

The Effects of Oxitropium Bromide on Exercise Performance in Patients with Stable Chronic Obstructive Pulmonary Disease

A Comparison of Three Different Exercise Tests

TORU OGA, KOICHI NISHIMURA, MITSUHIRO TSUKINO, TAKASHI HAJIRO, AKIHIKO IKEDA, and TAKATERU IZUMI

Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

The purpose of the present study was to compare the characteristics of three different exercise tests in evaluating the effects of oxitropium bromide on exercise performance. Thirty-eight males with stable chronic obstructive pulmonary disease (COPD) ($FEV_1 = 40.8 \pm 16.5\%$ predicted; mean \pm SD) completed randomized, double-blind, placebo-controlled, crossover studies for each exercise test. The exercise tests were performed 60 min after the inhalation of either oxitropium bromide 400 μ g or placebo. The patients performed 6-min walking tests (6MWT) on Days 1 and 2, progressive cycle ergometry (PCE) on Days 3 and 4, and cycle endurance tests at 80% of the maximal workload of PCE on Days 5 and 6. Spirometry was conducted before and at 45 and 90 min after the inhalation. Oxitropium bromide significantly increased FEV_1 as compared with placebo. Oxitropium bromide increased the endurance time significantly, by 19% ($p < 0.001$), and caused a small but significant increase in the 6-min walking distance by 1% ($p < 0.05$), but induced no significant increase in maximal oxygen consumption ($\dot{V}O_{2max}$) in PCE. The responses in these three exercise tests were different, and we conclude that the endurance test was the most sensitive in detecting the effects of inhaled anticholinergic agents on exercise performance in patients with stable COPD. An endurance procedure may be performed to detect clinical changes in evaluating the effects of oxitropium bromide on exercise performance.

Patients with chronic obstructive pulmonary disease (COPD) complain of exertional breathlessness and exercise intolerance, mainly due to reduced ventilatory capacity and impaired gas exchange. Inhaled anticholinergic agents are recommended as the first-line drugs to relieve these patients' symptoms and to improve their airflow limitation (1, 2). Although the bronchodilating effects of these drugs in COPD have been established (3, 4), there is sometimes controversy about whether anticholinergic agents affect exercise performance (5–10).

The effects of anticholinergic bronchodilators may depend on the type of exercise test performed. In investigating the effects of bronchodilators on exercise performance in patients with COPD, a walking test and progressive cycle ergometry (PCE) are often used (5–10). However, in assessing the effects of pulmonary rehabilitation, endurance tests are sometimes used because measures of endurance may be responsive to training. An effective pulmonary rehabilitation program usually results in an improvement in exercise endurance, but little or no change in maximal exercise capacity (11). Recently, O'Donnell and coworkers reported that after bronchodilator therapy, exercise time was a reliable measure of exercise en-

durance, being reproducible and responsive to changes in severe COPD (12).

There is no consensus about which measurement should be used in the clinical evaluation of exercise performance in patients with COPD. In the present study we applied an endurance test in addition to a walking test and PCE to patients with stable COPD. We hypothesized that the endurance test would be the most sensitive test for detecting the effects of oxitropium bromide on exercise performance, as previously reported in the field of pulmonary rehabilitation (11). The purpose of the present study was to compare the characteristics of three different exercise tests in evaluating the effects of oxitropium bromide on exercise performance in patients with COPD.

METHODS

Patients

Forty-two consecutive male patients with clinically stable COPD as defined by the American Thoracic Society (ATS) were recruited between November 1995 and September 1998 (1). The entry criteria for the study were: (1) age over 45 yr; (2) a history of cigarette smoking of more than 20 pack-years; (3) chest radiographs showing hyperinflation; (4) an FEV_1 of less than 80% of the predicted value; and (5) a best postbronchodilator FEV_1 -to-vital capacity (VC) ratio of less than 0.7. Reasons for exclusion included: (1) an exacerbation of airflow limitation within the preceding 3 mo; (2) a history of asthma; (3) other diseases likely to affect exercise; and (4) hypoxemia, defined as a Pa_{O_2} of less than 60 mm Hg at rest. None of the patients had taken oral or inhaled corticosteroids during the 4 wk preceding the study. Before the study, each subject had practiced how to use a metered dose inhaler (MDI) with a spacer device. Written informed consent was obtained from all patients prior to initiation of the study.

All patients underwent baseline pulmonary function testing and had an electrocardiogram (ECG) at least 12 h after administration of the bronchodilator used in the study. In accordance with the method recommended by the ATS, the spirometric testing for determining FEV_1 and FVC was done with a spirometer (Autospiro AS-600; Minato Medical Science Co. Ltd., Osaka, Japan) that was calibrated with a 3.0-L syringe before every measurement (13). The largest FEV_1 and largest FVC from three maneuvers were analyzed. The residual volume (RV) was measured with the closed-circuit helium method, and the diffusing capacity of carbon monoxide (D_{LCO}) was measured with the single-breath technique (Chestac-65V; Chest, Tokyo, Japan). The predicted values for the pulmonary function indices were those proposed by the Japan Society of Chest Diseases (14).

Exercise Tests

During the initial screening, the patients had undergone 6-min walking tests (6MWTs) and PCE on at least two occasions. Before entering the trial, patients were familiarized with the Borg scale (0 to 10) for evaluating their symptoms of breathlessness at rest and at the end of exercise (15).

The 6MWTs were performed in a hospital corridor 50 m long (16). No encouragement was given during the walk. In advance of the practice walk, we emphasized to the patients that the aim of the test was to walk as far as they could in 6 min, and that they would not be encouraged during the walk. Arterial oxygen saturation (Sa_{O_2}) and heart

(Received in original form May 13, 1999 and in revised form October 5, 1999)

Correspondence and requests for reprints should be addressed to Toru Oga, M.D., Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 53, Kawahara, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan.

Am J Respir Crit Care Med Vol 161, pp 1897–1901, 2000
Internet address: www.atsjournals.org

rate (HR) were monitored through pulse oximetry (N-200 pulse oximeter; Nellcor Inc, Hayward, CA). The Borg scores were recorded at rest and immediately after walking cessation. The distance the patients covered was measured as the 6-min walking distance (6MWD). The minimal Sa_{O_2} ($\text{Sa}_{\text{O}_2\text{min}}$) and the maximal HR (HRmax) reached during the 6MWT were also recorded.

The symptom-limited progressive exercise tests were performed on a calibrated, electrically-braked cycle ergometer (Corival WLP-400; Lode, Groningen, The Netherlands). A face mask connected to a low-resistance unidirectional valve (Rudolph Face Mask for Exercise Testing; Hans Rudolph Inc., Kansas City, MO) was placed on the patient's face without leakage. After unloaded pedaling for 3 min, the workload was increased automatically by increments of 1 W every 3 s until the patient could no longer continue the required cadence of 40 cycles per minute because of severe dyspnea or exhaustion. The exercise data were recorded with an automated exercise testing system (Desktop Diagnostics/CPX; Medical Graphics Corporation, St. Paul, MN) that converts breath-by-breath analog input to digital form in an on-line fashion. Minute ventilation (\dot{V}_E) and oxygen and carbon dioxide tension in the expired air were determined every eight breaths, and the mean \dot{V}_E , oxygen consumption (\dot{V}_{O_2}) and carbon dioxide production (\dot{V}_{CO_2}) were then calculated rapidly. The gas analyzer was calibrated just before the study with air and with a standard reference gas mixture (15% oxygen, 5% carbon dioxide). Sa_{O_2} was measured through pulse oximetry (N-200 pulse oximeter), and HR was recorded electrocardiographically (Life Scope 8; Nihon Koden Co., Tokyo, Japan). At rest and at the end of each exercise, symptoms of breathlessness were scored with the Borg scale. None of the tests was stopped by the physician unless untoward clinical signs or electrocardiographic changes suggestive of significant myocardial ischemia were recognized. The analysis of the expired gas and the monitoring of Sa_{O_2} and HR were continued for 3 min after the stopping of exercise. Maximal work rate (Wmax) was defined as the highest work level that was reached. Similarly, maximal \dot{V}_{O_2} ($\dot{V}_{\text{O}_2\text{max}}$) and maximal \dot{V}_E ($\dot{V}_{E\text{max}}$) were the endpoint levels reached during exercise.

The endurance tests were performed on the cycle ergometer at 80% of the maximal work rate in the PCE tests. After 3 min of unloaded pedaling, the power output increased to the work-rate level. The patients continued cycling at the constant submaximal workload until the test was stopped according to the same criteria as used in the symptom-limited progressive exercise tests, and the endurance time was measured. The Borg scores were also recorded as in the progressive cycle tests.

Study Design

The eligible patients performed the three types of exercise tests at the Kyoto University Hospital on six separate days within a period of 2 wk. They were requested to stop taking theophylline preparations and oral β_2 -stimulants for more than 48 h, and inhaled bronchodilators for at least 12 h before starting each test. The 6MWTs were performed on Days 1 and 2, the PCE tests on Days 3 and 4, and the endurance tests on Days 5 and 6. The endurance tests were performed at 80% of the higher maximal workload reached during the PCE tests on Days 3 and 4. The patients performed the exercise tests at 60 min after inhaling 400 μg of oxitropium bromide or an identical placebo in a randomized, double-blind, crossover fashion. The spirometric parameters were assessed before and at 45 and 90 min after the inhalation. Before each spirometric measurement, the patient's pulse rate and blood pressure were measured after at least 5 min of rest.

All patients inhaled either oxitropium bromide (Nippon Boehringer Ingelheim Ltd., Kawanishi, Japan) at a dose of 400 μg (4 puffs) or a matching placebo, from an MDI with a spacer device (InspirEase; Schering-Plough K.K., Osaka, Japan) (17). The spacer attached to the MDI was held in the mouth, and the canister was activated after the patient had exhaled to FRC. Patients inhaled very slowly until TLC was reached, and then held their breath for at least 10 s. To ensure that the study substances were administered correctly, the inhalation technique was carefully observed.

Statistical Analysis

The results of the study are expressed as mean \pm SD unless otherwise stated. Comparisons of the values observed with oxitropium bromide

and placebo were made with a two-tailed paired *t* test. The significance of the differences in the values observed for three exercise tests was determined with a repeated measures analysis of variance. When a significant difference was noted, *post hoc* analysis was done with Fisher's protected least squares difference method to identify where the differences were significant. Comparisons between PCE and endurance test results were made with a two-tailed paired *t* test. The dyspnea ratios were arbitrarily expressed as the ratio of the change in the Borg score (ΔBS) to: (1) the walking distance ($\Delta\text{BS-Distance}$); (2) maximal work rate ($\Delta\text{BS-Wmax}$); (3) change in \dot{V}_{O_2} ($\Delta\text{BS-}\Delta\dot{V}_{\text{O}_2}$); (4) change in \dot{V}_{CO_2} ($\Delta\text{BS-}\Delta\dot{V}_{\text{CO}_2}$); (5) change in \dot{V}_E ($\Delta\text{BS-}\Delta\dot{V}_E$); and (6) endurance time ($\Delta\text{BS-Time}$) (12, 18). Wilcoxon's signed ranks tests were used to compare the dyspnea ratios observed with oxitropium bromide and placebo. Spearman's rank correlation tests were performed for analyzing the correlations between the dyspnea ratios and between their changes after oxitropium bromide. A value of $p < 0.05$ was considered statistically significant for all analyses.

RESULTS

Subjects

Of the 42 patients enrolled, 38 completed the study. Their clinical backgrounds and the results of their baseline pulmonary function tests are presented in Table 1. The patients had moderate to severe airflow limitation, moderate hyperinflation, and reduced diffusing capacity. Four patients dropped out of the study during cycle tests. Respiratory exacerbations were the reason for the withdrawal of two of the patients. One patient had left knee pain, and one patient had uncontrolled atrial fibrillation.

Resting Physiologic Variables

The resting spirometric measurements, dyspnea, and Sa_{O_2} did not differ among the three exercise tests. FEV_1 and FVC at 45 min after placebo were 1.12 ± 0.42 L (mean \pm SD) and 2.34 ± 0.63 L, respectively, for the walking test, 1.12 ± 0.42 L and 2.37 ± 0.66 L, respectively, in PCE, and 1.12 ± 0.46 L and 2.35 ± 0.68 L, respectively, in the endurance test. The resting Borg score and Sa_{O_2} for each of the three types of tests were 0.8 ± 0.8 and $96 \pm 1\%$, 0.6 ± 0.4 and $96 \pm 2\%$, and 0.6 ± 0.5 and $96 \pm 2\%$, respectively.

Oxitropium bromide produced significant increases in FEV_1 and FVC at 45 min. The differences in FEV_1 and FVC at 45 min were 0.15 ± 0.16 L and 0.24 ± 0.30 L, respectively, with oxitropium bromide and placebo ($p < 0.001$ and $p < 0.001$, respec-

TABLE 1
CHARACTERISTICS OF THE 38 MALE PATIENTS WITH
STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE
WHO COMPLETED THIS STUDY

	Mean \pm SD	Range
Age, yr	69.0 \pm 6.6	47–80
Smoking, pack-years	55.4 \pm 26.0	20–112
FEV_1 , L	1.09 \pm 0.45	0.32–1.94
FEV_1 , % predicted	40.8 \pm 16.5	13.6–75.4
FVC, L	2.72 \pm 0.69	1.51–4.36
FVC, % predicted	79.2 \pm 17.9	43.6–122.2
FEV_1/FVC , %	39.3 \pm 10.7	15.4–61.3
TLC, L	5.99 \pm 1.05	3.97–8.69
TLC, % predicted	110.5 \pm 17.1	73.9–143.5
RV/TLC, %	51.1 \pm 10.3	32.3–75.3
D_{LCO} ml/min/mm Hg	15.19 \pm 4.99	8.72–30.17
D_{LCO} , % predicted	62.7 \pm 21.3	36.0–130.9
$\text{D}_{\text{LCO}}/\text{VA}$, ml/min/L/mm Hg	3.19 \pm 1.39	1.49–7.94
Resting Pa_{O_2} , mm Hg	76.4 \pm 7.8	60.4–92.0
Resting Pa_{CO_2} , mm Hg	42.7 \pm 4.9	31.9–53.0

Definition of abbreviations: D_{LCO} = diffusing capacity of carbon monoxide; VA = alveolar volume.

TABLE 2
PEAK PHYSIOLOGIC VARIABLES AFTER PLACEBO IN THREE EXERCISE TESTS IN 38 PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	6MWT	PCE	Endurance
Peak dyspnea, Borg	3.3 ± 1.8	5.5 ± 1.3 [†]	6.2 ± 1.5 [†]
Sa _O ₂ min, %	88 ± 7	90 ± 5	90 ± 4
HRmax, beats/min	112 ± 20	119 ± 19	125 ± 17 [†]
6-min walking distance, m	490 ± 67	—	—
Wmax, W	—	87 ± 25	—
ṀO ₂ max, ml/min	—	829 ± 239	875 ± 266 [¶]
ṀCO ₂ max, ml/min	—	943 ± 332	1,017 ± 357 [§]
ṀV _E max, L/min	—	39 ± 11	43 ± 13 [§]
Endurance time, s	—	—	189 ± 92

Definition of abbreviations: HRmax = maximum heart rate; 6MWT = 6-min walking test; PCE = progressive cycle ergometry; Sa_O₂min = minimal arterial oxygen saturation; ṀCO₂max = maximal carbon dioxide production; ṀV_Emax = maximal minute ventilation; ṀO₂max = maximal oxygen consumption; Wmax = maximal work rate.

* All values are expressed as mean ± SD.

[†] p < 0.001, significantly different from 6MWT.

[‡] p < 0.01, significantly different from 6MWT.

[§] p < 0.001, significantly different from PCE.

[¶] p < 0.01, significantly different from PCE.

tively) in the walking test; 0.12 ± 0.12 L and 0.14 ± 0.29 L, respectively (p < 0.001 and p = 0.007, respectively), in PCE; and 0.15 ± 0.12 L and 0.20 ± 0.34 L, respectively (p < 0.001 and p < 0.001, respectively), in the endurance test. However, oxitropium bromide induced no significant changes in resting dyspnea or Sa_O₂.

Peak Physiologic Variables

The peak physiologic variables in the three exercise tests after inhalation of placebo are shown in Table 2. The peak Borg score and HRmax during the exercise tests were highest in the cycle endurance test and lowest on the walking test, although Sa_O₂min during exercise did not differ among the three tests. ṀO₂max, ṀCO₂max, and ṀV_Emax were significantly higher in the endurance test than in PCE.

The changes in the peak physiologic variables after oxitropium bromide are shown in Table 3. Of the measures for exercise performance, the endurance time improved the most significantly after oxitropim bromide from 189 ± 92 s to 223 ±

TABLE 3

CHANGES IN PEAK PHYSIOLOGIC VARIABLES AFTER OXITROPIUM BROMIDE IN THREE EXERCISE TESTS IN 38 PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	6MWT	PCE	Endurance
ΔPeak dyspnea, Borg	-0.3 ± 1.2	0.2 ± 0.6 [§]	0.0 ± 0.9
ΔSa _O ₂ min, %	1 ± 3	1 ± 4	-1 ± 4
ΔHRmax, beats/min	-2 ± 10	2 ± 10	4 ± 8 [¶]
Δ6-minute walking distance, m	6 ± 19 [§]	—	—
ΔWmax, W	—	3 ± 8 [‡]	—
ΔṀO ₂ max, ml/min	—	20 ± 76	23 ± 78
ΔṀCO ₂ max, ml/min	—	51 ± 98 [†]	54 ± 119 [†]
ΔṀV _E max, L/min	—	2 ± 4 [‡]	2 ± 5 [‡]
ΔEndurance time, s	—	—	34 ± 53 [†]

Definition of abbreviations: ΔEndurance time = change in endurance time; ΔHRmax = change in maximum heart rate; Δ6MWT = change in 6-min walking test; ΔPCE = change in progressive cycle ergometric capacity; ΔPeak dyspnea, Borg = change in peak dyspnea according to the Borg scale; ΔSa_O₂min = change in minimal arterial oxygen saturation; ΔṀCO₂max = change in maximal carbon dioxide production; ΔṀV_Emax = change in maximal minute ventilation; ΔṀO₂max = change in maximal oxygen consumption; ΔWmax = change in maximal work rate.

* All values are expressed as mean ± SD.

[†] p < 0.001, significant change from placebo.

[‡] p < 0.01, significant change from placebo.

[§] p < 0.05, significant change from placebo.

[¶] p < 0.01, significantly different from 6MWT.

123 s, or by 34 ± 53 s (p < 0.001). The 6MWD increased significantly, to 497 ± 69 m, or by 6 ± 19 m (p = 0.048). Oxitropium bromide did not change ṀO₂max significantly during PCE or in the endurance test, although it produced significant increases in Wmax, ṀCO₂max, and ṀV_Emax. There were significant increases in peak dyspnea during PCE (p = 0.044), and in HRmax in the endurance test (p = 0.001).

The percent changes in the measures for exercise performance after oxitropium bromide in the three exercise tests are shown in Figure 1. The endurance time showed the most striking improvement, by 19%, among the exercise performance indices. The 6MWD improved a little, but significantly, by 1%. ṀO₂max increased by 3% in both PCE and in the endurance test, but the increase was not significant.

Dyspnea Ratios

Oxitropium bromide significantly reduced ΔBS-Time in the endurance test, from 0.035 ± 0.015 BS/s to 0.030 ± 0.013 (p = 0.003), and ΔBS-Distance in the walking test, from 0.0053 ± 0.0033 BS/m to 0.0047 ± 0.0036 (p = 0.037). Oxitropium bromide also changed ΔBS-ΔṀO₂ in PCE from 0.018 ± 0.021 BS/ml/min to 0.017 ± 0.018 BS/ml/min, but this was not a significant change. ΔBS-Wmax, ΔBS-ΔṀCO₂, and ΔBS-ΔṀV_E during PCE were also not significantly changed after oxitropium bromide.

There were significant correlations between ΔBS-Distance and ΔBS-ΔṀO₂ in PCE (r = 0.62, p < 0.001), as well as between ΔBS-ΔṀO₂ and ΔBS-Time (r = 0.55, p < 0.001) and between ΔBS-Time and ΔBS-Distance (r = 0.54, p = 0.001) in PCE after placebo. The change in ΔBS-Time after oxitropium bromide was not correlated with the change in ΔBS-Distance (r = -0.02, p = 0.92), although these two dyspnea ratios were both significantly reduced by oxitropium bromide.

DISCUSSION

This study showed that oxitropium bromide in a dose of 400 μg administered via an MDI brought about a large increase in cycle endurance time and a small but significant increase in 6MWD, but no significant changes in ṀO₂max in PCE. We showed that the effects of oxitropium bromide on exercise performance in patients with stable COPD could be determined differentially by the type of exercise test.

The endurance time showed the largest increase among the three exercise tests after oxitropium bromide. Endurance tests

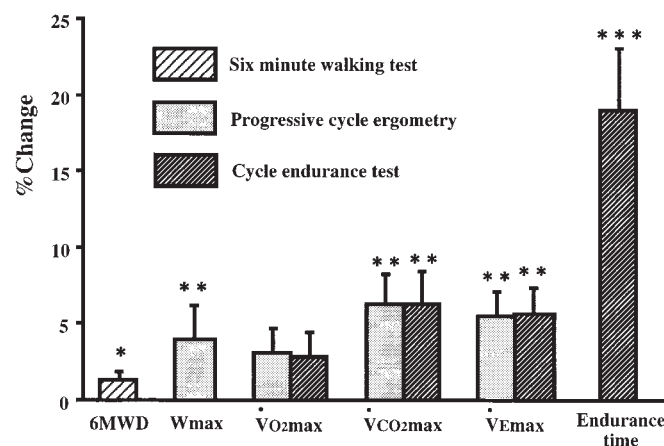


Figure 1. Changes in various measures of exercise performance after oxitropium bromide in three exercise tests. Changes are expressed as the percent change from placebo. Values are expressed as mean ± SE. *p < 0.05, **p < 0.01, ***p < 0.001 versus placebo.

measured the ability to sustain a submaximal exercise capacity, which could characteristically improve when there was no significant increase in maximal exercise capacity. O'Donnell and coworkers also reported the reliability of exercise endurance as being both reproducible and responsive to change (12). In the present study, $\dot{V}_{O_2\max}$ was an insensitive measure for improvement in a symptom-limited exercise test. In addition, Ikeda and coworkers reported that a dose of at least four times the standard dose of ipratropium bromide was necessary to improve the maximal cycle exercise capacity (19). Moreover, in the present study, the patients were more affected by reduced ventilatory capacity in PCE than in the endurance test. Therefore, it might be insufficient to measure the maximal exercise capacity in the incremental test in patients with COPD. In the 6MWT, patients sustained their steady state just below the maximum exercise capacity that they could reach within 6 min (20). Thus, the 6MWT would assess a mixture of endurance and maximal exercise capacity, although no physiologic data were obtained in the present study. Therefore, it is consistent that there was a small but significant improvement in the 6MWD when there was a large improvement in the endurance time and no significant increase in the maximal exercise capacity. The percent increase in the walking distance was small, partly because the patients' habitual walking speed prevented them from showing the maximal beneficial effect (20).

Endurance exercise tests had some other advantages besides being sensitive to changes in exercise performance after oxitropium bromide. In the present study, the endurance test imposed a greater load on the patients with respect to ventilation and circulation, which had been preserved by the exercise limitation of breathlessness in exercise performance tests in patients with COPD in a previous study (21). Our patients got closest to their true maximal exercise level in the endurance test. Furthermore, considering that the activities of daily living of patients with COPD are submaximal, measuring the submaximal exercise capacity might be more meaningful than measuring the maximal exercise capacity. This will be one of the reasons why endurance procedures are used more often in pulmonary rehabilitation.

Breathlessness is the symptom that most commonly limits exercise in patients with COPD, and this symptom should therefore be regarded as an important outcome measure when evaluating the effects of interventions. We compared dyspnea ratios with placebo and oxitropium bromide, because peak Borg scores were often similar before and after the intervention, and were not appropriate in evaluating dyspneic symptom responses to therapy (12). Oxitropium bromide significantly reduced Δ BS-Distance and Δ BS-Time, although it did not change any dyspnea ratios significantly in PCE. These reductions in exertional dyspnea may have been related to the improvements observed in exercise capacity. The baseline dyspnea ratios were significantly correlated with each other in three exercise tests. There was no significant relationship between the changes in Δ BS-Distance and Δ BS-Time, which were both significantly reduced by oxitropium bromide. Changes in breathlessness after oxitropium bromide were quite different according to the type of exercise test. Oxitropium bromide caused greater ventilation in both PCE and the endurance test, but the patients experienced higher peak dyspnea than with placebo only in PCE. The patients might also have been more susceptible to changes in ventilation in terms of breathlessness during the incremental test.

Some limitations in the present study should be mentioned. First, the order of the three exercise tests was not randomized. However, PCE was designed to be performed before the endurance test, in order to find the appropriate intensity of exer-

cise. Second, the incremental work rate of 1 W every 3 s in the present study might have been higher than in other trials. The progressive work rate has not been standardized for exercise performance tests for patients with pulmonary diseases. In our previous studies (9, 18, 19), this incremental rate was useful in detecting the effects of bronchodilators on exercise performance. $\dot{V}_{O_2\max}$ could be obtained from a ramp cycle exercise test of short duration (22), and a shorter exercise time will clear the reasons for stopping the exercise. We adopted a higher incremental rate for comparison with the endurance test, and to make the best use of the merits of PCE. However, further study will be required for determining an appropriate incremental rate in patients with COPD. Third, with respect to the higher intensity for the endurance test, an appropriate intensity, reported in the literature, has not been established. An ideal exercise performance test would place a greater load on patients during exercise, and a shorter exercise time would prevent a test from being stopped for psychological reasons in patients with COPD. This high intensity was effectively used in other studies (23, 24). Fourth, we evaluated symptoms mainly affected by dyspneic sensation and possible lower-extremity fatigue. However, separate evaluation for leg fatigue might have given us further useful information, since reduced peripheral muscle mass could limit exercise in patients with COPD.

In conclusion, our study showed that the three exercise tests examined had different capabilities in detecting changes produced by inhaled bronchodilators in exercise performance in patients with stable COPD. The endurance time showed the largest increase after oxitropium bromide, and the endurance test was considered to be the most appropriate indicator of effect on exercise performance. When cycle ergometry is performed to examine the effects of some interventions on exercise performance, an endurance procedure should be considered to detect those changes that may not be observed with an incremental test.

Acknowledgment: The authors would like to thank Nicholas R. Anthonisen, M.D., of the University of Manitoba, Winnipeg, Canada, for his helpful advice. They would also like to thank Ms. Kazuyo Haruna and Ms. Yumiko Tomita for conducting the pulmonary function tests, with additional thanks to Nippon Boehringer Ingelheim Ltd., for their kindness in providing the oxitropium bromide and the placebo used in the study.

References

1. Celli, B. R., G. L. Snider, J. Heffner, B. Tiep, I. Ziment, B. Make, S. Braman, G. Olsen, and Y. Phillips. 1995. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 152:S77-S120.
2. Siafakas, N. M., P. Vermeire, N. B. Pride, P. Paoletti, J. Gibson, P. Howard, J. C. Yernault, M. Decramer, T. Higenbottam, D. S. Postma, and J. Rees. 1995. Optimal assessment and management of chronic obstructive pulmonary disease. *Eur. Respir. J.* 8:1398-1420.
3. Braun, S. R., W. N. McKenzie, C. Copeland, L. Knight, and M. Ellersieck. 1989. A comparison of the effect of ipratropium and albuterol in the treatment of chronic obstructive airway disease. *Arch. Intern. Med.* 149:544-547.
4. Baigelman, W., and S. Chodos. 1977. Bronchodilator action of the anticholinergic drug, ipratropium bromide (Sch 1000), as an aerosol in chronic bronchitis and asthma. *Chest* 71:324-328.
5. Leitch, A. G., J. M. Hopkin, D. A. Ellis, S. Merchant, and G. J. R. McHardy. 1978. The effect of aerosol ipratropium bromide and salbutamol on exercise tolerance in chronic bronchitis. *Thorax* 33:711-713.
6. Tobin, M. J., J. A. Hughes, and D. C. Hutchison. 1984. Effects of ipratropium bromide and fenoterol aerosols on exercise tolerance. *Eur. J. Respir. Dis.* 65:441-446.
7. Brown, S. E., R. S. Prager, R. A. Shinto, C. E. Fischer, D. W. Stansbury, and R. W. Light. 1986. Cardiopulmonary responses to exercise in chronic airflow obstruction: effects of inhaled atropine sulfate. *Chest* 89:7-11.
8. Hay, J. G., P. Stone, J. Carter, S. Church, A. Eyre-Brook, M. G. Pearson, A. A. Woodcock, and P. M. A. Calverley. 1992. Bronchodilator re-

- versibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. *Eur. Respir. J.* 5:659-664.
9. Ikeda, A., K. Nishimura, H. Koyama, N. Sugiura, and T. Izumi. 1994. Oxitropium bromide improves exercise performance in patients with COPD. *Chest* 106:1740-1745.
 10. Spence, D. P. S., J. G. Hay, J. Carter, M. G. Pearson, and P. M. A. Calverley. 1993. Oxygen desaturation and breathlessness during corridor walking in chronic obstructive pulmonary disease: effect of oxitropium bromide. *Thorax* 48:1145-1150.
 11. Mahler, D. A. 1998. Pulmonary rehabilitation. *Chest* 113:263S-268S.
 12. O'Donnell, D. E., M. Lam, and K. A. Webb. 1998. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 158:1557-1565.
 13. Medical Section of the American Lung Association. 1994. Standardization of spirometry: 1994 update. *Am. Rev. Respir. Dis.* 152:1107-1136.
 14. Japan Society of Chest Diseases. 1993. The predicted values of pulmonary function testing in Japanese [in Japanese]. *Jpn. J. Thorac. Dis.* 31:Appendix.
 15. Borg, G. A. V. 1982. Psychophysical basis of perceived exertion. *Med. Sci. Sports Exerc.* 14:377-381.
 16. Butland, R. J. A., J. Pang, E. R. Gross, A. A. Woodcock, and D. M. Geddes. 1982. Two-, six-, and 12-minute walking tests in respiratory disease. *B.M.J.* 284:1607-1608.
 17. Tobin, M. J., G. Jenouri, I. Danta, C. Kim, H. Watson, and M. A. Sackner. 1982. Response to bronchodilator drug administration by a new reservoir aerosol delivery system and a review of other auxiliary delivery systems. *Am. Rev. Respir. Dis.* 126:670-675.
 18. Tsukino, M., K. Nishimura, A. Ikeda, T. Hajiro, H. Koyama, and T. Izumi. 1998. Effects of theophylline and ipratropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease. *Thorax* 53:269-273.
 19. Ikeda, A., K. Nishimura, H. Koyama, M. Tsukino, M. Mishima, and T. Izumi. 1996. Dose response study of ipratropium bromide aerosol on maximum exercise performance in stable patients with chronic obstructive pulmonary disease. *Thorax* 51:48-53.
 20. Swinburn, C. R., J. M. Wakefield, and P. W. Jones. 1985. Performance, ventilation, and oxygen consumption in three different types of exercise test in patients with chronic obstructive lung disease. *Thorax* 40: 581-586.
 21. Killian, K. J., P. Leblanc, D. H. Martin, E. Summers, N. L. Jones, and E. J. M. Campbell. 1992. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am. Rev. Respir. Dis.* 146:935-940.
 22. Whipp, B. J., J. A. Davis, F. Torres, and K. A. Wasserman. 1981. A test to determine parameters of aerobic function during exercise. *J. Appl. Physiol.* 47:1131-1135.
 23. Bye, P. T. P., S. D. Anderson, A. J. Woolcock, I. H. Young, and J. A. Alison. 1982. Bicycle endurance performance of patients with interstitial lung disease breathing air and oxygen. *Am. Rev. Respir. Dis.* 126:1005-1012.
 24. Simpson, K., K. Killian, N. McCartney, D. G. Stubbing, and N. L. Jones. 1992. Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. *Thorax* 47:70-75.