Twelve year clinical study of patients with hypoxic cor pulmonale given long term domiciliary oxygen therapy

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ABSTRACT Patients presenting with chronic obstructive airways disease and hypoxic cor pulmonale were assessed during a period of clinical stability. Seventy two patients (53 male) with a mean age of 60 years were selected for long term oxygen therapy. Mean FEV1 was 0.78 l and forced vital capacity 1.9 l. The mean arterial oxygen tension (Pao2) was 6.1 kPa (46 mm Hg) and the mean arterial carbon dioxide tension (PCo2) 6.9 kPa (52 mm Hg). All patients had a Pao2 of less than 8.0 kPa (60 mm Hg) and 57 patients had a PCo2 of more than 6.0 kPa (45 mm Hg). Pulmonary haemodynamics were measured in 45 patients yielding the following mean values: pulmonary artery pressure 28.3 mm Hg; cardiac output 5.9 l min⁻¹; total pulmonary vascular resistance 59.2 kPa l⁻¹ s. Oxygen delivery systems, including 23 oxygen concentrators, were installed in the patients' homes. Flow rates were adjusted to raise Pao2 to more than 8.0 kPa (60 mm Hg) for at least 15 hours each day and close supervision was maintained. Overall five year survival was 62%, which is better than previously reported for this type of patients; but the 10 year survival was only 26% owing to an observed acceleration in death rate at about this time. Progressive disturbances of the pulmonary circulation were arrested. Mortality was associated with the severity of airflow obstruction, reflecting a continuing pathological process affecting the airways.

Survival is poor in patients with cor pulmonale complicating chronic obstructive airways disease.¹⁻⁵ The benefits of long term oxygen therapy in these patients were examined in the nocturnal oxygen therapy (NOT) trial⁶ and the report of the Medical Research Council Working Party (MRC).⁷ In the MRC study survival in women appeared to be better than in men, although the female group was small and hence few deaths occurred during the period of follow up. In men the benefit of long term oxygen therapy on survival was not apparent until about 500 days, a delay that has never been adequately explained. The five year survival in men was 42%. The mean duration of follow up in the NOT trial was 19 months. The projected three year survival in the group having continuous oxygen therapy was 63%. Timms et al⁷ have recently reviewed the data from the NOT trial and report that survival up to eight years is related to the fall in mean pulmonary artery pressure during the first six months of long term oxygen therapy. Survival in the group treated with oxygen for 12 hours each day was correlated with pulmonary vascular resistance, but this relationship was not apparent for those having continuous oxygen therapy.

Our centre has a high incidence of cor pulmonale complicating chronic obstructive airways disease,⁸ and we have conducted a study over 12 years in patients given long term oxygen therapy. Now that expansion of domiciliary oxygen prescribing has gained the approval of the Department of Health and Social Security,⁹ it is important to identify those patients who are likely to benefit and to know what length of survival can be expected with this treatment. We have analysed survival and examined the prognostic value of some clinical characteristics.

Methods

The patients presented from 1971 to 1984 with a clinical diagnosis of chronic bronchitis and emphysema. Most were first encountered during an admission to hospital with an acute exacerbation of airflow obstruction associated with respiratory failure and oedema. After recovery they were assessed during
several weeks of clinical stability. Those fulfilling the following criteria were included in the study: (a) 
FEV₁, less than 50% of predicted normal values; (b) 
chronic hypoxaemia with an arterial oxygen tension 
(Pao₂) consistently less than 8-0 kPa (60 mm Hg); and 
(c) at least one recorded episode of peripheral 
œdema as evidence of cor pulmonale. Patients 
unlikely to be compliant with long term oxygen 
therapy and those whose homes could not be adequately 
fi tted and supplied with oxygen cylinders were 
excluded.

Physiological measurements were made on at least 
two occasions before the start of oxygen therapy and 
included age, height, weight, packed cell volume, 
FEV₁, forced vital capacity (FVC), lung volumes 
determined by helium mixing, and carbon monoxide 
transfer factor (TLCO) determined by the single breath 
technique. Blood gas tensions were measured while 
patients were breathing air and after two hours of 
breathing 30% oxygen. Many patients underwent 
right heart catheterisation, a balloon tipped flow 
directed catheter (Swan Ganz) being introduced via 
an antecubital vein. Mean pulmonary artery pressure 
was recorded with a transducer (SE Laboratories 648) 
and cardiac output was calculated by the Fick equation 
or by the thermal dilution method. Total pulmon-
ary vascular resistance was calculated on the 
assumption of a left atrial pressure of zero. Pulmonary 
haemodynamics were measured again after 12–18 
months of long term oxygen therapy.

Seventy two patients were included. Twenty two 
used oxygen concentrators at some stage during the 
study and the rest were supplied by regular deliveries 
of G (3600 l) or F (1360 l) size cylinders. A special 
maintenance and breakdown service ensured an un-
interrupted supply of oxygen and those patients using 
cylinders were taught to change the reducing valves 
themselves. Oxygen was given by nasal prongs and the 
flow rate (1-5–2-5 l min⁻¹) was regulated to maintain 
the Pao₂ at more than 8-0 kPa (60 mm Hg) during 
treatment. Patients were instructed to use the system 
night and for at least 15 hours in every 24 hours. 
Close supervision of patients is necessary to achieve 
the best compliance; so the patients were reassessed 
in hospital every three months and monitored by 
home visits during the intervals. Serial blood gas 
tensions were measured every two to three months, in 
hospital and at home, to confirm that the response to 
treatment was maintained.

Oedema was controlled by diuretic treatment, 
fluctuations of chronic obstructive airways disease 
were treated with β₂ sympathomimetic bronchidilators 
and occasionally with sustained release 
methyIxanthines. Infections were usually treated with 
apicillin or amoxycillin. All patients were discour-
ged from smoking during the study but it was clear 
from carboxyhaemoglobin measurements that some 
continued to do so. The amount smoked by individual 
patients could not be accurately assessed and it was 
not possible to make a reliable separation of patients 
into smokers and non-smokers for the purpose of 
further analysis. We were unable to determine the 
direct influence of smoking on survival.

The recruitment of patients was evenly distributed 
throughout the study and the median duration of fol-
low up was 5 years. Life tables were derived from 
fitting Cox’s proportional hazards model. 
Subgroup survival was compared using the Lee Desu statistic. 
Association of clinical characteristics with survival 
was examined by the χ² likelihood ratio test. A p value 
less than 0-05 was considered significant.

Results

Since 1971 in Sheffield 72 patients (53 men and 19 
women) have received domiciliary oxygen therapy 
according to the selection criteria. Thirty five reported 
that they were ex-smokers and 37 admitted that they 
continued to smoke. Their clinical characteristics are 
shown in table 1. While they were breathing oxygen 
(inspired oxygen concentration 30%) the mean Pao₂ 
increased from 6-1 to 9-1 kPa (a mean increase of 
3-0 kPa) while the mean arterial carbon dioxide 
tension (Paco₂) increased from 6-9 to 7-3 kPa (a mean 
increase of 0-39 kPa) (table 1). Repeated testing in 
hospital and at home gives convincing evidence of a 
sustained increase in Pao₂ in patients having domicili-
ary oxygen therapy.

Pulmonary artery catheterisation was carried out in 
45 patients before entry into the study and was 
repeated in 40 patients after 12 months of long term 
oxygen therapy. The values for pulmonary artery

Table 1 Clinical characteristics of the 72 patients 
(53 male, 19 female) starting domiciliary oxygen therapy 
(mean values with standard deviations in parentheses)

| Age (y) | 60(5-7) |
| Weight (kg) | 65(7-5) |
| FEV₁ (l) | 0-76(0-31) |
| % Pred FEV₁ | 29(10) |
| FVC (l) | 1-90(0-64) |
| TLC (l) | 5-65(1-36) |
| RV/TLC (%) | 60(10) |
| TLC0 (mmol min⁻¹ kPa⁻¹) | 3-48(1-87) |
| Pao₂ (air) (kPa) | 6-1(1-0) |
| Paco₂ (air) (kPa) | 6-9(1-2) |
| Paco₂ (O₂) (kPa) | 9-1(1-4) |
| Paco₂ (O₂) (kPa) | 7-3(1-4) |
| PCV (%) | 52(7) |

Conversion: SI to traditional units—Gas tensions: 1 kPa = 7-5 mm Hg; TLC0: 1 mmol min⁻¹ kPa⁻¹ = 2-99 ml min⁻¹ mm Hg⁻¹. FVC—forced vital capacity; TLC—total lung capacity; RV—residual volume; TLC0—carbon monoxide transfer factor; Pao₂—arterial oxygen tension; Paco₂—arterial carbon dioxide tension; (air)—breathing air; (O₂)—breathing oxygen; PCV—packed cell volume.
pulmonary arterial pressure; TPVR—total pulmonary vascular resistance.

The cumulative survival proportions for the whole group of patients are shown in figure 1. The survival proportions for normal subjects and untreated men in the MRC study have been plotted for comparison. The five year survival proportions for the three groups are 62% (patients in this study), 87% (normal subjects), and 16% (MRC controls). The survival curves suggest that the benefit of long term oxygen therapy follows the start of treatment immediately. The 10 year survival for the patients was 26%, indicating an acceleration in death rate at 10 years despite long term oxygen therapy. Thirty eight had died at the time of analysis (30 men, eight women).

Survival for males and females is plotted separately in figure 2. There was no difference in survival between the sexes (p = 0.583) and the survival curves lie between those of the treated male and female groups of the MRC study.

The association of various clinical characteristics with survival was analysed with a $\chi^2$ likelihood ratio test (table 3). Survival was clearly associated with indices of airflow obstruction (FEV$_1$; p = 0.019; FVC: p = 0.013), whereas no association was observed with blood gas tensions during the breathing of air, the rise in PaO$_2$ during the breathing of oxygen, pulmonary artery pressure or total pulmonary vascular resistance. When subgroups were compared, sur-

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**Table 2** Pulmonary haemodynamics (mean values with standard deviations in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAP (mm Hg)</td>
<td>28.3(10.2)</td>
<td>26.1(11.0)</td>
</tr>
<tr>
<td>(n = 45)</td>
<td>(n = 40)</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (l min$^{-1}$)</td>
<td>5.9(1.8)</td>
<td>6.7(2.8)</td>
</tr>
<tr>
<td>(n = 42)</td>
<td>(n = 37)</td>
<td></td>
</tr>
<tr>
<td>TPVR (kPa l$^{-1}$ s)</td>
<td>59.2(25.3)</td>
<td>51.1(24.7)</td>
</tr>
<tr>
<td>(n = 42)</td>
<td>(n = 37)</td>
<td></td>
</tr>
</tbody>
</table>

Conversion: SI to traditional units—TPVR: 1 kPa l$^{-1}$ s = 6.809 dynes cm$^{-1}$.5

PAP—mean pulmonary arterial pressure; TPVR—total pulmonary vascular resistance.

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**Table 3** Association of clinical characteristics at entry with survival of patients having long term oxygen therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>$\chi^2$</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.213</td>
<td>0.271</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>5.551</td>
<td>0.019</td>
</tr>
<tr>
<td>% Pred FEV$_1$</td>
<td>5.167</td>
<td>0.023</td>
</tr>
<tr>
<td>FVC</td>
<td>6.112</td>
<td>0.013</td>
</tr>
<tr>
<td>PaO$_2$ (air)</td>
<td>1.217</td>
<td>0.270</td>
</tr>
<tr>
<td>PaCO$_2$ (air)</td>
<td>0.386</td>
<td>0.534</td>
</tr>
<tr>
<td>PaO$_2$ (O$_2$</td>
<td>1.155</td>
<td>0.283</td>
</tr>
<tr>
<td>PaCO$_2$ (O$_2$</td>
<td>2.400</td>
<td>0.122</td>
</tr>
<tr>
<td>$\Delta$PaO$_2$</td>
<td>0.004</td>
<td>0.953</td>
</tr>
<tr>
<td>PAP</td>
<td>1.578</td>
<td>0.209</td>
</tr>
<tr>
<td>TPVR</td>
<td>1.423</td>
<td>0.233</td>
</tr>
</tbody>
</table>

*Likelihood ratio test from fitting Cox's proportional hazards model.

FVC—forced vital capacity; PaO$_2$—arterial oxygen tension; PaCO$_2$—arterial carbon dioxide tension; (air)—breathing air; (O$_2$)—breathing oxygen; $\Delta$PaO$_2$ = PaO$_2$ (O$_2$) — PaO$_2$ (air); PAP—mean pulmonary artery pressure; TPVR—total pulmonary vascular resistance.
vival was worse in patients with an FEV$_1$ below 30% predicted (p = 0.029), as shown in figure 3, but not significantly different in those with a pulmonary artery pressure greater than 25 mm Hg or a total pulmonary vascular resistance greater than 58.8 kPa s$^{-1}$ m$^{-5}$.

**Discussion**

The patients in this study form a carefully selected group with severe airflow obstruction, hyperinflation, arterial hypoxaemia at rest, and impairment of gas transfer. All had experienced acute episodes of cor pulmonale. They entered the study in a stable hypoxaemic state, 57 remaining hypercapnic (Paco$_2$ > 6.0 kPa).

Survival is considerably better than has previously been reported for hypoxic cor pulmonale in patients with similar degrees of airflow obstruction, hyperinflation, and pulmonary hypertension (table 4). The five year survival without treatment is less than 40%. In a study of patients with hypoxic cor pulmonale given continuous oxygen therapy two year survival was 72%. The predicted five year survival proportions for treated patients in the MRC and NOT trials were 53% (11.9% annual risk) and 39% (17.2% annual risk overall). These figures compare with a five year survival in the present study of 62% (8.8% annual risk) and a 10 year survival of 26%. The five year survival for an age and sex matched group of normal individuals is 87% according to English Life Tables 1970–1972. A selected group of patients with hypoxic cor pulmonale and oedema associated with chronic bronchitis and emphysema can expect a doubling of survival time as a result of long term oxygen therapy given for at least 15 hours each day. This conclusion is based on retrospective comparisons and therefore must be interpreted with caution. A change in the nature of the disease or general improvement in management of the patients may have contributed to the fall in mortality that we observed. Nevertheless, these are the best survival figures so far reported in hypoxic cor pulmonale and provide justification for selecting this type of patient for long term oxygen therapy.

There are discrepancies with the results of the MRC study, which had similar patients. Five hundred days elapsed before benefit was apparent in men and this delay has never been explained. Our findings suggest, however, that the benefit of long term oxygen therapy is immediate, but clearly large numbers of patients and controls would be required to prove a significant difference in survival early after the start of oxygen therapy. The greater number of female patients has

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**Table 4 Survival proportions in hypoxic cor pulmonale**

<table>
<thead>
<tr>
<th>Controls</th>
<th>Survival proportions %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual % risk</td>
</tr>
<tr>
<td>Stuart-Harris (1957)$^1$</td>
<td>76</td>
</tr>
<tr>
<td>Bousby and Coates (1964)$^2$</td>
<td>74</td>
</tr>
<tr>
<td>Renzetti et al (1966)$^3$</td>
<td>64</td>
</tr>
<tr>
<td>Ude and Howard (1971)$^4$</td>
<td>72</td>
</tr>
<tr>
<td>MRC, men (1981)$^5$</td>
<td>71*</td>
</tr>
</tbody>
</table>

**Oxygen**

| Neff and Petty (24h)$^6$  | 79          | 72  | 77  | 77  |
| NOT trial (12h)$^7$       | 88          | 78  | 68  | 60  |
| NOT trial (24h)$^8$       | 11-9        | 76  | 68  | 60  |
| MRC, men (15h)$^9$        | 88*         | 77* | 68* | 60* |
| Present study (15h)       | 87          | 83  | 72  | 66  | 62  |

*Predicted according to quoted annual risk factors.
NOT trial—Nocturnal Oxygen Therapy Trial.
eliminated the apparent difference in survival between the sexes and emphasises that the female survival curve accompanies that of the males.

A 10 year survival of only 26% is disappointing and probably relates to a continuing pathological process that exerts its effect on airway function rather than in the pulmonary circulation. Survival for patients having long term oxygen therapy was clearly associated with indices of airflow obstruction but not with pulmonary artery pressure or total pulmonary vascular resistance. The prognostic value of FEV$_1$ is recognised from large studies of patients with chronic obstructive Airways disease and when FEV$_1$ falls below 450 ml it contributes significantly to a poor prognosis. In severe hypoxic cor pulmonale without oxygen therapy progressive pulmonary hypertension becomes an important determinant of mortality, and this may mask the relationship between FEV$_1$ and survival. Acute administration of oxygen lowers pulmonary artery pressure and a fall greater than 5 mm Hg has been associated with better survival for patients having long term oxygen therapy. The fall in pulmonary artery pressure can be sustained with long term oxygen therapy. In this study pulmonary artery pressure and total pulmonary vascular resistance were unchanged at the end of the first year of treatment in those who had haemodynamic measurements at this time and stabilisation of pulmonary artery pressure and total pulmonary vascular resistance was confirmed in some patients up to six years later. Long term oxygen therapy appears to interrupt the progression of haemodynamic disturbances, as was also observed in the MRC study, and in doing so has displaced the correlation of pulmonary hypertension with mortality.

There are two possible explanations. Long term oxygen therapy may prevent death from disturbances of the pulmonary circulation, so that mortality is then related to the continuing disease process in the Airways and lung parenchyma. Alternatively, it is possible that the correlation of mortality with pulmonary hypertension is spurious, only masking important pathophysiological events elsewhere. The relevance of pulmonary hypertension has always been in doubt since the pulmonary artery pressure in chronic obstructive Airways disease is usually considerably lower than in primary pulmonary hypertension, where right ventricular afterload leads to a fall in cardiac output to very low values. In hypoxic cor pulmonale cardiac output remains normal or is raised and right ventricular function is only marginally impaired. Failure to adapt by an increase in cardiac output leads to a reduction in oxygen delivery to the tissues and a fall in mixed venous oxygen tension, which has been associated with a poor survival rate. Unfortunately the beneficial effect of oxygen may be counterbalanced by a fall in cardiac output, so that oxygen delivery remains unchanged. Generally the measurement of pulmonary artery pressure in chronic obstructive Airways disease is unhelpful but a detailed pathophysiological study of the Airways and pulmonary circulation is needed in patients having long term oxygen therapy.

This study confirms that long term oxygen therapy is of benefit in carefully selected patients with hypoxic chronic obstructive Airways disease. It is not yet clear whether it improves survival in hypoxic patients without oedema or in those with other forms of chronic respiratory disease. The analysis shows that there is no relationship between initial blood gas tensions and survival when hypoxia is subsequently corrected by long term oxygen therapy. Twenty nine of the 57 patients who were hypercapnic (Paco$_2$ greater than 6:0 kPa (45 mm Hg)) at entry died during the study but only three of the 15 normocapnic patients died. This suggests that chronic hypercapnia is associated with a poorer prognosis even though the five year survival in this subgroup was 59%. Survival was better in patients who started long term oxygen therapy within two months of first developing oedema (p = 0.039). This form of treatment should probably be considered in all hypoxic patients soon after the onset of oedema and before the development of severe hypercapnic respiratory failure. The proportion surviving after five years can be expected to double with long term oxygen therapy but the death rate accelerates at 10 years, indicating that the benefit is temporary. The progressive rise in pulmonary artery pressure is prevented and disturbances of the pulmonary circulation are no longer important determinants of survival. Mortality appears to be related to a continuing pathological process within the Airways.

We thank Dr J P Nicholl for assisting with the statistical analysis and the staff of the respiratory function unit who have been concerned with the assessment of the patients.

References

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