An Analysis of Sequential Physiologic Changes in Hypoxic Cor Pulmonale during Long-term Oxygen Therapy

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Physiologic changes were studied retrospectively in 37 patients with hypoxic cor pulmonale who died during long-term oxygen therapy (LTOT). The subjects were assessed during periods of clinical stability for each year on LTOT. At the onset of treatment, their mean age (±SEM) was 60.0±1.3 years, and at the time of death, they were aged 65.0±1.3 years. The median duration of LTOT was five years. For each year leading up to death, mean values of FEV₁, PaO₂, and PaCO₂ were obtained. A rate of decline of FEV₁ of 73±10 ml/yr was observed, and this was accompanied by a decline in PaO₂ of 0.47±0.01 kPa/yr. Patients died with a mean FEV₁ of 0.55±0.04 L and a PaCO₂ of 5.1±0.2 kPa. A small rise in PaCO₂ occurred, on average 0.25±0.09 kPa/yr, throughout the study, but accelerating in many cases during the three years before death. Hypoxic cor pulmonale appears to be associated with a rapid deterioration in airway function, a steady decline in PaO₂, and a slow rise in PaCO₂ during the years leading up to death. These physiologic changes measured in a stable clinical state while breathing air appear to occur in spite of LTOT. The LTOT may merely prevent death from episodes of severe hypoxemia while the pathophysiologic changes in the lung progress. Hence the benefit to be expected from LTOT is only temporary. Generally, those patients with lower levels of FEV₁ will obtain diminishing clinical benefit, inversely related to the severity of airflow obstruction at the time of commencement of LTOT.

(LTOT = long-term oxygen therapy; MRC = Medical Research Council)

Long-term oxygen therapy (LTOT) improves survival in hypoxic cor pulmonale associated with COPD.1-3 The benefit of LTOT is believed to be related to a lowering of pulmonary artery pressure,4,5 but the importance of pulmonary hypertension in cor pulmonale has been questioned6 because it is modest compared with primary pulmonary hypertension.7 In primary pulmonary hypertension the cardiac index falls to very low levels,8 whereas in COPD, while right ventricular performance may be impaired during exercise,9,10 the resting cardiac output is often normal.9-18 In patients receiving LTOT, although the progression of pulmonary hemodynamic disturbances is prevented,5 survival remains strongly associated with the severity of airflow obstruction at the start of treatment.3

There is continuing uncertainty as to what is primarily responsible for the death of patients with hypoxic cor pulmonale. The possible causes include decline of airway function, a deteriorating ventilation-perfusion relationship, progressive pulmonary hypertension, hypoventilation due to loss of respiratory drive, and episodes of severe hypoxemia. Previously, we have reported survival data in 72 patients who entered a 12-year study of LTOT in hypoxic cor pulmonale.3 In order to further investigate the pathophysiologic process leading to death in cor pulmonale, we examined data from 37 patients who died during this earlier study. We measured airway mechanics and arterial blood gas tensions for each year on LTOT. The pattern of change of these variables was closely observed and analyzed in relation to the time of death. Sequential measurements of pulmonary hemodynamics were not performed in every case, but we have previously reported stability of pulmonary artery pressure in some of these patients.5 Ventilation-perfusion relationships were not specifically examined in this study.

MATERIALS AND METHODS

We studied 37 consecutive patients who died while receiving LTOT. One patient who died during the previous study moved away from the investigating center and did not have sufficient data for inclusion in the present analysis. Twenty-seven were men and ten were women. They received LTOT for at least 13 h per day. Patient compliance was ensured by close supervision at home and by objective measurements of oxygen concentrator usage from hidden clocks, as described in a previous report from the same center.19 The clinical characteristics of the group at the beginning of the LTOT is shown in Table 1. All had at least one recorded episode of peripheral edema as evidence of cor pulmonale. The group showed moderately severe airflow obstruction, arterial hypoxemia, hypercapnia and polycythemia. Their mean age and initial values of forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and blood gas tensions breathing air were similar to those of patients in other studies of LTOT.4,5,19

The patients were assessed during a phase of clinical stability for each year on LTOT. Clinical stability was defined as an outpatient...
Table 1—Physiologic Measurements (Clinically Stable) at Entry into Study and within Year of Death*

<table>
<thead>
<tr>
<th>Data</th>
<th>Onset of LTOT</th>
<th>Prior to Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>60.0 (1.3)</td>
<td>65.0 (1.3)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.80 (0.06)</td>
<td>0.55 (0.04)</td>
</tr>
<tr>
<td>Percent of predicted FEV₁†</td>
<td>29 (2)</td>
<td>22 (2)</td>
</tr>
<tr>
<td>FVC, L</td>
<td>1.93 (0.13)</td>
<td>1.36 (0.09)</td>
</tr>
<tr>
<td>PaO₂ (air), kPa</td>
<td>6.6 (0.2)</td>
<td>5.1 (0.2)</td>
</tr>
<tr>
<td>PaCO₃ (air), kPa</td>
<td>6.7 (0.2)</td>
<td>7.2 (0.2)</td>
</tr>
<tr>
<td>Packed cell volume, %</td>
<td>51.0 (1.3)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Values are expressed as means, with SEM in parentheses. All patients had at least one recorded episode of peripheral edema as evidence of cor pulmonale. Conversion of SI to traditional units for gas tensions: 1 kPa = 7.5 mm Hg.
†European adult predicted values."n

Attended where the medical records indicated stability of symptoms for at least six weeks. Assessments within six weeks of hospital admission for exacerbation of airflow obstruction were not included. Maximum values of FEV₁ and FVC were recorded together with values of arterial oxygen tension (PaO₂) and arterial carbon dioxide tension (PaCO₃) while breathing air. Blood gas tensions during administration of oxygen were not considered because of the uncertainty of achieving a repeatable inspired oxygen concentration. Alterations in spirometry and blood gas tensions during periods of clinical deterioration were also disregarded. Where multiple data sets were available during a one-year period, two criteria were applied to the selection of results in the following order of priority: (a) the real-time interval from the previous results was as close as possible to one year, and (b) maximum values were selected. In most cases the last assessment was made during a routine attendance at the hospital outpatient clinic so that the results were not influenced by a terminal episode of respiratory failure.

A retrospective method of statistical analysis was chosen so that various clinical characteristics could be analyzed in relation to the time of death on LTOT. This was taken as a point of reference, allowing a comparison between patients for each year leading up to death. The statistical method reveals information about the clinical course of hypoxic cor pulmonale which cannot be derived by conventional prospective analysis because patients commence LTOT at different stages in the course of their disease.

Mean values (±SEM) for FEV₁, PaO₂, and PaCO₃ were calculated for each year leading up to death on LTOT. As the time on LTOT before death became shorter, there were more patients available for evaluation. Regression analysis was applied to the values of FEV₁, and blood gas tensions for each individual patient based on average time intervals of 12 months. In some cases, the real time intervals were not exactly one year, but they were close enough to make this assumption. A mean rate of change for these variables was obtained from the average of the individual regression slopes.

We divided the group into smokers and nonsmokers, as described in the previous study,"n and were therefore able to derive mean rates of decline of FEV₁ for these two subgroups.

**RESULTS**

The mean age of patients dying on LTOT was 65.0 ± 1.3 years, and the median duration of LTOT was five years. Table 1 shows the stable clinical characteristics of the patients at the introduction of LTOT and within the last year of life. They died with a mean FEV₁ of 0.55 ± 0.04 L and a mean PaO₂ of 5.1 ± 0.2 kPa when breathing air.

Figure 1 shows the mean FEV₁ of the group for each year leading up to death. The mean rate of decline in those who admitted smoking was 69 ± 13 ml/yr, and for those who denied smoking, it was 77 ± 16 ml/yr. A significant difference between these two subgroups was not found.

Figure 2 shows the mean PaO₂ and PaCO₃ of the group for each year leading up to death. The mean rate of decline of PaO₂ was 0.47 ± 0.01 kPa/yr. The mean change in PaCO₃ was an increase of 0.25 ± 0.09 kPa/yr.

**DISCUSSION**

This study reveals a steady decline of FEV₁ in a group of 37 patients with COPD who were receiving LTOT. The method of analysis deserves comment. Difficulties are encountered when studying the clinical course of cor pulmonale and the effects of LTOT, because patients tend to present to the investigators at different stages of the disease process. In this study the individual values of FEV₁ at entry varied from 1.7 L to 0.4 L. We attempted to time-align patients with respect to the stage of their disease process by utilizing the time of death as a fixed point in the analysis (Fig.

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**FIGURE 1.** Mean values (±SEM) of FEV₁. Number assessed for each year on LTOT is shown in parentheses. Subjects were time-aligned to point of death.

**FIGURE 2.** Mean values (±SEM) of PaO₂ and PaCO₃. Number assessed for each year on LTOT is shown in parentheses.
Physiologic Changes in Hypoxic Cor Pulmonale (Cooper, Howard)

1. A steady decline of mean FEV₁ occurred, from greater than 1.0 L ten years before death to less than 0.6 L within one year of death. The advantage conferred by this unconventional method of analysis is revealed by comparison of Figure 1 with Figure 3, in which serial values of FEV₁ have been plotted using the time of commencement of LTOT as the reference point. The decline in FEV₁ from year to year, which was demonstrated to occur by regression analysis of individual patient data, is completely masked by the conventional method of analysis (Fig 3), in which the mean values of FEV₁ at any stage throughout the study could have been influenced by patients' reaching the accelerated phase of deterioration.

In normal individuals the FEV₁ is expected to decline at a rate of about 30 ml/yr. This decline is accelerated by smoking in susceptible individuals. In chronic bronchitis the reported loss of forced expiratory volume is generally about 50 ml/yr but may exceed 80 ml/yr. The rate of decline of FEV₁ in this group was 73 ml/yr. Such a rapid decline appears to represent a terminal stage of the disease process. The Medical Research Council (MRC) Working Party reported a decrease in FEV₁ in control subjects and individuals receiving LTOT who died early (180 to 500 days) but suggested that physiologic variables remained stable in long-term survivors from the treated group. The present findings indicate that in hypoxic cor pulmonale, a rapid loss of airway function is to be expected despite LTOT and that the prognosis is poor once the FEV₁ has fallen below 0.6 L. Patients died with a mean FEV₁ of 0.57 L. Our observations are similar to those of Postma et al., who reported a mean rate of decline of FEV₁ of 54 ml/yr in 129 patients with COPD and a poor prognosis when FEV₁ had fallen below 0.45 L. The implication of these findings is that patients who already have a low FEV₁ at the commencement of LTOT have a particularly poor prognosis and will derive limited benefit from LTOT. Maximum benefit is achieved by commencing LTOT earlier in the disease process.

The progressive loss of airway function appears to be accompanied by a steady deterioration in PaO₂. In this group the rate of decline of PaO₂ was 0.47 kPa/yr, and the mean PaO₂ within one year of death was 5.1 kPa. Compared with FEV₁, values for PaO₂ are less strongly associated with survival, and Kawakami et al. have reported that mixed-venous oxygen tension is a better prognostic indicator, since it reflects the delivery of oxygen to the tissues. The mean annual change in PaCO₂ was an increase of 0.25 kPa. This represents an important change, but it should be adequately buffered by renal bicarbonate retention.

It seems unlikely, therefore, that the rise in PaCO₂ per se is a major determinant of the length of survival. The changes in blood gas tensions were gradual enough to give the impression of a period of clinical stability during which PaO₂ and PaCO₂ were about equal. Within three years of death, there was a clear divergence of blood gas tensions as PaO₂ fell and PaCO₂ rose. This important clinical observation may be predicted in the terminal years of COPD. Similar changes in PaO₂ and PaCO₂ were reported in the MRC study for patients who died early (180 to 500 days) on LTOT, but long-term survivors appeared to have stable blood gas tensions. Identification of the accelerated phase of respiratory failure may necessitate a review of treatment in these patients.

Progressive deterioration in airway function and blood gas tensions in hypoxic cor pulmonale is known to be accompanied by distinctive histopathologic changes in the lungs. Wilkinson et al., studied postmortem specimens from ten patients with hypoxic cor pulmonale and observed distinctive histopathologic changes of pulmonary vascular architecture which appeared to continue actively until the point of death, regardless of whether or not the patients received LTOT. Furthermore, quantitative histologic features were associated with severity of airflow obstruction, rather than PaO₂ or pulmonary artery pressure. These histopathologic observations, unique to hypoxic cor pulmonale, along with the physiologic changes observed in the present study, lend strength to the argument that the pathophysiologic process underlying hypoxic cor pulmonale is predominantly due to a decline in airway function which progresses despite LTOT.

We attempted to separate ex-smokers from those who continued smoking. Nineteen patients admitted smoking, and the rate of decline of their FEV₁ was 69 ml/yr. Eighteen patients denied smoking, although it was clear from carboxyhemoglobin measurements that some continued to do so. The rate of decline for this group was 77 ml/yr. It was difficult to make an accurate assessment of the quantity smoked by individual patients, but a significant difference in the rate of decline of FEV₁ was not detected between these two groups (unpaired t-test). Stopping smoking does not
appear to improve mortality in the terminal stages of hypoxic cor pulmonale when a serious deterioration in pulmonary function has already occurred.\textsuperscript{30} In less advanced stages of COPD, the rate of decline of FEV\textsubscript{1} is reduced by stopping smoking.\textsuperscript{30,34} We were unable to demonstrate an association between mortality and continued smoking,\textsuperscript{3} and two other studies have failed to show improvement in survival from advanced COPD after stopping smoking.\textsuperscript{21,31}

A common difficulty in the interpretation of this type of study is the reliance on historical controls. Only one study of LTOT has included a true control group,\textsuperscript{4} and now that there is convincing evidence of the benefit of LTOT, there are ethical difficulties in withholding the treatment from certain patients. In common with other studies, we rely on comparison with MRC controls. The clinical characteristics of these 37 patients at entry into the study were similar to those of the MRC control group (Table 1). Furthermore, it is unlikely that temporal influences have significantly altered the nature of the disease process, since there was some overlap in the period of recruitment to the two studies. The different survival times for the individuals in this study may reflect the varied stages of the disease process at which diagnosis was made or LTOT instituted. The median survival for this group was five years, showing that the prognosis is limited despite LTOT. The temporary nature of the benefit from LTOT was also an important finding in the 12-year study involving 72 patients with hypoxic cor pulmonale.\textsuperscript{3} Clearly, the severity of airflow obstruction at the commencement of LTOT is an important determinant of the length of survival. Patients with a poor FEV\textsubscript{1} (less than 0.6 L) who develop respiratory failure late in the course of their disease appear to have very limited benefit from LTOT. Improvement in the survival of this type of patient may be dependent on other methods of treatment. The consequences of loss of FEV\textsubscript{1}, indicate the need for optimal bronchodilator therapy. Bronchodilatation can be demonstrated in some patients with severe hypoxic cor pulmonale,\textsuperscript{32} and a trial of corticosteroid treatment is probably justified, provided that improvement is measured objectively.\textsuperscript{33,34} The need for therapeutic correction of pulmonary hypertension has not been proven. Pulmonary vasodilatation improves right ventricular performance and cardiac output\textsuperscript{35} but may lead to worsening hypoxemia, with an adverse effect on oxygen delivery to the tissues.\textsuperscript{36} Oxygen is the only vasodilator with a selective effect on pulmonary vessels and without risk of worsening hypoxemia. Other measures which support airway function, such as domiciliary physiotherapy and some form of intermittent mechanical ventilatory assistance, may become important in the management of the final stages of accelerated respiratory failure.

**REFERENCES**

21. Burrows B, Earle RH. Course and prognosis of chronic obstruc-

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