Risk Factors for Mortality in Chronic Obstructive Pulmonary Disease

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OBJECTIVE: Although the factors predictive of survival in patients with chronic obstructive pulmonary disease (COPD) have been widely studied, full consensus has yet to be reached. The objective of this study was to further clarify how lung function parameters, exercise tolerance, and quality of life influence survival in patients with COPD.

PATIENTS AND METHODS: This prospective study included 60 patients diagnosed with COPD. At the start of the study, patients underwent respiratory function tests, exercise testing, and 6-minute walk test. They also answered a chronic respiratory disease questionnaire to measure health-related quality of life. Follow-up lasted 7 years.

RESULTS: Five of the 60 patients withdrew from the study. Twenty-six of the remaining 55 patients (47%) died during the study. Univariate Cox regression analysis showed a correlation between survival and age, degree of obstruction, inspiratory capacity, carbon monoxide diffusing capacity, and peak exercise tolerance. No correlation was found between survival and body mass index, PaO2, PaCO2, total lung capacity, residual volume, maximal respiratory pressures, 6-minute walk test, or health-related quality of life.

Age, degree of obstruction (measured as the ratio of forced expiratory volume in 1 second to forced vital capacity after administration of bronchodilator), and maximum minute ventilation in the exercise test were introduced initially in the multivariate Cox stepwise regression analysis, but only maximum minute ventilation remained in the final model (relative risk, 0.926; P < .001).

CONCLUSIONS: Our findings show that peak exercise tolerance is the best predictor of survival in patients with COPD.

Key words: COPD. Exercise tolerance. Mortality. Survival.
concomitance.7 Although some authors have analyzed groups of factors, it has been impossible to draw firm conclusions or establish associations, and the prognostic factors for COPD are still the subject of debate.

To help determine which of the following factors was associated with survival and which was best able to predict survival: age, BMI, smoking habit (in pack-years), lung function variables, exercise test results, and CRQ score. One variable for every 8 events (deaths) was chosen to be introduced into a multivariable Cox regression model.13 The Kaplan–Meier method14 was used to analyze the effect on survival of the variable—stratified into quartiles—that was found to be the most relevant in the regression analysis.

**Patients and Methods**

**Patients and Design**

Sixty patients with COPD were selected according to the following inclusion criteria: age 75 years or less, forced expiratory volume in 1 second (FEV1) equal to or less than 70% of predicted; ratio of FEV1 to forced vital capacity (FVC) equal to or less than 65%; PaO2 greater than 55 mm Hg at rest; and no indication for home oxygen therapy on enrollment. Patients were excluded if they had been admitted to hospital in the preceding month or had documented clinically relevant heart disease or osteoarticular disease that might have prevented study procedures from being performed. Enrollment lasted from February 1992 to January 1995. The ethics committee of our hospital approved the study and patients gave their informed consent.

**Variables**

The primary outcome measure was survival at 7 years. The following series of tests were performed to collect information on independent variables possibly associated with survival: lung function tests, including spirometry under baseline conditions and spirometry after bronchodilation (FVC, FEV1/FVC, maximum voluntary ventilation (MVV), and inspiratory capacity (Datospir-92, Sibelmed, Barcelona, Spain)8) and lung volumes (total lung capacity [TLC] and residual volume [RV] by the helium dilution technique); carbon monoxide transfer coefficient (KCO) by the inhalation method (Sensormedis, Yorba Linda, California, USA)9; and resting arterial blood gas analysis (pH, PaO2, PaCO2, PaO2/FiO2 ratio of FEV1 to FVC equal to or less than 70% of predicted; IC, % pred 0.3 3.3 .24 KCO, % pred 0.3 3.3 .24 MVV, % pred 0.6 7.3 .011 Winex, kpm/min 0.3 0.9 <.001 VO2max, L/min 0.1 0.4 .3446 Arch Bronconeumol. 2007;43(8):445-9

**Results**

The study included 60 patients—all men. The mean (SD) age was 65 (7) years (range, 46-74 years), and the BMI was 26 (3.6) kg/m2 (range, 18-34 kg/m2). The following mean values were obtained in the lung function tests: FVC, 63% (15%) of predicted (range, 33%-94%); FEV1, 35% (14%) of predicted (range, 15%-68%); FEV1/FVC, 40% (11%) (range, 23%-64%); RV, 179% (45%) of predicted (range, 87%-278%); inspiratory capacity, 1.9 (0.4) L (range, 1.06-2.89 L); TLC, 112% (20%) of predicted (range, 82%-100%); PaO2, 70 (9) mm Hg (range, 56-89 mm Hg); PaCO2, 44 (5) mm Hg (range, 34-54 mm Hg). The mean value of peak exercise capacity in the exercise testing was 525 (168) kilopond meters (kpm) per minute (range, 200-1000 kpm/min), maximal minute ventilation (VEmax) was 39 (12) L/min (range, 19-65 L/min), and peak oxygen uptake (VO2max) was 1.1 (0.3) L/min (range, 0.6-1.9 L/min). The mean distance covered in the 6-minute walk test was 306 (57) m (range, 200-450 m), and the mean scores on the CRQ were 17.5 (3.8) (range, 10.1-26.8) for the overall scale; 3.2 (1) range, 1.0-6.6) for the dyspnea subscale; 4.5 (1.2) (range, 1.5-6.8) for the fatigue subscale; 4.8 (1.3) (range, 2.6-7) for the emotional subscale; and 5.1 (1.6) (range, 1-7) for the disease management subscale. There were no statistically significant differences between the 2 groups for the variables analyzed. Five of the patients withdrew from the study for personal reasons.

The overall survival after 7 years of follow-up was 53%. In this period, 26 of the 55 patients died (47%), 11 (42%) due to respiratory insufficiency, 7 (27%) due to lung cancer and 1 (4%) due to nonlung cancer, 2 (8%) due to acute myocardial infarction, and 5 (19%) due to other reasons.

**Examples and Tables**

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Δ Risk/Unit, %</th>
<th>P</th>
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</tr>
<tr>
<td>FEV1, % pred</td>
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<tr>
<td>FEV1/FVC abd, %</td>
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<tr>
<td>IC, % pred</td>
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<tr>
<td>KCO, % pred</td>
<td>0.3 0.24</td>
<td></td>
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<tr>
<td>MVV, % pred</td>
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<td>Winex, kpm/min</td>
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<tr>
<td>VO2max, L/min</td>
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<td></td>
</tr>
<tr>
<td>VEmax, L/min</td>
<td>0.4 &lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

**References**

1. **FEV1** indicates forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; KCO, carbon monoxide transfer coefficient; abd, after bronchodilation; pred, predicted value; kpm, kilopond meters; VO2max, maximum voluntary ventilation; Wmax, maximum work load.
In the univariate Cox regression analysis, an association was found between survival and age, degree of obstruction (FEV₁ and FEV₁/FVC after bronchodilation), inspiratory capacity (percentage of predicted), KCO (percentage of predicted), MVV (percentage of predicted), and peak exercise capacity assessed as peak workload (Wmax), VEmax, and VO₂max (Table 1).

We found no association between survival and the following variables: BMI, PaO₂, PacO₂, FVC after bronchodilation (%), TLC (percentage of predicted), RV (percentage of predicted), maximum respiratory pressures (percentage of predicted), distance covered in the 6-minute walk test, and quality of life according to the score on the CRQ for any of the subscales. The association between survival and pack-years was on the borderline of statistical significance (relative risk [RR], 1.01; P = .054). The variables entered were age, FEV₁/FVC ratio after bronchodilation, and VEmax. In the Cox regression analysis with a forward stepwise approach, only VEmax was included in the final model (RR, 0.926; P < .001). In the backwards stepwise analysis, both VO₂max (RR, 0.936; P < .001) and age (RR, 1.075; P < .054) were included in the model (Table 2). The models were run using the same procedure, that is, each of the other variables that measure peak exercise capacity (Wmax or VO₂max) were entered instead of VEmax (Table 2). Of the 6 models obtained, the most parsimonious was the one that included just VEmax.

Once VEmax had been chosen as the variable that best predicted survival, the patients were divided into quartiles according to this variable, and a Kaplan–Meier analysis was done with the 4 groups obtained. More than 75% of the patients with VEmax greater than or equal to 42 L/min survived the 7 years of follow-up, whereas fewer than 55% of the patients with VEmax below that value survived for 7 years (P = .0002, log-rank test).

Discussion

The most important finding of this study was that the risk factors for mortality in patients with COPD were associated with peak exercise capacity. The peak exercise capacity, assessed by exercise testing, was the best predictor of survival in these patients (all of whom were men with substantially deteriorated lung function). Many studies have analyzed predictors of survival in COPD, but few have assessed variables that reflect peak exercise capacity. Oga et al.15 studied a cohort of 144 patients with COPD for 5 years and, like us, came to the conclusion that peak exercise capacity—assessed with VO₂max in that particular study—predicted survival even better than the degree of airway obstruction or age. Those authors assumed that VO₂max was the principal measure of peak exercise capacity. In our study, however, not only VO₂max but also Wmax and VEmax were useful for predicting survival, and VEmax was a slightly stronger predictor than the other two.

COPD is a multisystem disease.16 Peak exercise capacity depends on many factors that could be related to survival, such as age, degree of obstruction, cardiovascular response,
nutritional status, and muscle characteristics. All of these are related to the functional reserve, and together they condition the specific response of a patient at peak exercise capacity. At the same time, any measure of peak exercise capacity is a good indicator of state of health and a predictor of survival.

Submaximal exercise capacity has been studied for its predictive value. In a sample of 138 patients with chronic respiratory disease (87% with COPD) who were participating in a respiratory rehabilitation program, Gerardi et al. found that the distance covered in the 6-minute walk test was a good predictor of survival. In another study of 149 patients with a 5-year follow-up, Bowen et al. reported similar findings. In both cases, the distance covered after a rehabilitation program was a better predictor than the distance covered before the intervention. Recently, Pinto-Plata et al. also observed that submaximal exercise capacity predicted survival better than the traditional markers of disease severity, such as FEV1, or BMI, and that the decrease in exercise capacity occurs regardless of the change in FEV1. The findings of the aforementioned studies differ from those of our study in the predictive value of the initial walk test, an observation which can probably be explained by the different characteristics of the patients in terms of disease severity and age. Our patients had more severe disease but they were younger. Finally, Celli et al. proposed a multifactorial variable denominated BODE, which comprises BMI, degree of obstruction, determined by FEV1 (percentage of predicted); dyspnea, as measured by the Medical Research Council scale from 0 to 4; and exercise capacity, measured with the 6-minute walk test. The authors did not assess peak exercise capacity and only compared the predictive value of BODE with that of FEV1.

The univariate Cox regression showed that the risk of death increased with age and decreased with degree of obstruction as assessed by FEV1, and the FEV1/FVC ratio after bronchodilation, inspiratory capacity, KCO, MVV, and variables derived from the exercise testing. No association was found between survival and body mass index, pack–years smoked, quality of life, or distance covered in the 6-minute walk test.

It is not surprising that age is associated with survival, and indeed this agrees with previous findings. The risk of death in our study increased with the degree of obstruction (RR=0.965 for FEV1, and RR=0.952 for FEV1/FVC, both after bronchodilation). This risk was similar to that reported in other studies, but it appears less marked than that calculated by Ries et al. (RR=0.84). However, in that study, risk was calculated for a clinically relevant unit change in FEV1, taken to be 100 mL, whereas, in our analysis, the risk was calculated per milliliter change. On the other hand, Schols et al. did not report an increased risk of death for FEV1 if adjustment was made for age, BMI or change in BMI, and PEF. Ries et al. also observed that submaximal exercise capacity was a better predictor of survival than the stage of the disease.

Several authors have reported that the distance covered increased with age and decreased with degree of obstruction as assessed by FEV1, and the FEV1/FVC ratio after bronchodilation, inspiratory capacity, KCO, MVV, and variables derived from the exercise testing. No association was found between survival and body mass index, pack–years smoked, quality of life, or distance covered in the 6-minute walk test.

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In conclusion, for all variables analyzed, peak exercise capacity alone was most useful for predicting survival, more so than other variables such as the degree of obstruction, quality of life, BMI, or age, in patients with COPD.

Acknowledgments

The authors thank Mary Ellen Kerans for her comments and advice on an earlier version of the manuscript.

REFERENCES