General Anesthetics and Regional Hypoxic Pulmonary Vasoconstriction

James Mathers, M.D.,* Jonathan L. Benumof, M.D.† Eric A. Wahrenbrock, M.D.‡

Administration of N₂O, fluoxetine and isoflurane to the left lower lobe (LLL) of dogs anesthetized with pentobarbital was previously shown to inhibit LLL hypoxic pulmonary vasoconstriction (HPV). Using the same experimental model, the present study examined the effect of whole-lung administration of N₂O, fluoxetine, isoflurane, halothane, and enflurane on left-lower-lobe HPV. Selective ventilation of the LLL with N₂ alone caused blood flow to the lobe to decrease 53.3 ± 3.0 per cent. Responses to LLL hypoxia were remeasured during administration of inhalation anesthetics at 1 and 2 MAC to both the LLL and the rest of the lung. Isoflurane and fluoxetine progressively inhibited and at 2 MAC halved lobar HPV. N₂O (one third MAC) caused slight but significant inhibition, while halothane and enflurane caused slight and nonsignificant changes in lobar HPV. These effects of whole-lung administration of anesthetics on HPV were almost identical to those obtained when the administration was confined to the test lobe alone. It is concluded that N₂O, isoflurane, and fluoxetine locally inhibit regional HPV and via this mechanism increase total venous admixture, while halothane and enflurane do not have this effect. (Key words: Lung, hypoxic pulmonary vasoconstriction; Hypoxia, pulmonary vascular response; Anesthetics, volatile.)

Previously, we demonstrated that N₂O, fluoxetine and isoflurane inhibit lobar hypoxic pulmonary vasoconstriction (HPV) when administered locally to a hypoxic test lobe of lung. Since the administration of anesthetics was confined to the test lobe, only the direct effects of anesthetics on HPV were determined. The experimental design, therefore, precluded assessment of the net effect of anesthesia on the distribution of perfusion in abnormal lungs. It is possible that in the clinical circumstance, where the entire organism is anesthetized, changes in cardiac output, metabolic rate, and pulmonary vascular pressures and resistances might alter the impact of anesthetics on HPV. Accordingly, we have examined the effect of whole-lung administration of halothane, fluoxetine, isoflurane, enflurane, and N₂O on regional test lobe HPV.

Methods

Our experimental preparation has been described and is only summarized here. Twenty mongrel dogs, anesthetized with 25 mg/kg pentobarbital, were endotracheally intubated and ventilated by one side of a dual-piston pump with 100% O₂. Through a left fifth–sixth intercostal thoracotomy, electromagnetic flow probes (Statham SP7515) were placed on the main and left-lower-lobe (LLL) pulmonary arteries. Both flow probes had been calibrated in vivo with known blood flows in excised vessels. The flow probe on the main pulmonary artery was further calibrated by simultaneous thermal dilution curves obtained in vivo; the maximum deviation was less than 6 per cent. Pulmonary arterial and left atrial pressures were measured directly.

The left-lower-lobe bronchus was incised distal to a ligature and ventilated independently but synchronously with the remainder of the lung with 100 per cent O₂ by a second respirator pump. External deadspace and tidal volume were manipulated to produce airway pressures and end-tidal CO₂ concentrations (Beckman LB-2) that were the same in both ventilated compartments. The respiratory rate was adjusted to achieve a PAO₂ of 40 mm Hg. LLL end-tidal Pao2 was monitored continuously with a rapidly responding Clark electrode. Arterial and mixed venous blood oxygen contents were measured in duplicate by the Klingenmeier method. Oxygen consumption was calculated by use of the Fick equation.

In all dogs, after baseline measurements were made, while the animals were ventilated with 100 per cent O₂, the control LLL hypoxic response was obtained by selectively ventilating the LLL with N₂ alone. During LLL N₂ ventilation CO₂ was added to the inspired gases to keep LLL end-tidal CO₂ concentration reasonably constant. The rest of the lung was ventilated with 100 per cent O₂ at all times and minute ventilation was kept constant in both compartments. Since changes in cardiac output alter LLL blood flow, the control vasoconstriction response to LLL hypoxia was calculated as the maximum percentage decrease in the fraction of the cardiac output perfusing the LLL (per cent decrease QLLL/Q).

The experimental sequence was as follows: a) measure control LLL hypoxic response; b) return to 100 per cent O₂ ventilation of the LLL and administer one anesthetic drug until a random stable
and the rest of the lung to a different MAC multiple; e) retest LLL hypoxic response. Five dogs were used to study each anesthetic drug; the dogs used to study halothane were also used to study N₂O. The end-tidal concentrations that were assumed to equal 1 MAC have been described.¹ Statistical significance of results was analyzed by Student's paired t analysis.

Results

EFFECTS OF ANESTHETICS ON PULMONARY CIRCULATION AND METABOLISM

Table 1 summarizes changes in hemodynamic and metabolic variables as a function of anesthetic depth before LLL hypoxia was induced. Compared with control conditions (0 MAC), halothane, isoflurane and enflurane at the greatest dose level significantly decreased pulmonary arterial pressure (Pₐp), cardiac output (Q₀), and metabolic rate (Vₒ₂).

Since Q₀ decreased more than Vₒ₂ with these three drugs, the arteriovenous oxygen content difference C(a – v)ₒ₂ was significantly increased at the greatest dose level. Pulmonary vascular resistance (PVR) was slightly but statistically significantly decreased at the highest dose level with halothane, isoflurane and enflurane, but was insignificantly affected by fluroxene. Except for fluroxene, changes in left atrial pressure (PₐL) were variable and inconsistent. Fluroxene, on the other hand, significantly elevated Pₐp and PₐL but was without significant effect on Q₀, PVR, C(a – v)ₒ₂ and Vₒ₂. Administration of N₂O produced no significant change in any of the variables.

EFFECT OF ANESTHETICS ON HYPOXIC PULMONARY VASOCONSTRICTION

Figure 1 shows the LLL hypoxic response (per cent decrease Qₒₒ(L/L)/Qₒ) as a function of anesthetic

<table>
<thead>
<tr>
<th>MAC</th>
<th>Pulmonary Arterial Pressure (Pₐp) (mm Hg ± SE)</th>
<th>Left Atrial Pressure (PₐL) (mm Hg ± SE)</th>
<th>Cardiac Output (Q₀) (ml/min ± SE)</th>
<th>Pulmonary Vascular Resistance (PVR) (dyne sec · cm⁻² ± SE)</th>
<th>Arteriovenous Oxygen Content Difference C(a – v)ₒ₂ (Vol %)</th>
<th>Oxygen Consumption (Vₒ₂) (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane 0</td>
<td>14.0 ± 0.9</td>
<td>4.4 ± 0.8</td>
<td>1896 ± 244</td>
<td>407 ± 36</td>
<td>5.3 ± 0.3</td>
<td>93 ± 8</td>
</tr>
<tr>
<td>Halothane 1.0</td>
<td>11.9 ± 1.6*</td>
<td>6.0 ± 1.2</td>
<td>1480 ± 117*</td>
<td>391 ± 60</td>
<td>5.5 ± 0.4</td>
<td>93 ± 8</td>
</tr>
<tr>
<td>Halothane 2.0</td>
<td>10.2 ± 1.4*</td>
<td>5.7 ± 0.4</td>
<td>1156 ± 156*</td>
<td>359 ± 79*</td>
<td>7.4 ± 0.7*</td>
<td>70 ± 4*</td>
</tr>
<tr>
<td>Isoflurane 0</td>
<td>15.2 ± 0.3</td>
<td>7.3 ± 0.7</td>
<td>2035 ± 464</td>
<td>330 ± 59</td>
<td>6.1 ± 0.8</td>
<td>104 ± 10</td>
</tr>
<tr>
<td>Isoflurane 1.0</td>
<td>13.8 ± 0.5*</td>
<td>7.0 ± 1.1</td>
<td>1306 ± 429*</td>
<td>316 ± 44</td>
<td>6.8 ± 1.2</td>
<td>71 ± 9*</td>
</tr>
<tr>
<td>Isoflurane 2.0</td>
<td>12.0 ± 0.6*</td>
<td>8.4 ± 2.4</td>
<td>1000 ± 336*</td>
<td>264 ± 41*</td>
<td>8.7 ± 1.9*</td>
<td>62 ± 15*</td>
</tr>
<tr>
<td>Enflurane 0</td>
<td>15.3 ± 1.3</td>
<td>4.9 ± 0.9</td>
<td>2085 ± 266</td>
<td>353 ± 38</td>
<td>4.6 ± 0.3</td>
<td>103 ± 10</td>
</tr>
<tr>
<td>Enflurane 1.0</td>
<td>10.8 ± 0.4*</td>
<td>4.4 ± 0.4</td>
<td>1370 ± 75*</td>
<td>338 ± 18</td>
<td>5.3 ± 0.4</td>
<td>76 ± 10*</td>
</tr>
<tr>
<td>Enflurane 2.0</td>
<td>10.7 ± 1.0*</td>
<td>5.7 ± 0.7</td>
<td>1370 ± 265*</td>
<td>321 ± 36*</td>
<td>6.7 ± 0.3*</td>
<td>69 ± 12*</td>
</tr>
<tr>
<td>Fluroxene 0</td>
<td>12.6 ± 0.8</td>
<td>4.4 ± 1.2</td>
<td>1894 ± 122</td>
<td>431 ± 54</td>
<td>6.2 ± 0.4</td>
<td>99 ± 9</td>
</tr>
<tr>
<td>Fluroxene 1.0</td>
<td>16.6 ± 1.4*</td>
<td>7.3 ± 1.0*</td>
<td>1800 ± 89</td>
<td>432 ± 40</td>
<td>6.0 ± 0.4</td>
<td>108 ± 9</td>
</tr>
<tr>
<td>Fluroxene 2.0</td>
<td>16.4 ± 2.0*</td>
<td>8.2 ± 1.4*</td>
<td>1781 ± 97</td>
<td>306 ± 68</td>
<td>5.3 ± 0.3</td>
<td>95 ± 8</td>
</tr>
</tbody>
</table>

* P < 0.05 compared with control conditions (0 MAC).
depth. Isoflurane progressively inhibited the hypoxic response at each anesthetic level \( P < 0.02 \). Inhibition of HPV by isoflurane was maximal when \( C(a - \bar{V}_O) \) was also maximal (table 1). Fluoxetine progressively decreased LLL HPV, but the effect was statistically significant only at the 2 MAC level \( P < 0.01 \). Enflurane and halothane had no significant effect on LLL HPV. \( N_2O \) caused a small but significant \( P < 0.02 \) inhibition of the LLL hypoxic response.

Figure 2 shows the changes in \( P_{aO_2} \) during LLL hypoxia caused by the anesthetic drugs. The changes in \( P_{aO_2} \) paralleled the effects of the drugs on HPV and had the same statistical significances as the HPV changes. During the LLL hypoxic responses the regression equation relating \( P_{aO_2} \) to the hypoxic response was \( P_{aO_2} = 5.6(\text{hypoxic response}) - 4.0 \) with a correlation coefficient \( r = 0.73 \), which was significant \( P < 0.01 \).

**Discussion**

The principal findings of this study were that 1) halothane, isoflurane and enfurane decreased PVR; 2) fluoxetine and isoflurane progressively inhibited HPV in a dose-dependent manner; 3) the inhibition of HPV by isoflurane was maximal when the \( C(a - \bar{V}_O) \) was maximal; 4) the magnitude of the hypoxic response correlated well, but not precisely, with \( P_{aO_2} \). Consideration should be given to the mechanism and importance of these findings. Sources of variability and errors related to our methods and experimental model have been described.\(^{1,4}\)

**Fig. 2.** The arterial partial pressure of oxygen \( (P_{aO_2}) \) during left-lower-lobe hypoxia as a function of anesthetic concentration (MAC multiple).

**Fig. 3.** Left-lower-lobe (LLL) responses to hypoxia during selective LLL administration of anesthetic (dashed lines) compared with whole-lung administration of anesthetic (solid lines) (MAC multiple). Response to hypoxia was defined as in figure 1. All control responses were grouped to facilitate comparison.

**DECREASED PVR**

Halothane, isoflurane and enfurane all caused between 30–40 per cent decreases in \( Q_t \). Decreases in \( Q_t \) are normally accompanied by passive increases in PVR because \( Q_t \) decreases more than \( P_{aO_2} \). In our study, anesthetic depth caused a decreased \( Q_t \) accompanied by a slightly decreased PVR. Thus, the observed decrease in \( P_{aO_2} \) was slightly out of proportion to the decrease in \( Q_t \). This may represent anesthetically induced relaxation of normally present tone in the pulmonary circulation.

**ANESTHETICS AND HPV**

\( N_2O \), fluoxetine and isoflurane inhibited HPV. Previous studies from our laboratory,\(^1\) in which the administration of anesthetics was confined to the LLL, had similar results. Figure 3 compares the LLL response to hypoxia during LLL (dotted line)...
versus whole-lung administration (solid line) of anesthetic. Although enfurane was not previously studied, all control responses in the single-lobe anesthetic experiments (per cent decrease $Q_{\text{LL}}/Q_{\text{L}} = 55.5 \pm 2.0$) were close to all control responses in this experiment (per cent decrease $Q_{\text{LL}}/Q_{\text{L}} = 55.0 \pm 3.0$, enfurane excluded), and in order to facilitate the comparison we have grouped them together. The effects of the anesthetics on HPV are remarkably similar in the two circumstances. This suggests that the mechanism of inhibition is a local pharmacological one and may be the result of interference with any of the metabolic processes responsible for the production, activation, inactivation, or release of the mediator of HPV, or direct alteration of the contractile mechanism of smooth muscle.

**Inhibition of HPV and Metabolism**

Inhibition of HPV by isofurane occurred at an anesthetic concentration that increased the $C(a - v)_{\text{O}_2}$ ($V_{\text{O}_2}/Q_{\text{L}}$ increased). This is important because it magnifies the deleterious effects on oxygenation of the blood resulting from anesthetic inhibition of HPV. Thus, the blood shunted through the LLL contained less oxygen.

**Inhibition of HPV and $P_{\text{aO}_2}$**

The determinants of $P_{\text{aO}_2}$ during LLL hypoxia are the magnitude of HPV, the initial $P_{\text{aO}_2}$ before LLL hypoxia, and $P_{\text{vO}_2}$, during LLL hypoxia. The correlation between the response to hypoxia and $P_{\text{aO}_2}$ was good, but because the initial $P_{\text{aO}_2}$ and $P_{\text{vO}_2}$ during LLL hypoxia varied among individual dogs and from one anesthetic level to another and from one anesthetic group to another, the correlation coefficient was not closer to 1.

These findings are important for several reasons. First, inhibition of HPV by fluroxene and isofurane can be expected to aggravate ventilation–perfusion inequalities in anesthetized patients who have pre-existing pulmonary disease, as well as patients in whom ventilation–perfusion inequalities develop during or as a consequence of anesthesia and surgery. Second, inhibition of HPV by isofurane and inhibition by $N_2O$ are additive, and coupled with isofurane limitations on $C_v_{\text{O}_2}$ and $N_2O$ limitations on $F_{\text{O}_2}$, this combination might result in serious arterial hypoxemia. Third, these findings indicate that the anesthetics studied have only slight effects on PVR. Last, these findings also emphasize the importance of considering the effect of anesthetics on HPV in studies of total venous admixture during anesthesia.

**References**