The Effects of Halothane on the Pulmonary Vascular Bed of the Dog

David C. Heitz, Ph.D., Peter J. Jebson, M.B.Ch.B., F.F.A.R.C.S.,†*
Azmy R. Boutros, M.B.Ch.B., F.F.A.R.C.S.,‡ Michael J. Brody, Ph.D.§

The effects of 0.5 and 1.5 per cent (end-tidal) halothane on the pulmonary circulation in the anesthetized dog were studied by measurement of left atrial pressure, pulmonary arterial pressure, and total pulmonary blood flow. Halothane, 1.5 per cent, decreased pulmonary arterial pressure and flow, while computed pulmonary vascular resistance remained unchanged. In order to establish whether halothane has a direct effect on the pulmonary vascular bed, the left diaphragmatic lobe was isolated from the pulmonary circulation and perfused at a constant rate with blood from an external oxygenating circuit. When halothane was added to the external circuit a sustained decrease in perfusion pressure occurred, indicating that pulmonary vascular resistance had decreased. In the same experiments when halothane was administered to the dog by inhalation no change in perfusion pressure occurred in the lobe. Thus, by a direct action on pulmonary vascular smooth muscle, halothane is capable of producing vasodilatation, which is masked in the intact animal by the decrease in pulmonary arterial pressure and/or the action of a circulating vasoconstrictor substance. (Key words: Halothane; Pulmonary vascular resistance; Pulmonary vascular tension; Isolated diaphragmatic lobe; Autoperfused lobe.)

THE EFFECTS of halothane (Fluothane) on the general circulation have been studied extensively since its introduction as a volatile anesthetic 14 years ago.[1-6] Despite the fundamental importance of the pulmonary circulation in the transfer and elimination of the anesthetic, relatively little is known about the effects of halothane on pulmonary vascular smooth muscle. Price *et al.*[7] reported that halothane does not alter pulmonary vascular resistance in man, while Wyant *et al.*[8] reported an increase in pulmonary arterial pressure following induction with the anesthetic, an effect which was interpreted by the authors as representing increased pulmonary vascular resistance. Buckley and co-workers[9] suggested that halothane may possess a pulmonary vasodilator effect since pulmonary vasoconstriction associated with hypoxia was antagonized in the presence of the anesthetic. The present investigation was undertaken to define the effect of halothane on the pulmonary circulation *per se* and to clarify the effect of halothane on pulmonary vascular smooth muscle.

Methods

Ten dogs of either sex were anesthetized with pentobarbital sodium, 30 mg/kg. Decamethonium (Syncurine), 0.25 mg/kg, was used to permit controlled pulmonary ventilation. The lungs were ventilated through a tracheal cannula at a fixed rate of 16/min and a tidal volume determined from a nomogram to maintain P_{CO_2} within normal limits (see table 1). Inspired oxygen concentration was 40 per cent. Systemic blood pressure was monitored from a brachial artery. Right atrial pressure was measured via a cannula passed into the right atrium from right external jugular vein. Measurement of pulmonary arterial pressure was accomplished by passing a catheter via the jugular vein and through the right heart into the pulmonary artery. A left thoracotomy was performed, through which an electromag-

* Predoctoral trainee in Pharmacology, supported by NIH Grant GM00141-13. Present address: Department of Physiology, Mayo Foundation, Rochester, Minnesota.

† Visiting Assistant Professor. Present address: Department of Anaesthetics, Royal Infirmary, University of Edinburgh, Edinburgh, Scotland.

‡ Professor of Anesthesia.

§ Professor of Pharmacology.

Received from the Departments of Pharmacology and Anesthesia, College of Medicine, University of Iowa, Iowa City, Iowa 52240. Accepted for publication March 19, 1971.

TABLE 1. *p*H and Blood–Gas Status of Animals Exposed to Halothane by Inhalation and Ventilated with 40 Per Cent O_2

	Control	Halothane	Mean Difference ± SE	*P*
Halothane, 0.5 per cent				
Arterial P_{O_2}	146	139	7 ± 4	NS*
Arterial *p*H	7.36	7.37	0.01 ± 0.01	NS
Arterial P_{CO_2}	37.8	34.5	3.3 ± 0.9	NS
Mixed venous P_{O_2}	39.5	36.2	3.3 ± 2	NS
Mixed venous *p*H	7.35	7.33	0.02 ± 0.01	NS
Mixed venous P_{CO_2}	43.2	41.9	1.3 ± 1.8	NS
Halothane, 1.5 per cent				
Arterial P_{O_2}	144	141	3 ± 8	NS
Arterial *p*H	7.39	7.38	0.01 ± 0.01	NS
Arterial P_{CO_2}	36.1	33.2	2.9 ± 2	NS
Mixed venous P_{O_2}	37.3	25.3	12 ± 1	< 0.001
Mixed venous *p*H	7.34	7.27	0.07 ± 0.03	< 0.05
Mixed venous P_{CO_2}	41.9	47.3	5.4 ± 2.3	< 0.05

* NS = not significant.

netic flow probe (Carolina Instruments) was placed around the main pulmonary artery to record total pulmonary blood flow. Zero flow was obtained by transient occlusion with a ligature distal to the probe. A cannula was sutured in the appendage of the left atrium to monitor left atrial pressure. All measurements were recorded on a Beckman Type R Dynograph. Experiments were performed with the chest closed and the pleural cavity evacuated of air.

Halothane was administered via a Fluotec (Cyprane Ltd., England) vaporizer in concentrations sufficient to reach 0.5 and 1.5 per cent end-tidal concentrations, determined by an Analytic Systems Model 10 halothane analyzer in series with a Rahn end-tidal sampler. Halothane administration was continued for 15 min after the desired end-tidal concentration was reached. Each dog was exposed to both concentrations of anesthetic (the order in which each animal received the high and low concentrations of halothane was alternated daily).

Samples of systemic and pulmonary arterial blood obtained immediately prior to halothane administration and just prior to discontinuation of halothane were analyzed for P_{O_2}, P_{CO_2}, and *p*H with an Instrumentation Laboratories Model 113 *p*H and gas analyzer.

In addition to the variables measured directly, four values were computed. Left ventricular stroke volume was found by dividing total pulmonary blood flow by heart rate. Left ventricular stroke work was defined as the product of left ventricular stroke volume and mean systemic blood pressure. Total peripheral resistance was calculated as the difference between mean systemic blood pressure and right atrial pressure, divided by total pulmonary blood flow. Pulmonary vascular resistance was computed by taking the difference between pulmonary arterial pressure and left atrial pressure and dividing by total pulmonary blood flow.

ISOLATED LOBE PERFUSION

Thirteen dogs ranging in weight from 24 to 29 kg were anesthetized basally with pentobarbital sodium, 30 mg/kg, and paralyzed with decamethonium, 0.25 mg/kg. A left thoracotomy was performed, the artery and vein of the left diaphragmatic lobe were carefully dissected, and after anticoagulation with heparin sodium, 5 mg/kg, were cannulated with 5-mm (i.d.) elbow-shaped catheters. The incision was covered with Vi-Drape self-adhering surgical film and the thoracic cavity evacuated of air. The lobe was perfused from an extracorporeal circuit (fig. 1) previously

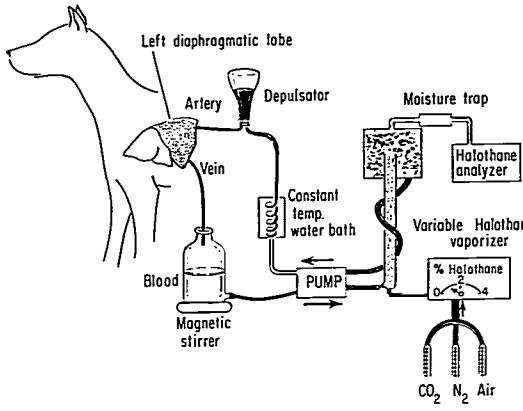

FIG. 1. Schematic representation of the method utilized to perfuse the left diaphragmatic lobe. See text for details.

primed with blood obtained from a donor dog. Blow flow to the lobe was set to give a perfusion pressure comparable to that of pulmonary arterial pressure in intact animals. Lobar venous blood was allowed to drain by gravity into a reservoir. The blood was then pumped from the reservoir by a Mark roller pump (model SH-51) to a modified Lillehei-Dewall bubble oxygenator. The blood was defoamed and pumped at a constant rate through a heat exchanger to the artery of the isolated lobe. Carbon dioxide, nitrogen, and air were admitted to the oxygenator column in amounts sufficient to produce gas tensions equivalent to those found in mixed venous blood. The bronchus of the autoperfused lobe remained intact and was ventilated along with the non-isolated lobes at a fixed rate and volume with 40 per cent O_2. Peak inflatation and intrathoracic pressures were monitored using Statham pneumatic transducers.

Halothane, 1.5 per cent, was administered to the perfused lobe with a Fluotec vaporizer placed in series with the gas-delivery system of the bubble oxygenator. Gas exhaust from the oxygenator was analyzed for halothane content as described above. Following the administration of halothane to the blood perfusate, ten of the 13 dogs used in this study received the same concentration of halothane by inhalation after basal conditions of the lobe had been re-established. The duration of halothane administration by either method was ten minutes after the onset of a response, as interpreted by a change in perfusion pressure in the lobe.

As a test of the functional status of the perfused lobe, pulmonary arterial and venous samples were obtained and analyzed for P_{O_2}, P_{CO_2}, and *p*H just prior to halothane administration.

Statistical analyses were performed using paired *t* tests.[10] A probability level of 0.05 or less was used as the criterion for statistical significance.

Results

HALOTHANE ADMINISTERED BY INHALATION TO THE INTACT DOG

Both high and low end-tidal concentrations of halothane produced significant decreases in systolic, mean, and diastolic blood pressures (fig. 2). The response to the high concentration of halothane was significantly different from the response to the low concentration after four minutes. This dose-related depressant effect of halothane on systemic blood pressure has been reported previously.[6]

Figure 3 illustrates changes in right atrial pressure, left ventricular stroke work, left ven-

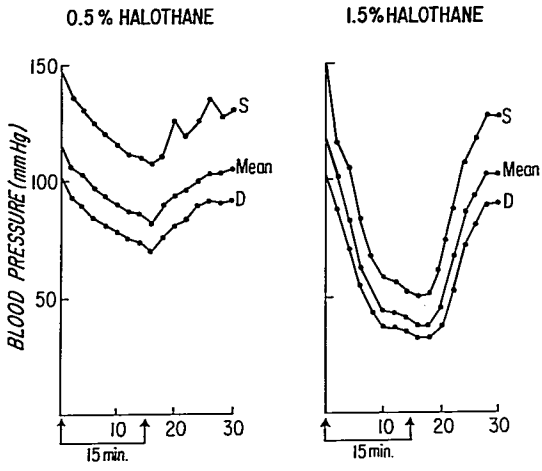

FIG. 2. The effects of 0.5 and 1.5 per cent end-tidal concentrations of halothane on systolic (S) mean and diastolic (D) blood pressures of ten dogs. The arrows indicate the duration of halothane administration. Mean, S, and D blood pressures were significantly reduced after two minutes of halothane administration ($P < 0.01$). Differences between the blood pressure responses at the high and low doses of halothane were significant after four minutes of administration ($P < 0.01$).

tricular stroke volume, and total peripheral resistance produced by 0.5 and 1.5 per cent end-tidal halothane. Right atrial pressure was not altered significantly by either the high or the low concentration. Left ventricular stroke work was significantly depressed by both concentrations of the anesthetic. Left ventricular stroke volume was not affected significantly by halothane. Total peripheral resistance was reduced significantly by both concentrations.

Figure 4 illustrates changes in pulmonary arterial pressure, left atrial pressure, total pulmonary blood flow, and pulmonary vascular resistance. Pulmonary arterial pressure was decreased significantly by the high dose of halothane. The peak decrease represents a 20 per cent reduction of pulmonary arterial pressure. The increases in left atrial pressure were significant at both 0.5 and 1.5 per cent end-tidal halothane. Total pulmonary blood

TABLE 2. Comparison of the Effects of Halothane Administered in the Perfusate of the Lobe and by Inhalation

	Perfusion, N = 13			Inhalation, N = 10		
	Control	Halothane	Mean Difference ± SE	Control	Halothane	Mean Difference ± SE
Lobar blood flow (ml/min)	106	106	0	118	118	0
Lobar perfusion pressure (mm Hg)	18.3	16.8	1.5 ± 0.3*	18.9	19.5	0.6 ± 0.3
Systemic blood pressure (mm Hg)	110	110	0	95	55	40 ± 6*
Peak inflation pressure (cm H_2O)	12.5	12.2	0.3 ± 0.3	12.4	12.7	0.3 ± 0.8
Thoracic pressure (cm H_2O)	−3 to −5	−3 to −5	0	−3 to −5	−3 to −5	0

* Significant difference from control, $P < 0.001$.

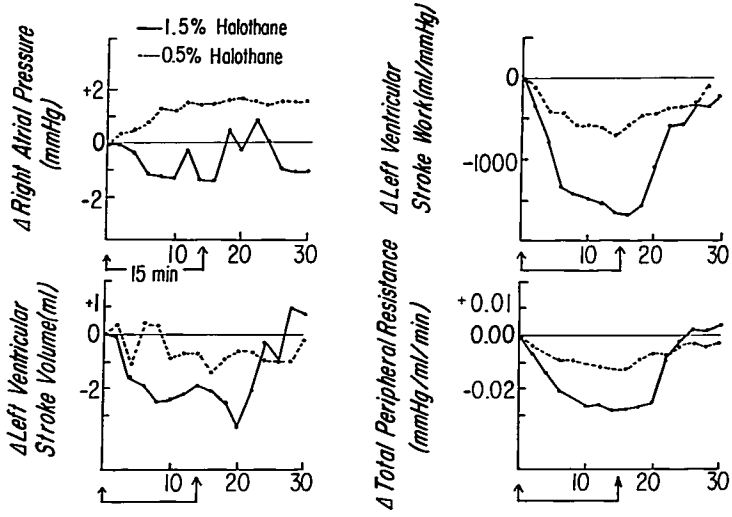

FIG. 3. The changes in right atrial pressure, left ventricular stroke work, left ventricular stroke volume, and total peripheral resistance produced by administration of 0.5 and 1.5 per cent halothane to ten dogs. The arrows indicate the duration of halothane administration. Right atrial pressure was not significantly altered. Left ventricular stroke work was reduced after two minutes of halothane administration ($P < 0.05$), and after six minutes the difference between the high and low doses was significant ($P < 0.01$). Left ventricular stroke volume was not significantly altered by either the high or the low dose. Total peripheral resistance was significantly reduced by both doses after two minutes ($P < 0.05$), and the differences between the doses were significant after four minutes.

flow was reduced by both concentrations of halothane, but not significantly. Calculated pulmonary vascular resistance was not significantly altered by the administration of either the high or the low dose.

Changes in heart rate induced by halothane were extremely variable, and no significant effects were noted.

The 0.5 per cent end-tidal concentration of halothane produced no significant changes in either arterial or mixed venous *p*H, P_{O_2} or P_{CO_2}. Arterial *p*H and blood gases were unaltered by 1.5 per cent halothane; however, mixed venous samples showed a significant decrease in P_{O_2} and *p*H and an increase in P_{CO_2}. Data summarizing the effects of the two concentrations of halothane on *p*H and blood gases are found in table 1.

HALOTHANE ADMINISTERED TO THE ISOLATED LOBE

Halothane equilibrated in the blood perfusing the isolated lobe produced a slight but significant decrease in lobar perfusion pressure. The onset of the response was slow, the average time being about four minutes. The decrease in perfusion pressure produced by halothane administered in this fashion was of long duration, on the average requiring 12 minutes to return to control levels after the anesthetic was discontinued. Halothane administered by inhalation in the same concentration to ten of the 13 dogs in the lobe-perfusion study produced no significant change in perfusion pressure, though systemic effects such as lowered arterial pressure were noted.

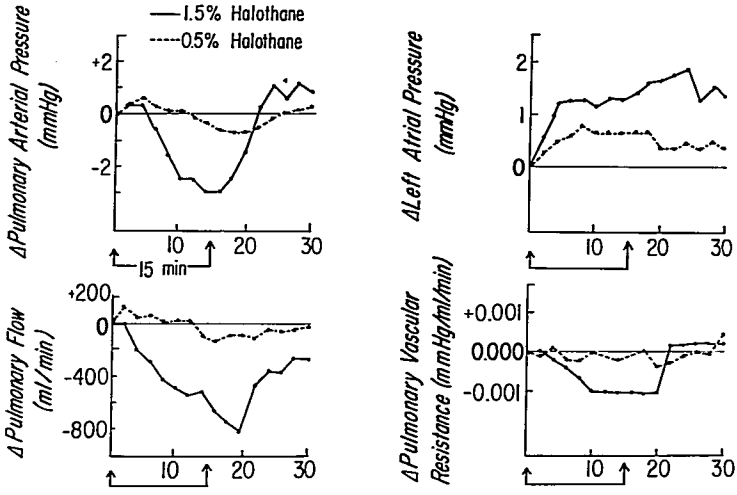

FIG. 4. The changes in pulmonary arterial pressure, left atrial pressure, total pulmonary blood flow, and pulmonary vascular resistance produced by administration of 0.5 and 1.5 per cent halothane to ten dogs. The arrows indicate the duration of halothane administration. Pulmonary arterial pressure was significantly reduced after eight minutes of halothane administration at the high concentration ($P < 0.01$). The low dose of halothane produced no significant changes in pulmonary arterial pressure. Left atrial pressure was significantly increased at two minutes by both concentrations of halothane. Pulmonary blood flow was not significantly altered by halothane, although the difference between the responses at the two doses was significant after four minutes ($P < 0.01$). There were no significant changes in pulmonary vascular resistance.

Peak inflation and intrathoracic pressures were unaltered by halothane administered to the perfusate or by inhalation. A comparison of the effects of halothane administered by equilibration in the perfusate and by inhalation is found in table 2.

Pulmonary arterial and venous blood gases were determined as an index of the functional status of the perfused lobe prior to halothane administration. Averaged arterial *p*H, P_{O_2}, and P_{CO_2} values were 7.38, 47 mm Hg, and 47 mm Hg, respectively; corresponding venous samples averaged 7.45, 154 mm Hg, and 36 mm Hg.

Discussion

Halothane administered to the intact dog produced generalized cardiovascular depression, a condition long known to be associated with use of the anesthetic. Since pulmonary blood flow and arterial pressure decreased in parallel, no significant change in pulmonary vascular resistance was detected in this study. These findings are in agreement with the work of Price *et al.*[7] However, despite the fact that halothane did not produce a significant change in pulmonary vascular resistance, the present results suggest that a pulmonary vascular smooth-muscle-depressant effect of halothane exists. If the overall radii of the vessels remained the same in face of a decrease in vascular distending pressure, the product of these variables, tension, probably was reduced. Theoretically, the reduction in pulmonary vascular tension could be the result of a withdrawal of neurogenically mediated tone since halothane has been demonstrated to possess sympathetic ganglionic and

peripheral and central vasomotor depressant properties.[6, 11, 12] The results of the present investigation suggest, however, that the pulmonary vascular depressant effect of halothane is the result of a direct effect of the anesthetic on the pulmonary vessels, since halothane in blood perfusing the isolated diaphragmatic lobe produced a significant decrease in perfusion pressure. The decrease in perfusion pressure occurred at a time when there was no change in peak inflation or intrathoracic pressure.

When halothane was administered by inhalation to the same dogs, thus confining the anesthetic to the intact animal and essentially denying halothane access to vessels of the perfused lobe, no changes in perfusion pressure occurred. Thus, during halothane-induced systemic hypotension, a condition which would be expected to increase, by reflex means, neurogenic pulmonary vasoconstrictor activity,[13] no pulmonary vascular adjustments were noted. It may be assumed from these data that the neural pathways associated with reflex regulation of pulmonary vascular resistance probably were depressed by the peripheral and central neural depressant actions of the anesthetic.

Since reflex pulmonary vasoconstriction did not occur in the isolated lobe during halothane-induced systemic hypotension, and the direct effect of halothane on pulmonary vessels was demonstrated to be vasodilating, the failure of pulmonary vascular resistance to decrease in the intact animal still requires explanation.

One explanation has already been alluded to. If active tension in pulmonary vascular smooth muscle is depressed by halothane, vasodilatation should ensue. If, however, pulmonary arterial pressure falls concomitantly, vascular caliber may remain unchanged. Thus, the demonstrated direct depressant effect of halothane on pulmonary vascular smooth muscle might not be translatable, in the intact animal, to a decrease in pulmonary vascular resistance.

It is also possible that the direct pulmonary vasodilatation produced by halothane is overridden by vasoconstriction produced indirectly as a consequence of the action of a circulating vasoconstrictor substance. Antidiuretic hormone (vasopressin) has been shown to be released from the hypothalamus in the dog upon inhalation or intracarotid injection of halothane.[14] This or other substances with pulmonary vasoconstrictor properties could well be involved in masking the pulmonary vasodilator effect of halothane.

References

1. Gander M, Veragut UP, Luthy E, *et al.*: Hemodynamic effects of halothane in the closed-chest dog. Helv Med Acta 33:351–362, 1967
2. Skovsted P, Price ML, Price HL: The effects of halothane on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. ANESTHESIOLOGY 31:507–514, 1969
3. Price HL, Price ML: Has halothane a predominant circulatory action? ANESTHESIOLOGY 77:764–769, 1966
4. Morrow DH, Pierce CE: The effect of halothane on systemic venous reactivity. J Surg Res 8:115–121, 1968
5. Ngai SH, Bolme P: Effects of anesthetics on circulatory regulatory mechanisms in the dog. J Pharmacol Exp Ther 153:495–504, 1966
6. Black GW: A review of the pharmacology of halothane. Brit J Anaesth 37:688–705, 1965
7. Price HL, Cooperman LH, Warden JC, *et al.*: Pulmonary hemodynamics during general anesthesia in man. ANESTHESIOLOGY 30: 629–636, 1969
8. Wyant GM, Merriman JE, Kilduff, CJ, *et al.*: The cardiovascular effects of halothane. Canad Anaesth Soc J 5:384–402, 1958
9. Buckley J, McLaughlin JS, Fort L III, *et al.*: Effects of anesthetic agents on pulmonary vascular resistance during hypoxia. Surg Forum 15:183–184, 1964
10. Steel RGD, Torrie JH: Principles and Procedures of Statistics. New York, McGraw-Hill Book Co., 1960
11. Price HL, Price ML: Relative ganglionic blocking potencies of cyclopropane, halothane and nitrous oxide and the interaction of nitrous oxide with halothane. ANESTHESIOLOGY 28:349, 1967
12. Biscoe TJ, Millar RA: The effect of cyclopropane, halothane and ether on sympathetic ganglion transmission. Brit J Anaesth 38:3, 1966
13. Van Den Heuvel-Heymans GM, Povati AL: Carotid sinus baroreceptors and pulmonary haemodynamics. Arch Int Pharmacodyn 71:169–175, 1959
14. Cristoforo MF, Brody MJ: Non-adrenergic vasoconstriction produced by halothane and cyclopropane anesthesia. ANESTHESIOLOGY 29:44–56, 1968