Response of Pulmonary Venous Admixture*  
A Means of Comparing Therapies?

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Patients who require cardiopulmonary bypass have a reproducible increase in interstitial pulmonary water and pulmonary venous admixture, a decrease in functional residual capacity, and a mild arterial hypoxemia. Therefore, such patients are good subjects for evaluating therapy with positive end-expiratory pressure and steroids, both of which are controversial. We sought to determine if the response of the pulmonary venous admixture to varying concentrations of inspired oxygen could affect the apparent efficacy of these types of therapy. Results of our study are presented.

The efficacy of various types of pulmonary therapy is often questioned. This may stem from investigative methods. Evaluation of pulmonary gas exchange usually involves the determination of arterial oxygen tension (PaO₂) and the calculation of the alveolar-to-arterial oxygen tension difference (P[Al-a]O₂) or pulmonary venous admixture, while pure oxygen is administered. Evaluation performed with a fractional concentration of inspired oxygen (FIO₂) of 1.0 allows right-to-left intrapulmonary shunting of blood to be measured; however, the contribution of such hypoxemia-producing derangements such as abnormalities of oxygen diffusion and pulmonary areas with low but finite ventilation-to-perfusion ratios cannot be appreciated. Since different treatments can affect each of these derangements uniquely, comparisons of various therapies may be difficult and incomplete if performed only at elevated FIO₂. In addition, because the administration of oxygen can affect each of these derangements differently, therapeutic efficacy may be difficult to determine with a single FIO₂.

We previously determined that patients with pulmonary venous admixture respond by an initial decrease and then an increase in venous admixture as the FIO₂ is increased.¹ This biphasic response of the venous admixture represents the interactions of the various sources of venous admixture in increasing FIO₂. Because therapies can affect the sources of venous admixture differently, the evaluation of therapies may be better performed by examining the biphasic response of venous admixture to increased concentrations of FIO₂ from 0.21 to 1.0.

Patients who undergo major operations may experience a decrease in PaO₂ secondary to an increase in pulmonary venous admixture. Often, such patients receive therapy with mechanical ventilation, especially with positive end-expiratory pressure (PEEP) and an elevated FIO₂. Systemic steroid administration has been recommended for such postoperative pulmonary dysfunction,²³ but the evidence of beneficial pulmonary effects of therapy with steroids and PEEP in such patients is controversial.¹⁸⁻¹⁰ Such controversy may be related to the FIO₂ and its effect on pulmonary venous admixture. Therefore, to test our hypothesis, we sought to determine if the biphasic response of pulmonary venous admixture can be useful in evaluating the effects of therapy with PEEP and steroids.

Materials and Methods

Written informed consent was obtained from 20 consecutive patients who required cardiopulmonary bypass for coronary artery-saphenous vein grafting operations. Before surgery, spirometric studies were performed and arterial blood sampled for determination of pH, PaO₂, and arterial carbon dioxide tension (PaCO₂) while patients breathed room air. Ten patients were assigned in random order to receive methylprednisolone sodium succinate diluent as a placebo, and the remaining ten patients received 30 mg of methylprednisolone sodium succinate per kilogram of body weight. Both the drug and the placebo were administered intravenously one hour prior to cardiopulmonary bypass and again six hours later. After induction of anesthesia and oral-endotracheal intubation, general anesthesia was maintained with halothane, intravenously administered fentanyl, or morphine combined with nitrous oxide and oxygen. Each patient had radial and pulmonary arterial catheters inserted.

Immediately after their operations, all patients were admitted to the surgical intensive care unit. Mechanical ventilatory support was maintained with a volume-cycled ventilator (J. H. Emerson Co.) that delivered a tidal volume of 12 ml/kg with a frequency sufficient to maintain a pH of the
arterial blood greater than 7.35. A threshold-resistor exhalation PEEP valve (J. H. Emerson Co.) provided all patients with 4 mm Hg of PEEP. A calibrated, high-flow air-oxygen blender (bird Corp.) with an accuracy of ±0.01 of the indicated FIO2 provided a continuous flow of gas with an FIO2 of 0.4, which was then heated and humidified. All patients were weaned from mechanical ventilation within an hour after the second dose of drug. At that time, therapy with PEEP was either maintained at 4 mm Hg or discontinued, and the FIO2 was decreased to 0.209 (room air). Samples of arterial and mixed venous or pulmonary arterial blood were collected anaerobically 30 minutes later. Blood gas tensions and pH were determined with a blood gas analyzer using a liquid calibrating system (Radiometer ABL-1).

Blood gas tensions were corrected to the patients' body temperature. Pulmonary venous admixture (Qsp/Qt) was calculated using the following equation:

\[
\text{Qsp/Qt} = \frac{\text{CcO}_2 - \text{CaO}_2}{\text{CcO}_2 - \text{CvO}_2}
\]

where \(\text{CaO}_2 = 1.34 \text{ (Hgb)} \times (\text{SaO}_2) + 0.0031 \text{ PaO}_2\); \(\text{CvO}_2 = 1.34 \text{ (Hgb)} \times (\text{SvO}_2) + 0.0031 \text{ PaO}_2\) and \(\text{CcO}_2 = 1.34 \text{ (Hgb)} \times (\text{ScO}_2) + 0.0031 \text{ (Pb} - \text{ PaO}_2) \text{ FIO2} - \text{ PaCO}_2\).

The oxygen saturation of arterial, pulmonary arterial, and pulmonary end-capillary hemoglobin (Hgb) is represented by

**Figure 1.** Pulmonary venous admixture (mean ± 1 SE) as function of FIO2 for patients who received placebo and PEEP (dotted line) and who received placebo alone (solid line). Asterisk indicates significant difference (P ≤ 0.05) between values with and without PEEP at one FIO2. Dagger indicates significant difference (P ≤ 0.05) compared to value obtained when FIO2 was 40 percent.

**Figure 2.** Pulmonary venous admixture (mean ± 1 SE) as function of FIO2 for patients who received methylprednisolone (dotted line) and who received placebo alone (solid line). Asterisk indicates significant difference (P ≤ 0.05) between values with and without methylprednisolone at one FIO2. Dagger indicates significant difference (P ≤ 0.05) compared to value obtained when FIO2 was 40 percent.

\(\text{SaO}_2\), \(\text{SvO}_2\), and \(\text{ScO}_2\), respectively; and \(\text{Pb}\) is barometric pressure, which was measured daily. Values were calculated by using the method described by Ruiz et al. The respiratory quotient was assumed to be equal to one; 1.34 is the oxygen capacity of hemoglobin in milliliters of oxygen per gram of hemoglobin; and 0.0031 is the solubility coefficient of oxygen in milliliters per millimeter of mercury per 100 ml of blood. The arterial-mixed venous oxygen content difference (C(a-v)O2) also was calculated. The FIO2 was increased to 0.4, 0.6, 0.8, and 1.0. Fifteen minutes after each increase, all measurements and calculations were repeated. Next, if therapy with PEEP had been discontinued initially, PEEP was readministered; if it had been continued initially, it was removed. In both cases the FIO2 was decreased to 0.21, and measurements and calculations were performed again at the same values for FIO2 as before. Throughout the period of study, patients remained in the supine position and received no medication or endotracheal suctioning. The PaO2 was measured 24 hours after tracheal extubation while patients breathed room air.

Data were expressed as the mean ± 1 SE. Measurements and calculations obtained at the same values for FIO2 were compared by an analysis of variance and by Duncan's multiple-comparison analysis. After tracheal extubation the values for PaO2 were compared using Student's t-test.
RESULTS

Patients who received methylprednisolone had a mean age (58 ± 3 years) that was not significantly different from those who received the placebo (57 ± 2 years). The results of preoperative spirometric testing were normal in all patients. Patients who received steroids had an average PaO₂ of 88 ± 3 mm Hg; that of patients who received placebo was not significantly different and averaged 85 ± 4 mm Hg. Times of anesthesia and of cardiopulmonary bypass for patients who received steroids averaged 4.16 ± 0.67 hours and 1.62 ± 0.42 hours, respectively. Patients who received placebo had times of anesthesia and of cardiopulmonary bypass of 4.32 ± 0.72 hours and 1.72 ± 0.88 hours, respectively; these times were not different from those for patients who received steroids.

Fluids added to the pump prime consisted of whole blood and Ringer’s lactate solution. Total volumes and types of fluid administered were similar. No patient had a pulmonary arterial occlusion pressure greater than 15 mm Hg during the postoperative period of study. The values for C(a-v)O₂ ranged from 5.50 to 6.42 volumes percent and were unaffected by PEEP, FIO₂, or administration of methylprednisolone. The PaCO₂ and arterial pH, which were unchanged throughout the period of study, ranged from 33 to 42 mm Hg and from 7.39 to 7.43, respectively.

The responses of venous admixture to varied levels of FIO₂ in patients who received placebo, PEEP, or steroids alone and in combination are presented in Figures 1 to 3. The highest venous admixture occurred when patients breathed room air and received the placebo only. When patients breathed room air, venous admixture was reduced equally by either therapy with PEEP or with steroids. When both were administered simultaneously, venous admixture was reduced twice as much. The lowest venous admixtures were unaffected by therapy with PEEP or with steroids. When the FIO₂ of those patients who did not receive steroids was increased to 1.0, venous admixture remained unchanged; however, when patients who were given steroids had the FIO₂ increased to 1.0, venous admixture increased. Right-to-left intrapulmonary shunting was greatest in those patients who received only steroids and was least in those patients who received placebo and PEEP when they breathed pure oxygen. Shunting of patients who received both steroids and PEEP or only placebo was intermediate.

The measurements of PaO₂ directly reflected venous admixture. When patients breathed room air, the highest values for PaO₂ occurred in those receiving PEEP and steroids (Table 1). Patients who received the placebo but not PEEP and breathed room air had significantly lower values for PaO₂. Increased FIO₂ caused PaO₂ to increase in all cases, but there appeared to be no difference between the values for PaO₂ of patients who did and did not receive PEEP or steroids. Twenty-four hours after

<p>| Table 1—Mean PaO₂ at Various Levels of FIO₂ |
| Mean PaO₂, mm Hg (±SE) |</p>
<table>
<thead>
<tr>
<th>FIO₂</th>
<th>Placebo Alone</th>
<th>Placebo and PEEP</th>
<th>Methylprednisolone Alone</th>
<th>Methylprednisolone and PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.21</td>
<td>53 ± 2</td>
<td>55 ± 3*</td>
<td>57 ± 3*</td>
<td>62 ± 3*</td>
</tr>
<tr>
<td>0.40</td>
<td>87 ± 6</td>
<td>92 ± 6</td>
<td>85 ± 7</td>
<td>97 ± 8</td>
</tr>
<tr>
<td>0.60</td>
<td>136 ± 11</td>
<td>143 ± 13</td>
<td>124 ± 12</td>
<td>150 ± 12</td>
</tr>
<tr>
<td>0.80</td>
<td>207 ± 19</td>
<td>227 ± 19</td>
<td>187 ± 20</td>
<td>208 ± 21</td>
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<tr>
<td>1.00</td>
<td>288 ± 25</td>
<td>327 ± 20*</td>
<td>265 ± 27*</td>
<td>294 ± 22</td>
</tr>
</tbody>
</table>

*P < 0.05 compared to placebo alone.
extubation, while breathing room air, patients who had received the placebo had a significantly lower mean PaO$_2$ (61.4 ± 2.4 mm Hg) than those who had received steroids (69.5 ± 3.2 mm Hg) (P ≤ 0.05).

**DISCUSSION**

We previously evaluated pulmonary gas exchange in patients with respiratory failure varying in degrees of severity. The arterial and mixed venous blood gas tensions and pH were determined while patients breathed inspired oxygen in increments from room air to pure oxygen. Using the two-compartment model shunt equation, venous admixture was calculated. All patients had a uniform response. Venous admixture decreased significantly as FIO$_2$ was increased from 0.21 to 0.4, remained unchanged until the FIO$_2$ was increased to 0.7, and then increased as FIO$_2$ was increased to 1.0 (Fig 4); this resulted in a biphasic response.

We thought that the initial decrease in venous admixture resulted from an increased alveolar oxygen tension (PaO$_2$), which either increased the diffusion of oxygen across the alveolar capillary space or masked the venous admixture, producing effects of pulmonary areas with low but finite ventilation-to-perfusion ratios. Venous admixture with intermediate levels of FIO$_2$ primarily reflected right-to-left intrapulmonary shunting of blood. The increase in calculated venous admixture with an FIO$_2$ of greater than 0.7 was thought to result from two possible factors. Critical ventilation-to-perfusion ratios may exist, which promote alveolar collapse even when FIO$_2$ is less than 1.0. After such collapse, intrapulmonary shunting of blood would be increased.

The second factor which might promote increased venous admixture is an alteration of hypoxic pulmonary vasoconstriction. Normally, pulmonary perfusion is decreased to areas of lung with low ventilation-to-perfusion ratios because pulmonary arteriolar vasoconstriction is increased. Such a change would tend to normalize the matching of ventilation to perfusion. Were the FIO$_2$ increased enough, the PaO$_2$ would also increase, which, in turn, would depress hypoxic pulmonary vasoconstriction and thereby increase both perfusion and venous admixture. Thus, the biphasic response of venous admixture implies that the evaluation of pulmonary gas exchange with a single FIO$_2$ can lead to wrong conclusions about the efficiency of a specific therapy. In addition, because the biphasic response of venous admixture to increasing FIO$_2$ reflects the sources of admixture, this response may be useful in evaluating various types of therapy. We investigated this possibility.

Abnormal pulmonary gas exchange is manifested by arterial hypoxemia and increased pulmonary venous admixture and often occurs in patients who undergo cardiopulmonary bypass during open-heart operations. Some investigators believe that pulmonary dysfunction is caused by aggregation of white blood cells and platelets within the pulmonary microvasculature. Methylprednisolone has been shown to reduce such sequestration and, thus, is thought to have potentially beneficial effects. Patients who undergo cardiopulmonary bypass also have a decrease in functional residual capacity (FRC). The cause of diminished pulmonary volume is unclear, but some authors have speculated that the diminished volume reflects closure of small airways secondary to increased interstitial pulmonary water. The recommended therapy has been the application of PEEP to increase FRC, which, in turn, may improve alveolar-capillary gas exchange, decrease venous admixture, and increase PaO$_2$. Therapy with steroids has been shown to reduce pulmonary water after aspiration of acid; this suggests that steroid therapy might also improve the ventilation of patients who are likely to develop
edema of the small airways. Thus, there is evidence to suggest that the use of therapy with both steroids and PEEP might improve intrapulmonary gas exchange after cardiopulmonary bypass; however, results of previous studies have been conflicting.\textsuperscript{15-19}

The conflict may result because the various sources of pulmonary venous admixture might be affected differently by therapy with systemic steroids and PEEP. Most studies have evaluated pulmonary gas exchange through determinations of venous admixture or PaO\textsubscript{2} while elevated concentrations of oxygen are breathed. Under these conditions the effects of therapy on sources of venous admixture other than direct right-to-left intrapulmonary shunting may not be recognized. Such problems may be avoided by considering the effect of therapy on the biphasic curve of venous admixture, since the curve reflects the cumulative effects of various causes of venous admixture. If we consider both the magnitude of change in venous admixture and the shape of the curve, a more accurate and useful way to evaluate therapies to improve pulmonary function may be provided. For this reason, we evaluated the separate and combined effects of therapy with systemic steroids and with PEEP on postoperative pulmonary function in the present study at various levels of FI\textsubscript{O}\textsubscript{2}.

We calculated pulmonary venous admixture while patients breathed room air. We believed that this would make venous admixture most apparent when it resulted from impaired diffusion of oxygen across the alveolar space to the pulmonary capillary blood and from areas with low, but finite, ventilation-to-perfusion ratios. Since a low FI\textsubscript{O}\textsubscript{2} would be most likely to reveal symptoms of these abnormalities, it would, therefore, be most likely also to reveal any effect which therapy with PEEP and methylprednisolone might have on these symptoms. We found that methylprednisolone and PEEP equally reduced pulmonary venous admixture when patients breathed room air. Patients who received methylprednisolone and also received PEEP had twice as much reduction in venous admixture as those receiving either therapy alone; this indicates that the effects were additive. When patients breathed 40 percent oxygen, venous admixture decreased to similar levels in all patients, whether or not PEEP or steroids were administered. Thus, the effects of therapy with PEEP and steroids were not apparent when 40 percent oxygen was inspired. This suggests that these agents may help reduce arterial hypoxemia secondary to ventilation-to-perfusion mismatching, to defects in oxygen diffusion, or to both; but the agents did not reduce intrapulmonary shunting.

Several mechanisms may account for the reduction in pulmonary venous admixture after administration of methylprednisolone, PEEP, or both while patients breathed room air. The first is an alteration of pulmonary vascular resistance. Regional pulmonary vasoconstriction normally occurs after a reduction in PaO\textsubscript{2}. Although the mechanism primarily responsible for increased vasoconstriction is unknown, we do know that various vasoactive agents are released into the pulmonary circulation after a reduction in PaO\textsubscript{2}.\textsuperscript{26,28} One of these agents, prostaglandin E\textsubscript{1}, a vasodilator, is released from pulmonary parenchymal cells.\textsuperscript{30-32} The role of prostaglandin E\textsubscript{1} is unknown, but possibly it modulates the hypoxic vasoconstrictive response. Methylprednisolone inhibits the release of prostaglandin E\textsubscript{1}.\textsuperscript{33,34} By this inhibition the hypoxic vasoconstrictor response may be enhanced.\textsuperscript{35,36} This would then cause better matching of ventilation to perfusion. A second possibility is that methylprednisolone may inhibit formation of edema.\textsuperscript{28} Cardiopulmonary bypass can cause an increase in interstitial pulmonary water\textsuperscript{4,7} and thereby reduce the diameter of small airways, which may decrease ventilation to some areas. Such an inhibitive effect of methylprednisolone could prevent both the mismatch of ventilation to perfusion and the increase of venous admixture observed in patients who received the placebo. It is possible that both may have been operative. The improvement in PaO\textsubscript{2} induced by therapy with steroids was not transient, as evidenced by the increased PaO\textsubscript{2} 24 hours after surgery.

The reduction in venous admixture by the administration of PEEP during the breathing of room air most likely reflects improvement in matching of ventilation to perfusion secondary to an increase in FRC. We previously have shown that 4 mm Hg of PEEP returned FRC to normal in patients who underwent cardiopulmonary bypass;\textsuperscript{28} however, we found no effect with an FI\textsubscript{O}\textsubscript{2} of 0.4. Similarly, Millbern et al\textsuperscript{19} observed no effect of PEEP on PaO\textsubscript{2} when patients breathed an FI\textsubscript{O}\textsubscript{2} of 0.4 following major abdominal operations. Based on this observation, these authors\textsuperscript{19} concluded that PEEP had no therapeutic effect. Had they investigated the effect of PEEP at other levels of FI\textsubscript{O}\textsubscript{2}, they may have reached a different conclusion. This emphasizes the need to employ more than a single FI\textsubscript{O}\textsubscript{2} when evaluating various types of therapy.

When FI\textsubscript{O}\textsubscript{2} was increased to 1.0 in patients who received steroids, we found no improvement in gas exchange. In fact, while breathing pure oxygen, patients who received steroids had an increase in intrapulmonary shunting. This phenomenon has been observed previously. Schwartz and co-workers\textsuperscript{17} found that dogs breathing oxygen and receiving 30
mg methylprednisolone per kilogram of body weight had increased right-to-left intrapulmonary shunting of blood through an atelectatic right lower lobe. This appeared to be caused by an increase in the flow of blood to that lobe. Lozman et al8 observed similar increases in intrapulmonary shunting when patients with respiratory failure received methylprednisolone. The mechanism that decreases pulmonary vascular resistance after steroid administration is unknown but may be related to the release of hypoxic pulmonary vasoconstriction by an elevated PAO2, to direct vasodilation, or to the inhibition by methylprednisolone of pulmonary vasoconstrictors.29 Since the PAO2 would be equivalent whether patients received steroids or placebo, the increased intrapulmonary shunting in patients after steroid administration suggests a steroid-induced vasodilation or an inhibition of the release of pulmonary vasoconstrictors.

One might be tempted to interpret the steroid-induced increase in intrapulmonary shunt fraction as a detrimental effect; however, it is possible that the increased right-to-left intrapulmonary shunting represents an increased flow of blood to nonventilated pulmonary units. In other words, steroids may unmask "silent" pulmonary units, which may occur in large numbers in these patients.26 In this event the increase in shunting might even be considered beneficial. Again, the need to evaluate therapy at more than one FIO2 is apparent.

When patients received PEEP and breathed pure oxygen, venous admixture was decreased. Since an elevated FIO2 will reduce all contribution to venous admixture except right-to-left intrapulmonary shunting, it appears that PEEP may decrease shunting. Such may result if FRC is increased and alveolar collapse prevented by PEEP during the breathing of oxygen.

Differences in C(a-v)O2 were similar in all patients regardless of therapy with steroids, PEEP, or oxygen. Therefore, it is unlikely that the changes in PaO2 and venous admixture were secondary to changes in oxygen consumption or cardiac output. Left atrial pressure also may influence intrapulmonary shunting and hypoxic pulmonary vasoconstriction;37 however, left atrial pressure was not elevated in our patients, as reflected by normal pulmonary arterial occlusion pressures.

In summary, we found that the response of venous admixture to varied levels of FIO2 was useful in evaluating two commonly used types of therapy. In addition, the response of venous admixture appears to provide a sensitive means to detect the effects of different types of therapy on pulmonary gas exchange.

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