REVERSAL OF NITROUS OXIDE-INDUCED DEPRESSION OF HYPOXIC PULMONARY VASOCONSTRICTION BY LIGNOCAINE HYDROCHLORIDE DURING COLLAPSE AND VENTILATION HYPOXIA OF THE LEFT LOWER LOBE

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Decreases in alveolar $P_{O_2}$ as a result of relative underventilation or regional alveolar collapse give rise to vasoconstriction in the pulmonary vascular bed—the diversion of blood flow away from the hypoxic area improving the match of perfusion to ventilation. A number of studies have shown that this mechanism is depressed by anaesthetic agents such as nitrous oxide, with a consequent decrease in arterial oxygenation. Thus ventilation of the isolated perfused cat lung with 100% nitrous oxide produced a smaller increase in pulmonary vascular resistance than ventilation with 100% nitrogen (Hurtig et al., 1977). Similarly, in a preparation in which the distribution of blood flow was examined in intact dogs, ventilation of the left lung or lower lobe with nitrous oxide instead of nitrogen increased flow to the hypoxic segment (Benumof and Wahrenbrock, 1975a; Sykes et al., 1977). Recently, it was shown that ventilation of the left lower lobe with 7% oxygen in nitrous oxide produced a smaller increase in pulmonary vascular resistance than ventilation with 100% nitrogen (Bindslev, Cannon and Sykes, 1986). However, the addition of lignocaine hydrochloride to the lobar perfusate restored the lobar PVR to the value existing during ventilation with 7% oxygen in nitrogen. The present investigations examined the influence of lignocaine and nitrous oxide on the diversion of blood flow from the independently ventilated left lower lobe in the open chest dog.

SUMMARY

The blood flow to the left lower lobe ($QL$), and total ($QT$) pulmonary blood flow, were measured in 10 open-chest dogs using electromagnetic flowmeters. Ventilation of the left lower lobe with 7% oxygen in nitrogen produced a greater reduction in $QL/QT$ (41%) than lobar ventilation with 7% oxygen in nitrous oxide (33%). Lobar collapse reduced $QL/QT$ by 65%, but there was no change in $QL/QT$ when 50% nitrous oxide was administered to the right lung. The i.v. infusion of lignocaine hydrochloride during ventilation of the lobe with 7% oxygen in nitrogen produced no change in $QL/QT$. However, lignocaine infusion during lobar ventilation with 7% oxygen in nitrous oxide produced a further reduction in $QL/QT$ to a value which was not significantly different from that observed during ventilation with 7% oxygen in nitrogen. Lignocaine had no effect on $QL/QT$ during lobar collapse whether the right lung was ventilated with 50% oxygen in nitrogen or 50% oxygen in nitrous oxide. It is concluded that lignocaine reverses the depression of hypoxic pulmonary vasoconstriction produced by lobar ventilation with nitrous oxide.

MATERIALS AND METHODS

Ten dogs of different breeds weighing between 18 and 30 kg were anaesthetized with thiopentone 30 mg kg$^{-1}$ i.v. and pentobarbitalone 2-3 mg kg$^{-1}$ following premedication with morphine 2-3 mg kg$^{-1}$. Anaesthesia was maintained with bolus doses of pentobarbital 10-30 mg i.v., as required. The dogs were maintained in the supine position throughout each investigation. After
intubation of the trachea a 10-mm i.d. cuffed tracheal tube, artificial ventilation was instituted with a Cape–Waine ventilator at 10 b.p.m., the tidal volumes being adjusted to give an end-tidal carbon dioxide concentration of 4.5–5.0%. Blood and fluid loss was replaced by a continuous infusion of Haemaccel Polygeline (Hoechst U.K. Ltd) and any non-respiratory acidosis corrected by an infusion of 8.4% sodium bicarbonate. Fluid and drugs were administered through a catheter in the right external jugular vein and femoral arterial pressure was monitored throughout the study.

A left lateral thoracotomy was performed and the fifth rib was excised. The upper and cardiac lobes of the lung were removed to improve exposure and the bronchus to the lower lobe was intubated via the left upper bronchial stump so that the right lung and left lower lobe could be ventilated synchronously, although independently, by a double "bellows-in-box" system, each side of which was supplied by a separate bank of flow meters and synchronously compressed by the Cape–Waine ventilator. Cannulae were introduced to the pulmonary artery through the right ventricular infundibulum and to the left atrial appendage for pressure recording and blood sampling. The connective tissue adhering to the pulmonary artery and lower lobe artery was stripped and Statham electromagnetic cuff flow probes (Gould Statham Flo-Probe Blood Flow Transducer SP7516, Gould Statham Blood Flow Meter SP2204) placed around the vessels. The flow probes were fed with synchronous excitation currents to prevent cross interference. Intravascular pressures were measured by Druck PDCR75 transducers and blood-gas tensions were analysed on an automated blood-gas analyser (ABL2, Radiometer, Copenhagen).

The ventilation of the right lung and of the left lower lobe was adjusted so that the peak airway pressures were equal when the end-expiratory pressure was 2.5 mm Hg on each side. The end-expired carbon dioxide concentrations were maintained at 4.5–5.0% by adding carbon dioxide to the lobar inspirate during ventilation hypoxia. Before the start of each study the lobe was subjected to repeated periods of hypoxic ventilation (7% oxygen in nitrogen) until a maximal response was achieved. This period varied from 20 min to 4 h.

The investigation was divided into 12 stages (table I, fig. 1). During the first three stages the effects of an i.v. infusion of lignocaine hydrochloride 0.15 mg kg⁻¹ min⁻¹ were examined whilst the right lung and left lower lobe were being ventilated with 50% oxygen in nitrogen. The inspired gases to the left lower lobe were then changed to 7% oxygen in nitrogen (stage 4) and the effects of lignocaine tested again (stage 5). The lobe was then ventilated with 7% oxygen in nitrous oxide (stage 6) and the right lung was ventilated with 50% oxygen in nitrous oxide in order to decrease the loss of nitrous oxide from the circulation. Measurements were made before and during the infusion of lignocaine (stages 6 and 7) and the lobe ventilated with 100% oxygen for nine or ten breaths (stage 8) before the lobar endobronchial tube was clamped to produce collapse. A further set of measurements was made 20–30 min later when collapse appeared complete (stage 9) and these were followed by measurements during the infusion of lignocaine (stage 10), right lung ventilation with 50% oxygen in nitrous oxide (stage 11) and the combined administration of lignocaine and ventilation of the right lung with 50% oxygen in nitrous oxide (stage 12).

After each new set of conditions had been established a period of 10–15 min was allowed to ensure stability, during which the measuring and recording apparatus was calibrated. Each complete study took a maximum of 5 h to complete. The results were analysed by a two-way analysis of variance, followed where appropriate by Duncan's Multiple Range test at the $P < 0.01$ level of significance.

Lobar PVR (pulmonary vascular resistance) was calculated from the equation:

$$PVR = (P_{PA} - P_{LA})/Q_L$$

where $P_{PA}$ and $P_{LA}$ were mean pulmonary artery and left atrial pressures (mm Hg) and $Q_L$ was lobar blood flow (litre min⁻¹).

RESULTS

There were no significant changes in $Q_L/Q_T$ between the control stages (stages 1, 3 and 8) (table I) or in cardiac output, mean pulmonary arterial or mean left atrial pressures throughout the investigation (figs 1 and 2). The arterial $P_{O_2}$ values decreased during ventilation hypoxia and lobar collapse but were always greater than 25 kPa. There were no significant changes in arterial $P_{CO_2}$ and $pH$, mixed venous $P_{O_2}$ or end-tidal carbon dioxide concentration throughout the investigation.

Ventilation of the lobe with 7% oxygen in
Table I. Means and standard deviations for left lower lobar vascular resistance (PVRl), ratio of lobar flow to cardiac output (QL/QT), cardiac output (QT), left atrial pressure (PLX) and pulmonary artery pressure (PFX). Condition of the left lower lobe (LLL) is shown at the left. Right lung was ventilated with 50% oxygen in nitrogen during stages 1-5 and 8-10 and with 50% oxygen in nitrous oxide during stages 6, 7, 11 and 12. L = i.v. infusion of lignocaine; C = left lower lobe collapse.

<table>
<thead>
<tr>
<th>Stage</th>
<th>LLL status</th>
<th>PVRL (mm Hg litre(^{-1}) min(^{-1}))</th>
<th>( \frac{Q_L}{Q_T} ) (%)</th>
<th>( \bar{Q}_T ) (litre min(^{-1}))</th>
<th>PLX (mm Hg)</th>
<th>PFX (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>50% O(_2)/N(_2), L</td>
<td>21.2 ± 8.3</td>
<td>17.7 ± 3.54</td>
<td>1.98 ± 0.26</td>
<td>5.9 ± 1.7</td>
<td>12.8 ± 2.6</td>
</tr>
<tr>
<td>(2)</td>
<td>50% O(_2)/N(_2), L</td>
<td>24.8 ± 7.9</td>
<td>17.4 ± 2.81</td>
<td>1.91 ± 0.26</td>
<td>6.2 ± 1.7</td>
<td>14.1 ± 2.6</td>
</tr>
<tr>
<td>(3)</td>
<td>50% O(_2)/N(_2), L</td>
<td>21.4 ± 7.6</td>
<td>17.6 ± 3.52</td>
<td>2.01 ± 0.26</td>
<td>6.1 ± 1.7</td>
<td>13.3 ± 2.5</td>
</tr>
<tr>
<td>(4)</td>
<td>7% O(_2)/N(_2), L</td>
<td>44.0 ± 8.3</td>
<td>10.3 ± 1.86</td>
<td>1.88 ± 0.26</td>
<td>6.3 ± 1.8</td>
<td>14.7 ± 2.6</td>
</tr>
<tr>
<td>(5)</td>
<td>7% O(_2)/N(_2), L</td>
<td>41.7 ± 8.6</td>
<td>10.3 ± 1.81</td>
<td>1.79 ± 0.27</td>
<td>7.5 ± 1.8</td>
<td>15.2 ± 2.4</td>
</tr>
<tr>
<td>(6)</td>
<td>7% O(_2)/N(_2), L</td>
<td>31.4 ± 8.2</td>
<td>13.5 ± 2.42</td>
<td>1.83 ± 0.25</td>
<td>7.4 ± 1.7</td>
<td>14.9 ± 2.6</td>
</tr>
<tr>
<td>(7)</td>
<td>7% O(_2)/N(_2), L</td>
<td>38.0 ± 8.1</td>
<td>10.6 ± 1.96</td>
<td>1.72 ± 0.24</td>
<td>8.5 ± 1.8</td>
<td>15.4 ± 2.4</td>
</tr>
<tr>
<td>(8)</td>
<td>50% O(_2)/N(_2), L</td>
<td>20.9 ± 6.9</td>
<td>19.7 ± 3.08</td>
<td>1.95 ± 0.25</td>
<td>6.1 ± 1.7</td>
<td>13.8 ± 2.6</td>
</tr>
<tr>
<td>(9)</td>
<td>C, L</td>
<td>61.7 ± 9.3</td>
<td>6.9 ± 1.11</td>
<td>2.01 ± 0.19</td>
<td>5.8 ± 1.7</td>
<td>14.1 ± 2.4</td>
</tr>
<tr>
<td>(10)</td>
<td>C, L</td>
<td>58.8 ± 7.3</td>
<td>7.4 ± 1.53</td>
<td>1.91 ± 0.26</td>
<td>7.2 ± 1.8</td>
<td>15.4 ± 2.6</td>
</tr>
<tr>
<td>(11)</td>
<td>C, O(_2)</td>
<td>58.7 ± 8.5</td>
<td>7.9 ± 1.51</td>
<td>1.98 ± 0.25</td>
<td>6.7 ± 1.7</td>
<td>15.8 ± 2.6</td>
</tr>
<tr>
<td>(12)</td>
<td>C, O(_2), L</td>
<td>57.3 ± 7.5</td>
<td>7.8 ± 1.83</td>
<td>1.81 ± 0.26</td>
<td>7.9 ± 1.7</td>
<td>16.0 ± 2.5</td>
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Fig. 1. Pulmonary arterial (P\(\text{PA}\)) and left atrial (P\(\text{LA}\)) pressures at each stage of the experiment. Values are given as mean ± SEM. The periods of lobar ventilation hypoxia and lobar collapse are indicated under the abscissa. Nitrous oxide was administered to both the right lung and left lower lobe during hypoxia, and to the right lung during collapse. L = lignocaine infusion.

Nitrogen (stage 4) and the induction of lobar collapse (stage 9) resulted in significant decreases in \( \frac{Q_L}{Q_T} \) and increases in lobar PVR. However, these changes were significantly greater during lobar collapse. Substitution of nitrous oxide for nitrogen during ventilation hypoxia (stage 6) produced a significant increase in \( \frac{Q_L}{Q_T} \) and decrease in lobar PVR, but there were no changes when 50% nitrous oxide was administered to the right lung during the period of collapse of the left lower lobe (stage 11) (figs 2 and 3).

The i.v. infusion of lignocaine produced no significant changes in \( \frac{Q_L}{Q_T} \) or lobar PVR during ventilation of the lobe with 50% oxygen in nitrogen, with 7% oxygen in nitrogen or with lobar collapse, but there was a significant decrease in \( \frac{Q_L}{Q_T} \) and increase in lobar PVR when lignocaine was infused during the ventilation of...
the lobe with 7% oxygen in nitrous oxide, the values at this stage (stage 7) not being significantly different from those existing during ventilation of the lobe with 7% oxygen in nitrogen (stage 4). The infusion of lignocaine during lobar collapse (when the right lung was ventilated with 50% oxygen in nitrogen (stage 10) or with 50% oxygen in nitrous oxide (stage 12) produced no significant changes in lobar PVR or $Q_L/Q_T$.

DISCUSSION

This study demonstrated that ventilation hypoxia (7% oxygen in nitrous oxide) of the left lower lobe produced a smaller reduction in $Q_L/Q_T$ and a less marked increase in lobar PVR than ventilation with 7% oxygen in nitrogen. The administration of 50% oxygen in nitrous oxide to the right lung during lobar collapse had no effect on $Q_L/Q_T$, although $Q_L/Q_T$ was lower during lobar collapse than during ventilation with 7% oxygen in nitrogen. The infusion of lignocaine hydrochloride did not produce any significant effects on $Q_L/Q_T$ or lobar PVR except when given during the administration of nitrous oxide in association with lobar ventilation with 7% oxygen in nitrous oxide. Under the latter conditions $Q_L/Q_T$ was decreased to a value not significantly different from that observed during ventilation with 7% oxygen in nitrogen. These results suggest that nitrous oxide decreases hypoxic pulmonary vasoconstriction and that lignocaine restores the response to normal.

There are, however, a number of inherent limitations associated with the use of this preparation. First, the lung and lobe are probably denervated during the surgery so that reflex effects such as those resulting from chemoreceptor stimulation are eliminated (Levitzky, 1979). Second, there is a decrease in pulmonary vascular volume as a result of the removal of the left upper and cardiac lobes so that the diversion of flow away from a hypoxic segment may be reduced. Third, the thorax is open to atmosphere so that the regional differences in pleural pressure normally associated with regional collapse in the closed chest are not present. This may result in a different distribution of blood flow between the open- and closed-chest preparations (Quebbeman and Dawson, 1976).

The regional distribution of perfusion is governed by regional transpulmonary pressures, the recruitment pattern of blood vessels, vascular pressures and the vasoactive state of the regional vascular bed. In the present study there were no significant changes in transpulmonary pressure during lobar ventilation or collapse. Furthermore, changes in mean pulmonary artery and left atrial pressures were small and unlikely to have had any effect on the pattern of flow distribution (Benumof and Wahrenbrock, 1975b; West, 1977). Under these circumstances the distribution of blood flow was dependent on the vasoactive state of the blood vessels, a major determinant of which is alveolar $P_{O_2}$.

The magnitude of the hypoxic pulmonary vasoconstrictor response is governed by a number of factors. The main factors are the alveolar $P_{O_2}$ and $P_{CO_2}$ in the ventilated segment or the mixed venous blood $P_{O_2}$ and $P_{CO_2}$ in the collapsed segment (Benumof, Mathers and Wahrenbrock, 1976; McFarlane, Gardaz and Sykes, 1984), the size of the hypoxic segment (Marshall et al., 1981) and the vascular pressures (Benumof and Wahrenbrock, 1975a). The response is also known to be decreased by surgical trauma as a result of the release of vasodilator prostaglandins (Weir et al., 1976) and augmented by time, although whether this is the result of the number of responses (Benumof, 1983) or simply of time (Marshall, 1981) is not yet clear. In the present experiments the effects of the latter variables were minimized.
by ensuring that several baseline responses of comparable magnitude were obtained before the production of alveolar hypoxia.

The decrease in $Q_L/\dot{Q}_T$ during lobar collapse was greater than that resulting from lobar ventilation hypoxia (7% oxygen in nitrogen). The use of 7% oxygen as the hypoxic stimulus in ventilation hypoxia has been shown to produce pulmonary venous $P_{O_2}$ values close to the normal mixed venous values (unpublished data), so that the hypoxic stimulus should be the same during ventilation hypoxia and collapse. The difference in $Q_L/\dot{Q}_T$ between the two conditions is now thought to be caused by higher $P_{CO_2}$ values in the lobe following equilibration of the alveolar gas with mixed venous $P_{CO_2}$ and to the mechanical factors associated with the reduction in lobar volume (McFarlane, Gardaz and Sykes, 1984).

The administration of nitrous oxide in conjunction with ventilation hypoxia (7% oxygen in nitrous oxide) produced a smaller decrease in $Q_L/\dot{Q}_T$ than ventilation hypoxia alone (7% oxygen in nitrogen), thus suggesting that nitrous oxide depresses the hypoxic vasoconstrictor mechanism. Another explanation for the decrease in the response to alveolar hypoxia in the presence of nitrous oxide is that the alveolar $P_{O_2}$ may have been increased by the "second gas" effect (Eger, 1974). This latter effect is the result of the moderate solubility of nitrous oxide, which leads to a rapid initial uptake and a concentration of the remaining alveolar gases with a consequent decrease in the hypoxic stimulus (Heller and Watson, 1962). As the blood becomes saturated with nitrous oxide the uptake is decreased and the alveolar $P_{O_2}$ returns to its previous value. However, if there is a continued loss of nitrous oxide from the circulation, for example via a lung region in which there is no nitrous oxide in the inspired gas, the alveolar $P_{O_2}$ may be maintained at a value greater than that predicted from the inspired oxygen concentration. The sensitivity of the vasoconstrictor response to alveolar hypoxia is greatest in the range of 4–8 kPa (Barer, Howard and Shaw, 1971) so that small changes in alveolar $P_{O_2}$ caused by this second gas effect would be likely to produce significant changes in $Q_L/\dot{Q}_T$.

Although the administration of 50% oxygen in nitrous oxide to the right lung during lobar ventilation with 7% oxygen in nitrous oxide should have reduced the loss of nitrous oxide from the right lung, there may still have been some nitrous oxide uptake from the lobe with a consequent decrease in the hypoxic stimulus. However, there is other evidence which suggests that nitrous oxide does diminish the vasoconstrictor response to alveolar hypoxia. Thus it has been shown that ventilation of a lung or lobe with pure nitrous oxide produces a weaker hypoxic response than does ventilation with pure nitrogen (Benumof and Wahrenbrock, 1975a; Sykes et al., 1977). Although there must have been some uptake of oxygen into the alveolus from venous blood in these studies, it seems unlikely that the alveolar $P_{O_2}$ could have increased to values which could have altered the hypoxic stimulus. Furthermore, experiments using the isolated perfused cat lung preparation in which there was negligible loss of nitrous oxide from the circuit demonstrated a dose-dependent inhibition of the pressor response (Hurtig et al., 1977).

The failure of right lung ventilation with 50% oxygen in nitrous oxide to inhibit hypoxic pulmonary vasoconstriction during lobar collapse was probably the result of the low nitrous oxide concentrations in the blood perfusing the lobe. Hurtig and colleagues (1977) showed that alveolar concentrations of 50% nitrous oxide failed to inhibit HPV in cats. However, in the present investigation, the mixed venous nitrous oxide concentrations must have been much less, for only one lung was ventilated with the gas mixture and the arterial blood would have given up nitrous oxide to the tissues before returning to the lobe. The possibility of tolerance to the effects of prolonged exposure to nitrous oxide cannot be excluded.

Lignocaine produced no change in $Q_L/\dot{Q}_T$ during normoxic ventilation, during ventilation hypoxia (7% oxygen in nitrogen) or during lobar collapse with or without the administration of nitrous oxide via the right lung. However, when lignocaine was infused during ventilation of the lobe with 7% oxygen in nitrogen, $Q_L/\dot{Q}_T$ decreased to a value not significantly different from that found with ventilation using 7% oxygen in nitrogen. This suggests that lignocaine antagonizes the specific effects of nitrous oxide upon the mechanism of HPV although, here also, the possibility of a nitrous oxide tolerance effect may not be ruled out. The failure of lignocaine to exert an effect upon lobar PVR during nitrous oxide ventilation and lobar collapse (stage 12) was probably the result of absence of nitrous oxide-induced inhibition of HPV. Indeed, the absence of the nitrous oxide-induced reduction in lobar PVR...
during collapse may itself be dependent on the antagonistic effects of residual lignocaine in the perfusate. The disposition kinetics of lignocaine result in a prolonged half-time for elimination (Benowitz et al., 1974) of about 100 min in man (Goodman and Gilman, 1980) so that increased concentrations are likely to be present in the perfusate for some time after the end of the previous stages of lignocaine infusion (stages 5, 7, 10).

It is concluded that nitrous oxide may depress hypoxic pulmonary vasoconstriction and that this effect may be reversed by the i.v. infusion of lignocaine. Although this action may improve ventilation–perfusion mismatch in the patient with diseased lungs, it could also increase pulmonary vascular resistance and so increase the load on the right heart, which in turn may prove detrimental to the patient. Since there is still no evidence that nitrous oxide depresses hypoxic pulmonary vasoconstriction in patients, these results should not be extrapolated to the human situation.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the technical support of Mr R. Madgewick. The work was supported by the Medical Research Council. Dr Bindsley was supported by a Smith and Nephew Research Fellowship.

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