The Influence of Nitric Oxide in Adult Respiratory Distress Syndrome when \( P_{O_2} \) Is Varied

In recent years, there have been several investigations of the adult respiratory distress syndrome (ARDS) that are remarkable for the extensive measurements performed and for the new insights that they provide. In this issue, Benzing et al. (page 1254) from the University of Freiburg, Germany, provide another such study. These authors measured indices of pulmonary oxygen exchange and vascular characteristics in 11 patients with severe ARDS, whose gas exchange was being supported by venovenous extracorporeal lung assistance. By adjusting the flow rate through the extracorporeal circuit, the mixed venous tension (\( P_{V_{O_2}} \)) was systematically adjusted to 47, 54, 64, and 84 mm Hg, whereas the carbon dioxide tension and cardiac output (Qt) remained unchanged and in the presence and absence of 15 ppm inhaled nitric oxide (NO). Addition of NO was observed to cause a greater reduction of perfusion pressure (PP) at low \( P_{V_{O_2}} \), than at high \( P_{V_{O_2}} \), whereas reduction of shunt was almost constant (table 1) at all \( P_{V_{O_2}} \). Identification of the mechanisms underlying such apparently dissociated responses is of special interest.

Ventilation was with 100% \( O_2 \), and with the highest \( P_{V_{O_2}} \), the fractional shunt (fQs) was 0.67. Hypoxic pulmonary vasoconstriction (HPV) would be minimal during these conditions, and therefore throughout the study, 68% of the lung can be represented as one nonventilated compartment in parallel with the remaining 32% that is ventilated. When Rt, Ra, and Rb are the total, nonventilated, and ventilated lung vascular resistances, respectively, then 1/Rt = 1/(Ra + 1/Rb), and distribution of flow to the nonventilated (fQs) and ventilated (1 - fQs) compartments is given by [(1 - fQs)/fQs] = Ra/Rb. Table 1 lists the essential observed and derived values. Benzing et al. explains these results intuitively with the assumptions that HPV acts only on the nonventilated compartment, and NO acts only on the ventilated compartment. These conditions can be simulated with a sophisticated computer model (V/Q - P/Q model), which demonstrates three important principles illustrated in figure 1. First (fig. 1A), even if there is no HPV present and no other cause of small artery constriction (SAC), so that fQs is constant, the \( P_{A_{O_2}} \) increases dramatically as \( P_{V_{O_2}} \) is increased. Second (fig. 1B), if HPV alone is present, then PP decreases with increasing \( P_{V_{O_2}} \), but NO has no effect. Conversely, if small pulmonary arteries are actively constricted but if HPV is absent, then NO reduces PP (and shunt), although by a constant amount independent of \( P_{V_{O_2}} \). Only when HPV and SAC are present (fig. 1C) is a \( P_{V_{O_2}} \)-dependent response to NO revealed, although shunt also changes similarly. This computer simulation and consideration of the equations applicable to the simple model of two parallel compartments do not demonstrate dissociation of the pressure and shunt responses to NO, and therefore the assumptions of Benzing et al. are reexamined. Undoubtedly, HPV is inactive in the hypoxic ventilated compartment, but the pattern of changes shown in table 1, for Ra and Rb when NO was administered, suggest that the action of NO is not confined to the ventilated compartment.

One difficulty with comparing Ra and Rb are the different sizes of the compartments. It is useful to normalize these resistances to what they would be if the whole lung had either the resistance, \( a_{TOT} \) of the nonventilated compartment or the resistance, \( b_{TOT} \), of the ventilated compartment so \( Ra = a_{TOT}/fa \) and \( Rb = b_{TOT}/fb \), where \( fa \) and \( fb \) are the fraction of lung in each compartment and are 0.68 and 0.32 for the data of Benzing et al. Thus, the total vascular resistance of each of the normalized parallel compartments (\( a_{TOT} \) and \( b_{TOT} \)) derived from the data of Benzing et al. can be reconstructed as three resistances in series consisting of HPV, SAC, and everything else (OTHer). Thus, \( a_{TOT} = a_{HPV} + a_{SAC} + a_{OTH} \) and \( b_{TOT} = b_{HPV} + b_{SAC} + b_{OTH} \). Quantities can be assigned to each of these resistances with the following assumptions: \( b_{OTH} \) is zero throughout; \( a_{OTH} = b_{OTH} \); \( a_{TOT} \) and \( b_{TOT} \) for the highest \( P_{V_{O_2}} \), differ only by the minimal \( a_{HPV} \) and \( b_{SAC} \) is zero with NO at the lowest \( P_{V_{O_2}} \). The estimated values are shown in table 2 and reveal as expected that \( a_{HPV} \) decreases systematically as \( P_{V_{O_2}} \) increases, but more interestingly, the

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Key words: parallel resistance, series resistance, hypoxic pulmonary vasoconstriction, computer models.
Table 1. Basic Observed and Derived Values for Pulmonary Perfusion Pressures, Compartment Flows and Resistances

<table>
<thead>
<tr>
<th>PV_{O_2} (mmHg)</th>
<th>Qt (l/min)</th>
<th>fQs</th>
<th>PP (mmHg)</th>
<th>Rt (U)</th>
<th>Ra (U)</th>
<th>Rb (U)</th>
<th>Ra/Rb</th>
</tr>
</thead>
<tbody>
<tr>
<td>46.6</td>
<td>7.48</td>
<td>0.595</td>
<td>23.6</td>
<td>3.16</td>
<td>5.30</td>
<td>7.79</td>
<td>0.68</td>
</tr>
<tr>
<td>NO + 48.8</td>
<td>7.65</td>
<td>0.555</td>
<td>19.5</td>
<td>2.55</td>
<td>4.59</td>
<td>5.73</td>
<td>0.80</td>
</tr>
<tr>
<td>54.1</td>
<td>7.31</td>
<td>0.604</td>
<td>22.0</td>
<td>3.01</td>
<td>4.98</td>
<td>7.60</td>
<td>0.66</td>
</tr>
<tr>
<td>NO + 55.2</td>
<td>7.48</td>
<td>0.559</td>
<td>19.2</td>
<td>2.57</td>
<td>4.59</td>
<td>5.82</td>
<td>0.79</td>
</tr>
<tr>
<td>64.3</td>
<td>7.31</td>
<td>0.645</td>
<td>19.4</td>
<td>2.65</td>
<td>4.11</td>
<td>7.48</td>
<td>0.55</td>
</tr>
<tr>
<td>NO + 66.7</td>
<td>7.48</td>
<td>0.602</td>
<td>17.6</td>
<td>2.35</td>
<td>3.91</td>
<td>5.91</td>
<td>0.66</td>
</tr>
<tr>
<td>83.6</td>
<td>7.48</td>
<td>0.674</td>
<td>18.5</td>
<td>2.47</td>
<td>3.67</td>
<td>7.59</td>
<td>0.48</td>
</tr>
<tr>
<td>NO + 87.7</td>
<td>7.65</td>
<td>0.631</td>
<td>17.4</td>
<td>2.27</td>
<td>3.60</td>
<td>6.16</td>
<td>0.58</td>
</tr>
</tbody>
</table>

PV_{O_2} = mixed venous oxygen tension. Qt = cardiac output. fQs = fractional shunt. PP = perfusion pressure. Rt = total vascular resistance. Ra = nonventilated vascular resistance. Rb = ventilated vascular resistance.

Changes induced by the administration of NO differ in two important respects from the assumptions. First, although the small artery constriction of the ventilated lung (b_{SAC}) decreases each time NO is administered, the change decreases as PV_{O_2} increases. Second, with administration of NO to the ventilated lung, the small artery constriction, b_{SAC}, and the strength of HPV, a_{HPV}, of the nonventilated lung also decrease. The changes again are reduced with increasing PV_{O_2}. Therefore, the inhibitory effects of NO are exerted on the ventilated and nonventilated compartments, and the efficacy of the NO action on either compartment is oxygen-dependent, as has been shown with other pulmonary vasoactive compounds.

With these modifications, the V/Q-P/Q model is able to simulate the observed results of Benzing et al., and therefore the apparently dissociated changes in PP and shunt are accounted for quantitatively. PP is determined by PP = Qt/(1/Ra + 1/Rb). At the lowest PV_{O_2}, change of PP with NO is a result of reduction of resistance in both compartments, and the reduction in the change of PP with NO as PV_{O_2} increases is a result of the oxygen-dependent loss of efficacy of NO and the interaction with the decreased influence of HPV. Conversely, shunt is determined by fQs = 1/[(Ra/Rb) + 1] so that the relatively

![Graph A](image)

![Graph B](image)

![Graph C](image)

**Fig. 1.** Computer modeling illustrates the effects of increasing PV_{O_2} when (A) neither HPV nor other active small pulmonary artery constriction are present. (B) Above, dotted lines are when small pulmonary artery constriction is present but not HPV, in the absence (solid circles) and presence (open circles) of NO. Below, the solid line is in the presence of HPV, but with and without NO are superimposed. (C) HPV and another cause of active small pulmonary artery constriction are present, without (solid circles) and with (open circles) NO.

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constant change of shunt with NO at all \( P_{V_{O2}} \) results from the approximately proportionate change of the \( R_{a/R_b} \) ratio, which also is a result of the same influences and is presumably independent of the size of the nonventilated compartment. It is not surprising that NO acts on both compartments because in patients with ARDS, the nonventilated and ventilated lung regions are distributed contiguously throughout the lungs. However, this effect and the nature and extent of the oxygen dependence of NO action require confirmation and further study.

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References