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Dyspnoea with activities of daily living versus peak dyspnoea during exercise in male patients with COPD

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Summary Dyspnoea measurements in chronic obstructive pulmonary disease (COPD) can be broadly divided into two categories: those that assess breathlessness during exercise, and those that assess breathlessness during daily activities. We investigated the relationships between dyspnoea at the end of exercise and during daily activities with clinical measurements and mortality in COPD patients.

We examined 143 male outpatients with moderate to very severe COPD. The peak Borg score at the end of progressive cycle ergometry was used for the assessment of peak dyspnoea rating during exercise, and the Baseline Dyspnea Index (BDI) score was used for dyspnoea with activities of daily living. Relationships between these dyspnoea ratings with other clinical measurements of pulmonary function, exercise indices, health status and psychological status were then investigated. In addition, their relationship with the 5-year mortality of COPD patients was also analyzed to examine their predictive ability.

Although the BDI score was significantly correlated with airflow limitation, diffusing capacity, exercise indices, health status and psychological status, the Borg score at the end of exercise had non-existent or only weak correlations with them. The BDI score was strongly significantly correlated with mortality, whereas the Borg score was not.

Abbreviations: BDI, Baseline Dyspnea Index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; HADS, Hospital Anxiety and Depression Scale; HR, heart rate; RV, residual volume; SaO_2, arterial oxygen saturation; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity; TLCO, carbon monoxide transfer factor; $\dot{V}_E$, minute ventilation; $\dot{V}_{O_2}$, oxygen uptake

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Dyspnoea during daily activities was more significantly correlated with objective and subjective measurements of COPD than dyspnoea at the end of exercise. In addition, the former was more predictive of mortality. Dyspnoea with activities of daily living is considered to be a better measurement for evaluating the disease severity of COPD than peak dyspnoea during exercise.

Introduction

Exertional dyspnoea is one of the most common complaints of patients with chronic obstructive pulmonary disease (COPD), and often leads these patients to seek medical attention, although the mechanism responsible for dyspnoea is complex and multifactorial.[1] However, dyspnoea can be relatively easily measured in clinical settings, and is evaluated under various circumstances in patients with COPD.

The outcome measurements of dyspnoea can be broadly divided into those that assess breathlessness during exercise, and those that assess overall breathlessness during daily activities.[2] The relationships between dyspnoea during daily activities and other objective or subjective measurements[3–5] or mortality[6,7] have been reported, and its measurement is recommended as an indicator of disease severity in COPD management guidelines.[8,9]

In comparison, it is still uncertain what researchers actually evaluate by measuring peak dyspnoea during exercise, and whether it is related to disease severity in COPD. Furthermore, peak dyspnoea has been reported to evaluate different aspects from dyspnoea with activities of daily living.[4] Therefore, in the present study, we investigated what peak dyspnoea during exercise actually represented in patients with COPD, and whether it was related to mortality in order to investigate its relationship with disease severity, and compared it with dyspnoea during daily activities.

Methods

Subjects

We previously recruited male outpatients with COPD from the Kyoto University Hospital, and analyzed the relationships between baseline clinical parameters and mortality, focusing on exercise capacity and health status.[10] In the present study, we retrospectively reviewed these data and re-analyzed the relationships between the dyspnoea measurements during exercise and during daily activities, as well as other clinical parameters and mortality, in 143 patients with moderate to very severe COPD. The definition of COPD was based on published guidelines,[8] and the subjects met the following criteria: (1) a smoking history of more than 20 pack-years; (2) maximal forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of less than 0.7 and a postbronchodilator FEV_1 of less than 80% of the predicted value; (3) no uncontrolled comorbidities likely to affect mortality such as malignant disorders, cardiovascular diseases or cerebrovascular diseases; (4) regular attendance of over 6 months; and (5) no exacerbations in the preceding 6 weeks. Pulmonary function testing, progressive cycle ergometry, and the assessments of dyspnoea, health status, psychological status and body mass index (BMI) were performed on the same day. The present study was performed as part of our standard outpatient treatment and care.

Measurements

Pulmonary function

Pulmonary function tests were performed at least 12 h after the withdrawal of inhaled bronchodilators. According to the recommended method,[11] the subjects underwent spirometry before and at 15 and 60 min after inhaling salbutamol (400 μg) and ipratropium bromide (80 μg), using a metered-dose inhaler with a spacer device (InspirEase™, Schering-Plough K.K., Osaka, Japan). The residual volume (RV) was measured by the closed-circuit helium method, and the carbon monoxide transfer factor (TLCO) was measured by the single-breath technique (CHESTAC-65V, Chest, Tokyo, Japan). Predicted values were based on data from the Japan Society of Chest Diseases.[12]

Exercise tests

Symptom-limited progressive cycle ergometry was performed at 60 min after the inhalation of bronchodilators on a calibrated, electrically braked cycle ergometer, as described in detail elsewhere.[13] The patients wore a face mask and began

unloaded pedaling for 3 min, after which the workload was increased progressively by increments of 1 W every 3 s to the limit of tolerance. The exercise data were recorded using an automated exercise testing system. Minute ventilation ($\dot{V}_E$) and oxygen tension in the expired air were determined every eight breaths, and the mean $\dot{V}_E$, oxygen uptake ($\dot{V}_{O_2}$) and carbon dioxide production were then calculated. The peak values were defined as the highest levels reached during exercise. Arterial oxygen saturation (SaO_2) was measured through pulse oximetry, and the heart rate (HR) was recorded electrocardiographically. At the end of the exercise, the symptoms of breathlessness were scored with the Borg scale (0–10),[14] with 0 indicating the absence of dyspnoea and 10 representing ''the most severe level of dyspnoea you could imagine or have ever undergone''.

Clinical dyspnoea

Dyspnoea during daily activities was evaluated by the Japanese version of the Baseline Dyspnea Index (BDI).[4,15] The BDI recognizes five grades from 0 (severe) to 4 (not impaired) for each of the following three categories: functional impairment, magnitude of task, and magnitude of effort.

Health status

Health status was measured by the St. George's Respiratory Questionnaire (SGRQ)[16] whose Japanese version has been previously validated.[17] The SGRQ consists of 50 items divided into three components of symptoms, activity and impacts, and the total score was also calculated, with scores ranging from 0 to 100. Lower scores indicate less impairment on the SGRQ.

Psychological status

Psychological status related to anxiety and depression was evaluated by the Japanese version of the Hospital Anxiety and Depression Scale (HADS).[17,18] It consists of 14 items, seven for anxiety and seven for depression. Each item is scored from 0 to 3, where 3 represents a state corresponding to the worst anxiety or depression. The sum of these items produces 2 subscales ranging from 0 to 21.

Follow-up data

Among the 143 COPD patients, five were unavailable for follow-up and 31 died during the 5-year period. With respect of the causes of deaths, 20 died of COPD or COPD-related disease, four due to malignant disorders, and one each due to myocardial infarction and hepatic failure, respectively. Five deaths were due to unknown causes.

Statistical analysis

The results are presented as mean $\pm$ SD, unless otherwise stated. The relationships between the dyspnoea scores and other clinical measurements were analyzed by Spearman's rank correlation tests. When significant relationships were observed, stepwise multiple regression analyses were performed to identify those variables that could best predict the dyspnoea score, using the variables that were significantly correlated to it as explanatory variables.[17]

The survival status of all subjects after 5 years was assessed. The duration from entry to the last attendance or death was then recorded. Univariate Cox proportional hazards analyses were performed to investigate the relationship between the clinical indices and mortality. The results of the regression analysis were presented in terms of the estimated relative risks (RR) with the corresponding 95% confidence intervals (CI). *P* values of less than 0.05 were considered to be statistically significant.

Results

The baseline characteristics of the patients with COPD are presented in Table 1. Their average age

Table 1 Baseline characteristics in 143 male patients with COPD.

Characteristic	Mean $\pm$ SD
Age, years	68.8 $\pm$ 6.7
Body mass index (kg/m^2)	21.0 $\pm$ 2.9
Postbronchodilator FEV_1, % predicted	45.7 $\pm$ 15.9
RV/TLC (%)	47.1 $\pm$ 10.3
TLCO, % predicted	64.7 $\pm$ 20.3
Exercise data	
Borg score at the end of exercise (0–10)	6.5 $\pm$ 1.5
Peak $\dot{V}_{O_2}$ (mL/min)	817 $\pm$ 256
Peak $\dot{V}_E$ (L/min)	40 $\pm$ 11
Lowest SaO_2 (%)	91 $\pm$ 5
Peak HR, beats/min	125 $\pm$ 18
BDI (0–12)	7.9 $\pm$ 2.6
SGRQ total (0–100)	36.7 $\pm$ 16.3
HADS anxiety (0–21)	3.9 $\pm$ 3.4
HADS depression (0–21)	4.7 $\pm$ 3.7

The numbers in parentheses indicate the theoretical score range.

was 68.8±6.7 years, and the postbronchodilator FEV_1 was 1.21±0.43 L and 45.7±15.9% predicted. The peak dyspnoea during exercise evaluated by the Borg score at the end of progressive cycle ergometry was 6.5±1.5, and the dyspnoea with activities of daily living evaluated by the BDI score was 7.9±2.6. The frequency distributions of the Borg score at the end of exercise and the BDI score in COPD patients are shown in Fig. 1. These histograms showed virtually normal distributions.

Table 2 shows the Spearman's rank correlation coefficients (Rs) between the dyspnoea scores and various clinical variables. The Borg score at the end of exercise was significantly correlated with postbronchodilator FEV_1 ($Rs = -0.27$, $P = 0.0017$), the health status score evaluated by the SGRQ ($Rs = 0.31$, $P = 0.0002$), and the depression score from the HADS ($Rs = 0.19$, $P = 0.026$). In contrast, the BDI score was significantly correlated with pulmonary function from postbronchodilator FEV_1 and TLCO, and the exercise indices of peak $\dot{V}_{O_2}$, peak $\dot{V}_E$, lowest SaO_2 and peak HR ($Rs = 0.22-0.46$, $P<0.05$). The BDI was also moderately correlated with the health status by the SGRQ ($Rs = -0.71$, $P<0.0001$) and with anxiety and depression from the HADS ($Rs = -0.31$, $P = 0.0002$; and $Rs = -0.44$, $P<0.0001$, respectively). These significant relationships of the BDI with other objective and subjective measurements were stronger than those of the peak Borg score, judging from the Spearman's rank correlation coefficients. The relationship between the Borg score and the BDI score was significant but weak ($Rs = -0.33$, $P<0.0001$).

Table 2 Spearman's rank correlation coefficients between the dyspnoea scores and other clinical variables.

	Borg score at the end of exercise	BDI score
Age	—	—
Body mass index	—	—
Postbronchodilator FEV_1	−0.27	0.30
RV/TLC	—	—
TLCO	—	0.34
Exercise data		
Peak $\dot{V}_{O_2}$	—	0.46
Peak $\dot{V}_E$	—	0.30
Lowest SaO_2	—	0.23
Peak HR	—	0.22
SGRQ total	0.31	−0.71
HADS anxiety	—	−0.31
HADS depression	0.19	−0.44

Missing data (—) indicate that there were not statistically significant relationships.

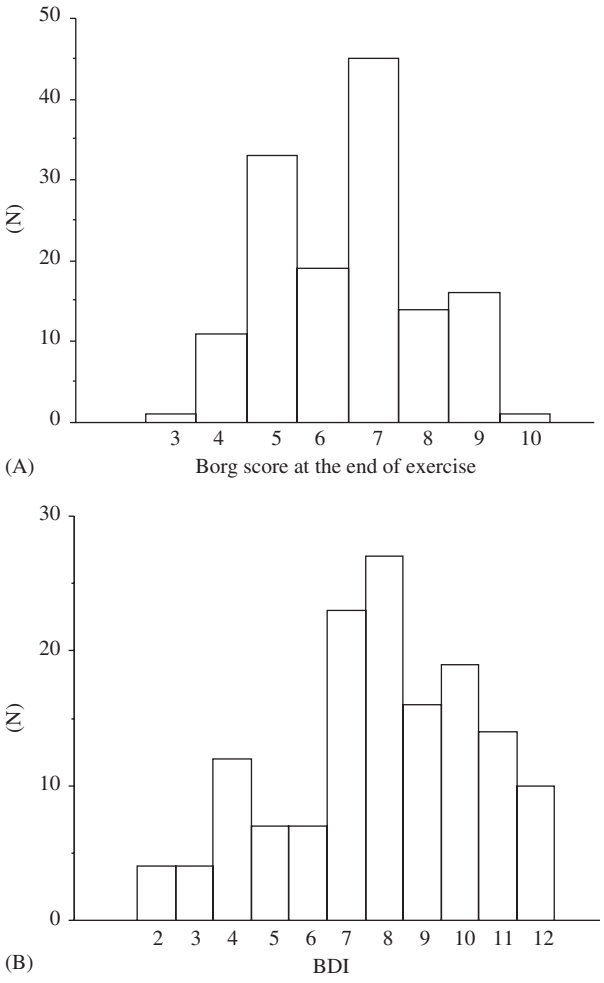

Figure 1 Frequency distributions of the Borg score at the end of exercise (A) and the BDI score (B) in patients with COPD. On the Borg score, lower scores indicate less dyspnoea, and on the BDI score, lower scores indicate more severe dyspnoea.

Table 3 shows the stepwise multiple regression analyses performed to identify those variables that could best predict the dyspnoea scores. Regarding the Borg score at the end of exercise, the SGRQ total score and FEV_1 accounted for 8% and 5% of the variance, respectively. Regarding the BDI, the SGRQ total score significantly accounted for 50% of the variance, and the lowest SaO_2 also accounted for 4% of the variance.

Table 4 shows the results from the univariate Cox proportional hazards model in analyzing the relationship between dyspnoea and the other major clinical measures with mortality in COPD. The Borg score at the end of exercise was not significantly correlated with all causes and COPD-related mortality in COPD ($RR = 1.084$, $P = 0.51$; and $RR = 1.030$, $P = 0.85$, respectively). In comparison, the

BDI score was significantly correlated with all causes and COPD-related mortality (RR = 0.824, $P = 0.0049$; and $RR = 0.792$, $P = 0.0061$, respectively). BMI, FEV_1, RV/total lung capacity (TLC), TLCO, peak $\dot{V}_{O_2}$ and the SGRQ total score had significant correlations with mortality, although the psychological status evaluated by the HADS did not.

Discussion

We found out that the Borg score at the end of progressive cycle ergometry was less significantly correlated with pulmonary function, exercise indices, health status and psychological status than the BDI score. In addition, we demonstrated that although health status and airflow limitation accounted for the Borg score at the end of exercise, their relative contributions were very small. Furthermore, this peak score was not significantly correlated with all causes and COPD-related mortality, which contrasted with the strong and significant relationship of the BDI score with mortality.

As compared to dyspnoea during daily activities, there is still more study required for investigating the properties of peak dyspnoea during exercise. Physicians measure dyspnoea during exercise in COPD in order to identify those patients with more severe exertional dyspnoea (discriminatory purposes), and to investigate the benefits of some interventions (evaluative purposes).[19] The near normal distribution in Fig. 1 shows that the Borg score at the end of exercise has discriminatory power like the BDI. However, regarding its evaluative property, peak dyspnoea during exercise sometimes shows no significant changes after an intervention which is apparently beneficial by other measurements.[13,20–24] By calculating the dyspnoea rating at isotime or expressed over the slopes of time, $\dot{V}_{O_2}$ or $\dot{V}_E$, exertional dyspnoea became an improved outcome.[13,20–22]

The ability to predict mortality (predictive property) is important in COPD,[10,25] in addition to discriminatory and evaluative properties, considering that COPD is ranked high as a cause of death in the world.[26] In the present study, peak dyspnoea on progressive cycle ergometry was not well correlated with mortality in COPD, unlike the BDI. It should be noted that the relationship of dyspnoea with mortality was completely different according

Table 3 Relative contribution of each variable to the dyspnoea scores on the stepwise multiple regression analyses.

	Borg score at the end of exercise	BDI score
Postbronchodilator FEV_1	0.05	—
TLCO		—
Peak $\dot{V}_{O_2}$		—
Peak $\dot{V}_E$		—
Lowest SaO_2		0.04
Peak HR		—
SGRQ total	0.08	0.50
HADS anxiety		—
HADS depression	—	—
Cumulative R^2	0.13	0.54

Missing data (—) indicate that the independent variables were not statistically significant.
All values represent coefficients of determination (R^2).

Table 4 Univariate Cox proportional hazards analyses on the relationship between major clinical measurements and mortality.

	All deaths		COPD deaths	
	Relative risk (95% CI)	*P* value	Relative risk (95% CI)	*P* value
Borg score	1.084 (0.853–1.378)	0.51	1.030 (0.763–1.392)	0.85
BDI	0.824 (0.720–0.943)	0.0049	0.792 (0.670–0.935)	0.0061
BMI (kg/m^2)	0.795 (0.693–0.911)	0.0010	0.786 (0.659–0.939)	0.0078
FEV_1, % predicted	0.944 (0.918–0.970)	<0.0001	0.909 (0.871–0.948)	<0.0001
RV/TLC (%)	1.069 (1.033–1.105)	0.0001	1.092 (1.047–1.139)	<0.0001
TLCO, % predicted	0.948 (0.926–0.972)	<0.0001	0.945 (0.916–0.975)	0.0004
Peak $\dot{V}_{O_2}$ (mL/min)	0.994 (0.992–0.996)	<0.0001	0.994 (0.991–0.996)	<0.0001
SGRQ total	1.032 (1.011–1.054)	0.0024	1.039 (1.013–1.066)	0.0028
HADS anxiety	1.033 (0.933–1.144)	0.53	0.992 (0.867–1.134)	0.90
HADS depression	1.078 (0.984–1.182)	0.11	1.040 (0.923–1.171)	0.52

to the situation measured, such as during exercise versus during daily activities. The predictive property of peak dyspnoea during exercise has not been well investigated thus far. Barreiro et al.[27] recently reported that blunted dyspnoea at the end of exercise was a good predictor of near fatal asthma, and asthma is a disease characterized by airflow limitation and breathlessness, like COPD. However, in COPD, it is difficult to postulate that peak dyspnoea during exercise reflects disease severity from the viewpoint of mortality, unlike asthma.

The peak Borg score on progressive cycle ergometry was less correlated with objective physiological severity as assessed by pulmonary function or exercise indices, unlike the BDI, in Table 2. This explains the stronger relationship of the BDI with mortality, because these physiological measures have been reported to be factors responsible for predictable mortality.[7,10,28] Furthermore, the relationship between the peak Borg score and subjective measures of health status and psychological disturbances was also weak in the present study, which contrasted with the results for the BDI. Dyspnoea is a subjective experience of breathing discomfort caused due to physiological and psychological interrelationships. In this sense, dyspnoea during daily activities is a more appropriate measurement for evaluating systemic individual impairment due to COPD.

These relationships between breathlessness and clinical measurements were analyzed further by multiple regression analyses. Although health status and lowest oxygen level during exercise explained 54% of the BDI score, health status and airflow limitation contributed to only 13% of the Borg score at the end of exercise. Although the exercise limitations of COPD are diverse, and dyspnoea is the main cause, limitations due to dyspnoea are not universal, and over- or underrating in individual patients can be a confounding issue.[29] This is one reason why that type of multiple regression analysis in the present study was not significant with regard to peak dyspnoea during exercise.

When the present study started, peak values were the primary outcome for dyspnoea ratings during exercise. However, as we explained, their predictive and evaluative properties were worse, and it still remains uncertain what they evaluate. The current statement[30] says that there is more information available if a range of continuum of perceptual responses is examined. Therefore, in addition to peak values, dyspnoea rating at each minute or work is also necessary in assessing dyspnoea during exercise.

In conclusion, we demonstrated that the relationships between clinical dyspnoea measures with activities of daily living and objective and subjective measurements in COPD were stronger than those of dyspnoea at the end of progressive cycle ergometry. In addition, this tendency held true for the relationship between dyspnoea measurements and mortality. Although both dyspnoea measurements are used as an outcome for exertional breathlessness in patients with COPD, dyspnoea during daily activities is considered to evaluate the disease severity of COPD better than peak dyspnoea during exercise.

References

1. American Thoracic Society. Dyspnea: mechanisms, assessment, and management; a consensus statement. *Am J Respir Crit Care Med* 1999;**159**:321–40.
2. Zuwallack RL, Haggerty MC, Jones P. Clinically meaningful outcomes in patients with chronic obstructive pulmonary disease. *Am J Med* 2004;**117**:49S–59S.
3. Mahler DA, Harver A. A factor analysis of dyspnea ratings, respiratory muscle strength, and lung function in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992;**145**:467–70.
4. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Analysis of clinical methods used to evaluate dyspnea in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**158**:1185–9.
5. Nguyen HQ, Altinger J, Carrieri-Kohlman V, Gormley JM, Stulbarg MS. Factor analysis of laboratory and clinical measurements of dyspnea in patients with chronic obstructive pulmonary disease. *J Pain Symptom Manage* 2003;**25**:118–27.
6. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002;**121**:1434–40.
7. 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.
8. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;**23**:932–46.
9. O'Donnell DE, Aaron S, Bourbeau J, et al. Canadian thoracic society recommendations for management of chronic obstructive pulmonary disease—2003. *Can Respir J* 2003;**10**:11A–65A.
10. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease. Role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003;**167**:544–9.
11. Medical Section of the American Lung Association. Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med* 1994;**152**:1107–36.
12. Japan Society of Chest Diseases. The predicted values of pulmonary function testing in Japanese. *Jpn J Thoracic Dis* 1993;**31** Appendix [in Japanese].
13. Oga T, Nishimura K, Tsukino M, Hajiro T, Ikeda A, Izumi T. The effects of oxitropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease.

A comparison of three different exercise tests. *Am J Respir Crit Care Med* 2000;**161**:1897–901.
14. Borg GAV. Psychophysical basis of perceived exertion. *Med Sci Sports Exercise* 1982;**14**:377–81.
15. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea: contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984;**85**:751–8.
16. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;**145**:1321–7.
17. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Comparison of discriminative properties among disease-specific questionnaires for measuring health-related quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**: 785–90.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.
19. Mahler DA, Guyatt GH, Jones PW. Clinical measurement of dyspnea. In: Mahler DA, editor. Dyspnea. New York: Marcel Dekker, 1997. pp. 149–198.
20. O'Donnell DE, Fluge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;**23**:832–40.
21. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**158**:1557–65.
22. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T, Mishima M. A comparison of the effects of salbutamol and ipratropium bromide on exercise endurance in patients with COPD. *Chest* 2003;**123**:1810–6.
23. Griffiths TL, Burr ML, Campbell IA, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;**355**:362–8.
24. Casaburi R, Kukafka D, Cooper CB, Witek Jr TJ, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest* 2005;**127**:809–17.
25. Oga T, Nishimura K, Tsukino M, et al. Health status measured with the CRQ does not predict mortality in COPD. *Eur Respir J* 2002;**20**:1147–51.
26. World Health Report. World Health Organization, Geneva, 2000.
27. Barreiro E, Gea J, Sanjuas C, Marcos R, Broquetas J, Milic-Emili J. Dyspnoea at rest and at the end of different exercises in patients with near-fatal asthma. *Eur Respir J* 2004;**24**:219–25.
28. Anthonisen NR, Wright EC, Hodgkin JE, the IPPB Trial Group. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;**133**:14–20.
29. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJ. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992;**146**:935–40.
30. American Thoracic Society/American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;**167**:211–77.