Anesthesiology
72:125–133, 1990

The Effects of Halothane in Hypoxic Pulmonary Vasoconstriction

D. Johnson, M.D.,* I. Mayers, M.D.,† T. To, Ph.D.‡

Human and animal experiments have not consistently shown halothane to inhibit hypoxic pulmonary vasoconstriction (HPV). The authors used a canine lung lobe perfused *in situ* to more precisely characterize the effects of halothane on HPV. The pulmonary vasculature can be divided into inflow, middle, and outflow segments by sequentially occluding the lobar inflow and outflow of blood. The lobes were ventilated with four different gas mixtures (normoxia, hypoxia, normoxia/halothane, hypoxia/halothane) and measured inflow, outflow, and middle segment (Rm) resistances using this stop-flow technique. All values are shown as means ± standard deviation. The authors found that hypoxia increased Rm from normoxia values of .006 ± .005 $cmH_2O \cdot ml^{-1} \cdot min^{-1}$ to .025 ± .008 $cmH_2O \cdot ml^{-1} \cdot min^{-1}$ ($P < 0.05$). During hypoxia/halothane Rm returned to .005 ± .004 $cmH_2O \cdot ml^{-1} \cdot min^{-1}$. The relationship between pressure and flow (P-$\dot{Q}$) for the lobes for each gas mixture was also determined. The slopes of the P-$\dot{Q}$ lines by linear regression were all similar. The zero-flow pressure intercepts of the P-$\dot{Q}$ lines for normoxia (3.2 ± .9 cmH_2O) and hypoxia (4.4 ± 1.1 cmH_2O) were significantly decreased after the administration of halothane (1.7 ± 1.0 cmH_2O and 2.6 ± 1.0 cmH_2O, respectively). Since the zero-flow intercept likely reflects the tone at alveolar vessel level, the authors conclude that halothane inhibits HPV by decreasing the tone in the middle vascular segment. (Key words: Anesthetics, volatile: halothane. Lung blood flow: critical closing pressure; pulmonary vascular resistance.)

ALVEOLAR OXYGEN CONCENTRATION plays an important role in matching ventilation and perfusion.[1] Decreased regional partial pressure of oxygen causes regional pulmonary vasoconstriction, thus diverting blood from the hypoxic region and minimizing venous admixture. The state of anesthesia can induce regional alveolar hypoxia due to atelectasis, positive pressure ventilation, one-lung ventilation, and postural changes.[2] Halothane has been shown to variably inhibit hypoxic pulmonary vasoconstriction in animal[3–7] and in human studies.[8] The animal studies were able to directly measure the effects of halothane on hypoxic pulmonary vasoconstriction while the human studies used changes in oxygenation as an index of hypoxic pulmonary vasoconstriction. These studies have been only partially successful in distinguishing between the direct effects of inhalational anesthetics on the pulmonary vasculature due to the direct action of halothane from those effects due to the indirect hormonal or neurogenic compensatory reflexes.[9]

We sought to more precisely characterize the direct effects of halothane in the normal lung vasculature under normoxic and under hypoxic conditions. In an isolated lobe, pulmonary vascular resistance can be partitioned into inflow, outflow, and middle segment resistances by a stop-flow technique.[10] By sequentially occluding the arterial and venous flow of the isolated lobe, it is possible to obtain the subdivisions of pulmonary vascular resistance following various interventions. Using the technique of arterial and venous occlusions, hypoxia has been shown to primarily increase the middle segment resistance in both dogs[11] and pigs[12] while other drugs primarily altered either inflow resistance or outflow resistance.[10,13] The pressure required to drive blood flow through the pulmonary vasculature can also be viewed as being composed of a pressure decrease related to flow and a pressure decrease related to opening vessels with tone.[12] Hypoxia has also been shown to preferentially increase the pressure decrease related to vessels with tone.[12] We wondered if halothane acted to specifically inhibit hypoxic pulmonary vasoconstriction or if it acted as a nonspecific vasodilator uniformly decreasing all segments of resistance throughout the pulmonary circulation. We found that halothane diminished the hypoxia induced increase in middle-segment resistance. The decrease in resistance caused by halothane was likely on the basis of a decrease in vascular tone. Halothane and hypoxia both appear to exert their effects on the same vessels but with opposing actions.

Methods

Animal Preparation

Six mongrel dogs (weights 20–24 kg) were anesthetized (thiopental 500 mg iv) and the trachea intubated with a #10 cuffed endotracheal tube. These studies were carried out following approval from the university animal care committee. The lungs were mechanically ventilated (Harvard ventilator) at a tidal volume (Vt) of 20 ml/kg with room air. Throughout the remainder of the surgical procedure, anesthesia was maintained with intermittent doses of pentobarbital (50 to 100 mg iv) as necessary. A large-bore catheter inserted into the abdominal aorta *via* the femoral artery was used for phlebotomy and drug administration.

* Associate Professor of Medicine, Departments of Anaesthesia and Medicine, University Hospital.

† Associate Professor of Medicine, Department of Medicine, University Hospital.

‡ Assistant Professor of Medicine, Department of Community Health and Epidemiology, University of Saskatchewan.

Received from the Departments of Anaesthesia, Medicine and Community Health and Epidemiology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada. Accepted for publication August 25, 1989. Supported by a grant from the Saskatchewan Heart Foundation, and a Scholarship from the Saskatchewan Lung Association.

Address reprint requests to Dr. Johnson: Department of Anaesthesia, Box 95, University Hospital, Saskatoon, Saskatchewan, S7N OXO Canada.

Following muscle paralysis (succinylcholine 40 mg iv), the left upper lobe was exposed through the left fifth intercostal space. Positive end-expiratory pressure (PEEP) of 3 cmH_2O was added during the surgical procedures. The left upper lobe was surgically removed to facilitate exposure of the left lower lobe. Heparin (300 U/kg) was administered and a stainless steel cannula was inserted into the left lower lobar vein *via* the left atrial appendage. We inserted a #6 cuffed endotracheal tube into the lobar bronchus *via* a bronchotomy and the endotracheal cuff was inflated. We ensured that the entire lobe could be inflated before suturing the bronchial tube in place. The left lower lobar artery was dissected and a plastic cannula was inserted; 400 ml of blood was obtained from the femoral artery catheter and diluted with saline and heparin (5,000 U) to a total volume of 600 ml. The blood was initially passed through a filter to remove any aggregates or particles. After the cannulae were inserted and the lobe effectively isolated, the animals were killed by injection of 10 ml of supersaturated KCl solution and 40 mg of succinylcholine. The cannulated lobe was left *in situ* within the thoracic cavity and was connected to an extracorporeal circuit. The lobe was perfused by gravity from an arterial reservoir. Pulmonary venous blood passively drained into a venous reservoir was pumped by a roller pump through a heat exchanger and filter and was then returned to the arterial reservoir. Lobar blood flow ($\dot{Q}_L$) was measured near the venous cannula by a previously calibrated electromagnetic flow probe (Carolina Instruments). Care was taken to prevent air embolization during cannula insertion and subsequent perfusion.

The lobar bronchus was ventilated independently of the remainder of the lung by a second Harvard ventilator (Vt = 150–200 ml, PEEP = 0). Lobar inflow pressure (Pa) and outflow pressure (Pv) were set by adjusting the height of the respective reservoirs. Pa and Pv were measured at pressure ports near the arterial and venous cannulae, respectively. The ports were connected to pressure transducers by low-compliance tubing and all pressures zero referenced to the top of the lobe. Before commencing the experimental protocol, at least 30 min was allowed for the preparation to stabilize as assessed by constant $\dot{Q}_L$ over a 5-min period. Heparin (1000 U) and 50% dextrose (1 ml) were added to the extracorporeal circuit every 30 min. The dextrose maintained a glucose level of between 7–9 mmol/l.

Calculations

Using methodology described by Hakim *et al.*,[10] pulmonary vascular resistance was divided into inflow segment resistance (Ra), middle segment resistance (Rm), and outflow segment resistance (Rv). We calculated the distribution of resistances using the pressure changes following a venous or arterial occlusion (fig. 1). After a rapid arterial occlusion an initial rapid decrease in pressure (ΔPa) followed by a slow decrease in pressure was recorded at the inflow port. The value of ΔPa was calculated by manually fitting a straight line through the first 1 s of the slow decrease in pressure and extrapolating this straight line back to the time of occlusion. The change from Pa to the pressure extrapolated to the time of occlusion was assumed to be ΔPa. Following return of flow, the venous cannula was occluded and a rapid rise in pressure (ΔPv) followed by a slow rise in pressure was recorded at the outflow port. ΔPv was calculated in a similar manner to ΔPa. Total resistance (R_T) was calculated as $Pa - Pv/\dot{Q}_L$. Ra and Rv were calculated as $\Delta Pa/\dot{Q}_L$ and $\Delta Pv/\dot{Q}_L$, respectively. Rm was calculated as $R_T - (Ra + Rv)$.

Critical closing pressure (P_{CRIT}) of the pulmonary vasculature was calculated using the linear relationship between driving pressure and flow. Under zone 2 conditions for flow, the driving pressure was equal to Pa since alveolar pressure was set at zero. We obtained at least eight different pressure-flow points by decreasing inflow pressure in steps of 2–3 cmH_2O. The pressure-flow points from all animals were fit to a straight line by linear regression and the straight line was then extrapolated to zero flow. The zero-flow pressure intercept was assumed to be the mean P_{CRIT}. The slopes of the pressure flow relationship were also obtained by linear regression and the flow related resistance was then equal to the inverse of the slope.

Experimental Protocol

Following stabilization of flow, baseline flow was set by adjusting Pa to near 15 cmH_2O and Pv to 7 cmH_2O. This ensured zone 3 conditions for flow during subsequent vascular occlusion measurements. Each lobe was sequentially ventilated with four different gas mixtures. Each lobe was initially ventilated with a control gas mixture (35% O_2, 7% CO_2, and 58% N_2). The lobe was next ventilated with a hypoxic gas mixture (3% O_2, 7% CO_2, and 90% N_2). The lobe was then ventilated with the original control mixture of gas diverted through a precalibrated Ohio halothane vaporizer at a flow of 3 l/min. This generated a control gas mixture with 0.5% halothane. The lobe was next ventilated with the hypoxic gas mixture with 0.5% halothane added as previously described. In order to verify that the lobe could still respond to a hypoxic stimulus, the lobe then received a ventilatory period with the original control mixture of gases alone and finally was ventilated with the hypoxic gas mixture alone. We refer to the six ventilatory periods as $normoxia_1$, $hypoxia_1$, normoxia/halothane, hypoxia/halothane, $normoxia_2$ and $hypoxia_2$, respectively.

Venous and arterial occlusions were performed in triplicate at the end of each ventilation period. The occlusions

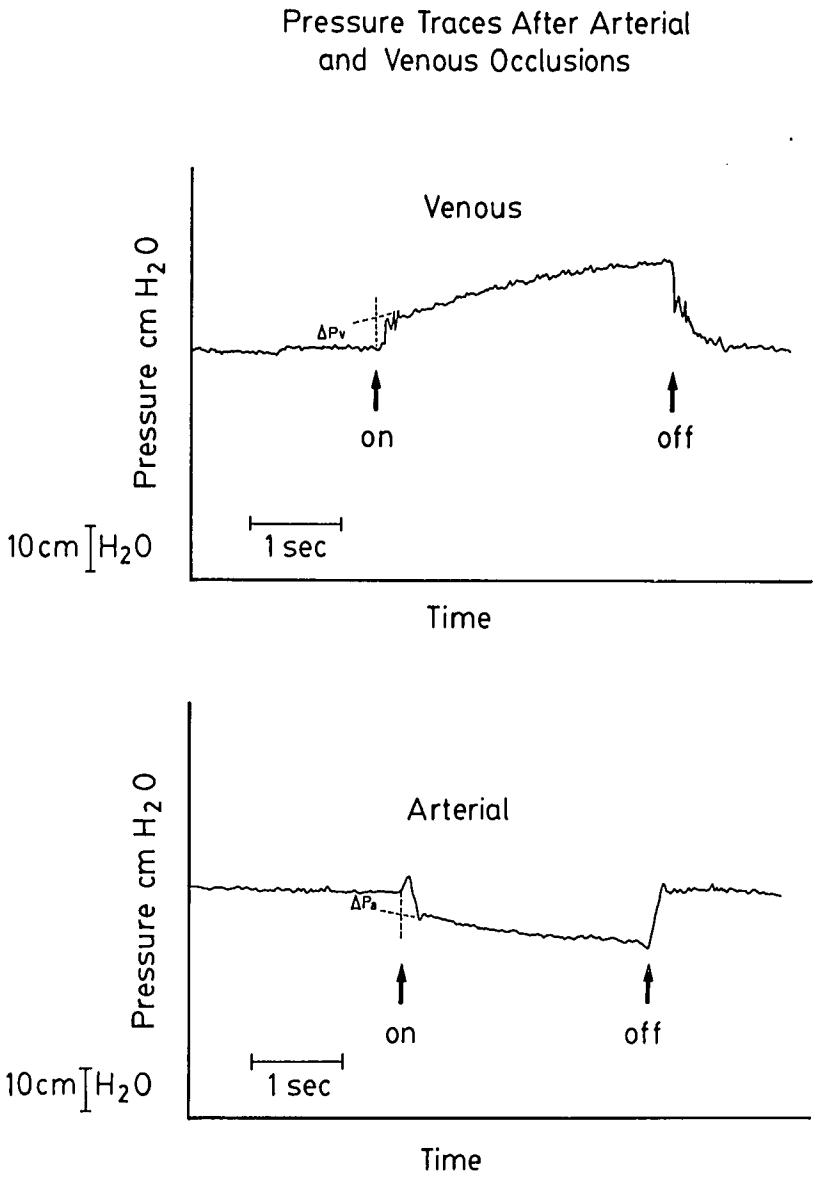

FIG. 1. This illustrates a representative venous occlusion (*upper curve*) and arterial occlusion (*lower curve*). The arrows represent the beginning and end of each occlusion. Each occlusion would last for 2–3 s. The change in pressure would be calculated from the stable baseline preceding the occlusion. Each slow pressure change would be extrapolated back to the instant of occlusion. The calculated changes in pressure (ΔPa and ΔPv) are shown.

were obtained after stopping the ventilator at end expiration. Prior to occlusions, blood was withdrawn from the venous cannula for blood gas and hematocrit determinations. Blood gases were analyzed for P_{O_2}, P_{CO_2}, and pH at 37° C (Corning 162-2) using appropriately calibrated electrodes and then corrected for blood reservoir temperature[14] after calculating hemoglobin saturation from a standard nomogram.[15] Inspired gas was withdrawn just prior to occlusions and was analyzed for N_2, O_2, CO_2, and halothane concentrations using an S.A.R.A. mass spectrometer.

After vascular occlusions were completed for each of the first four ventilatory periods, the venous reservoir was set below the lung base (Pv less than -10 cmH_2O). Varying flows were obtained by altering the height of the inflow reservoir in steps of 2–3 cmH_2O. To allow for flow stability, $\dot{Q}_L$ was measured at each driving pressure after stopping the ventilator at end expiration for 20 s. Following these determinations, Pv was reset to near 7 cmH_2O and the next ventilatory period was started. In this manner we obtained measurements of driving pressures and their respective flows in zone 2 conditions for ventilatory periods $normoxia_1$, $hypoxia_1$, normoxia/halothane, and hypoxia/halothane. We did not obtain pressure-flow measurements for periods $normoxia_2$ or $hypoxia_2$.

STATISTICS

Values of blood gases, inspired gases, and hemodynamics were compared between ventilatory periods using

a one-way analysis of variance (ANOVA). Where the F statistic showed a significant difference, paired t tests were used to determine which groups were different. Sidak's multiplicative inequality was used to correct for the number of comparisons made between groups.[16] Since the t value required to achieve significance increases with increasing number of comparisons, we did not compare each period to every other period, but instead prospectively decided on only five comparisons. These comparisons were normoxia$_1$ with hypoxia$_1$, normoxia$_2$ with hypoxia$_2$, normoxia$_1$ with normoxia/halothane, hypoxia$_1$ with hypoxia/halothane, and finally normoxia/halothane with hypoxia/halothane.

The eight pressure-flow values for each ventilatory period in each experiment were fit to a straight line using linear regression. Slopes and zero-pressure intercepts were also calculated using linear regression. The slopes and zero-pressure intercepts calculated from each experiment were averaged to yield a mean P_{CRIT} and mean 1/slope. The linear regressions for each experiment were compared using a repeated measure analysis of variance as described by Feldman.[17] $P < 0.05$ was considered to show a significant difference. Values are represented as means ± standard deviations.

Results

By ANOVA there were no differences between ventilatory periods for values of Pv_{CO_2}, pH, Fi_{CO_2}, or hematocrit (table 1). There were small but statistically significant differences between periods for temperature with the first two periods being cooler than the remaining periods. As expected, lobar Pv_{O_2} was lower in the hypoxic periods when compared to the other periods. In addition, there was a significant difference in lobar Pv_{O_2} between the normoxia$_1$ and normoxia/halothane periods when compared with normoxia$_2$. Inspired halothane concentrations were similar between normoxia/halothane and hypoxia/halothane periods (0.5 ± 0.06% and 0.54 ± 0.05%, respectively).

There were no significant differences between periods for values of Pa or Pv. $\dot{Q}_L$ was significantly lower during the hypoxia$_1$ and hypoxia$_2$ periods when compared with the other four ventilatory periods. Values for total resistance were similar between all six periods by ANOVA (table 2). Ra and Rv were also similar between the six periods. Rm was significantly higher in the hypoxia$_1$ and hypoxia$_2$ periods when compared with the other four periods.

In order to decrease the scatter in values due to inherent variation between animals, we normalized resistance values as a percent change of their normoxia$_1$ values (table 2). By definition, mean resistance values during normoxia$_1$ were set to 100% ± 0%. For meaningful statistical comparisons between normoxic ventilation and the other conditions, we therefore made comparisons with resistance measurements obtained in the normoxia$_2$ period. Total resistance was similar between normoxia$_1$ to normoxia$_2$ periods. By this analysis, total resistance increased in the hypoxia$_1$ and hypoxia$_2$ periods when compared to normoxia$_2$ ($P < 0.05$). Total resistance in period normoxia/halothane decreased significantly compared to period normoxia$_2$ ($P < 0.05$). Total resistance also decreased between the hypoxia$_1$ and hypoxia/halothane periods. The normoxia/halothane and the hypoxia/halothane periods showed similar changes in resistance from baseline and were not different from each other. We also normalized the subdivisions of resistance as a percent change of the normoxia$_1$ values. Middle segment resistance increased significantly between normoxia$_2$ compared with hypoxia$_1$ period. Similarly, middle segment resistance increased significantly between normoxia$_2$ and hypoxia$_2$. Middle segment resistance decreased significantly between hypoxia$_1$ and hypoxia/halothane pe-

TABLE 1. Mean Hemodynamic, Inspired Gas, and Blood Gas Values during the Six Ventilatory Periods

	Normoxia$_1$	Hypoxia$_1$	Normoxia Halothane	Hypoxia Halothane	Normoxia$_2$	Hypoxia$_2$
Pv_{CO_2} (mmHg)	40 ± 1.8	39 ± 0.8	39 ± 1.9	38 ± 1.6	38 ± 3.0	40 ± 1.0
Pv_{O_2}* (mmHg)	190 ± 11.3	42 ± 2.5	177 ± 23.8	42 ± 2.7	162 ± 17.5	40 ± 4.3
pH	7.16 ± 0.03	7.19 ± 0.03	7.18 ± 0.03	7.16 ± 0.04	7.14 ± 0.04	7.15 ± 0.03
Hct (%)	21 ± 2	21 ± 2	21 ± 2	21 ± 1	21 ± 1	21 ± 1.5
Fi_{O_2}* (%)	33.1 ± 0.1	5.3 ± 0.2	33.0 ± 0.1	5.5 ± 0.1	32.7 ± 0.2	5.3 ± 0.6
Fi_{CO_2} (%)	6.0 ± 0.1	6.1 ± 0.4	5.9 ± 0.1	5.9 ± 0.1	5.8 ± 0.2	6.0 ± 0.2
Temp* (°C)	36.7 ± 0.2	36.7 ± 0.1	36.9 ± 0.2	37.0 ± 0.1	37.0 ± 0.1	37.0 ± 0.2
Pa (cmH_2O)	14.2 ± 1.2	14.5 ± 0.8	14.1 ± 1.1	14.2 ± 1.7	14.2 ± 1.2	14.3 ± 1.0
Pv (cmH_2O)	6.8 ± 0.9	7.2 ± 0.4	7.3 ± 0.8	7.3 ± 0.8	7.1 ± 0.7	7.2 ± 1.2
$\dot{Q}_L$* (ml/min)	156 ± 17	125 ± 16	180 ± 18	172 ± 18	159 ± 17	133 ± 10

Pv_{O_2}, Pv_{CO_2}, and pH refer to lobar venous blood gases. Fi_{O_2} and Fi_{CO_2} refer to inspired O_2 and CO_2 concentration, Hct = lobar hematocrit, Temp = reservoir temperature, Pa = lobar inflow pressure, Pv = Lobar outflow pressure, and $\dot{Q}_L$ = lobar flow.

* denotes a difference between periods by ANOVA ($P < 0.01$).

TABLE 2. Pulmonary Vascular Resistance and its Subdivisions during the Six Ventilatory Periods

	$Normoxia_1$	$Hypoxia_1$	Normoxia Halothane	Hypoxia Halothane	$Normoxia_2$	$Hypoxia_2$
R_T	0.048 ± 0.016	0.060 ± 0.014	0.039 ± 0.011	0.041 ± 0.013	0.045 ± 0.013	0.056 ± 0.015
Ra	0.016 ± 0.004	0.018 ± 0.003	0.016 ± 0.003	0.017 ± 0.003	0.015 ± 0.004	0.017 ± 0.003
Rm	0.006 ± 0.005	0.025* ± 0.008	0.004 ± 0.004	0.005 ± 0.004	0.006 ± 0.004	0.022* ± 0.01
Rv	0.026 ± 0.009	0.017 ± 0.007	0.019 ± 0.005	0.020 ± 0.007	0.023 ± 0.009	0.016† ± 0.006
R_T% (%)	100	132†§ ± 26	83† ± 7	88 ± 6	98 ± 8	116† ± 11
Ra% (%)	100	112 ± 26	101 ± 24	106 ± 25	95 ± 6	107 ± 17
Rm% (%)	100	509†§ ± 167	50† ± 41	75 ± 36	131 ± 82	410† ± 117
Rv% (%)	100	68 ± 18	76 ± 15	81 ± 13	92 ± 22	62 ± 10
P_{CRIT} (cmH_2O)	3.2‡ ± 0.9	4.4§ ± 1.1	1.7 ± 1.0	2.6 ± 1.0	—	—
1/slope	0.038 ± 0.009	0.043 ± 0.009	0.037 ± 0.004	0.038 ± 0.004	—	—

R_T = total resistance, Ra = inflow segment resistance, Rm = middle segment resistance and Rv = outflow segment resistance. RT%, Ra%, Rm%, Rv% refer to normalized values of resistance subdivisions. P_{CRIT} = extrapolated critical closing pressure; 1/slope = inverse of the slope of the pressure-flow relationship (by linear regression). The inverse of the slope would equal the resistance to flow. Note all resistance values and the values of 1/slope of the lines are in units of $cmH_2O \cdot ml^{-1} \cdot min^{-1}$.

* Denotes a significant difference from the other periods tested by *t* test. †denotes a significant difference from $normoxia_2$. ‡ denotes a significant difference from normoxia/halothane. § denotes a significant difference from hypoxia/halothane.

Not all possible interactions between periods were compared by *t* test.

riods. Neither Ra nor Rv showed any significant changes from its baseline values in any of the subsequent periods.

Figure 2 shows the individual pressure-flow lines for the periods $normoxia_1$, $hypoxia_1$, normoxia/halothane, and hypoxia/halothane in each of the six individual animals. By linear regression the correlation coefficients of the pressure-flow lines for each of the periods was significant ($P < 0.01$); 1/slope and pressure intercepts (P_{crit}) are shown in table 2. The differences in intercepts between the four periods were small. Using the analysis described by Feldman,[17] mean P_{CRIT} during period normoxia/halothane was significantly lower when compared with period $normoxia_1$ ($P < 0.01$). Similarly mean P_{CRIT} was significantly lower during period hypoxia/halothane when compared with period $hypoxia_1$ ($P < 0.01$). Although P_{CRIT} tended to be slightly greater during $normoxia_1$ compared with $hypoxia_1$, and between normoxia/halothane compared with hypoxia/halothane, these differences were not statistically significant; 1/slope of the lines were similar between all four periods.

Discussion

We found that halothane inhibited hypoxic pulmonary vasoconstriction as it decreased total pulmonary vascular resistance. We more precisely characterized the effects of halothane into those altering critical closing pressure and those altering the slope of the linear pressure-flow relationship. Our experiments suggest that halothane acts primarily to decrease the critical closing pressure of the pulmonary vasculature. Other experiments in isolated lungs, as well as *in vivo* and human lungs, have shown conflicting effects of halothane on hypoxic pulmonary vasoconstriction as measured directly[3-7] or indirectly.[8] The isolated lobe is unique in that secondary neuronal and humoral influences can be eliminated and the specific effect of halothane on the pulmonary vasculature can be tested. We were also able to control vascular pressures to a degree not possible in the intact animal or in the clinical setting. In turn, the disadvantage of these experiments is that they cannot be directly applied to the clinical setting where there may be secondary neural or humoral reflexes that might alter the specific actions of halothane.

We used methodology similar to that described Hakim *et al.*[10] to subdivide pulmonary vascular resistance into inflow, middle, and outflow segment resistances. Hakim *et al.* have described the lobar vasculature as though the vasculature was similar to a resistance-capacitance-resistance model.[18] It is also possible to model the lung as if it were an electrical circuit composed of three resistors (Ra, Rm, and Rv) in series separated by two parallel capacitors.[19] Using this electrical analogy, breaking the circuit results in the measured voltage to immediately take on the value set by the capacitors. The measured voltage change corresponds to voltage drop across its resistor. With either model, acutely occluding flow allows pressure to rapidly equilibrate with the capacitance vessels. This change in pressure divided by flow is equivalent to the value of resistance across the vascular segment being tested. By this method the resistance across the inflow and outflow segments can be measured. The resistance of the middle segment can then be calculated as the measured total resistance minus the inflow and outflow segment resistances. Most vasoactive agents in the lung have been shown to act primarily on inflow or outflow resistance and to have minimal effects on the middle segment.[10,19] In preliminary experiments we found that hypoxia acted primarily to increase the middle segment re-

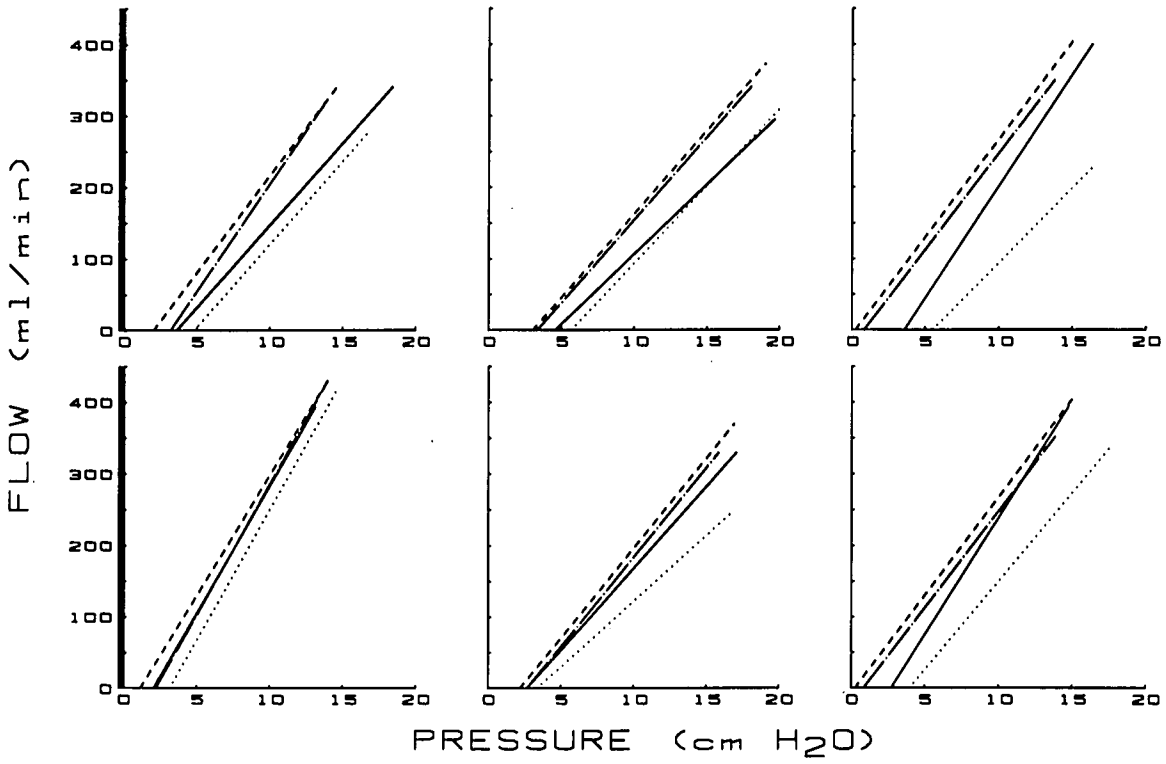

FIG. 2. This illustrates the relationship between pressure and flow for four ventilatory periods: Normoxia 1 (*solid line*), hypoxia 1 (*dotted line*), normoxia/halothane (*dashed line*), and hypoxia/halothane (*dashed and dotted line*). Each panel represents the linear regression for the four ventilatory periods in a single animal. The linear regression for normoxia$_1$ and hypoxia/halothane are superimposed in the first panel of the lower row. The correlation coefficient for each line was greater than 0.99 by linear regression ($P < 0.05$). Note that although the slopes of the lines tended to be similar, the zero-flow pressure intercepts tended to be different between the ventilatory periods. The intercepts (P_{CRIT}) in order from smallest to largest were normoxia/halothane, hypoxia/halothane, normoxia$_1$ and hypoxia$_1$.

sistance.[20] This was in keeping with prior observations by Hakim *et al.* in dogs[11] and cats,[13] and those of Rock *et al.* in pigs.[12] We hypothesized that halothane would be a nonspecific vasodilator and that it would antagonize the effects of hypoxia by decreasing resistance through all segments of the pulmonary vasculature.

We attempted to control other parameters that might alter resistance and thereby confound interpretation of our results. Lobar blood P_{CO_2}, *p*H, and hematocrits were similar between conditions. We allowed lobar venous *p*H to remain in an acidotic range (below 7.20) in order to potentially augment the strength of the hypoxic response.[21] Although it is possible that the H^+ ion is not responsible for the increased vasoconstriction seen with hypoxia and acidosis,[22] we allowed the acidosis to persist since, in any event, the level of acidemia was similar between the ventilatory periods. Lobar Pv_{O_2} varied between the different ventilatory periods. It was similar between the two hypoxic periods. The final normoxic ventilatory period had a lower Pv_{O_2} than the first two periods ventilated with 35% O_2. However, the values of Pv_{O_2} remained above 130 mmHg in every animal and was therefore unlikely to influence resistance. Inspired halothane concentrations were also similar between the normoxia/halothane and the hypoxia/halothane periods. Only temperature showed significant differences between periods and this was so small a difference (0.3° C) that it is unlikely to have any physiological significance. We prospectively set inflow and outflow pressures during vascular occlusions in zone 3 conditions for flow. This would ensure that vascular recruitment was similar between periods and that it did not influence our measured distribution of resistances.

Our model and calculations of resistance varied from that of Hakim *et al.* in several other details. They fixed flow and allowed driving pressure to vary with resistance. We do not believe that this difference in methodology was significant since Townsley *et al.*[23] could not find any differences in the subdivisions of resistance using either a constant flow or a constant pressure in vitro system. Of potentially greater significance was the manner in which the rapid arterial pressure change with occlusion (ΔPa) was calculated. Hakim *et al.*[10–13] have calculated ΔPa by fitting the slow arterial pressure curve to an exponential

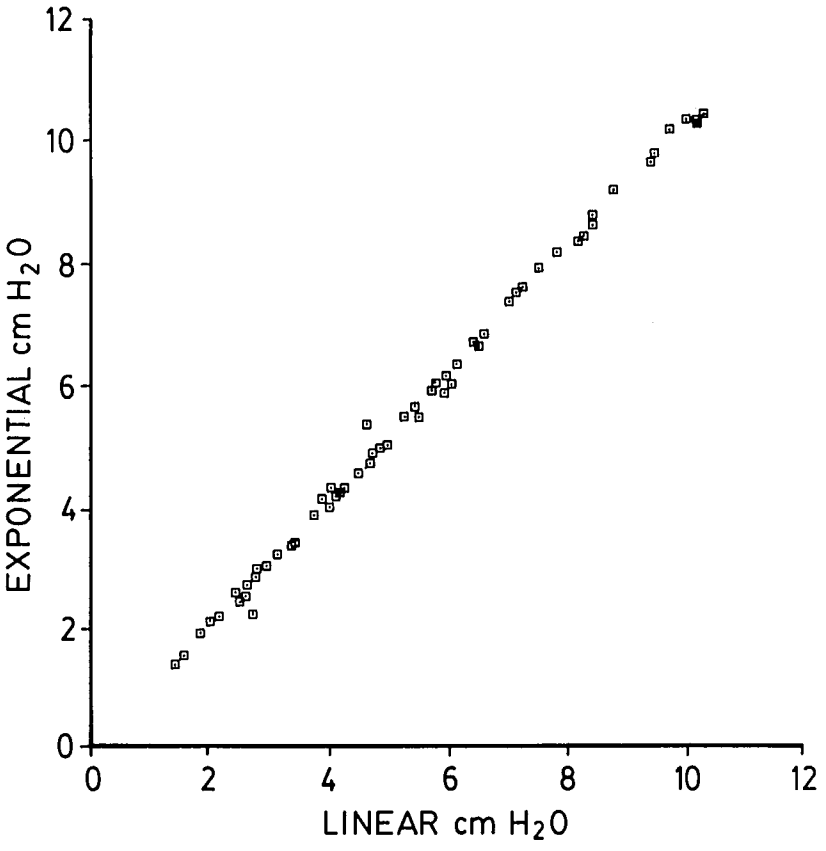

FIG. 3. This illustrates the relationship between the arterial pressure drop (ΔPa) calculated by fitting the slow pressure decrease to a linear (x axis) or to an exponential (y axis) function. The values of (ΔPa) are represented as pressures that were calculated from the digitized voltages collected on computer. The equation describing the linear relationship between these is (ΔPa) exp = 0.97*(ΔPa) lin −0.008 with r = 0.999. ΔPa exp (represented by squares in the figure) equals the rapid arterial pressure decrease calculated using an exponential function. ΔPa lin (represented by dots in the figure) equals the rapid arterial pressure decrease calculated using a linear function.

function by plotting the pressure fall on logarithmic paper and extrapolating the resultant curve to the instant of occlusion. ΔPa was then determined as the rapid fall in pressure to the point of intersection with the extrapolated slow-pressure curve. Rather than use an exponential function, we have calculated values of ΔPa by fitting a straight line to the slow arterial pressure decrease and extrapolated this linear curve back to the instant of occlusion. We are confident that this method closely approximates the values that would be obtained by using an exponential extrapolation. In preliminary experiments with the identical experimental model, using a data acquisition board (Isaac, Cyborg®) we had sampled the pressure signals of arterial occlusions at 300 Hz and stored the digitized data on computer (Compax). We then displayed the signals and fit each slow pressure decrease to both a linear and an exponential function. We then calculated ΔPa for 55 arterial occlusions using linear and exponential back extrapolation and found that ΔPa was accurately measured by a linear extrapolation when compared with exponential extrapolation. Figure 3 shows the relationship between values of ΔPa calculated by both linear and exponential extrapolation. The values are shown as pressures calculated from the voltages sampled by the data acquisition unit. There is excellent agreement between the two methods with the resultant equation having a slope of 0.97 and an r value greater than 0.99 by linear correlation. This implies that the slow arterial pressure decrease can be represented by a capacitor discharging through a resistor, but that the system has a very long-time constant. In this setting we believe that using a linear fit is much simpler and as reliable as the more cumbersome exponential fit method.

Total pulmonary vascular resistance was similar between all periods by ANOVA. Neither inflow segment resistance nor outflow segment resistance was significantly different between any of the ventilatory periods. Only middle segment resistance was different between ventilatory periods by ANOVA ($P < 0.01$) and this difference was related to the increased middle segment resistance seen during the hypoxia periods compared with the preceding normoxic periods. At the conclusion of the experiments, we repeated ventilation with a normoxic gas mixture followed by one final period of hypoxia. With this we were able to demonstrate that the lobes were still able to respond to hypoxia by increasing middle segment resistance. In order to decrease the variability in resistance values between dogs, we also analyzed the changes in resistance for each individual dog between the different ventilatory periods. We normalized resistance to the first

normoxia period and calculated subsequent resistance values as a percent change from this value. By this analysis we found that hypoxia caused an increase in total resistance from its baseline values. This was due to the large increase in middle segment resistance. We also found that during normoxia/halothane the normalized total resistance decreased from the normoxic baseline values. The middle segment resistance tended to decrease compared to normoxia$_2$ and this may account in part for reduction in total resistance. During hypoxic ventilation with halothane, the middle segment resistance returned back to its normoxic baseline values. This suggests that halothane preferentially causes a decrease in middle segment resistance under hypoxic conditions and that even under normoxic conditions halothane may cause a reduction in the middle segment resistance.

A complementary model of the pulmonary vasculature includes the further division of resistances into flow dependent and flow independent resistances.[12] Plotting the pressure-flow relationship of the pulmonary vasculature yields a component of resistance related to the slope of line (flow dependent) and a component of resistance related to the zero-flow pressure intercept (flow independent). The slope of the linear regression corresponds to the conductance to flow. The conductance to flow is the inverse of resistance. This resistance corresponds to the resistance to flow through a rigid pipe and is described by the Poiseuille equation.[24] The zero-flow pressure intercept (critical closing pressure) corresponds to a Starling resistor.[25] The pressure gradient through a rigid pipe increases with increasing flow. In distinction, once flow is established across a Starling resistor, the pressure gradient across the Starling resistor is constant and therefore it is independent of the flow. Similarly, once the critical closing pressure of the vascular bed is exceeded it no longer influences flow and is therefore considered flow independent.

We found that in zone 2 conditions for flow, the slopes of the relationship were similar during ventilation with all four gas mixtures. Neither hypoxia nor halothane appear to influence the flow-dependent portion of vascular resistance. With all four gas mixtures we measured the critical closing pressure to be greater than atmospheric pressure. The differences in resistance seen with hypoxia can be explained by a parallel shift of the pressure-flow lines. The effects of hypoxia in our experiments are similar to those observed by Sylvester *et al.*[26] in the isolated pig lung. Halothane caused the critical closing pressure to return to its baseline values. There was still an effect of hypoxia seen on the critical closing pressure, *i.e.*, P_{CRIT} tended to be higher in all animals during hypoxia/halothane compared with normoxia/halothane. This implies that at a concentration of 0.5%, halothane only partially antagonized the effects of hypoxia.

That halothane reduces critical closing pressure suggests that it acts to reduce tone in the vessels that set the level of the Starling resistor. Rock *et al.* have described a Starling resistor at the arterial end of the middle vascular segment.[12] Since our inflow and outflow resistances did not change but critical closing pressures did change, our results would also place the site of critical closure within the middle vascular segment. Therefore our data supports the hypothesis that hypoxia acts to increase the value of the Starling resistor and in turn halothane acts to decrease the value of the Starling resistor back toward its baseline levels. These results suggest that halothane does not act to dilate vessels but rather it acts specifically to cause a reduction in the tone of the Starling resistor with a resultant decrease in total pulmonary vascular resistance. Graham *et al.*[25] have hypothesized that the vessels responsible for the phenomenon of critical closure are the alveolar vessels. This would also situate the site of the Starling resistor within the middle segment.

In summary, we have confirmed that hypoxia tends to increase the critical closing pressure of the pulmonary vasculature. Halothane in the concentrations that we used antagonized the effects of hypoxia and returned the components of resistance back toward their baseline states. Our data also suggest that in the normoxic lobe, halothane can act to decrease pulmonary vascular resistance specifically by decreasing critical closing pressure. In both normoxic and hypoxic conditions, halothane does not appear to affect the flow dependent components of resistance.

The authors wish to thank Ms. T. Ekersly, Ms. J. Healy, and Ms. D. Lefaivre for technical and secretarial assistance, and Mr. B. R. Wiggs for the repeated measure analysis of variance, whose development of the computer program was supported by the Medical Research Council of Canada grant 7246.

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