Prognostic Factors in COPD Patients Receiving Long-term Oxygen Therapy*

Importance of Pulmonary Artery Pressure

Monique Oswald-Mammosser, MD; Emmanuel Weitzenblum, MD; Elisabeth Quoix, MD; Gabrielle Moser, MD; Ari Chaouat, MD; Catherine Charpentier, MD; and Romain Kessler, MD

Prognostic factors in COPD patients receiving long-term oxygen (LTO) therapy were recently analyzed, but very few studies considered the prognostic value of pulmonary artery pressure (PAP) in these patients. We investigated 84 patients who had undergone a right heart catheterization just before the onset of LTO. There were 75 men and 9 women, with a mean age of 63.0±9.9 (SD) years, at the onset of LTO. When PaO₂ was persistently less than 55 mm Hg, LTO was initiated. This therapy was started in some patients with PaO₂ in the range of 55 to 60 mm Hg if they had signs of cor pulmonale or a resting PAP of 25 mm Hg or greater at right heart catheterization. The daily duration of LTO was 16 h/d or more. Oxygen flow was adapted to achieve a PaO₂ of 65 mm Hg or more. The patients were subdivided into subgroups according to the median value of age (cutoff value=63 years); vital capacity (2,250 mL); FEV₁ (800 mL); residual volume-total lung capacity ratio (38%); PaO₂ value (52 mm Hg), PaCO₂ level (45 mm Hg); and PAP (25 mm Hg). The cumulative 5-year survival rate was 48% for the group as a whole. Actuarial survival curves were plotted for the two subgroups of patients subdivided according to the initial median value of the variables just listed. There was no significant difference in survival rate between subgroups except when taking into account the level of PAP and age. In patients with an initial PAP of 25 mm Hg or less (n=44), the 5-year survival was of 62.2 vs 36.3% in the remainder (n=40) [p<0.001]. We performed a multivariate analysis of survival using Cox’s model of the proportional hazards regression including sex and the variables with the same categorization in the stepwise procedure: PAP and age were the only variables included in the final model. We conclude that the best prognostic factor in COPD patients receiving LTO is not the FEV₁, nor the degree of hypoxemia or hypercapnia, but the level of PAP.

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In patients with advanced COPD, FEV₁ and arterial blood gas values (PaO₂ and PaCO₂) have been shown to be good indicators of prognosis.1-4 Further studies have indicated that pulmonary artery mean pressure (PAP) also had a good prognostic value: the higher the PAP, the shorter the life expectancy.5-7 These studies concerned patients treated with conventional methods, not including long-term oxygen therapy (LTO). The well known Nocturnal Oxygen Therapy Trial (NOTT)⁸ and Medical Research Council (MRC) studies⁹ have showed that LTO, given 15 h or more per day, improved survival in hypoxemic COPD patients. LTO also has favorable effects on pulmonary hypertension since it stabilizes, and sometimes reverses, the progression of pulmonary hypertension.10,11 Consequently, the prognostic value of PAP, well shown in patients not receiving LTO, could no longer be present in patients receiving LTO. Few studies have considered the prognostic value of pulmonary hemodynamic variables in COPD patients receiving oxygen therapy.12-14 Thus, the aim of the present study was to evaluate the prognostic factors including respiratory functional variables and PAP, in a relatively large series (n=84) of COPD patients receiving LTO.

METHODS

Clinical Data

Eighty-four COPD patients were included in this study. There were 75 men and 9 women and the mean age at the onset of LTO was 63.0±9.9 (SD) years. The COPD was assessed on clinical grounds as history of productive cough with progressive exertional dyspnea and functional criteria: FEV₁-vital capacity (VC) ratio of less than 60%, the total lung capacity (TLC) being more than 80% of the predicted value. Patients with an associated lung disease, eg, sequelae of pulmonary tuberculosis, pneumoconiosis, left heart diseases, marked obesity (body mass index more than 32), sleep apnea syndrome, or any other severe disease were excluded from the study. Therapy with LTO was initiated when the PaO₂ value was persistently less than 55 mm Hg, patients being in a stable state of their disease, and in patients with PaO₂ levels in the

LTO=long-term oxygen; MRC=Medical Research Council; NOTT=Nocturnal Oxygen Therapy Trial; PAP=pulmonary artery pressure; RV=residual volume; TLC=total lung capacity; VC=vital capacity

Key words: chronic hypoxemia; COPD; long-term oxygen therapy; prognosis; pulmonary hypertension

*From the Services de Pneumologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France.

Reprint requests: Dr. Weitzenblum, Service de Pneumologie, Hôpital de Hautepierre, 67098 Strasbourg Cedex, France.
range of 55 to 59 mm Hg, provided that they had signs of clinical cor pulmonale or a resting PAP of 25 mm Hg or more at right heart catheterization. The stability of hypoxemia before the onset of LTO was checked by repeated arterial blood gas measurements, the follow-up period being at least 1 month and 3 months whenever possible. 15

The daily duration of oxygen therapy was 16 h or more. Oxygen was provided in most of the patients by concentrators and was given by nasal prongs. The oxygen flow was adapted and checked at least once a year to achieve a PaO2 of 65 mm Hg or more. At the onset of LTO, the flow of O2 ranged between 1 and 3 L per minute. The patients included in that study were regularly followed up (once every 2 to 3 months) at the outpatient clinic. Long-term therapy usually included inhaled β2-agonists, long-acting theophylline, and chest physiotherapy. Corticosteroids were prescribed only during acute episodes of respiratory failure.

Conventional spirometry was performed with a 10-L closed-circuit water-sealed spiromet. Static lung volumes were measured by the closed-circuit helium dilution method. Reference values were those of the European Community. 16 Right heart catheterization was performed as previously described. 17 Briefly, the hemodynamic measurements were always done while the patient was in the supine position, in the morning, without premedication, 2 h after a light breakfast. For the purpose of this study, we used small-diameter Grandjean 18 catheters (4F, Plastimed; Saint-Leu-la-Forêt, France). Arterial blood samples were obtained through a Cournand needle inserted in the humeral artery during right heart catheterization. In our department, right heart catheterization belongs to the investigations usually performed before the onset of LTO in hypoxemic COPD patients 19 after an informed consent has been obtained.

The LTO was initiated from 1976 to 1991 and the endpoint for the analysis of the data was February 1992. The duration of the follow-up ranged from 1 to 12 years. The possible influence of the following variables on mortality was assessed by statistical analysis, as discussed later: age at the onset of LTO, pulmonary volumes (VC, FEV1, FEV1/VC ratio; residual volume (RV)-TLC ratio), and arterial blood gases levels with patients breathing on ambient air (PaO2, PaCO2) and PAP.

### Statistical Methods

Quantitative variables were compared by the Student's t test for unpaired data. Survival was calculated from the date of onset of LTO until death or up to the closing date of the study: February 28, 1992. Survival curves were established according to the actuarial method. Comparison between the survival curves defined for different groups was done by the log rank test. All quantitative variables were categorized before analysis and only clinically meaningful grouping was carried out. A multivariate analysis of survival using Cox's model of the proportional hazards regression was then performed. A stepwise regression using the maximum partial likelihood ratio method was used. All the variables without missing values were included in the stepwise procedure with a probability to enter set at 0.15 and a probability to remove value set at 0.10. Data were processed using the BMDP package from the University of California, Los Angeles.

### Results

The mean and median values of age, pulmonary volumes, arterial blood gas levels, and PAP of the 84 patients, at the onset of LTO, are given in Table 1. Bronchial obstruction was generally severe with mean and median FEV1 values less than 900 mL. By definition, all the patients were markedly hypoxemic and the median PaO2 was 51.6 mm Hg. In 29 of 84 patients, the initial PaO2 value was less than 50 mm Hg. Half of the patients (44 of 84) were hypercapnic (≥45 mm Hg), and the median PaCO2 was exactly 45 mm Hg. In only seven patients was the initial PaCO2 more than 55 mm Hg. For the group as a whole, PAP was mildly elevated with a mean value of 27.2 ± 8.9 mm Hg and a median value of 25 mm Hg. Sixty-five of 84 patients (77%) had pulmonary hypertension (PAP>20 mm Hg), PAP was 30 mm Hg or greater in 31 patients.

The cumulative survival rate for the group as a whole was 71% at 3 years and 48% at 5 years (Fig 1). Actuarial survival curves were plotted for groups of patients subdivided according to the initial level of

### Table 1—Pulmonary Volumes, Arterial Blood Gas Levels, and Hemodynamic Data of the 84 Patients Included in the Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Range)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>63.0 (44.0)</td>
<td>62.9 ± 9.9</td>
</tr>
<tr>
<td>VC, mL</td>
<td>2,272 (3,775)</td>
<td>2,430 ± 718</td>
</tr>
<tr>
<td>FEV1, mL</td>
<td>775 (1,380)</td>
<td>852 ± 340</td>
</tr>
<tr>
<td>FEV1/VC ratio, %</td>
<td>33.0 (41.3)</td>
<td>36.0 ± 11.0</td>
</tr>
<tr>
<td>RV/TLC ratio, %</td>
<td>58.0 (43.0)</td>
<td>57.6 ± 9.8</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>51.6 (25.0)</td>
<td>52.0 ± 5.4</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>45.0 (44.0)</td>
<td>45.3 ± 7.6</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>25.0 (40.0)</td>
<td>27.2 ± 8.9</td>
</tr>
</tbody>
</table>

* Range is the difference between the extreme values.
age, pulmonary volumes, arterial blood gas levels, and PAP. The patients were subdivided into two groups according to the median value of age (cutoff value=63 years); VC (2,250 mL); FEV₁ (800 mL); RV/TLC ratio (58%); PaO₂ value (52 mm Hg); PaCO₂ level (45 mm Hg), and PAP (25 mm Hg).

There was no significant difference in survival rates between subgroups except when taking into account the level of PAP and age (Table 2, Figs 2 and 3). In patients with an initial PAP of 25 mm Hg or less (n=44), the 5-year survival rate was 62.2 vs 36.3% in the remainder (n=40), with an initial PAP greater than 25 mm Hg, the difference being highly significant (p<0.001). Identical results were observed when the cutoff value was of 27 mm Hg (mean value) or 30 mm Hg: in patients with an initial PAP greater than 30 mm Hg (n=31), the 5-year survival rate was 15 vs 63.9% in the remainder (n=53), with an initial PAP of 30 mm Hg or less (p<0.001). We also chose to analyze our results with a cutoff value of 30 mm Hg because this value corresponds to the generally accepted limit between mild and moderate to severe pulmonary hypertension. Age, VC, FEV₁, RV/TLC ratio, PaO₂ level, and PaCO₂ value did not differ in the two subgroups with mild and moderate pulmonary hypertension whatever cutoff value (25, 27, or 30 mm Hg) was considered.

The multivariate proportional hazards analysis included the sex and the following variables: age, PAP, PaO₂ value, PaCO₂ level, and FEV₁/VC ratio with the same categorization. PAP and age were the only variables included in the final model. Estimate of the relative risk of dying for each variable is given in Table 3. The data supported the proportional assumption. Adequation of the model is satisfying and shown in Table 4. Figure 4 shows the survival curves estimated with Cox’s model of prognostic categories (age ≤63 or >63 years and PAP ≤25 or >25 mm Hg). It can be seen that estimated survival is the best in patients having both an age of 63 years or less and a PAP of 25 mm Hg or less; it is the worst in patients having both an age of greater than 63 years and a PAP greater than 25 mm Hg; the estimated survival curves are between these two extremes for the two other combinations of age and PAP.

**Discussion**

Undoubtedly the major finding of this study was that the univariate as well as the multivariate analysis could identify PAP (and age) as a significant predictor of survival in COPD patients receiving LTO, whereas pulmonary volumes and arterial blood gas levels had no predictive value. The difference in survival at 5 years between patients with a PAP greater than 30 mm Hg and those with a PAP less than 30 mm Hg was highly significant (15 vs 63.9%;

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21713/)

**Figure 2.** Actuarial survival curves according to age at the onset of LTO therapy.

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21713/)

**Figure 3.** Actuarial survival curves according to the level of PAP at the onset of LTO therapy.
p<0.001) and when the cutoff value was 25 mm Hg (median value of PAP in our group) the results were similar (p<0.001). These results raise at least two questions: Why were pulmonary volumes and arterial blood gases of poor prognostic value? Why, on the other hand, did PAP appear as a good indicator of prognosis?

First, it is important to underline that our series is well representative of COPD patients in whom O₂ therapy is needed. The criteria for prescribing O₂ were those commonly accepted (NOTT) and particular attention was paid to assess the stability of hypoxemia before initiating the treatment. The mean initial PaO₂ of our patients was identical to that of the patients included in both NOTT and MRC studies, and the mean PaCO₂ was comparable to that of the NOTT patients. Furthermore, the overall 5-year survival rate of our 84 patients was 48%, which is rather similar to the life expectancy of the men receiving O₂ for 15 h or more per day in the MRC study. In COPD patients given LTO, the 5-year survival rate varies, according to the series, from 30 to 62%. Thus, our figure of 48% agrees well with previous results obtained in patients with a comparable degree of severity.

We were surprised that the degree of airway obstruction and the level of hypoxemia and hypercapnia had no prognostic value in our series, which is different from the results of some earlier studies, but does agree with results of others. Our finding could be explained by the fact that our cohort was perhaps too small to allow us to detect the influence of FEV₁, FEV₁/VC ratio, PaO₂ level, and PaCO₂ value on survival. Of interest are the studies of Keller et al and our own where similar numbers of patients (87 and 84, respectively) with a comparable degree of severity were included that showed no influence of FEV₁ and PaO₂ on survival; however, the multicentric study by Chailleux et al, which had included as many as 1,775 COPD patients receiving LTO, showed a marked influence of FEV₁, FEV₁/VC ratio, and PaO₂ level on survival, but only in men. On the other hand, Cooper et al., who have followed up a relatively small number of patients (n=72), have observed a good correlation between FEV₁ and survival, while Dubois et al., who could include 217 patients, reported no difference in FEV₁ between those who died and those who were still alive after 2 years. It, thus, appears that the discrepancies between the results reported in the literature cannot be satisfactorily explained by differences in the numbers of patients included.

Another possible explanation is that some series of

Table 3—Prognostic Factors: Results of Cox’s Regression Analysis in the 84 Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>RR*</th>
<th>CI†</th>
<th>Probability Value</th>
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<tbody>
<tr>
<td>PAP &gt;25 mm Hg</td>
<td>2.17</td>
<td>1.14-3.78</td>
<td>0.016</td>
</tr>
<tr>
<td>Age &gt;63 yr</td>
<td>2.18</td>
<td>1.15-4.11</td>
<td>0.018</td>
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</table>

*RR is the relative risk of dying. †CI is the 95% confidence interval.

![Figure 4: Survival related to prognostic categories (age and PAP) obtained with the Cox model.](image)

Table 4—Adequation of Cox’s Model and Actuarial Survival Rate*

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>Cox, %</th>
<th>Actuarial, %</th>
<th>SE, %</th>
<th>Cox, %</th>
<th>Actuarial, %</th>
<th>SE, %</th>
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</thead>
<tbody>
<tr>
<td>PAP &lt;25 mm Hg and Age &lt;63 yr</td>
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<td></td>
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<td></td>
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<tr>
<td>12</td>
<td>97.5</td>
<td>100</td>
<td>...</td>
<td>94.7</td>
<td>95.4</td>
<td>4</td>
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<tr>
<td>24</td>
<td>92.1</td>
<td>94.7</td>
<td>5</td>
<td>83.7</td>
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<tr>
<td>36</td>
<td>85.2</td>
<td>89.2</td>
<td>7</td>
<td>70.5</td>
<td>72.8</td>
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<tr>
<td>48</td>
<td>78.8</td>
<td>82.8</td>
<td>9</td>
<td>59.5</td>
<td>72.8</td>
<td>11</td>
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<tr>
<td>60</td>
<td>70.0</td>
<td>70.0</td>
<td>11</td>
<td>46.0</td>
<td>53.1</td>
<td>14</td>
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<tr>
<td>PAP &gt;25 mm Hg and Age &lt;63 yr</td>
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<tr>
<td>12</td>
<td>94.9</td>
<td>95.6</td>
<td>4</td>
<td>89.3</td>
<td>85.2</td>
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<td>24</td>
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<tr>
<td>48</td>
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<td>34.1</td>
<td>14.1</td>
<td>12</td>
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<tr>
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<td>45.0</td>
<td>10</td>
<td>20.0</td>
<td>14.1</td>
<td>12</td>
</tr>
</tbody>
</table>

*Cox refers to the survival rate according to the Cox model; actuarial, actuarial survival rate; and SE, standard error.
the medical literature, including our own, are relatively homogenous with a small variability of arterial blood gas levels and pulmonary volumes from one patient to another, whereas other series are quite different in this regard. If most FEV1, PaO2, and PaCO2 values are included in a narrow range, it is easy to understand that these variables will not turn out to be good indicators of prognosis, particularly when the group comprises fewer than 100 subjects.

This applies to our study where the dispersion of PaO2, PaCO2, and FEV1 values from the mean value was limited. As an example, the average PaO2 was 52 mm Hg, with a standard deviation of only 5 mm Hg, which means that subgroups of patients—those with less than 52 mm Hg or greater than 52 mm Hg (Table 2) had average values of PaO2, which were not markedly different; this probably explains why the level of PaO2 did not influence the life expectancy. Conversely, Skwarsky et al12 have observed that in their 154 patients with an initial PaO2 level of 60 mm Hg or less, FEV1 and PaO2, at the time of prescription of LTO, predicted survival, the cutoff values being 350 mL and 42 mm Hg, respectively. This indicates that the range of FEV1 and PaO2 values was large in this series and, in addition, that many patients were in an advanced stage of the disease. In our series, only 3 of 84 patients had an initial PaO2 of 42 mm Hg or less, and no one had an initial FEV1 of 350 mL or less (lowest FEV1=425 mL). Of interest, the range of PAP values in our patients was proportionally larger than that of arterial blood gas values, with a mean value of 27±9 (SD) mm Hg, and extreme values of 14 and 44 mm Hg.

The relatively poor prognostic value of PaO2 is also accounted for by the fact that in patients receiving O2 therapy for more than 16 h in a 24-h period and particularly in those having O2 therapy during 18 h or more in a 24-h period, the relevant PaO2 is no longer PaO2 obtained in ambient air conditions but rather PaO2 obtained during O2 therapy. This has been emphasized by Cooper et al21 and may apply to our patients whose daily duration of LTO was generally more than 16 h in a 24-h period.

The influence of initial PAP on the survival of COPD patients receiving LTO has been investigated in a limited number of studies10,12,13,14,21 which all had methodologic limitations with the exception of the NOTT study10 that was not particularly devoted to the prognostic value of physiologic variables. Keller et al13 observed that initial PAP was of high prognostic value since patients surviving after 2 years of LTO therapy significantly differed from the remainder (PAP of 29±9 [SD] vs 40±12 [SD] mm Hg), but these results were limited to 38 of 87 patients in whom right heart catheterization could be performed. On the other hand, Cooper et al21 did not observe that PAP was an indicator of prognosis but hemodynamic variables were available in 45 of 72 patients. Würtemberger et al14 investigated a larger series of 127 patients and reported a higher survival rate in patients whose initial PAP was less than 30 mm Hg, but LTO therapy was given for a minimum of only 8 to 12 h per day, whereas a minimum of 15 to 16 h per day is generally required,5,8 particularly if the aim of LTO therapy is to improve pulmonary hypertension.24 Skwarsky et al12 have investigated the largest group of patients (n=179) and have shown that a cutoff value of 30 mm Hg (for PAP) had a good prognostic significance, but 25 of 179 patients had an initial PaO2 more than 60 mm Hg, and hemodynamic variables were not measured in all patients (they were available in 115 of 179 patients). To our knowledge, the present study is the first where the following criteria were all fulfilled: measurement of PAP; initial PaO2 of 60 mm Hg or less and most often less than 55 mm Hg, according to the NOTT criteria;8 daily duration of O2 therapy of 16 h or more per day.

That age is a determinant factor of survival in patients with severe COPD receiving LTO or not is easy to understand and has been underlined in almost all series.8,14,20,23 In this regard, our results agree well with those of the medical literature. The prognostic value of PAP, in patients receiving LTO therapy, is more difficult to explain. Indeed, PAP is known to be a good indicator of prognosis in COPD patients not treated with O2 therapy5-7 but this may not apply to patients receiving LTO therapy since this treatment allows the stabilization9 and sometimes the reversal10,11 of the progression of pulmonary hypertension. Cooper et al21 have noticed that LTO therapy “appears to interrupt the progression of hemodynamic disturbances . . . and in doing so has displaced the correlation of pulmonary hypertension with mortality.” In our opinion, the level of PAP at the onset of O2 therapy is an overall index of the severity of the disease and can be considered as a marker of the deleterious effects of chronic hypoxia, which concern the pulmonary circulation but also other organs including the myocardium, the kidneys, and the brain. PAP could be a good indicator of prognosis even if LTO therapy allows the stabilization of pulmonary hypertension. Furthermore, most of the patients are not given O2 continuously, and some of them discontinue the treatment for several hours each day. We know from the study by Selinger et al25 that removing O2 in 2 to 3 h leads to a significant increase of PAP. The deleterious hemodynamic effects of removing O2 are probably more pronounced in those patients whose PAP is higher (>30 mm Hg). These patients are at a higher risk of harmful consequences of acute alveolar hypoxia: repetitive bouts of
worsening of pulmonary hypertension could favor the development of right heart failure.

In conclusion, our study has shown that the level of PAP (together with age) is a good indicator of survival in COPD patients receiving LTO therapy. When PAP is moderately to markedly elevated (>30 mm Hg) at the onset of LTO therapy, the survival rate is decreased in comparison with patients with no or mild (<30 mm Hg) pulmonary hypertension. These results may suggest that LTO should be started earlier in hypoxemic COPD patients at a stage of mild (or even absent) pulmonary hypertension.

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