Effects of Pulmonary Blood Flow and Mixed Venous O₂ Tension on Gas Exchange in Dogs

Michael J. Bishop, M.D.,* and Frederick W. Cheney, M.D.†

The authors investigated whether the increases in venous admixture and intrapulmonary shunt which occur with increases in cardiac output (Qc) result from an effect mediated by mixed venous PVo₂ (PVVQ) or an effect mediated by the increase in pulmonary blood flow. Using a veno-venous bypass system they were able to alter PVo₂ independent of variations in Qc and vice versa. During room air ventilation of dogs with normal lungs at constant Qc, an increase in PVo₂ from 53 ± 7 (mean ± SD) to 54 ± 9 mmHg (P < 0.05) resulted in a decrease in venous admixture from 22 ± 11 to 13 ± 4% (P < 0.05). During room air ventilation of normal dogs at a constant PVo₂, increasing Qc from 2.16 ± .53 to 3.49 ± .91 l/min (P < 0.05) increased venous admixture from 10 ± 5 to 16 ± 5% (P < 0.05). During oxygen ventilation in these two groups of dogs, changes in PVo₂ and Qc had no effect on shunt.

During oxygen ventilation of dogs with significant shunts from oleic-acid-induced pulmonary edema, independent increases in either PVo₂ or pulmonary blood flow resulted in increased shunt. At constant Qc, an increase in PVo₂ from 30 ± 8 to 52 ± 5 mmHg (P < 0.05) resulted in an increase in shunt from 35 ± 12 to 45 ± 12% (P < 0.05). When PVo₂ remained constant, increasing Qc from 1.97 pm 0.42 to 3.61 ± 0.50 l/min (P < 0.05) resulted in an increase in shunt from 47 ± 17 to 53 ± 15% (P < 0.05).

The authors conclude that during oxygen ventilation, normal dogs have shunts which are unaffected by changes in blood flow or PVo₂. Increases in pulmonary blood flow increase venous admixture during room air ventilation, while increases in PVo₂ decrease venous admixture during air ventilation. In edematous lungs, increases in either PVo₂ or pulmonary blood flow increase shunt. (Key words: Ventilation; perfusion. Lungs; blood flow; edema; respiratory distress syndrome.)

MEASUREMENTS OF INTRAPULMONARY SHUNT (Qs/ Qc) or venous admixture (QVA/Qc) frequently are used to monitor the progress of patients with lung disease and are often considered indices of the success or failure of therapeutic interventions. The perception that QVA/Qc and Qs/Qc reflect the ventilatory efficiency of the lung led to the principle that increases in cardiac output (Qc), which increase mixed venous oxygen tension (PVo₂), should increase arterial oxygen tension (Pao₂). However, this theoretical analysis has not been borne out by clinical experience in patients with diffuse lung disease. Instead, Qs/Qc and QVA/Qc have varied directly with Qc, resulting in little or no improvement in Pao₂ despite increases in Qc. Laboratory investigations in dogs have largely supported the observation that both Qs/Qc and QVA/Qc increase with increases in Qc. The cause of these apparent decreases in the efficiency of gas exchange in the lungs with increases in Qc remains undefined. Some investigators have suggested that the effects are mediated by changes in the distribution of pulmonary blood flow, possibly by the dilation of vessels constricted in response to hypoxia. The present study was planned to define better the factors that govern the influence of Qc on both Qs/Qc and QVA/Qc.

We investigated the independent effects of changes in total pulmonary blood flow (Qc) and of changes in the mixed venous oxygen tension (PVo₂), a parameter which usually varies directly with Qc, when oxygen consumption remains constant.

Methods

Studies were performed on 22 mongrel dogs, weighing 22–33 kg, anesthetized with 30 mg/kg pentobarbital sodium and paralyzed with intramuscular succinylcholine. After orotracheal intubation, the animals were ventilated supine to achieve a Pao₂ of 25–30 mmHg. Femoral arterial catheters were placed via cutdown and 7F Swan-Ganz® thermodilution catheters were placed via jugular vein cutdown.

The animals were prepared for veno-venous bypass by inserting large-bore cannulae for blood withdrawal into the inferior and superior vena cavea via peripheral cutdown. A blood return cannula was advanced into the right atrium from a femoral vein. All dogs were then heparinized with 0.5 mg/kg of heparin supplemented with doses of 2.5 mg/kg every two hours.

The veno-venous bypass system (fig. 1) included a Bentley Temptrol Q-200A bubble oxygenator to which blood was pumped from the withdrawal cannulae using a Sarns model 3500 pump. The oxygenator was primed with 500 ml of lactated Ringer’s solution mixed with 500 ml of citrated dog blood obtained from previously killed animals. The blood passing through the oxygenator was exposed to a 7 l/min flow of gas consisting of nitrogen, oxygen, and carbon dioxide in proportions determined with two Bennett AO-1 air-oxygen mixers. The blood was then pumped into the right atrium using a Cole-Parmer Masterflex pump. This system permitted the gas tensions in mixed venous blood to be varied.

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over a wide range. In addition, intravascular volume could be varied rapidly and \( Q_1 \) altered by withdrawing blood from the animal into the reservoir or by infusing blood from the oxygenator reservoir into the animal.

Cardiac output was measured in triplicate using the thermodilution technique. The Swan-Ganz catheters were supplied with proximal ports 15 cm from the tip as opposed to the conventional 30 cm. This prevented the bypass withdrawal cannula from removing the cold solution from the superior vena cava.

Arterial and mixed venous blood-gas tensions were determined from samples stored in ice immediately and measured no more than five minutes after sampling. Gas tensions were measured using a Radiometer BMS3MK2 blood-gas and pH analyzer and were corrected to blood temperature recorded from the indwelling pulmonary arterial catheter. The oxygen electrode was calibrated at 0%, 21%, and 100% oxygen. Blood-gas correction factors determined at 89% oxygen using a Dynex tonometer were used to correct \( P_{\text{O}_2} \) in normal animals ventilated with oxygen.\(^{15}\) Hemoglobin was measured using an IL-OXimeter Model 182. \( Q_{\text{VA}}/Q_t \) and \( Q_1/Q_t \) were calculated by computer program from the standard Berggren equation.\(^{16,17}\) \( Q_{\text{VA}}/Q_t \) refers to this calculation for \( F_{\text{O}_2} = 0.21 \), while \( Q_1/Q_t \) refers to the calculation for \( F_{\text{O}_2} = 1.0 \).

The study consisted of three groups of animals. In animals in Group 1 (\( N = 8 \)), we studied the effects of \( P_{\text{V}_2} \) on \( Q_{\text{VA}}/Q_t \) and \( Q_1/Q_t \) while \( Q_1 \) remained constant. In animals in Group 2 (\( N = 8 \)), we studied the effects of high and low \( Q_1 \) on \( Q_{\text{VA}}/Q_t \) and \( Q_1/Q_t \) while \( P_{\text{V}_2} \) remained constant. In animals in Group 3 (\( N = 6 \)), we studied the effects of \( P_{\text{V}_2} \) and \( Q_1 \) and \( Q_1/Q_t \) in dogs with diffuse lung injury.

Data were analyzed using Student’s \( t \) test for paired observations to compare effects at high vs. low \( P_{\text{V}_2} \), and high vs. low \( Q_1 \). Changes were considered significant if \( P < 0.05 \).

**Group 1: Effect of \( P_{\text{V}_2} \) at Constant \( Q_1 \)**

Veno-venous bypass of up to 30% of \( Q_1 \) was achieved without collapsing the return vessels. Variation of \( P_{\text{V}_2} \) was achieved by flowing either 95% \( \text{N}_2 \)/5% \( \text{CO}_2 \) or 95% \( \text{O}_2 \)/5% \( \text{CO}_2 \) through the oxygenator, alternating the sequence of alternate animals. Measurements of arterial and mixed venous blood gases as well as pulmonary and systemic pressures were made at both high and low \( P_{\text{V}_2} \) during both room air and oxygen ventilation. Two animals were studied during room air ventilation only. Although \( Q_1 \) generally remained constant when the gas in the oxygenator was varied, several dogs required the appropriate transfer of blood between the animal and the oxygenator reservoir to keep \( Q_1 \) constant. When switching from low to high or high to low \( P_{\text{V}_2} \), \( Q_1 \) was measured and sampling performed only when \( Q_1 \) remained within 10% of the value obtained initially.

**Group 2: Effect of \( Q_1 \) at Constant \( P_{\text{V}_2} \)**

After measurement of baseline \( Q_1 \) and \( P_{\text{V}_2} \), veno-venous bypass was initiated. Blood was withdrawn from the animal into the oxygenator reservoir to lower \( Q_1 \) to 75% of baseline, or blood was infused into the animal to raise \( Q_1 \) to 125% of baseline. The order in which \( Q_1 \) was changed was alternated among animals. Once the desired \( Q_1 \) was reached, \( P_{\text{V}_2} \) was adjusted to within 10% of baseline by altering the proportions of nitrogen and oxygen flowing through the oxygenator. When \( Q_1 \) and \( P_{\text{V}_2} \) were adjusted appropriately, blood-gas and hemodynamic measurements were made in duplicate. All measurements were performed during room air ventilation and repeated while the animal was ventilated with pure oxygen.

**Group 3: Effect of Independent \( Q_1 \) and \( P_{\text{V}_2} \) Variation during Lung Injury**

Because of the small \( Q_1/Q_t \) in the normal dog lung,\(^{18}\) we also studied the mechanisms of \( Q_1/Q_t \) increases with increased \( Q_1 \) in six animals with diffuse lung injury induced by oleic acid. Oleic acid injection produces a diffuse lung injury which becomes a stable lesion after 24 h, and heals over 3-7 days. Animals underwent right
Table 1. Effects of P\textsubscript{O\textsubscript{2}} on Hemodynamic and Blood-gas Values in the Normal Lung with Q\textsubscript{i} Constant

<table>
<thead>
<tr>
<th></th>
<th>Room Air Ventilation</th>
<th>Oxygen Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low P\textsubscript{O\textsubscript{2}}</td>
<td>High P\textsubscript{O\textsubscript{2}}</td>
</tr>
<tr>
<td>Q\textsubscript{i} (/min)</td>
<td>2.86 ± 0.47</td>
<td>2.88 ± 0.71</td>
</tr>
<tr>
<td>P\textsubscript{a}O\textsubscript{2} (mmHg)</td>
<td>33 ± 7</td>
<td>54 ± 9*</td>
</tr>
<tr>
<td>Q\textsubscript{VA}/Q\textsubscript{i} (%)</td>
<td>22 ± 11</td>
<td>13 ± 4*</td>
</tr>
<tr>
<td>Q\textsubscript{i}/Q\textsubscript{a} (%)</td>
<td>5 ± 2</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>P\textsubscript{a}O\textsubscript{2} (mmHg)</td>
<td>64 ± 10</td>
<td>98 ± 7*</td>
</tr>
<tr>
<td>P\textsubscript{a}CO\textsubscript{2} (mmHg)</td>
<td>26 ± 6</td>
<td>25 ± 5</td>
</tr>
<tr>
<td>P\textsubscript{a}CO\textsubscript{2} (mmHg)</td>
<td>34 ± 8</td>
<td>34 ± 10</td>
</tr>
<tr>
<td>pH\textsubscript{E}</td>
<td>7.34 ± 0.09</td>
<td>7.36 ± 0.10</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>10 ± 1</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>3 ± 1</td>
<td>2 ± 0</td>
</tr>
<tr>
<td>PVR (dyn·s·cm\textsuperscript{-5})</td>
<td>251 ± 83</td>
<td>256 ± 79</td>
</tr>
</tbody>
</table>

Values are mean values ± SD. n = 8 during room air ventilation and n = 6 during oxygen ventilation. PAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance.

* P < 0.05.

atrial injection of 0.06 ml/kg oleic acid 24 h prior to study. The oleic acid was injected while the dog was awake and resulted in some initial coughing and vomiting, but animals continued to behave normally otherwise. The lesion remained stable with the dog in either the awake or anesthetized state, but usually rose upon induction of anesthesia. Only Q\textsubscript{VA}/Q\textsubscript{i} was evaluated in injured animals because the severity of the induced lung lesion necessitated a high F\textsubscript{CO\textsubscript{2}}. Studies at constant P\textsubscript{a}O\textsubscript{2} with changing Q\textsubscript{i} at constant Q\textsubscript{i} with changing P\textsubscript{a}O\textsubscript{2} were performed in each animal using the methods described for Group 1 and 2 animals. The order in which these studies were performed was alternated.

Results

Group 1: Effect of P\textsubscript{a}O\textsubscript{2} at Constant Q\textsubscript{i}

With Q\textsubscript{i} stable, we were able to vary P\textsubscript{a}O\textsubscript{2} between 33 ± 7 and 54 ± 9 mmHg (mean ± SD) (table 1). With the increase in P\textsubscript{a}O\textsubscript{2}, Q\textsubscript{VA}/Q\textsubscript{i} decreased from 22 ± 11 to 13 ± 4%, resulting in an increase in P\textsubscript{a}CO\textsubscript{2} from 64 to 98 mmHg. Mean pulmonary artery pressure, pulmonary artery wedge pressure, and pulmonary vascular resistance (PVR) all remained unchanged.

During ventilation with oxygen, changing P\textsubscript{a}O\textsubscript{2} from 33 ± 2 to 61 ± 11 mmHg resulted in an insignificant change in Q\textsubscript{i}/Q\textsubscript{a} (table 1). Again, pulmonary artery pressure, pulmonary artery wedge pressure, and PVR remained unchanged.

Group 2: Effects of Changes in Q\textsubscript{i} at Constant P\textsubscript{a}O\textsubscript{2}

During room air ventilation, increasing Q\textsubscript{i} from 2.16 ± 0.53 to 3.49 ± 0.91 l/min at constant P\textsubscript{a}O\textsubscript{2} resulted in an increase in Q\textsubscript{VA}/Q\textsubscript{i} from 10 ± 5 to 16 ± 5% (table 2). Pulmonary artery wedge pressure was increased from 2 to 5 mmHg to achieve this difference in Q\textsubscript{i}.

Table 2. Effects of Q\textsubscript{i} on Hemodynamic and Blood-gas Values in the Normal Lung with P\textsubscript{a}O\textsubscript{2} Constant

<table>
<thead>
<tr>
<th></th>
<th>Room Air Ventilation</th>
<th>Oxygen Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Q\textsubscript{i}</td>
<td>High Q\textsubscript{i}</td>
</tr>
<tr>
<td>Q\textsubscript{i} (/min)</td>
<td>2.16 ± 0.53</td>
<td>3.49 ± 0.91*</td>
</tr>
<tr>
<td>P\textsubscript{a}O\textsubscript{2} (mmHg)</td>
<td>37 ± 6</td>
<td>37 ± 6</td>
</tr>
<tr>
<td>Q\textsubscript{VA}/Q\textsubscript{i} (%)</td>
<td>10 ± 5</td>
<td>16 ± 5*</td>
</tr>
<tr>
<td>P\textsubscript{a}CO\textsubscript{2} (mmHg)</td>
<td>73 ± 9*</td>
<td>73 ± 9*</td>
</tr>
<tr>
<td>P\textsubscript{a}CO\textsubscript{2} (mmHg)</td>
<td>31 ± 3</td>
<td>41 ± 5</td>
</tr>
<tr>
<td>pH\textsubscript{E}</td>
<td>7.27 ± 0.04</td>
<td>7.26 ± 0.07</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>10 ± 2</td>
<td>13 ± 5</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>2 ± 1</td>
<td>5 ± 3*</td>
</tr>
<tr>
<td>PVR (dyn·s·cm\textsuperscript{-5})</td>
<td>294 ± 58</td>
<td>180 ± 106*</td>
</tr>
</tbody>
</table>

Values are mean values ± SD. n = 8. PAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance.

* P < 0.05.
TABLE 3. Effects of Varying F\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} or \textit{Q}\textsubscript{i} during Oxygen Ventilation in Animals with Oleic Acid Lung Injury

<table>
<thead>
<tr>
<th>\textit{Q}\textsubscript{i} (l/min)</th>
<th>\textbf{Low P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2}}</th>
<th>\textbf{High P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2}}</th>
<th>\textbf{Low \textit{Q}\textsubscript{i}}</th>
<th>\textbf{High \textit{Q}\textsubscript{i}}</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textbf{2.48 ± 0.40}</td>
<td>\textbf{2.51 ± 0.38}</td>
<td>\textbf{1.97 ± 0.42}</td>
<td>\textbf{3.61 ± 0.50*}</td>
<td></td>
</tr>
<tr>
<td>\textbf{30 ± 8}</td>
<td>\textbf{52 ± 3*}</td>
<td>\textbf{43 ± 8}</td>
<td>\textbf{44 ± 8}</td>
<td></td>
</tr>
<tr>
<td>\textbf{39 ± 12}</td>
<td>\textbf{43 ± 12*}</td>
<td>\textbf{47 ± 17}</td>
<td>\textbf{55 ± 15*}</td>
<td></td>
</tr>
<tr>
<td>\textbf{111 ± 110}</td>
<td>\textbf{186 ± 140*}</td>
<td>\textbf{152 ± 147}</td>
<td>\textbf{126 ± 117}</td>
<td></td>
</tr>
<tr>
<td>\textbf{30 ± 4}</td>
<td>\textbf{28 ± 3}</td>
<td>\textbf{28 ± 5}</td>
<td>\textbf{29 ± 6}</td>
<td></td>
</tr>
<tr>
<td>\textbf{40 ± 6}</td>
<td>\textbf{40 ± 4}</td>
<td>\textbf{39 ± 7}</td>
<td>\textbf{39 ± 6}</td>
<td></td>
</tr>
<tr>
<td>\textbf{7.32 ± 0.01}</td>
<td>\textbf{7.29 ± 0.05}</td>
<td>\textbf{7.27 ± 0.05}</td>
<td>\textbf{7.27 ± 0.05}</td>
<td></td>
</tr>
<tr>
<td>\textbf{11 ± 4}</td>
<td>\textbf{11 ± 2}</td>
<td>\textbf{8 ± 2}</td>
<td>\textbf{13 ± 5*}</td>
<td></td>
</tr>
<tr>
<td>\textbf{2 ± 3}</td>
<td>\textbf{1 ± 3*}</td>
<td>\textbf{0 ± 3}</td>
<td>\textbf{2 ± 3*}</td>
<td></td>
</tr>
<tr>
<td>\textbf{318 ± 126}</td>
<td>\textbf{352 ± 156}</td>
<td>\textbf{370 ± 120}</td>
<td>\textbf{256 ± 72}</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean values ± SD. n = 6. P\textsubscript{\textit{A}}P = mean pulmonary artery pressure; P\textsubscript{\textit{A}P\textsubscript{\textit{W}}} = mean pulmonary artery wedge pressure; P\textsubscript{\textit{V}}\textsubscript{\textit{R}} = pulmonary vascular resistance. *P < 0.05.

Pulmonary vascular resistance decreased significantly with the increased \textit{Q}\textsubscript{i} from 294 ± 58 to 180 ± 106 dyn·s·cm\textsuperscript{-5}. There was a nonsignificant rise in mean pulmonary artery pressure from 10 ± 2 to 13 ± 5 mmHg.

During oxygen ventilation in dogs with normal lungs, an increase in \textit{Q}\textsubscript{i} from 1.90 ± 0.35 to 3.36 ± 0.89 l/min at constant P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} did not cause a rise in P\textsubscript{\textit{A}}\textsubscript{P} or P\textsubscript{\textit{A}}\textsubscript{P\textsubscript{\textit{W}}}, pulmonary artery pressure, and P\textsubscript{\textit{V}}\textsubscript{\textit{R}} did not change significantly.

**GROUP 3: DIFFUSE LUNG INJURY**

Animals in Group 3 had a one-day-old oleic-acid-induced diffuse lung injury that resulted in a mean pre-bypass \textit{Q}/\textit{Q}\textsubscript{i} of 37%.

In these animals, an increase in P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} from 30 to 52 mmHg resulted in a rise in P\textsubscript{\textit{A}}\textsubscript{P} from 39 ± 12 to 43 ± 12% (table 3). Pulmonary vascular resistance again remained unchanged. Despite the increase in calculated shunt, the large rise in venous O\textsubscript{2} content resulting from the increased P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} caused P\textsubscript{\textit{A}}\textsubscript{O\textsubscript{2}} to rise from 111 ± 110 mmHg to 186 ± 140 mmHg.

With P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} constant, an increase in \textit{Q}\textsubscript{i} from 1.97 ± 0.42 to 3.61 ± 0.50 l/min caused an increase in \textit{Q}/\textit{Q}\textsubscript{i} from 47 ± 17 to 53 ± 15% and an increase in mean pulmonary arterial pressure (P\textsubscript{\textit{A}}} from 8 ± 2 to 13 ± 5 mm. P\textsubscript{\textit{A}}\textsubscript{O\textsubscript{2}} did not change significantly despite the increased \textit{Q}\textsubscript{i}.

**Discussion**

The purpose of this study was to clarify the factors responsible for an increase in shunt or venous admixture when cardiac output increases. Normally, when \textit{Q}\textsubscript{i} increases without a rise in oxygen consumption, P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} will rise. However, using veno-venous bypass, we were able to vary pulmonary blood flow and P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} independently without having to resort to the use of vasoactive substances which alter the regional distribution of pulmonary blood flow.\textsuperscript{16}

**EFFECTS OF VARYING \textit{Q}\textsubscript{i} WITH P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} CONSTANT**

In dogs with normal lungs, increases in pulmonary blood flow during air ventilation with P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} constant resulted in increases in Q\textsubscript{\textit{VA}}/Q\textsubscript{i} (table 1). During 100% oxygen ventilation, Q\textsubscript{\textit{VA}}/Q\textsubscript{i} showed a nonsignificant rise from 5 ± 2 to 9 ± 4%. This trend became significant in dogs with edematous lungs.

The increased shunt during oxygen ventilation must result from either an increase in anatomic shunts or increased flow past unventilated alveoli. The former has been demonstrated not to be likely.\textsuperscript{19} More likely is the recruitment of vessels in areas previously unperfused. The increase in P\textsubscript{\textit{A}}} from 8 ± 2 to 13 ± 5 mmHg (table 3) may well have overcome the ability of some vessels in hypoxic regions to constrict appropriately. Left atrial pressure rises also have been shown to affect the pulmonary vascular response to hypoxia,\textsuperscript{20} but the small rise from 0 to 2 mmHg would not produce a significant inhibition of hypoxic vasoconstriction.

The increase in Q\textsubscript{\textit{VA}}/Q\textsubscript{i} may be explicable by the increase in true shunt. However, the possible role of alterations in ventilation/perfusion (V\textsubscript{\textit{A}}/Q\textsubscript{i}) ratios also must be considered.\textsuperscript{21} Since pulmonary blood flow increased from 2.16 ± 0.53 to 3.49 ± 0.91 l/min, the V\textsubscript{\textit{A}}/Q\textsubscript{i} ratios for individual lung units obviously decreased. Because of the nonlinearity of the oxygen-hemoglobin dissociation curve, there is a much greater effect on P\textsubscript{\textit{A}}\textsubscript{O\textsubscript{2}} in units with V\textsubscript{\textit{A}}/Q\textsubscript{i} ratios of less than 1, and an increase in calculated Q\textsubscript{\textit{VA}}/Q\textsubscript{i} is predictable even in the absence of redistribution of flow.\textsuperscript{22}

**EFFECTS OF VARYING P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} WITH \textit{Q}\textsubscript{i} CONSTANT**

V\textsubscript{\textit{A}}/Q\textsubscript{i} changes are also important in determining P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} effects at constant \textit{Q}\textsubscript{i}. When P\textsubscript{\textit{V}}\textsubscript{\textit{O}}\textsubscript{2} increases, the
PO₂ in low Vₐ/Q units rises more than that of lung units with high Vₐ/Q ratio. In a lung unit with a high Vₐ/Q ratio, PᵥO₂ affects the PO₂ of the unit relatively little. One extreme example is found with dead space (Vₐ/Q = ∞) when PᵥO₂ has no effect on alveolar PO₂. A lung unit with a low Vₐ/Q ratio has a PO₂ that is determined largely by the PᵥO₂. As Vₐ/Q decreases, there is less fresh gas in the alveolus, and the PO₂ will approach that of the mixed venous blood perfusing the lung unit. Increases or decreases in the alveolar PO₂ of lung units whose PO₂ is on the steep portion of the oxygen hemoglobin dissociation curve will result in changes in PO₂ despite little or no change in overall ideal alveolar PAO₂. Consequently, QᵥVA/Q is the term that should theoretically decrease with increased PᵥO₂ even in the absence of redistribution of pulmonary blood flow. The extent of the decrease will depend on hemoglobin concentration, PᵥO₂, and the actual Vₐ/Q ratios. Such a decrease was indeed observed in our animals during room air ventilation.

However, PᵥO₂ might have an opposite effect on QᵥVA/Q, by contributing to a redistribution of blood flow through inhibition of hypoxic pulmonary vasoconstriction (HPV). Although the predominance of current thought favors the alveolus as the receptor site for the HPV response, evidence of a PᵥO₂ effect on HPV has been provided by several authors. In addition, PᵥO₂ affects PAO₂, and, thus, influences regional pulmonary vascular tone. Presumably, any inhibition of HPV by increased PᵥO₂ would increase flow to low Vₐ/Q units and result in increased QᵥVA/Q. But, since increased PᵥO₂ also must have increased PAO₂ in low Vₐ/Q units as discussed previously, we are unable to accurately define whether there was significant inhibition of HPV with consequent increased flow to these units.

The effect was not great enough to cause a rise in QᵥVA/Q with high PᵥO₂.

During ventilation with 100% oxygen in animals with large shunts due to oleic acid injury, a significant rise occurred in Q/V, when PᵥO₂ was increased. In dogs with normal lungs, the slight increase in Q/V was not significant. These changes confirm the rise in Q/V with increased PᵥO₂ reported by Smith et al. using a similar system. The most likely mechanism here is a redistribution of blood flow in the lungs due to inhibition of HPV. Such an effect might be predicted whether the HPV receptor is purely alveolar or alveolar plus vascular in location, since in unventilated lung units the PᵥO₂ would determine the PO₂ present at an alveolar receptor site. Any increase would be expected to inhibit HPV.

Investigators using the multiple inert gas technique in dogs during ventilation with oxygen have shown that the primary effect of a fall in Q/V on perfusion distribution is to reduce flow to regions of true shunt. Our studies demonstrate that this redistribution of blood flows results from at least two factors: 1) change in total pulmonary blood flow, and 2) change in PᵥO₂.

The factors determining the direct relationship between QᵥVA/Q and Q/V in intact animals must be considered in light of the altered Vₐ/Q relationships resulting from changing Q/V. Although a rise in total pulmonary blood flow will increase QᵥVA/Q, this effect may be partially counterbalanced during a rise in Q/V by a fall in QᵥVA/Q, resulting from increased PᵥO₂. The net result, a rise in QᵥVA/Q, agrees with the prediction by West using computer models of a lung with substantial Vₐ/Q inequality.

An important clinical implication resulting from this study is the relatively greater effect in treating arterial hypoxemia of increasing PᵥO₂ by decreasing oxygen consumption rather than of increasing PᵥO₂ by increasing Q/V. Thus, in a patient with hypoxemia resulting largely from Vₐ/Q inequality, reducing peripheral oxygen demand should result in a higher PAO₂ and lower QᵥVA/Q.

During the use of high inspired oxygen tensions, the effects of Vₐ/Q inequality are minimized. Consequently, decreasing peripheral oxygen consumption may not have as beneficial results on the PAO₂ because Q/V might increase as it did in our experimental model. The ultimate effect of changes in PᵥO₂ on PAO₂ will be a function of both the increase in Q/V, Q/V, and the rise in PᵥO₂. In our dogs, a large rise in the venous oxygen content occurred when PᵥO₂ rose from 30 to 52 mmHg (table 3), but this is reflected in only a small rise in the arterial oxygen content with a rise in PAO₂ from 111 to 186 mmHg. This rise remains small because of the concurrent increase in Q/V, from 39 to 43%.

The effects we have shown of PᵥO₂ and pulmonary blood flow on gas exchange demonstrate a caveat noted by other authors as well: changes in QᵥVA/Q or Q/V/Q do not necessarily imply a progression or remission of the intrinsic pulmonary process but may reflect circulatory changes. We conclude that the pulmonary blood flow and PᵥO₂ affect calculated QᵥVA/Q and Q/V. The magnitude and direction of these effects depend on the inspired oxygen concentration and the presence or absence of Vₐ/Q inequality.

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