The Influence of Halothane and Isoflurane on Pulmonary Collateral Ventilation

Christian M. Alexander, M.D.,* Linda Chen, M.D.,† Roberta Ray, M.B., Ch.B.,‡ Bryan E. Marshall, M.D., F.R.C.P.§

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 (Vcoll) was measured with a flowmeter and delivered through one lumen of the catheter, while the other lumen measured distal pressure (Pd). At FRC, the resistance to collateral ventilation (Rcoll) was calculated as Rcoll = Pd/Vcoll. The rest of the lung was ventilated with air, while air (hypocapnia), 10% CO2 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% CO2, the average increase in Rcoll was calculated and called Rmax. When 10% CO2 in air was infused into segments the mean Rcoll (n = 50) was 0.0196 ± 0.0022 cmH2O·ml⁻¹·min⁻¹. This increased to 0.0285 ± 0.0051 cmH2O·ml⁻¹·min⁻¹ (mean ± SD) when air was infused, a mean increase in resistance of 52 ± 8%. 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 but the effect of anesthetics on collateral resistance is unknown.

The response of collateral channels to changes in Pco2 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 CO2 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 (Pd), and the other was used to place a flow of test gas into the isolated segment at a known constant flow (Vcoll) via a flowmeter (Mathesafe Co.). To measure resistance to collateral ventilation, the ventilator was stopped at functional residual capacity (FRC). The segment pressure, Pd, then reached a steady state value.

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Calculated

The driving pressure for collateral flow at FRC is $P_b - P_{ab}$, where $P_{ab}$, 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 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 $R_{coll} = (P_b - P_{ab})/V_{coll}$ where $P_{ab}$ is zero at FRC.

In the sequence for each segment, there were five values for Rcoll with 10% CO₂ 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% CO₂ in air readings. The anesthetic in air challenge also was preceded and followed by 10% CO₂ in air values. Thus, a typical sequence would be 10% CO₂-air-10% CO₂-air-10% CO₂-air-10% CO₂-air-10% CO₂-air.

For each wedge position, the mean of the five Rcoll (10% CO₂) 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.
EFFECT OF ANESTHETICS ON COLLATERAL VENTILATION

Fig. 2. Sample experimental record during a measurement of collateral resistance, showing \( V_{coll} \) flow, distal pressure (\( P_b \)), and airway pressure (\( P_{alv} \)). After the ventilator is stopped, \( P_b \) plateaus. When the \( V_{coll} \) 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 \( R_{coll} \) values for the two bracketing 10% \( CO_2 \) runs were calculated. Then, using the \( R_{coll} \) 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 \( R_{coll} \) over baseline \( (R_{max}) \) when anesthetic was present could be calculated in the same manner. Thus, the average percentage increase in \( R_{coll} \) when air replaced 10% \( CO_2 \) \( (R_{max}) \) and the percentage increase when anesthetic plus air replaced 10% \( CO_2 \) \( (R_{max}) \) was calculated. Therefore,

\[
\frac{R_{max}}{R_{max}} \times 100 = R_{\%max}
\]

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

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**Table 1. Effect of Halothane on \( R_{coll} \) Increases with Hypocapnia**

(mean ± standard error)

<table>
<thead>
<tr>
<th>Test Gas Composition</th>
<th>( R_{coll} ) (cmHg·mL⁻¹·min⁻¹)</th>
<th>( R_{max} )</th>
<th>( R_{%max} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% ( CO_2 ) in air (( n = 26 ))</td>
<td>0.0185 ± 0.0017</td>
<td>53 ± 5</td>
<td>100</td>
</tr>
<tr>
<td>Air (( n = 26 ))</td>
<td>0.0196 ± 0.0021</td>
<td>76 ± 12</td>
<td>150</td>
</tr>
<tr>
<td>0.4% Halothane in air (0.5 MAC) (( n = 7 ))</td>
<td>0.0240 ± 0.0055</td>
<td>43 ± 9</td>
<td>110</td>
</tr>
<tr>
<td>0.9% Halothane in air (1 MAC) (( n = 7 ))</td>
<td>0.0240 ± 0.0055</td>
<td>43 ± 9</td>
<td>110</td>
</tr>
<tr>
<td>1.7% Halothane in air (2 MAC) (( n = 6 ))</td>
<td>0.0132 ± 0.0038</td>
<td>25 ± 3</td>
<td>100</td>
</tr>
<tr>
<td>2.6% Halothane in air (3 MAC) (( n = 6 ))</td>
<td>0.0116 ± 0.0027</td>
<td>25 ± 3</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 2. Effect of Isoflurane on \( R_{coll} \) Increases with Hypocapnia**

(mean ± standard error)

<table>
<thead>
<tr>
<th>Test Gas Composition</th>
<th>( R_{coll} ) (cmHg·mL⁻¹·min⁻¹)</th>
<th>( R_{max} )</th>
<th>( R_{%max} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% ( CO_2 ) in air (( n = 24 ))</td>
<td>0.0263 ± 0.0038</td>
<td>51 ± 4</td>
<td>100</td>
</tr>
<tr>
<td>Air (( n = 24 ))</td>
<td>0.0383 ± 0.0053</td>
<td>64 ± 9</td>
<td>100</td>
</tr>
<tr>
<td>0.7% Isoflurane in air (0.5 MAC) (( n = 5 ))</td>
<td>0.0390 ± 0.0126</td>
<td>46 ± 7</td>
<td>100</td>
</tr>
<tr>
<td>1.5% Isoflurane in air (1 MAC) (( n = 7 ))</td>
<td>0.0391 ± 0.0122</td>
<td>46 ± 7</td>
<td>100</td>
</tr>
<tr>
<td>3.0% Isoflurane in air (2 MAC) (( n = 6 ))</td>
<td>0.0286 ± 0.0064</td>
<td>30 ± 5</td>
<td>100</td>
</tr>
<tr>
<td>4.4% Isoflurane in air (3 MAC) (( n = 6 ))</td>
<td>0.0192 ± 0.0051</td>
<td>12 ± 5</td>
<td>100</td>
</tr>
</tbody>
</table>
Airway pressure was 14.3 ± 0.3 cmH₂O, the temperature was 37.2 ± 0.6°C, and the end-tidal CO₂ was 3.1 ± 0.1%. The \( P_{\text{aO}_2} \) was 105 ± 3 mmHg, \( P_{\text{aCO}_2} \) was 24 ± 1 mmHg, and the \( \text{pH} \) was 7.54 ± 0.01. The \( P_{\text{aCO}_2} \) values during air alone and with 10% CO₂ administered to the test segment were not statistically different.

Previous studies, as well as this study, show a large variability in the values for \( R_{\text{coll}} \) 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 \( R_{\text{coll}} \).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 \( R_{\text{max}} \) for each segment normalizes the data for the effect of segment size variations. Thus, in spite of the differences in absolute numbers, the calculated \( R_{\text{max}} \) values for the halothane and isoflurane groups were (55 ± 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 \( R_{\text{coll}} \), when 10% CO₂ 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). \( R_{\text{max}} \), 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% CO₂ in air was infused into the segments, the mean \( R_{\text{coll}} \) for the pooled data (n = 50) was 0.0196 ± 0.0022 cmH₂O · ml⁻¹ · min (mean ± SE). This value

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

**Fig. 4.** Graph of data showing \( R_{\text{max}} \) 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.
EFFECT OF ANESTHETICS ON COLLATERAL VENTILATION

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 $0.0285 \pm 0.0031$ cmH$_2$O $\cdot$ 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 $R_{coll}$ was $52 \pm 3\%$. 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 $R_{coll}$ 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

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>$n$</th>
<th>% Delivered</th>
<th>Blood Level (mmHg) (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 MAC</td>
<td>6</td>
<td>0.4</td>
<td>0.102 ± 0.014</td>
</tr>
<tr>
<td>1.0 MAC</td>
<td>6</td>
<td>0.9</td>
<td>0.150 ± 0.036</td>
</tr>
<tr>
<td>2.0 MAC</td>
<td>6</td>
<td>1.7</td>
<td>0.342 ± 0.043</td>
</tr>
<tr>
<td>3.0 MAC</td>
<td>6</td>
<td>2.6</td>
<td>0.372 ± 0.064</td>
</tr>
<tr>
<td>Isoflurane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 MAC</td>
<td>4</td>
<td>0.7</td>
<td>0.192 ± 0.036</td>
</tr>
<tr>
<td>1.0 MAC</td>
<td>4</td>
<td>1.5</td>
<td>0.257 ± 0.050</td>
</tr>
<tr>
<td>2.0 MAC</td>
<td>4</td>
<td>3.0</td>
<td>0.456 ± 0.100</td>
</tr>
<tr>
<td>3.0 MAC</td>
<td>5</td>
<td>4.4</td>
<td>0.905 ± 0.135</td>
</tr>
</tbody>
</table>
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.\textsuperscript{13}

Halothane and isoflurane attenuate the increase in collateral resistance with hypcapnia 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,\textsuperscript{14} vagal stimulation, histamine,\textsuperscript{3} and hypcapnia in isolated dog lobes,\textsuperscript{4} as well as during cardiopulmonary bypass in humans.\textsuperscript{15–17} Isoflurane also has been shown to reverse elevated arterial resistance when ascaris antigen is the stimulus\textsuperscript{14} and was not found to be significantly different from halothane. These drugs may be bronchodilators directly by relaxation of 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,\textsuperscript{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\textsubscript{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 hypcapnia, 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,\textsuperscript{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\textsubscript{50} (dose to reduce response by 50\%) of 1.3\% for both agents.

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References