

# The Effects of Halothane and Cyclopropane on Total Pulmonary Resistance in the Dog

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The authors compared the effects of halothane and cyclopropane on total pulmonary resistance ( $R_L$ ) in dogs before (unstimulated) and during airway constriction produced by histamine or vagal nerve stimulation. In two dogs, direct measurements of airway diameter were obtained from bronchograms and compared with simultaneously obtained values of  $R_L$ . At equipotent concentrations halothane was the more potent dilator of both constricted and unstimulated airways. (Key words: Airway resistance; Bronchodilation; Halothane; Cyclopropane.)

STUDIES of the effects of halothane and cyclopropane on airway size have produced divergent results. Changes in airway size have been evaluated indirectly by measuring total pulmonary resistance ( $R_L$ ).  $R_L$  is the resistance to gas flow in the airway plus the viscous resistance associated with mechanical deformation of the lung. Resistance to flow is related inversely to airway size. Colgan<sup>1</sup> observed no change in  $R_L$  with the administration of 2.5 per cent halothane or 17 to 33 per cent cyclopropane to dogs lightly anesthetized with pentobarbital. In contrast, Klide and Aviado<sup>2</sup> found a progressive reduction in  $R_L$  in dogs as the inspired halothane concentration was increased from 0.5 to 3 per cent (15 to 30 mg/100 ml blood), and they interpreted

their findings as indicating that halothane is a bronchodilator.

Conflicting results have also been obtained in studies of the effects of halothane and cyclopropane on airways previously constricted by histamine or acetylcholine. In one study, cyclopropane, but not halothane, attenuated the bronchoconstrictive effect of histamine<sup>3</sup>; in another, halothane antagonized histamine-induced and acetylcholine-induced constriction of tracheal smooth muscle.<sup>4</sup>

Observed differences in anesthetic effects on airways may result from: (1) species variation; (2) comparison of isolated with intact preparations; (3) variability in resting airway tone; (4) simultaneous use of more than one anesthetic agent; and (5) variations in the method for determining  $R_L$ . Minimizing the factors that produce conflicting results, we compared the effects of halothane and cyclopropane alone and with chloralose on  $R_L$  in the intact dog. Measurements were made at constant respiratory flow rates before and after airway constriction produced by histamine or by stimulation of the vagal nerve. In two dogs anesthetized with halothane or cyclopropane,  $R_L$  was compared with direct measurements of airway diameter from bronchograms before and during vagal nerve stimulation.

## Methods

We performed experiments on 30 dogs weighing 10.6 to 13.6 kg. Anesthesia was induced with halothane or cyclopropane in oxygen, using a conventional circle system with CO<sub>2</sub> absorber or with intravenous chloralose (90 to 150 mg/kg). Oxygen inflow was 3 l/min in animals anesthetized with halothane or chloralose and 1.5 l/min in animals anesthetized with cyclopropane. These inflow rates were maintained for a minimum of two

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hours prior to the start of measurements. Ventilation was controlled with a ventilator\*\* to maintain arterial carbon dioxide partial pressure ( $P_{aCO_2}$ ) at about 40 torr. End-expired halothane concentration was determined with a Beckman LB-1 infrared halothane analyzer, sampling from a small catheter in the tracheostomy tube. A calibration curve for halothane was prepared as previously described.<sup>4</sup> End-expired cyclopropane concentration was taken as the difference in oxygen concentration from that observed during breathing of pure oxygen. Oxygen concentration was sampled from the tracheostomy tube during expiration with a Beckman Model D oxygen analyzer.

The effects of halothane and cyclopropane on  $R_L$  were compared at constant and equivalent depths of anesthesia using the concept of minimum alveolar (anesthetic) concentration (MAC).<sup>5</sup> In the dog MAC for halothane is 0.87 per cent; for cyclopropane, 17.5 per cent. A constant end-expired anesthetic concentration was established and held for a minimum of ten minutes before  $R_L$  was measured. In those animals anesthetized with halothane, the inspired end-tidal anesthetic partial pressure difference was less than 12 per cent throughout the ten-minute period.

$R_L$  was determined by measuring airflow and transpulmonary pressure ( $P_{TP}$ ) simultaneously and projecting these measurements in an X-Y display on an oscilloscope. We integrated airflow to obtain tidal volume and subtracted an electrical signal proportional to lung volume from  $P_{TP}$  to eliminate that portion of pressure due to elastic recoil (i.e., compliance pressure).<sup>6</sup> The slope of the resulting line is  $R_L$ .

Airflow was measured through a tracheostomy tube with a Fleisch pneumotachograph and a Satham PM15TC transducer. Flow was produced by a small bellows pump driven by an electrical motor or by a loudspeaker powered by a variable-frequency sine-wave generator. A sine-wave flow was produced with each of the two systems, and we maintained respiratory frequency and airflow constant in each animal. The pneumotachograph

was calibrated with a Fischer-Porter rotameter using oxygen. Since the flow signal from the pneumotachograph is dependent on viscosity, and since the relative viscosities of oxygen (0.02) and cyclopropane (0.0087) are dissimilar,<sup>7</sup> we prepared a calibration curve relating flow to cyclopropane concentration and corrected all flow values for differences in viscosity.

Transpulmonary pressure was measured with a Satham PM131TC as the difference between airway and intrapleural pressure. Airway pressure was measured with a 13-gauge needle inserted into the tracheostomy tube. Intrapleural pressure was obtained from a catheter inserted into a right mid-chest interspace.

To permit measurement of  $R_L$ , a three-way valve was turned to bypass the anesthetic apparatus and connect the dog's airway to the sine-wave generator.  $R_L$  was measured in duplicate at resting lung volume and the airway was then returned to the anesthetic circuit. Measurements were completed within a ten-second period.

Resistance of the tracheostomy tube and connecting tubing was subtracted from the value obtained, so the  $R_L$  reported is that of the animal only. Esophageal temperature was monitored and maintained between 35.8 and 38.9 C. We measured arterial blood  $P_{O_2}$ ,  $P_{CO_2}$ , and pH after induction of anesthesia and at least every two hours thereafter. Metabolic acidosis, if present, was treated by intravenous infusion of sodium bicarbonate.

Three types of experiments were performed to determine the effects of halothane and cyclopropane on resting airways and on airways constricted by histamine or vagal nerve stimulation:

#### RESTING (UNSTIMULATED) AIRWAY

$R_L$  was measured in eight dogs anesthetized with halothane (mean weight = 12.6 kg) and in 12 dogs anesthetized with cyclopropane (mean weight = 13 kg). Six dogs in each group had  $R_L$  measured at various anesthetic concentrations ranging from 0.5 to 2.4 MAC for halothane and 0.5 to 4.0 MAC for cyclopropane. In the remaining eight dogs,  $R_L$  was measured at one anesthetic concentration

\*\* Air Shields Ventimeter Ventilator, Hatboro, Pennsylvania.

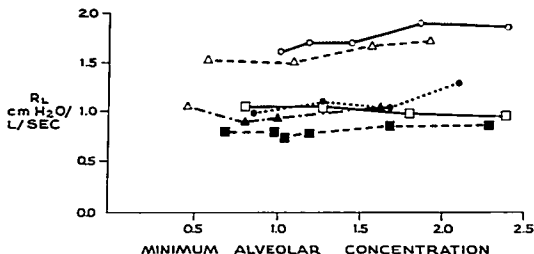


FIG. 1. Effects of halothane on  $R_L$  in six dogs. Levels of halothane anesthesia are shown as multiples of MAC.

only. Airflow from the sine-wave generator was held constant for each dog. Peak airflow for the group varied from 0.43 to 0.60 l/sec.

#### AIRWAY CONSTRICTED BY HISTAMINE

Effect of histamine on  $R_L$  was measured in five dogs anesthetized with halothane and six dogs anesthetized with cyclopropane. MAC ranged from 0.65 to 1.9 for halothane and from 0.6 to 2.9 for cyclopropane. Histamine, 125  $\mu$ g dissolved in 1 ml saline, was injected into a 3-ml catheter in a femoral vein and the catheter was rapidly flushed with 10 ml of saline.  $R_L$  was measured continuously for 90 seconds after injection, by which time the

maximum rise in  $R_L$  had occurred. Duplicate determinations were made when  $R_L$  had returned to prehistamine control for a minimum of five minutes. Changes in  $R_L$  induced by 50 and 250  $\mu$ g of histamine were also determined in three of the above animals anesthetized with halothane and three anesthetized with cyclopropane.

#### AIRWAY CONSTRICTED BY VAGAL NERVE STIMULATION

Under chloralose anesthesia, a bilateral cervical vagotomy was performed in each of 12 dogs, the distal end of the transected vagus nerves stimulated (10 to 12 volts; frequency,

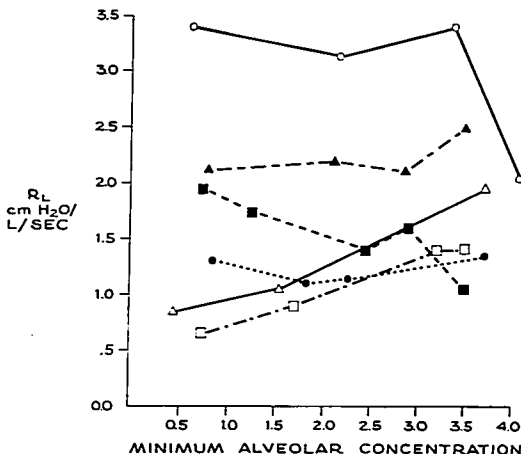
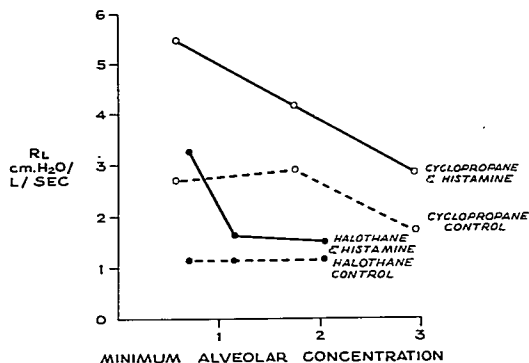


FIG. 2. Effects of cyclopropane on  $R_L$  in six dogs. Levels of cyclopropane anesthesia are shown as multiples of MAC.

FIG. 3. Effects of halothane and cyclopropane on the increase in  $R_L$  produced by 125  $\mu$ g histamine given intravenously. Anesthetic concentration is given in multiples of MAC. Closed circles are halothane; open circles are cyclopropane. Dashed lines indicate  $R_L$  measurements made prior to histamine administration; solid lines are  $R_L$  measurements made with histamine.



15 Hertz; duration, 3 msec) for 20 seconds and the resultant maximal increase in  $R_L$  measured. The inspired gas was then changed from pure oxygen to halothane-oxygen (six dogs) or cyclopropane-oxygen (six dogs) and  $R_L$  measured before and during vagal stimulation. These measurements were made at stable MAC multiples ranging from 0.1 to 2.3 for halothane and from 0.5 to 4.6 for cyclopropane. To exclude the effect of chloralose on the airway, two dogs were anesthetized with halothane and two dogs with cyclopropane and  $R_L$  determined before and after vagal nerve stimulation at several multiples of MAC. The anesthetic concentration was then lowered to about 0.6 MAC and the dogs were given chloralose (80 mg/kg) intravenously. Measurements of  $R_L$  were made at MAC values as low as 0.1 for halothane and 0.5 for cyclopropane.

In two additional dogs anesthetized with chloralose, airway diameter was measured directly from tantalum bronchograms<sup>8</sup> and compared with simultaneously-obtained values of  $R_L$ . Six airways ranging from 1.5 to 20 mm in diameter were measured prior to and during stimulation of the vagus nerve. These measurements were repeated during the inhalation of halothane (0.6 to 2.2 MAC) in one dog and during the inhalation of cyclopropane (0.8 to 3.1 MAC) in the second dog.

## Results

### RESTING (UNSTIMULATED) AIRWAY

Animals anesthetized with halothane had significantly lower  $R_L$  (mean  $1.1 \pm 0.3$  cm  $H_2O/l/sec$ ) than those anesthetized with cyclopropane (mean  $2.0 \pm 0.8$  cm  $H_2O/l/sec$ ) ( $P < 0.01$ ).  $R_L$  ranged from 0.7 to 1.9 cm  $H_2O/l/sec$  during halothane anesthesia (fig. 1) and from 0.6 to 3.4 cm  $H_2O/l/sec$  during cyclopropane anesthesia (fig. 2).  $R_L$  did not vary significantly with changes in anesthetic concentration for either agent ( $P > 0.5$ ).

### AIRWAY CONSTRICTED BY HISTAMINE

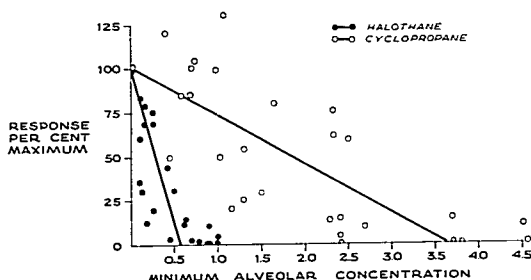
At 0.6 to 0.7 MAC, control  $R_L$  was lower in animals anesthetized with halothane than in animals anesthetized with cyclopropane.  $R_L$  measurements made prior to administration of histamine averaged 1.1 cm  $H_2O/l/sec$  for those dogs anesthetized with halothane and 2.2 cm  $H_2O/l/sec$  for those anesthetized with cyclopropane (fig. 3). After histamine 125  $\mu$ g intravenously, mean  $R_L$  increased to 3.2 cm  $H_2O/l/sec$  in the animals anesthetized with halothane and to 5.5 cm  $H_2O/l/sec$  in the animals anesthetized with cyclopropane (fig. 3). Increasing the concentration of either anesthetic antagonized the bronchoconstrictive effect of histamine, but at near-equivalent MAC values,  $R_L$  was always lower with halothane than with cyclopropane ( $P < 0.05$ ). Histamine dosages of 50 and 250  $\mu$ g changed

TABLE 1. Effects of Halothane and Cyclopropane on the Increase in  $R_L$  Produced by Electrical Stimulation of the Vagus Nerves

Dog	Halothane Concentration Vol Per Cent	$\Delta R_L^*$	Per Cent Max.†	Dog	Cyclopropane Concentration Vol Per Cent	$\Delta R_L^*$	Per Cent Max.
1	0.00	1.9	100	10	0	7.4	100
	0.15	1.5	78		18	3.6	49
	0.22	1.4	74		47	0.7	10
	0.40	0.7	37	11	0	7.5	100
	0.88	0.2	11		8	3.7	49
	1.40	0.0	0		20	1.4	20
2	0.00	5.2	100		40	1.0	13
	0.25	1.0	19	12	0	4.4	100
	0.58	0.1	2		8	5.0	120
	0.74	0.2	2		17	4.3	98
	0.88	0.0	0		41	3.3	75
	0.95	0.0	0	13	0	7.2	100
3	0.00	8.0	100		11	6.1	83
	0.16	1.0	12		29	5.7	79
	0.88	0.0	0		41	3.5	61
	1.92	0.0	0		81	0.7	10
4	0.00	5.2	100	14	0	2.4	100
	0.10	1.5	29		19	3.1	130
	0.60	0.6	12		26	0.6	28
	1.25	0.0	0		42	0.0	0
	1.35	0.4	8		67	0.0	0
5	0.00	5.1	100	15	0	2.3	100
	0.13	3.5	68		13	2.4	104
	0.22	3.5	68		43	1.4	59
	0.43	0.1	3		65	0.3	14
	1.10	0.0	0		81	0.0	0
7	0.00	4.6	100	16	0	5.7	100
	0.10	3.8	83		12	5.7	100
	1.05	1.0	22		23	3.1	54
	1.95	0.9	20		42	0.2	3
8	0.00	18.2	100		65	0.1	1
	0.10	10.1	59	17	0	2.9	100
	0.60	2.6	14		12	2.4	83
	1.00	3.2	18		23	0.7	25
	1.25	1.3	7		41	0.4	14
9	0.00	2.9	100		61	0.1	3
	0.15	1.0	35				
	0.46	0.9	31				
	0.97	0.1	4				
	1.52	0.4	14				

\*  $\Delta R_L$  is the increase in total lung resistance in  $\text{cm}/\text{H}_2\text{O}/\text{l}/\text{sec}$  produced by vagal nerve stimulation.† Per cent max. is the per cent of the maximum increase in  $R_L$  observed during vagal nerve stimulation when 100 per cent is defined as the increase in  $R_L$  during anesthesia with chloralose only.

FIG. 4. Effects of halothane and cyclopropane on the increase in  $R_L$  produced by electrical stimulation of the vagus nerves. Closed circles are halothane; open circles are cyclopropane. Anesthetic concentration is given in multiples of MAC. Response per cent maximum is defined in table 1. Regression lines for each agent were calculated by the method of least squares.



the degree of bronchoconstriction seen, but irrespective of histamine dosage,  $R_L$  was always lower in animals anesthetized with halothane than those anesthetized with cyclopropane.

#### AIRWAY CONSTRICTED BY VAGAL NERVE STIMULATION

Halothane at all anesthetic concentrations attenuated the increase in  $R_L$  that occurs with vagal nerve stimulation ( $P < 0.001$ ) (table 1). Cyclopropane did not alter significantly the airway response to vagal nerve stimulation until the mean concentration exceeded 19 per cent (1.1 MAC) (table 1). Comparison of the slopes of the regression lines for these two agents indicate that they are significantly different ( $P < 0.01$ ) (fig. 4).

Bronchograms confirmed that both anesthetics lessened bronchoconstriction induced by vagal nerve stimulation, but of the two agents, halothane was the more potent antagonist (figs. 5-8). Vagal stimulation decreased airway diameter by an average of 44 per cent during chloralose anesthesia, by an average of 38 per cent during chloralose anesthesia plus 0.8 MAC cyclopropane, and by 18.5 per cent during chloralose anesthesia plus 0.6 MAC halothane. These changes in diameter extended throughout all major airways.

#### Discussion

Essential to any study of anesthetic effect on airways is the determination of drug action on the stimulated (constricted) as well as the unstimulated airway. In both circumstances,

our study indicates that halothane is a more potent bronchodilator than cyclopropane. At equivalent multiples of MAC, mean  $R_L$  in the unstimulated airways of animals anesthetized with halothane was half the mean value obtained in similar animals anesthetized with cyclopropane. Likewise, halothane more effectively antagonized the bronchoconstrictive effects of histamine and vagal stimulation. At equivalent multiples of MAC (figs. 3 and 4) halothane was distinctly the more potent antagonist. Bronchographic studies with direct measurement of airway diameter confirmed the indirect (physiologic) evaluation of airway size by measurement of  $R_L$  (figs. 5-8). The tantalum bronchograms demonstrated that: 1) both anesthetics will prevent the severe bronchoconstriction of vagal nerve stimulation, but halothane is the more potent antagonist; and 2) the antagonistic actions of both anesthetics occur in both small and large airways.

Dissimilar lung volumes between the groups of dogs might explain the difference in  $R_L$  observed between halothane and cyclopropane in the unstimulated airway. However, mean body weights were similar in the two groups of dogs, hence resting lung volumes in the two groups would presumably be similar. Furthermore, recent evidence suggests that anesthesia, *per se*, does not alter end-expiratory lung volume appreciably.<sup>9</sup>

Differences in viscosity of inhaled gases, like changes in lung volume, will influence  $R_L$ . With laminar flow,  $R_L$  is directly proportional to viscosity, decreasing as viscosity decreases. Viscosity of cyclopropane is ap-

CONTROL,  $R_L$  0.9VAGAL STIMULATION,  $R_L$  17.8CONTROL,  $R_L$  0.6VAGAL STIMULATION,  $R_L$  2.6

FIG. 5 (above, left). Tantalum bronchograms and  $R_L$  measurements prior to (control) and during vagal nerve stimulation in one dog anesthetized with chloralose and breathing oxygen.

FIG. 6 (below, left). Effects of vagal nerve stimulation on airway size and  $R_L$  in the same dog shown in fig. 5 following the addition of halothane anesthesia to 0.6 MAC to the basal chloralose anesthesia.

proximately half that of air or oxygen. As the concentration of cyclopropane in the airway increases, viscosity decreases, thereby decreasing  $R_L$  even though airway dimensions remain constant. This would tend to minimize the differences in  $R_L$  between these two agents and thus oppose our findings. A decrease in viscosity also lowers the flow rate at which laminar flow changes to turbulent flow. With turbulent flow,  $R_L$  increases, although airway dimensions are unchanged. However, we found no evidence of turbulent flow in that we saw no change in pressure-flow slopes with increasing gas flow at any cyclopropane concentration.

Our observation that  $R_L$  did not change appreciably with increases in halothane concentration above 0.5 per cent differs from that of Klide and Aviado.<sup>2</sup> They found a mean reduction of  $R_L$  of 40 per cent in spontaneously-breathing dogs as the inspired halothane concentration was increased from 0.5 to 3.0 per cent. We question Klide and Aviado's interpretation of their results. They cited as evidence that halothane is a bronchodilator, the finding that as halothane concentration was increased, the slope of the pressure-flow loop increased and that transpulmonary pressure decreased at a constant air flow. In the one illustration of pressure-flow loops provided, Klide and Aviado report a 72 per cent reduction in  $R_L$  as the halothane concentration increased from 23.2 to 35.4 mg/100 ml blood. Examining their data, we found that the pressure-flow loops could be exactly superimposed on each other, and we propose that the slopes of these loops were not significantly different at different halothane concentrations.

The question whether halothane dilates the unstimulated airway of the dog is not answered by our study.  $R_L$  was low at the lowest halothane concentration studied and did not decrease as the halothane concentration was increased (fig. 1). We suggest that the unstimulated airway is fully dilated at 0.5 per cent, so that increasing the halothane

dose has no further effect on  $R_L$ . The marked reduction in  $R_L$  (50 per cent) observed with a low concentration of halothane (0.25 per cent) in the stimulated airway would support this conclusion (fig. 4).

Anesthetics probably act at multiple sites to affect airway size. Fletcher *et al.*<sup>3</sup> found that 10 mg/100 ml halothane in blood antagonized histamine-induced contraction of an isolated preparation of guinea pig tracheal chain. They concluded that halothane has a direct relaxed effect on tracheobronchial smooth muscle. We support this conclusion since we found that halothane antagonized the bronchoconstrictive effect of histamine in an intact preparation. However, severe hypocapnia may also produce bronchoconstriction, presumably by a direct effect on the airway.<sup>10</sup> Patterson and associates recently have demonstrated that halothane at airway concentrations ranging from 1.0 to 3.0 per cent was completely ineffective in reversing the bronchoconstriction of severe hypocapnia.<sup>11</sup> Why halothane was ineffective in this circumstance is unknown.

No studies of the effect of cyclopropane on histamine-induced constriction of isolated airway smooth muscle are available. Colgan<sup>12</sup> has shown that cyclopropane inhibits the effect of histamine on airways in the intact dog. Our study confirms his findings. The mechanism for cyclopropane inhibition of histamine-induced bronchoconstriction may be direct action on the smooth muscle, an unknown reflex mechanism, or, as suggested by Colgan, secondary to increased catecholamines liberated by cyclopropane. Whether cyclopropane changes pulmonary resistance from that found in unanesthetized dogs is not answered by this study.

### Conclusions

Comparison of the effects of halothane and cyclopropane on airway size by measurement of  $R_L$  and by direct measurement of the diameter of airways indicates that: (1) Dogs

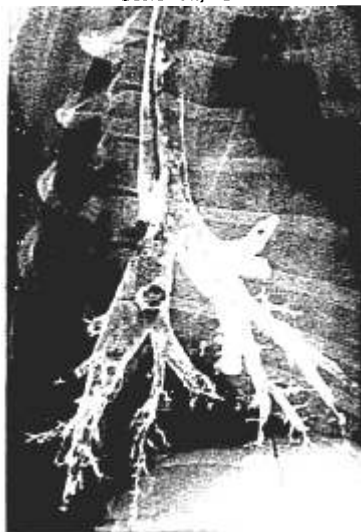
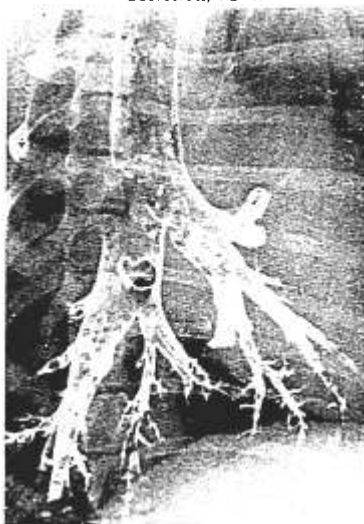
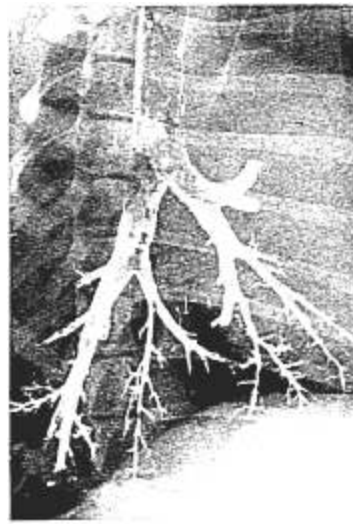
CONTROL, R<sub>L</sub> 0.9VAGAL STIMULATION, R<sub>L</sub> 13.9CONTROL, R<sub>L</sub> 0.9VAGAL STIMULATION, R<sub>L</sub> 6.6

FIG. 7 (above, left). Tantalum bronchograms and  $R_L$  measurement prior to (control) and during vagal nerve stimulation in an animal anesthetized with chloralose only.

FIG. 8 (below, left). Effect of vagal nerve stimulation on airway size and  $R_L$  in the same dog shown in fig. 7 following the addition of cyclopropane anesthesia to 0.8 MAC to the basal chloralose anesthesia.

anesthetized with halothane have a significantly lower  $R_L$  than those anesthetized with cyclopropane; (2) There is no correlation between the depth of halothane or of cyclopropane and  $R_L$  in concentrations ranging from 0.5 to 3.5 MAC; (3) Both anesthetics block neurally-mediated bronchoconstriction and the bronchoconstriction of direct-acting histamine. Halothane is the more potent antagonist.

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