

Insufflated Halothane Increases Venous Admixture Less Than Nitroprusside in Canine Atelectasis

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Although it generally is agreed that halothane is a pulmonary vasodilator, its effect on venous admixture and hypoxic pulmonary vasoconstriction are more controversial. The effects of 2.4% halothane on pulmonary vascular resistance and venous admixture were investigated in an isolated canine lobe made atelectatic. Halothane was administered by three different methods: insufflation, addition to the pulmonary artery blood through a bubble deoxygenator, or a combination of both techniques. Pulmonary vascular resistance was divided into arterial, venous, and middle segmental resistance by a vascular occlusion technique. Middle resistance increased with 3% O₂ ventilation (0.0238 ± 0.0092 cmH₂O · ml⁻¹ · min⁻¹) or after production of atelectasis (0.0225 ± 0.0074 cmH₂O · ml⁻¹ · min⁻¹), compared to control ventilation in the nonatelectatic lung (0.01 ± 0.0067 cmH₂O · ml⁻¹ · min⁻¹). Halothane by any delivery method variably decreased middle resistance, with increasing potency from addition of halothane through the bubble deoxygenator (0.0118 ± 0.0047 cmH₂O · ml⁻¹ · min⁻¹) to halothane insufflation (0.0072 ± 0.0058 cmH₂O · ml⁻¹ · min⁻¹), and finally to a combination of both techniques (0.0026 ± 0.0041 cmH₂O · ml⁻¹ · min⁻¹). In contrast to vascular resistance, venous admixture in the atelectatic ($8 \pm 5\%$) and nonatelectatic lobes ($7 \pm 4\%$) was increased with halothane insufflation ($11 \pm 4\%$), addition of halothane through the bubble deoxygenator ($26 \pm 16\%$), and a combination of both techniques ($22 \pm 13\%$). Compared to intravenous nitroprusside ($26 \pm 12\%$), halothane insufflation was less potent in increasing venous admixture when total pulmonary vascular resistances were of similar magnitude (0.0526 ± 0.0112 and 0.0484 ± 0.0088 cmH₂O · ml⁻¹ · min⁻¹, respectively). It was speculated that halothane insufflation decreases pulmonary vascular resistance in the atelectatic lobe by selectively vasodilating nonatelectatic vessels, thereby preserving hypoxic pulmonary vasoconstriction. (Key words: Anesthetics, volatile: halothane. Lung(s), circulation: hypoxic; vasoconstriction. Pulmonary vascular resistance.)

ANESTHESIA DECREASES pulmonary compliance, resulting in small airway closure with subsequent lung atelectasis.^{1,2} Atelectasis also can occur because of supine positioning or direct pulmonary compression. Despite these potential reasons for development of hypoxemia, intraoperative arterial blood oxygenation often is decreased only minimally.³ The mechanism to preserve arterial oxygenation may involve active vasoconstriction within small pulmonary vessels, which divert blood flow

away from atelectatic alveoli.⁴ If regional diversion of blood away from low ventilation units is dependent primarily on hypoxic pulmonary vasoconstriction, administration of vasodilating agents in the presence of regional lung hypoxia should increase venous admixture (\dot{Q}_{VA}/\dot{Q}_T) and subsequently further impair arterial oxygenation. A number of intravenous agents (e.g., nitroprusside, prostaglandin I₂, nitroglycerin) have been shown to increase \dot{Q}_{VA}/\dot{Q}_T in proportion to their inhibition of the hypoxic pressor response.⁵⁻¹¹ Similarly, halothane, which also impairs regional control of blood flow, may be expected to increase \dot{Q}_{VA}/\dot{Q}_T . Halothane, however, has been inconsistently shown to inhibit hypoxic pulmonary vasoconstriction in animal¹²⁻¹⁴ and human¹⁵ studies. Marshall and Marshall¹⁶ have speculated that this variability can be explained by the direct effects of halothane on cardiac output¹⁷ and mixed venous oxygen content ($P\bar{v}O_2$),¹⁸ which concurrently influence hypoxic pulmonary vasoconstriction.

Using an isolated lobe globally ventilated with 3% O₂, we have shown recently that halothane is a potent inhibitor of hypoxic pulmonary vasoconstriction when vascular recruitment and $P\bar{v}O_2$ are held constant.¹⁹ When hypoxic pulmonary vasoconstriction is augmented in the isolated lobe by producing patchy atelectasis,²⁰ however, halothane becomes a less potent inhibitor of hypoxic pulmonary vasoconstriction. We also found in the atelectatic lobe that the increase in \dot{Q}_{VA}/\dot{Q}_T was not proportional to the degree of vasodilation induced by halothane. We speculated that the inhibition of hypoxic pulmonary vasoconstriction induced by insufflated halothane was localized selectively to nonatelectatic alveoli, thereby preserving \dot{Q}_{VA}/\dot{Q}_T .

These experiments were designed to investigate the effects of halothane on pulmonary vascular resistance and \dot{Q}_{VA}/\dot{Q}_T in the atelectatic canine lobe when halothane was delivered to the lung by an air and blood route or by a blood route only. Halothane was administered either by airway insufflation or by being mixed directly with pulmonary artery blood through a bubble deoxygenator. In the same atelectatic lobes, the effects of halothane on \dot{Q}_{VA}/\dot{Q}_T and hypoxic pulmonary vasoconstriction also were compared to those of an intravenous vasodilator, nitroprusside. An isolated lobe was used to control other potentially confounding variables, such as changes in $P\bar{v}O_2$ or cardiac output.^{17,18} The isolated lobe also permits sequential occlusion of the pulmonary artery and vein, which is used to partition pulmonary vascular resistance into arterial, middle, and venous segmental resistances.²¹

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The effects of hypoxia and specific drug interactions then can be characterized more fully than they can in the intact animal.

Materials and Methods

ANIMAL PREPARATION

These studies were carried out with approval of the University Animal Care Committee. The surgical preparation of the isolated lobe has been described in detail elsewhere.²⁰ In brief, eight mongrel dogs weighing 20–30 kg were anesthetized with 25 mg/kg thiopental. After tracheal intubation, the lungs were ventilated (Harvard ventilator) with room air at a tidal volume of 20 ml/kg. A catheter was inserted into the abdominal aorta *via* the femoral artery for subsequent removal of blood and for drug administration. The left upper lobe was surgically removed to facilitate exposure of the left lower lobe. The left lower lobe artery and vein were dissected and cannulated. A #6 cuffed tracheal tube was inserted into the lobar bronchus through a bronchostomy. After the cannulae were inserted and the lobe isolated, the animals were killed by injection of supersaturated KCl (10 ml) solution. The cannulated lobe was left *in situ* within the thoracic cavity and was connected to an extracorporeal circuit. The lobe was perfused with 400 ml of phlebotomized autologous blood diluted to 500 ml with heparin (1,000 U) and normal saline. Pulmonary venous blood passively drained into a venous reservoir, was pumped by a roller pump through a heat exchanger, filter, and bubble deoxygenator (95% N₂, 5% CO₂), and then was returned to the arterial reservoir. The lobar bronchus was ventilated independent of the remainder of the lung by a second Harvard ventilator (tidal volume [V_t] = 150–200 ml), positive end-expiratory pressure (2 cmH₂O). To adjust lobar arterial pressure (Pa) and venous pressure (Pv), heights of the respective reservoirs were varied. Lobar Pa and Pv were measured at pressure ports near the arterial and venous cannulae, respectively. Airway pressure was measured with an air-phase transducer connected with low-compliance tubing to a port near the endobronchial tube. Before the experimental protocol was begun, at least 30 min was allowed for the preparation to stabilize, as assessed by a constant flow (\dot{Q}_L) over a 5-min period. Heparin (1,000 U) and 50% dextrose (1 ml, with glucose concentration maintained at 4–12 mM) were added to the circuit every 30 min.

CALCULATIONS

Using methodology similar to that described by Hakim *et al.*,²¹ total pulmonary vascular resistance (Rt) was divided into arterial segment resistance (Ra), middle segment resistance (Rm), and venous segment resistance (Rv). The pressure changes after a venous or arterial occlusion

were used to calculate the distribution of resistances.¹⁹ After an arterial occlusion, an initial rapid decrease in pressure (ΔP_a) followed by a slow decrease in pressure was recorded at the arterial pressure port. Similarly, after venous occlusion a rapid increase in venous pressure (ΔP_v), followed by a slow increase in pressure, was recorded. Total, arterial, venous, and middle resistances were calculated as follows: $R_t = (P_a - P_v)/\dot{Q}_L$, $R_a = \Delta P_a/\dot{Q}_L$, $R_v = \Delta P_v/\dot{Q}_L$, and $R_m = R_t - (R_a + R_v)$, respectively. Venous admixture through the lobe was calculated as follows: $\dot{Q}_{VA}/\dot{Q}_T = [Cc'_{O_2} - Cp_{vO_2}]/[Cc'_{O_2} - Cpa_{O_2}]$, where Cc'_{O_2} is the end-capillary O₂ content, Cp_{vO_2} is the lobar pulmonary venous O₂ content, and Cpa_{O_2} is the pulmonary arterial O₂ content. Oxygen saturations and hemoglobin concentrations in the arterial and venous blood were directly measured with an co-oximeter (OSM2, Radiometer, Copenhagen, Denmark). The alveolar gas equation²² was used to calculate PA_{O_2} ; PA_{O_2} and Pv_{O_2} were measured directly.

Halothane was measured with a gas chromatograph (model 5790, Hewlett-Packard, Boston, MA) with a ⁶³Ni electron-capture detector. A packed, coiled glass (1 m × 2 mm ID) filled with SP1200/15 H₃PO₄ coated on 100–120-mesh chromosorb W and connected to a packed column injector was used. The column oven was held constant at 70° C, injection port at 200° C, and detection at 300° C. The carrier gas was 5% methane in argon, with a flow rate of 20 ml/min. Peak height responses were recorded on an integrator (model 3390A, Hewlett-Packard). Halothane (Fluothane®, Ayerst Laboratories, Montreal, Quebec, Canada) was diluted in N-hexane to 10 mg/ml and stored as a stock solution at –20° C. Standard solutions of halothane in fresh whole blood were prepared daily by volumetric addition of the stock solution. Standard samples and unknown samples (100 μ l) were added to deionized water (100 μ l) and N-hexane (2 ml) in a Pyrex test tube capped with nonstick screw caps (Teflon, DuPont, Wilmington, DE). The tubes were tightly capped, mixed by vortex, and allowed to separate. Aliquots (1–2 μ l) of the N-hexane layer were directly injected into the gas chromatograph. At least 12 calibration standards at six different concentrations were measured daily along with spiked quality control samples (n = 6). Calibration curves were based on plotting of the peak height of halothane against the peak height of N-hexane. The resulting curve was fit to its best quadratic equation and used to estimate the concentration of halothane in the unknown and quality-control samples. Blood concentrations of halothane also were expressed in equivalent gas-phase partial pressures, corrected for temperature and barometric pressure.²³

EXPERIMENTAL PROTOCOL

After the stabilization period, baseline flow was set by adjustment of Pa to near 17 cmH₂O and Pv to 6 cmH₂O.

This ensured zone 3 conditions for flow during the remainder of the experiment. The lobes were ventilated initially for 10 min (fig. 1) with a control gas mixture (35% O₂, 7% CO₂, 58% N₂), followed by ventilation with a hypoxic gas mixture (3% O₂, 7% CO₂, 90% N₂). After these baseline ventilatory periods with control and hypoxic gas mixtures (period control and period hypoxia, respectively), the lobe was denitrogenated by ventilation with 100% O₂ for 10 min.²⁴ Sublobar atelectasis then was produced by introduction of steel ball bearings (4.5 mm diameter) into the left lobar bronchus.²⁵ The number of ball bearings introduced (range: 20–30) was titrated to decrease lobar P_{vO₂} by 20 mmHg from baseline. After introduction of the steel ball bearings, tidal volume was reduced by 0–50 ml to maintain peak inspiratory pressure similar to that measured during period control. After production of atelectasis, the lobes again were ventilated with control gas (period atelectasis 1).

Halothane (2.4%) then was administered to the lobe by insufflation to the airway (period insufflated halothane), added to the bubble deoxygenator gas (period deoxygenator-administered halothane) or a combination of both insufflated- and deoxygenator-administered halothane (period combined-administration halothane). The manner of administration of halothane to lobes was randomized from a number of preselected sequences to ensure that no method of delivery predominantly occurred first, second, or third. An Ohio vaporizer was used at a constant flow rate of 3 l/min to generate the 2.4% halothane delivered. After the randomized periods of halothane administration, the lobe was ventilated with the control gas without halothane (atelectasis 2), and measurements were made after 15 min of ventilation. Nitroprusside (5-mg bolus, followed by an 8-μg · kg⁻¹ · min⁻¹ infusion) then was administered intravenously to the lobe (period nitroprusside).

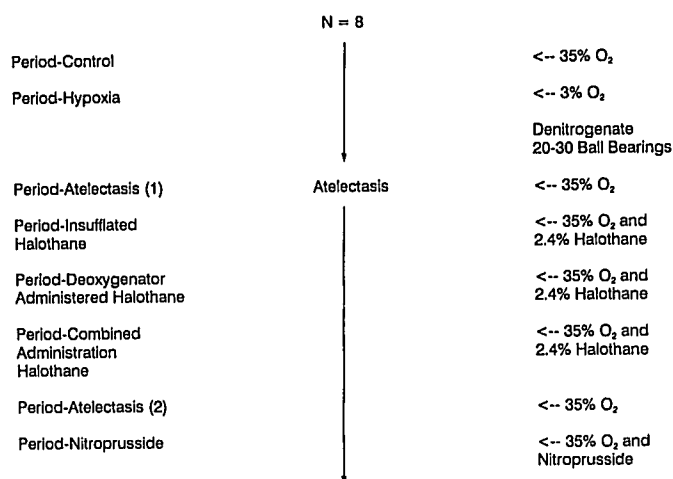


FIG. 1. The experimental protocol. Note that sufficient time was allowed for elimination of halothane before resistance measurements were made in period atelectasis (2).

Venous and arterial occlusions were performed in triplicate at the end of each ventilatory period. The occlusions were produced after the ventilator was stopped at end expiration. Immediately preceding the occlusion, blood was withdrawn from the arterial and venous cannulae for blood gas and hematocrit determination. Blood (5 ml) also was withdrawn for halothane-concentration determinations and placed within a Teflon-lined, capped glass tube. Blood gases were analyzed for P_{O₂}, P_{CO₂}, and pH at 37° C with appropriately calibrated electrodes (model 162-2, Corning) and then were corrected for blood reservoir temperature.²² Inspired and expired halothane concentrations in the airway gas as well as gas to the blood deoxygenator was measured continuously with a photoacoustics halothane detector (Brüel and Kjaer, Naerum, Denmark).

STATISTICS

Values of blood gases, inspired gases, and hemodynamic functions were compared between ventilatory periods with a one-way analysis of variance. When Scheffe's F statistic showed a significant difference, paired Student's *t*-tests were used to determine which groups were different. Because the requisite *t* value for significance increases with multiple comparison, were limited prospectively to no more than 7 of the possible 27 comparisons:

- Comparison A: period control *versus* period hypoxia
- Comparison B: period control *versus* period atelectasis 1
- Comparison C: period atelectasis 1 *versus* period insufflated halothane
- Comparison D: period atelectasis 1 *versus* period deoxygenator-administered halothane
- Comparison E: period atelectasis 1 *versus* period combined-administration halothane
- Comparison F: period atelectasis 1 *versus* period atelectasis 2
- Comparison G: period atelectasis 2 *versus* period nitroprusside.

Sidak's multiplicative inequality was used to correct for the number of comparisons made between groups.²⁶ Interactions between resistance and \dot{Q}_{VA}/\dot{Q}_T were evaluated with a linear regression analysis. A statistically significant difference was set at *P* < 0.05. Values are shown as mean plus or minus standard deviation.

Results

Analysis of variance showed no differences between periods in temperature (36.5 ± 0.6° to 37 ± 0.6° C), hematocrit (23 ± 2% to 24 ± 2%), hemoglobin (8.5 ± 1 to 9.4 ± 1 mg/dl), lobar P_{vCO₂} (45 ± 4 to 49 ± 4 mmHg), lobar Pa_{CO₂} (42 ± 4 to 47 ± 4 mmHg), lobar venous pH (7.23 ± 0.04 to 7.28 ± 0.04), lobar arterial pH (7.27 ± 0.05 to 7.31 ± 0.03), Pa (17 ± to 18 ± 1 cmH₂O), or

TABLE 1. Selected pH and Blood Gas Variables

	PpvO ₂ *	SpvO ₂	PpaO ₂	SpaO ₂	Q _{VA} /Q _T *
Control	177 ± 27	98 ± 1	43 ± 11	64 ± 17	7 ± 4
Hypoxia	42 ± 6†	61 ± 10†	41 ± 11	61 ± 17	—
Atelectasis (1)	145 ± 40†	97 ± 2	46 ± 11	67 ± 18	8 ± 5
Insufflated halothane	124 ± 35	97 ± 2	48 ± 9	72 ± 14	11 ± 4‡
Deoxygenator-administered halothane	107 ± 32‡	94 ± 5	51 ± 16	72 ± 12	26 ± 16‡
Combined-administration halothane	107 ± 32‡	94 ± 6	49 ± 13	71 ± 12	22 ± 13‡
Atelectasis (2)	145 ± 37	98 ± 2	41 ± 8	62 ± 14	6 ± 4
Nitroprusside	106 ± 29§	95 ± 5	49 ± 12	72 ± 15	26 ± 12§

PpvO₂ = lobar venous P_{O₂} (mmHg); SpvO₂ = venous saturation (%); PpaO₂ = lobar arterial P_{O₂} (mmHg); SpaO₂ = arterial saturation (%); and Q_{VA}/Q_T = venous admixture (%).

* Significance by ANOVA.

† Significant difference ($P < 0.05$) from period control.

‡ Significant difference ($P < 0.05$) comparing period atelectasis (1) to all other atelectatic periods with halothane administration.

§ Significant difference ($P < 0.05$) comparing period atelectasis (2) to period nitroprusside.

Pv ($5 \pm$ to 7 ± 2 cmH₂O). Table 1 illustrates values of lobar PaO₂ and PvO₂. Lobar PaO₂ and arterial O₂ saturation (SaO₂) were similar during all ventilatory periods. Lobar PvO₂ and venous O₂ saturation (SvO₂) were significantly greater during comparison B. As expected, PvO₂ and SvO₂ decreased significantly with the decreased inspired O₂ concentration during period hypoxia. SvO₂ was similar between all atelectatic periods, although PvO₂ was significantly less in comparisons D and E. PvO₂ also was significantly less after comparison G. During period hypoxia, mean values of saturation were the same between lobar arterial and venous blood, and therefore values of Q_{VA}/Q_T were not calculated. Induction of atelectasis did not significantly influence values of Q_{VA}/Q_T because these values were similar between period control and period atelectasis 1 ($P > 0.05$). Administration of halothane during comparisons C, D, and E caused increases in Q_{VA}/Q_T. Similarly, period 7 also caused significant increases in Q_{VA}/Q_T.

Table 2 illustrates measured values of halothane in blood and air during each period. As expected, halothane was not present in air or blood during period atelectasis 1. Inspired and expired gas concentrations of halothane were similar during periods insufflated halothane and combined-administration halothane. Halothane blood concentration was significantly higher during period combined-administration halothane compared to either period insufflated halothane or period deoxygenator-administered halothane. During period deoxygenator-administered halothane, low concentrations of halothane were measured in the expired gas and none was measured in the inspired gas. Venous halothane concentration during period deoxygenator-administered halothane was similar to arterial halothane concentration during period insufflated halothane. Arterial and venous halothane concentrations were similar during these same two periods, respectively. Expiratory halothane concentration was near zero during periods nitroprusside and atelectasis 2. There also was a barely detectable concentration of halo-

thane in either pulmonary arterial or venous blood during period atelectasis 2.

Table 3 illustrates values of pulmonary vascular resistance during all ventilatory periods. During comparisons A and B, Q_L was reduced significantly; it increased significantly during comparisons C, E, and G. Values of Rt, Rm, and Rv were significantly greater during comparison A. Values of Rt and Rm also were increased significantly during comparison B. Comparisons C, D, E, and G decreased both Rt and Rm. During all ventilatory periods, Ra was similar. During period nitroprusside, values of Rv were significantly lower than during period atelectasis 2.

The change in Q_{VA}/Q_T was compared with the change in Rt for each lobe by linear regression for periods insufflated halothane, deoxygenator-administered halothane, combined-administration halothane, and nitroprusside. Period atelectasis 1 was used as a baseline to calculate changes during periods insufflated halothane, deoxygenator-administered halothane, and combined administration halothane; atelectasis 2 was used as a baseline to calculate changes during period nitroprusside. By linear regression, only during period nitroprusside did the change in Q_{VA}/Q_T significantly correlate to the change in resistance ($R = -0.685$, $P < 0.05$). By linear regression, the change in Q_{VA}/Q_T was not related to the change in resistance (neither Rt nor any subdivision) during any other period.

Discussion

RATIONALE

The effects of halothane on hypoxic pulmonary vasoconstriction have yielded conflicting results.¹⁶ In animal studies directly measuring hypoxic pulmonary vasoconstriction and controlling cardiac output and P_{VO₂}, halothane has been found to inhibit hypoxic pulmonary vasoconstriction.^{11,14,19,20} In contrast, human studies using changes in oxygenation as an index of hypoxic pulmonary vasoconstriction have not universally found halothane to

TABLE 2. Inhaled and Blood Concentration of Halothane

	Halothane Inhaled	Halothane Expired	Halothane Arterial	Halothane Venous
Control	0	0	—	—
Hypoxia	0	0	—	—
Atelectasis (1)	0	0	0	0
Insufflated halothane	16.9 ± 1.4	16.9 ± 1.3	200 ± 48 (5.7 ± 1.4)	351 ± 42 (10.1 ± 1.2)
Deoxygenator-administered halothane	0	4.5 ± 0.45	302 ± 87 (8.7 ± 2.5)	193 ± 74 (5.5 ± 2.1)
Combined-administration halothane	17.8 ± 1.0	17.8 ± 0.9	469 ± 71 (13.4 ± 2.0)	482 ± 51 (13.8 ± 4.9)
Atelectasis (2)	0	0.8 ± 0.5	23 ± 24 (0.7 ± 0.7)	40 ± 23 (1.1 ± .7)
Nitroprusside	0	0.3 ± 0.5	—	—

Halothane contents are expressed in partial pressures (mmHg). Blood halothane contents (halothane arterial and halothane venous) were measured in micrograms per milliliter and converted to equivalent concentrations in the gas phase values (in parentheses) and expressed as partial pressures (mmHg). All measured values were significantly

different from all other periods except inhaled and expired halothane, which were similar in periods insufflated halothane and combined-administration halothane. Arterial and venous halothane blood contents also were similar in period insufflated halothane and deoxygenator-administered halothane.

be a potent inhibitor.¹⁵ In an attempt to explain this discrepancy, we used an isolated canine lobe exposed to halothane by either the blood or airway route. The isolated canine lobe allows for careful control of confounding variables during measurement of pulmonary vascular resistance and \dot{Q}_{VA}/\dot{Q}_T . The isolated lobe also allows halothane to be delivered through the airway or pulmonary artery in the absence of secondary neural and systemic humoral influences.

EXPERIMENTAL MODEL

Using the technique of vascular occlusions to obtain segmental resistance distribution, we characterized the pulmonary vascular response to halothane and nitroprusside in the atelectatic lobe. The segmental distribution of resistance allows a better description of the interactions of drugs with hypoxia.^{19,20} That is, the hypoxic pressor response is predominantly an increase in R_m ; therefore any drugs that directly alter hypoxic pulmonary vasoconstriction primarily should alter R_m . Previously, we described in detail our method of calculating the distribution

of resistances.^{19,20} Unlike our model, the model of Hakim *et al.*²¹ fixed flow and allowed driving pressure to vary with resistance. We do not believe that this methodologic difference is significant because the subdivisions of resistance are similar if measured with either a constant driving pressure or a constant flow system.²⁷ We prospectively controlled parameters that might independently affect pulmonary vascular resistance and thereby confound our results. The lobar perfusion pressure was similar during all ventilatory periods in each group; therefore neither changes in vascular recruitment nor vascular distension would influence our measurements.¹⁷ Similarly, Pa_{O_2} and Sa_{O_2} were maintained constant by the bubble deoxygenator and would not independently influence pulmonary vascular resistance.¹⁸ Factors such as pH, hematocrit, and temperature that might influence resistance also were similar among periods.

To potentially augment the strength of the hypoxic vascular response, we elected to maintain pH in a slightly acidotic range.²⁸ We maintained Pv_{O_2} and Sv_{O_2} high enough during all periods of control ventilation (greater

TABLE 3. Pulmonary Vascular Resistance and Subdivision Values

	Flow*	Rt*	Ra	Rm*	Rv*
Control	202 ± 7	0.0563 ± 0.0064	0.0101 ± 0.0032	0.0100 ± 0.0067	0.0271 ± 0.0048
Hypoxia	152 ± 13†	0.0857 ± 0.0099†	0.0180 ± 0.0053	0.0238 ± 0.0092†	0.0440 ± 0.0109†
Atelectasis (1)	166 ± 15†	0.0731 ± 0.0125†	0.0182 ± 0.0055	0.0225 ± 0.0074†	0.0315 ± 0.0112
Insufflated halothane	200 ± 20‡	0.0526 ± 0.0112‡	0.0185 ± 0.0046	0.0072 ± 0.0058‡	0.0269 ± 0.0076
Deoxygenator-administered halothane	179 ± 20	0.0628 ± 0.0131	0.0158 ± 0.0047	0.0118 ± 0.0047‡	0.0352 ± 0.0126
Combined-administration halothane	206 ± 27‡	0.0477 ± 0.0086‡	0.0168 ± 0.0053	0.0026 ± 0.0041‡	0.0278 ± 0.0135
Atelectasis (2)	158 ± 15	0.0782 ± 0.0136	0.0146 ± 0.0063	0.0236 ± 0.0092	0.0400 ± 0.0154
Nitroprusside	223 ± 29§	0.0484 ± 0.0088§	0.0156 ± 0.0031	0.0070 ± 0.0056§	0.0257 ± 0.0074§

All resistance measurements are in $\text{cm H}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{min}^{-1}$. Flow is measured in $\text{ml} \cdot \text{min}^{-1}$.

Rt = total resistance; Ra = arterial resistance; Rm = middle resistance; Rv = venous resistance.

* Significance by ANOVA.

† Significant difference ($P < 0.05$) from period control.

‡ Significant difference ($P < 0.05$) comparing period atelectasis (1) to all other atelectatic periods with halothane administration.

§ Significant difference ($P < 0.05$) comparing period atelectasis (2) to period nitroprusside.

than 100 mmHg and 90%, respectively, in every animal) such that P_{VO_2} should not have independently altered hypoxic pulmonary vasoconstriction and confounded our results. It also is unlikely that significant atelectasis was present in the control period, as demonstrated by a $PA_{O_2} - Pa_{O_2}$ gradient of less than 5 mmHg. The $PA_{O_2} - Pa_{O_2}$ gradient increased to more than 30 mmHg during the atelectatic periods. We also did not observe free reflux of edematous fluid into the airways during the experiment, another factor that can independently influence the distribution of resistances.²⁹ Finally, our anesthetic agent (pentobarbital) previously has been found not to affect pulmonary vascular resistance.³⁰ We therefore are confident that any differences in pulmonary vascular resistance were a direct consequence of the specific drug or route of drug administration.

Previously, we also described in detail our model of atelectasis.²⁰ Lee *et al.*,²⁵ using a multiple inert gas method, showed that introduction of steel balls of 4.8-mm diameter into the lower and middle lobes of dogs produces a bimodal pattern of ventilation/perfusion distribution. They found increased low ventilation/perfusion regions and increased intrapulmonary shunt after induction of atelectasis. We used a modification of this model of sublobar atelectasis to mimic the common clinical situation of patchy atelectasis found during surgery.¹⁻³ To minimize any effects of transmitted airway pressures on pulmonary vascular resistance, we adjusted tidal volume to maintain similar peak airway pressure throughout the experiment.²⁴ We decided prospectively that the degree of atelectasis would be standardized in every animal to produce at least a 20-mmHg decrease in P_{VO_2} from the initial control value. In this manner, we induced a standard and reproducible inhomogeneity of ventilation/perfusion. We expected that hypoxic pulmonary vasoconstriction would be a potent countervailing force that would optimize the ventilation/perfusion matching. From our previous experiments,²⁰ we found that pulmonary vascular resistance, its subdivisions, and hypoxic pulmonary vasoconstriction were constant throughout a protocol of similar duration to these current experiments. In these experiments, we also found that the lobe is stable and that values of resistance and \dot{Q}_{VA}/\dot{Q}_T did not change over time; *i.e.*, values were similar between periods atelectasis 1 and atelectasis 2.

We found that global hypoxia (hypoxic gas ventilation) or regional hypoxia (atelectasis) caused an increase in R_t and R_m . During hypoxic gas ventilation, R_v also was increased. These findings were similar to those of Hakim *et al.*²¹ More than 70% of the change in resistance could be attributed to the R_m with sublobar atelectasis. This suggests that our model of atelectasis stimulates regional hypoxic pulmonary vasoconstriction and is consistent with our previous observations using this same model.²⁰ Alternatively, local trauma induced by airway occlusion with

ball bearings may increase R_v by release of vasoactive mediators²⁵ such as histamine or serotonin. Such mediators, however, primarily increase R_a or R_v and have not been shown to result in significant changes in R_m .²¹ It also is unlikely that mechanical obstruction was a major factor increasing resistance in the atelectatic lung because this effect was reversibly diminished by use of vasodilators both in our model²⁰ and in others.³¹ Therefore we believe that stimulation of hypoxic pulmonary vasoconstriction is a more likely explanation for the increased pulmonary vascular resistance induced by atelectasis.

PULMONARY VASCULAR RESISTANCE AND VENOUS ADMIXTURE

As noted previously, in the normal isolated lobe, 0.5% halothane inhibits hypoxic pulmonary vasoconstriction,¹⁹ whereas in the atelectatic lung, only a higher concentration of halothane (2.3%) does so.²⁰ The present study confirms our previous findings^{19,20} that halothane specifically decreases R_t , exerting this effect on the middle vascular segment. In another study, we also showed that intravenous vasodilator nitroprusside is a more generalized vasodilator, decreasing both R_m and R_v .³² In the present study, the absolute magnitude of R_t and its subdivisions was similar in the halothane and nitroprusside periods, compared to the control atelectasis period most closely associated with halothane (*i.e.*, atelectasis 1) or nitroprusside (*i.e.*, atelectasis 2), however, we also demonstrated that R_v and R_m subdivisions decreased with nitroprusside, whereas only R_m decreased with halothane. To compare halothane (middle resistor vasodilation) and nitroprusside (middle and venous resistor vasodilation), it is more meaningful to compare changes in R_t . Although nitroprusside was our single chosen agent, we wished to illustrate a more generalized concept of the effects of intravenous vasodilators. The dose of nitroprusside was arbitrarily chosen to achieve a similar decrease in R_t to that observed with insufflated halothane.

The route of halothane administration did not alter its specificity for reduction of the middle vascular segment. The inhibition of hypoxic pulmonary vasoconstriction, as suggested by decreased R_m , occurred with halothane insufflation or with addition of halothane through the bubble deoxygenator. The potency of halothane as a vasodilator, however, was dependent on the route. Bjertnaes *et al.*³³ reported that the relative potency of halothane as an inhibitor of hypoxic pressor response *via* the alveolar, pulmonary artery, and pulmonary venous routes was 0.65, 0.25, 0.10, respectively. Our study confirms their results: we found that 2.4% insufflated halothane (alveolar route) decreased R_t to a greater degree than 2.4% halothane added to the bubble deoxygenator (pulmonary arterial route). This differentially increased potency of insufflated

halothane *versus* deoxygenator-administered halothane also may be noted in the values of R_m . We did not achieve a solely insufflated delivery of halothane because halothane concentration in the pulmonary artery was 60% of that found in the pulmonary vein. The same proportion was present with deoxygenator-administered halothane: pulmonary venous concentration was 60% of that found in the pulmonary artery. Thus, we were comparing the effects of halothane delivered by airway and blood routes during insufflation to that of halothane delivered by blood route during deoxygenator administration. The partial pressures of halothane in the alveoli during deoxygenator administration of halothane were low and, based on our previous experiments in the atelectatic isolated lobe, not likely to inhibit hypoxic pulmonary vasoconstriction.²⁰ Despite the greater decrease in resistance during insufflation, \dot{Q}_{VA}/\dot{Q}_T was less affected during this period. The changes in \dot{Q}_{VA}/\dot{Q}_T and R_t induced by halothane or nitroprusside are illustrated in figure 2. Nitroprusside administration resulted in the same magnitude of resistance change as did insufflated halothane administration, but it produced a greater increase in \dot{Q}_{VA}/\dot{Q}_T .

We speculate that halothane insufflation protects the lung from loss of hypoxic pulmonary vasoconstriction compared to that induced by intravenous administration of vasodilators. In any alveoli receiving ventilation, some halothane would enter and cause vasodilation. In atelectatic alveoli, assuming no collateral ventilation, only intravenous halothane would be present. Halothane is three or four times as potent in preventing hypoxic pulmonary vasoconstriction when administered by the alveolar route than by the pulmonary artery, and therefore atelectatic alveoli would tend to preserve their hypoxic pulmonary vasoconstriction. The selective vasodilation in nonatelectatic alveoli and relative preservation of hypoxic pulmonary vasoconstriction in atelectatic alveoli would result in smaller increases in \dot{Q}_{VA}/\dot{Q}_T than we would have expected otherwise. This is similar to the effects of oxygen itself, where alveolar oxygen modulates hypoxic pulmonary vasoconstriction to a much greater degree than does $P\bar{V}O_2$.¹⁷ Thus, there is discordance between the changes in resistance and the changes in \dot{Q}_{VA}/\dot{Q}_T induced by halothane. Alternately, the vasodilator potency of nitroprusside has been shown to increase if the initial resting tone of the pulmonary vessels is high.⁸ Therefore, the degree of vasodilation would be greatest in those atelectatic alveoli and would result in a greater increase in \dot{Q}_{VA}/\dot{Q}_T due to antagonism of hypoxic pulmonary vasoconstriction. This process would be analogous to emergence from anesthesia when intravenous *versus* alveolar concentrations of halothane are greater, as was noted in the deoxygenator-administered halothane period. We found that \dot{Q}_{VA}/\dot{Q}_T was of similar magnitude in the nitroprusside and deoxygenator-administered halothane periods

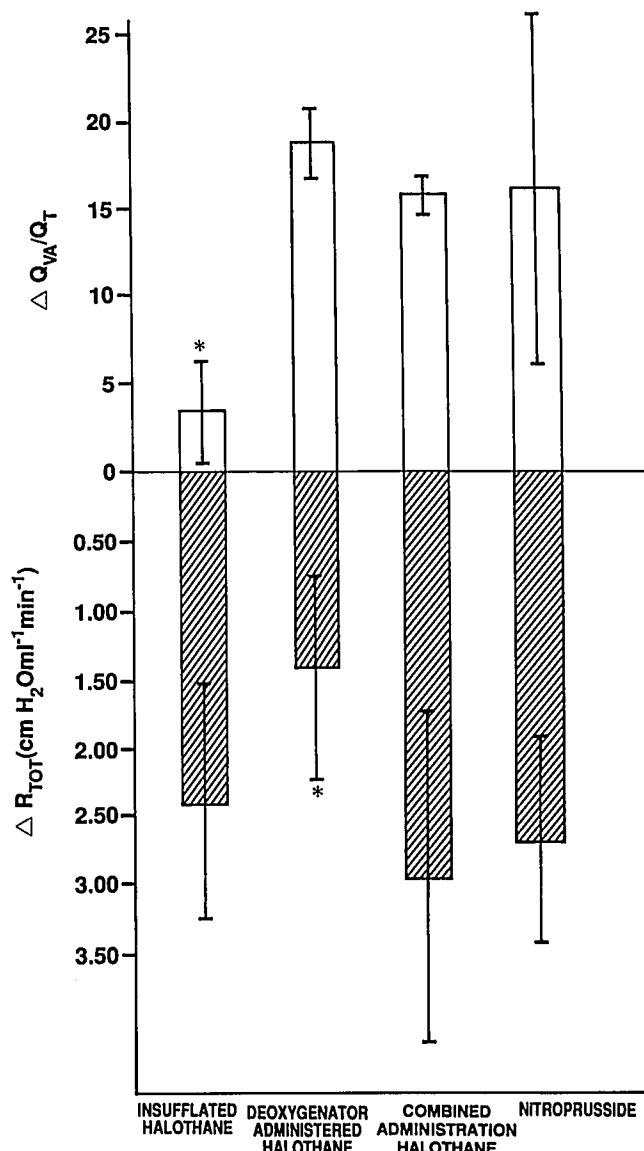


FIG. 2. The increases in venous admixture ($\Delta \dot{Q}_{VA}/\dot{Q}_T$, open bars) and the decreases in total resistance (ΔR_{TOT} hatched bars) during periods insufflated halothane, deoxygenator-administered halothane, and combined-administration halothane. The baseline values for calculation of changes were chosen from period atelectasis (1) except period nitroprusside, in which baseline changes were calculated from period atelectasis (2). Changes in \dot{Q}_{VA}/\dot{Q}_T and total resistance also are illustrated for period nitroprusside. *Significant difference ($P < 0.05$) from all other periods for values of \dot{Q}_{VA}/\dot{Q}_T or total resistance.

and postulate that the loss of hypoxic pulmonary vasoconstriction with intravenously delivered halothane and nitroprusside may be of more similar magnitude.

In summary, we have shown that halothane decreases pulmonary vascular resistance and increases \dot{Q}_{VA}/\dot{Q}_T in the atelectatic lobe. The potency of vasodilation by halothane is likely dependent on the route of delivery (air or blood route). When regional hypoxia stimulates pulmo-

nary vasoconstriction, insufflated halothane may act to minimize changes in \dot{Q}_{VA}/\dot{Q}_T compared to equipotent intravenous vasodilators such as nitroprusside. This discordance between pulmonary vascular resistance changes and \dot{Q}_{VA}/\dot{Q}_T changes due to selective vasodilation in nonatelectatic alveoli may explain the discordance in studies that use arterial oxygenation or \dot{Q}_{VA}/\dot{Q}_T to quantitate the loss of hypoxic pulmonary vasoconstriction with inhalational agents.

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