Myocardial and Total Oxygen Consumption with Halothane

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In paralyzed dogs, with steady systemic flow rates of 2.0 liters/minute/m.^{2} assured by right-heart bypass, increasing halothane from 0.1 to 0.9 per cent resulted in an 8 per cent reduction in rate of whole-body O_2 consumption ($\dot{V}_{O_2}$) in the presence of vagotomy and spinal anesthesia. The decrease in non-myocardial $\dot{V}_{O_2}$ was 7 per cent and unrelated to changes in arterial pressure. The latter change in $\dot{V}_{O_2}$ is believed due to a direct depressant effect of halothane. Reductions in myocardial $\dot{V}_{O_2}$ were related to decreases in external work of the heart and are considered to represent indirect depressant effects of halothane.

UNCERTAINTY exists concerning the effects of gaseous anesthetics on rate of oxygen consumption ($\dot{V}_{O_2}$).[1] Though clinical studies made during halothane (Fluothane) anesthesia have suggested a reduction in $\dot{V}_{O_2}$, the information obtained has been unreliable because of the interplay of other variables, including temperature, premedication, and skeletal-muscle tone.[2-4] In dogs a 17 per cent reduction in $\dot{V}_{O_2}$ occurred as the mean expired concentration of halothane was increased from 0.8 to 2.5 per cent; but cardiac output and arterial pressure decreased concomitantly and direct effects of halothane on $\dot{V}_{O_2}$ could not be distinguished from indirect effects mediated by circulatory changes.[5] The presently reported study was designed to make this distinction possible by use of right-heart bypass and spinal anesthesia to minimize changes in cardiac output and arterial pressure during the observation of effects of halothane on total and myocardial $\dot{V}_{O_2}$.

Material and Methods

Unpremedicated dogs of 0.7 to 0.9 m.^{2} surface area were anesthetized with halothane * in air and maintained supine on a heated mattress. Succinylcholine, 30 mg., was administered before placement of a cuffed tracheal cannula and thereafter at 150 mg./hour. The gases to be inspired were delivered to a non-rebreathing system by flowmeters and a halothane vaporizer. Ventilation by pump was constant after initial adjustment to provide approximately normal Pa_{CO_2} levels.

The chest was opened by median sternotomy and the azygous vein was ligated. Catheters were placed in the left common carotid artery, the left atrium, and the superior vena cava (SVC) and inferior vena cava (IVC), for measurement of pressures and sampling. After administration of heparin, 3 mg./kg., venous return by gravity to a reservoir was separated into three streams by cannulation of the SVC through the wall, the IVC via the right atrium, and the outflow tract of the right ventricle (RV) directly. This blood was pumped through a heat exchanger and into the distal main pulmonary artery. The priming volume of the apparatus consisted of 1.5 to 2.0 liters of heparinized blood, 0.5 to 1.0 liter of 6 per cent dextran in normal saline,† and 50 to 100 mEq. of $NaHCO_3$.

Total right-heart bypass was established by tightening of tapes around each caval cannula and ligating the proximal main pulmonary artery. Thus myocardial blood flow returning to the right heart was diverted through the cannula previously placed in the RV outflow

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* Provided by Ayerst Laboratories, New York City.

† Provided by Abbott Laboratories, North Chicago, Illinois.

tract. A temperature of 37.0 ± 0.1° C. in IVC drainage blood and flow rates ($\dot{Q}$) of 2.0 liters/minute/m.^{2} were established.

Spinal anesthesia, when employed, was induced by injection of 5 ml. of 0.15 per cent tetracaine in Ringer's solution via a catheter in the midcervical portion of the subarachnoid space. This was repeated at 1-hour intervals. Arterial pressure fell with the initial administration but not subsequently. When spinal anesthesia was used, the right and left vagus nerves and accompanying cervical sympathetic trunks were divided previously in the neck. Under this circumstance, electrical stimulation of the central ends of the divided vagus nerves did not change the heart rate and arterial pressure.

SVC and myocardial $\dot{Q}$ were determined by timed collection. Total $\dot{Q}$ was calculated from pump speed (rpm) and stroke volume. IVC $\dot{Q}$ was obtained by difference (total $\dot{Q}$, less SVC $\dot{Q}$, less myocardial $\dot{Q}$) and checked at intervals by timed collection. Oxygen content in each venous stream and in arterial blood was determined by an O_2 electrode method [6]; and the difference in arteriovenous O_2 content, (a-v)O_2, was obtained. The rate of O_2 consumption, $\dot{V}_{O_2}$, was calculated ($\dot{Q}$ times (a-v)O_2). Other measurements included Pa_{CO_2}, Pa_{O_2}, and pH by calibrated electrode at 37° C., hemoglobin concentration by the cyanmethemoglobin method, pressures by strain gauges, and end-expiratory halothane concentration by column chromatography. Left-ventricular (LV) external work (kg.-m./minute) was obtained by multiplying total $\dot{Q}$ (liters/minute) times the product of mean arterial pressure (mm. of mercury) and a constant, 0.0144.

TABLE 1. Effect of Halothane on $\dot{V}_{O_2}$, $\dot{Q}$, and (a-v)O_2 (10 Dogs, Vagotomy and Spinal Anesthesia)

	Control Value, (mean)	With Halothane, % of Control	
		Mean	S. E.
$\dot{V}_{O_2}$, ml./min./m.^{2}			
SVC drainage	31.0	91*	2.0
IVC drainage	67.8	94*	1.4
Myocardial	10.4	83*	3.4
Whole-body	109.2	92*	1.0
$\dot{Q}$, l./min./m.^{2}			
SVC	0.649	101	1.4
IVC	1.253	101	1.0
Myocardial	0.108	94	6.5
Whole-body	2.010	100	0.3
(a-v)O_2, ml./100 ml.			
SVC drainage	4.91	90*	2.2
IVC drainage	5.42	93*	1.4
Myocardial	9.67	90	5.0

* Significantly different from 100 by t test ($P < 0.05$).

TABLE 2. Arterial and Venous Blood O_2 and Acid-Base Values (10 Dogs, Vagotomy and Spinal Anesthesia)

	Control Value		Halothane Value	
	Mean	S. E.	Mean	S. E.
Arterial				
pH	7.44	0.01	7.46	0.01
P_{CO_2}, mm. Hg	38	1	35	1
Buffer base, mEq./L.	48	1	48	1
P_{O_2}, mm. Hg	235	46	248	46
O_2 saturation, %	100	1	100	1
Hemoglobin, g./100 ml.	11.6	0.6	11.8	0.5
Venous drainages, O_2 saturation, %				
SVC	69	3	71	3
IVC	66	3	67	3
Myocardial	38	3	44	4

Observations were made during the final 30 minutes of 1-hour periods in which the inspired gas consisted, alternatively, of 30 to 100 per cent O_2, and 70 to 0 per cent N_2O for control values; or 1 per cent halothane, 30 to 99 per cent O_2, and 69 to 0 per cent N_2 for halothane values. Results were combined for presentation, since variability in inspired P_{O_2} and presence or absence of N_2O or N_2 appeared to influence the absolute blood levels of O_2 but not the metabolic or circulatory response to halothane. Halothane values for individual dogs were obtained by averaging observations from 1 to 3 halothane periods, and comparisons were made with the averages from 1 to 3 control periods. The effects of lapse of time and sequence were minimized by alternating the conditions of the initial period and, in five dogs, by returning to the initial conditions. Consequently, halothane was

TABLE 3. Effect of Halothane on Circulatory System (10 Dogs, Vagotomy and Spinal Anesthesia)

	Control Value	With Halothane, % of Control	
		Mean	S. E.
Pressures, mean, mm. Hg			
Arterial	78	88*	4.6
Left atrial	13	103	4.8
SVC†	1	100	—
IVC†	7	100	—
Heart rate, beats/min.	159	90*	1.8
External work, kg.-m./min.	1.77	90	4.9

* Significantly different from 100 by t test ($P < 0.05$).
† Measured in 4 dogs.

present in the expired gas during some control periods, but in small amounts (average, 0.07 per cent; range, 0 to 0.11 per cent). During halothane administration, concentrations averaged 0.85 per cent (range, 0.70 to 0.93 per cent). Each study required 6 to 8 hours.

Catheter positions were confirmed at autopsy, at which time the heart, empty and devoid of atria and great vessels, was weighed (average, 146 g.; range, 124 to 177 g.).

Results

Regional and whole-body $\dot{V}_{O_2}$ decreased with halothane administration in each of the 10 dogs studied after preparation by vagotomy and spinal anesthesia. The average reduction in whole-body $\dot{V}_{O_2}$, 8 per cent, was similar to the decrease in each caval drainage and approximately one half that of the myocardium (table 1). The overall decrease in $\dot{V}_{O_2}$ in tissue exclusive of the heart (non-myocardial) averaged 7 per cent. Regional and total $\dot{Q}$ were not altered significantly by halothane. Regional venous O_2 saturation values were increased with halothane (table 2), and caval (a-v)O_2 values were reduced significantly. Otherwise, gas and acid-base values for arterial and venous blood were generally unchanged (table 2). The steadiness of $\dot{Q}$ and arterial O_2 levels implies that the reductions in $\dot{V}_{O_2}$ were not based upon impaired transport of O_2 to the tissues.

Systemic arterial pressure was reduced 12 per cent with halothane, but other pressures were not significantly changed (table 3). Systemic vascular resistance (not tabulated) decreased to a similar degree in the region drained by each caval cannula. The reduction in non-myocardial $\dot{V}_{O_2}$ is not considered to be based upon decreased arterial pressure, since in two dogs a reduction in $\dot{V}_{O_2}$ was seen with increased arterial pressure and in the 14 dogs as a group the degree of reduction in $\dot{V}_{O_2}$ was not related to the degree of reduction in arterial pressure (fig. 1).

Heart rate slowed with halothane (table 3). External work decreased with halothane, because of lower arterial pressure and unchanged cardiac output. The reduction in myocardial $\dot{V}_{O_2}$ (10 per cent) was less than the reduction in myocardial $\dot{V}_{O_2}$ (17 per cent). The increase in values for myocardial efficiency, however, did not prove to be significant (t test). Figure 2 relates external work and myocardial $\dot{V}_{O_2}$. The regression line, myocardial $\dot{V}_{O_2} = 1.4 + 2.1$ LV external work, was calculated by the method of least squares, SD ± 0.95 ml. O_2/minute/100 g. Values calculated with assumptions of no external work and of a normal work load are similar to the findings of others in both man and dog.[7]

The response of total $\dot{V}_{O_2}$ and arterial pressure to halothane was similar in the absence of vagotomy and spinal anesthesia (table 4). While only 4 dogs were studied and significance was not tested, omission of spinal anesthesia resulted in increased arterial pressure

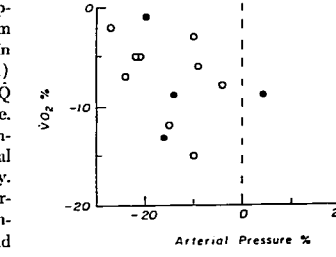

FIG. 1. Relation of decrease in non-myocardial (total, less myocardial) $\dot{V}_{O_2}$ to change in mean arterial pressure with halothane in presence (circles) and absence (disks) of spinal anesthesia. $\dot{V}_{O_2}$ decreased in all without apparent relation of degree to arterial pressure change.

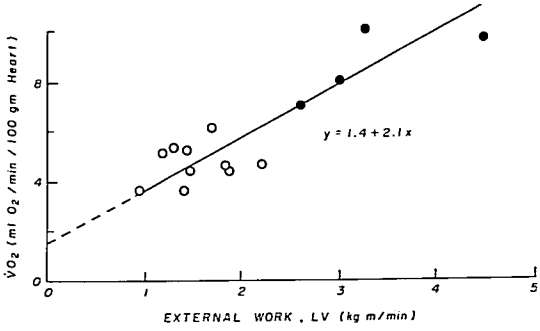

FIG. 2. Relation of myocardial $\dot{V}_{O_2}$ to external work of heart during halothane anesthesia in presence (circles) and absence (disks) of spinal anesthesia.

and, consequently, increased myocardial external work and $\dot{V}_{O_2}$. These observations are included primarily in order to expand the range of values used in preparation of figures 1 and 2. The similarity of decrease in arterial pressure with halothane in the presence (table 3) and absence (table 4) of spinal anesthesia suggests a direct vasodilatory action of halothane, not altered in apparent magnitude by interruption of autonomic-nervous-system transmission. Comparison with other observations in table 1 is limited by differences in total $\dot{Q}$, temperature, and knowledge of regional flow.

Comment

This study was designed to separate and quantitate direct and indirect effects of halothane on $\dot{V}_{O_2}$. Right-heart bypass provided for determination of effects due directly to the presence of halothane at the intracellular site of metabolism, without interference from variations in $\dot{Q}$ and body temperature. Spinal anesthesia and vagotomy minimized variations in peripheral autonomic-nervous-system activity. Separation of myocardial blood flow permitted determination of those effects produced indirectly by halothane on myocardial $\dot{V}_{O_2}$ by inducing changes in the external work of the heart.

Direct effects on myocardial $\dot{V}_{O_2}$ could not be evaluated accurately, since to do so would have required measurements in the absence of external work, that is, in the arrested or fibrillating heart. This limitation does not appear to be serious, however, since calculated values for the situation of no external work were small (1.4 ml. O_2/100 g./minute). Thebesian venous drainage into the left heart was not collected, but ordinarily it is of little magnitude and can be ignored safely.[8] The usefulness of estimates of myocardial $\dot{V}_{O_2}$ is not considered to be impaired because the RV was performing no external work. Ordinarily only one seventh of the total myocardial $\dot{V}_{O_2}$ is performed by the RV, and though this would be decreased it would not be eliminated by the absence of right ventricular work.[7]

While these arrangements permitted the direct and indirect effects to be observed separately, certain limitations existed. Only a narrow range of halothane concentrations could be studied, since at concentrations exceeding 1 per cent left ventricular failure and pulmonary edema usually developed with loss of the preparation. Although this risk was less at

TABLE 4. Effect of Halothane Without Vagotomy and Spinal Anesthesia (Mean Values, 4 Dogs)

	Control	With Halothane, % of Control
$\dot{V}_{O_2}$, total, ml./min./m.^{2}	120	92
$\dot{Q}$, total, l./min./m.^{2}	2.4	100
Arterial pressure, mean, mm. Hg	138	89
External work, kg.-m./min.	3.76	89
Myocardial $\dot{V}_{O_2}$, ml./min./m.^{2}	18.4	95
Temperature, esophageal, °C.	36.4	100

lower flow rates, flows lower than 2.0 liters/minute/m.^{2} are generally considered inadequate and hence were not suitable.

The risk of left ventricular failure could have been avoided entirely by total cardiopulmonary bypass. This course was not chosen because of the inherent abnormalities of such perfusion and the lack of opportunity for determining associated myocardial effects; but total bypass was used occasionally, as noted later, in order to extend the range of halothane concentrations studied. Similarly, in order to determine the relation of external myocardial work and $\dot{V}_{O_2}$ over a more useful range, it was necessary to include values observed in the absence of vagotomy and spinal anesthesia and at increased total $\dot{Q}$. Efforts to increase $\dot{Q}$ greatly in the presence of spinal anesthesia were generally unsuccessful because of the development of left ventricular failure.

Direct depression of $\dot{V}_{O_2}$ by halothane is believed evident in the reduction of $\dot{V}_{O_2}$ that occurred in each caval drainage while there was no change in temperature, rate of blood flow, perfusing pressure, Pa_{O_2} and Pa_{CO_2}, and autonomic-nervous-system activity. There was no evidence that these findings resulted from redistribution of blood flow: none of the changes in buffer-base were detected which would accompany the increase of anaerobic metabolism to be expected with deprivation of flow to metabolically active tissues. The direct depressant effect was small (a 7 per cent reduction in non-myocardial $\dot{V}_{O_2}$ when halothane was increased from 0.1 to 0.9 per cent) and was less with similar increments at greater concentrations during total cardiopulmonary bypass. In the latter circumstance, $\dot{V}_{O_2}$ decreased on an average of 15 per cent (4 dogs) and 40 per cent (2 dogs) as halothane was increased from 0.8 to 3.2 and 10 per cent, respectively.†

It seems likely that the direct depressant effects were general, involving all organs to some degree. Certainly for the SVC drainage, some decrease in $\dot{V}_{O_2}$ in tissues in addition to the brain must be supposed in order to account for the decrease of 2.8 ml. O_2/minute/m.^{2} in this drainage, since the *total* $\dot{V}_{O_2}$ for dog-brain is not much greater than 3.0 ml. O_2/minute/m.^{2}. This estimate is based upon the average brain weight of approximately 100 g./m.^{2} surface area and average values for cerebral $\dot{V}_{O_2}$ of 3 ml./100 g./minute at 37° C. in conscious man.[9] The other tissue is most likely skeletal muscle. Although direct depression of $\dot{V}_{O_2}$ in the brain, heart, and liver of the rat has been demonstrated,[10] similar information regarding skeletal muscle, skin, and bone is not available.

Indirect depression of $\dot{V}_{O_2}$ by halothane was apparent in the decrease of myocardial $\dot{V}_{O_2}$ as external work lessened. The overall effect on myocardial $\dot{V}_{O_2}$ reflects both the influence of halothane on external work and on myocardial efficiency. External work was reduced generally because of a reduction in arterial pressure consequent to a lowering of systemic vascular resistance. The increase in efficiency is not regarded as having any great import, since calculations of efficiency consider only mechanical work, a trivial item in the total energy exchange of the heart.[11] Each change contributed, however, to a reduction in myocardial $\dot{V}_{O_2}$.

The changes in myocardial $\dot{V}_{O_2}$ recorded during the present study are probably minimal values for the effect of halothane, because the usual reduction in cardiac output with halothane was prevented. A more realistic appraisal of the potential effect of halothane on myocardial $\dot{V}_{O_2}$ was obtained by estimating the change in myocardial $\dot{V}_{O_2}$ that occurred during previous studies with halothane concentrations of 0.8 and 2.5 per cent and cardiac outputs of 3.8 and 1.8 liters/minute/m.^{2}, respectively.[5] Myocardial $\dot{V}_{O_2}$ values of 19 and 7 ml./minute/m.^{2} at 0.8 and 2.5 per cent halothane, respectively, were calculated by use of the relationships between external work and myocardial $\dot{V}_{O_2}$ (fig. 2) and of body surface area and heart weight in the present study. This suggests that of the 23 ml./minute/m.^{2} by which $\dot{V}_{O_2}$ was reduced when halothane was increased from 0.8 to 2.5 per cent, approximately 12 ml. was related to reduction of myocardial work, and approximately 11 ml. was related to direct depressant effects of halothane. By the same means, it has been estimated that the increase in myocardial $\dot{V}_{O_2}$

† A. D. Sessler and R. A. Theye, unpublished observations.

alone could account for the increase in whole-body $\dot{V}_{O_2}$ observed when the halothane concentration was unchanged but cardiac output and arterial pressure were increased by means of infusion of blood and administration of digitalis.[5] Other indirect effects of halothane on $\dot{V}_{O_2}$ may be mediated by flow and pressure changes in the renal and splanchnic circulation.

These findings apply only in a general way to the clinical situation. During anesthesia and operation, an increase in halothane concentration would tend to decrease total $\dot{V}_{O_2}$, both by direct metabolic depression and by reduction of the external work and thereby the $\dot{V}_{O_2}$ of the heart. The overall effect, however, depends upon whether other potent influences on $\dot{V}_{O_2}$ are operative. For example, as the halothane concentration is increased, body temperature may fall—as a result of either increased heat loss or decreased heat production, or both. Reduction in body temperature results in a decrease in $\dot{V}_{O_2}$. If, however, the lowered temperature causes increased skeletal-muscle activity through shivering, with associated increased consumption of O_2, the overall $\dot{V}_{O_2}$ tends to increase.[4] This possibility can be eliminated by the use of muscle relaxants, leaving unopposed the effect of lowered temperature. Similar considerations apply to the onset and fading of the metabolic depressant effects of thiopental and meperidine, used either as premedicants or as adjuvants. Conversely, increased levels of catecholamines from either exogenous or endogenous sources would likely result in increase of $\dot{V}_{O_2}$, as would an increase in body temperature. This list is by no means considered complete.

Summary

Direct and indirect effects of halothane on $\dot{V}_{O_2}$ were determined in dogs, during right-heart bypass with vagotomy and spinal anesthesia. A direct depressant effect of approximately 7 per cent was demonstrated as the end-expiratory concentration of halothane was increased from 0.1 to 0.9 per cent. Evidence from other studies during total cardiopumonary bypass suggests that the magnitude of this effect may be less with similar increments at greater concentrations. An indirect depressant effect of halothane on $\dot{V}_{O_2}$ was evident in the decrease of myocardial $\dot{V}_{O_2}$ as external work of the heart lessened. The magnitude of this effect was related to the degree of reduction in cardiac output and arterial pressure. The implications of these findings are discussed.

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