Prognosis of Severely Hypoxemic Patients Receiving Long-term Oxygen Therapy*

Pierre Dubois, M.D., F.C.C.P.; Jacques Janmart, M.D.; Jacques Machiels, M.D., F.C.C.P.; Freddy Smeets, M.D., F.C.C.P.; and Jean Lulling, M.D.

Two hundred seventy severely hypoxemic (\(\text{PaO}_2 \leq 55\) mm Hg; mean ± SD = 48 ± 6) COPD patients (232 men) were selected for long-term oxygen therapy (LTOT). They were old (mean = 66 ± 8 years), with severe airflow limitation (FEV₁ = 30 ± 12 percent of predicted), some CO₂ retention (\(\text{PaCO}_2 = 47 ± 9\) mm Hg), and compensated respiratory acidosis. Eighteen percent of the patients presented some complicating pleuropulmonary diseases (pleural thickening, sequelae of tuberculosis, etc.). Overall survival proportion was poor: 70, 50, and 43 percent at 1, 2, and 3 years, respectively. The Cox model showed that the factors which independently reduced survival were lower CO transfer coefficient, smaller intrathoracic gas volume, more severe bronchial obstruction, the fact that oxygen administration did not increase \(\text{PaO}_2\) above 65 mm Hg, increasing age, and the presence of chest wall abnormalities. When the patients were divided into three groups according to mortality risk, the mean clinical and functional profile of the high-mortality risk group was consistent with the prevalence of emphysematous lesions. Moreover, the best survivors fitted better into the "bronchitic" type; they showed a higher mean \(\text{PaCO}_2\), suggesting that some degree of hypoventilation could delay muscular fatigue and improve survival. The difference in the proportion of "emphysematous" and "bronchitic" patients is a possible explanation for the variability of the mortality rate reported in literature. (Chest 1994; 105: 469-74)

For many years, long-term oxygen therapy (LTOT) has shown its favorable impact on the well-being and the survival of patients with COPD in the stage of severe chronic hypoxemia. This treatment seems to stabilize for quite a long time the blood gases, \(\text{PaO}_2\), and \(\text{PaCO}_2\) while breathing air, although it cannot prevent a deterioration in the long run. Moreover, LTOT reduces polycythemia. The regression of pulmonary arterial hypertension has been demonstrated in several series.

Since the studies monitored by the National Institutes of Health (NIH) and the British Medical Research Council (MRC), certain series have shown a satisfactory, and even excellent, survival of severely hypoxemic COPD patients receiving LTOT. Nevertheless, recent clinical studies have indicated a higher mortality than that shown in earlier studies, especially in male subjects.

A number of scientific associations have made recommendations for the eligibility of patients for LTOT.

*From the Service de Pneumologie (Drs. Dubois and Lulling) and the Consultation Biostatistique of the Cliniques Universitaires de Mont-Godinne (Dr. Janmart), Université Catholique de Louvain, Yvoir, Belgium; the Clinique St Pierre, Ottignies (Dr. Machiels); and Centre Hospitalier de St Ode, Bacofo (Dr. Smeets). Manuscript received January 29, 1993; revision accepted May 28.

**Methods**

**Patients**

The patients were admitted to three hospitals from 1985 to 1990 with respiratory insufficiency and severe hypoxemia. Most were admitted for an acute exacerbation of airflow obstruction, some with right heart failure. After recovery, they were assessed during several weeks for clinical stability.

According to the Belgian Social Security regulations for reimbursement of LTOT, the patients were selected for oxygen treatment if their
PaO₂ while breathing air was equal to or lower than 55 mm Hg in a controlled steady state of at least 3 weeks, with a control at 3 months, and if their PaCO₂ did not increase "excessively" during oxygen administration. However, the degree of induced hypercapnia was not precisely determined in the regulations.

The sole exclusion criterion for entry into the study was a severe disease that might be expected to influence short-term mortality, eg, evolutionary cancer, severe renal or hepatic insufficiency. No patient has had previous LTOT.

From 365 patients subjected to LTOT, we selected the 276 whose diagnosis was COPD; six patients who improved their PaO₂ above 55 mm Hg within 3 months of treatment were rejected, and we finally included 270 severe hypoxic COPD patients: 232 were male and 38 were female. Moreover, 15 patients had late sequelae of tuberculosis, 9 had pneumonia, and 3 had radiologic bronchovascular accentuation; 4 patients had undergone pulmonary resections and 18 had various degrees of chest wall abnormalities, such as pleural thickening, costal fracture, or slight kyphoscoliosis.

All patients were discouraged from smoking but it was clear from carboxyhemoglobin measurements that some continued to do so. It was impossible to make a reliable separation into smokers and nonsmokers for further analysis.

Treatment other than oxygen was given according to the discretion of the clinician in charge of the patient and usually included sympathomimetic agonists, inhaled corticosteroids, and/or sustained-release methylxanthines; diuretics and antibiotics were used as clinically indicated; therapeutic phlebotomies were not done. The patients were controlled once a year in the hospital and admitted for other treatments if necessary. Otherwise the patients stayed at home and were visited every 3 months by a trained nurse or technician to assure their compliance to oxygen therapy and to assess changes in the clinical state.

**Physiologic Measurements**

The baseline studies included history and clinical examination, electrocardiogram, chest radiograph, and usual blood and urine analysis. Spirometry, measurement of the single breath transfer factor for carbon monoxide (TLCO) (Morgan Transfer Test or Alveolo Diffusion Test, Jaeger), and body plethysmography (Body Test, Jaeger) were performed in all patients able to do so; 65 patients were unable to maintain the 10-s apnea for TLCO measurement. Predicted values were those published in Quanjer.²⁸

Arterial blood was analyzed by a pH and blood gas analyzer (Corning 175, ABL Radiometer, submitted to regular quality controls by an independent institution) and in 116 cases, oxyhemoglobin and carboxyhemoglobin were directly measured (CO-Oxymeter IL 282); measurements were made when breathing air at rest and after 30 min oxygen administration through nasal prongs or a reservoir canula²⁹ at a flow rate of about 2 L/min in order to increase as much as possible the resting PaO₂.

**Oxygen Treatment**

Oxygen therapy was prescribed for at least 15 h/d, usually 18 h, and was administered in the conditions determined during the physiologic measurements in the laboratory. Patients and their families were carefully instructed in the use of their oxygen concentrators. Oxygen concentrators were fitted with timers that recorded the duration of gas flow. Treatment was interrupted for a few noncompliant patients (mean O₂ concentrator use < 5 h/d) who were not included in the study.

**Statistical Methods**

Numeric data were expressed as mean ± standard deviation. Survival curves were estimated by Kaplan-Meier product limit method and compared for each categorical variable by log-rank test and for each ordinal or continuous variable by Cox model. The Cox proportional hazards model was used to study the simultaneous influence of all variables, selected by a stepwise forward procedure with Wald likelihood ratio test. The goodness of fit of the model was checked by incorporating interaction time-variate terms into the model.

The patients were further divided into three equal groups of low, medium, and high risk, according to their individual risk score, ie, the exponential factor of the model, including all significant variables. Other variables were compared among these three groups by analysis of variance, Fisher's Exact Test, Cochran test, or test for linear trend in survival. All tests were two tailed. Analysis was performed with a statistical package (SC, Lambda-Plus, Gembloux, Belgium).

**RESULTS**

On an average, the patients were old (mean age, 66 ± 8 years), with severe airway obstruction (FEV₁ = 30 ± 12 percent of predicted values) and pulmonary hyperdistention (intrathoracic gas volume [ITGV] = 151 ± 44 percent). The mean transfer coefficient TLCO/VA of the patients able to perform the maneuver was reduced to 57 ± 31 percent of predicted.

The patients were severely hypoxic with some CO₂ retention and compensated respiratory acidosis (Table 1). Oxygen breathing drastically improved the PaO₂ without noticeable mean increase of PaCO₂ or arterial acidosis. No patient was excluded for so-called "excessive" increase of PaCO₂, and only five exceeded an increase of 10 mm Hg with a maximum of 18.

The overall survival curve for the whole group of patients is shown in Figure 1. The survival proportion was 70, 50, and 43 percent at 1, 2, and 3 years, respectively.

The significance of the clinical diagnosis and of each initial physiological measurement was examined extensively to see if there was any combination of values that

![Figure 1. Estimation of survival rate (Kaplan-Meier) of our 270 patients.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21689/)
Table 2—Significance of the Evaluated Variables on Survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate Probability Value</th>
<th>Multivariate Probability Value</th>
<th>Coefficient b</th>
</tr>
</thead>
<tbody>
<tr>
<td>TL CO/VA</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>-0.019</td>
</tr>
<tr>
<td>TLCO</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>0.005</td>
<td>0.043</td>
</tr>
<tr>
<td>Hb</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococosis</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2</td>
<td>0.015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITGV</td>
<td>0.02</td>
<td>0.004</td>
<td>-0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>0.027</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC</td>
<td>0.044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2 with O2</td>
<td>0.252</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2 with O2 ≥ 65 mm Hg</td>
<td>0.1</td>
<td>0.014</td>
<td>-0.544</td>
</tr>
<tr>
<td>FEV/FVC</td>
<td>0.115</td>
<td>0.02</td>
<td>-0.03</td>
</tr>
<tr>
<td>Chest wall abnormalities</td>
<td>0.61</td>
<td>0.022</td>
<td>1.064</td>
</tr>
</tbody>
</table>

*TLCO/VA = transfer coefficient for carbon monoxide in apnea; TLCO = transfer factor; HC = hematocrit; Hb = hemoglobin; ITGV = intrathoracic gas volume; BMI = body mass index; RBC = red blood cell count; FEV/FVC = forced expiratory volume in 1 s/forced vital capacity; TLC = total lung capacity; SGaw = specific conductance of the airways.

†Variables which are not significant, neither by univariate nor by multivariate analysis are not mentioned (ie, PaCO2; PaCO2 and pH with O2; TLC; SGaw; FVC; FEV1; sex; right heart failure; sequelae of tuberculosis).

could predict early mortality. By univariate analysis, many factors were highly significant. However, the Cox model showed that there were six factors that were independently associated with reduced survival, namely lower TLCO/VA, smaller ITGV, higher age, a PaO2 level below 65 mm Hg under oxygen administration, severe bronchial obstruction as indicated by a lower FEV/FVC, and chest wall abnormalities (Table 2).

The patients were selected and treated in three closely connected hospitals, which apply exactly the same principles of selection and treatment. A log rank test showed a higher mortality in one of the centers (relative risk of 1.5; p = 0.02). The introduction of the origin of the patients in the Cox model did not show any influence on survival (p = 0.712), and we concluded that there was no difference among centers when really predictable variables were taken into account.

The patients in whom all significant variables from the Cox model were available (n = 189) were then distributed into three equal-size groups of low-, medium-, and high-mortality risk, according to their individual risk score computed from the model, ie, score = exp (-0.019 [TLCO/VA (percent pred)] - 0.010 [ITGV (percent pred)] + 0.043 [age (years)] - 0.544 [PaO2 with O2 ≥ 65 mm Hg] - 0.030 [FEV1/FVC] + 1.604 [chest wall lesion (1 or 0)]). The survival curves of those three groups are displayed on Figure 2.

Table 3 shows the mean values and SDs of the physiologic measurements and the percentage of clinical diagnosis, which were significantly different between the three groups, and some other data pertinent for the discussion.

The PaCO2 was significantly different among the three groups in Table 3. Moreover, the proportion of hypercapnic patients (PaCO2 > 46 mm Hg) was significantly different (p = 0.013) within those groups (60, 54, and 38 percent, respectively). We then performed a new univariate analysis on all the 270 patients, divided into hypocapnic, normocapnic, and hypercapnic groups (PaCO2 < 34; 34 to 46; > 46 mm Hg, and n = 14, 116, and 140, respectively). The survival rate was significantly different between these groups (log rank test: p = 0.039, and linear trend test: p = 0.017), and the relative mortality risk was 1.9 for hypocapnic, 1.14 for normocapnic, and 0.86 for hypercapnic patients.

Discuss

The mean PaO2 while breathing air (48 ± mm Hg) of the patients from the present series was lower than that of other LTOT series,5,7,11,17,18,35 where mean PaO2 exceeded 50 mm Hg. Under O2 therapy, our patients and those from the MRC reached, nevertheless, a slightly higher PaO2 than in the other series. As far as PaCO2 is concerned, most studies report, as we do, a moderate hypercapnia,5,8,11,13,18,19 while others5,13,14 show a mean PaCO2 within normal limits. All of the studies reported that O2 administration slightly increases PaCO2.

Mortality rate in the present study is comparable with some recently published data, especially for male subjects,17,18 and it is higher than the level observed in the nocturnal treatment group from the NIH study6 (30 vs 20.6 at 1 year; 50 vs 40.8 at 2 years; 57 vs 55 at 3 years). Survival was nevertheless much better in other series.5,8,15 Differences in the selection criteria are of great importance in order to explain those differences. According to the regulations of the Belgian Society Security, which are in agreement with the usually admitted indications.

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21689/)
Table 3—Differences Among Three Groups Distributed According to Mortality Risk

<table>
<thead>
<tr>
<th>Variables†</th>
<th>Group 1 (Low Risk) Mean</th>
<th>SD</th>
<th>Group 2 (Medium Risk) Mean</th>
<th>SD</th>
<th>Group 3 (High Risk) Mean</th>
<th>SD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLCO, % pred</td>
<td>57</td>
<td>24</td>
<td>38</td>
<td>16</td>
<td>25</td>
<td>13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FVC, % pred</td>
<td>52</td>
<td>13</td>
<td>50</td>
<td>16</td>
<td>59</td>
<td>13</td>
<td>0.008</td>
</tr>
<tr>
<td>sGaw, % pred</td>
<td>32</td>
<td>36</td>
<td>20</td>
<td>16</td>
<td>18</td>
<td>26</td>
<td>0.009</td>
</tr>
<tr>
<td>TLC, % pred</td>
<td>116</td>
<td>24</td>
<td>123</td>
<td>20</td>
<td>120</td>
<td>22</td>
<td>0.229</td>
</tr>
<tr>
<td>FEV1, % pred</td>
<td>32</td>
<td>13</td>
<td>30</td>
<td>12</td>
<td>31</td>
<td>11</td>
<td>0.465</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>49</td>
<td>8</td>
<td>47</td>
<td>8</td>
<td>45</td>
<td>9</td>
<td>0.045</td>
</tr>
<tr>
<td>PaCO2, with O2, mm Hg</td>
<td>51</td>
<td>9</td>
<td>48</td>
<td>8</td>
<td>47</td>
<td>10</td>
<td>0.044</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>50</td>
<td>5</td>
<td>50</td>
<td>5</td>
<td>48</td>
<td>5</td>
<td>0.15</td>
</tr>
<tr>
<td>PaO2, with O2, mm Hg</td>
<td>70</td>
<td>11</td>
<td>70</td>
<td>11</td>
<td>69</td>
<td>12</td>
<td>0.605</td>
</tr>
<tr>
<td>pH, mm Hg</td>
<td>7.39</td>
<td>0.04</td>
<td>7.39</td>
<td>0.04</td>
<td>7.4</td>
<td>0.05</td>
<td>0.256</td>
</tr>
<tr>
<td>Hb, g</td>
<td>16.1</td>
<td>2.3</td>
<td>15.6</td>
<td>1.9</td>
<td>15.1</td>
<td>1.9</td>
<td>0.046</td>
</tr>
<tr>
<td>HC, %</td>
<td>49</td>
<td>7</td>
<td>47</td>
<td>6</td>
<td>46</td>
<td>6</td>
<td>0.062</td>
</tr>
<tr>
<td>RBC</td>
<td>5.2</td>
<td>0.72</td>
<td>5.07</td>
<td>0.72</td>
<td>4.94</td>
<td>0.64</td>
<td>0.16</td>
</tr>
<tr>
<td>BMI</td>
<td>25</td>
<td>6</td>
<td>23</td>
<td>4</td>
<td>23</td>
<td>4</td>
<td>0.002</td>
</tr>
<tr>
<td>Age, yr</td>
<td>62</td>
<td>7</td>
<td>64</td>
<td>7</td>
<td>69</td>
<td>7</td>
<td>...‡</td>
</tr>
<tr>
<td>TLCO/VA, % pred</td>
<td>85</td>
<td>31</td>
<td>52</td>
<td>22</td>
<td>56</td>
<td>18</td>
<td>...‡</td>
</tr>
<tr>
<td>ITOV, % pred</td>
<td>161</td>
<td>54</td>
<td>157</td>
<td>37</td>
<td>139</td>
<td>29</td>
<td>...‡</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>45</td>
<td>12</td>
<td>38</td>
<td>9</td>
<td>37</td>
<td>10</td>
<td>...‡</td>
</tr>
<tr>
<td>% SE(%) PaO2 with O2 ≥65 mm Hg</td>
<td>70</td>
<td>6</td>
<td>68</td>
<td>6</td>
<td>54</td>
<td>6</td>
<td>...‡</td>
</tr>
<tr>
<td>Chest wall abnormalities</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>11</td>
<td>4</td>
<td>...‡</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>33</td>
<td>6</td>
<td>21</td>
<td>5</td>
<td>14</td>
<td>4</td>
<td>0.011</td>
</tr>
</tbody>
</table>

*Abbreviations: see Table 2. The patients were equally distributed into three groups of 63 patients each, according to the calculated risk of mortality: group 1 <0.186; group 2 between 0.186 and 0.410; group 3 >0.410 (see statistical methods and results).

†All variables are expressed as mean ± SD and compared by analysis of variance, except chest wall abnormalities (Fisher’s Exact Test for groups 1 and 2 vs group 3) and PaO2 with O2 ≥65 mm Hg and right heart failure (Cochran test), those three variables being expressed in percentage terms ± SE of the 63 patients in each group.

‡Statistical test irrelevant for those variables that are implied in the definition of the groups.

for LTOT,20-22 all our patients had a PaO2 ≤55 mm Hg in a closely controlled steady state for several weeks and during 3 months follow-up. The strict observance of those very severe selection criteria probably explains the small number of patients (n = 6) who increased “spontaneously” their PaO2 above 55 mm Hg. Most of other published studies included patients with PaO2 up to 60 mm Hg and some applied even much more liberal guidelines.35 Some studies19,19 showed an influence of initial PaO2 on survival under LTOT while most of the others5,7,13,15 did not confirm this observation.

We included all severely hypoxemic COPD patients while other studies carried out some kind of selection: the NIH study2 excluded some patients because they were thought to be “too sick,” because they lived too far away from the hospital, and on account of their dubious compliance or ability to give informed consent. The MRC clinical trial6 excluded patients older than 70 years, as well as patients who presented with fibrotic or infiltrative lung disease, kyphoscoliosis, pulmonary embolism, systemic hypertension, and coronary arterial disease. In the Sheffield study,5 patients unlikely to be compliant with LTOT and those whose homes could not be adequately fitted and supplied with oxygen were excluded. Most studies of LTOT are focused on patients with pure COPD. There are some articles that include other diseases, often complicating COPD. Brambilla et al13 reported on 62 percent COPD patients, 24 percent sequelae of tuberculosis, and 14 percent other diseases; the sex ratio was 3.7 (male/female). The series by Ström and Boë17 included 70 percent COPD patients, 18 percent sequelae of tuberculosis, 8 percent interstitial fibrosis, and 7 percent kyphoscoliosis; strangely enough, 52 percent of the patients were female. In the present study, all patients had COPD; 18 percent of whom had other complicating conditions that may have influenced the prognosis.

The compliance with the treatment is difficult to evaluate with certainty. In this study, the exclusion of some obviously noncompliant patients and the regular controls at home ensured that the majority of the patients used their oxygen concentrator for at least 15 h/d. This is probably the case in all well-controlled studies and does not explain the differences between survival rates.

There is a great deal of controversy about the influence of the sex on survival of patients receiving LTOT. The remarkably better results of LTOT on female subjects, reported in the MRC study,4 could be accidental owing to the small number of cases. Cooper et al13 did not find any difference between the sexes. The Swedish
confirmed

The French study\textsuperscript{19} had a more usual sex ratio for COPD patients and survival was also better for female subjects.

Hemoglobin, hematocrit, and RBC correlated significantly with survival in our univariate analysis and hemoglobin was significantly higher in the lower-mortality groups. The positive correlation between these oxygen transporters and survival seems logical, but is not completely in accordance with data from the MRC study that showed that there was a higher mortality rate at 500 days in male patients with the highest sum of PaCO\textsubscript{2} and RBC mass.

Age was another important prognostic factor in the present study, as well as in others, using multivariate methods.\textsuperscript{17,19,36}

Using the Cox model, the most significant predictor of mortality was a low TLCO/VA, as we have already demonstrated by simple univariate statistical methods.\textsuperscript{16} It is really surprising that, as far as we know, there is only one other study on LTOT that mentioned the transfer factor\textsuperscript{15} but without analyzing its prognostic significance. The transfer coefficient is nevertheless a good indicator of the efficiency of lung parenchyma and is markedly lower in severe emphysema.

The mean clinical and lung functional profile of our high-mortality risk group 3 in Table 3 was moreover consistent with the prevalence of emphysematous lesions: lower body mass index (BMI) and lower proportion of right heart failure as compared with other groups, severely reduced transfer factor and coefficient, and major bronchial obstruction. When such emphysematous patients become severely hypoxic, as they were in this study according to inclusion criteria, their prognosis is quite poor.

The BMI did not appear in our multivariate hazard equation but was actually significant in the univariate analysis and was also significantly lower in high-mortality risk groups. The Antadir study\textsuperscript{19} also demonstrated the poor outcome of underweight patients, confirming previous studies.\textsuperscript{23,37}

Bronchial obstruction, as evaluated by FEV\textsubscript{1}/FVC, showed a significant correlation with mortality in our multivariate analysis, and the specific conductance of the airways (sGaw) was lower in the high-mortality risk group. Other studies\textsuperscript{6,7,8,14,18,36} confirmed the prognostic importance of FEV\textsubscript{1} or its rate of decline, but this was not found by all the observers.\textsuperscript{5,13,14,17}

As far as lung volumes are concerned, it is interesting to observe that total lung capacity (TLC) was not statistically different among the three risk groups in Table 3, while the ITGV actually was. As we already stated, the high-risk group 3 had many characteristics compatible with emphysema, and this implies a mean shift to the left of the volume/elastic pressure relationship (V/Pel).

On the other hand, group 1 was more of the bronchitic type with a mean V/Pel curve probably closer to normal. We can speculate that lower-risk patients from group 1 showed two mechanical advantages, as compared with the high-risk group 3: a smaller decrease of elastic recoil, due to the more favorable position of the V/Pel curve, and an upward shift along that curve, due to a greater pulmonary distension, as objectivated by a higher mean ITGV.

The PaCO\textsubscript{2} while breathing air or oxygen, was significantly higher in our lower-mortality groups (Table 3), and the mortality risk was lower in hypercapnic patients (relative risk = 0.86). Keller et al\textsuperscript{14} also observed a tendency to hypercapnia in survivors. Hypercapnia is nevertheless considered a bad prognostic factor in many studies,\textsuperscript{5,8,15} while others\textsuperscript{6,8} insist on the rate of increase of PaCO\textsubscript{2} in the preterminal phase of the disease, which suggests a lethal chronic respiratory failure.

In order to explain this apparently contradictory significance of hypercapnia in the prognosis of severely hypoxemic patients, we suggest a distinction should be made between (1) hypercapnia due to pump failure and (2) an "adaptative" hypercapnia, where the respiratory centers are tuned on a higher PaCO\textsubscript{2} in order to lessen the respiratory work. In some chronic ventilatory failures, the respiratory centers could be tuned for higher PaCO\textsubscript{2} values, and this could be the case in patients with a weak response to CO\textsubscript{2} (ΔVE/ΔPaCO\textsubscript{2}). If this should be true, then it is conceivable that patients who "fight" in order to lower their PaCO\textsubscript{2} will fatigue their respiratory muscles and decompensate earlier than patients who tolerate a higher PaCO\textsubscript{2} level. Actually, our hypoxic patients showed a higher relative mortality risk (= 1.9), and the French study\textsuperscript{19} showed that low values of PaCO\textsubscript{2} (< 43 mm Hg) had a poor prognostic significance. On the other hand, in the terminal stage, there will appear a final increase of carbon dioxide, and that was the case in the study by Cooper and Howard, and is compatible with the results of Antadir, who showed a bad prognosis for patients with a PaCO\textsubscript{2} > 55 mm Hg.

**Conclusion**

In conclusion, the mortality rate of our severely hypoxemic COPD patients (PaO\textsubscript{2} < 55 mm Hg) remained considerably high, in spite of LTOT. According to the Cox model, the best predictors of a poor outcome were the following: a low TLCO/VA, a small ITGV, a severe airflow limitation, the fact that O\textsubscript{2} therapy does not increase PaO\textsubscript{2} above 65 mm Hg and, from the clinical point of view, increasing age, and the presence of chest wall abnormalities.

The clinical and functional profile of the patients, too, had a prognostic value: when dividing the population into three mortality-risk groups, the patients with a poor outcome under LTOT showed a mean "emphysematous"
profile, while the best survivors showed more "bronchitic" characteristics. Some degree of hypventilation, as assessed by hypercapnia, seemed to be associated with prolonged survival, possibly reflecting delayed muscular fatigue and exhaustion.

ACKNOWLEDGMENTS: The authors wish to thank their colleagues L. Delaunois, Y. Sibille, and P. Weynants for providing the records of many patients; the technical staff: J. P. Delwiche, F. Wautelet, F. Licope, F. Wanther, F. Fisron, CL. Goffin, and J. Duplyc; and M. Laureys for improving the English style of the paper and preparing the typescript.

REFERENCES
8 Cooper CB, Howard P. An analysis of sequential physiologic changes in hypoxic cor pulmonale during long-term oxygen therapy. Chest 1991; 100:76-80
12 Timms RM, Khaja FY, Williams GW, the Nocturnal Oxygen Therapy Trial Group. Hemodynamic response to oxygen therapy in 1985; 102:29-36
15 Cooper CB, Waterhouse J, Howard P. Twelve years clinical study of patients with hypoxic cor pulmonale given long term domiciliary oxygen therapy. Thorax 1967; 42:105-10