Combined Effects of Sodium Nitroprusside and Propranolol on Hypoxic Pulmonary Vasoconstriction

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Recent clinical experience and previous experimental work indicate that propranolol may reverse sodium-nitroprusside-induced inhibition of hypoxic pulmonary vasoconstriction (HPV). Accordingly, the authors decided to test this possibility in an experimental model that allows direct examination of pharmacologic influence on HPV. Six mongrel dogs were anesthetized with pentobarbital and intubated. Following a left thoracotomy, the left lower lobe (LLL) was ventilated independently but synchronously with the rest of the lung. Selective hypoxia of the LLL (95% nitrogen and 5% CO₂) caused a 39 ± 6% (mean ± SE) decrease in the electromagnetically measured fraction of the cardiac output perfusing the LLL and a 287 ± 65% increase in the pulmonary vascular resistance of the LLL from their respective prehypoxic values. Propranolol, 1 mg/kg intravenously, caused a 76 ± 5% beta-blockade, as determined by an isoproterenol infusion test, but did not cause a significant change in the LLL HPV response. Sodium nitroprusside (SNP) infusion, caused a 38 ± 4% decrease in systemic arterial pressure, and nearly abolished LLL HPV. Most important, the addition of propranolol to sodium nitroprusside did not significantly change the SNP induced inhibition of LLL HPV. The authors conclude that in acute lung disease, propranolol does not alter lobar HPV and does not reverse sodium nitroprusside inhibition of lobar HPV. (Key words: Anesthetic techniques; hypotensive, nitroprusside. Interactions: drug: Lung: blood flow; hypoxic pulmonary vasoconstriction; vascular resistance. Pharmacology: nitroprusside; propranolol. Sympathetic nervous system: sympatholytic agents; propranolol.)

Hypoxic pulmonary vasoconstriction (HPV) diverts blood flow away from hypoxic areas of the lung to better ventilated normoxic regions of the lung. Sodium nitroprusside (SNP), a potent vasodilator has been shown to inhibit regional HPV in a dose-dependent manner. Conversely, other experimental studies have suggested that propranolol may cause pulmonary vasoconstriction, enhance HPV, and reverse inhibition of HPV caused by minoxidil.

The findings of a recent preliminary study in humans appears to demonstrate both the known effects of sodium nitroprusside and the suggested effects of propranolol on HPV. Ten surgical patients with scoliosis and restrictive lung disease received sodium nitroprusside (controlled hypotension) which caused a significant increase in venous admixture and a decrease in PaO₂ and pulmonary vascular resistance. Subsequent administration of propranolol, in order to blunt sodium-nitroprusside-induced tachycardia, caused a significant decrease in venous admixture and increase in PaO₂ and pulmonary vascular resistance. The authors suggested that propranolol may have reversed the known inhibitory effects of sodium nitroprusside on HPV. We thought it important to test this intriguing hypothesis in an experimental model that allows direct examination of pharmacologic influence on HPV.

Methods

Six mongrel dogs of either sex, weighing 16–22 kg, were anesthetized with 25 mg/kg intravenous pentobarbital, paralyzed with 4 mg/kg gallamine, intubated with auffed endotracheal tube, and ventilated with 100% O₂ with one side of a dual piston Harvard® ventilator. Via peripheral vessels, catheters for pressure measurement and blood sampling were placed in the femoral artery (Pₐa), pulmonary artery (PAP), and after a left fifth intercostal space thoracotomy, a catheter was placed directly into the left atrium (LAP). All pressures were transduced (Bell-Howell #4-327-I®) and zeroed against atmospheric pressure at the level of the left atrium, and then recorded as a mean value (Hewlett Packard 7788A®). Electromagnetic flow probes (Statham SP-7515®) were placed around the main and left lower lobe (LLL) pulmonary arteries (Qₐ and Qₙₐ respectively) after minimal dissection. Both flow probes had been calibrated in vivo with known blood flows through excised vessels. The main flow probe calibration was further confirmed by in vivo thermodilution cardiac output with deviation less than 6% at all levels of flow. We express blood flow to the LLL as a fraction of the cardiac output (Qₙₐ/Qₐ).

The LLL bronchus was intubated distal to a ligature and ventilated independently and synchronously with the rest of the lung (RL) with 100% O₂ with the second piston of the respirator. The inspired gas composition to the LLL was controlled by a separate bank of flowmeters. Appropriate ventilation of the LLL compared to the rest of the lung was achieved by manipulating the two tidal volumes and external dead spaces so that the end-tidal CO₂ concentrations (Beckman LB-2) and airway pressures were equal in both airways. The expiratory hoses from both airways were immersed in water.
TABLE 1. Pulmonary Vascular Pressures, Flows and Resistances as a Function of Left Lower Lobe Hyperoxia and Hypoxia and Infusion of Sodium Nitroprusside and Propranolol* (Mean ± SE)

<table>
<thead>
<tr>
<th>LLL Condition</th>
<th>PAP (mmHg)</th>
<th>LAP (mmHg)</th>
<th>Qo (l/min)</th>
<th>QLLL (ml/min)</th>
<th>QLLL/Qo (%)</th>
<th>QLLL/Qo (% decrease)</th>
<th>PVRLLL (dyn·s·cm⁻⁵)</th>
<th>PVRLLL (% increase)</th>
<th>PPa₁ (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without P</td>
<td></td>
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<tr>
<td>O₂</td>
<td>15.9 ± 0.4</td>
<td>6.9 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>420 ± 34</td>
<td>20.2 ± 1.0</td>
<td>—</td>
<td>1884 ± 171</td>
<td>—</td>
<td>482 ± 8</td>
</tr>
<tr>
<td>N₂</td>
<td>17.9 ± 0.4†</td>
<td>6.9 ± 0.4</td>
<td>2.3 ± 0.3</td>
<td>191 ± 43†</td>
<td>8.1 ± 1.3†</td>
<td>59.2 ± 5.7</td>
<td>8108 ± 1976†</td>
<td>286.5 ± 64.7</td>
<td>351 ± 17†</td>
</tr>
<tr>
<td>N₂ + SNP</td>
<td>16.0 ± 0.8‡</td>
<td>5.0 ± 0.3‡</td>
<td>2.4 ± 0.3</td>
<td>376 ± 48‡</td>
<td>16.6 ± 1.5‡</td>
<td>33.7 ± 8.8</td>
<td>2911 ± 332‡</td>
<td>33.7 ± 8.8</td>
<td>256 ± 13‡</td>
</tr>
<tr>
<td>With P</td>
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<tr>
<td>O₂</td>
<td>17.1 ± 0.3</td>
<td>8.8 ± 0.3*</td>
<td>1.7 ± 0.3*</td>
<td>380 ± 46</td>
<td>22.9 ± 1.0</td>
<td>—</td>
<td>1973 ± 130</td>
<td>—</td>
<td>462 ± 11</td>
</tr>
<tr>
<td>N₂</td>
<td>19.1 ± 0.4†</td>
<td>10.2 ± 0.6*</td>
<td>1.9 ± 0.6*</td>
<td>142 ± 45†</td>
<td>8.0 ± 1.5†</td>
<td>64.9 ± 5.1</td>
<td>7440 ± 1760†</td>
<td>278.7 ± 74.5</td>
<td>344 ± 36†</td>
</tr>
<tr>
<td>N₂ + SNP</td>
<td>16.1 ± 0.7‡</td>
<td>6.7 ± 0.4‡</td>
<td>1.8 ± 0.3*</td>
<td>318 ± 54‡</td>
<td>17.8 ± 1.0‡</td>
<td>37.4 ± 6.4</td>
<td>2801 ± 337‡</td>
<td>37.4 ± 6.4</td>
<td>242 ± 26‡</td>
</tr>
</tbody>
</table>

* P = propranolol; LLL = left lower lobe; O₂ = ventilation of LLL with 100% O₂; N₂ = ventilation of LLL with 95% N₂ and 5% O₂; SNP = sodium nitroprusside; PAP = pulmonary artery pressure; LAP = left atrial pressure; Qo = cardiac output; QLLL = LLL blood flow; QLLL/Qo = fraction of the cardiac output perfusing the LLL; PVRLLL = pulmonary vascular resistance in the left lower lobe; PPa₁ = partial pressure of O₂ in systemic arterial blood.

† P < 0.05 LLL condition with propranolol compared to similar LLL condition without propranolol.
‡ P < 0.05 LLL-N₂ compared to LLL-O₂.
D. = (9) LLL-O₂; (10) LLL-N₂; (11) LLL-N₂ + SNP; (12) LLL-N₂ + SNP + P; (Administration of P after establishment of LLL-N₂ + SNP)

E. = (13) LLL-O₂ + P; (14) LLL-O₂ + P + I (Isoproterenol infusion test after P blockade)

F. = (15) LLL-O₂ + P; (16) LLL-N₂ + P; (17) LLL-N₂ + P + SNP (Administration of P before establishment of LLL-N₂ + SNP)

G. = (18) LLL-O₂ + P; (19) LLL-O₂ + P + I (Isoproterenol infusion test after P blockade)

We computed the LLL response to hypoxia in two ways: first, as the maximum percentage reduction in the fraction of the cardiac output perfusing the LLL (% decrease $Q_{\text{LLL}}/Q_o$) from its prehypoxic (hyperoxic) control value; and second, as the maximum percentage increase in the pulmonary vascular resistance of the LLL (% increase PVR$_{\text{LLL}}$) from its prehypoxic control value. SNP-induced changes in systemic arterial pressure and isoproterenol-induced changes in heart rate (HR) were referenced to the immediately preceding LLL-O₂ value. The degree of beta-blockade was determined by:

$$\% \text{beta-blockade} = 1 - \left( \frac{\text{HR}_1 \text{ change after P}}{\text{HR}_1 \text{ change before P}} \right) \times 100$$

where HR$_1$ = heart rate change caused by isoproterenol bolus. All results are expressed as means ± SE and were analyzed by Student’s paired t analysis with $P < 0.05$ considered significant. When the animals showed signs of light anesthesia and/or lack of paralysis, 3 mg/kg pentobarbital and/or 0.5 mg/kg gallamine, respectively, were administered.

**Results**

There were no significant differences in pulmonary vascular pressures (PAP, LAP), flows ($Q_{\text{LLL}}$, $Q_o$, $Q_{\text{LLL}}/Q_o$), and resistances ($\text{PVR}_{\text{LLL}}$, PVR$_c$) between the multiple periods of LLL-O₂ alone (steps 1, 4, 7, and 9); LLL-N₂ alone (steps 2 and 10); LLL-N₂ + SNP (steps 3, 6, and 11); LLL-O₂ + P (steps 13, 15, and 18); LLL-N₂ + SNP + P (steps 12 and 17) and, therefore, the values for these pulmonary vascular variables were combined together for each group of steps in the above parentheses (table 1, fig. 1).

Sodium nitroprusside infusion caused a decrease in the mean arterial pressure of 38 ± 4% (from 116 ± 4 to 73 ± 3 mmHg). Propranolol infusion caused a 76 ± 5% beta-blockade. During every comparable LLL condition (LLL-O₂, LLL-N₂, LLL-N₂ + SNP), beta-blockade caused a significant decrease in heart rate and cardiac output and a significant increase in LAP (table 1). LLL hypoxia alone (LLL-N₂) did not cause a significant change in $P_{\text{aw}}$, PAP, LAP, cardiac output, or heart rate.

Beta-blockade alone (without SNP infusion) did not cause a significant change in the LLL vasconstrictor response to hypoxia (% decrease $Q_{\text{LLL}}/Q_o$ and % increase PVR$_{\text{LLL}}$) (fig. 1, table 1). SNP infusion alone (without beta-blockade) nearly abolished the LLL response to hypoxia. Most important, the addition of beta-blockade during SNP infusion did not significantly change the SNP-induced inhibition of LLL HPV.

**Discussion**

This study has three major findings. First, we have confirmed that SNP is a potent inhibitor of HPV. Second, propranolol alone (without SNP) has no significant effect on HPV. Third, the combination of propranolol beta-blockade and SNP infusion causes the same degree of HPV inhibition as does SNP infusion alone. Thus, propranolol has no effect on HPV alone or on SNP inhibition of HPV. Before discussing these results con-
sideration should be given to a few special features of our experimental model and design.

First, our experimental design ruled out possible differences in drug effects due to the temporal sequence of drug administration and/or LLL hypoxia. Thus, SNP was administered before and after LLL hypoxia (sequence A vs. B) and before and after propranolol administration (sequence D vs. F), and left lower lobe hypoxia was induced before and after SNP administration (sequence A vs. B) and before and after propranolol administration (sequence D vs. F).

Second, both propranolol and SNP were administered in doses sufficient to cause significant changes in appropriate physiologic end points. As indicated by our isoproterenol infusion test, once propranolol was administered, a large beta-blockade (76%) was present for the duration of the rest of the experiment. We administered SNP so as to cause a decrease in systemic artery pressure (40%) which is similar to changes that would be desired clinically during controlled hypotension or control of acute systemic hypertension. As indicated by our small standard errors, these physiologic end points were achieved consistently.

Third, our LLL model results in a reasonably consistent and replicable degree of regional HPV.7–10 Induction of regional HPV in our model does not cause systemic changes (i.e., $P_{\text{aSa}}$, PAP, LAP, and $Q_v$). Since we expressed blood flow to the LLL as a fraction of the cardiac output ($Q_{\text{LLL}}/Q_v$), passive changes in LLL blood flow, which are due to changes in cardiac output, are taken into account.

We found that SNP greatly decreased the HPV response. Despite rather widespread agreement on the direction and magnitude of SNP effect on HPV,1 the mechanism of this action is obscure. Recent evidence indicates that increased levels of either cellular cAMP and/or cGMP cause vasodilation.11–13 Although it has been previously hypothesized that HPV may be mediated by decreases in cellular ATP levels (and therefore by mass action, decreases in cAMP levels),14 more recent studies of the effects of SNP on vascular smooth muscle indicate that SNP does not change intracellular levels of cAMP, but rather activates guanylate cyclase increasing cGMP.12 It is possible, therefore, that SNP may inhibit HPV via a pathway different from that which causes HPV.

We found that beta-receptor blockade caused no change in the magnitude of lobar HPV. Since it is well-known that beta-receptor stimulation causes pulmonary vasodilation,5 inhibits the HPV response,15 and increases cAMP,13 it is reasonable to suggest that the mechanism of isoproterenol inhibition of HPV is via increasing intracellular cAMP. Based on these considerations, one would anticipate that the HPV response would be enhanced by beta-blockade since the beta-receptor vaso-

dilator effect would be decreased. However, we found no improvement in HPV after propranolol administration, despite the fact that we had a demonstrated beta-receptor blockade. Since alpha-receptors numerically and functionally predominate over beta-receptors in the pulmonary circulation,16,17 it may be that achievement of a major blockade of a normally minor influence on HPV resulted in minimal effect on HPV. Other studies have previously reported that propranolol does not diminish HPV.18,19

Similarly, SNP-induced inhibition of HPV was unaffected by propranolol beta-blockade. The lack of significant interaction between these two drugs may be related to the possibilities that beta-blockade caused only minor changes in cAMP activity, and that SNP effects on HPV may be via a different pathway, namely changes in cGMP.

Our results with SNP and propranolol infusion in dogs are not in good agreement with the results of infusion of these drugs in humans with chronic lung disease caused by scoliosis.6 Two explanations for these differences seem possible. First, the noncompatible results of these two studies may be due to species differences. For example, exposure of several different species to high altitude has resulted in a clear-cut difference in the magnitude of increased pulmonary perfusion pressure.20,21 Similarly, in cattle, propranolol enhances HPV and reverses inhibition of HPV caused by minoxidil, whereas in dogs, propranolol has no effect on HPV alone (as we have confirmed) and does not restore inhibition of HPV due to minoxidil.5 Although HPV in the dog and human seem to be similar,1,14 drug interactions, such as propranolol and sodium nitroprusside, may not be extrapolated from one species to another.

Second, the difference in the results between these studies also may be related to differences in the pulmonary circulation caused by acute versus chronic regional hypoxia. Scoliosis creates widespread and regional hypoventilation as a result of restrictive lung changes. The regional defects in ventilation are matched by appropriate defects in perfusion (presumably caused by HPV).22 There is evidence to indicate that prolonged regional HPV will result in selective regional vascular smooth muscle hypertrophy.23,24 It is possible that propranolol may have a greater effect on chronically hypoxic and hypertrophied vessels (i.e., results in a greater amount of alpha-receptor-mediated vasoconstriction2,23,26) than it has on acutely hypoxic and relatively normal vessels. Thus, if propranolol administration resulted in more vasoconstriction in hypertrophied and chronically hypoxic areas of the lung, then changes compatible with an enhancement of HPV would result (i.e., decrease in venous admixture and an increase in total pulmonary vascular resistance). On this basis, we speculate that the
favorable interaction between propranolol and SNP observed in patients with chronic lung disease might not be present in patients with acute lung disease.

References