Pulmonary Exercise Testing Predicts Prognosis in Patients with Chronic Obstructive Pulmonary Disease

Naoko Tojo, Masahiko Ichikawa*, Mamoru Chida**, Itsuro Miyazato***, Yasuyuki Yoshizawa**** and Nobuyuki Miyasaka*****

Abstract

Objective

In patients with chronic obstructive pulmonary disease (COPD), patient age and initial value of forced expiratory volume in 1 second (FEV₁) have been considered the most accurate predictors of mortality among the parameters obtained from pulmonary exercise tests. However, few studies have examined the predictive variables of prognosis among exercise parameters in COPD. We therefore attempted to identify the best index for predicting long-term survival in patients with COPD among the cardiopulmonary variables obtained during exercise testing.

Patients and Methods

Fifty-eight patients with COPD (50 men and 8 women) without hypoxemia at rest or other serious complications performed resting pulmonary function tests followed by a symptom-limited ramp exercise test on a cycle ergometer with breath-by-breath gas analysis and arterial blood gas sampling.

Results

After 3,570±1,373 days follow-up (mean±SD), 21 died because of deaths by respiratory failure. The overall survival rates calculated by the Kaplan-Meier method were 92.9% and 75.8% at 5 years and 10 years, respectively. In univariate Cox hazards analysis, age, FEV₁, VC, RV/TLC, V̇ₑₘₓ, V̇ₒ₂ₘₓ, V̇₃₄₀₂ₘₓ, Pₐₒ₂ₘₓ, Pₐ₃₄₀₂ₘₓ, and Pₐₒ₂ at rest were found to be significant prognostic indices of survival. However, multivariate analysis revealed only FEV₁, Pₐₒ₂ₘₓ, and age as independent predictors of mortality. In severe COPD patients (FEV₁ <50% predicted, n=35), Pₐₒ₂ₘₓ and age also correlated with prognosis, whereas FEV₁ did not.

Conclusion

Pulmonary exercise testing is useful in predicting prognosis in patients with COPD.

Key words: COPD, exercise, exercise-induced hypoxia, prognosis, hypoxemia

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation in the lung. Both age and FEV₁ are reported to be closely related to subsequent survival in patients with COPD (1–5).

In patients with COPD, few studies have examined predictors of prognosis among the parameters of cardiopulmonary exercise testing. Anthonisen and colleagues (4) demonstrated a weak association between maximal exercise tolerance and survival over a 34.7-month follow-up period in patients with COPD. Bowen and colleagues (6) revealed that 6-min walking distance was associated with survival following pulmonary rehabilitation. Fujii et al (7) performed incremental treadmill exercise testing in 77 COPD patients, and found that patients showing exercise-induced hypoxemia had a poorer prognosis. However, no definite variables for predicting prognosis in patients with COPD have so far been identified in exercise testing.

Exercise testing evaluates systemic cardiopulmonary oxygen transport. Parameters obtained from exercise testing, such as maximum oxygen consumption (V̇ₒ₂ₘₐₓ), have been considered to reflect the severity of COPD. In contrast, resting pulmonary function tests can predict neither exercise performance (8) nor exercise-induced hypoxemia in patients with COPD (9). It has been shown that preoperative measurement of oxygen uptake (V̇ₒ₂) during exercise is predictive of postoperative mortality and morbidity (10). In addition, parameters obtained from exercise tests are known to reflect the efficacy of lung volume reduction surgery (LVRS) in patients with emphysema (11, 12).
In the present study, we performed expired gas analysis and blood gas analysis during exercise testing together with resting pulmonary function tests in patients with COPD, and subsequently examined the relationship between these variables and patient mortality. We found that cardiopulmonary exercise testing can predict long-term survival in patients with COPD.

Patients and Methods

Patients

We studied 69 patients (61 men and 8 women) with a diagnosis of COPD based on FEV1/forced vital capacity (FVC) of less than 70%. None of the patients had a clinical history of coexisting asthma or lung, cardiac, peripheral vascular, or neuromuscular disease. They performed both resting pulmonary function tests and exercise testing with respiratory gas analysis between October 1983 and November 1992. They were followed up for 3,570±1,373 days (mean±SD). Patients whose arterial oxygen tension (PaO₂) was less than 60 mmHg at rest and those who had received long-term home oxygen therapy were excluded from the study. Patients with cor pulmonale or left ventricular failure were excluded from the study. Informed consent was obtained from each patient after the purpose of the study and the risk associated with it had been thoroughly explained.

Vital capacity (VC), FEV1, FVC and maximal minute volume (MVV) were measured with a hot-wire spirometer (system 45 between October 1983 and December 1987, system 55 between January 1988 to November 1992, Minato Medical Science, Osaka) by two skilled technicians after calibration was performed. Functional residual capacity (FRC) was determined by the N₂ washout method. The diffusing capacity for carbon monoxide (DL CO ) was measured using a single-breath technique.

Survival analysis was performed every 2 years by examining patients’ medical records or by conducting direct or telephone interviews with the patients or their families until December 2003.

Exercise testing

All patients underwent ramp exercise testing by cycle ergometer (380B Siemens Elema, Solna, Sweden) starting at 20 w and increasing by 1 w every 3 seconds to the symptom-limited maximum. During the test, heart rate, oxygen uptake (VO₂), carbon dioxide production (VCO₂), and minute ventilation (VE) were continuously recorded by a medical cart (RM300, Minato Medical Science, Osaka). Arterial blood sampling was performed every 1 minute via a plastic catheter placed percutaneously into a brachial artery, and analyzed at 37°C for pH, partial pressure of oxygen (PaO₂), and partial pressure of carbon dioxide (PaCO₂) (IL813, Instrumental Laboratory, Lexington, MA, USA). Normal values were referenced from those of Baldwin et al (13) for VC, those of Crapo et al (14) for FEV1, those of Burrows et al (15) for DLCO, and those of Wasserman et al (16) for VO₂ max.

Statistics

Data are expressed as means±SD. Analysis to measure the impact of variables on survival time was carried out as follows. Univariate Cox proportional hazard analysis was initially performed using data obtained from the resting pulmonary function test and exercise test. Multivariate Cox proportional hazards analysis was subsequently done using 10 correlated variables shown in Table 1 (age, FEV1, VC, and residual volume/total lung capacity (RV/TLC)) and Table 2 (VE max, VO₂ max, VCO₂ max, PaO₂ max, PaCO₂ max, and PaO₂ at rest) using forward stepwise regression techniques. Maximum heart rate (HR max) was excluded from this analysis since seven values were missing. Multivariate Cox proposal hazards analysis was performed only in patients who had all the variables entered in the analysis. Any patients with missing values were excluded from the analysis. Kaplan-Meier analysis and the log-rank test were performed after stratifying the level of FEV1 with a cutoff line of 50% according to the Global Institute for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria (17) and PaO₂ max with that of 60 mmHg according to the diagnostic criteria of chronic respiratory failure (18). For all comparisons, p <0.05 was considered statistically significant.

Results

Of 69 patients with COPD, 32 died during the follow-up period (3,570±1,373 days). The cause of death was respiratory failure in 21 patients (66%), malignancy in 9 patients (28%), and myocardial infarction in 2 patients (6%). After excluding 11 patients who died of non-respiratory complications, data on the remaining 58 patients were subjected to analysis.
During the follow-up period, 22 patients started long-term oxygen therapy and 16 died among them. Five patients died without starting long-term oxygen therapy. The overall survival rates were 92.9% at 5 years and 75.8% at 10 years. Mean age at death time was 74.4±7.5 years in males (mean±SD, n=19), and 84.0±7.7 years in females (n=2). Clinical profiles of the patients and data of resting pulmonary function tests at the initiation of the study are shown in Table 1. The mean age of patients at the start of this study was 63.0±6.5 years. There were 9 nonsmokers and 49 smokers including ex-smokers, and mean smoking history was 43.6±32.7 pack-years. The mean percentage of the predicted value of FEV1 was 46.4±18.0%, indicating that the grade of COPD was severe in our patient population (17). The results of exercise tests are shown in Table 2. VO2 max was decreased (76.5±19.9% predicted), and arterial gas analysis showed an increase of PaCO2 and decrease of PaO2, as expected.

We initially employed univariate Cox proportional hazard analysis to examine whether or not a relationship existed between variables obtained either from resting pulmonary function tests or exercise test and survival periods. Among resting pulmonary function test variables, age (p<0.027), VC (p=0.017), FEV1 (p=0.0003), and RV/TLC (p=0.001) were non-adjusted prognostic factors (Table 3). Among exercise variables, VE max (p=0.027), VO2 max (p=0.017), VC02 max (p=0.029), PaO2 at rest (p=0.020), PaO2 max (p=0.005), PaCO2 max (p=0.029), and HRmax (p=0.047) were found to be significantly correlated with prognosis, and, among them, PaO2 max was demonstrated to be the best predictor of patient survival (Table 4).

Table 5 shows the results of multivariate Cox proportional hazard analyses for age, VC, FEV1, RV/TLC, VE max, VO2 max, VCO2 max, PaO2 at rest, PaO2 max, and PaCO2 max. PaO2 max (p=0.043) and FEV1 (p=0.002) were negatively correlated with mortality, whereas age (p=0.045) was positively correlated with mortality. These were independent predictors of mortality.

Kaplan-Meier survival curves of the two groups of patients stratified by PaO2 max level with a cutoff line of PaO2 60 mmHg; i.e., patients with PaO2 max <60 mmHg (n=11) and those with PaO2 max ≥60 mmHg (n=44), are shown in Fig. 1. The cumulative survival rate of patients with PaO2 max ≥60 mmHg was significantly better than that of patients with PaO2 max <60 (p<0.001).

When the patients were stratified by FEV1 with a cutoff line of 50%, i.e., patients with FEV1 ≥50% (n=23) and those

*Table 2. Data with Gas Exchange before and during Ramp Exercise Test*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>Exercise**</th>
</tr>
</thead>
<tbody>
<tr>
<td>WR, w</td>
<td>–</td>
<td>113±32</td>
</tr>
<tr>
<td>VO2, ml•min⁻¹•kg⁻¹</td>
<td>0.23±0.05</td>
<td>1.11±0.36</td>
</tr>
<tr>
<td>VCO2, ml•min⁻¹</td>
<td>4.4±1.0</td>
<td>20.5±5.8</td>
</tr>
<tr>
<td>% pred</td>
<td>–</td>
<td>76.5±19.9</td>
</tr>
<tr>
<td>VO2 max, ml•min⁻¹</td>
<td>0.19±0.03</td>
<td>1.22±0.46</td>
</tr>
<tr>
<td>VE, ml•min⁻¹</td>
<td>12.0±3.2</td>
<td>46.2±16.1</td>
</tr>
<tr>
<td>HR, beat•min⁻¹</td>
<td>80±11</td>
<td>143±21</td>
</tr>
<tr>
<td>VE/Max • MVV</td>
<td>–</td>
<td>1.03±0.25</td>
</tr>
<tr>
<td>Blood gas analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2, mmHg</td>
<td>85.3±10.3</td>
<td>74.2±16.4</td>
</tr>
<tr>
<td>PaCO2, mmHg</td>
<td>39.3±4.2</td>
<td>45.0±5.4</td>
</tr>
<tr>
<td>pH</td>
<td>7.408±0.036</td>
<td>7.327±0.047</td>
</tr>
</tbody>
</table>

*Data are shown as mean±SD. **Exercise at maximum. WR: work rate, VO2: oxygen uptake, % pred: percentage of predicted value, VCO2: carbon dioxide production, VE: minute ventilation, HR: heart rate, PaO2: arterial oxygen tension, PaCO2: arterial carbon dioxide tension.
with FEV<sub>1</sub> < 50% (n=35), patients with FEV<sub>1</sub> < 50% had a significantly worse prognosis than those with FEV<sub>1</sub> ≥ 50% (p=0.001) (Fig. 2). In patients with FEV<sub>1</sub> < 50% (mean±SD, 34.7±9.4 %, range 17.3–49.4 %), PaO<sub>2</sub> max was negatively correlated, whereas age was positively correlated with mortality when analyzed by stepwise regression. None of the other eight baseline characteristics, including FEV<sub>1</sub>, was associated with mortality (Table 6).

**Discussion**

We performed expired gas analysis and blood gas analysis during exercise testing together with the resting pulmonary function test in patients with COPD, and subsequently examined the relationship between these variables and patient survival. We identified PaO<sub>2</sub>max during exercise testing, FEV<sub>1</sub>, and age as strong independent predictors of survival in patients with COPD. These findings suggest that patients without exercise-induced hypoxemia might live longer than those with exercise-induced hypoxemia. In this respect, Fujii et al (7) found that COPD patients who showed exercise-induced hypoxemia in incremental treadmill exercise testing had a poor prognosis. They used ΔPaO<sub>2</sub>/ΔVo<sub>2</sub> as an index of the severity of exercise-induced hypoxemia, and found that survival was significantly better in the group with ΔPaO<sub>2</sub>/>
\( \Delta V_{O_2} < 20 \text{ mmHg} \cdot l^{-1} \cdot \text{min} \) than in the group with \( \Delta P_{A\text{O}_2} < 20. \) The present study confirmed these findings. However, their study did not demonstrate any other predictive variables for survival. To our knowledge, no other studies that have systematically assessed the relationship between exercise-induced hypoxemia and prognosis in patients with COPD have been reported in the literature. Why do patients with exercise-induced hypoxemia have a poor prognosis? In the present study, we had no patients with hypoxemia at rest \( (P_{A\text{O}_2} < 60 \text{ mmHg}) \), and mean \( P_{A\text{O}_2} \) at rest was 80.3±9.0 mmHg. However, \( P_{A\text{O}_2}\text{max} \) was negatively correlated with mortality by stepwise proportional hazards regression analysis. The exercise-induced hypoxemia seen in patients with COPD is ascribed to ventilation-perfusion \((V/A)\) inequality (19). Hypoxemia induces vasoconstriction of the pulmonary artery, and repeated episodes of such vasoconstriction are thought to be responsible for the development of irreversible pulmonary hypertension followed by cor pulmonale. In patients with moderate to severe COPD, prognosis was reported to be significantly worse when pulmonary hypertension \((\text{pulmonary arterial pressure} > 20 \text{ mmHg})\) was present (5). It is therefore conceivable that, even in patients without hypoxemia at rest, common daily activities often induce hypoxemia, leading to cor pulmonale and resulting in poor prognosis in these patients.

We found that both age and \( F_{E\text{V}_1} \), influenced the survival of patients with COPD, confirming the results of previous studies (1–5). We noted that mortality was not correlated with \( V_{O_2}\text{max} \), which is well known as a good index of predicting severity and for selecting candidates for lung surgery in patients with COPD. Also mortality was not associated with other exercise variables including \( V_{O_2,\text{max}}, V_{C\text{O}_2,\text{max}}, V_{E\text{max}}, \) and \( P_{A\text{CO}_2,\text{max}} \). Anthonisen et al (4) found maximal exercise tolerance to be a useful predictor of mortality after adjustment for age and \( F_{E\text{V}_1} \), while we did not (Table 4). It is possible that the difference could be ascribed to patient selection and exercise protocol. Our patients tended to be milder than their patients, and they did not include other exercise variables in their analysis.

Some limitations of the study should be pointed out. First, the entry of our study lasted for approximately 10 years, and the hot-wire spirometer was changed to a new type during this period. However, it was calibrated beforehand by skilled technicians and spirogram was periodically measured in healthy nonsmokers as standard subjects to assure the overall accuracy of the system, we therefore consider that the differences of machines were within an acceptable range. Secondly, treatment and prevention during the follow-up period, in some part, might influence the prognosis for each patient. The long-term administration of oxygen \((>15 \text{ hours per day})\) to patients with chronic respiratory failure has been shown to increase survival \((20\)\). During the follow-up period, 22 patients started long-term oxygen therapy. Long-term oxygen therapy was not considered to be an indication for the health insurance system until 1985 in Japan, and the starting criteria of long-term oxygen therapy was solely dependent on each doctor’s judgment. Third, we do not have exact data on smoking cessation among our patients.

We consider that patients with COPD should undergo exercise testing in order to detect exercise-induced hypoxia, and also to determine the indication of oxygen therapy. Oxygen therapy for preventing exercise-induced hypoxemia may also protect against the development of pulmonary hypertension (21, 22) and may contribute to prolonged life (23).

The present study thus highlights the importance of exercise testing to evaluate prognosis in patients with COPD.

**References**