

# Dose response study of ipratropium bromide aerosol on maximum exercise performance in stable patients with chronic obstructive pulmonary disease

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## Abstract

**Background** - Although the bronchodilating effect of inhaled anticholinergics has been established in patients with chronic obstructive pulmonary disease (COPD), their effects on exercise capacity are still controversial. Previous studies have suggested that the standard dosage hardly affects exercise tolerance, whereas higher doses might elicit an improvement. The aim of the present study was to determine the dose of ipratropium bromide aerosol that improves exercise performance using progressive cycle ergometry in patients with stable COPD.

**Methods** - Twenty men with stable COPD of mean (SD) age 69.2 (4.6) years and forced expiratory volume in one second (FEV<sub>1</sub>) 1.00 (0.37) l were studied in a randomised double blind manner. Each patient received ipratropium bromide in doses of 240 µg, 160 µg, 80 µg, 40 µg, and placebo from a metered dose inhaler (MDI) with an InspirEase spacer on five separate days. Spirometric parameters were assessed before and at 30, 60, 90, and 120 minutes after each inhalation, and pulse rate and blood pressure were also measured immediately before each spirometric measurement. Symptom limited progressive (20 watts/min) cycle ergometer exercise tests were performed 90 minutes after each inhalation.

**Results** - Ipratropium bromide in doses of 160 µg and 240 µg produced a greater increase in FEV<sub>1</sub> than 40 µg or 80 µg ipratropium bromide at all time points. Doses of 160 µg and 240 µg ipratropium bromide also produced greater increases in maximal work load and maximal oxygen consumption than placebo, whereas 40 µg and 80 µg ipratropium bromide did not. There was a weak correlation between the change in FEV<sub>1</sub> and the change in maximal work load ( $r=0.45$ ). No differences were found in pulse rate or blood pressure between the treatment and placebo groups, and no side effects were noted throughout the study.

**Conclusions** - A dose of at least four times the standard dose of ipratropium bromide from an MDI with a spacer device was necessary to improve maximal cycle exercise capacity in patients with stable

COPD. Although the data from cycle ergometry cannot be directly applied to exercise performed during day to day activities, it is conceivable that the recommended doses of ipratropium bromide do not elicit the optimal clinical benefits.

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Keywords: chronic obstructive pulmonary disease (COPD), ipratropium bromide, exercise capacity.

The goal of treatment of chronic obstructive pulmonary disease (COPD) with bronchodilators is to improve airways obstruction and to improve exercise tolerance. While the dilating effect of inhaled bronchodilators in patients with COPD has been established,<sup>1-5</sup> their effects on exercise capacity are still controversial. To date, several studies have examined the relationship between short term bronchodilator response and exercise capacity,<sup>6-10</sup> but only a few studies have shown that exercise capacity, assessed using cycle ergometry, is improved by an inhaled anticholinergic agent. In each study only a single small dose of an inhaled anticholinergic was evaluated, and the results suggested that the standard dosage hardly affects exercise tolerance whereas higher doses might elicit an improvement.

The purpose of the present study was to determine the dose of ipratropium bromide that produces the maximum improvement in exercise performance, evaluated by progressive cycle ergometry, and also to determine if there is a significant relationship between this improvement in airways obstruction and exercise capacity in patients with COPD.

## Methods

### PATIENTS

Twenty men with clinically stable COPD<sup>11</sup> were recruited from about 200 patients attending the outpatient clinic at the Chest Disease Research Institute, Kyoto University. Entry criteria included age over 55 years, a smoking history, chest radiographs showing hyperinflation, a forced expiratory volume in one second (FEV<sub>1</sub>) of less than 80% of the predicted value, a best post-bronchodilator FEV<sub>1</sub>/forced vital capacity (FVC) of less than 0.7, and the absence of other disorders likely to affect exercise. Those

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with an exacerbation of their pulmonary disease within the last three months, a history of asthma, severe hypoxaemia ( $P_{aO_2}$  less than 8 kPa at rest), or treatment with oral bronchodilators, including theophylline, were excluded. None of the patients had taken oral or inhaled corticosteroids in the preceding three months. All were ex-smokers. In order to familiarise the patients with the testing technique and to confirm that their exercise tolerance was limited by mechanical ventilatory capacity, each subject underwent progressive exercise studies on at least two occasions before entering the trial. Written informed consent was obtained prior to the initiation of the study. The study protocol was approved by the ethics committee of our institute.

#### PULMONARY FUNCTION TESTS

Spirometric tests were performed using the methods described in the American Thoracic Society 1987 update.<sup>12</sup> Three consecutive flow volume curves were recorded with a spirometer (Autospiro AS-600, Minato Medical Science Co Ltd, Osaka, Japan) which was calibrated with a three litre syringe before each day of testing. The highest  $FEV_1$  and FVC from triplicate measurements were analysed.

Baseline pulmonary function tests were performed within the three months preceding the study and at least 12 hours after the administration of bronchodilators had been suspended. In addition to usual spirometric testing (Chestac-65, Chest, Tokyo), maximum voluntary ventilation (MVV) was performed with the patient breathing maximally into a pneumotachograph for 12 seconds, and then multiplied to obtain a per minute value. Functional residual capacity (FRC) was measured by body plethysmography (MBR-600, Nihon Kohden Co, Tokyo, Japan), and residual volume (RV) was calculated as the FRC minus the expiratory reserve volume measured by spirometric testing. Total lung capacity (TLC) was determined as the sum of the vital capacity and RV. Static compliance (Cst) and airways resistance (Raw) were also measured by plethysmography. The transfer factor of the lung for carbon monoxide (TLCO) was measured by the single breath technique (Chestac-65, Chest, Tokyo). The predicted values for the pulmonary function indices were those given by the Japan Society of Chest Diseases.<sup>13</sup>

#### PROGRESSIVE EXERCISE TESTS

An electrically braked cycle ergometer (Corival WLP-400, Lode, Groningen, The Netherlands) was used to increase the exercise workload progressively. After unloaded pedalling for three minutes, the workload was increased automatically at increments of one watt every three seconds to the limit of tolerance. Patients maintained a pedalling frequency above 40 cycles per minute throughout the test. A face mask connected to a low resistance unidirectional valve (Rudolph Face Mask Exercise Testing, Hans Rudolph Inc, Kansas City, USA) was placed on the patient's face without leak-

age. Exercise data were recorded using an automated exercise testing system (Desktop Diagnostics/CPX, Medical Graphic Corporation, St Paul, USA) which converts breath-by-breath analog input to digital form in an on-line fashion. The testing system included a pneumotachograph with a gas analyser module and a personal computer interfaced to the measuring instrument. Minute ventilation ( $\dot{V}E$ ) and oxygen and carbon dioxide tensions in the expired air were determined every eight breaths, and from these measurements the mean  $\dot{V}E$ , oxygen uptake ( $\dot{V}O_2$ ), and carbon dioxide production ( $\dot{V}CO_2$ ) were rapidly calculated. Routine volume calibration was accomplished with a three litre syringe. A gas analyser was calibrated just before the study with air and a standard reference gas mixture (15% oxygen, 5% carbon dioxide). Arterial oxygen saturation ( $SaO_2$ ) was measured by pulse oximetry (N-200 pulse oximeter, Nellcor Inc, Hayward, USA), and heart rate (HR) and waveform were measured by electrocardiography (Life Scope 8, Nihon Kodens Co, Tokyo, Japan). At the end of each exercise test symptoms of leg effort and breathlessness were scored with the Borg scale (0 to 10), which was presented within easy vision of the subject. None of the tests was terminated by the attending physician because of untoward clinical signs or electrocardiographic changes suggestive of significant myocardial ischaemia. Analysis of the expired gas and monitoring of  $SaO_2$  and HR continued for three minutes after stopping the exercise. Maximal work rate ( $W_{max}$ ) was defined as the highest work level that was reached. Similarly, maximal HR,  $\dot{V}O_{2max}$ , and  $\dot{V}E$  ( $\dot{V}E_{max}$ ) were the end point levels reached during the exercise. All the exercise tests were performed by the same doctor (HK) who was blinded to the results of the spirometric tests.

#### STUDY DESIGN

The present study, conducted between September 1992 and October 1993, was performed in a randomised, double blind, placebo controlled crossover fashion at about the same time on five separate days within a two week period (the interval between testing ranged from two to four days). The patients were requested to stop taking inhaled bronchodilators for at least 12 hours before entering the study.

All of the patients received ipratropium bromide (20  $\mu$ g/puff) in doses of 240  $\mu$ g, 160  $\mu$ g, 80  $\mu$ g, 40  $\mu$ g, and placebo from a metered dose inhaler (MDI) with a spacer device, InspirEase (Schering-Plough, Japan).<sup>14</sup> The drug doses were given in random order. The spacer attached MDI was held in the mouth and, after the patient had exhaled to functional residual capacity, the canister was activated. Patients inhaled very slowly until total lung capacity was reached, and then the breath was held for at least ten seconds. To ensure that the drugs were administered always in the same way, the inhalation technique was carefully observed by the same doctor (AI) who

Table 1 Clinical data of the 20 patients entered in the study

	Mean (SD)	Range
Age	69.2 (4.6)	61-76
Smoking (pack years)	69.8 (31.6)	20-165
VC (% predicted)	85.1 (15.9)	54.2-111.7
FEV <sub>1</sub> (l)	1.00 (0.34)	0.43-1.88
FEV <sub>1</sub> (% predicted)	40.5 (13.7)	19.5-78.0
FEV <sub>1</sub> /FVC (%)	43.2 (9.6)	21.7-62.4
TLC (% predicted)*	126.9 (21.1)	71.3-134.8
RV/TLC (%)*	48.0 (10.3)	31.1-71.8
TLco (% predicted)	62.7 (13.8)	48.0-110.1
Kco (mmol/min/l/kPa)	1.11 (0.35)	0.84-2.38
MVV (% predicted)	50.8 (17.0)	17.7-56.4
Cst (l/kPa)†	3.57 (2.55)	1.02-12.2
Raw (kPa/l/s)*	0.55 (0.13)	0.36-0.84
PaO <sub>2</sub> (kPa)	10.6 (0.8)	9.0-12.4
Paco <sub>2</sub> (kPa)	5.6 (0.4)	4.6-6.4

VC=vital capacity; FEV<sub>1</sub>=forced expiratory volume in one second; FVC=forced vital capacity; TLC=total lung capacity; RV=residual volume; TLco=carbon monoxide transfer factor; Kco=carbon monoxide transfer coefficient; MVV=maximum voluntary ventilation; Cst=static compliance; Raw=airways resistance; PaO<sub>2</sub>, Paco<sub>2</sub>=arterial oxygen and carbon dioxide tensions.

\*Not measured in two patients because of severe airways limitation.

†Not measured in four patients because of severe airways limitation.

also carefully observed all of the spirometric measurements.

Spirometric parameters were assessed before and at 30, 60, 90, and 120 minutes after the inhalation. Before each spirometric measurement, pulse rate and blood pressure were measured after at least five minutes of rest. After obtaining the spirometric measurement at 90 minutes, symptom limited progressive cycle ergometry was performed. The patients were asked to note any side effects at each time period.

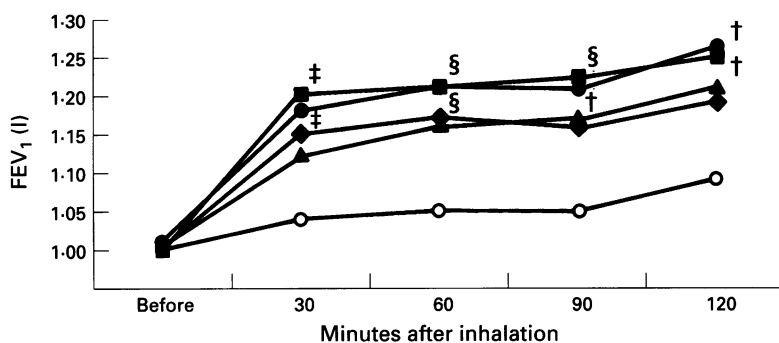


Figure 1 Time-response curve of forced expiratory volume in one second (FEV<sub>1</sub>) after inhalation of ipratropium bromide in doses of 40 µg (◆), 80 µg (▲), 160 µg (●), and 240 µg (■). FEV<sub>1</sub> was significantly greater than in the placebo group (○) at all time points ( $p < 0.01$ ). †  $v$  40 µg  $p < 0.05$ ; ‡  $v$  80 µg  $p < 0.05$ ; §  $v$  40 and 80 µg ( $p < 0.05$ ).

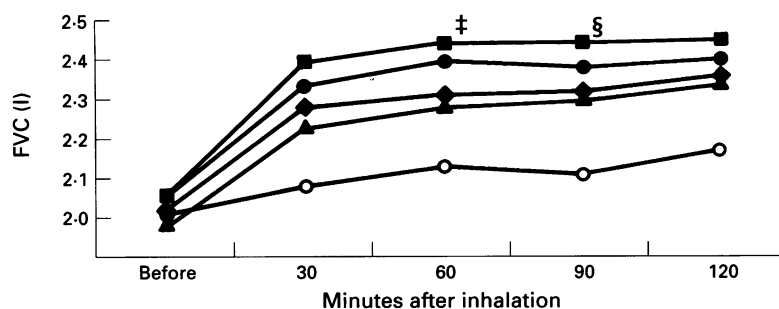


Figure 2 Time-response curve of forced vital capacity (FVC) value after inhalation of ipratropium bromide in doses of 40 µg (◆), 80 µg (▲), 160 µg (●), and 240 µg (■). FVC was significantly greater than in the placebo group (○) at all time points ( $p < 0.01$ ). ‡  $v$  80 µg ( $p < 0.05$ ), §  $v$  40 and 80 µg ( $p < 0.05$ ).

## STATISTICAL ANALYSIS

All data are expressed as mean (SD). The significance of differences among values observed for the five treatment groups was determined by repeated measures analysis of variance. When a significant difference existed among groups, a two tailed paired  $t$  test was used to identify where differences were significant. The relationship between two sets of data was analysed by Pearson's correlation coefficient. A  $p$  value of less than 0.05 (two tailed) was considered significant for all tests.

## Results

All 20 patients completed the entire study. On average, patients had spirometric evidence of moderate to severe airways obstruction and were mildly hypoxaemic when breathing room air (table 1).

There were no differences in FEV<sub>1</sub> and FVC before inhalation in the treatment groups. At 90 minutes, treatment with 160 or 240 µg ipratropium bromide produced greater improvements in FEV<sub>1</sub> than 40 or 80 µg ipratropium bromide (fig 1). No differences were observed between 160 and 240 µg ipratropium bromide, or between 40 and 80 µg ipratropium bromide. Nearly the same results were obtained for FVC values, but differences among the results at 40, 80, and 160 µg ipratropium bromide did not reach significance (fig 2).

The mean Wmax in the second exercise test before entering the study was 85.0 (20.6) watts, and no significant difference was found between this value and the placebo test during the study. This difference did not change significantly as the placebo test came later in the series of the study. Thus, the reproducibility of the exercise tests was considered to be good. Furthermore, because the order of the different drug doses was randomised, the effects of learning, training, or motivation were considered to be negligible.

At rest, no significant differences were observed in indices such as VO<sub>2</sub>, VE, respiratory rate, or heart rate among the five treatment groups. At maximum exercise, treatment with 160 or 240 µg ipratropium bromide produced significantly greater increases in Wmax, VO<sub>2</sub>max, and VEmax than the placebo, whereas treatment with 40 or 80 µg ipratropium bromide did not (table 2). The values of VEmax were obtained at approximately Wmax for each individual, and the ratio of VEmax/MVV was more than 1.0 in each group. No differences were observed in mean maximal heart rates, which were approximately 75% of the predicted values. Dyspnoea on the Borg scale at the end of exercise and SaO<sub>2</sub> at maximum exercise were not different between any of the treatment groups.

To determine whether the observed improvement in exercise capacity was related to individual improvements in airways limitation we examined the relationship between the changes in FEV<sub>1</sub> at 90 minutes and the changes in Wmax (fig 3). The data represent the differ-

Table 2 Mean (SD) maximum exercise data for different dosage groups

	Placebo	40 µg	80 µg	160 µg	240 µg
Wmax (watts)	86.5 (21.0)	88.8 (16.7)	89.6 (22.0)	91.7 (19.8)‡	90.1 (19.5)†
$\dot{V}O_2$ max (ml/min)	865 (184)	879 (167)	878 (183)	908 (182)‡	904 (159)†
$\dot{V}CO_2$ max (ml/min)	894 (245)	925 (237)	929 (249)	963 (253)‡	950 (230)†
$\dot{V}E$ max (l/min)	37.2 (8.7)	39.4 (8.5)	39.7 (8.3)†	41.4 (9.8)‡	40.5 (9.2)‡
$\dot{V}E$ max/MVV (%)	103 (27)	108 (25)	109 (24)†	113 (27)‡	111 (26)‡
HR (beats/min)	126 (16)	125 (16)	125 (17)	125 (15)	128 (16)
SaO <sub>2</sub> (%)	94 (4)	93 (4)	94 (4)	93 (4)	94 (4)
Borg scale	7.5 (1.4)	7.6 (1.4)	7.7 (1.4)	7.7 (1.4)	7.5 (1.1)

Wmax = maximum work rate;  $\dot{V}O_2$ max,  $\dot{V}CO_2$ max = maximum oxygen and carbon dioxide consumption;  $\dot{V}E$ max = maximal ventilation; MVV = maximum voluntary ventilation; HR = heart rate; SaO<sub>2</sub> = arterial oxygen saturation.

† p < 0.05 versus placebo; ‡ p < 0.01 versus placebo.

ences in these two parameters between each of the 40, 80, 160, and 240 µg ipratropium bromide groups and the placebo treatment group in all of the 80 tests – that is, four tests for 20 patients. A significant correlation was found between the change in FEV<sub>1</sub> and the change in Wmax ( $r = 0.45$ ,  $p < 0.005$ ).

Individual resting pulse rates and blood pressures did not differ between the active treatment group and the placebo group for any of the measurements. No patients complained of adverse symptoms.

### Discussion

The results of this study show that the administration of 160 µg or more ipratropium bromide with an MDI has a small but significant effect on exercise capacity in patients with COPD evaluated with progressive cycle ergometry, whereas doses below 80 µg were less effective.

In the studies of Leitch *et al.*,<sup>6</sup> Tobin *et al.*,<sup>7</sup> and Brown *et al.*<sup>8</sup> the significant improvement in airway mechanics produced by inhaled anticholinergics did not result in a significant increase in maximum exercise capacity. One possible reason for this discrepancy with our results is that these workers used a smaller dose of inhaled anticholinergic agent, and thus maximal bronchodilation was not achieved. In our study at least 160 µg ipratropium bromide, which is four times more than the recommended dose, was necessary for optimal

bronchodilation. The currently recommended dose of ipratropium bromide produces less than maximal bronchodilation, and the dose can be doubled or tripled without notable side effects.<sup>15</sup> According to bronchodilator responses following 40 µg ipratropium bromide via an MDI and the results from a dose response study of nebulised ipratropium bromide, Gross *et al.*<sup>16</sup> speculated that the optimal dose of ipratropium bromide delivered by MDI in patients with stable COPD may be as much as four times the recommended dose. This speculation is consistent with our results. Ipratropium bromide does not have significant effects on the cardiovascular system – that is, heart rate or blood pressure<sup>17,18</sup> – even when given at eight times the currently recommended doses.<sup>19</sup> Even in hypoxaemic patients this drug does not affect arterial blood gases.<sup>20</sup> The present study also confirmed these findings.

Although non-asthmatic patients with COPD were included in the present study, FEV<sub>1</sub> increased by an average of more than 15% after administration of the drugs under study. However, the mean absolute change in FEV<sub>1</sub> was at most 250 ml, and this value is compatible with the changes reported in previous studies.<sup>3–5</sup> Thus, our patients had partially reversible chronic airways limitation.

There was a significant correlation between the change in Wmax and the change in FEV<sub>1</sub>, but this correlation was too weak to conclude that the improvement in exercise tolerance depended solely on the reduction in airways limitation. The  $\dot{V}E$  at Wmax was almost equal to  $\dot{V}E$ max in each individual, and the ratio of  $\dot{V}E$ max/MVV was over 1.0 in every group. Although less convincing, this evidence would suggest that ventilatory mechanics were the limiting factor in the exercise tests. Carter *et al.*<sup>21</sup> reported that the equation  $37.5 \times FEV_1$  was an accurate and robust predictor of  $\dot{V}E$ max when applied to patients with moderate to severe COPD ( $FEV_1$  0.56–1.61 l). Applying this rule to our data, the mean actual  $\dot{V}E$ max in each group did not reach the predicted value (about 90% of the predicted value in each group). This could imply that the patients in the present study still had some ventilatory reserve. Killian has shown that patients with obstructive airways disease generally stop exercising when the level of dyspnoea reaches 6 on the Borg scale, or when the perceived exertion of the working muscles reaches 7 on the same scale.<sup>22</sup> The data from the present study show that all scores on the Borg scale were 7.5 or more at Wmax. This could suggest that

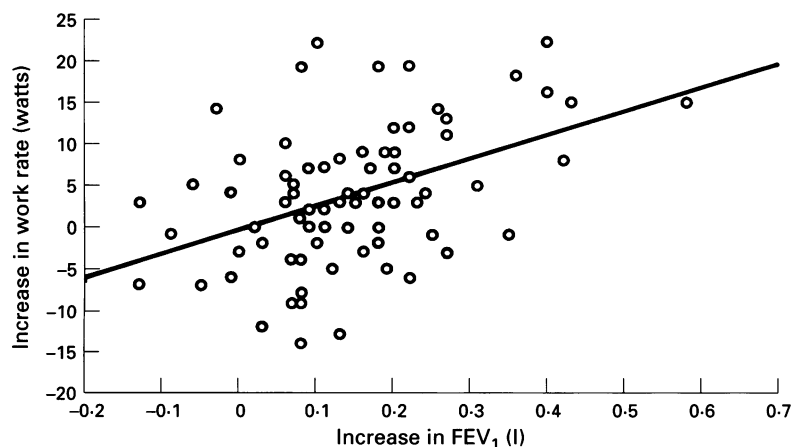


Figure 3 Correlation between the change in forced expiratory volume in one second (FEV<sub>1</sub>) before exercise (at 90 minutes) and the change in maximal work load. The data represent the differences in these two parameters between the ipratropium bromide and placebo treatment groups in all of the 80 tests. The correlation was significant ( $r = 0.45$ ,  $p < 0.005$ ).

dyspnoea and leg effort were the limiting factors rather than ventilatory mechanics. It is conceivable that ipratropium bromide at higher doses improves FEV<sub>1</sub>, thus improving dyspnoea, which allows for a higher W<sub>max</sub>.

Spence *et al* demonstrated that 200 µg oxitropium bromide increased the six minute walking distance but not the duration of cycle exercise.<sup>23</sup> They found that bicycle ergometry underestimates haemoglobin desaturation more than a corridor walking test, suggesting that self-paced exercise may be a more sensitive method, although the reason for this is not clear. In fact, the mean SaO<sub>2</sub> was 97% at rest in the present study, and it did not drop below 93% at maximal exercise. Almost the same results were obtained in previous studies using cycle ergometry.<sup>24,25</sup> The possibility that a dose of ipratropium bromide of less than 160 µg could improve exercise performance can be evaluated using the six minute walking distance test. Furthermore, a tightly fitting face mask can alter the breathing pattern<sup>26</sup> and cycle exercise may also produce different data from a six minute walking test. Although there were only small changes in the exercise parameters in the present study, a small improvement in severely disabled patients with COPD may be of benefit. However, since data from cycle ergometer exercise tests are not directly relevant to usual exercise patterns,<sup>27</sup> it is difficult to evaluate how much improvement in exercise capacity would be experienced in daily life.

Hay *et al* reported that the increase in six minute walking distance seen with 200 µg oxitropium bromide was unrelated to bronchodilation.<sup>9</sup> These results suggest that anticholinergic therapy can improve dyspnoea and exercise tolerance in COPD, and that reversibility testing is not a good predictor of symptomatic benefits. The present study does not address the possibility that mechanisms other than bronchodilation could improve exercise tolerance. Anticholinergics might affect afferent vagal reflexes from the airways and lung, though their role in mediating the respiratory sensation of dyspnoea is not presently known. Theophylline may improve exercise tolerance by affecting respiratory muscle performance rather than by bronchodilation,<sup>25,28</sup> but anticholinergics are not considered to have such an effect. LoRusso reported that the maximum voluntary ventilation which requires inspiratory and expiratory effort was the single best predictor of  $\dot{V}O_2$  in patients with COPD.<sup>29</sup> Dillard *et al* demonstrated that factors other than ventilatory capacity also have a quantitative effect on  $\dot{V}O_{2,max}$ , and that peak inspiratory pressure has an effect on maximal exercise capacity.<sup>30</sup> Thus, inspiratory muscle function may be an important determinant of exercise performance.

We conclude that, although cycle ergometry is not directly relevant to exercise performed as daily activities, ipratropium bromide at doses of 160 µg or more from an MDI with a spacer may be optimal for improving the maximal exercise capacity in patients with stable COPD.

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