

Dose-dependent Depression of Cardiac Function and Metabolism by Halothane in Swine (*Sus scrofa*)

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Halothane depresses myocardial blood flow and metabolism in the dog, but no studies in man have been published. However, the coronary circulation of the pig is remarkably similar to that of man. The authors investigated the effects of halothane-nitrous oxide anesthesia on cardiac function and metabolism in piglets. Thermodilution cardiac output, catheter-tip-manometer measurement of left ventricular function, electromagnetic flowmeter measurement of coronary blood flow, and blood and tissue measurements of gases and metabolites were made during 0.04 (control), 0.46 (low concentration) and 1.04 (high concentration) per cent halothane vaporized in nitrous oxide, 60 per cent: oxygen, 40 per cent. Compared with control, the low concentration decreased cardiac output (CO) by 10 per cent, left ventricular systolic pressure (LVSP) by 30 per cent, peak contractile element velocity (V_{max}) by 34 per cent, coronary blood flow (CBF) by 36 per cent, and cardiac oxygen uptake (\dot{V}_{O_2}) by 55 per cent. Compared with control, the high concentration decreased CO by 32 per cent, LVSP and V_{max} by 53 per cent, CBF by 63 per cent and \dot{V}_{O_2} by 62 per cent. This indicates that the dose-related depression in left ventricular function produced by halothane was accompanied by equivalent decreases in coronary blood flow and oxygen consumption. There was minimal evidence of anaerobic metabolism in these depressed ventricles. Tissue levels of the high-energy phosphates, adenosinetriphosphate and creatine phosphate, and glycogen were unchanged. It is concluded that changes in cardiac oxygenation and metabolism in the pig during halothane anesthesia result from the changes in ventricular function. (Key words: Anesthetics, volatile, halothane; Heart, blood flow, myocardial; cardiac output; metabolism; myocardial function; oxygen consumption; vascular pressures; Metabolism, adenosinetriphosphate; glucose; lactate.)

THE EFFECT OF HALOTHANE on cardiac function in the dog has been well defined.^{1,2} The same statement can be made concerning man,^{3,4} although because of the limited instrumentation that can be applied to man, there have been no data published concerning the relationship between myocardial function, coronary blood flow and tissue

oxygenation. Studies in dogs have indicated that halothane decreases myocardial perfusion and oxygenation in concert with the decrease in cardiac function.^{2,5} However, the canine coronary circulation differs from that of man, particularly in terms of transmural flow distribution.⁶ The coronary circulation, conducting system and general function of the heart of the domestic swine, *Sus scrofa*, resembles that of man more than those of other subprimate mammals.^{7,8} Consequently, we have documented the myocardial metabolic and functional effects of three concentrations of halothane with 60 per cent nitrous oxide in 3-month-old Yorkshire piglets.

Methods

Anesthesia was induced with halothane-nitrous oxide by face mask in 11 fasted 21-28-kg piglets. After orotracheal intubation, ventilation was controlled by use of a volume-cycled ventilator guided by airway and arterial blood carbon dioxide measurements. A standard Cape anesthesia ventilator§ was modified for use with a nonrebreathing system, and the negative expiratory phase was changed so that positive end-expiratory pressure could be applied when the pleura was open. Halothane was delivered from a calibrated vaporizer¶ in 60-70 per cent nitrous oxide: 30-40 per cent oxygen. Sodium chloride, 0.9 per cent, was administered by infusion pump through an ear-vein cannula at a rate of 3 ml/kg/hr. Body temperature was controlled by external heating.

INSTRUMENTATION

Cardiac catheterization was performed with the aid of image intensification fluoroscopy. A single 8F Cournand catheter was positioned in the thoracic aorta via the left femoral artery. The lumen was used for aortic pressure measurements (Statham P 23 Db pressure transducer) and withdrawal of blood samples for determination of hemoglobin, blood-gas, and biochemical values. Through the right femoral vein, a 7F triple-lumen balloon-tipped thermal dilution catheter** was positioned in the pulmonary artery for determination of cardiac output. Through the left carotid artery, an 8 MMC Dal-

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Received from the Thoraxcenter, Erasmus University, Rotterdam, The Netherlands. This work was done during Dr. Merin's tenure as Senior Visiting Scientist.

Accepted for publication February 11, 1977.

Supported in part by DHEW grants HL 13257 and HL 31752 and by the Dutch Heart Foundation. Presented at 1975 annual meeting of the American Society of Anesthesiologists, Chicago, Illinois.

§ Cape Engineering Company, Ltd., Warwick, England.

¶ Fluomatic, Foregger Corporation, New York.

** Edwards Corporation, Santa Ana, California.

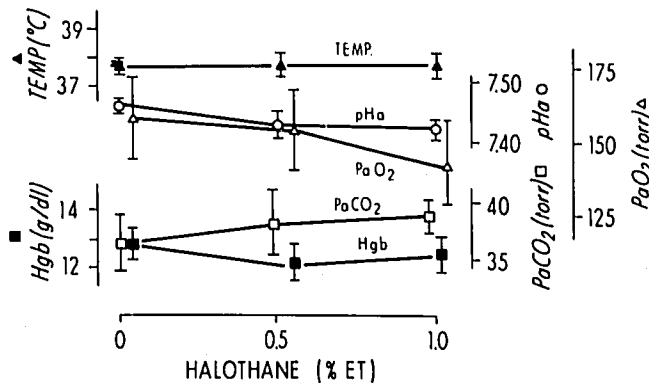


FIG. 1. Controlled variables. ET = end-tidal; I = SEM.

lons-Telco†† tip-manometer catheter, with a frequency response flat to 1,000 Hz, was placed in the left ventricle for the recording of left ventricular pressure. Through the right jugular vein, an 8F Cournand catheter was placed in the right atrium. The catheter was intermittently connected to a Statham P23 Db pressure transducer for determination of right atrial pressure. The anterior wall of the left ventricle was exposed by means of a mid-sternal incision. The left anterior descending coronary artery was dissected from its origin to its first branch, which usually gave about 1.5 cm of free artery. After a bolus injection of lidocaine, 30 mg, biopsy sutures were placed along the distribution of the left anterior descending coronary artery. An electromagnetic flow probe‡‡ (20–25 mm inner diameter) was placed around the free part of the left anterior descending coronary artery. Zero flow was obtained by occluding the artery with an atraumatic forceps. A 1.2-mm polyvinyl cannula was inserted in the anterior ascending coronary vein, parallel to the artery, approximately halfway from the apex. The cannula was connected to a plastic catheter and the system was kept patent with intermittent flushes of dilute heparin.

EXPERIMENTAL PROTOCOL

After the instrumentation and catheterization were completed, halothane was discontinued and succinylcholine, 2–3 mg/kg/hr, was added to the infusion. At least 60 min were allowed for stabilization of the animal and halothane washout before control measurements were made. The end-tidal halothane concentration during control studies averaged 0.04 ± 0.01 per cent (\pm SE). Thermodilution cardiac output curves were recorded in duplicate. Between cardiac output determinations, left ventricular pressure (LVP), its first derivative (LVdP/dt), aortic pressure, right atrial pressure and leads 1, 2 and 3 of the electrocardiogram were recorded at a paper speed of 200 mm/sec. During the high-

speed recording period, the ventilator was switched off to avoid respiratory artifacts. All traces were recorded on a pressurized ink system with high-frequency response.§§ For an accurate assessment of left ventricular end-diastolic pressure, the gain of the left ventricular pressure signal was magnified during part of the recording. Heart rate was counted from the electrocardiogram, while peripheral resistance was calculated from the difference between mean aortic and right atrial pressures divided by cardiac output. Left ventricular dP/dt/LVP was calculated on-line as a function of left ventricular pressure, visualized on a Textronic oscilloscope,¶¶ and photographed. From the oscilloscopic pictures, two pressure-derived indices of contractility were obtained: maximum contractile element velocity (V_{max}) and peak contractile element velocity (peak V_{ce}).⁹ Mean left anterior descending coronary artery flow was continuously recorded by integrating the area under the flow curve. Blood samples were collected simultaneously from the aorta and the coronary vein for analysis of pH, carbon dioxide tension, oxygen tension and saturation, hemoglobin concentration, glucose, potassium, inorganic phosphate and lactate. An epicardial biopsy (10–30 mg) was rapidly cut and plunged immediately into liquid nitrogen in a Dewar bottle. Finally, end-tidal gas samples were collected in an airtight flask especially designed to allow multiple gas chromatographic analysis.***

Two end-tidal concentrations of halothane were tested. The low concentration, 0.46 ± 0.01 per cent, was just sufficient to keep the animal from moving or breathing against the ventilator after the succinylcholine was discontinued. The high concentration, 1.04 ± 0.04 per cent, was the highest percentage that would allow a mean aortic pressure of more than 50 mm Hg. The sequence of administration of the two concentrations was randomized to offset the effect of any deterioration of the preparation. At least 45 minutes were allowed for equilibration after anesthetic concentrations were changed.

BIOCHEMICAL ANALYSIS

Blood

Serum was separated and frozen for subsequent determinations of glucose, inorganic phosphate, and potassium by AutoAnalyzer techniques.††† Whole blood was immediately deproteinized with an equal volume of cold perchloric acid, 8 per cent. The supernatant was frozen for lactate analysis†††

§§ Siemens Oscillomink B recorder, Erlangen, GFR.

¶¶ Textronix Corporation, Type 502A-Dual Beam, Beaverton, Oregon.

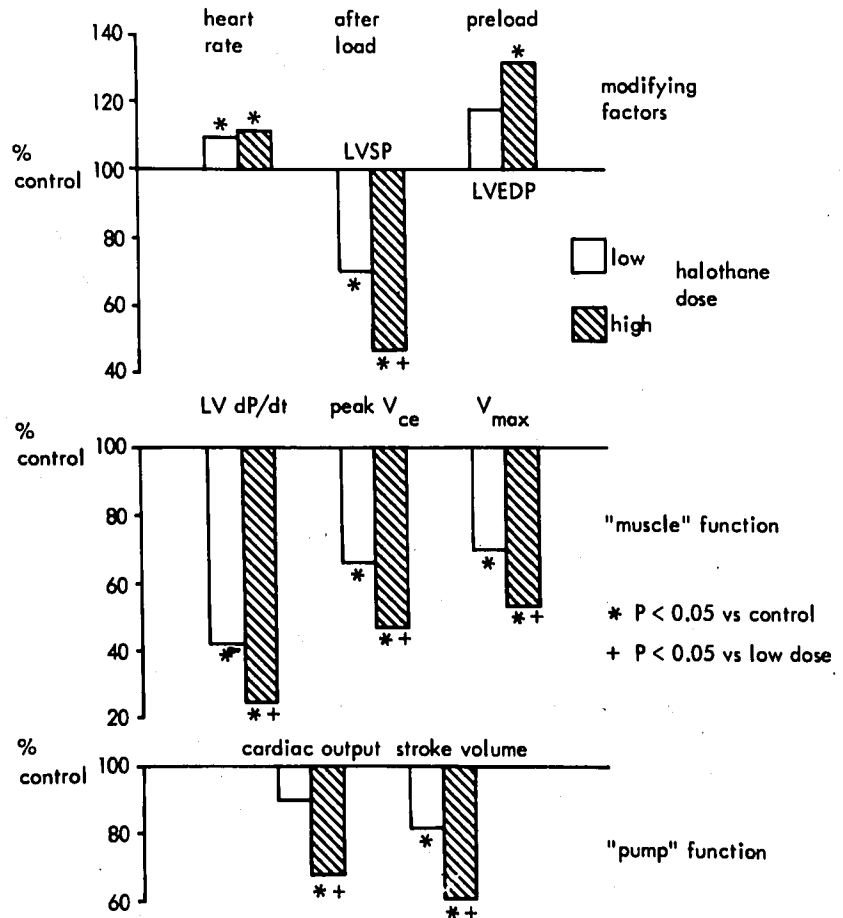
*** Courtesy of Glass Blowing Laboratory, Erasmus University, Rotterdam.

††† Technicon Instrument Corporation, Tarrytown, New York.

†† Thompson, Paris, France.

‡‡ Skalar Instruments, Transflow 600, Delft, The Netherlands.

FIG. 2. Cardiac function. LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; LV dP/dt = maximum rate of rise of LVSP; peak V_{ce} = peak contractile element velocity; V_{max} = extrapolated maximum contractile element velocity.



at a later date.¹⁰ Blood-gas measurements were performed on standard electrodes.††† Oxygen content was calculated from measured oxyhemoglobin saturation,§§§ hemoglobin concentration, and ar-

terial blood oxygen tension, using 1.39 ml oxygen/g hemoglobin as the fully saturated value.

Tissue

The frozen-muscle biopsy was homogenized with perchloric acid, 0.2 ml of 4 per cent, and transferred to a centrifuge tube with two acid washes of

††† Instrumentation Labs, Milan, Italy.
§§§ American Optical Company, Framingham, Massachusetts.

TABLE 1. Cardiovascular Function (Means ± SEM)

	Control	Halothane Concentration	
		Low	High
Halothane, per cent end-tidal	0.04 ± 0.01	0.46 ± 0.01	1.04 ± 0.04
Heart rate (beats/min)	95.9 ± 5.5	105.1 ± 3.1*	106.5 ± 3.2*
Mean aortic pressure (mm Hg)	115.0 ± 4.8	77.2 ± 3.2*	51.5 ± 1.7*†
Right atrial pressure (mm Hg)	3.5 ± 1.5	4.2 ± 0.4	5.2 ± 0.6*†
Left ventricular end-diastolic pressure (mm Hg)	6.8 ± 0.6	8.0 ± 1.1	9.0 ± 0.8*†
Left ventricular systolic pressure (mm Hg)	135.7 ± 5.2	92.0 ± 3.9*	62.4 ± 2.0*†
Left ventricular dP/dt (mm Hg/sec)	1788 ± 219	757 ± 35*	452 ± 18*†
Maximum contractile element velocity (l/sec)	67.0 ± 2.9	46.7 ± 2.2*	35.3 ± 1.8*†
Peak contractile element velocity (l/sec)	57.7 ± 2.7	38.1 ± 1.8*	27.1 ± 1.5*†
Cardiac output (l/min)	2.11 ± 0.17	1.89 ± 0.10	1.43 ± 0.26*†
Stroke volume (ml)	22.3 ± 1.8	18.2 ± 3.9*	13.5 ± 2.5*†
Left ventricular stroke work (g/m)	34.3 ± 2.6	19.2 ± 1.8*	9.48 ± 0.73*†
Left ventricular minute work (kg/m)	3.25 ± 0.35	2.04 ± 0.17*	1.01 ± 0.08*†
Systemic vascular resistance (mm Hg/l/min)	55.2 ± 5.2	39.4 ± 2.4*	31.3 ± 2.2*†

* $P < 0.05$ vs. control.
† $P < 0.05$ vs. low.

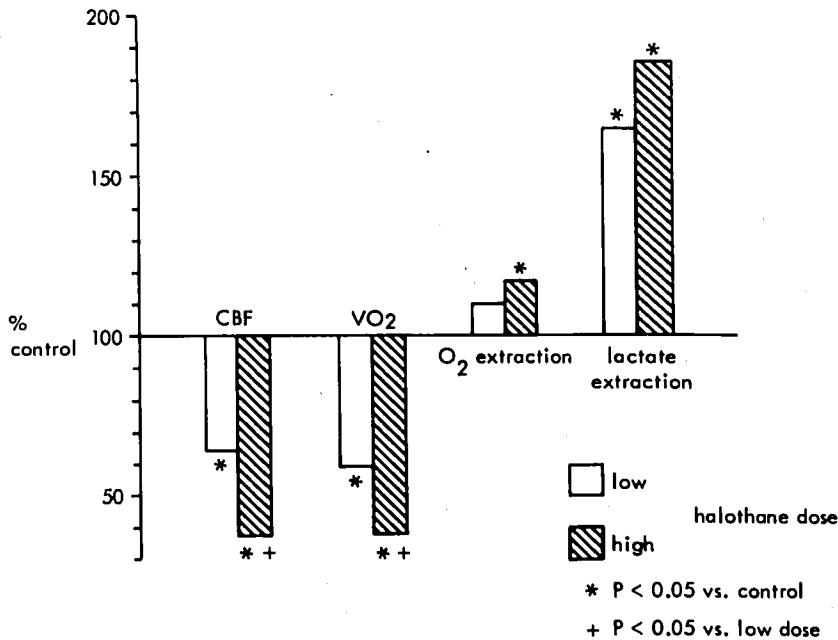


FIG. 3. Coronary blood flow and oxygenation. CBF = left anterior descending coronary artery blood flow; V_{O_2} = myocardial oxygen uptake from the left anterior descending coronary artery.

0.2 ml. The homogenate was centrifuged and the pellet frozen for protein and glycogen determinations. The supernatant fluid was adjusted to pH 6.5 with 0.5 M potassium hydroxide and recentrifuged. The precipitate was discarded and the supernatant frozen for analysis of high-energy phosphates. All tissue analyses were performed within 24 hours of the biopsy. Glycogen was assayed enzymatically.¹¹ The Folin assay was used for protein.¹² Adenosinetriphosphate (ATP) and creatine phosphate (CP) were assayed by the enzymatic method of Lamprecht *et al.*¹³ All assays were performed in duplicate. Statistical analysis utilized Student's *t* test for paired determinations.¹⁴

Results

There was no significant difference in the controlled variables (fig. 1).

VENTRICULAR FUNCTION

The marked negative inotropic effect of halothane was evident from analysis of the function of the intact heart as a muscle under isovolumic conditions (before the aortic valve opened) by the use of left ventricular pressure indices (fig. 2, table 1). The pumping function was measured by cardiac output and stroke volume was also depressed, but to a lesser extent than muscle function (fig. 2, table 1). The major factors modifying cardiac function must also be considered.¹⁵ A significant decrease in heart rate or preload (left ventricular end-diastolic pressure) will decrease both pump and muscle function. Both were significantly increased (table 1, fig. 2). Decreased afterload (aortic pressure) can decrease left ventricular *dP/dt*. However,

the derived indices, V_{max} and peak V_{ce} are much less sensitive to changes in afterload.¹⁵ In addition, the effects of afterload on ventricular function in the dog during halothane anesthesia have been dissociated.^{2,16} On the other hand, decreased afterload (best estimated for pump function by vascular resistance) will increase pump function, which it obviously did not do (table 1). Consequently, there seems to be little doubt that halothane caused a dose-related negative inotropic effect on the heart of the intact pig.

MYOCARDIAL PERFUSION, OXYGENATION AND METABOLISM

Blood flow in the left anterior descending coronary artery decreased, as did aortic pressure, cardiac work, and other estimates of ventricular function (fig. 3, table 1). Oxygen consumption in the distribution of that vessel decreased as well, entirely because of the decrease in blood flow, since there was a slight increase in oxygen extraction. However, lactate extraction increased markedly and tissue concentrations of ATP, CP and glycogen were unchanged. There was no coronary venous efflux of inorganic phosphate, although there was a small increase in potassium efflux. Although arterial glucose concentrations decreased, extraction increased somewhat at the high halothane concentration. Arterial concentrations of both inorganic phosphate and potassium increased progressively with increasing halothane concentrations (table 3).

Discussion

The halothane concentration in the control state was low, but it is important to realize that the

TABLE 2. Coronary Blood Flow and Oxygenation (Means ± SEM)

	Control	Halothane Concentration	
		Low	High
Coronary blood flow (ml/min)	26.7 ± 3.1	17.1 ± 0.9*	10.0 ± 1.1*†
CaO ₂ (ml/dl)	17.1 ± 0.7	16.2 ± 0.7	16.3 ± 0.7
Arterial–coronary venous O ₂ difference (ml)	7.94 ± 0.52	8.28 ± 0.44	8.9 ± 0.54*†
V̇O ₂ (ml/min)	2.32 ± 0.23	1.38 ± 0.09*	0.89 ± 0.11*†
Coronary vascular resistance (mm Hg/ml/min)	3.95 ± 0.33	4.24 ± 0.26	5.09 ± 0.78

Coronary blood flow = left anterior descending coronary artery blood flow.

V̇O₂ = myocardial oxygen uptake from the left anterior descending coronary artery.

* P < 0.05 vs. control.

† P < 0.05 vs. low.

animals had previously been equilibrated with halothane for two hours or more. Had we allowed the halothane washout to continue for more than 75 minutes, the animals' heart rates would have begun to increase. The hemodynamic values obtained during the control state closely resemble those recorded in awake trained miniature pigs.¹⁷ Consequently, we believe that the animals were analgesic during the control period.

Previous investigations in dogs have strongly suggested that halothane decreases myocardial oxygen demands as much as or more than myocardial oxygen supply, based on no change or decreased oxygen extraction and increased lactate extraction.^{2,5} This study adds several more indicators of anaerobic metabolism in the pig heart, whose coronary circulation closely resembles that in the human heart.

With myocardial cellular ischemia there may be leakage of intracellular potassium, leading to a higher coronary venous than arterial concentration.¹⁸ Because of continuing ATP use without corresponding synthesis, inorganic phosphate also is higher in coronary venous blood during ischemia.¹⁹ Finally, when hypoxia or ischemia becomes severe enough to interfere with myocardial function, ATP and CP levels are decreased by more than 50 per cent.²⁰ In these pigs, where left ventricular function was decreased by more than 50 per cent during administration of high concentrations of halothane, only potassium efflux showed a small increase. In addition, ventricular tissue glycogen content did not change. Since glycolysis is the only pathway for ATP synthesis during severe hypoxia and ischemia,²¹ glycogen content should be de-

TABLE 3. Metabolism (Means ± SEM)

	Control	Halothane Concentration	
		Low	High
Lactate			
art (mmol/l)	1.11 ± 0.09	1.21 ± 0.16	1.52 ± 0.14*†
a - cv† (mmol/l)	0.26 ± 0.05	0.43 ± 0.06*	0.67 ± 0.10*†
Uptake (μmol/min)	6.92 ± 1.88	6.81 ± 1.13	6.07 ± 1.28
Extraction (per cent)	23.9 ± 4.7	38.8 ± 4.7*	44.3 ± 6.3*
Glucose			
art (mmol/l)	5.75 ± 0.38	4.20 ± 0.33*	3.81 ± 0.37*
a - cv† (mmol/l)	0.12 ± 0.15	0.10 ± 0.08	0.25 ± 0.10
Uptake (μmol/min)	4.92 ± 3.31	1.37 ± 1.65	2.62 ± 1.33
Extraction (per cent)	1.44 ± 2.81	1.86 ± 1.67	6.34 ± 2.02†
Potassium (mmol/l)			
art	5.34 ± 0.11	5.15 ± 0.11	5.56 ± 0.12†
a - cv†	0.11 ± 0.07	-0.05 ± 0.04	-0.31 ± 0.19
Phosphate, inorganic (mmol/l)			
art	2.12 ± 0.14	2.57 ± 0.20*	2.77 ± 0.20*
a - cv†	-0.01 ± 0.03	0.02 ± 0.03	0.02 ± 0.03
ATP (μmol/g protein)	33.8 ± 2.3	33.0 ± 4.2	32.8 ± 4.2
Creatine phosphate (μmol/g protein)	58.0 ± 4.4	52.5 ± 8.6	55.1 ± 7.5
Glycogen (mg/g protein)	25.5 ± 3.3	25.8 ± 4.1	23.7 ± 5.6

* P < 0.05 vs. control.

† P < 0.05 vs. low.

‡ Arterial–coronary venous difference.

creased when ischemia is present. There is some evidence that halothane interferes with glycolysis in heart muscle,²² so the observation that tissue glycogen was unchanged may not be pertinent. However, myocardial glucose extraction actually increased during this study with increasing halothane concentrations in spite of decreased arterial levels. This is in contrast to previous findings in dogs.^{2,5} Whether this is a species variation or the result of the different experimental preparation is not clear.

The changes in arterial lactate, which are not dose-dependent, were seen in the dog,² and may relate to the effect of halothane on hepatic lactate metabolism. The increases in arterial potassium and inorganic phosphate have not been reported previously and are puzzling. Again, this may be a species variation.

Although there can be little doubt that halothane has a dose-related negative inotropic effect in yet another species, it is interesting that the left ventricular pressure derivatives were more sensitive to the drug than was pump function. Admittedly, only one aspect of pump function, stroke volume, was measured, but it appears that the increases in heart rate and preload compensated for the pump dysfunction more than the muscle dysfunction produced by halothane.

Since our control preparation utilized nitrous oxide, we chose to continue the nitrous oxide during halothane administration. Nitrous oxide decreases the hypotensive effect of halothane in dog²³ and man²⁴ without changing cardiac function. In the closed-chest pig anesthetized with 1.4 per cent end-tidal halothane, only a small decrease in left ventricular dP/dt was seen when nitrous oxide was substituted for nitrogen (unpublished results). There was no change in other measures of ventricular function. Contrary to previous studies in dog and man,^{23,24} systemic vascular resistance decreased with increasing halothane concentration during constant nitrous oxide administration (table 1). Although it is likely that the pigs would have tolerated more halothane without nitrous oxide, we believe our results reflect primarily a halothane effect. However, we cannot be sure that nitrous oxide did not modify either the functional or the metabolic effects slightly.

The mechanism of the negative inotropic effect of halothane remains in doubt.²⁵ There is some evidence to suggest that halothane might interfere with energy (ATP) synthesis through either glycolytic or oxidative pathways.^{25,26} There is equally good work indicating that the predominant effect is on energy utilization, probably through interference with myocardial cellular calcium fluxes.^{25,27} Stong *et al.* examined the relationship between the negative inotropic effect and ATP synthesis in cultured beating heart cells exposed to halothane.²⁸

During a decrease in beating amplitude of 50 per cent produced by halothane, there was no change in ATP concentration. However, since the rate of labeled inorganic phosphate incorporation into ATP was decreased, they hypothesized that the primary effect was on energy synthesis. In view of the very tight feedback control of energy metabolism in muscle, however, a decrease in energy utilization would very shortly be accompanied by a corresponding decrease in synthesis and, hence, the concentration of ATP in the cell.²⁰ Inasmuch as no-one has been able to show reversible interference by halothane with succinate-linked mitochondrial electron transport,²⁰ it appears unlikely that decreased ATP synthesis is responsible for the negative inotropic effect. Although the maintained concentration of ATP in this study suggests that energy synthesis is not defective during the negative inotropic effect of halothane, the same feedback argument mentioned above can be made; that is, energy synthesis and utilization are so tightly coupled that a decrease or increase in one is rapidly compensated by the same directional change in the other. However, decreases in CP by more than 50 per cent during hypoxia or ischemia are accompanied by decreases in cardiac function.²⁰ Since there was no change in the concentration of the more labile CP, we feel that the predominant subcellular effect of halothane in the heart is on energy utilization.

The effects of halothane on the pig heart appear to be similar to effects previously found in the dog heart. The dose-dependent decreases in coronary blood flow, oxygen consumption, and metabolism are probably related to the negative inotropic effect. There is no evidence for tissue hypoxia during this functional depression. Maintenance of ATP, CP and glycogen concentrations suggests that there is no defect in energy synthesis, although more definitive metabolic studies are necessary to confirm this.

The authors are grateful to J. W. Meilink, Ph.D., Department of Pharmacy, Erasmus University, Rotterdam, for the gas chromatography. The expert technical assistance of Marita Rutteman, Rob van Bremen, Sally Basch, and Liesbeth Eysbroek-Sipman made this work possible. The halothane used in this study was generously supplied by Imperial Chemical Industries, Holland.

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