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Are the Myocardial Functional and Metabolic Effects of Isoflurane Really Different from Those of Halothane and Enflurane?

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The effects of low (1.6 per cent end-tidal) and high (3.2 per cent end-tidal) concentrations of isoflurane were compared in a closed-chest dog preparation. Hemodynamics were evaluated using cardiac catheterization for measuring mean right atrial (RAP) and aortic (MAP) pressures; left ventricular end-diastolic (LVED) and peak systolic (LVSP) pressures and maximum rate of pressure rise (LVdP/dt); and the cardiac output (CO) by the dye dilution technique. Myocardial blood flow (MBF) and metabolism were estimated by ^{133}Xe washout from the great cardiac vein and measurement of oxygen and various substrates in aortic and coronary venous blood. Ventricular functional responses to altering preload (LVEDP) by blood infusion or withdrawal, and afterload (systemic vascular resistance, SVR) by balloon occlusion of the aorta were measured at low and high isoflurane concentrations. Body temperature, Pa_{O_2} and Pa_{CO_2} were maintained constant. High concentrations of isoflurane (as compared to low concentrations) produced 40–60 per cent decreases in MAP, CO, LVSV, LVdP/dt, and SVR without changing heart rate or LVEDP. MBF and myocardial O_2 uptake were decreased to the same extent without change in O_2 or lactate extraction by the heart. Increased preload resulted in small increases in cardiac output at low LVEDP (13–15 torr), but little or no change at higher values (18–23 torr) during both high and low isoflurane concentrations. Likewise, increased afterload decreased ventricular function at both concentrations of isoflurane. When the effects of halothane and enflurane were compared in identical, acute and chronic preparations, the results were similar except the filling pressures (LVEDP) were significantly increased by high concentrations (more than two times MAC) of the other two anesthetics. In addition, there was no change in systemic vascular resistance produced by halothane or enflurane. Thus, although isoflurane produces a dose-related depression of ventricular function in the intact dog, the degree appears to be somewhat less than that seen with halothane and enflurane. This difference may be related to the decreased afterload resulting from the administration of isoflurane and perhaps a minor degree of cardiac sympathetic stimulation. Myocardial perfusion was decreased to the same degree as function and oxygenation was well maintained. (Key words: Anesthetics, volatile: isoflurane; halothane; enflurane; fluroxene. Heart: blood flow, myocardial; cardiac output; contractility; metabolism; myocardial function, anesthetics; oxygen consumption; vascular pressures. Metabolism: fatty acids; glucose; lactate; oxygen consumption; pyruvate. Oxygen: blood levels; consumption, heart; tension. Sympathetic nervous system: anesthesia; catecholamines.)

THE MAJOR PHARMACOLOGIC EFFECTS of isoflurane were first described in five human and two animal studies published in 1971.[1-7] Prominent among the advantages claimed for the anesthetic over its isomer, enflurane, and halothane, was minimal myocardial depression. This was based on the observation that cardiac ouput and several indicators of myocardial contractile function were minimally affected by isoflurane anesthesia in a carefully controlled study in human volunteers.[1] However, there was a concomitant increase in heart rate which accounted for the cardiac output effect (stroke volume was diminished). Increased heart rate also stimulates cardiac contractile performance.[8] Subsequent studies in dogs have shown that high concentrations of isoflurane depress cardiac output and stroke volume,[9-11] as well as more sensitive indicators of myocardial function.[11] Horan *et al.* compared isoflurane with halothane and enflurane at minimum inspired concentrations (similar to MAC), and found that heart rate, mean arterial pressure, stroke volume, cardiac output, and systemic vascular resistance were comparable for all three anesthetics.[11] However, the absolute values of the more sensitve indices of myocardial function (left ventricular dP/dt and aortic acceleration) were greater during isoflurane anesthesia than during either enflurane of halothane anesthesia in dogs.

The influence of isoflurane on myocardial perfusion and metabolism has been controversial. Using a right heart bypass preparation, Theye and Michenfelder reported a dose-related depression in myocardial blood flow and oxygen consumption.[12] In closed-chest dogs during basal anesthesia with a synthetic narcotic, 65 per cent nitrous oxide, and neuromuscular blockade, Tarnow *et al.* saw no change in myocardial blood flow at 0.75 (0.5 MAC) and 1.5 per cent (1.0 MAC) isoflurane in spite of decreases in aortic pressure, cardiac output and left ventricular dP/dt.[13] Myocardial oxygen extraction decreased at the same time. Consequently they felt that isoflurane produced coronary vasodilation and hyperperfusion of the heart.

The present study was designed to address the following questions: 1) Is isoflurane depressant to the intact *in vivo* dog heart? 2) Does isoflurane produce coronary vasodilation and increase myocardial oxygenation? 3)

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Are these effects different from the effects of halothane, enflurane, and fluroxene?

Methods

Male mongrel dogs were conditioned for at least four weeks. After an overnight fast, anesthesia was induced by mask with nitrous oxide, oxygen, and isoflurane. After tracheal intubation, ventilation was adjusted to produce a Pa_{CO_2} of 30–35 torr and nitrous oxide was discontinued. An intravenous cannula was placed in a foreleg vein and 0.9 per cent sodium chloride was infused at 3–5 $ml \cdot kg^{-1} \cdot h^{-1}$ for the duration of the experiment. With fluoroscopic guidance, the following Goodale-Lubin catheters were placed in all animals: an 8 or 9 F through a femoral artery in the descending thoracic aorta; an 8 F through a carotid artery into the left ventricle; a 7 F through a femoral vein into the right atrium; and a 6 F in the great cardiac vein through an external jugular vein. Blood pressures were transduced through Statham® transducers and recorded on a polygraph. The rate of rise of left ventricular pressure was differentiated by a resistance-capacitance circuit. All measurements were made at end expiration. At least 60 min after the completion of the catheterization and after 20 min at a constant end-tidal isoflurane concentration, vascular pressures and cardiac output were measured. Myocardial blood flows were estimated in duplicate. Aortic and coronary venous blood samples were withdrawn. The inspired concentration was then changed; another 20 min of constant end-tidal isoflurane concentration was maintained; and the measurement sequence was repeated. The low concentration of isoflurane (1 + MAC) was that which abolished response to paw pinch in approximately three-quarters of the animals and the high concentration (2 + MAC) was the highest at which mean aortic pressure could be maintained between 50 and 60 torr. The order of the administration of the concentration was varied.

Effect of Succinylcholine

Control of tachypnea was impossible in most animals at 1 + MAC and in several at 2 + MAC isoflurane concentrations in spite of Pa_{CO_2} of less than 30 torr. Consequently, neuromuscular blockade with succinylcholine (0.5 mg/kg bolus dose, infusion of 1 $mg \cdot kg^{-1} \cdot h^{-1}$) was used on these occasions. In order to be certain that succinylcholine had no cardiovascular effect, six animals were studied with and without succinylcholine neuromuscular blockade. Ventilation, body temperature, and isoflurane concentration were maintained constant. The order of the anesthetic concentrations and the administration of succinylcholine were varied.

Effect of Inspired Oxygen Concentration

Previous experiments in chronically instrumented animals had been conducted at an FI_{O_2} of 0.21–0.25.[14] In order to ascertain whether the FI_{O_2} of 0.97 to 0.99 used in the acute studies had an effect on myocardial function and metabolism, eight acutely prepared animals were studied at the respective FI_{O_2}s in question. As in the succinylcholine study, only the FI_{O_2}s was changed during low and high concentrations of isoflurane.

Effect of Preload

Four animals were acutely prepared as previously described except that 10 ml/kg of blood was withdrawn and replaced with 20 ml/kg of 0.9 per cent sodium chloride as soon as they were anesthetized. This blood together with previously collected donor dog blood was used to increase preload, defined for this study as left ventricular end-diastolic pressure (LVEDP). The blood was anticoagulated with 2 units/ml of sodium heparin. After completion of catheterization, the animals were stabilized at either a low or high concentration of isoflurane. LVEDP was varied through a range of 5–26 torr in an attempt to achieve at least a twofold difference at each anesthetic concentration. Blood was infused or withdrawn depending on the change desired. It is of some interest that usually blood had to be infused at the low concentrations to produce higher LVEDPs and withdrawn during high concentrations to achieve lower LVEDPs. After blood infusion or withdrawal, at least 10 min was allowed for equilibration. Arterial blood gases and body temperatures were maintained constant throughout the course of the study.

Effect of Afterload

In the same animals used for the preload studies, the effect of increasing mean aortic pressure and systemic vascular resistance by inflating a balloon catheter in the descending thoracic aorta was studied at low and high isoflurane concentrations. The occlusion was maintained for 20 to 30 min in order to accomplish this study. Again body temperature and arterial blood gases were unchanged throughout the study.

Measurement Techniques

Cardiac output was estimated by indocyanine green dye dilution, injected into the right atrium and withdrawn and recorded from the thoracic aorta by a Gilford® densitometer system. The determinations were repeated until the estimates were within 5 per cent. Stroke volume, stroke work and vascular resistance were calculated from standard formulae. Myocardial blood flow was estimated

from the coronary venous washout of ^{133}Xe injected into the left ventricle. The on-line technique has been described in detail.[14] Blood gases were measured on standard electrodes. Blood oxygen contents were estimated both by the Van Slyke manometric technique and by measuring O_2 tension, hemoglobin concentration and oxygen saturation (using 1.39 ml O_2/g of hemoglobin at 100 per cent saturation). Isoflurane concentration was continuously monitored from a carinal catheter using a Beckman® LB-2 infrared analyzer. The analyzer was calibrated against standard gases every hour. Temperature was measured from an esophageal thermister and maintained by external heating. Plasma glucose, non-esterified fatty acids, blood lactate and pyruvate were measured as previously described.[14] Inasmuch as each animal served as his own control, Student's *t* test for paired samples was used to evaluate statistical significance.

Results

In six animals at near one MAC (1.6–1.63 per cent) and two MAC (3.23 per cent) concentrations of isoflurane, neuromuscular blockade with succinylcholine had no effect on hemodynamics or myocardial oxygenation. Consequently, the total number of acute preparations included 12 animals studied with and without succinylcholine neuromuscular blockade.

The high isoflurane concentrations produced a small degree of metabolic acidosis and decrease in arterial hematocrit, but there were no physiologically significant changes in the controlled parameters (table 1, section A). Isoflurane 3.3 per cent produced marked decreases in the pressures delivered by the left ventricle (table 1, section B). Systolic pressure decreased by 40 per cent and mean aortic pressure by almost 50 per cent. Although right atrial pressure rose significantly, there was no significant increase in LVEDP. Since cardiac output was depressed by only about 35 per cent, systemic vascular resistance was also significantly less at the higher concentrations. Inasmuch as these was no change in heart rate, stroke volume decreased to the same extent as cardiac output. Left ventricular dP/dt was depressed by more than 50 per cent and left ventricular stroke work was depressed by more than 65 per cent.

Myocardial blood flow and oxygen consumption appeared to follow the changes in cardiovascular function (table 1, section C). There were no significant changes in coronary vascular resistance, lactate or oxygen extraction. The only significant change in arterial concentration, myocardial extraction or uptake of substrates was the decrease in arterial non-esterified fatty acid concentrations seen during deep isoflurane anesthesia (table 1, section D).

Increasing LVEDP by volume infusion resulted in increasing cardiac outputs in most animals at both low and high isoflurane concentrations (fig. 1, table 2). However, the response was decreased during 1.5 per cent isoflurane and was abolished during 3.1 per cent isoflurane at the highest end-diastolic pressures. Although the end-diastolic pressures tended to be higher at high isoflurane concentrations, the finding was not consistent in all animals. Overall, increases in preload appeared to increase cardiac function to a similar degree at both isoflurane concentrations, although the cardiac outputs at any given ventricular end diastolic pressure were much higher during low isoflurane concentrations (table 2).

Balloon occlusion of the thoracic aorta indeed produced a marked increase in afterload, whether estimated as mean aortic pressure or systemic vascular resistance (table 3 and fig. 2). Even though filling pressures were increased (LVEDP and RAP) cardiac outputs and stroke volume decreased. Both myocardial blood flow and oxygen consumption responded to the afterloading with increases during low isoflurane concentration. However, only myocardial oxygen extraction increased at the high concentration as myocardial blood flow was unchanged. Significant lactate extraction continued during all conditions.

Discussion

If a drug is a myocardial depressant, increasing doses should produce significant decreases in myocardial function. By this definition, isoflurane is certainly a myocardial depressant in the dog. Marked and significant decreases in cardiac output, left ventricular systolic pressure, stroke volume and dP/dt occurred at high end-tidal concentrations without a change in heart rate in contrast to the effects seen in human studies.[1] However, there was no change in left ventricular filling pressure (which could not be measured in the human experiments). Previous studies from this laboratory using the same model have demonstrated similar effects for halothane,[15] methoxyflurane,[16] and fluroxene[17] (figs. 3 and 4). With halothane and methoxyflurane, however, there was a significant increase in left ventricular end-diastolic pressure. Fluroxene did not produce such a change. Horan *et al.* (also in the dog), noted that heart rate, aortic pressure, cardiac output, and stroke volume were nearly identical at MAC levels of halothane, methoxyflurane, enflurane, and isoflurane.[11] However, when more sensitive indicators of myocardial function (dP/dt and aortic acceleration) were compared, the values were significantly higher for isoflurane. They concluded that isoflurane did not produce as much myocardial functional depression as the other anesthetics. In order to examine further the degree of depression produced by isoflurane, we tested

TABLE 1. Effect of Low and High Isoflurane Concentrations on Myocardial Performance and Metabolism (n = 12)

A) Controlled Parameters		
Isoflurane Per cent ET	1.66 ± 0.05	3.30 ± 0.10
pH_a	7.43 ± 0.01	7.37 ± 0.01*
Pa_{CO_2} (torr)	32.0 ± 1.0	34.0 ± 1.0
Base excess ($mEq \cdot L^{-1}$)	−2.2 ± 1.0	−5.3 ± 0.7*
Pa_{O_2} (torr)	394.0 ± 30.0	357.0 ± 36.0
Hct (Per cent)	41.0 ± 1.4	38.0 ± 1.2*
T (°C)	38.0 ± 0.3	38.1 ± 0.3
B) Hemodynamics		
MAP (torr)	106 ± 5	55 ± 2*
CO ($ml \cdot min^{-1}$)	2680 ± 240	1760 ± 190*
HR (min^{-1})	129 ± 5	126 ± 2
RAP (torr)	1.2 ± 0.3	3.6 ± 0.5*
LVEDP (torr)	9.0 ± 0.7	9.6 ± 1.0
LVdP/dt ($torr.5^{-1}$)	23 ± 2	11 ± 1*
LVSV (ml)	20.9 ± 1.9	14.0 ± 1.6*
LVSW ($g \cdot m$)	28.9 ± 3.2	9.2 ± 1.3*
SVR (pru)	2.6 ± 0.3	2.0 ± 0.2*
C) Myocardial Blood Flow + Oxygenation		
MBF ($ml \cdot 100g^{-1} \cdot min^{-1}$)	61.1 ± 5.4	36.6 ± 3.5*
Ca_{O_2} ($ml \cdot dl^{-1}$)	19.5 ± 0.6	18.5 ± 0.6*
$a\text{-}cv_{O_2}$ (ml)	10.0 ± 0.9	10.1 ± 0.8
$\dot{V}_{O_2}$ ($ml \cdot 100g^{-1} \cdot min^{-1}$)	5.7 ± 0.3	3.5 ± 0.3*
O_2 Per cent ext.	51.5 ± 4.3	54.2 ± 3.8
Lactate Per cent ext.	22.6 ± 10.8	38.2 ± 4.4
CVR pru	1.84 ± 0.14	1.64 ± 0.14
D) Myocardial Metabolism		
Isoflurane Per cent ET	1.66	3.30
Glucose		
Art. ($mg \cdot dl^{-1}$)	87.0 ± 7	96.0 ± 14
Art.-c.v. ($mg \cdot dl^{-1}$)	−1.3 ± 6.5	1.3 ± 8.2
Uptake ($mg \cdot 100\ g^{-1} \cdot min^{-1}$)	1.9 ± 6.5	1.3 ± 3.7
NEFA		
Art. ($\mu El \cdot l^{-1}$)	325 ± 51	210 ± 18*
Art.-c.v. ($\mu Eq \cdot l^{-1}$)	86 ± 34	44 ± 21
Uptake ($\mu Eq \cdot 100\ g^{-1} \cdot min^{-1}$)	32.9 ± 17.8	10.7 ± 7.5
D) Myocardial Metabolism		
Lactate		
Art. ($mg \cdot dl^{-1}$)	12.0 ± 1.7	13.4 ± 1.8
Art.-c.v. ($mg \cdot dl^{-1}$)	3.5 ± 1.2	5.4 ± 1.1
Uptake ($mg \cdot 100\ g^{-1} \cdot min^{-1}$)	1.2 ± 0.8	2.2 ± 0.6
Pyruvate		
Art. ($mg \cdot dl^{-1}$)	1.09 ± 0.10	1.20 ± 0.10
Art.-c.v. ($mg \cdot dl^{-1}$)	0.45 ± 0.12	0.56 ± 0.12
Uptake ($mg \cdot 100\ g^{-1} \cdot min^{-1}$)	0.24 ± 0.10	0.19 ± 0.04

Values are means ± SEM. ET = end-tidal; Hct = arterial hematocrit; T = esophageal temperature; HR = heart rate; MAP = mean aortic pressure; CO = cardiac output; RAP = right atrial pressure; LVEDP = left ventricular end diastolic pressure; LV dP/dt = maximum rate of rise of left ventricular pressure; LVSV = left ventricular stroke volume; LVSW = left ventricular stroke work; SVR = systemic vascular resistance; MBF = myocardial (coronary) blood flow; a−cv O_2 = arterial- coronary venous O_2 content difference; $\dot{V}_{O_2}$ = myocardial oxygen consumption; Per cent extraction - a-cv/art. × 100; CVR = coronary vascular resistance; LVSP = left ventricular systolic pressure.

* $P < 0.05$ *vs.* low isoflurane.

myocardial functional response to changing left ventricular filling pressures. Although cardiac output increased with increasing left ventricular end-diastolic pressures at both high and low concentrations, the increase was much smaller at the high concentration. Of more significance is the fact that the animals anesthetized with more than 3 per cent isoflurane (high concentration) would not tolerate as low end-diastolic pressures as those anesthetized with 1.5 per cent (low concentration). At a mean left ventricular end-diastolic pressure of 11.6 torr, cardiac output was only 1220 ml/min and mean aortic pressure 44 torr at the high isoflurane concentrations. In order to maintain stable left ventricular filling pressures, only 10 min could be allowed for equilibration.

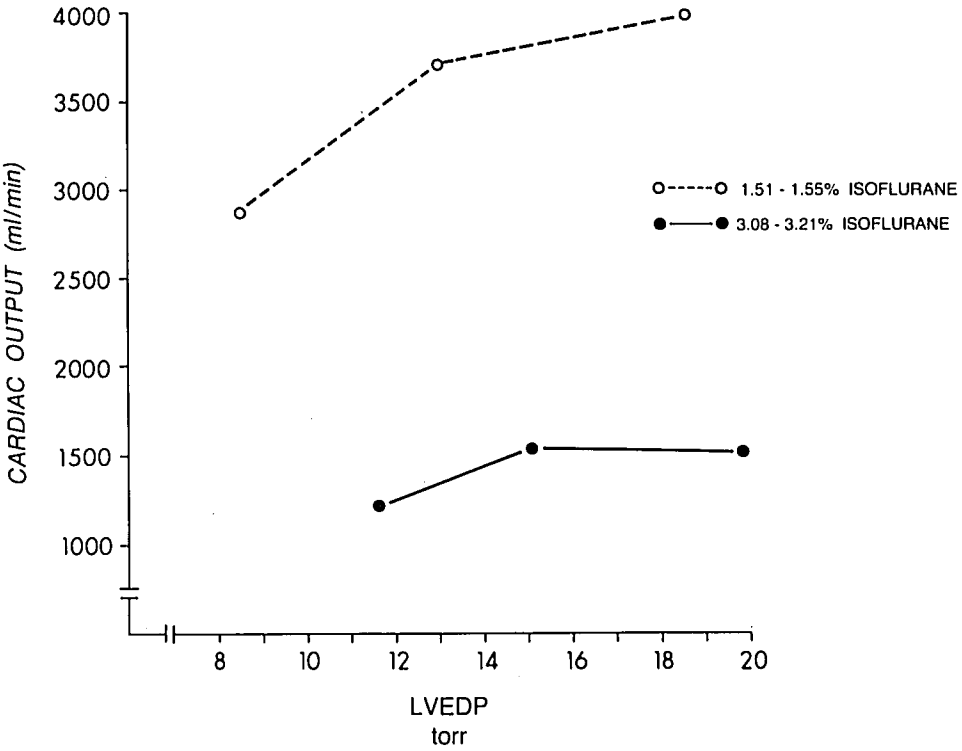

FIG. 1. Effect of changes in preload on cardiac output during low and high concentrations of isoflurane (n = 4). Preload expressed as left ventricular end-diastolic pressure (LVEDP) was changed by infusing or withdrawing blood from the dogs during steady end-tidal isoflurane concentrations and cardiac output measured after 10 minutes of stabilization.

Evidently with more time, as in the acute steady-state experiments reported above, the dog's cardiovascular system was able to partially compensate for the depression and maintain aortic pressure (55 torr) and cardiac output (1760 ml/min) at lower left ventricular end-diastolic pressures (9.6 torr) (table 1, section B). Another index of the level of myocardial function is the response to afterloading. The nondepressed heart responds to an increase in afterload by increased contractile performance.[18,19] However, the heart with compromised function from either disease or drugs will usually fail further with increased afterload.[19] Prys-Roberts *et al.* indicated that increasing afterload with phenylephrine decreased contractile performance during halothane anesthesia in the dog.[20] We have seen the same response using balloon occlusion of the thoracic aorta with halothane.[14] In the present study, a 20- to 24-torr increase in mean aortic pressure produced significant depression of cardiac output and stroke volume with no change in left ventricular dP/dt during both low and high isoflurane concentrations (table 3). Of particular note was the marked increases in left ventricular end-diastolic pressure at both anesthetic levels. Thus, the pumping function of the heart anesthetized with low and high concentrations of isoflurane was markedly depressed by increased afterload.

These experiments have examined the effect of high

TABLE 2. Effects of Changes in Preload on Cardiac Function during High and Low Isoflurane Concentrations (n = 4)

	Low Isoflurane			High Isoflurane		
LVEDP (torr)	8.5	13*	18.6*	11.6	15.1*	21.5*
Isoflurane (Per Cent ET)	1.51	1.47	1.55	3.21	3.08	3.17
CO ($ml \cdot min^{-1}$)	2,890 ± 1,200	3,715 ± 1,353	3,980 ± 1,100*	1,222 ± 135	1,535 ± 424	1,524 ± 500*
HR (min^{-1})	142 ± 7	151 ± 26	143 ± 6	135 ± 9	132 ± 5	132 ± 8
MAP (torr)	98 ± 4	110 ± 3	113 ± 10	44 ± 7	54 ± 5*	66 ± 12*
RAP (torr)	1.0 ± 0.4	2.1 ± 0.7*	4.3 ± 3.1*	2.2 ± 0.8	3.2 ± 0.1	5.9 ± 1.4*
LV dP/dt ($torr \cdot 5^{-1}$)	19.8 ± 7.0	19.3 ± 7.0	20.6 ± 4.0	9.5 ± 1.0	10.1 ± 1.6	12.1 ± 0.4*
LVSV (ml)	21 ± 10	25.5 ± 10.0	18.9 ± 9.0*	9.2 ± 1.3	11.9 ± 3.4	13.7 ± 3.0
LVSW (g·m)	26.2 ± 8.0	33.9 ± 13.9	37.6 ± 13.0*	4.1 ± 1.0	8.1 ± 2.0	8.9 ± 4.0*
SVR pru	2.6 ± 0.5	2.3 ± 0.6	2.0 ± 0.4*	2.1 ± 0.4	2.8 ± 1.1	2.5 ± 0.6

Values are means ± SEM.

LVEDP = left ventricular end-diastolic pressure; ET = end-tidal; CO = cardiac output; HR = heart rate; MAP = mean aortic pressure; RAP = right atrial pressure; LV dP/dt = maximum rate of rise of left ventricular pressure; LVSV = left ventricular stroke volume, LVSW = left ventricular stroke work; SVR = systemic vascular resistance.

* Same directional change in all animals.

TABLE 3. Effects of Change in Afterload on Myocardial Function, Perfusion and Oxygenation at High and Low Isoflurane Concentrations (n = 4)

	Low Isoflurane		High Isoflurane	
Aortic occlusion	0	+	0	+
Isoflurane (Per cent ET)	1.53 ± 0.10	1.50 ± 0.10	3.19 ± 0.10	3.18 ± 0.10
MAP (torr)	99 ± 4	121 ± 3*	52 ± 2	76 ± 13*
SVR (pru)	2.30 ± 0.41	4.28 ± 1.50*	2.04 ± 0.33	4.07 ± 1.06*
CO ($ml \cdot min^{-1}$)	3,280 ± 1,130	2,216 ± 630*	1,620 ± 270	1,275 ± 290*
HR (min^{-1})	140 ± 6	132 ± 10	132 ± 7	125 ± 5
RAP (torr)	0.9 ± 0.5	1.4 ± 0.8	2.6 ± 0.8	4.0 ± 0.8*
LVSP (torr)	120 ± 7	143 ± 8*	75 ± 3	96 ± 9*
LVEDP (torr)	8.0 ± 1.3	14.9 ± 1.7*	12.7 ± 2.3	18.9 ± 0.8*
LV dP/dt ($torr \cdot s^{-1}$)	17.7 ± 3.7	19.1 ± 8	10.6 ± 0.6	13 ± 1.6
LVSV ($ml \cdot kg^{-1}$)	23.6 ± 8	19.1 ± 8.1*	12.6 ± 2.2	10.6 ± 3.2*
LVSW ($g \cdot m$)	30.2 ± 11.2	27.5 ± 10.7	6.7 ± 0.9	8.7 ± 3.3
MBF ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	53.7 ± 4.7	78.7 ± 5.9*	49.6 ± 7.9	49.7 ± 9.5
$\dot{V}_{O_2}$ ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	5.95 ± 0.7	7.17 ± 0.6*	4.54 ± 0.5	7.13 ± 1.23*
O_2 extract per cent	54.7 ± 7.5	59.5 ± 6.9	48.6 ± 4.1	67.6 ± 3.0*
Lactate extract per cent	22.7 ± 16.0	—	34.8 ± 10.0	43.2 ± 3.0

Values are means ± SEM.

LVEDP = left ventricular end diastolic pressure; ET = end-tidal; CO = cardiac output; HR = heart rate; MAP = mean aortic pressure; RAP = right atrial pressure; LV dP/dt = maximum rate of rise of left ventricular pressure; LVSV = left ventricular stroke volume; LVSW = left ventricular stroke work; SVR = systemic vascular resistance; LVSP = left ventricular systolic pressure; MBF = myocardial (coronary) blood flow; $\dot{V}_{O_2}$ = myocardial oxygen consumption; O_2 extract per cent = a-cv/art. × 100; Lactate extract per cent = a-cv/art. × 100.

* Same directional change in all animals.

concentrations of isoflurane compared with low concentrations. It is important to know how both these circumstances compare with the awake nonmedicated animal. Utilizing the same chronically instrumented animal model previously published for halothane[14] and enflurane,[21] the cardio-dynamic effects of isoflurane were compared to those of enflurane in four experiments using the same animals. Low concentrations of enflurane and isoflurane produced remarkably similar changes (fig. 5). Heart rate was markedly increased; stroke volume, left ventricular dP/dt, and aortic pressure were moderately decreased; and there was no change in left atrial pressure,

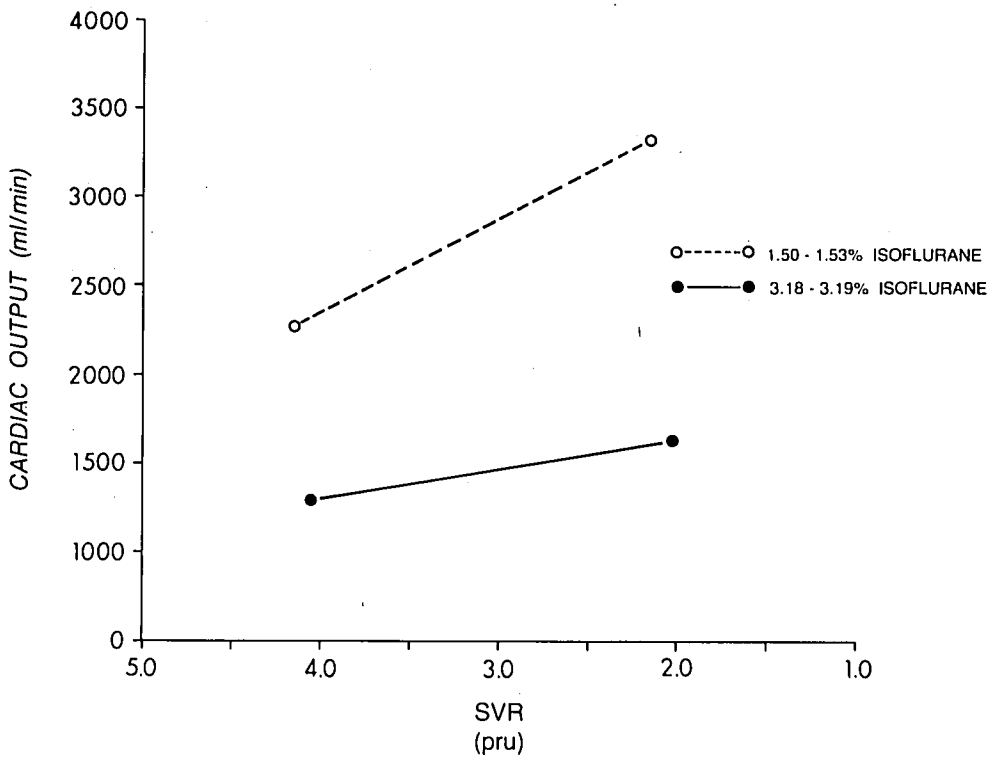

FIG. 2. Effect of changes in afterload on cardiac output during low and high concentrations of isoflurane (n = 4). Afterload expressed as systemic vascular resistance (SVR) was increased by balloon occlusion of the descending thoracic aorta during low and high concentrations of isoflurane and cardiac output was measured after 10 minutes.

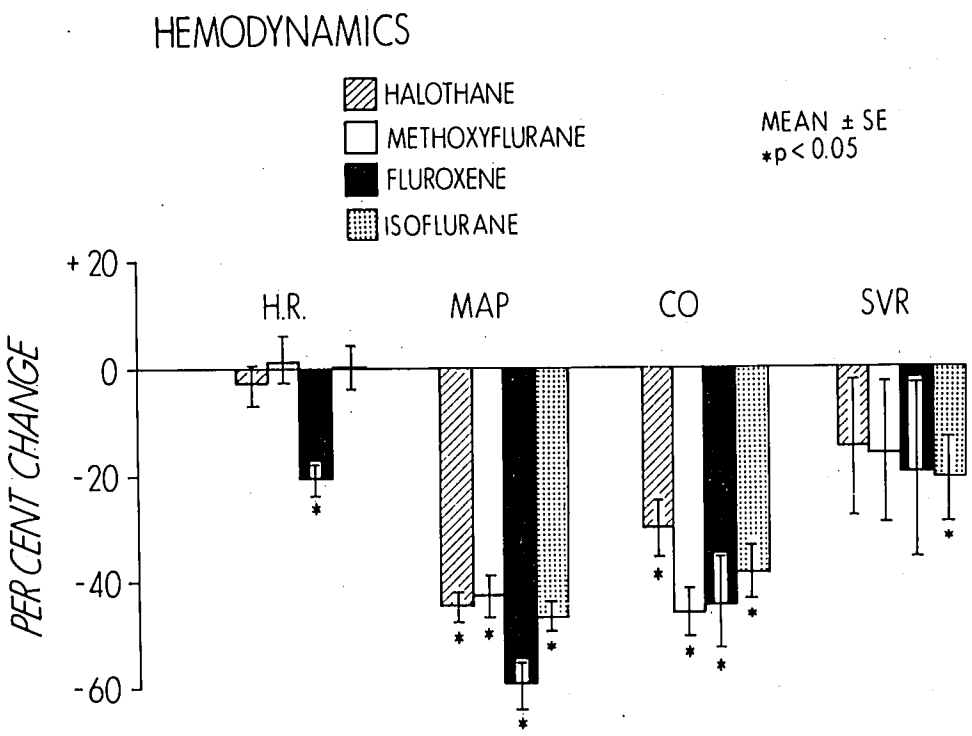

FIG. 3. Comparison of the systemic hemodynamic effects of several halogenated anesthetics in an acute dog preparation. The effects of the high concentration of isoflurane compared with the low concentration (per cent change) reported in this study are graphically compared with those from previous studies in our laboratory.[15-17] HR = heart rate; MAP = mean aortic pressure; CO = cardiac output; SVR = systemic vascular resistance.

cardiac output, or systemic vascular resistance. With higher anesthetic concentrations, stroke volume, dP/dt and aortic pressure were further decreased and, with no further change in heart rate, cardiac output was also decreased (fig. 6). The changes were essentially the same as those seen with enflurane. However, with isoflurane, left ventricular filling pressures (left atrial pressure) were not changed, in contrast to enflurane. As with halothane[14] and enflurane,[21] isoflurane caused an increase in heart rate at low anesthetic concentrations which tended to

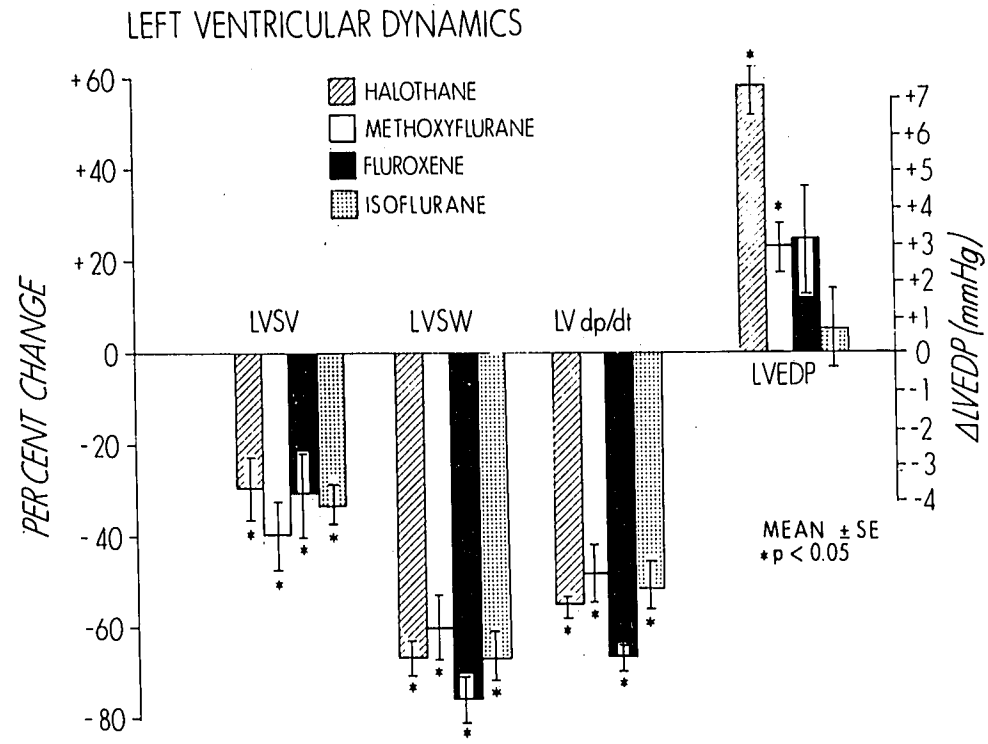

FIG. 4. Comparison of the effect of several halogenated anesthetics on left ventricular dynamics in an acute dog preparation. The effects of the high concentration of isoflurane compared with the low concentration (per cent change) reported in this study are graphically compared with those from previous studies in our laboratory.[15-17] LVSV = left ventricular stroke volume; LVSW = left ventricular stroke pressure; LVdP/dt = maximum rate of rise of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure.

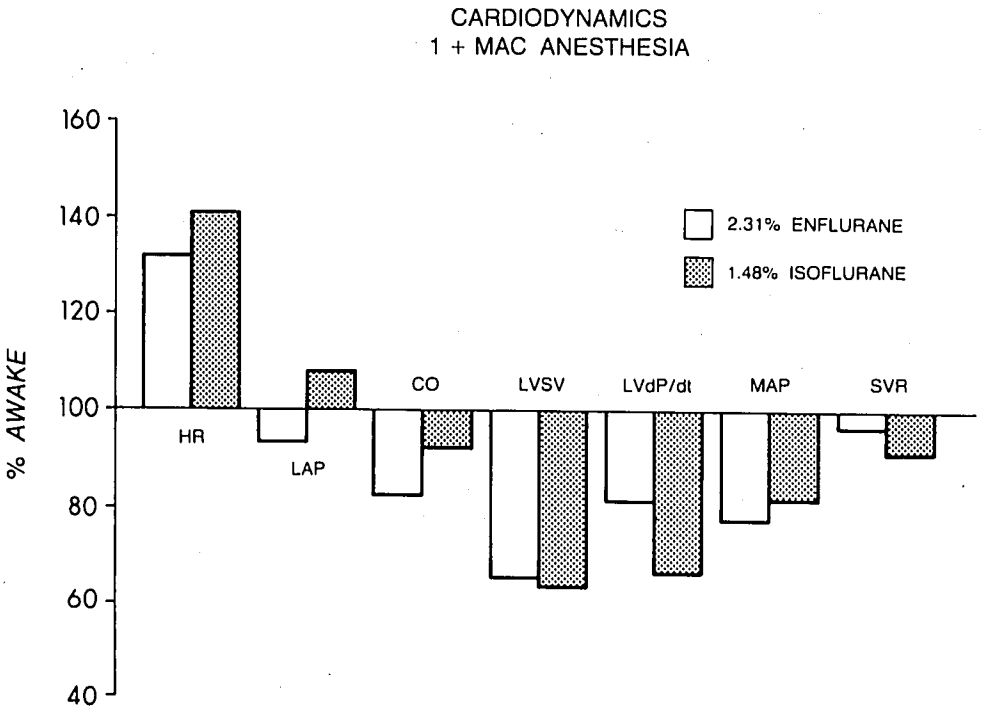

FIG. 5. Comparison of the cardiodynamic effects of enflurane and isoflurane in a chronic dog preparation (n = 4). The effects of 1 + MAC anesthetic concentrations in the same chronically instrumented dogs are graphically expressed as the percentage of the measured values in the awake animals (per cent awake). The enflurane data have been previously published.[21] HR = heart rate; LAP = left atrial pressure; CO = cardiac output; LVSV = left ventricular stroke volume; LVdP/dt = maximum rate of rise of left ventricular pressure; MAP = mean aortic pressure; SVR = systemic vascular resistance.

counteract the direct cardiac depressant effect.[8] With higher concentrations, more depression became obvious. However, as in the acute dog preparation, during high concentrations of isoflurane, the heart was able to empty more effectively so that left ventricular filling pressures were not elevated. Thus, the effects in the chronically instrumented animal closely resemble those in the acute preparation if the effect of the heart rate increase is recognized.

From the above experiments, I conclude that isoflur-

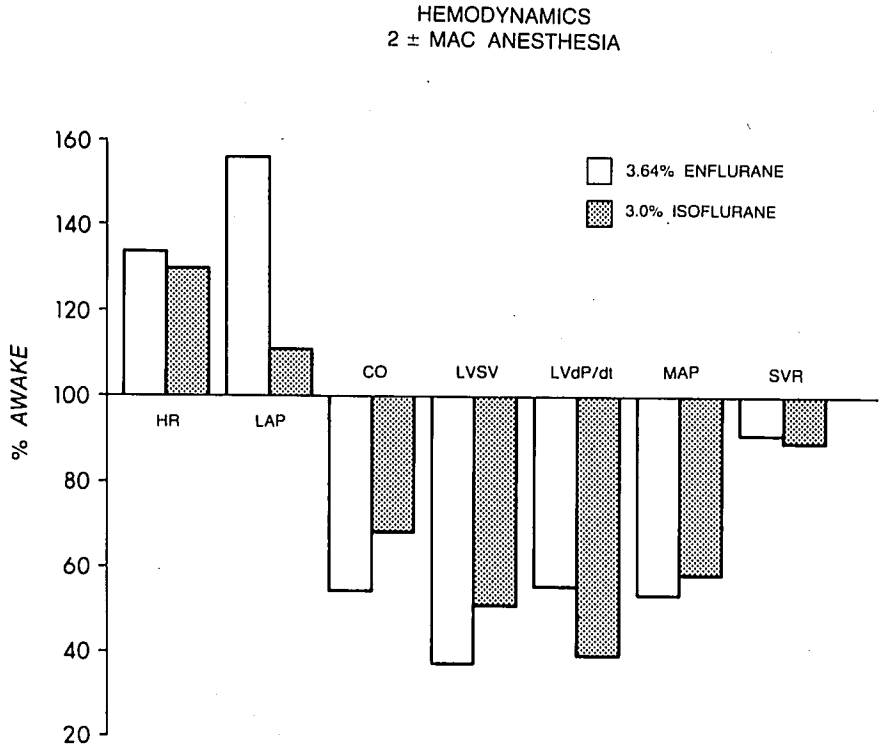

FIG. 6. Comparison of the cardiodynamic effects of enflurane and isoflurane in a chronic dog preparation (n = 4). The effects of 2 + MAC anesthetic concentrations in the same chronically instrumented dogs are graphically expressed as the percentage of the measured values in the awake animals (per cent awake). The enflurane data have been previously published.[21] HR = heart rate; LAP = left atrial pressure; CO = cardiac output; LVSV = left ventricular stroke volume; LVdP/dt = maximum rate of rise of left ventricular pressure; MAP = mean aortic pressure; SVR = systemic vascular resistance.

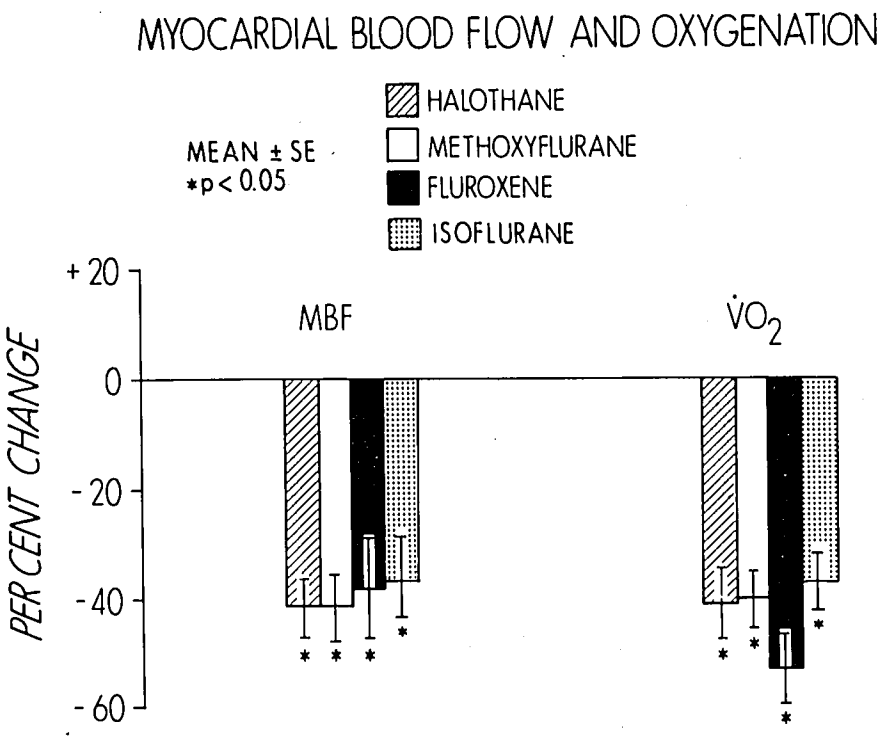

FIG. 7. Comparison of the effects of several halogenated anesthetics on myocardial blood flow and oxygen consumption in an acute dog preparation. The effects of the high concentration of isoflurane compared with the low concentration (per cent change) reported in this study are graphically compared with those from previous studies in our laboratory.[15-17] MBF = myocardial (coronary) blood flow; $\dot{V}_{O_2}$ = myocardial oxygen consumption.

ane does produce myocardial depression in a dose-dependent manner in the dog. However, since the decrease in the pumping of the heart is not accompanied by an increase in left ventricular filling pressure as has been seen with halothane and enflurane, the depression appears to be less than with these anesthetics. Increasing preload does produce some increase in myocardial function at both low and high concentrations. However, the hearts are more preload dependent at high isoflurane concentrations suggesting more cardiovascular depression. Increasing afterload decreases function at both high and low isoflurane concentrations suggesting that the afterload decrease produced by high concentrations of isoflurane may partially compensate for the direct myocardial depression.

Myocardial blood flow and oxygenation appeared to follow the functional demands of the heart. The changes were entirely similar to those seen with halothane,[15] methoxyflurane,[16] and fluroxene[17] (fig. 7). Myocardial oxygenation appeared adequate as oxygen extraction did not change and lactate uptake continued (table 1, section C). Thus the findings of Theye and Michenfelder were confirmed.[12] However, it is interesting that myocardial blood flow did not increase with the increased oxygen demands produced by the increased afterload during high isoflurane concentration (table 3). Increased oxygen extraction was necessary to increase myocardial oxygen consumption. Myocardial fuel usage followed the same pattern seen with the other anesthetics. Lactate and fatty acids provided the primary energy source for the work of the heart. During the chronic preparations referred to previously, myocardial blood flow decreased less than myocardial oxygen consumption so there was marked decrease in myocardial oxygen extraction (figs. 8 and 9). Coronary vascular resistance was also decreased during high concentrations of isoflurane, in contrast to enflurane. There appeared to be some degree of "luxury perfusion" and coronary vasodilation in this circumstance confirming the observations of Tarnow and co-workers.[13] The different instrumentation in the two types of experiments might have been responsible for the different coronary blood flow responses. Catheters were surgically implanted in coronary artery and vein in the chronic preparation. Although an attempt was made not to strip the vessels of their innervation, it is possible that the healing process interfered with autonomic control of the coronary circulation. However, in the same chronic preparation, halothane and enflurane produced similar coronary vascular effects to those which had been seen in the acute experiments.[14,21] The smaller number of chronically instrumented experiments leaves some doubt as to the validity of these observations, however. At the present time, therefore, there is no convincing evidence that the effect of isoflurane on myocardial perfusion and oxygenation is different from the other halogenated anesthetics.

However, isoflurane does appear to be less cardiodepressant in the intact animal in contrast to isolated papillary muscle.[22] Stevens *et al.* suggested that sympathetic activation might be responsible.[1] Although Philbin and Lowenstein concluded that beta adrenergic blockade with

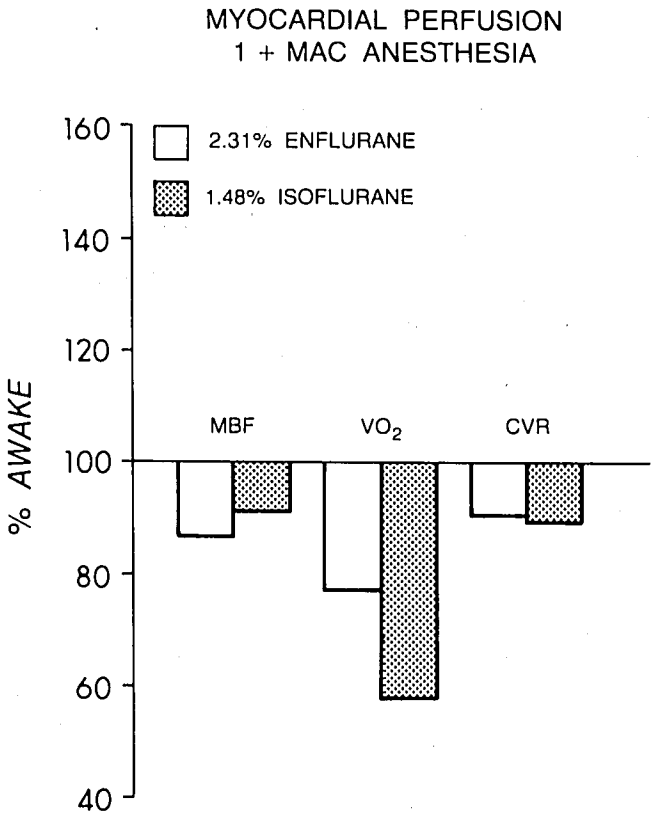

FIG. 8. Comparison of the effects of enflurane and isoflurane on myocardial perfusion and oxygen uptake in a chronic dog preparation. The effects of 1 + MAC anesthetic concentrations in the same chronically instrumentd dogs are graphically expressed as the percentage of the measured values in the awake animals (per cent awake). The enflurane data have been previously published.[21] MBF = myocardial (coronary) blood flow; $\dot{V}_{O_2}$ = myocardial oxygen consumption; CVR = coronary vascular resistance.

propranolol did not change hemodynamics during one and two MAC isoflurane,[9,10] there were, in fact, significant decreases in cardiac output and increases in left ventricular filling pressures in their first study.[9] Horan *et al.* saw no effect of propranolol during one MAC anesthesia, but significant cardiac depression was produced during higher isoflurane concentrations.[11] Using a sensitive radioenzymatic assay,[23] plasma norepinephrine levels in coronary venous blood were measured during the experiments on the chronically instrumented animals. There was an increase in every experiment at the high isoflurane concentration averaging 57 per cent. These observations coupled with the published beta-blocking data suggest that there is some cardiac sympathetic stimulation at the higher isoflurane concentrations. Such an effect combined with the decrease in vascular resistance also seen with the high isoflurane concentrations could account for the lesser cardiodepression seen with isoflurane as contrasted with halothane and enflurane.

Although it is possible that the dog may respond to inhaled anesthetics differently than humans, previous studies with halothane[24] and enflurane[25] suggest that the differences are minor. Ongoing studies in our laboratory in swine with halothane, enflurane, and isoflurane are producing results similar to those seen in the dog. On the other hand, fluroxene was much more depressant to the canine[17] than the human heart.[26] Consequently, these results may not be directly transferable to the clinic. However, I believe the differences are quantitative rather than qualitative.

In answer to the three questions posed in the introduction: 1) Isoflurane does depress cardiac function in a dose-related fashion in the intact dog. 2) There is no convincing evidence at present that isoflurane produces coronary vasodilation or uncouples myocardial oxygen demand and coronary blood flow. 3) Isoflurane depresses left ventricular performance less at high concentrations than halothane or enflurane, in a manner similar to fluroxene in the dog.

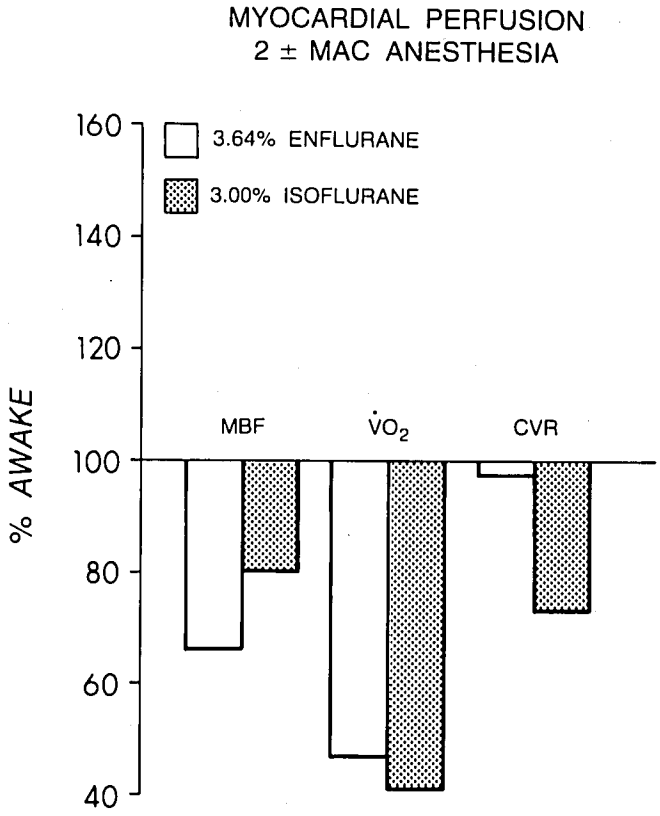

FIG. 9. Comparison of the effects of enflurane and isoflurane on myocardial perfusion and oxygen uptake in a chronic dog preparation. The effects of 2 + MAC anesthetic concentrations in the same chronically instrumented dogs are graphically expressed as the percentage of the measured values in the awake animals (per cent awake). The enflurane data have been previously published.[21] MBF = myocardial (coronary) blood flow; $\dot{V}_{O_2}$ = myocardial oxygen consumption; CVR = coronary vascular resistance.

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