,[29] possibly because of species variation. In addition, Larach *et al.*[5] used hearts arrested with tetrodotoxin, which may have a direct action on vascular smooth muscle.[30] Thus, results obtained from *in vitro* studies of anesthetics are variable and may depend on the concomitant use of other drugs, the specific model, or the species.

The effect of halothane on coronary flow at a constant perfusion pressure has been studied in the dog during cardiopulmonary bypass.[15] Halothane added to a baseline pentobarbital anesthetic increased diastolic coronary vascular resistance. In contrast, Domenech *et al.*[31] demonstrated that halothane produced a reduction in coronary vascular resistance in thiopental-anesthetized, open-chest dogs and canine nonworking hearts. Vatner and Smith,[16] using conscious chronically instrumented dogs, showed a reduction in coronary flow by halothane. Sill *et al.*[32] demonstrated in dogs anesthetized with fentanyl and pentobarbital that isoflurane increased coronary blood flow in a dose-related manner. By calculating regression lines at a specific myocardial oxygen demand, these investigators suggested that at a given rate of oxygen consumption, coronary blood flow was greater after isoflurane and hence that coronary vasodilation had occurred.

Other investigators[33] have found that halothane decreased but isoflurane increased coronary flow in isolated perfused rat hearts. These investigators[33] suggested that isoflurane increased the myocardial oxygen supply–demand ratio more than did halothane. Recent results by Stowe *et al.*[34] in a similar preparation, however, did not document a decrease in coronary flow with halothane or a reduction in oxygen extraction with isoflurane. In the present study, isoflurane increased coronary blood flow in excess of myocardial oxygen demand. These results agree with data obtained in previous experiments in chronically instrumented dogs but may be concentration-dependent. For example, Bernard *et al.*[35] noted no changes in coronary blood flow during 3.3% isoflurane, whereas 2 MAC isoflurane led to an increase in coronary blood flow. Recent results of Crystal *et al.*[36] indicated that isoflurane is a potent coronary vasodilator, increasing flow to peak levels within 5–10 min after intracoronary administration of blood containing isoflurane. Thus, results from different laboratories and within the same laboratory have considerable variability.[21–23,33–35]

Coronary blood flow is tightly coupled to myocardial oxygen consumption. Recent reexamination of the determinants of myocardial oxygen demand has emphasized that oxygen consumption closely correlates with indices using stroke work.[37] When stroke volume can be estimated, the pressure–work index provides a reasonable estimate of myocardial oxygen consumption.[38] Rooke and Feigl[19] have provided an experimental basis for the use of the pressure–work index as an estimate of myocardial oxygen consumption. This index has been further validated in the presence of volatile anesthesia.[39] Direct coronary vasodilation may be defined as an increase in coronary blood flow in excess of myocardial oxygen demand. Such direct coronary vasodilation should lead to a decrease in myocardial arteriovenous oxygen content difference and an increase in oxygen tension in coronary venous blood. In the present investigation, the pressure–work index was used as an estimate of myocardial oxygen demand. Furthermore, the ratio of diastolic coronary blood flow to the pressure–work index was calculated as an estimate of the balance between myocardial oxygen supply and demand. The present results using the pressure–work index are in close agreement with those of Smith *et al.*,[40] who measured myocardial oxygen consumption directly in a canine model. In addition, myocardial oxygen consumption as estimated by the pressure–work index in the present study was in the same range as that previously noted by others.[41] Habazettl *et al.*[6] investigated the effect of isoflurane on myocardial oxygen balance and myocardial tissue oxygen tensions in opioid-anesthetized open-chest dogs and described an increase

** Hartman JC, Kampine JP, Schmeling WT, Warltier DC: Volatile anesthetics and regional myocardial perfusion in chronically instrumented dogs: halothane versus isoflurane in a single-vessel disease model with enhanced collateral development. Journal of Cardiothoracic Anesthesia 4:588–603, 1990

in the ratio of oxygen delivery to consumption. The present results are in close agreement with this study.

In many previous reports describing actions of volatile anesthetics on the coronary circulation, a baseline anesthetic was used, acute surgery was performed, or the contribution of myocardial oxygen consumption to coronary blood flow was not quantified. The present investigation avoided basal anesthesia, eliminated acute surgical trauma, and provided for a quantitative evaluation of myocardial oxygen consumption. Furthermore, the effects of the volatile anesthetics were compared between dogs with intact autonomic nervous reflexes and the same dogs with autonomic nervous system blockade to partially prevent hemodynamic alterations that may cause an increase in coronary flow independent of any direct vasodilator action.

In the presence of intact reflexes, halothane produced an increase in coronary blood flow concomitant with an increased myocardial oxygen demand. As systemic pressure and myocardial contractility decreased, coronary blood flow declined. The ratio of myocardial oxygen supply to demand as estimated by the ratio of diastolic coronary blood flow to pressure–work index was unchanged by halothane. When autonomic reflex increases in heart rate and pressure were eliminated, no change in coronary blood flow was produced by halothane. In contrast, isoflurane produced a quantitatively greater increase in coronary blood flow, and flow was maintained at a greater level than demand in the presence of a decreased driving pressure. The ratio of flow to demand also was significantly increased by isoflurane. The increase in coronary blood flow produced by isoflurane could not be solely attributed to systemic hemodynamic alterations, because the increase in flow was still present when autonomic reflexes were abolished and when any increase in pressure–work index was prevented. Furthermore, the return of blood flow to baseline levels could not be related solely to a decrease in driving pressure because adenosine still was capable of increasing flow.

The mechanism(s) responsible for the elevation of coronary blood flow produced by isoflurane was not readily apparent. Vasodilation produced by a rapidly degraded, endogenous mediator with a direct effect on vascular smooth muscle could explain the coronary vasodilator action of isoflurane. Endothelium-derived relaxing factor is one such potent endogenous vasodilator. Blaise *et al.*,[12] using isolated coronary arteries, suggested that vasodilation produced by isoflurane may be mediated *via* vascular endothelium. Vasodilation produced by isoflurane has also been previously suggested to be due to a vasodilating prostanoid,[42] although Blaise *et al.*[12] found that inhibition of the cyclooxygenase enzyme complex that generates prostaglandins from arachidonic acid did not prevent isoflurane-induced vasodilation. Thus, the transient increase in coronary blood flow might be caused by an isoflurane-mediated release of endothelium-derived relaxing factor, although further investigations are necessary to confirm this.

Study Limitations

In this investigation, high concentrations of halothane and isoflurane were studied. Although the MAC multiple of halothane was higher than that of isoflurane, the peak effect on coronary blood flow occurred very early (before intubation). In addition, the time to intubation was similar in both groups (10 ± 1 min *vs.* 8 ± 1 min). While substantial excitement during inhalation induction may account for some of the hemodynamic changes independent of the direct effects of the anesthetics, it does not explain the transient increase in coronary blood flow produced by isoflurane in dogs with autonomic nervous blockade, because coronary blood flow increased when the perfusion pressure and the pressure–work index declined. The changes in coronary blood flow were associated with changes in the pressure–work index in dogs with intact reflexes, but this represents an association and not necessarily a result of alteration in myocardial oxygen consumption.

The effect of the volatile anesthetics in the coronary circulation is controversial and depends partly on the definition of "vasodilation." Coronary vasodilation may be defined as an increase in blood flow relative to control (absolute flow), as no change in flow but an increase in epicardial coronary artery diameter, as a decrease in coronary vascular resistance, or as a preserved flow at control levels in the presence of reduced myocardial oxygen consumption. In the current investigation, when autonomic reflexes were eliminated to prevent increases in oxygen demand, isoflurane only transiently increased coronary blood flow relative to control values. Diastolic coronary vascular resistance also transiently decreased. The ratio of diastolic coronary blood flow to the pressure–work index suggested that there was also a relatively greater increase in myocardial oxygen delivery as compared to demand produced by isoflurane; this was maintained over 30 min.

This study would benefit from a methodology in which arterial pressure, heart rate, and myocardial metabolism could be held constant such that arteriolar dilation could be estimated. Furthermore, direct measurement of coronary venous blood oxygen saturation and calculation of myocardial oxygen consumption and extraction would have yielded valuable information; however, this was not technically feasible in chronically instrumented dogs that underwent different portions of an experimental protocol at widely different times. Although myocardial oxygen consumption was not measured directly, the major de-

terminants of myocardial oxygen consumption are incorporated in the pressure–work index, which has recently been validated[39] as an excellent index of oxygen consumption in dogs. Furthermore, although we did not measure coronary sinus oxygen tension, the present results imply an increase in coronary sinus oxygen content without an increase in absolute coronary blood flow. These results are in agreement with those of Reiz *et al.*,[1] who suggested that isoflurane is a "powerful" coronary vasodilator. Efficacious coronary vasodilators such as adenosine increase total coronary blood flow independent of change in oxygen consumption. Although the current investigation did not compare the effects of high concentrations of desflurane on coronary blood flow, two recent studies[43,44] comparing the effects of desflurane, halothane, enflurane, and/or isoflurane on coronary and systemic hemodynamics have demonstrated that lower concentrations of isoflurane and desflurane have similar effects on coronary hemodynamics in chronically instrumented dogs with intact autonomic reflexes. If autonomic reflexes are eliminated, desflurane produced no absolute or relative increase in coronary blood flow. The temporal effects of high concentration of desflurane, however, warrant further investigation.

In summary, the present results demonstrate that the increase in coronary flow produced by halothane during inhalation induction is related to an increase in myocardial oxygen demand. The increase in coronary blood flow produced by isoflurane exceeds that of oxygen demand but is transient. In general, the results indicate that isoflurane is a weak coronary vasodilator.

The authors extend their appreciation to John Tessmer, Doug Hettrick, and David Schwabe for excellent technical assistance and to Mimi Mick and Suzanne Emmrich for preparation of the manuscript.

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