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Enflurane Depresses Myocardial Function, Perfusion, and Metabolism in the Dog

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Trained dogs with chronically implanted catheters and left ventricular (LV) pressure transducers were anesthetized with 2.3 per cent (1 + MAC) and 3.6 per cent enflurane. Left ventricular function and metabolism were studied while the dogs were awake and during exposure to the two anesthetic concentrations. Enflurane depressed LV function in a dose-dependent fashion. Myocardial blood flow and oxygenation mirrored the functional changes. Myocardial oxygen extraction decreased and lactate extraction increased during enflurane anesthesia, suggesting adequate oxygen delivery to the myocardium. Low concentrations of halothane in the same dogs on different days had similar effects. However, 2 MAC halothane resembled 1.6 MAC enflurane, suggesting that the cardiovascular dose–effect curve for enflurane is steeper than that for halothane. Both anesthetics produce dose-dependent negative inotropic effects in the intact dog, accompanied by equivalent decreases in cardiac oxygen demand. Contrary to previous suggestions, enflurane appears to be at least as depressant to the dog heart as halothane. (Key words: Anesthetics, volatile, enflurane: Heart, myocardial function; Metabolism, myocardial.)

ALTHOUGH the recently introduced halogenated ether, enflurane, has been shown to decrease the function of cardiac muscle *in vitro* in a dose-dependent manner,[1,2] the effect on cardiac function in the intact animal is less clear. Three studies in animals either superimposed the drug on other anesthetics,[3,4] or started with a high control heart rate which obscured the final result.[5] The studies in man have suggested that there is a minimal negative inotropic effect of enflurane.[6–8] One of the animal studies also looked at myocardial perfusion and oxygenation, but only low concentrations (0.5 and 1.0 MAC) were compared with values in narcotic-anesthetized controls.[4] In the investigations reported here, we studied the effects of two concentrations of enflurane on cardiac function, perfusion and metabolism in five chronically instrumented hounds. In addition, we compared the effects of enflurane and halothane in the same animals on different days.

Methods

Our techniques have been described in detail.[9] Briefly, catheters were surgically implanted in the thoracic aorta, left atrium, pulmonary artery, left anterior descending coronary artery, and great cardiac vein. In some animals, a large catheter was placed in the external jugular vein for subsequent catheterization of the coronary sinus in the awake dog. A miniature high-fidelity pressure transducer was implanted in the left ventricle, and a pacing electrode was sewn to the right atrial appendage. Before and after the surgical procedure, the animals were trained to lie quietly on a laboratory table and breathe through a canine anesthesia mask. Between two and 26 weeks after the surgical procedure, when the dogs were afebrile and not receiving any medication, they were brought to the laboratory after a 12-hour fast. A Teflon catheter was placed in a foreleg vein. During a quiet period in which the dogs were awake, breathing room air, pressures in the left atrium, left ventricle and thoracic aorta were recorded. Cardiac output was measured in duplicate by the dye-dilution technique with the injection of cardiogreen dye in the pulmonary artery and sampling from the thoracic aorta. Aortic and coronary vein samples of blood were taken for analysis of gases and metabolites. Myocardial blood flow was estimated from the coronary venous washout of ^{133}Xe that had been injected

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TABLE 1. Controlled Variables (Mean Values ± SEM)

	Awake	Low Dose	High Dose
Enflurane (per cent end-tidal)	0	2.3 ± 0.2	3.6 ± 0.4
Temperature (C)	36–38.5	37.8 ± 0.4	37.8 ± 0.2
Hct_a (per cent)	31.7 ± 1.8	30.4 ± 1.7	31 ± 1.7
pH_a	7.45 ± 0.02	7.46 ± 0.01	7.43 ± 0.01
Pa_{CO_2} (torr)	30.4 ± 0.7	29.6 ± 1.2	31.2 ± 1.2
Pa_{O_2} (torr)	84.6 ± 3.3	86 ± 0.9	83.6 ± 0.9

(dissolved in saline solution) into the left anterior descending coronary artery. Coronary vein blood was passed continuously through a glass coil in a sodium iodide crystal well gamma counter by means of a roller-pump system that returned the blood to the peripheral vein. The output of the crystal was transmitted via phone lines to a remote computer, where it was scaled in 5-second intervals and returned to the laboratory on an oscilloscope display over closed-circuit television and on a teletype. At the end of a 5-minute washout period, the teletype operator in the laboratory selected the appropriate portion of the washout curve for calculation of myocardial blood flow. Most of the myocardial blood flows were determined in duplicate and were within 5 per cent of the mean. The animals were then anesthetized by mask with nitrous oxide–oxygen–enflurane (in one dog 5 mg/kg thiopental was used). As soon as possible, the trachea was intubated with a cuffed tube, nitrous oxide was discontinued, and $F_{I_{O_2}}$ was adjusted with a nitrogen–oxygen mixture so that Pa_{O_2} approximated the measured awake value. Ventilation was controlled so that Pa_{CO_2} was also maintained close to the value in the awake animal. Hydration was maintained by constant infusion of 3 to 4 ml/kg/hr of 0.9 per cent sodium chloride, given by an infusion pump. Esophageal temperature was measured from an esophageal thermistor probe and maintained between 36.5 and 38.7 C by external heating. Two concentrations of enflurane were studied. The low dose was that dose which would keep most of the animals from responding to a painful stimulus (Kocher clamp on hind paw) and the high dose was the highest concentration during which mean aortic blood pressure could be maintained above 50 torr. Even when the enflurane concentration was high enough to prevent response to the painful stimulus, tachypnea was troublesome in spite of low Pa_{CO_2} (table 1). Consequently, in some of the studies of the low concentration of enflurane an infusion of 1 mg/kg/hr of succinylcholine was employed. Previous observations in our laboratory have

TABLE 2. Cardiodynamics (Mean Values ± SEM)

	Awake	Enflurane	
		2.3 Per Cent	3.6 Per Cent
Measured			
Heart rate	91 ± 7.3	120 ± 5.1*	122.4 ± 5.6*
Mean aortic pressure (torr)	99 ± 5.6	76.4 ± 3.2*	52.6 ± 3.7*†
Cardiac output (ml/min)	3650 ± 580	2980 ± 510*	1970 ± 340*†
LV systolic pressure (torr)	121.3 ± 12.1	91.3 ± 7.3*	68.5 ± 5.0*†
L atrial pressure (torr)	4.6 ± 0.9	4.3 ± 1.4	7.2 ± 1.2*†
LV dP/dt (per cent awake)	100	81*	54.6*†
Calculated			
Cardiac output/kg (ml/min/kg)	158 ± 20	130 ± 19*	87 ± 13*†
LV stroke volume (ml)	39.6 ± 4.8	25.3 ± 4.9*	16.1 ± 2.6*†
LV stroke vol/kg (ml/kg)	1.75 ± 0.18	1.11 ± 0.19*	0.72 ± 0.11*†
LV stroke work (g·m)	52.2 ± 9.0	24.8 ± 4.9*	10.2 ± 2.1*†
LV minute work (kg·m)	4.85 ± 0.98	2.91 ± 0.49*	1.24 ± 0.27*†
Systemic vascular resistance (p.r.u.)	1.68 ± 0.22	1.64 ± 0.33	1.53 ± 0.27

* $P < 0.05$ vs. awake.
† $P < 0.05$ vs. 2.3 per cent enflurane.

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TABLE 3. Myocardial Perfusion and Oxygenation (Mean Values ± SEM)

	Awake	Enflurane	
		2.3 Per Cent	3.6 Per Cent
Myocardial blood flow (ml/100 g/min)	56.8 ± 3.5	49.5 ± 3.7*	31.4 ± 2.4*†
Ca_{O_2} (ml/dl)	14.2 ± 1.0	13.7 ± 1.0	13.8 ± 1.0
Aortic–coronary venous Ca_{O_2} (ml/dl)	11.1 ± 0.7	9.2 ± 0.8	9.6 ± 0.4
O_2 extraction (per cent)	78.6 ± 1.5	67.4 ± 4.0*	70.2 ± 3.0*
Myocardial oxygen consumption (ml/100 g/min)	6.28 ± 0.47	4.56 ± 0.48	3.00 ± 0.22*†
Coronary vascular resistance (torr/ml/100 g/min)	1.76 ± 0.12	1.58 ± 0.14	1.73 ± 0.23
Percentage of cardiac output perfusing left anterior descending coronary artery	1.73 ± 0.27	1.92 ± 0.40	1.87 ± 0.42
Unit of external cardiac work per unit of oxygen consumption (g·m/ml/100 g/min)	754 ± 134	722 ± 206	452 ± 135*†

* $P < 0.05$ vs. awake.
† $P < 0.05$ vs. 2.3 per cent enflurane.

indicated that this dose of succinylcholine has little effect on cardiovascular function. The order of the dose administration of enflurane was alternated. Studies were only done after 20 to 30 minutes of a steady end-tidal enflurane concentration as measured by infrared analysis. Blood-gas analysis was performed using standard electrodes. Oxygen content was calculated from measured saturation, tension and hemoglobin concentration. Glucose, lactate, and pyruvate levels were assayed by enzymatic methods.[9] Nonesterified fatty acids were measured using a colorimetric method.[10] Statistical evaluation utilized Student's t test for paired samples.[11]

Results

Aside from the programmed increase in anesthetic concentration, there was no significant change in the controlled variables during anesthesia with enflurane (table 1). Four of the five dogs did not respond to a painful stimulus at the low enflurane concentration, so that this concentration was

TABLE 4. Myocardial Metabolism (Mean Values ± SEM)

	Awake	Enflurane	
		2.3 Per Cent	3.6 Per Cent
Lactate			
Arterial (mg/dl)	3.79 ± 0.47	8.17 ± 1.53*	13.74 ± 4.69*
Aortic–coronary venous (mg/dl)	1.00 ± 0.41	4.09 ± 1.48*	4.76 ± 0.82*
Extraction (per cent)	22.3 ± 8.4	44.0 ± 8.1*	43.2 ± 6.7*
Uptake (mg/100 g/min)	0.63 ± 0.27	2.03 ± 0.69*	1.46 ± 0.24*
Pyruvate			
Arterial (mg/dl)	0.33 ± 0.04	0.36 ± 0.11	0.45 ± 0.13
Aortic–coronary venous (mg/dl)	−0.03 ± 0.05	0.07 ± 0.13	0.14 ± 0.26
Extraction (per cent)	−13.7 ± 13.4	−40.3 ± 57	18.6 ± 15.8
Uptake (mg/100 g/min)	−0.01 ± 0.03	0.03 ± 0.06	0.04 ± 0.03
Glucose			
Arterial (mg/dl)	88.9 ± 9.5	67.2 ± 4.9*	88.0 ± 11.0†
Aortic–coronary venous (mg/dl)	20.2 ± 6.1	−5.8 ± 5.8*	5.4 ± 1.9
Extraction (per cent)	22 ± 4.6	−11 ± 10.3*	5.5 ± 1.9
Uptake (mg/100 g/min)	10.9 ± 3.3	−3.1 ± 1.4*	1.8 ± 0.7
Nonesterified Fatty Acids			
Arterial (mEq/l)	368 ± 42 (n = 4)	244 (n = 3)	169 (n = 3)
Aortic–coronary venous (mEq/l)	91 ± 28	13.4	12.8
Uptake (mEq/100 g/min)	5 ± 1.5	0.4	0.3

* $P < 0.05$ vs. awake.
† $P < 0.05$ vs. 2.3 per cent enflurane.

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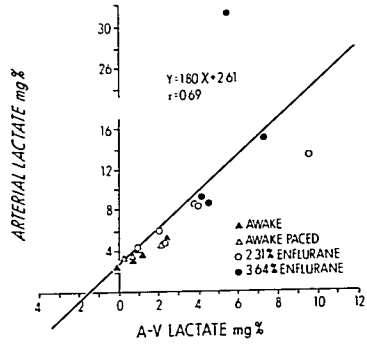

FIG. 1. Relationship between arterial concentration and cardiac extraction of lactate. $r = 0.69$, $P < 0.01$.

slightly more than MAC. Most of the animals manifested some spontaneous movements of non-respiratory muscles, particularly in response to noise. Two of the five animals had convulsive movements at some time during the experiments, one at a low concentration and the other at a high concentration.

Heart rate increased at both concentrations of enflurane, but the increase was not dose-related (table 2). Left atrial pressure (a reflection of left ventricular filling pressure) did not change with the low concentration but increased with the high concentration. All other measures of ventricular function decreased in a dose-related manner (table 2).

Myocardial blood flow and oxygen consumption also declined in a dose-related fashion (table 3). There was no change in calculated coronary vascular resistance. Oxygen extraction decreased during both low- and high-dose anesthesia. The proportion of the cardiac output perfusing the left anterior descending coronary artery did not change, while the amount of external work performed by the left ventricle per unit of oxygen consumed declined with the high concentration only.

Arterial lactate concentrations increased markedly during both high- and low-dose enflurane anesthesia. Myocardial uptake and extraction followed the arterial changes (table 4 and figure 1). Pyruvate metabolism remained the same. Arterial glucose levels decreased with the low concentration, but were not changed with the high concentration. Again, uptake and extraction mirrored the arterial concentration. No significant change was seen in nonesterified fatty acid, arterial level or uptake, although the trend was down-

TABLE 5. Effects of Tachycardia on Awake Dogs (Mean Values ± SEM)

	Awake	Atrial Pacing
Hemodynamics		
Heart rate	80.3 ± 3.6	129.1 ± 3.6*
Mean aortic pressure (torr)	94.1 ± 2.8	101.5 ± 2.4*
Cardiac output (ml/min)	3230 ± 170	3760 ± 180*
LV stroke volume (ml)	40.5 ± 1.8	29.3 ± 1.5*
LV dp/dt (per cent awake)	100	109.6 ± 2.6*
LV stroke work (g·m)	49.7 ± 3.3	39.6 ± 2.7*
LV work (kg·m)	4.00 ± 0.34	5.10 ± 0.32*
Left atrial pressure (torr)	4.4 ± 0.7	2.2 ± 0.7*
Systemic vascular resistance (pru)	1.70 ± 0.05	1.63 ± 0.06
Myocardial perfusion and oxygenation		
Myocardial blood flow (ml/100 g/min)	56.5 ± 2.8	63.5 ± 2.8*
Ca_{O_2} (ml/dl)	13.9 ± 0.5	14.1 ± 0.5
Aortic–coronary venous Ca_{O_2} (ml/dl)	10.6 ± 0.4	10.8 ± 0.4
Extraction (per cent)	76.6 ± 1.3	76.8 ± 1.6
Myocardial oxygen consumption (ml/100 g/min)	6.0 ± 0.4	6.8 ± 0.4*
Percentage of cardiac output perfusing left anterior descending coronary artery	1.81 ± 0.13	1.73 ± 0.10
Unit of external cardiac work per unit of oxygen consumption (g·m/ml/100 g/min)	687 ± 59	760 ± 54
Coronary vascular resistance (torr/ml/100 g/min)	1.70 ± 0.09	1.64 ± 0.08

* $P < 0.05$ *vs.* awake.

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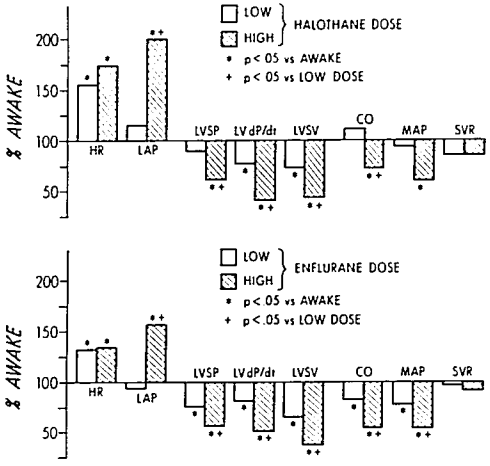

FIG. 2. Comparison of cardiodynamic effects of halothane and enflurane in the same dogs. HR = heart rate, LAP = left atrial pressure, LVSP = left ventricular systolic pressure, LVSV = left ventricular stroke volume, CO = cardiac output, MAP = mean aortic pressure, SVR = systemic vascular resistance, pru = peripheral resistance units.

ward with increasing concentrations of enflurane.

Discussion

On the basis of this study, there can be little doubt that the high concentration of enflurane caused marked depression in left ventricular function. Although heart rate and filling pressure (left atrial) increased, cardiac output, stroke volume, stroke work, and left ventricular dP/dT were all decreased to less than 50 per cent of control (table 2). Since with the low concentration of enflurane left atrial pressure did not increase and there was less depression of the aforementioned indicators of ventricular function, the situation is not as clear as with the high concentration. However, atrial pacing to an equivalent heart rate in our laboratory under the same conditions in this group of dogs produced a decrease in left atrial pressure and increases in all the measures of ventricular function except stroke volume and stroke work (table 5). Consequently, it would appear that the negative inotropic effect of the low enflurane concentration was partially masked by the tachycardia. Thus, there is evidence that enflurane depresses cardiac performance in the intact dog even at the lowest concentration necessary for surgical anesthesia.

Although early studies in man suggested that enflurane produced only slight to moderate depression of ventricular function, none examined the problem in a rigorous fashion.[6-8] More recently, a dose- and time-related investigation with careful controls of modifying factors has shown that enflurane is a potent cardiac depressant in human volunteers (Smith, N.T., *et al.*, personal communication). At equipotent concentrations (MAC multiples), in fact, the drug was more depressant than halothane.[12] We have been able to compare the cardiodynamic effects of halothane and enflurane in the same chronically instrumented dogs on different days. The dogs were a little more hyperdynamic on the days they were given enflurane (table 6). With this

TABLE 6. Awake Measurements on the Day of the Study

	Halothane	Enflurane
Ratio between high and low anesthetic concentrations	2.02	1.57
Pa_{CO_2} (torr)	33	30
pH_a	7.44	7.45
Pa_{O_2} (torr)	83	84
Heart rate (/min)	73	91
Aortic pressure (torr)	95.4	99
Cardiac output (ml/min)	2680	3650
LV stroke volume (ml)	37.2	39.6
Left atrial pressure (torr)	3.4	4.6
Myocardial blood flow (ml/100 g/min)	46.8	56.8

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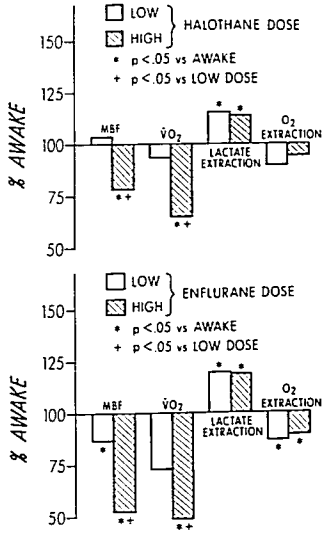

FIG. 3. Comparison of effects of halothane and enflurane on myocardial blood flow and oxygenation in the same dogs. MBF = myocardial blood flow, $\dot{V}_{O_2}$ = myocardial oxygen consumption.

difference in mind, the changes in cardiodynamics from the awake state with both anesthetics showed a marked resemblance (fig. 2). The greater percentage increase in heart rate with halothane is probably a result of the lower awake heart rate (table 6). The low enflurane concentration produced somewhat more depression than the low halothane concentration, but the changes with the high concentrations were quite similar. It must be noted, however, that only 1.5 MAC enflurane could be given when the mean aortic pressure was to be maintained above 50 torr, compared with 2.0 MAC halothane. Consequently, it would appear that enflurane is at least as (if not more) depressant to the intact canine cardiovascular system than halothane. The results of other animal studies suggest the same conclusion.[3-5]

As has been seen previously with enflurane and other anesthetics,[4,9,13-16] myocardial blood flow and oxygenation followed the changes in cardiac function and oxygen demand (table 3). Although both were depressed in a dose-dependent manner, oxygen supply to the heart was adequate for the demand. As arterial blood lactate concentrations increased with anesthesia, so did myocardial extraction and uptake (table 4). The only pathway for cardiac catabolism of lactate involves conversion to pyruvate via an oxidative enzyme and then oxidative phosphorylation through the tricarboxylic acid cycle.[15] Consequently, a heart that is using lactate must have an adequate oxygen supply. In addition, myocardial oxygen extraction decreased significantly during enflurane anesthesia, further suggesting a surfeit of oxygen. Although both myocardial blood flow and oxygen consumption decreased more during enflurane than during halothane anesthesia, oxygen extraction did not decrease significantly with halothane (fig. 2). It is tempting to suggest that enflurane might have a more favorable effect on the relationship between myocardial oxygen supply and demand than halothane, but coronary vascular resistance and the proportion of cardiac output perfusing the left anterior descending coronary artery were unchanged, and the external work performed per unit of oxygen consumed decreased significantly during deep anesthesia, similar to the effects seen with halothane.[9] Finally, the ischemic heart is the one where a decrease in oxygen demand would be most beneficial. Unfortunately, the marked aortic hypotension might well produce a greater decrease in oxygen supply in these hearts, where perfusion is markedly pressure-dependent.[17] Consequently, a definitive statement on the use of enflurane in this disease must await further study in ischemic hearts of animal and man. At this time, the cardiac functional and metabolic effects of halothane and enflurane are essentially the same, so that the choice of one anesthetic over the other must be decided on the basis of other properties.

The decrease in arterial blood glucose concentration with low concentrations of enflurane, with a return to normal during anesthesia with high concentrations, is puzzling. However, in a study such as this, there is no way of determining which of the many controls of systemic glucose availability is affected.[18,19] Changes in autonomic nervous activity, glucagon, insulin secretion and receptor effect, glycogen stores, glycogenolysis, or gluconeogenesis could play a role. From

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this study, it would appear that myocardial extraction of glucose was dependent on the arterial blood concentration, unlike the results seen previously with halothane,[9,15] where hypoinsulinemia was probably a factor. However, the small number and wide standard error of the glucose determinations preclude a definitive statement concerning enflurane on the basis of this study.

The increase in plasma lactate seen with enflurane was also seen with halothane,[9] methoxyflurane and fluroxene (unpublished results). There has been little documentation of the effect of inhalation anesthetics on blood lactate concentrations in the dog. Galla reported increases with diethyl ether,[20] similar in magnitude to those seen by us with fluroxene. It is probable that the lactic acidosis is related either to interference with gluconeogenesis in the liver[21] or to sympathetic nervous activation.[22]

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