Respiratory Medicine (2007) **101**, 561–567

ELSEVIER

respiratoryMEDICINE

Distance and oxygen desaturation in 6-min walk test predict prognosis in COPD patients

Nagio Takigawa[a,b,*], Atsuhiko Tada[a], Ryo Soda[a], Hiroshi Date[c], Motohiro Yamashita[d], Shigeto Endo[d], Syuji Takahashi[a], Noriko Kawata[a], Takuo Shibayama[a], Noboru Hamada[a], Motoi Sakaguchi[a], Atsushi Hirano[a], Goro Kimura[a], Chiharu Okada[a], Kiyoshi Takahashi[a]

[a]*Department of Internal Medicine, National Hospital Organization, Minami-Okayama Medical Center, 4066 Hayashima, Okayama 701 0304, Japan*
[b]*Department of Respiratory Medicine, Okayama University Hospital, 2-5-1 Shikata-cho, Okayama 700 8558, Japan*
[c]*Department of Thoracic Surgery, Okayama University Hospital, 2-5-1 Shikata-cho, Okayama 700 8558, Japan*
[d]*Department of Surgery, National Hospital Organization, Minami-Okayama Medical Center, 4066 Hayashima, Okayama 701 0304, Japan*

Received 29 March 2006; accepted 18 June 2006

KEYWORDS
COPD;
Prognosis;
Oxygen desaturation;
6-min walk test;
Pulmonary rehabilitation;
Lung volume reduction surgery

Summary
The aim of the present study was to predict the prognosis of Chronic obstructive pulmonary disease (COPD) patients who underwent comprehensive pulmonary rehabilitation (PR). A total of 144 patients who performed PR between 1992 and 1999 was assessed. After PR, 67 patients underwent lung volume reduction surgery (LVRS). Baseline data before PR consisted of body mass index, serum albumin levels, use of supplement oxygen at home, pulmonary function, arterial blood gas analysis, and distance and fall of hemoglobin oxygen saturation (ΔSpO_2) in 6-min walk test. In addition to pre-PR factors, treatment with LVRS was taken into the analysis. The prognostic significance of variables influencing survival was determined by univariate analysis with Log rank test or multivariate analysis using Cox's proportional hazard model. By a median follow-up time of 8.4 years, the median survival time was 8.1 years (95% confidence interval: 6.9–9.4 years). Albumin level, $PaCO_2$, distance and ΔSpO_2 were significant prognostic factors in univariate analysis. LVRS did not affect the prognosis. The multivariate analysis showed short distance and increase of ΔSpO_2 as significant independent predictors of the risk of death. 6-min walk test was very useful for predicting the prognosis of the COPD patients.

*Corresponding author. Department of Respiratory Medicine, Okayama University Hospital, 2-5-1 Shikata-cho, Okayama 700 8558, Japan. Tel.: +81 86 235 7227; fax: +81 86 232 8226.
E-mail address: ntakigaw@md.okayama-u.ac.jp (N. Takigawa).

0954-6111/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2006.06.017

Introduction

Chronic obstructive pulmonary disease (COPD) has become a common disease worldwide.[1] The prevalence of COPD in subjects aged $\geqslant$40 years increased 10.9% more than expected according to a Japanese epidemiology study conducted in 2000.[2] COPD is currently the fourth leading cause of death in the world, and further increases in the prevalence and mortality of the disease can be predicted in the coming decades.[3] Several factors including reduced expiratory volume in 1 s (FEV_1), hypoxia, hypercapnea, a short distance walked in a fixed time, a high degree of functional breathlessness, and a low body mass index (BMI) were associated with an increased risk of death.[3,4]

Pulmonary rehabilitation (PR) is an effective intervention in patients with COPD.[1,5] Troosters et al. reported that the current best estimate using 7 randomized studies (total 596 patients) was that PR reduced the short-term (1–1.5 year) risk of dying by 31% although this reduction was not statistically significant.[6] In addition, lung volume reduction surgery (LVRS) has been proposed as a palliative treatment for severe COPD patients.[3] Overall, LVRS offered no survival benefit; however, their subgroup analysis demonstrated that patients with predominantly upper-lobe emphysema and low base-line exercise capacity had an advantage in survival.[7] Accordingly, PR and LVRS may prolong survival for COPD patients.

We started our comprehensive PR program for COPD in 1992 at Minami-Okayama Medical Center and LVRS was performed in eligible patients after PR. The aim of this study was to predict the prognosis of COPD by evaluating prognostic factors in all patients participating in our PR program despite LVRS.

Methods

The diagnosis of COPD and classification of severity was defined according to the global strategy for the diagnosis, management, and prevention of COPD updated 2004.[3] The patients have symptoms of cough, sputum, or dyspnea, and/or a history of exposure to risk factors for the disease. The presence of a postbronchodilator $FEV_1 < 80\%$ of the predicted value in combination with an FEV_1/forced vital capacity (FVC) $< 70\%$ confirms the presence of airflow limitation that is not fully reversible. Reversibility was defined as an increase in FEV_1 greater than 12% and/or 200 mL after inhalation of β-agonist. Classification of severity was as follows: mild COPD (stage I), $FEV_1 > 80\%$ predicted; moderate COPD (stage II), $50\% \leqslant FEV_1 < 80\%$; severe COPD (stage III), $30\% \leqslant FEV_1 < 50\%$; very severe COPD (stage IV), $FEV_1 < 30\%$.[3] Inclusion criteria of this study were as follows: (1) the ability to walk for 6 min, (2) never having participated in a rehabilitation program before, (3) absence of a comorbid disease that would make it unlikely that the patient could participate in a PR program, for example, severe pulmonary hypertension with dizziness or syncope on exercise, severe congestive heart failure refractory to medical management, unstable coronary disease, and mental deterioration. The patients received optimal medical treatment including β-agonists, anticholinergic drugs, theophylline, and/or (inhaled or oral) steroids. A stable condition whilst receiving medical treatment was required before PR commenced. This study was performed as part of our standard inpatient treatment and care.

Baseline data before PR consists of height, body weight, BMI, serum albumin level, and use of supplement oxygen at home. Pulmonary function data such as FEV_1% predicted, FEV_1/FVC, and % vital capacity (VC) were assessed with spirometry (Chestac-25, Chest, Tokyo, Japan). Predicted FEV_1 values were obtained from the guidelines of the Japanese Respiratory Society[8]: FEV_1 (L) for men = 0.036 × height (cm) − 0.028 × age (yr) − 1.178; FEV_1 (L) for women = 0.022 × height (cm) − 0.022 × age (yr) − 0.055. Arterial blood gases were taken at rest. Patients with hypoxemia at rest (< 55 Torr) were prescribed oxygen therapy, so that PaO_2 and $PaCO_2$ were measured while they were receiving oxygen. The patients performed 6-min walk (6MW) tests. Six-min walk distance (6MWD) was defined as the longest distance possible in 6MW without encouragement. A practice walk was not included. They were allowed to stop and rest if necessary. They walked with hemoglobin oxygen saturation (SpO_2) monitors. ΔSpO_2 (SpO_2 level just before 6MW − minimum SpO_2 level during 6MW) was also assessed. All the data were before PR.

The comprehensive PR including exercise and educational activities, which are described elsewhere in detail,[9] were performed using a hospitalized program from 4 to 8 weeks. Briefly, patients attended the rehabilitation unit on 5 half-days per week. Exercise included cycle ergometer training, treadmill training, upper and lower extremity strength training, breathing therapies, and relaxation therapies. The education program was also given on weekdays. Inclusion criteria for LVRS were as follows: (1) marked restriction in the activity of daily life despite maximal medical therapy; (2) marked hyperinflation (% total lung capacity > 120%) by dilutional method; (3) diffuse but inhomogeneous emphysema (existence of target areas); (4) ability to participate in a vigorous PR program before and after LVRS; (5) smoking cessation for at least 3 months. Exclusion criteria for LVRS were as follows: (1) pulmonary hypertension (mean pulmonary artery pressure > 30 mmHg) measured by Swan-Ganz catheter; (2) active bronchopulmonary infection; (3) severe bronchial asthma; (4) severe pleural adhesion (for example, prior thoracotomy or chemical pleurodesis); (5) hypercapnea ($PaCO_2 > 60$ Torr).[10] The patients underwent PR for 4 weeks after LVRS.

Statistical analyses were performed with the SPSS Base System™ and Advanced Statistics™ programs (SPSS, Chicago, IL, USA). To compare categorized variables between two groups, Pearson χ^2 was used. The influence of variables on survival was studied by univariate and multivariate analyses. We categorized potential prognostic variables, which were dichotomized into normal and abnormal values based on standard norms ($PaCO_2$: 45 Torr, %VC: 80%); the usual baseline of the supplemental oxygen for hypoxemic patients (PaO_2: 60 Torr); the cutoff line in stage III and IV (FEV_1% of predicted: 30%), or median values for age, BMI, albumin, 6MWD and ΔSpO_2 in this study. All survival data have been updated to 13 December 2004. The overall survival time from the beginning of PR was calculated using the method of Kaplan-Meier. We determined the prognostic significance of variables by univariate analysis with Log rank test or multivariate analysis using Cox's proportional hazard model

in a stepwise backward fashion. The variables incorporated into the multivariate analysis are those that were $P<0.3$ in the univariate analysis. In addition to pretreatment factors, the LVRS was taken into the variables because LVRS might affect survival. Pearson's correlation coefficient (r) was used to examine the degree of association of 6MWD and ΔSpO_2. For all comparisons, $P<0.05$ was considered statistically significant.

Results

Between 13 July 1992 and 10 December 1999, 132 men and 12 women participating in our PR program were assessed for this study. Of the 144 patients in this study, 9 were classified as having stage II COPD, 47 stage III, and 88 stage IV. The median age was 67 years and range of 45–79 years. The median BMI was 18 kg/m^2 (range: 12.4–28.4 kg/m^2); albumin level: 3.9 g/dL (range: 2.6–4.6 g/dL); 6MWD: 340 m (range: 60–510 m); ΔSpO_2: 6% (range: 0–33%); FEV_1% predicted: 26.9% (range: 11.9–71.9%); FEV_1/FVC: 40.1% (range: 22.7–66.9%); %VC: 69.0% (range: 26–129%); PaO_2: 68.2 Torr (range: 45.7–100 Torr); $PaCO_2$: 43.7 Torr (range: 28.8–93.8 Torr). When clinical stage was categorized in two groups of patients based on FEV_1% of predicted ($<30\%$ vs. $\geqslant 30\%$), the median values were 46.4 Torr vs. 40.0 Torr in $PaCO_2$; 67.7 Torr vs. 69.5 Torr in PaO_2; 60.5% vs 85.2% in %VC; 22.6% vs. 35.0% in FEV_1% of predicted, respectively. There were 127 patients who had smoked and 17 who had never smoked. 75 patients received home oxygen therapy at the time of PR and 67 underwent LVRS after PR. At the time of analysis, 55 patients were dead, 89 were alive. Cause of death was as follows: cardiopulmonary insufficiency: 48 (cause of cardiopulmonary insufficiency: myocardial infarction 2, bacterial pneumonia 1, congestive heart failure 2, not specified cause 43); lung cancer: 4; stomach cancer: 1; rupture of abdominal aortic aneurysm: 1; bleeding of duodenal ulcer: 1. By a median follow-up time of 8.4 years, the median survival time was 8.1 years (95% confidence interval [CI]: 6.9–9.4 years).

Univariate survival analysis showed that the following characteristics were highly significant prognostic factors favoring longer survival (with associated P value <0.05): 6MWD ($\geqslant 340$ m), ΔSpO_2 ($<6\%$), $PaCO_2$ (<45 Torr), and albumin level ($\geqslant 3.9$ g/dL) (Table 1) (Fig. 1a–d). Other variables that may be discriminant for survival (with associated P values between 0.05 and 0.3) were FEV_1% predicted (Fig. 1e), sex (Fig. 1f), and home oxygen therapy. LVRS did not discriminate for survival ($P = 0.59$) (Fig. 1g). Comparison of characteristics with or without LVRS was shown in Table 2. The younger patients underwent LVRS ($P = 0.003$) and those with higher albumin level received LVRS ($P = 0.078$), which might be associated with being favorable for longer survival. On the other hand, the patients with lower FEV_1% predicted ($P = 0.000$), those with higher $PaCO_2$ level ($P = 0.016$) and those with higher ΔSpO_2 level ($P = 0.078$) underwent LVRS, which might be unfavorable for survival.

Using multivariate analysis, patients were analyzed to determine factors affecting their prognosis. The variables incorporated into this analysis are sex, serum albumin level, use of supplement oxygen at home, 6MWD, ΔSpO_2, $PaCO_2$, FEV_1% predicted, and LVRS. Independently significant factors influencing survival were 6MWD ($P = 0.005$) and ΔSpO_2 ($P = 0.004$) (Table 3). There was no correlation between 6MWD and ΔSpO_2 ($r = -0.028$, $P = 0.744$). When all patients were categorized into 2 using 6MWD and ΔSpO_2, 105 patients with 6MWD $\geqslant 340$ m and/or $\Delta SpO_2 < 6\%$ had better prognosis (median survival time: 11.4 year; 95% CI: not determined, mean survival time: 8.4 years, 95% CI: 7.5–9.3 years); 39 patients with 6MWD <340 m and $\Delta SpO_2 \geqslant 6\%$ had worse prognosis (median survival time: 4.0 years; 95% CI: 2.7–5.3 years, mean survival time: 4.5 years, 95% CI: 3.6–5.4 years). There was a significant difference between the 2 categorized patients ($P = 0.000$) (Fig. 2).

Table 1 Univariate analysis by Log rank test.

Variable	n	MST, year (95% CI)	P
Age (year)			
<67	65	8.1 (n.d.)	0.59
$\geqslant 67$	79	7.0 (5.2–8.8)	
Sex			
Men	132	7.6 (5.8–9.4)	0.089
Women	12	8.3 (n.d.)	
Body-mass index			
<18 kg/m^2	68	8.1 (n.d.)	0.89
$\geqslant 18$ kg/m^2	76	7.6 (5.6–9.7)	
Albumin			
<3.9 g/dL	65	5.6 (3.6–7.6)	0.015
$\geqslant 3.9$ g/dL	79	Not reached	
6MWD			
<340 m	70	5.8 (3.0–8.6)	0.024
$\geqslant 340$ m	74	8.1 (n.d.)	
ΔSpO_2			
$<6\%$	65	11.4 (n.d.)	0.0033
$\geqslant 6\%$	79	5.8 (3.9–7.7)	
$PaCO_2$			
<45 Torr	84	Not reached	0.012
$\geqslant 45$ Torr	60	6.8 (4.2–9.4)	
PaO_2			
<60 Torr	30	8.1 (n.d.)	0.60
$\geqslant 60$ Torr	114	7.6 (6.1–9.1)	
%VC			
$<80\%$	98	7.6 (5.8–9.5)	0.62
$\geqslant 80\%$	46	8.1 (n.d.)	
FEV_1, % predicted			
$<30\%$	88	7.6 (5.7–9.6)	0.10
$\geqslant 30\%$	56	Not reached	
LVRS			
Yes	67	7.6 (6.6–8.9)	0.59
No	77	11.4 (n.d.)	
HOT			
Yes	75	8.3 (3.7–13.0)	0.24
No	69	7.6 (6.1–9.1)	

MST: median survival time; CI: confidence interval; LVRS: lung volume reduction surgery; HOT: home oxygen therapy; n.d. not determined.

Discussion

Predictors of mortality from COPD include FEV_1, BMI, respiratory symptoms, exercise capacity, PaO_2, $PaCO_2$,

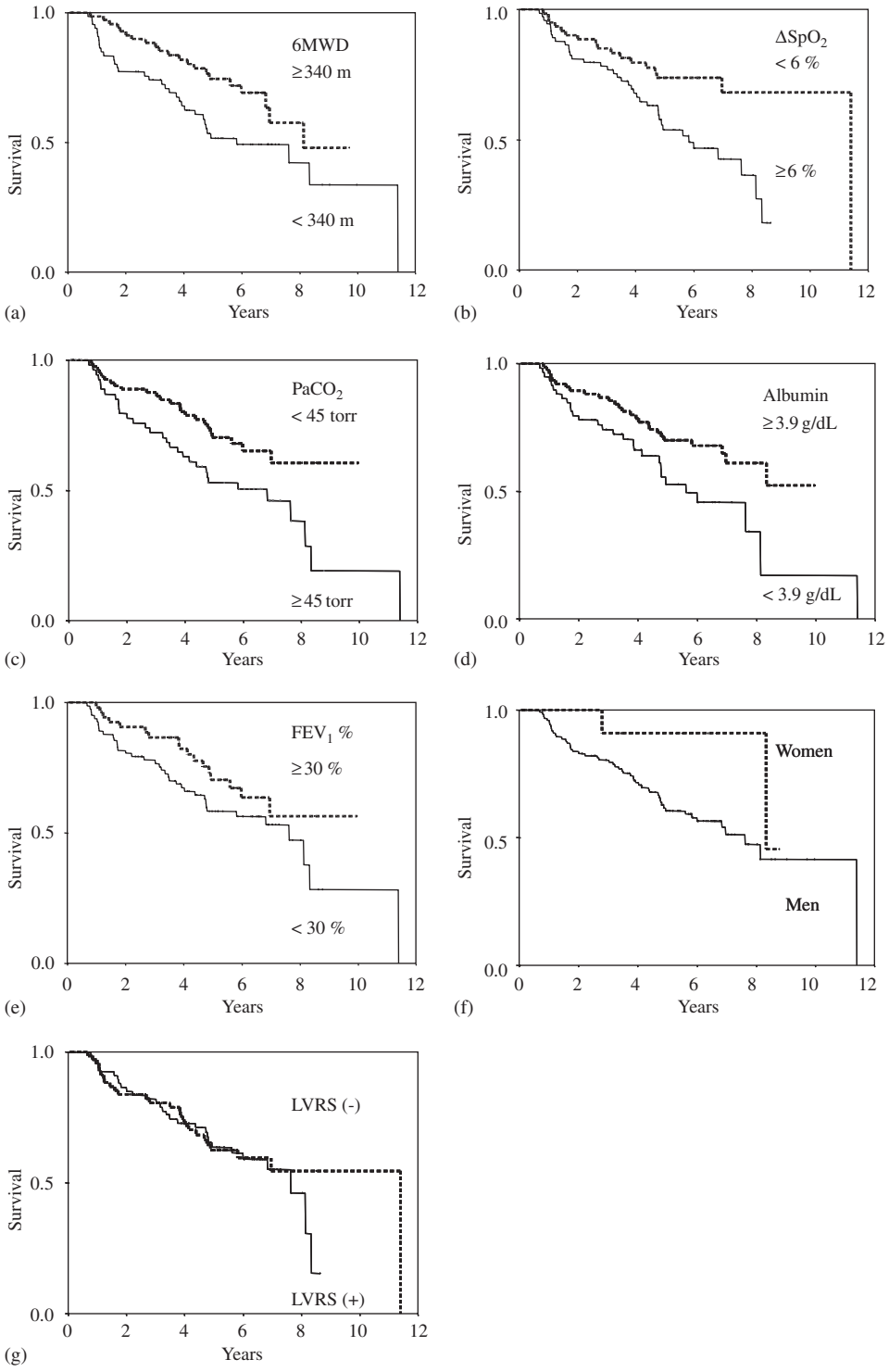

Figure 1 Survival curves according to the 6MWD (a), ΔSpO_2 (b), $PaCO_2$ (c), albumin level (d), FEV_1% predicted (e), sex (f), and LVRS (g).

exacerbations, and their combinations.[3] Among them, the combination index using BMI, FEV_1, dyspnea scale and 6MWD was a more powerful indicator than the previously reported prognostic factors in predicting the risk of death.[4] However, treatment such as PR or LVRS was not described there. The patients with $FEV_1 < 80\%$ were recommended to perform PR.[3] There have been three indications of survival benefits by PR.[11–14] Ries et al.[11] reported that survival rates were 61% in PR group and 56% in control group after 6 years of follow-up, and the difference was a slight but not significant ($P = 0.32$). Griffiths et al.[12] found that six of 99 patients (6%) in PR group and 12 of 101 (12%) in control group died during 1-year of follow-up. A tendency for greater survival in patients who underwent PR after hospitalization for an acute exacerbation of COPD was also reported.[14] However, these were insufficient to demonstrate improved survival

Table 2 Comparison of characteristics with or without LVRS.

	LVRS			
	−	+	Total	*P*
Age, year				
<67	26	39	65	0.003
$\geqslant 67$	51	28	79	
Sex				
Men	69	63	132	0.34
Women	8	4	12	
Body mass index				
$<18\,kg/m^2$	38	30	68	0.58
$\geqslant 18\,kg/m^2$	39	37	76	
Albumin				
$<3.9\,g/dL$	40	25	65	0.078
$\geqslant 3.9\,g/dL$	37	42	79	
6MWD				
$<340\,m$	36	34	70	0.63
$\geqslant 340\,m$	41	33	74	
ΔSpO_2				
$<6\%$	40	25	65	0.078
$\geqslant 6\%$	37	42	79	
$PaCO_2$				
<45 Torr	52	32	84	0.016
$\geqslant 45$ Torr	25	35	60	
PaO_2				
<60 Torr	16	14	30	0.99
$\geqslant 60$ Torr	61	53	114	
%VC				
$<80\%$	52	46	98	0.89
$\geqslant 80\%$	25	21	46	
FEV_1, % predicted				
$<30\%$	35	53	88	0.00
$\geqslant 30\%$	42	14	56	

Pearson χ^2 test was used for comparison between two groups.
LVRS: lung volume reduction surgery.

Table 3 Multivariate analysis by Cox proportional hazard model.

	Exp (β)	95% CI	*P*
Sex	0.320	0.076–1.354	0.122
Albumin	0.588	0.338–1.023	0.060
6MWD	0.447	0.256–0.779	0.005
ΔSpO_2	2.393	1.317–4.346	0.004

after PR. Troosters et al.[6] also reported that PR might prolong survival as a result of analysis using 7 randomized studies. In addition, LVRS for patients with predominantly upper-lobe emphysema and low base-line exercise capacity had produced survival benefits.[7] Accordingly, we planned to evaluate prognostic factors in COPD patients participating in our PR programs and take LVRS into consideration in this analysis.

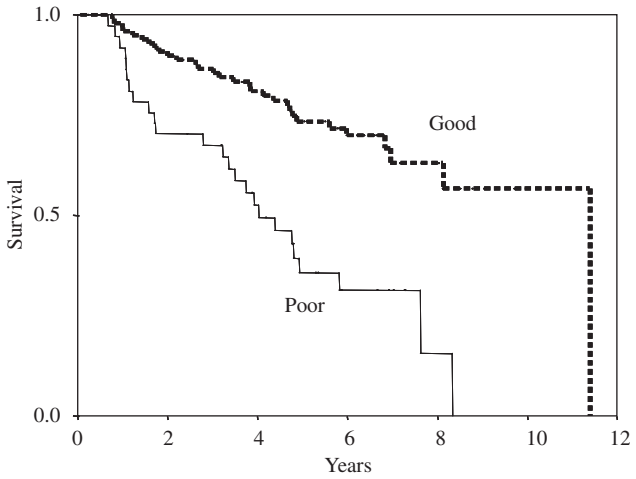

Figure 2 When all patients were categorized into two groups using 6MWD and ΔSpO_2, patients with 6MWD $\geqslant 340$ m and/or $\Delta SpO_2 < 6\%$ had good prognosis and patients with 6MWD < 340 m and $\Delta SpO_2 \geqslant 6\%$ had poor prognosis.

Our multivariate analysis showed that only distance and oxygen desaturation in 6MW test were independent prognostic factors. 12MWD was reported to be a significant prognostic factor.[15] We cannot tell which (6MWD or 12MWD) is better for predicting prognosis. The mean FEV_1% predicted ($38 \pm 19\%$) in their study[15] was much higher than that ($29.2 \pm 11.3\%$) in our study. Actually, some patients in our study could not walk for 12 min. In the severe COPD patients at least, 6MWD seems more useful than 12MWD. There have been a few studies on exercise-induced hypoxemia as a prognostic factor. Poulain et al. reported that 28% of COPD patients showed $\Delta SpO_2 \geqslant 4\%$ and the reproducibility of this phenomenon was confirmed.[16] They also showed that ΔSpO_2 was not correlated with 6MWD, which is consistent with our result. Mak et al.[17] also reported that ΔSpO_2 was not related to 6MWD, the degree of perceived exertion, nor perceived breathlessness. There have been a few reports concerning the relationships between exercise-induced hypoxemia and survival. Hiraga et al.[18] showed that the cardiopulmonary exercise test by treadmill was most closely associated with survival. They found $\Delta PaO_2/\Delta VO_2$ more accurately and quantitatively reflected the degree of the exercise-induced hypoxemia than ΔSpO_2. However, the measurement of $\Delta PaO_2/\Delta VO_2$ was quite costly and might not be standard clinical practice as they referred to in the discussion. Tojo et al.[19] recently reported that fall of PaO_2 during cycle ergometer was an independent predictor of mortality. They speculated that repeated exercise-induced hypoxemia induced vasoconstriction of the pulmonary artery, which were responsible for the development of irreversible pulmonary hypertension and resulted in poor prognosis. We also speculate that cardiopulmonary dynamics associated with cardiac output and pulmonary artery pressure cannot compensate the oxygen desaturation during exercise in such patients. This may be due to loss of functional reserve capacity of the cardiopulmonary system, leading to poor prognosis. In respect of the method of detecting exercise-induced hypoxemia, the cardiopulmonary exercise test using

cycle ergometer was compared to the 6MW test.[17] They found that the 6MW test was more sensitive than the cardiopulmonary exercise test for detecting oxygen desaturation. They also suggested that the 6MW test might have the potential to become a diagnostic test as well, either to measure dynamic hyperinflation or unmask exercise-induced hypoxemia. Desaturation was also proven to be a prognostic indicator for patients with interstitial pneumonia although the definition was a fall in oxygen saturation to 88% or less during 6MW test.[20] In the present study, ΔSpO_2 and 6MWD were independently significant factors influencing survival. These two parameters can be easily obtained because the 6MW test is carried out as clinical practice.

Our study has limitations. Firstly, we did not evaluate the degree of dyspnea. We estimated it by the scale for the patients with home oxygen therapy in Japan; however, it has not been validated so far. Accordingly, we omitted the evaluation of perceived breathlessness. Secondary, the cut-off value of BMI (18 kg/m^2), 6MWD (340 m) and ΔSpO_2 (6%) was determined by the median value in this study population. In the report of Celli et al.,[4] the cut-off value of BMI was 21 kg/m^2; those of 6MWD were 350, 250, and 150 m. 4% fall of ΔSpO_2 was validated in a study of exercise-induced hypoxemia in athletes and this 4% fall was defined as a fall of 2% to account for potential inaccuracy of oximetry plus another fall of 2% to account for the right shift of the hemoglobin saturation curve induced by exercise metabolic acidosis.[16,21] The median values of these parameters should be validated in another population and prospective design. Thirdly, we did not analyze the patients who underwent LVRS in detail. The present study could not show survival benefits of LVRS. Preliminary data[22] revealed that LVRS produced temporary palliation without operative deaths, and there were lower rates of upper lobe type emphysema, which was associated with survival advantage from LVRS, compared to previous reports.[7,13] The detailed analysis regarding LVRS will be published in the near future. Fourthly, we did not analyze the data after PR in this study. Gerardi et al.[15] identified the 12MWD after PR was the best predictor of mortality. The mechanism for improving survival might be through improvement secured by the PR. The interaction of the effect of the program with survival should be examined in the future. Finally, only 12 (8%) women were included in this study and to say something meaningful on gender and mortality may be difficult.

In conclusion, both short distance and increase of ΔSpO_2 showed significant independent poor prognosis. 6MWT was very useful for predicting the prognosis in COPD patients. To improve the outcome for the patients with poor prognosis, new strategies including early intervention of PR for stage I patients, drugs such as antioxidants, testosterone, and erythropoietin, and intensive nutritional support should be established.[6]

Acknowledgments

We are grateful to the specialist respiratory nurses, physical therapists and dietetic staffs who supported this rehabilitation program.

References

1. Sutherland ER, Cherniack RM. Management of chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**: 2689–97.
2. Fukuchi Y, Nishimura M, Ichinose M, et al. COPD in Japan: the Nippon COPD epidemiology study. *Respiratology* 2004;**9**: 458–65.
3. National Institutes of Health, National Heart, Lung and Blood Institute. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Workshop Report. Update 2004. www.goldcopd.com.
4. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**: 1005–12.
5. Lacasse Y, Wong E, Guyatt GH, King D, Cook DJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *Lancet* 1996;**348**: 1115–9.
6. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;**172**:19–38.
7. National Emphysema treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;**348**: 2059–73.
8. Japan Society of Chest Diseases. The predicted values of pulmonary function testing in Japanese. *Jpn J Thoracic Dis* 1993;**31** appendix (in Japanese).
9. Takigawa N, Tada A, Soda R, et al. Comprehensive pulmonary rehabilitation according to severity of COPD. *Respir Med* 2006; [Epub ahead of print].
10. Date H, Goto K, Souda R, et al. Predictors of improvement in FEV_1 (forced expiratory volume in 1 s) after lung volume reduction surgery. *Surg Today* 2000;**30**:328–32.
11. Ries AL, Kaplan RM, Limberg TMK, et al. Effects of pulmonary rehabilitation on physiological and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995;**122**:823–32.
12. Griffiths TL, Burr ML, Campbell IA, et al. Results at 1 year of patient multidisciplinary pulmonary rehabilitation: a randomized controlled trial. *Lancet* 2000;**355**:362–8.
13. Decramer M. Treatment of chronic respiratory failure: lung volume reduction surgery versus rehabilitation. *Eur Respir J* 2003;**22**(Suppl):47s–56s.
14. Troosters T, Gosselink R, De Paepe K, Decramer M. *Am J Resp Crit Care Med* 2002;**165**:A16.
15. Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL. Variables related to increased mortality following out-patient pulmonary rehabilitation. *Eur Respir J* 1996;**9**: 431–5.
16. Poulain M, Durand F, Palomba B, et al. 6-minute walk testing is more sensitive than maximal incremental cycle testing for detecting oxygen desaturation in patients with COPD. *Chest* 2003;**123**:1401–7.
17. Mak VH, Bugler JR, Roberts CM, Spiro SG. Effect of arterial oxygen desaturation on six minute walk distance, perceived effort, and perceived breathlessness in patients with airflow limitation. *Thorax* 1993;**48**:33–8.
18. Hiraga T, Maekura R, Okuda Y, et al. Prognostic predictors for survival in patients with COPD using cardiopulmonary exercise testing. *Clin Physiol Funct Imag* 2003;**23**:324–31.
19. Tojo N, Ichioka M, Chida M, Miyazato I, Yoshizawa Y, Miyasaka N. Pulmonary exercise testing predicts prognosis in patients with

chronic obstructive pulmonary disease. *Intern Med* 2005;**44**: 20–5.
20. Lama VN, Flaherty KR, Toews GB, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003;**168**: 1084–90.
21. Prefaut C, Durand F, Mucci P, Caillaud C. Exercise-induced arterial hypoxaemia in athletes: a review. *Sports Med* 2000;**30**: 47–61.
22. Date H, Goto K, Souda R, et al. Bilateral lung volume reduction surgery via median sternotomy for severe pulmonary emphysema. *Ann Thorac Surg* 1998;**65**:939–42.