The Management of Arterial Hypoxia in Chronic Obstructive Pulmonary Disease*

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The relief of hypoxia is an immediate and essential therapeutic goal in the management of acute respiratory failure associated with chronic pulmonary disease. This primary objective, though long recognized, became obscured following the observation that frequently the administration of oxygen without regard to the inspired concentration was associated with the development of profound respiratory acidosis and coma.4 In the absence of generally available and reliable blood gas determinations, estimates of the need for oxygen therapy were of necessity based on bedside observation, which can detect only the grossest abnormalities in oxygenation and ventilation.4,5 When these inadequate bedside observations were coupled with the fear of precipitating serious hypercapnia, it is not surprising that in many patients with chronic pulmonary disease oxygen therapy tended to be withheld when this in fact was their greatest therapeutic need.

In addition to overemphasis of the importance of carbon dioxide retention in respiratory failure, three developments occurred which led to further misunderstanding and inappropriate therapy. First, it was observed that the ventilatory response to carbon dioxide was diminished in subjects with chronic obstructive pulmonary disease.6,7 If then hypoxia remained the major chemical stimulus to breathing, the removal of the stimulatory effect of hypoxia could result in a reduction in ventilation and further carbon dioxide retention.8 Thus, it was considered that the primary cause of hypercapnia was a defect in ventilatory control although overall ventilation tends to be increased in subjects with chronic obstructive pulmonary disease.9 It was suggested that serious worsening of preexisting hypercapnia might be avoided if oxygen were given intermittently,10 a technique that could result in serious hypoxia,11,12 or via nasal catheter at low flowrates with or without graded increases,13 a technique the effect of which has been shown to be unpredictable14,15 insofar as the mean inspired oxygen concentration is variable. Secondly, clinically applicable techniques for measuring carbon dioxide pressure (Pco2) and hydrogen ion activity were available prior to the general deployment of similar techniques for determining oxygen pressure. As a result, in the search for an objective parameter, respiratory failure became defined in terms of an elevated arterial Pco2. Thirdly, the availability of a variety of mechanical devices for artificial ventilation enabled oxygen to be given while maintaining an adequate ventilation, defined in terms of the arterial carbon dioxide pressure. Frequently, efforts were made to lower and maintain the arterial Pco2 within the normal range and it was felt justifiable to treat chronic hypercapnia with mechanical ventilation and respiratory stimulants even when it was unaccompanied by symptoms specifically attributable to an elevated arterial Pco2.14,15

An important reorientation of the whole approach to therapy in respiratory failure was made by Campbell who emphasized the importance of concentrating on the treatment of hypoxia rather than hypercapnia.11,16-20 He demonstrated that a small but precise increment in the inspired oxygen concentration would result in marked improvement in the arterial oxyhemoglobin saturation without increasing carbon dioxide retention to a significant extent. He attributed the development of extreme degrees of hypercapnia occasionally seen in clinical practice to high inspired oxygen concentrations19 due to uncontrolled oxygen administration. Most of the techniques for administering oxygen at that time resulted in a variable but generally a high inspired oxygen concentration.20 The introduction of a mask based upon the Venturi principle solved this problem and the validity of this approach has been repeatedly demonstrated.20-22 As important, however, was the emphasis by Campbell of the underlying concept that oxygen is a drug.
with a dose measured in terms of the inspired concentration.

The assessment of hypoxia, and thus the need for oxygen therapy, is usually made by determining the oxygen and carbon dioxide pressures and the pH of arterial blood, and likewise the adequacy of oxygen therapy may be assessed by whether or not a predetermined level of arterial oxygenation has been achieved without further serious carbon dioxide retention. In chronic obstructive pulmonary disease, the therapeutic goals for oxygen administration, when recommended, vary greatly ranging from arterial oxygen pressures (PaO₂) of 40 to 80 mm Hg.10,23-25,32 No specific limits need be set for patients without carbon dioxide retention as, in the absence of marked worsening of the gas exchange function of the lung, it is unusual for hypercapnia to develop in such patients even with high inspired oxygen concentrations. In spite of this fact, it is not uncommon to see all forms of respiratory failure, with or without respiratory acidosis, associated with chronic pulmonary disease treated with oxygen at a low concentration whether or not it is necessary or in fact inappropriate.35

It is now well established that in chronic obstructive pulmonary disease arterial hypoxia is the result of venous admixture due to an increase in the distribution of areas of the lung where alveolar ventilation is low with respect to perfusion (low \( V_{\text{A}}/Q \)) and that carbon dioxide retention results from an increase in alveolar deadspace (high \( V_{\text{A}}/Q \)) rather than from overall hypoventilation.26-29

Venous admixture, being due primarily to a maldistribution of ventilation, is sensitive to the inspired oxygen concentration.30 The response of the calculated venous admixture to oxygen administration observed in two patients is shown in Figure 1. The study in patient A and one study in patient B (B-1) were obtained at times when their disease was stable, and it can be seen that the venous admixture falls as the inspired oxygen concentration is increased. The change in the admixture being in part dependent on the degree of venous admixture present when breathing air. This change was reflected by a concomitant rise in the arterial PaO₂. The second study in patient B (B-2) was undertaken during a superimposed episode of acute respiratory failure and demonstrates the marked reduction in the venous admixture effect that may be obtained with 24 percent and 21 percent oxygen. This variability in the response of the venous admixture largely accounts for the variability in response of the arterial PaO₂ among patients with different degrees of severity of their pulmonary disease.

In spite of this variation in response, some precision has been introduced in prescribing an appropriate inspired oxygen concentration based upon the fact that the response of the venous admixture, and thus the arterial PaO₂, to a given inspired oxygen concentration will depend upon the degree of severity of the underlying pulmonary disease as reflected in the arterial PaO₂ during air breathing.28-30 When the arterial oxygen pressure on air breathing is known, an estimate of the arterial PaO₂ that will result from breathing known inspired oxygen concentrations may be made from the regression lines shown in Figure 2.1 Furthermore, if arterial PaO₂ is measured in a patient receiving a known inspired oxygen concentration it is possible to estimate from these regression lines the arterial PaO₂ that would result from changing the inspired gas to air or a different oxygen concentration.

Adjustment of the dose of oxygen in terms of the inspired oxygen concentration requires that it be known accurately and this implies the use of a fixed performance system that is patient-independent, such as a Venturi mask or an accurately regulated gas mixing device.31 Variable performance systems such as nasal cannulae, where the inspired oxygen concentration is dependent on the level and pattern of ventilation, may give an unpredictable response in terms of arterial oxygenation, and this is demonstrated in Figure 3 with data from one reported study32 where the initial arterial PaO₂ noted with air breathing is plotted against the arterial PaO₂ observed when oxygen was administered at a flowrate.

The originally published diagram was incorrectly drawn30 but has been corrected.31

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of 2 liters/minute via a nasal cannula or plastic oronasal mask. The regression lines on the graph represent the observed relationship between the arterial Po2 with air breathing and four known inspired oxygen concentrations. It is seen that great variation occurred in the response of the arterial Po2 with oxygen administered in this manner and by inference a similar variation existed in the effective inspired oxygen concentration. Thus while minor directional changes in the arterial Po2 may be interpreted as reflecting changes in overall response of the lungs, the ability to detect minor changes in lung function is lost when the effective inspired oxygen concentration is also subject to fluctuation.

In establishing therapeutic goals for the arterial Po2 with oxygen therapy, the major concern is to improve overall oxygenation. In the presence of hypercapnia, efforts to elevate the arterial oxygen pressure beyond 60 mm Hg are frequently associated with further serious carbon dioxide retention and inspection of the oxyhemoglobin dissociation curve reveals that little is accomplished in terms of oxygen transport by hemoglobin above an arterial Po2 of 50-60 mm Hg. Below an oxygen pressure of 50 mm Hg the oxyhemoglobin dissociation curve becomes progressively steeper, and though as a therapeutic compromise in the presence of severe hypercapnia arterial oxygen pressures in the range of 40-50 mm Hg may have to be accepted, our recent studies indicate that an arterial oxygen pressure in the region of 40 mm Hg or less is associated with markedly impaired oxygen transport and thus probably represents borderline tissue hypoxia. In chronic obstructive pulmonary disease without hypercapnia, oxygen therapy does not normally cause further carbon dioxide retention, providing lung function is stable or improving and accordingly there is no need to maintain the arterial Po2 below 60 mm Hg. Therefore, advantage should be taken of the small increase in oxygen transport that will result by increasing the arterial Po2 to the region of 90-100 mm Hg and on occasion higher.

While to date attention toward controlled oxygen therapy has been focused upon the arterial Po2 since this is a convenient measurement, it is intuitively apparent that more to the point is a consideration of tissue oxygenation. In this regard it must be remembered that the function of the lungs represents only one component of the gas transport system. The amount and distribution of the systemic blood flow, together with the amount and qualitative properties of the hemoglobin must all be considered. These parameters determine the oxygen delivery and normally about 4 to 5 ml of oxygen are delivered to the tissues for each ml of oxygen utilized. A patient with only moderately severe pulmonary disease who is anemic or whose cardiac output is depressed may have more severe tissue hypoxia than one in whom pulmonary function is severely compromised but who nevertheless is able to maintain an adequate oxygen delivery by compensatory polycythemia or normal cardiac function. Data obtained during right heart catheterization from the two patients previously discussed are given in Table 1. It can be seen that when in a stable state of their disease, the arterial Po2 in both patients was similar. However, in spite of severe lung dysfunction (venous admixture 46 percent)
Table 1—Physiologic Data on Individual Patients with Respiratory Failure Breathing Ambient Air

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>B-1</td>
</tr>
<tr>
<td>Hemoglobin (gms %)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Sat, (%)</td>
<td>82.7</td>
<td>89.2</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>52</td>
<td>39</td>
</tr>
<tr>
<td>pHa</td>
<td>7.40</td>
<td>7.49</td>
</tr>
<tr>
<td>Deadspace/Tidal Volume ratio</td>
<td>0.39</td>
<td>0.37</td>
</tr>
<tr>
<td>Venous admixture (%)</td>
<td>46</td>
<td>21</td>
</tr>
<tr>
<td>a-V O2 difference (mm Hg)</td>
<td>3.5</td>
<td>7.7</td>
</tr>
<tr>
<td>Cardiac Index (L/min/m2)</td>
<td>3.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Oxygen delivery (ml/min/1.73 m2)</td>
<td>445</td>
<td>351</td>
</tr>
<tr>
<td>Oxygen delivery/oxygen uptake</td>
<td>5.1</td>
<td>2.4</td>
</tr>
<tr>
<td>P5O2 (mm Hg)</td>
<td>37</td>
<td>27</td>
</tr>
</tbody>
</table>

Symbols:
- Sat = arterial oxygen saturation
- PaO2 = arterial oxygen pressure
- PaCO2 = arterial carbon dioxide pressure
- pHa = arterial pH
- a-V O2 difference = arterial to mixed venous oxygen difference
- O2 = mixed venous oxygen pressure

patient A was able to maintain normal oxygen delivery with respect to oxygen uptake by maintaining normal cardiac output in association with some polycythemia. On the other hand, patient B (Study B-1), while having less severe pulmonary disease (venous admixture 21 percent), had low cardiac output and under these circumstances, oxygen delivery was reduced even though hemoglobin concentration was identical to patient A. When in this patient a superimposed episode of acute respiratory failure developed in the continued presence of a low cardiac output (Study B-2), severe hypoxia resulted, though the impaired lung function as measured by the venous admixture was the same as that observed in the study on patient A. These data demonstrate the importance of the cardiac output in maintaining oxygen transport and similar changes may occur as a result of quantitative and qualitative changes in hemoglobin.

Oxygen delivery is a function of both the arterial oxygen content and the cardiac output and mixed venous oxygenation represents the end result of the balance between oxygen delivery and oxygen utilization. It may well be that in the future we will find it useful in critical situations to monitor mixed venous oxygen pressure as a reflection of overall tissue oxygenation. A sustained pressure gradient is required for the adequate transfer of oxygen from the capillary to the tissue and it has been suggested that in terms of mixed venous oxygenation a critical level lies in the region of 20 to 30 mm Hg. Ideally, oxygen therapy should restore oxygen delivery and therefore mixed venous oxygenation to normal levels, though the presence of an inadequate cardiac output or hemoglobin concentration or the concomitant development of severe hypercapnia may prevent this objective from being achieved.

Patients with chronic obstructive pulmonary disease may be separated into two groups, those with and those without hypercapnia, 46 a separation reflecting the degree of abnormality in the relationship between ventilation and perfusion. 47 Preliminary studies of the interaction between arterial and mixed venous oxygenation in subjects with chronic obstructive pulmonary disease 48 indicate that the following guidelines may be used to determine initial oxygen therapy:

Patients with normocapnia (arterial Pco2 < 45 mm Hg)

When the arterial PaO2 at rest is above 65 mm Hg, oxygen delivery and the mixed venous Po2 will be near normal and oxygen therapy is not required. When arterial hypoxia (PaO2 less than 65 mm Hg) is present, an inspired oxygen concentration of 40 percent will raise the mixed venous Po2 to 35 mm Hg and there will be little danger of hypercapnia, in spite of the level of arterial Po2 achieved unless pulmonary function deteriorates.

Patients with hypercapnia (arterial Pco2 > 44 mm Hg)

When the arterial PaO2 is 50 mm Hg or above, oxygen therapy is usually not required for oxygen delivery will probably be normal. In fact, the mixed venous Po2 can be raised above normal (40 mm Hg) by 28 percent oxygen.

When the arterial PaO2 is less than 50 mm Hg mixed venous hypoxia is usually present and is significant when the arterial PaO2 is less than 40 mm Hg. This can be corrected in most cases by an inspired oxygen concentration of 28 percent though occasionally an inspired oxygen concentration of 35 percent will be required. Generally in these patients when the arterial oxygen pressure is raised above 50 mm Hg, the mixed venous oxygen pressure will be at a satisfactory level of greater than 35 mm Hg.

After oxygen therapy has been started, the arterial PaO2 should be measured to ensure that the therapeutic goals have been achieved and maintained. While in the presence of hypercapnia, some further carbon dioxide retention may be anticipated, precise limits defining the permissible rise in arterial Pco2 cannot be set for other factors, including the overall clinical status of the patient must be considered. It has been stated that nursing procedures directed toward encouraging spontaneous coughing and sputum production are valuable adjuncts to therapy 49 and attention should always be given to these aspects of the care of the patient with respiratory failure. Mechanical ventilation should...
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remain an absolute last resort to be reserved for those occasions when an adequate arterial Po2 cannot be achieved without precipitating carbon dioxide narcosis.

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