Myocardial Metabolism in the Halothane-depressed Canine Heart

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In order to assess the mechanism of the myocardial depression produced by halothane, myocardial oxygen and substrate uptake as well as myocardial blood flow and hemodynamics were studied in the intact closed-chest dog. Using each animal as his own control with very light halothane, the negative inotropic effect of deep halothane was documented. Myocardial blood flow, oxygen uptake and stroke work decreased significantly, with no evidence of myocardial hypoxia as myocardial excess lactate changed from positive in the control state to negative in the depressed state. There was little glucose uptake in either state and an elevated myocardial threshold for glucose utilization was demonstrated. Fatty acid and pyruvate uptake decreased while lactate uptake remained unchanged.

HALOTHANE decreases myocardial contractile force in increasing dosage.[1, 2] The mechanism of this pharmacologic effect of the anesthetic remains unknown. Inasmuch as the heart has tremendous energy requirements, some insight into the cardiac action of halothane might be gained by looking at the way in which the heart obtains its energy. Olson has divided energy kinetics in the heart into liberation, conservation and utilization (fig. 1).[3] Liberation refers to the processes by which the organ metabolizes fuels or substrates to obtain energy; conservation is the storage and release of this energy; and utilization is the conversion of energy to function. The major energy for the work of the heart must come from the oxidation of glucose, nonesterified fatty acids (NEFA), lactate and pyruvate through the aerobic pathways of the Krebs cycle. Although there are anaerobic mechanisms for energy liberation in the heart, these are so inefficient that the heart is unable to function for more than a few minutes without oxygen. Consequently, utilization of the heart's principal fuels, myocardial blood flow and oxygen uptake have been studied in the intact, closed-chest dog under light and deep halothane anesthesia.

Methods

Fourteen healthy mongrel dogs weighing 17–26 kg were fasted overnight and brought to the laboratory unpremedicated. Following intravenous injection of thiopental (20 mg/kg), the tracheas were intubated with cuffed orotracheal tubes. Ventilation was controlled with a Bird Mark IV ventilator with 100 per cent oxygen and halothane vaporized in a Fluotec Mark II vaporizer and delivered through a Sierra nonrebreathing valve. Mixed expired halothane was analyzed continuously with an ultraviolet analyzer.* Approximately 100 ml/hour of 0.9 per cent sodium chloride was administered to replace insensible fluid loss. An esophageal thermistor probe was inserted to the level of the heart and temperature continually monitored and controlled by external heating. With the aid of fluoroscopy, catheters were placed in the femoral artery and the left ventricle through femoral cutdowns and in the right atrium and coronary sinus through jugular cutdowns. Patency was maintained by periodic flushing with a dilute

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Received from the University of Rochester School of Medicine and Dentistry, Rochester, New York. Accepted for publication March 5, 1969. Presented at the 1968 American Society of Anesthesiologists meeting, Washington, D. C. Supported in part by a grant from the Genesee Valley Heart Association.

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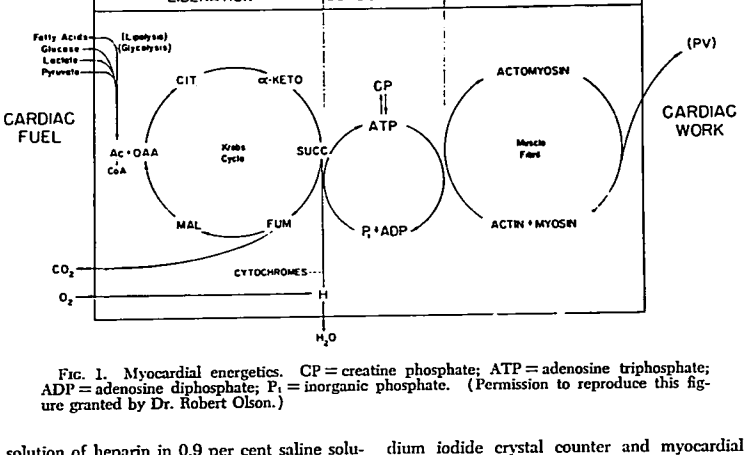

FIG. 1. Myocardial energetics. CP = creatine phosphate; ATP = adenosine triphosphate; ADP = adenosine diphosphate; P_i = inorganic phosphate. (Permission to reproduce this figure granted by Dr. Robert Olson.)

solution of heparin in 0.9 per cent saline solution. The coronary sinus catheter was placed at least 4 cm into the great cardiac vein so that only coronary venous blood was being withdrawn, but not more than 8–10 cm, to ensure that the majority of the left ventricular venous drainage was being sampled. Pressures were recorded through Statham p23 Aa transducers on a Sanborn 350 polygraph, along with the electrocardiogram and the first derivative of the left ventricular pressure pulse (dp/dt), which was differentiated electronically. Mean pressures were determined by electrical damping. After catheterization, the initial anesthetic concentration was set and ventilation was managed so as to keep pH_a and Pa_{CO_2} within normal limits. After at least 60 minutes, cardiac output was determined by the dye-dilution method, in duplicate, using indocyanine green and a Gilford densitometer. Injection was made into the right atrium and withdrawal from the femoral artery. A bolus of 1–3 millicuries of ^{85}krypton dissolved in physiologic saline solution was injected into the left ventricle. Blood samples of 2 ml were then withdrawn anaerobically over the following two and a half minutes at 15–20-second intervals through the coronary venous catheter. The samples were counted in a well-type sodium iodide crystal counter and myocardial blood flow estimated according to the method of Cohen *et al.*[4] as modified by Privatera and Rosenblum.[5] Simultaneous arterial and coronary venous samples were taken for gas and substrate determinations. Blood sampling loss was replaced by donor dog blood.

The anesthetic dose was then changed, the animal allowed to equilibrate for 30–60 minutes, and the entire protocol repeated. Terminally, the animals were sacrificed for verification of catheter placement and the absence of cardiopulmonary pathology. The control, or low, anesthetic dose (light anesthesia) was the lowest concentration of halothane which would keep the animals from moving or breathing against the ventilator. The depressing, or high, anesthetic dose (deep anesthesia) was two to three times the control dose. Dose was limited so that systolic arterial pressure remained above 75 mm Hg in order to prevent a gross arterial pressure effect on myocardial blood flow. The order in which the doses were administered was altered in successive animals to minimize the effect of sequence.

Gas tensions and *p*H were measured on conventional electrodes. Oxygen contents were determined using the manometric method of Van Slyke and Neill.[6] Glucose was estimated

TABLE 1. Controlled Parameters

	Control—low halothane concentration ± SEM	Depressed—high halothane concentration ± SEM
Per cent halothane	0.63 ± 0.04	1.64 ± 0.07
pH_a	7.41 ± 0.02	7.39 ± 0.07
Pao_2 (mm Hg)	487 ± 9.5	485 ± 8.6
$Paco_2$ (mm Hg)	33 ± 1.3	34 ± 2.1
Arterial hematocrit	42.5 ± 1.5	36.5 ± 4.2*
Esophageal temperature (C)	35.9 ± 0.18	36.0 ± 0.24

* $P < 0.01$.

TABLE 2. Hemodynamics

	Control—low halothane concentration ± SEM	Depressed—high halothane concentration ± SEM
Heart rate	120 ± 6.8	114 ± 4.5
Right atrial pressure (mm Hg)	2.6 ± 0.2	6.73 ± 0.62*
Left ventricular end-diastolic pressure (mm Hg)	4.07 ± 1.09	11.39 ± 1.11*
Mean arterial pressure (mm Hg)	119.6 ± 5.6	63.9 ± 3.02*
Left ventricular dp/dt	16 ± 1.5	7.1 ± 0.61*
Cardiac output (l/min)	2.63 ± 0.17	1.71 ± 0.14*
Left ventricular stroke work (gm meters)	37.33 ± 2.05	10.02 ± 0.82*
Peripheral vascular resistance	2.82 ± 0.29	2.24 ± 0.29

* $P < 0.01$.

by the glucose oxidase technique (Worthington Corp.)[7]; NEFA by the colorimetric method of Duncombe [8]; and lactate and pyruvate with enzymatic methods (Sigma Corp.) according to

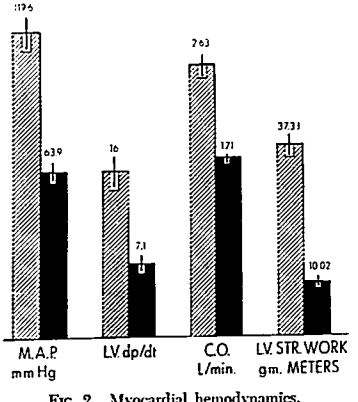

FIG. 2. Myocardial hemodynamics. Striped = control; solid = depressed.

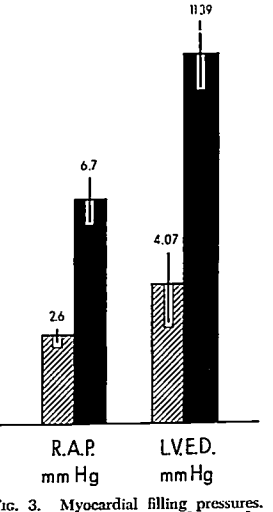

FIG. 3. Myocardial filling pressures. Striped = control; solid = depressed.

the techniques of Hohorst.[9] All determinations were done in duplicate. Myocardial uptake was calculated by multiplying arterial–venous difference by the blood flow. Stroke work and peripheral resistance were calculated using standard formulae.[10, 11] Statistical analyses were performed using Student's t test for paired samples.[12]

Results

The control parameters, pH_a, Pa_{CO_2}, Pa_{O_2} and esophageal temperature, were within normal limits and identical within the two groups (table 1). The hematocrit and, consequently, the arterial oxygen content, tended to be lower in the depressed group.

Decreases in mean arterial pressure, left ventricular dp/dt, cardiac output and left ventricular stroke work were accompanied by increased right atrial pressure and left ventricular end-diastolic pressure in the depressed animals. No change in heart rate or peripheral vascular resistance was observed (table 2, figs. 2, 3, 4).

Myocardial blood flow declined markedly in the depressed animals, with a decrease in oxygen uptake and excess lactate (table 3, fig. 5). There was no change in arterial substrate levels, while NEFA and pyruvate uptake declined (table 4, fig. 6). Lactate uptake was unchanged. There was little glucose uptake in either the control or the depressed heart. Indeed, four of the 13 control animals and six of the 13 depressed animals had higher coronary venous glucose levels than arterial glucose levels (table 4).

Discussion

Although no unanesthetized controls were used, low concentrations of halothane have been shown to have little or no effect on the heart.[1, 2] Inasmuch as the cardiac effects of the basal anesthetics have been incompletely studied, light halothane seemed a reasonable control when studying inotropy. At least two hours elapsed between the single induction dose of thiopental and the first study period. This fact and the alternate sequence of the dosage made any residual effect of the thiopental unlikely.

Documentation of the negative inotropic effect of deep halothane has again been provided in this study with the decrease in left ventricular dp/dt and cardiac output in the face of increased filling pressures and maintained heart rate. The unchanged arterial blood gases, pH and body temperature suggest that the halothane was responsible for this change. Although the hematocrit was lower in the depressed animals, the arterial oxygen content was still well within normal limits and it is doubtful if this could have affected myocardial function.

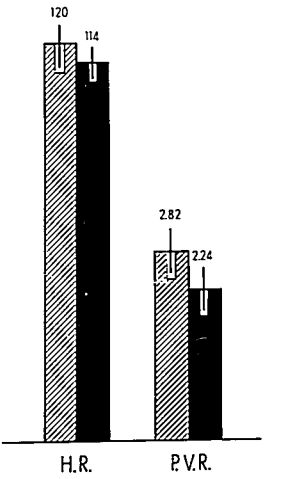

FIG. 4. Heart rate and peripheral vascular resistance. Striped = control; solid = depressed.

It has been shown that the canine spleen has a large storage capacity for red blood cells.[13] Sympathetic stimulation causes splenic contraction and the release of the cells into the circulation. It seems likely that the lower hematocrit seen in the deeply anesthetized animals is a reflection of the lack of sympathetic effect, splenic relaxation and sequestration of red blood cells.

Little information about the effects of halothane on myocardial blood flow is available, in contrast to the well-documented hemodynamic changes seen with increasing concentrations of the drug. Bagwell demonstrated a

TABLE 3. Myocardial Blood Flow and Oxygenation

	Control—low halothane concentration ± SEM	Depressed—high halothane concentration ± SEM
Myocardial blood flow (ml/100 gm/min)	42.02 ± 3.11	22.98 ± 2.07*
Excess lactate	6.1 ± 2.08	−2.12 ± 2.05†
O_2 uptake (ml/100 gm/min)	5.53 ± 0.40	3.06 ± 0.34*
Arterial O_2 content (vol per cent)	19.86 ± 0.84	19.06 ± 0.94†

* $P < 0.01$.
† $P < 0.05$.

TABLE 4. Myocardial Substrate Kinetics

	Control—low halothane concentration ± SEM	Depressed—high halothane concentration ± SEM
Arterial glucose c uptake (mg/100 ml)	N = 9 127.67 ± 11.86	N = 7 122.07 ± 10.19
Glucose uptake (mg/100 gm/min)	3.84 ± 0.72	4.05 ± 1.73
Arterial glucose c production	N = 4 96.25 + 6.4	N = 6 100.08 + 5.25
Glucose production (mg/100 gm/min)	6.00 ± 2.27	1.52 ± 0.47
NEFA, arterial (mEq/l)	376.14 ± 37.91	345.11 ± 28.28
NEFA uptake (micro Eq/100 gm/min)	4.733 ± 1.608	2.192 ± 0.517†
Pyruvate, arterial (mg/100 ml)	1.66 ± 0.11	1.49 ± 0.08
Pyruvate uptake (mg/100 gm/min)	0.34 ± 0.08	0.17 ± 0.03*
Lactate, arterial (mg/100 ml)	24.88 ± 4.53	22.54 ± 2.65
Lactate uptake (mg/100 gm/min)	3.18 ± 0.65	2.54 ± 0.75

* $P < 0.01$.
† $P < 0.05$.

progressive decrease in coronary flow with increasing halothane concentrations, accompanied by decrease in mean arterial pressure and aortic flow in an open-chest electromagnetic flow probe preparation in the dog.[14] He was unable to demonstrate significant excess lactate, and concluded that there was no evidence for myocardial hypoxia under these circumstances. Saito *et al.* likewise showed a marked fall in coronary blood flow with increasing halothane concentration,[15] utilizing an open-chest coronary cannulation technique. They found an increased coronary arteriovenous oxygen difference at the same time and a decrease in the cardiac output–coronary blood flow ratio. They interpreted their data as demonstrating a deleterious effect of halothane on the coronary circulation. Using a closed-chest coronary sinus drainage technique, Eberlein showed decreasing coronary blood flow with increasing halothane concentrations, but saw no change in coronary sinus oxygen saturation and felt that there had been a concomitant decrease in oxygen consumption.[16]

The present study supports the observations of Bagwell and of Eberlein. There was no change in the cardiac output–myocardial blood flow ratio, in contrast to the findings of Saito. In spite of the marked decrease in myocardial function, blood flow and oxygen uptake, myocardial excess lactate actually changed from positive (indicating anaerobic metabolism) to negative (indicating aerobic metabolism). Although Huckabee's concept of excess lactate as an indicator of anaerobic metabolism and hypoxia[17] has been questioned by Olson,[18] this remains one of the few means for assessing this function *in vivo*.[19] The additional observation that lactate uptake was maintained in these depressed hearts makes it extremely unlikely that anaerobic glycolysis was occurring to any significant degree, in contrast to the effect seen in cell cultures by Kenny and Fink.[20] In disagreement with the work of Bagwell and Saito, there was no significant correlation between mean arterial pressure and myocardial blood flow in this study. This is partly explained by the maintenance of mean arterial pressure about 60 mm Hg, and may indicate the de-

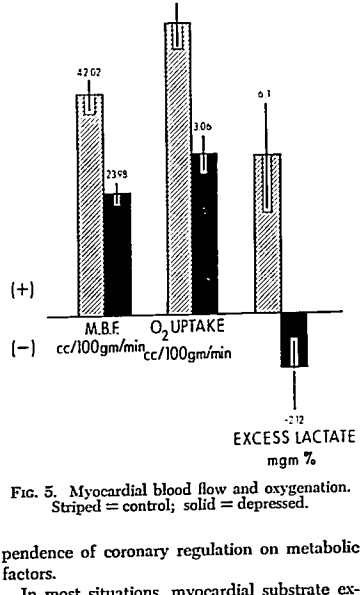

FIG. 5. Myocardial blood flow and oxygenation. Striped = control; solid = depressed.

pendence of coronary regulation on metabolic factors.

In most situations, myocardial substrate extraction has been shown to depend on arterial concentration.[21] As the arterial substrate levels in this study were the same in the two groups, this aspect cannot be implicated in the changes seen in uptake.

The fasted heart derives most of its energy from lipid sources, particularly NEFA,[22] so that the decrease in NEFA uptake along with the functional depression is not surprising.

For most substrates, a threshold has been demonstrated for myocardial extraction (arterial level below which no extraction occurs) but, except for glucose, it is much lower than usual *in vivo* concentrations and is of no functional importance. In the normal dog or human heart, the threshold for glucose is around 60 mg/100 ml.[22] This rises to about 100 mg/100 ml in diabetic animals (both pancreatectomized and Alloxan-treated). In both the normal and the diabetic animal, the threshold is markedly decreased by insulin.[22, 23] Galla and Wilson have shown in dogs that halothane produces a diabetic-like glucose tolerance curve which can be reversed by insulin.[24] The same phenomenon has been seen in regard to myocardial glucose transport in this study. As in the diabetic animals referred to above, the hearts in this study seemed to take up glucose above an arterial level of about 100 mg/100 ml (mean arterial level of the animals not taking up glucose) rather than above the 60 mg/100 ml threshold of the normal dog (fig. 7). (The glucose "production" seen is probably indicative of zero uptake due to the inherent error of the methodology.) Greene has shown that halothane impedes glucose transport across the erythrocytic membrane,[25] so that the same mechanism could be responsible for the effect seen in these hearts. Since in this respect no clear difference could be demonstrated between the control and depressed hearts, this aspect of the metabolic effect of halothane cannot be implicated as present in the myocardial depression of halothane, although several investigators have seen abnormal glucose metabolism with changes in inotropy.[26, 27, 28]

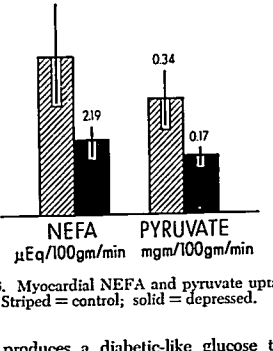

FIG. 6. Myocardial NEFA and pyruvate uptake. Striped = control; solid = depressed.

Conclusion

The significant negative inotropic effect of deep halothane anesthesia has been demonstrated. Although myocardial blood flow and oxygen uptake also decreased markedly, there was no evidence of myocardial hypoxia or ischemia. Glucose uptake was low or even nonexistent in both lightly- and deeply-anesthe-

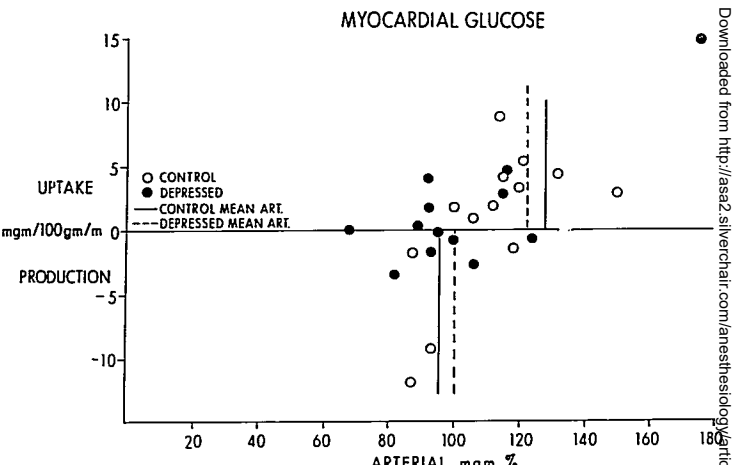

FIG. 7. Relationship between myocardial glucose uptake and arterial glucose level.

tized animals, so that the functional import of this observation remains unclear. NEFA and pyruvate uptake were decreased in the depressed hearts while lactate uptake remained unchanged. It would appear that the halothane-depressed heart, although it functions at a very low level, is being nourished adequately. No firm conclusions as to the mechanism of the depression can be drawn from this study.

The author acknowledges the advice and assistance of Drs. Pravin Shah, Paul Yu, Irwin Spar and Frank Colgan. Ayerst Laboratories provided the halothane used in the study.

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