Local Effects of Anesthetics on Regional Hypoxic Pulmonary Vasoconstriction

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The hypothesis that halogenated anesthetics and N₂O locally inhibit hypoxic pulmonary vasoconstriction (HPV) was tested. Selective ventilation of the left lower lobe of the lung with N₂ in dogs anesthetized with pentobarbital caused blood flow to the lobe to decrease 33.5 ± 2.0 per cent and lobar vascular resistance to increase 148 ± 8 per cent. Responses to hypoxia were remeasured during administration of various MAC multiples of inhalation anesthetics to the left lower lobe and following systemic administration of intravenous anesthetics. Isoflurane and fluoroxyne progressively inhibited and finally almost extinguished the vasoconstriction response as anesthetic concentration increased to 3 MAC. N₂O moderately diminished HPV. Halothane had little, and intravenous anesthetics had no significant effect on HPV. It is concluded that N₂O, isoflurane, and fluoroxyne locally inhibit regional HPV and via this mechanism may increase total venous admixture. (Key words: Lung, hypoxic pulmonary vasoconstriction; Hypoxia, pulmonary vascular response; Anesthetics, volatile.)

RESPIRATORY GAS EXCHANGE in the lung is determined by the relative amounts of ventilation and blood flow: Although the distribution of pulmonary blood flow is governed mainly by gravity, there is ample evidence in many species, including man, that alveolar oxygen concentration plays an important role in the matching of perfusion to ventilation at the alveolar level in abnormal lung. Decreased regional alveolar PₐO₂ causes regional pulmonary vasoconstriction, which diverts blood flow and so minimizes venous admixture from underventilated or nonventilated lung units. Drugs that inhibit regional hypoxic pulmonary vasoconstriction (HPV) might impair arterial oxygenation by permitting increased venous admixture from hypoxic or atelectatic areas of the lung. Indeed, intravenously administered pulmonary vasodilators, such as aminophylline and isoproterenol, reduce PₐO₂ in subjects with abnormal lungs. We suspected that anesthetic drugs might also diminish HPV, either by relaxation of preanesthetic hypoxic vasoconstriction or by inhibition of hypoxic vasoconstriction intraoperatively should conditions sufficient to induce HPV develop. In either instance, total venous admixture would be increased by the anesthetic drug.

We therefore investigated the effects of inhalational and intravenous anesthetics on HPV in dogs anesthetized with pentobarbital, and found that N₂O, isoflurane and fluoroxyne inhibited HPV, halothane had little effect, and thiopental, ketamine, meperidine, lidocaine and chlorpromazine had little effect. Anesthetics that depressed HPV caused substantial increases in total venous admixture (Q/O₂) and significantly reduced arterial oxygen tension.

Methods

Thirty-two mongrel dogs of either sex, weighing 12–24 kg, were each anesthetized with pentobarbital, 25 mg/kg, iv, paralyzed with 1 mg/kg gallamine, intubated with a cuffed endotracheal tube and ventilated with one side of a dual-piston Harvard respirator. Three additional dogs were anesthetized with fentanyl, 0.06 mg/kg, im, and droperidol, 3 mg/kg, im, and anesthesia was maintained with meperidine, 1 mg/kg, and gallamine, 1 mg/kg, iv, both repeated as needed. Catheters were placed in the femoral artery and inferior vena cava, and a Swan-Ganz catheter was positioned in the pulmonary artery. Following a thoracotomy through the left fifth and sixth intercostal space, a catheter was placed directly into the left atrium. Femoral and

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FIG. 1. Responses to left lower lobe (LLL) hypoxia. LLL blood flow (QLL) decreased when the LLL was made hypoxic. Total pulmonary blood flow (Q) and the pressures in the pulmonary artery (Ppa) and left atrium (Pia) changed only slightly. The change in LLL blood flow represents a decrease in QLL/Q from 20.6 to 9.8 per cent and an increase in the pulmonary vascular resistance of the LLL (PRLL) from 2,221 to 5,351 dynes·sec·cm\(^{-5}\).

The lung was achieved by manipulating tidal volumes and external deadspaces so that end-tidal CO\(_2\) concentrations (Beckman LB-2) and airway pressures (Statham transducers) were equal in the two airways. The CO\(_2\) analyzer head was filled with N\(_2\)O. Arterial P\(_{CO_2}\) levels of 40 mm Hg (SE = ± 2) were achieved by altering respiratory rate. Metabolic acidosis was controlled, when necessary by infusion of sodium bicarbonate to obtain pH = 7.38 (SE = ± .01) (Radiometer BMG-3). The expiratory hoes from both the LLL and the rest of the lung were immersed in water to maintain a positive end-expiratory pressure of 4 mm Hg.

The LLL end-tidal P\(_{CO_2}\) was monitored continuously with a rapidly responding Clark electrode maintained at body temperature by a warming coil. LLL end-tidal N\(_2\)O and concentration of halogenated anesthetic were measured with Beckman LB-2 infrared analyzers, which were calibrated frequently throughout the experiment with gas chromatographically determined concentrations of these agents. The N\(_2\)O analyzer head was filled with CO\(_2\).

Responses to hypoxia were measured before and after responses in the presence of inhalational anesthetics. Responses to hypoxia in the absence of anesthetics were induced by changing the ventilating gas mixture of the LLL from O\(_2\) and N\(_2\) (LLL P\(_{10}\), 160–200 mm Hg) to pure N\(_2\). The rest of the lung was ventilated with 100 per cent O\(_2\) at all times. To test the effect of N\(_2\)O, the LLL was ventilated with O\(_2\) and N\(_2\)O to obtain a LLL P\(_{10}\), between 160 and 200 mm Hg, but the hypoxic response was obtained with pure N\(_2\)O. To test the halogenated anesthetics, both individually and in combination with N\(_2\)O, the LLL was ventilated with halogenated agents, which were vaporized first in either O\(_2\) and N\(_2\) or O\(_2\) and N\(_2\)O, to obtain reasonably stable end-tidal concentrations of anesthetic which corresponded to various MAC multiples, and then in either pure N\(_2\) or N\(_2\)O. Expressed as a percentage of one atmosphere, we assumed 1 MAC for isoflurane equaled an end-tidal concentration of 1.5 per cent, for fluroxene, 6 per cent, for

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1 Joas, T., and Stevens, W. C., personal communication.
halothane, 0.9 per cent, and for N₂O, 180 per cent. When studied with N₂O, the concentration of halogenated anesthetic was reduced by an amount equivalent to the partial MAC of 70 per cent N₂O. Seven dogs were studied for each halogenated agent, and the effect of N₂O was studied in all dogs (n = 35).

We computed the response to hypoxia in two ways: first, as the maximum percentage reduction in the fraction of the cardiac output perfusing the LLL (per cent decrease QPLL/Qₘ) from its prehypoxic value; second, as the maximum percentage increase in the pulmonary vascular resistance of the LLL (per cent increase PVRPLL) from its prehypoxic value. All results were analyzed by Student's t test, with the test responses paired with the average of the corresponding before and after control responses.

Intravenous anesthetics were tested in six or seven dogs for each agent. Test responses in the presence of intravenous agents were measured subsequent to a control response as soon as pulmonary blood flows and blood pressures had stabilized following as rapid an intravenous administration as the animal's condition would permit. Pentobarbital, 100 mg, iv, was tested in the three dogs anesthetized with fentanyl, droperidol and meperidine.

After instrumentation, the experimental period required approximately four hours. Rectal or esophageal temperature was monitored and maintained at 37 ± 2°C with a heat lamp and a warming blanket, and pulmonary vascular pressures were maintained within normal limits by the appropriate infusion of fluids. Anesthesia was maintained with pentobarbital when the dog showed signs of inadequate anesthesia, and gallamine was given to suppress spontaneous respiration. The dogs were studied in the supine position.

**Results**

**INDIVIDUAL LLL HYPOXIA-RESPONSE CURVE AND AVERAGE HEMODYNAMIC DATA**

Figure 1 is an example of a typical reduction in LLL blood flow when the lobe was made hypoxic by ventilating with N₂ alone. The response, which consisted of a 52.5 per cent decrease in QPLL/Qₘ and a 141 per cent increase in PVRPLL, was first detectable at an LLL PA₉₅ of 100 mm Hg, reached its maximum by seven minutes, and remained stable thereafter. The rate of change in the LLL blood flow was identical to that in a previous study in dogs.

Table 1 shows the average pulmonary vascular pressures, and the various compartmental flows and resistances and their percentage changes, for all the control responses (n = 255) in this study. LLL hypoxia

**Table 1. Pulmonary Vascular Pressures, Flows, and Resistances during Left-lower-lobe (LLL) Normoxia and Hypoxia Produced by Ventilating the LLL with N₂**

<table>
<thead>
<tr>
<th>Variables</th>
<th>LLL Normoxia</th>
<th>LLL Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>P₉₅, mm Hg ± SE</td>
<td>16.3 ± 0.3</td>
<td>16.7 ± 0.3†</td>
</tr>
<tr>
<td>P₉₅, mm Hg ± SE</td>
<td>5.9 ± 0.2</td>
<td>5.6 ± 0.2†</td>
</tr>
<tr>
<td>QPLL, ml/min ± SE</td>
<td>331 ± 11</td>
<td>144 ± 6†</td>
</tr>
<tr>
<td>Qₘ, ml/min ± SE</td>
<td>1,588 ± 58</td>
<td>1,541 ± 58†</td>
</tr>
<tr>
<td>QPLL, ml/min ± SE</td>
<td>1,256 ± 48</td>
<td>1,392 ± 54†</td>
</tr>
<tr>
<td>QPLL/Qₘ, per cent ± SE</td>
<td>30.9 ± 0.3</td>
<td>9.3 ± 0.2†</td>
</tr>
<tr>
<td>Per cent decrease, QPLL/Qₘ ± SE</td>
<td>55.5 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>PVRPLL, dynes·sec/cm² ± SE</td>
<td>2,507 ± 57</td>
<td>6,207 ± 8†</td>
</tr>
<tr>
<td>Per cent increase, PVRPLL ± SE</td>
<td>148 ± 8</td>
<td></td>
</tr>
<tr>
<td>PVR₉₅, dynes·sec·cm² ± SE</td>
<td>528 ± 18</td>
<td>580 ± 21†</td>
</tr>
<tr>
<td>Per cent increase, PVR₉₅ ± SE</td>
<td>12 ± 1</td>
<td></td>
</tr>
<tr>
<td>PVRPLL, dynes·sec·cm² ± SE</td>
<td>660 ± 25</td>
<td>638 ± 27†</td>
</tr>
<tr>
<td>Per cent decrease, PVRPLL ± SE</td>
<td>4 ± 1</td>
<td></td>
</tr>
</tbody>
</table>

* P₉₅ = left atrial pressure; P₉₅ = pulmonary artery pressure; QPLL = blood flow to the left lower lobe; Qₘ = total pulmonary flow; PVR = pulmonary vascular resistance; RL = remainder of the lung.
† P < 0.1.
caused HPV in the LLL and an increase in the PVR\textsubscript{LLL}. The diversion of blood flow away from LLL caused an increase in blood flow to the remainder of the lung (RL) and a small decrease in $Q_l$. The passive increase in $Q_l$ passively decreased PVR\textsubscript{LLL}. The algebraic addition of an increased PVR\textsubscript{LLL} and a decreased PVR\textsubscript{LLL} and the effect of a small decrease in $Q_l$ resulted in a net small increase in PVR\textsubscript{t}.

**Effect of Inhalation Anesthetic Agents on the Vasoconstriction Response to Hypoxia**

Figure 2 shows the fractional blood flow and pulmonary vascular resistance of the LLL during normoxia and hypoxia, caused by both N\textsubscript{2} and N\textsubscript{2}O. N\textsubscript{2}O caused a significant decrease in the redistribution of blood flow away from the hypoxic LLL and impeded the increase in PVR\textsubscript{LLL} when compared with the average of the two corresponding control responses ($P < 0.01$).

Responses (as defined by percentage decrease in $Q_{LLL}/Q_l$) in the presence of different halogenated anesthetics were similarly compared with the control responses. In figure 3, both isoflurane and fluoroane caused significant ($P < 0.01$) progressive decreases in the response to hypoxia. Since the control vasoconstriction responses to hypoxia vary by a few percentage points between dogs, relative effects of anesthetics are best shown using normalized data. Halothane enhanced the responses to hypoxia at the 2- and 3-MAC levels, but the effect is exaggerated by the method of computing percentage changes and was significant ($P < 0.05$) only at the 2-MAC level. The addition of N\textsubscript{2}O to isoflurane and halothane shifted these curves downward by an amount approximately equal to the effect of N\textsubscript{2}O by itself. This additive effect of N\textsubscript{2}O was statistically significant at all MAC levels for isoflurane ($P < 0.01$) but only at the 2-MAC level for halothane ($P < 0.02$), and was not present with fluoroane. The relative effects of the anesthetics were not altered by computing the responses to hypoxia as percentage increases in PVR\textsubscript{LLL} and by comparing test responses in this manner against the average of the corresponding control responses. The control responses before and after exposure to all inhalation anesthetics did not differ by more than 4 per cent. Total and LLL prehypoxic pulmonary vascular flows, resistances, and pressures were not significantly altered by the introduction of any concentration of any of the inhalation anesthetics into the LLL, since end-tidal anesthetic concentration in the remainder of the lung never exceeded 7 per cent of the LLL concentration.

In three of the dogs used to study fluoroane and in three of the dogs used to study isoflurane, $P_{A_{O_2}}$, $Q_{LLL}/Q_l$, and $Q_l/Q_t$ (by the Berggren method\textsuperscript{17} were measured during LLL normoxia ($P_{A_{O_2}} = 180$ mm Hg), LLL hypoxia ($P_{A_{O_2}} = 28$ mm Hg), and LLL hypoxia plus the addition of 2–3 MAC
anesthetic concentration. Figure 4 shows that when the LLL was ventilated with N₂ alone, \( Q_{\text{LLL}}/Q_1 \) decreased from the control value of 22 per cent to 9 per cent, \( Q_2/Q_1 \) increased by an amount approximately equal to the remaining \( Q_{\text{LLL}}/Q_1 \), and \( P_{O_2} \) decreased. When the LLL was then ventilated with 2–3 MAC fluoxetine or isoflurane in N₂, \( Q_{\text{LLL}}/Q_1 \) increased by 8 per cent, \( Q_2/Q_1 \) increased further by an amount approximately equal to the increase in \( Q_{\text{LLL}}/Q_1 \), and \( P_{O_2} \) decreased still further. The changes in \( Q_2/Q_1 \) do not precisely correspond to the changes in \( Q_{\text{LLL}}/Q_1 \) because the blood that is shunted through the LLL differs in \( P_{O_2} \) from the mixed venous blood due to reverse oxygen diffusion.

**EFFECT OF INTRAVENOUS ANESTHETIC AGENTS ON THE RESPONSE TO HYPOXIA**

The effect of intravenous anesthetics on the response to hypoxia, as defined by percentage decrease \( Q_{\text{LLL}}/Q_1 \), is summarized in table 2. None of the anesthetics produced statistically significant changes in the hypoxic response.

**Discussion**

Our results demonstrate that inhalation anesthetics alter HPV, depending on the anesthetic and its concentration, whereas the intravenous drugs are without effect. Before discussing these results, consideration should be given to sources of variability related to the methods used and the experimental model.

**Methods.** The response to hypoxia was calculated from change in the ratio of two blood flows recorded electromagnetically, or from change in vascular resistance, for which pressures are also required. Since *in-vitro* calibration of the main pulmonary-artery flow probe agreed well with *in-vivo* dye dilution determination, and since the average \( Q_{\text{LLL}}/Q_1 \) (20.9 ± 0.3 per cent for the average control responses) agreed well with the predicted fraction of 22 per cent,¹⁸ we are confident of the flowmeter calibrations. In addition, small errors in absolute flows would not seriously affect our assessments of HPV, which depended primarily upon detecting a change in flow.

Measurements of vascular pressures and respiratory gas tensions were straightforward. The left atrial catheter contained several side ports and was always shown to lie free in the left atrial cavity by palpation. Blood and gas electrodes and the infrared \( N_2O \) and halogenated agent analyzers were calibrated against room air and against gas mixtures, which we analyzed and which were stable throughout the course of each experiment.

**Experimental Model.** The response to hypoxia in our experimental model is self-limited, for two reasons. First, as the LLL blood flow decreases approximately 50 per cent in response to LLL alveolar hypoxia, the LLL \( P_{ACO_2} \) also decreases by approximately half. This change in LLL \( P_{ACO_2} \) does not alter the mixed arterial blood \( P_{CO_2} \), but it may affect responsiveness of the LLL pulmonary vessels to hypoxia by a local effect.¹⁶¹⁹ Sec-
ond, due to reverse diffusion of O₂, the extent to which the LLL PaO₂ can decrease during ventilation with N₂ alone is partially a function of PaO₂. However, the relationship between alveolar hypoxia and lobar blood flow is sigmoid, not linear, and small differences in the minimum measured LLL PaO₂, probably secondary to variation in PaO₂, would not appreciably affect the vasoconstriction response.

We do not feel that use of pentobarbital as our basic anesthetic materially affected the response to hypoxia, for two reasons. First, the response to hypoxia could be elicited in all dogs, and subsequent doses of pentobarbital, even if they were large (50–100 mg), did not change the magnitude of the response. Second, in the three dogs anesthetized with droperidol, fentanyl, and meperidine instead of pentobarbital, initial responses were similar to those observed in the pentobarbital group and subsequent large doses of pentobarbital did not alter this response. This is in contrast to the report that dogs anesthetized with fentanyl and droperidol responded to hypoxia more consistently and to a greater extent than did dogs anesthetized with pentobarbital. However, in that study the hypoxic stimulus consisted of a PaO₂ of 56 mm Hg, which is only a mild stimulus (see figure 1 and reference 16). Furthermore, since the dogs anesthetized with pentobarbital were significantly more hypocapnic than those anesthetized with fentanyl and droperidol, HPV would be expected to be diminished.

Buckley et al. proposed that halothane might depress HPV and N₂O might enhance the response. However, their abstract did not include any baseline data such as cardiac output, PaO₂, or PaO₂, and since the hypoxia was systemic, changes in these hemodynamic variables would cause secondary changes in the pulmonary circulation. In addition, Levitzky, et al. have suggested that systemic hypoxia by itself attenuates HPV.

**Table 2. Effects of Intravenous Anesthetics on Response to Hypoxia**

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Dose (mg)</th>
<th>Number</th>
<th>Control Response*</th>
<th>Test Response*</th>
<th>Paired t Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Per Cent ± SE</td>
<td>Per Cent ± SE</td>
<td></td>
</tr>
<tr>
<td>Thiopental</td>
<td>100</td>
<td>6</td>
<td>58.0 ± 7.5</td>
<td>63.9 ± 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>Ketamine</td>
<td>50</td>
<td>7</td>
<td>54.6 ± 5.6</td>
<td>57.1 ± 7.1</td>
<td>NS</td>
</tr>
<tr>
<td>Meperidine</td>
<td>50</td>
<td>6</td>
<td>56.3 ± 10.9</td>
<td>41.6 ± 13.2</td>
<td>NS</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>100</td>
<td>7</td>
<td>79.7 ± 4.1</td>
<td>78.7 ± 5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>30</td>
<td>6</td>
<td>62.4 ± 9.2</td>
<td>58.5 ± 10.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Responses = per cent decrease Q₉₀/Q₀.
Sykes et al. reported that 5 per cent halothane limited HPV in isolated perfused cat and dog lungs. However, in their study, control conditions were abnormal and changed with time, perfusion difficulties were encountered, and the hypoxic response was not determined in the presence of halothane. For these reasons, comparison of our results with theirs is not helpful.

We confined the inhaled anesthetics to the LLL in order to minimize any systemic changes (in fact, there were almost none). This permitted us to determine the direct effect of the anesthetics on HPV but precluded any assessment of the net effect of anesthesia on the distribution of perfusion in abnormal lung. It is possible that in the in-vitro situation where the entire organism is anesthetized, with attendant changes in cardiac output, pulmonary vascular pressures, and temperature, and increased drug concentration in the whole lung, the effect of the anesthetics on HPV might be different. Our experimental design enabled us to examine only the direct effect of anesthetics on the distribution of blood flow in lung that had a hypoxic compartment, and thus, on arterial oxygenation.

HPV is probably mediated by a local vasoconstrictor metabolite. Anesthetics could act by interfering with any of the metabolic processes responsible for the production, activation, inactivation, or release of the vasoactive metabolite, or by altering the contractile mechanism of smooth muscle. Our study does not permit conclusions concerning how specific anesthetics depress or enhance HPV. However, our results indicate that halothane, which slightly enhanced HPV, either acts at a different site from isoflurane and fluoroxyene or acts at the same site but with an opposite effect. Both isoflurane and fluoroxyene progressively abolished HPV. In addition, our results indicate that the effects of N2O are additive to those of halothane and isoflurane.

These findings are important for a number of reasons. First, inhibition of HPV can be expected to aggravate ventilation-perfusion inequalities in anesthetized patients with pre-existing pulmonary disease, as well as in patients in whom ventilation-perfusion in-

equalities develop during or as a consequence of anesthesia and operation. Second, the effects of several of the increasing number of maneuvers influencing HPV may be additive, and because of this, further contribute to venous admixture. These include acid-base state and CO₂ tension, pulmonary vascular pressure, body temperature and the ratio of abnormal to normal lung (unpublished observations), several other drugs, and perhaps systemic hypoxia. To these must now be added the effects of anesthetics. The present findings also emphasize the importance of considering the effect of anesthetics on HPV during studies of total venous admixture during anesthesia.

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References
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