Characteristics and survival of patients prescribed long-term oxygen therapy outside prescription guidelines

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ABSTRACT: Criteria for the prescription of long-term oxygen therapy (LTOT) have been published by academic societies and regulatory bodies, but many prescriptions for LTOT do not fulfil these criteria.

Demographic, functional data and survival were compared in chronic obstructive pulmonary disease (COPD) patients with different levels of oxygenation, i.e. arterial oxygen tension ($P_{a,O_2}$) <8 kPa or $\geq$8 kPa (60 mmHg), at the time of initial registration in the ANTADIR Observatory. Data were collected between 1984–1995. Selection criteria were a diagnosis of COPD or emphysema with forced expiratory volume in one second (FEV1) <80% pred, FEV1/vital capacity (VC) <70% and age between 18–75 yrs.

Of 7,700 patients prescribed LTOT 18.5% had stable $P_{a,O_2}$ $\geq$8 kPa. While the FEV1 was the same they differed from the patients with more severe hypoxaemia in having a higher rate of diagnosis of primary emphysema and a lower arterial carbon dioxide tension ($P_{a,CO_2}$). In this group of patients LTOT was more frequently administered as liquid oxygen than in other patients on LTOT. The survival of these patients was reduced compared to the general population of the same age and sex but comparable to that of patients with a $P_{a,O_2}$ between 6.7–8 kPa (50–60 mmHg).

Patients prescribed long-term oxygen therapy with an arterial oxygen tension $\geq$8 kPa (60 mmHg) in the ANTADIR network were shown to have severe chronic obstructive pulmonary disease on the basis of spirometry and their survival was similar to that of more hypoxaemic patients. Randomized controlled trials of the effect of long-term oxygen therapy in patients with arterial oxygen tension $\geq$8 kPa are needed.

Studies have shown that long-term oxygen therapy (LTOT) improves survival in patients with chronic obstructive pulmonary disease (COPD) [1, 2]. These initial studies were carried out using strictly defined protocols and in narrowly defined groups of patients. Subsequently, patients have been widely prescribed LTOT on the basis of these studies. In 1995 it was reported that close to 800,000 patients (~280/100,000) in the USA were receiving LTOT at an annual cost of US$1.8 billion [3]. In France in 1996 17,500 patients were receiving LTOT in the ANTADIR network and an estimated similar number in the private sector (~70/100,000).

Criteria for the prescription of LTOT have been published by academic societies and regulatory bodies [4–6]. Surveys have shown that many prescriptions for LTOT do not fulfil published criteria [7–9]. MORRISON et al. [10] showed that only 14% of patients with COPD and receiving LTOT in Scotland fulfilled all of the relative criteria for the prescription of LTOT.

Association Nationale pour le Traitement à Domicile de l'Insuffisance Respiratoire (ANTADIR) is the co-ordinating headquarters for 33 federated nonprofit associations delivering home treatment to patients with chronic respiratory insufficiency (CRI) in France [11]. The federated associations manage the homecare of nearly 70% of all patients treated at home for CRI. ANTADIR collects data on all patients managed by its regional associations and this forms the basis of a database called the Observatory. An appreciable proportion of patients with COPD in the Observatory do not fulfil the established criteria for starting LTOT [11]. This has led us to analyse the data in this Observatory to describe the situation of patients prescribed LTOT outside guidelines.

Follow-up studies on unselected groups of patients showed a two-year survival of only 46% in 217 COPD patients on LTOT in the Belgian register [12] and similar results (54%) for 393 patients in the Swedish register [13]. Thus, as a secondary aim the survival of patients with arterial oxygen tension ($P_{a,O_2}$) $\geq$8 kPa (60 mmHg) was examined, to determine whether this cut-off point clearly demarcated a different category of patient.

Patients and methods

Collection of data

Since 1984, the characteristics of patients and their outcome have been collected prospectively in 25 associations,
managing 79% of the patients of the ANTADIR network. Information concerning the patient’s characteristics was taken from the Social Security form filled in by the prescribing physician. At entry, this form contains information about the patient’s age, sex, height, weight, the cause of their CRI, the forced expiratory volume in one second (FEV1) and vital capacity (VC) and arterial blood gases (ABG) in room air. The form specifies the equipment being used at home, the daily use of oxygen therapy, the mode of administration and the flow rate prescribed. On follow-up, treatment modifications, treatment withdrawal or death is noted. All of these data are collected, entered into a computerized database in each regional association and centralized at ANTADIR for an annual report and a national database. The anonymous registration of patients was approved by the Commission Nationale de l’Informatique et des Libertés (CNIL), the French equivalent of the Data Protection Council.

Patient selection

The patients selected were those equipped with LTOT between January 1 1984 and December 31 1995 who were registered with the diagnosis of chronic bronchitis and/or emphysema without any other contributing cause of respiratory failure. Patients studied were aged 18–74 yrs inclusive with an FEV1/VC <70% and an FEV1 <80% predicted [14]. Older patients were likely to have multiple pathologies and a very high rate of transfer to long-term care units.

Statistical analysis

The patients were divided into two classes according to whether their $P_aO_2$ in air at the time of installation of LTOT was <8 kPa or $\leq 8$ kPa (60 mmHg). The demographic and functional characteristics of the patients in these two classes were compared by the Chi-squared test and the Student t-test. A graphic analysis of the variations of each of these variables in relation to the $P_aO_2$ divided into classes of 1.3 kPa (10 mmHg) was also carried out. Survival was calculated by the actuarial method from the first day of home treatment. Patients lost to follow-up were excluded from the survival analysis on the day of withdrawal from LTOT or transfer to long-term care units. The comparison of survival of patients according to their initial $P_aO_2$ was performed using the log-rank test. The survival of the patients was also compared to that of the general population calculated for a population of the same age and sex from the French national statistics (Institut National de la Statistique et des Études Economique) [15].

Results

A total of 7,700 patients fulfilled the inclusion criteria. These were mostly males (6,655) and the mean age overall was 63.7±7.6 yrs (mean±SD). The principal cause of respiratory failure was chronic bronchitis in 7,086 cases. At the closing date (January 1 1996) 3,940 patients had died, 2,570 were known to be alive and 1,190 patients were lost to follow-up (75% because of cessation of therapy and 25% because of transfer to long-term care units).

Figure 1 shows the $P_aO_2$ data at the time of prescription of LTOT. Of the patients studied, 18.5% (1,425) had a $P_aO_2 >8$ kPa (60 mmHg) on initial blood gases. Table 1 compares the functional and demographic characteristics of these patients with those for the group with a $P_aO_2 <8$ kPa (60 mmHg) at the time of prescription. There were no age or sex differences between the groups or in body mass index (BMI). The spirometric data were not different and the severity of airflow obstruction was comparable whether or not the patients had a $P_aO_2 <8$ kPa. The patients with a higher $P_aO_2$ had a significantly lower arterial carbon dioxide tension ($P_aCO_2$). Figure 2 shows FEV1 as a percentage predicted in relation to the $P_aO_2$ and figure 3 shows the relationship between $P_aO_2$ and the $P_aCO_2$.

The daily duration of oxygen therapy prescribed was shorter in the patients with better oxygenation but was near 15 h per 24 h (fig. 4) and LTOT was more frequently administered as liquid oxygen to these patients. The proportion of patients labelled as having emphysema was increased in the group with a higher $P_aO_2$ (fig. 5).

Table 1. – Demographic and physiological data according to arterial oxygen tension ($P_aO_2$)

<table>
<thead>
<tr>
<th>$P_aO_2$ (60 mmHg)</th>
<th>$P_aO_2$ (60 mmHg)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8 kPa</td>
<td>$\leq 8$ kPa</td>
<td></td>
</tr>
<tr>
<td>5417/858</td>
<td>1238/187</td>
<td>0.591</td>
</tr>
<tr>
<td>63.7±7.5</td>
<td>63.9±7.8</td>
<td>0.25</td>
</tr>
<tr>
<td>24.0±6.0</td>
<td>24.2±6.0</td>
<td>0.221</td>
</tr>
<tr>
<td>61.2±17.7</td>
<td>61.9±18.0</td>
<td>0.186</td>
</tr>
<tr>
<td>32.3±12.6</td>
<td>32.2±13.2</td>
<td>0.877</td>
</tr>
<tr>
<td>40.6±12.0</td>
<td>40.1±12.8</td>
<td>0.173</td>
</tr>
<tr>
<td>90.2±23.0</td>
<td>93.7±23.6</td>
<td>0.014</td>
</tr>
<tr>
<td>47.7±8.5</td>
<td>43.6±7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>16.2±2.9</td>
<td>14.9±3.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are shown as mean±SD. M: male; F: female; BMI: body mass index; VC: vital capacity; % pred: per cent of predicted value; FEV1: forced expiratory volume in one second; TLC: total lung capacity; $P_aCO_2$: arterial carbon dioxide tension. (1 mmHg=0.133 kPa.)

![Fig. 1. – Number and proportion of patients at different levels of arterial oxygen tension ($P_aO_2$). (1 mmHg=0.133 kPa.)](image-url)
Figure 6 shows the survival of the patients in relation to the initial \(P_aO_2\). The survival of patients with an initial \(P_aO_2\) \(\geq 8\) kPa (60 mmHg) was identical to that of patients with a \(P_aO_2\) between 6.7 and 7.2 kPa (50 and 54 mmHg) and between 7.3 and 7.9 kPa (55 and 59 mmHg). Only patients with a \(P_aO_2\) <6.6 kPa (50 mmHg) at the time of prescription had a significantly worse survival (p<0.001) than the other groups. The survival of patients with a \(P_aO_2\) \(\geq 8\) kPa was greatly reduced compared with that of the general population of the same age and sex as derived from French national statistics [15] (fig. 6). It should be noted that rate of entry into long-term care was similar for all groups, but the level of discontinuation of LTOT was 14% in patients with \(P_aO_2\) \(\geq 8\) kPa (60 mmHg) and only 9% in patients with \(P_aO_2\) <8 kPa (60 mmHg).

**Discussion**

In a study of 7,700 patients prescribed LTOT it was shown that 18.5% of patients with a diagnosis of COPD in the ANTADIR network in France were prescribed LTOT with initial stable blood gases outside published guidelines. These patients, however, had reduced survival which was comparable to that of patients with a \(P_aO_2\) between 6.7 and 8 kPa (50 and 60 mmHg). They differed from the patients on LTOT, with more severe hypoxaemia being more frequently labelled as emphysema. They also had a lower \(P_aCO_2\) and a shorter duration of LTOT prescribed and were more frequently given liquid oxygen.

The results show a wide range of \(P_aO_2\) with a few patients having normal oxygenation. This may have been a miscoding in a few of the 7,700 patients. This wide variation in \(P_aO_2\) was associated with a constantly poor level of FEV1 of around 40% pred. This may reflect the wide range in the morphotype of patients with COPD, traditionally described as pink puffers and blue bloaters. This possibility is reinforced by the finding of a gradual increase in \(P_aCO_2\) as the \(P_aO_2\) declines (fig. 3), but this may also reflect the stage of evolution of the COPD. There is considerable variability in the relationship between \(P_aCO_2\) and FEV1 [16].

The guidelines published by academic societies or regulatory bodies are based on the two controlled studies which have proven the efficacy of LTOT in hypoxaemic COPD patients. Criteria for entry for these studies were for the Medical Research Council (MRC) study, a \(P_aO_2\) between 5.3 and 8 kPa (40 and 60 mmHg) with one or more episodes of heart failure with ankle oedema [2], and for the Nocturnal Oxygen Therapy Trial (NOTT) study, a \(P_aO_2\) \(\geq 7.2\) kPa (55 mmHg) or a \(P_aO_2\) >8 kPa (60 mmHg) plus either oedema, haematocrit \(\geq 55\)% or P pulmonale on electrocardiography (ECG) [1]. Precise prescription rules
exist in France for oxygen therapy [17]. This treatment is reimbursed if \( P_aO_2 \) under room air is 7.3 kPa (55 mmHg) or lower at two measurements in a steady state. The minimum interval between the two measurements should be at least 2 weeks and daily oxygen treatment should be given for at least 15 h. The reimbursement criteria also state that the prescription can be applied for the existence of polycythaemia and desaturation during sleep or exercise [18].

In the present study, \( P_aO_2 \) was >7.3 kPa (55 mmHg) in 45% of patients and >8 kPa (60 mmHg) in 18%. Daily oxygen was prescribed for <15 h in 18% of patients (16% in patients with \( P_aO_2 \) <8 kPa and 33% for patients with \( P_aO_2 \), 8 kPa). Several surveys performed in the UK have shown that compliance with guidelines is often weak. In the study by Walsh et al. [7], 27 of 61 patients had been prescribed LTOT by a doctor other than a respiratory specialist and only 32 of 61 patients fulfilled official criteria for the prescription of LTOT at the time of prescription of therapy. Only 54% of the patients had basal arterial oxygen saturation (\( S_aO_2 \)) of <90% for the study of Waterhouse et al. [9] and only 14% fulfilled all of the relative criteria for the prescription of LTOT in the study of MacRae et al. [10]. Only Restick et al. [8] observed that guidelines were largely followed.

No precise data were available on the reasons for prescription of LTOT in the group of patients with \( P_aO_2 \), 8 kPa (60 mmHg), but it may be speculated that these patients were prescribed LTOT for nocturnal desaturation or because of exercise-related desaturation, among other causes. Fletcher et al. [19] examined the effect of nocturnal oxygen in patients with a daytime \( P_aO_2 \) >8 kPa and found a nonsignificant trend increased survival in 39 oxygen-treated versus 38 non-oxygen-treated desaturating patients, where nocturnal desaturation was defined as a fall in \( S_aO_2 \), 90% for 5 min or more, with a nadir \( S_aO_2 \), reaching 85% or less. While American guidelines do not set any criteria for nocturnal desaturation the recent French guidelines [6] would consider LTOT for nocturnal desaturation only if the patient passes over 30% of the night with a \( S_aO_2 \), <90%. These guidelines state, however, that this treatment should not yet be applied systematically but only in carefully considered cases.

Many patients who are hypoxaemic at rest worsen during exertion, while others develop hypoxaemia only during exertion. Some short-term studies have shown that supplemental oxygen during exercise can prevent transient increases in pulmonary artery pressure and pulmonary vascular resistance [20]. Home supplemental oxygen is commonly prescribed for exercise-related desaturation, even though studies designed to determine the long-term benefit of oxygen solely for exercise have yet to be conducted [5]. Figure 5 shows a sharp rise in the proportion of patients given liquid oxygen with a \( P_aO_2 \) above 7.3 kPa (55 mmHg), implying that above this figure a large proportion of patients were prescribed ambulatory oxygen. These patients were more likely to have a diagnosis of emphysema and therefore have severe breathlessness and exercise-related desaturation.

Prognosis in COPD depends not on hypoxaemia alone but equally on other factors such as sex, nutritional status, type of COPD (emphysematous or bronchitic) and bronchial obstruction [11]. FEV1 is independently predictive of survival even when mildly impaired [21]. Cooper and Howard [22] have shown that deterioration in airway function continues despite LTOT and thus reduces survival. Indeed, in the present study a \( P_aO_2 \) of 6.7 kPa (50 mmHg) seems to be a more cut prognostic figure for survival than 8 kPa (60 mmHg), as the survival was similar for all groups of patients with a \( P_aO_2 \), 7.3 kPa. This could reflect the beneficial effect of LTOT in hypoxaemic patients in improving the survival into the same range as that of patients with a \( P_aO_2 \), 8 kPa. Antinnes et al. [21] showed that oxygen therapy improved survival in patients with a \( P_aO_2 \) ranging 7.4–8.7 kPa (55–60 mmHg) to the same level as in patients with a similar level of obstruction but without hypoxaemia (\( P_aO_2 \), 7.3 kPa). Randomized, controlled trials with well-defined groups of patients and an assessment of quality of life, healthcare consumption and costs are needed.

Compliance with LTOT plays a role in outcome. No precise data are available on these individual patients, but Dinn et al. [23] studied compliance in 950 patients in the ANTADIR network and found an average compliance of 14.5±5 (mean±SD) from clock counters in the concentrators. Factors influencing compliance included a reduced compliance in patients with a \( P_aO_2 \) >7.3 kPa and the prescribed duration of LTOT. This strengthens the implication that prescription of LTOT to such patients is for effort or nocturnal desaturation.

It seems important to understand the reasons why physicians prescribe LTOT for patients with \( P_aO_2 \) outside guidelines. Furthermore, prospective studies on the use of LTOT in circumstances outside those verified by the MRC and NOTT studies are needed in order to validate or justify the use of oxygen in circumstances such as nocturnal or exercise-related hypoxaemia, dyspnoea, cardiac failure, pulmonary arterial hypertension and polycythaemia.
groups are treated. Whether these two groups would have had the same survival if both were untreated is a vexed question which our study does not answer. Since the functional impairment as shown by FEV1 was the same in both groups one could only speculate that the same survival advantage accrued to all.

In conclusion, patients prescribed long-term oxygen therapy with an arterial oxygen tension \(8\) kPa (60 mmHg) in the ANTADIR network have been shown to have severe chronic obstructive pulmonary disease on the basis of spirometry. Their survival is similar to that of more hypoxaemic patients who were also treated with long-term oxygen therapy and below that of the general population of the same age and sex. The current guidelines may need revision and prospective studies of the effect of long-term oxygen therapy in these patients are needed.

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References


