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The Influence of Halothane and Isoflurane on Pulmonary Collateral Ventilation

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The effects of halothane and isoflurane on hypocapnic increases in pulmonary collateral resistance were studied in dogs. A bronchoscope with a double lumen catheter in the suction port obstructed a peripheral airway and allowed gas to flow out of the isolated segment of lung only via collateral channels. The collateral gas flow ($\dot{V}$coll) was measured with a flowmeter and delivered through one lumen of the catheter, while the other lumen measured distal pressure (P_b). At FRC, the resistance to collateral ventilation (Rcoll) was calculated as Rcoll = $P_b/\dot{V}$coll. The rest of the lung was ventilated with air, while air (hypocapnia), 10% CO_2 in air, or air and halothane or isoflurane were delivered to the isolated segment. A measurement of resistance was made after 4 min of test gas flow. For each segment, when air replaced 10% CO_2, the average increase in Rcoll was calculated and called R_{max}. When 10% CO_2 in air was infused into segments the mean Rcoll (n = 50) was 0.0196 ± 0.0022 $cmH_2O \cdot ml^{-1} \cdot min$. This increased to 0.0285 ± 0.0031 $cmH_2O \cdot ml^{-1} \cdot min$ (mean ± E) when air was infused, a mean increase in resistance of 52 ± 3%. When halothane or isoflurane was added to air the hypocapnic increase in Rcoll was attenuated with a 50% decrease at 1.3% (1.4 MAC and 0.8 MAC, respectively). These two inhalational anesthetics reduce active changes in the flow resistance to collateral ventilation. When collateral resistance acts to adjust ventilation perfusion deviations, this action of halothane and isoflurane may make this regulation less effective. (Key words: Anesthetics, volatile: halothane; isoflurane. Ventilation: collateral.)

PERIPHERAL AIRWAYS can allow respired gas to pass between contiguous lung segments under physiologic conditions. This collateral ventilation may pass through three types of channels: interalveolar pores of Kohn, bronchoalveolar communications of Lambert, and interbronchiolar connections discovered by Martin (fig. 1). Like small airways, these collateral channels increase their flow resistance with hypocapnia.[1,2] Halothane can reverse the increase in airway resistance seen with hypocapnia[3,4] but the effect of anesthetics on collateral resistance is unknown.

The response of collateral channels to changes in P_{CO_2} suggests that collateral channels may have a role in adjusting ventilation perfusion deviations from ideal. If inhalational anesthetics interfered with the normal responses of collateral channels, then the effectiveness of collateral ventilation could be affected by these drugs. The purpose of this study was to compare the effects of different doses of halothane and isoflurane on hypocapnia-induced increases in collateral resistance.

Methods

Sixteen female dogs, weighing 14–25 kg, were anesthetized with sodium pentobarbital (30 mg/kg). Ventilation was maintained with the use of a Harvard® piston ventilator through an endotracheal tube, and the tidal volume was adjusted to maintain an end-tidal CO_2 between 3 and 3.5% when the rate was between 10 and 12 breaths/min. The dogs were paralyzed with 0.1 mg/kg of pancuronium, and supplemental anesthetic and muscle relaxant were infused as required. Airway pressure was measured through a side arm of the endotracheal tube and systemic arterial pressure measured through a percutaneous femoral artery catheter.

Measurements of collateral ventilation were made according to the method of Menkes and Traystman.[5] A fiberoptic bronchoscope (Machida Co.), with an outside diameter of 5.5 mm, was introduced through a Portex® swivel adapter and passed peripherally in the lung under direct vision until it wedged in a subsegmental airway (fig. 1). The segment of lung thus isolated received ventilation only through the bronchoscope and collateral channels. A double lumen catheter (5F Swan-Ganz® cut off proximal to the balloon) was inserted into the suction channel of the bronchoscope until its tip approached the wedged end of the bronchoscope. One lumen of the catheter monitored pressure in the isolated segment (P_b), and the other was used to place a flow of a test gas into the isolated segment at a known constant flow ($\dot{V}$coll) via a flowmeter (Matheson Co.). To measure resistance to collateral ventilation, the ventilator was stopped at functional residual capacity (FRC). The segment pressure, P_b, then reached a steady state value

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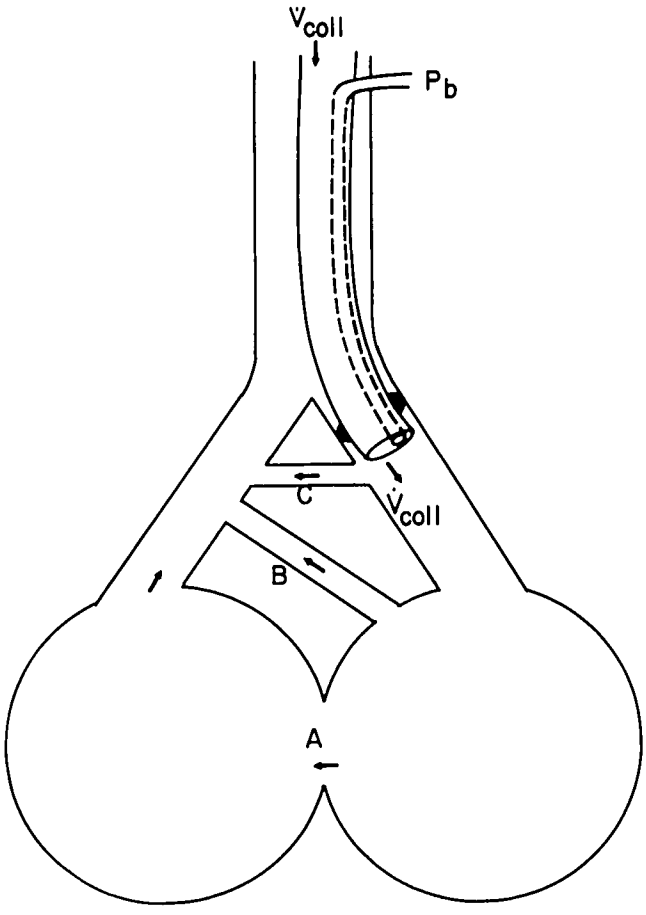

FIG. 1. Pathways for collateral ventilation. Diagram shows bronchoscope wedged into a lung segment with double lumen catheter in place. $\dot{V}$coll represents flow of gas into the isolated lung segment and P_b is distal pressure monitored through the catheter. The lettered pathways represent the different types of collateral airways: A = Interalveolar pores of Kohn; B = Bronchioalveolar communications of Lambert; C = Interbronchiolar channels of Martin.

above zero because of the continuing flow of test gas into the segment (fig. 2).

Experimental Design

Each dog was anesthetized on two occasions with two to four bronchoscope wedge positions per anesthetic. For each isolated segment, $\dot{V}$coll was adjusted so that the end-expiratory P_b with air was between 2.5 and 4 cmH_2O. $\dot{V}$coll ranged from 48 ml/min to 275 ml/min. Once the flow for a given wedge position was set, it remained constant for every test gas in that segment. The calibration of the flowmeter did not change with the gases used.

Each segment then was exposed to a series of test gases so that each segment served as its own control. After a baseline measurement with 10% CO_2 in air flowing into the isolated lung as $\dot{V}$coll, a series of three challenges with air (hypocapnia) and one with air and a randomized concentration of halothane or isoflurane in air were performed. Each challenge was bracketed by 10% CO_2 in air readings, and the anesthetic plus air was randomized between the second and third positions, so that a CO_2–air–CO_2 exposure occurred at the beginning and end of each segment's sequence. Each gas was infused at a constant $\dot{V}$coll for 4 min with measurements of Rcoll at that time. Anesthetic concentrations included: 0.4, 0.9, 1.7, and 2.6% halothane and 0.7, 1.5, 3.0, and 4.4% isoflurane where MAC in dogs = 0.87% for halothane and 1.48% for isoflurane.[6,7] At least five segments were obtained for each concentration of anesthetic.

The test gas passed through a Drager® vaporizer and was sampled continuously by a mass spectrometer (Perkin–Elmer® Model MGA 1100). Gas ($\dot{V}$coll) was sampled at each exposure and the anesthetic levels measured by gas chromatograph. Arterial blood was sampled 3 min after the start of each anesthetic trial and blood halothane or isoflurane concentrations assayed by the method of Butler *et al.*[8] Systemic arterial blood samples were obtained for each segment tested and analyzed for *p*H, P_{CO_2} and P_{O_2}.

Calculations

The driving pressure for collateral flow at FRC is $P_b - P_{alv}$ where P_{alv}, the pressure in the surrounding lung, is zero at FRC. This gradient reflects resistance to flow through collateral channels (Rcoll) as well as the resistance to flow through small airways (Rsaw) between the bronchoscope and the alveoli. We and other investigators[9,10] do not partition this resistance, because the small airway contribution to the total resistance is small. The results show the total resistance through the collateral system. Collateral resistance is calculated from Rcoll = $(P_b - P_{alv})/\dot{V}$coll where P_{alv} is zero at FRC.

In the sequence for each segment, there were five values for Rcoll with 10% CO_2 as the test gas, three values for Rcoll with air as the test gas, and one value for anesthetic plus air. These were ordered so there were three challenges with air, each bracketed by 10% CO_2 in air readings. The anesthetic in air challenge also was preceded and followed by 10% CO_2 in air values. Thus, a typical sequence would be 10% CO_2–air–10% CO_2–air–10% CO_2–air and halothane–10% CO_2–air–10% CO_2.

For each wedge position, the mean of the five Rcoll (10% CO_2) values and the mean of the three Rcoll (air) readings were calculated. These were the segment values for Rcoll for the two gases. The mean values for all segments in the halothane study (n = 26) and the isoflurane study (n = 24) are reported in the first two rows of tables 1 and 2 for the eight dogs in the halothane series and the eight dogs in the isoflurane study.

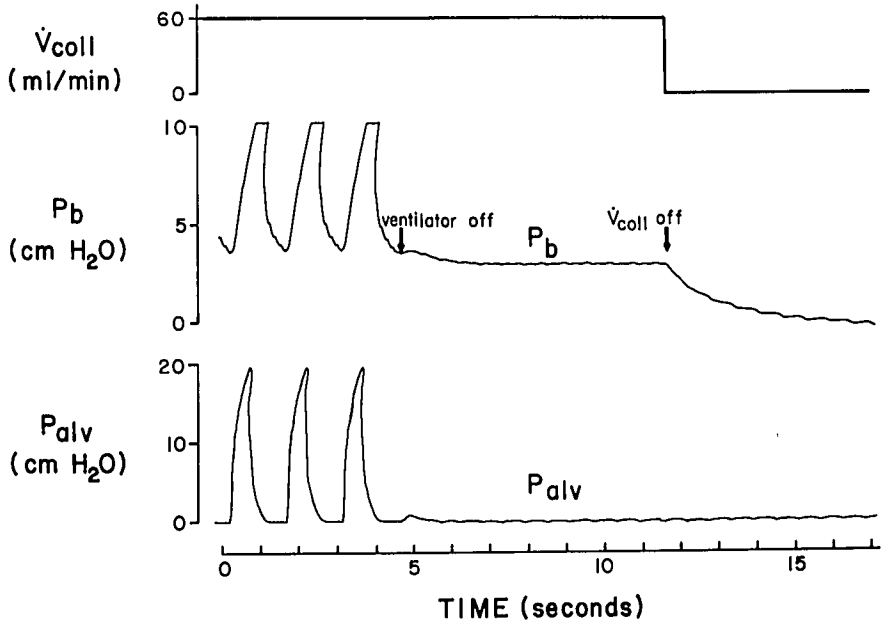

FIG. 2. Sample experimental record during a measurement of collateral resistance, showing V̇coll flow, distal pressure (P_b), and airway pressure (P_{alv}). After the ventilator is stopped, P_b plateaus. When the V̇coll is discontinued, P_b decays with time.

For each segment the average increase in collateral resistance with air (R_{max}) was calculated. Within each segment there were three trials with air as the test gas, a trial consisting of a 10% CO_2–air–10% CO_2 sequence. The mean Rcoll values for the two bracketing 10% CO_2 runs were calculated. Then, using the Rcoll value for air as the test gas, the percentage increase with air was calculated. Thus, three R_{max} values were generated for each segment, and their mean was the overall segment R_{max}. The anesthetic exposure of the segment (air plus halothane/isoflurane) also was bracketed by 10% CO_2 test gas so the percentage increase in Rcoll over baseline (R_{anes}) when anesthetic was present could be calculated in the same manner. Thus, the average percentage increase in Rcoll when air replaced 10% CO_2 (R_{max}) and the percentage increase when anesthetic plus air replaced 10% CO_2 (R_{anes}) was calculated. Therefore,

$$\frac{R_{anes}}{R_{max}} \times 100 = R_{\%max}$$

or the per cent of the maximum system response for each segment that was observed when anesthetic was present.

Linear regression analysis was used to construct dose–response curves for the four doses of each anesthetic drug.

Results

For the 50 lung segments tested, the systemic arterial pressure was 134 ± 3 mmHg (mean ± SE), the peak

TABLE 1. Effect of Halothane on Rcoll Increases with Hypocapnia (mean ± standard error)

Test Gas Composition	Rcoll ($cmH_2O \cdot ml^{-1} \cdot min$)	R_{max}	$R_{\%max}$
10% CO_2 in air (n = 26)	0.0135 ± 0.0017	—	—
Air (n = 26)	0.0196 ± 0.0021	53 ± 5	100
0.4% Halothane in air (0.5 MAC) (n = 7)	0.0170 ± 0.0023	—	76 ± 12
0.9% Halothane in air (1 MAC) (n = 7)	0.0240 ± 0.0055	—	65 ± 8
1.7% Halothane in air (2 MAC) (n = 6)	0.0132 ± 0.0038	—	43 ± 9
2.6% Halothane in air (3 MAC) (n = 6)	0.0116 ± 0.0027	—	25 ± 3

TABLE 2. Effect of Isoflurane on Rcoll Increases with Hypocapnia (mean ± standard error)

Test Gas Composition	Rcoll ($cmH_2O \cdot ml^{-1} \cdot min$)	R_{max}	$R_{\%max}$
10% CO_2 in air (n = 24)	0.0263 ± 0.0038	—	—
Air (n = 24)	0.0383 ± 0.0053	51 ± 4	100
0.7% Isoflurane in air (0.5 MAC) (n = 5)	0.0390 ± 0.0126	—	64 ± 9
1.5% Isoflurane in air (1 MAC) (n = 7)	0.0391 ± 0.0122	—	46 ± 7
3.0% Isoflurane in air (2 MAC) (n = 6)	0.0286 ± 0.0064	—	30 ± 5
4.4% Isoflurane in air (3 MAC) (n = 6)	0.0192 ± 0.0051	—	12 ± 5

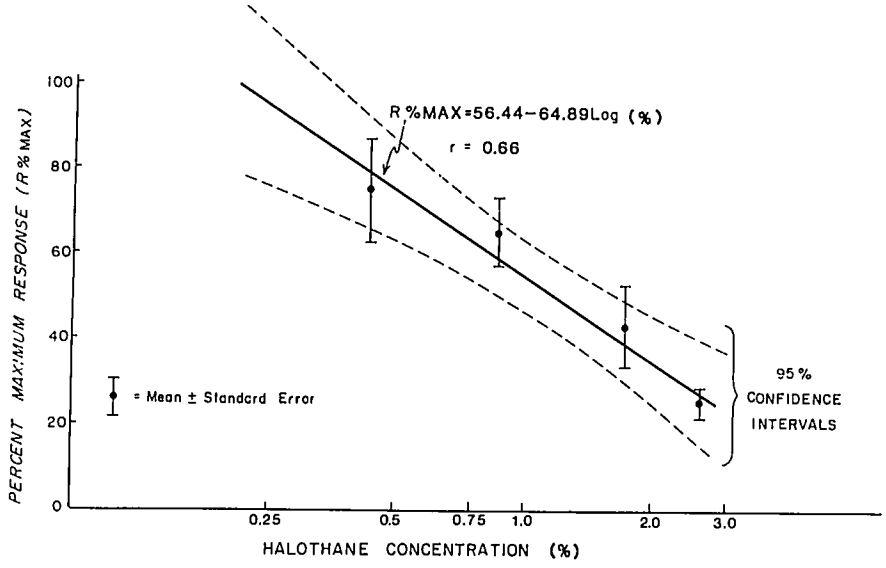

FIG. 3. Graph of data showing $R_{\%max}$ *versus* per cent halothane delivered to test segment on a log scale. As the halothane concentration increases, the $R_{\%max}$ decreases. Data points are mean ± SE. Ninety-five per cent confidence intervals and linear regression line are shown.

airway pressure was 14.3 ± 0.3 cmH_2O, the temperature was 37.2 ± 0.6° C, and the end-tidal CO_2 was 3.1 ± 0.1%. The Pa_{O_2} was 105 ± 3 mmHg, Pa_{CO_2} was 24 ± 1 mmHg, and the pH_a was 7.54 ± 0.01. The Pa_{CO_2} values during air alone and with 10% CO_2 administered to the test segment were not statistically different.

Previous studies, as well as this study, show a large variability in the values for Rcoll from segment to segment.[2,9] This occurs because segments of different sizes are obstructed and because of anatomic differences such as the location of the segment.[11] Decreased lung volume causes an increase in Rcoll.[12]

Segments used for the two anesthetic studies show different average values for resistances because the dogs used for the isoflurane series were smaller and therefore have smaller lung volumes distal to the wedged bronchoscope. The calculation of R_{max} for each segment normalizes the data for the effect of segment size variations. Thus, in spite of the differences in absolute numbers, the calculated R_{max} values for the halothane and isoflurane groups were (53 ± 5%) and (51 ± 4%), respectively.

Although the variability between segments for resistance values is large, we found that measurements within each segment were reproducible, and our study design used each segment as its own control. The baseline Rcoll, when 10% CO_2 was the test gas, was measured five times during each segment's sequence, and the mean coefficient of variation for the 50 segments studied was 7.0% ± 0.6 (mean ± SE). R_{max}, the maximum increase in resistance the system could generate (measured three times per segment), was more variable and the coefficient of variation was 22.7% ± 1.8 (mean ± SE).

When 10% CO_2 in air was infused into the segments, the mean Rcoll for the pooled data (n = 50) was 0.0196 ± 0.0022 $cmH_2O \cdot ml^{-1} \cdot min$ (mean ± SE). This value

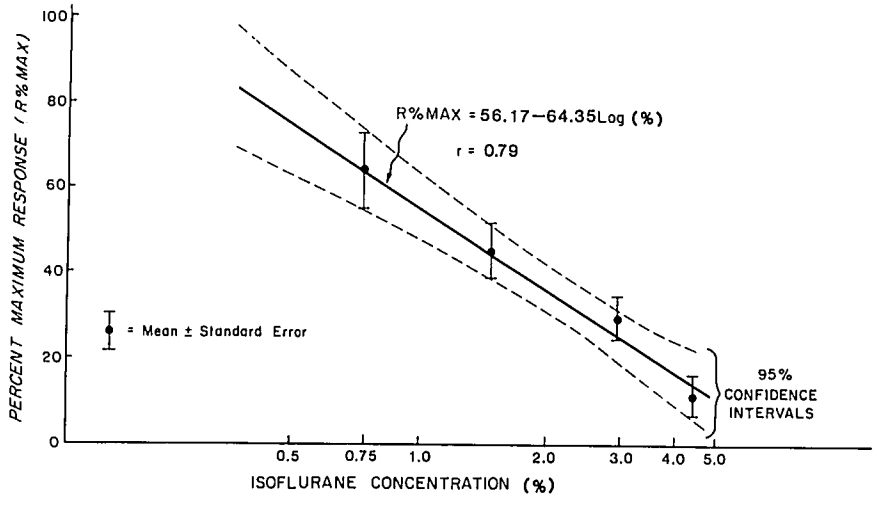

FIG. 4. Graph of data showing $R_{\%max}$ *versus* per cent isoflurane delivered to test segment on a log scale. As the isoflurane concentration increases, the increased resistance normally seen with air decreases.

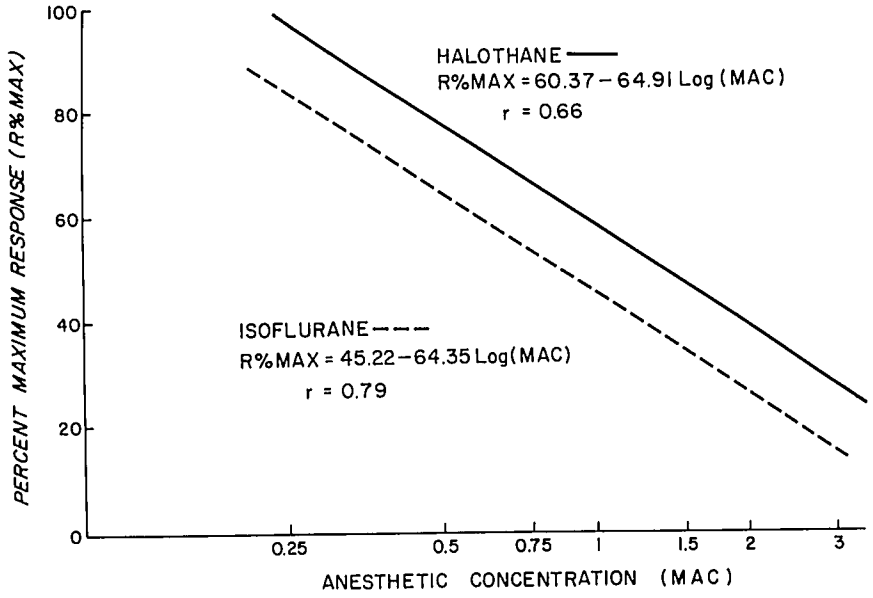

FIG. 5. Graph of data showing $R_{\%max}$ *versus* MAC of anesthetic on a log scale. The line for halothane is solid, the line for isoflurane is dashed.

increased to 0.0285 ± 0.0031 $cmH_2O \cdot ml^{-1} \cdot min$ when CO_2 in air was replaced by air and is significantly different at the $P < 0.05$ level. The mean percentage increase in Rcoll was 52 ± 3%. Tables 1 and 2 show the effect of halothane and isoflurane on collateral resistance. Each value in the tables represents the mean results of the values obtained four minutes after change of test gas. The initial values are pooled results from all air and 10% CO_2 measurements (three air challenges per segment bracketed by 10% CO_2). The Rcoll values for anesthesia are means for the group of segments exposed to the particular anesthetic concentration. $R_{\%max}$ is the percentage of R_{max} observed for each anesthetic exposure.

The dose–response curves for the effect of the four concentrations of the two anesthetics on the normal increase in collateral resistance are seen in figures 3 and 4. As the concentration of anesthetic delivered to the segment increased, the expected increase in resistance with air was attenuated with both drugs. The ED_{50} (the dose of drug necessary to observe only 50% of the expected maximum response) for halothane was 1.3% (1.4 MAC), with a confidence interval of 1.0–1.7%, and the isoflurane ED_{50} was 1.3% (0.8 MAC) (0.9–1.5%). The linear regression equations for the two anesthetics are essentially identical.

Figure 5 shows the drugs plotted together with the use of log MAC on the abscissa. Using analysis of covariance at the $P < 0.01$ level, the lines were not significantly different in their variances or slopes but did have different elevations, indicating that isoflurane was significantly more potent than halothane when compared by MAC levels.

Blood levels of halothane and isoflurane are shown in table 3. They document that the systemic levels of anesthetic were extremely low.

Discussion

This study has shown that halothane and isoflurane progressively can reduce the increase in collateral resistance normally seen with hypocapnia with the use of a segment occlusion technique in dogs. Dose–response curves were derived with an ED_{50} of approximately 1.3% (1.4 MAC for halothane and 0.8 MAC for isoflurane). Our data show that when $R_{\%max}$ is graphed *versus* the log dose in per cent, the curves from the two anesthetics are almost identical.

TABLE 3. Blood Levels of Anesthetics

	n	% Delivered	Blood Level (mmHg) (Mean ± SE)
Halothane			
0.5 MAC	6	0.4	0.102 ± 0.014
1.0 MAC	6	.9	0.150 ± 0.036
2.0 MAC	6	1.7	0.342 ± 0.043
3.0 MAC	6	2.6	0.372 ± 0.064
Isoflurane			
0.5 MAC	4	.7	0.192 ± 0.036
1.0 MAC	4	1.5	0.257 ± 0.050
2.0 MAC	4	3.0	0.456 ± 0.100
3.0 MAC	5	4.4	0.905 ± 0.135

The effect of inhalational anesthetics on collateral ventilation apparently has not been reported previously. One paper noted no difference in the values obtained when pentobarbital and chloralose were the anesthetic agents.[13]

Halothane and isoflurane attenuate the increase in collateral resistance with hypocapnia and make this regulation less effective. This effect is consistent with the reported action of halothane on airways. Although it has no effect on total pulmonary resistance in the unstimulated state, when increased bronchial tone is induced, halothane administration decreases the response. This effect has been shown with a variety of airway stimulants, including ascaris antigen and methacholine in greyhounds,[14] vagal stimulation, histamine,[3] and hypocapnia in isolated dog lobes,[4] as well as during cardiopulmonary bypass in humans.[15–17] Isoflurane also has been shown to reverse elevated airway resistance when ascaris antigen is the stimulus[14] and was not found to be significantly different from halothane. These drugs may be bronchodilators directly by relaxation of airway smooth muscle or indirectly by blocking airway reflexes, but little is known about direct effects of anesthetics on airways. Clinical concentrations of halothane do relax tracheal smooth muscle *in vitro,*[18] suggesting the bronchodilation due to halothane is at least partially due to a nonspecific direct effect on smooth muscle cells. In the present studies the anesthetics and CO_2 were acting locally on the airways, since systemic blood concentrations of the agent were extremely low, with the anesthetic delivered only to the segment tested. In this study, isoflurane was a more potent inhibitor of collateral airway constriction than halothane when compared according to clinical standards of potency (MAC) but was equipotent at the same per cent level. Since these two agents have identical dose–response curves, they appear to act in the same way, despite their different chemical structures.

Changes in collateral resistance, such as that seen with hypocapnia, may act in conjunction with hypoxic pulmonary vasoconstriction to actively reduce ventilation perfusion deviations from ideal and compensate for airway closure. The contribution of collateral ventilation to gas exchange in humans is unknown. However, in emphysematous lungs *in vivo,* it has been suggested that Rcoll is relatively less than in young healthy individuals,[19] indicating that collateral channels may be important ventilatory pathways in this disease state.

In summary, this study has demonstrated that halothane and isoflurane significantly reduce the resistance of collateral ventilation in dog lungs. A dose–response relationship was derived with an ED_{50} (dose to reduce response by 50%) of 1.3% for both agents.

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