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# Evaluation of Acute Bronchodilator Reversibility in Symptomatic GOLD Stage I COPD

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**Running head:** Effects of ipratropium in mild COPD

**Key words:** exercise, lung hyperinflation, dyspnoea, anticholinergic, efficacy.

## ABSTRACT

***Background***: Symptomatic patients with GOLD stage I COPD can have significant abnormalities of ventilatory mechanics with greater exertional symptoms and exercise limitation than age-matched healthy subjects. In such patients, the impact of bronchodilator therapy remains unknown and is difficult to evaluate.

***Methods***: We measured the acute effects of nebulized ipratropium bromide 500μg (IB) on resting pulmonary function and on dyspnoea and ventilatory parameters during symptom-limited constant work-rate cycle exercise. In a randomized, double-blind, crossover study, 16 patients with COPD [post-bronchodilator forced expiratory volume in one second ($FEV_1$)=90±7 %predicted, $FEV_1$/forced vital capacity (FVC)=59±7%; mean±SD] with a significant smoking history (44±16 pack-years) inhaled either IB or placebo (PL) on each of two separate visits. Pulmonary function tests and cycle exercise at 80-85% of each subject's maximal work capacity were performed 2-hours after dosing.

***Results***: After IB compared with PL: $FEV_1$ increased 5±9 %predicted; residual volume decreased 12±20 %predicted; and specific airway resistance decreased 81±93 %predicted (all $p<0.05$). At a standardized time during exercise: dynamic inspiratory capacity and tidal volume significantly increased in tandem by 0.12 and 0.16 L, respectively (each $p<0.05$); dyspnoea fell by 0.9±1.8 Borg units ($p=0.07$) and dyspnoea/ventilation ratios fell significantly ($p<0.05$). The fall in dyspnoea intensity at higher submaximal ventilations correlated with the concurrent decrease in end-expiratory lung volume ($p<0.05$).

***Conclusion***: In symptomatic GOLD stage I COPD, IB treatment was associated with modest but consistent improvements in airway function, operating lung volumes and dyspnoea intensity during exercise. Our results provide a physiological rationale for a trial of bronchodilator therapy in selected patients with milder but symptomatic COPD.

## INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) who have relatively preserved measurements of forced expiratory flow rates, may have extensive small airway dysfunction.[1-4] Such patients report greater intensity of exertional dyspnoea than healthy age-matched controls as a result of the combined effects of abnormal dynamic ventilatory mechanics and higher ventilatory requirements during exercise.[5] This physiological impairment of the respiratory system may explain, at least in part, reports of poor perceived health status in subpopulations of patients with apparently mild airway obstruction.[6] Successful smoking cessation is the only proven intervention that has been shown to improve small airway function in patients with mild COPD.[2, 4] However, the optimal clinical management of these symptomatic smokers with mild COPD is not established and remains largely unstudied. It is not known, for example, whether inhaled bronchodilator therapy, which has established efficacy in moderate to severe COPD,[7-10] is effective in alleviating activity-related dyspnoea in those with milder disease. Moreover, it remains uncertain whether traditional spirometric criteria for bronchodilator reversibility, based on arbitrary improvement in the forced expiratory volume in one second ($FEV_1$), are applicable in mild COPD. This information becomes important for clinical practice and for the design of future clinical trials to evaluate the efficacy of therapeutic interventions in early COPD.

The purpose of the present study was therefore to evaluate the acute effects of an anticholinergic bronchodilator on airway function and exertional dyspnoea in patients with mild COPD, as defined by GOLD stage I criteria.[10] Based on the results of a previous mechanistic study in symptomatic mild COPD,[5] we hypothesized that inhaled bronchodilator therapy would improve airway function and lung volumes at rest and reduce the rate of dynamic pulmonary hyperinflation during exercise, thus permitting greater tidal volume expansion and reduced dyspnoea intensity at higher submaximal ventilations. To test this hypothesis we undertook a randomized placebo-controlled study in 16 well characterized symptomatic patients with mild COPD. We compared the acute effects of nebulized ipratropium bromide and placebo on detailed resting pulmonary function measurements, as well as dyspnoea ratings, operating lung volumes, breathing pattern and gas exchange during constant work cycle exercise. To explore potential mechanisms of dyspnoea relief, we also measured esophageal pressure (Pes)-derived indices of dynamic ventilatory mechanics in a small subsample of patients who consented to undertake these more invasive measurements.

## METHODS

### Subjects

We studied 16 symptomatic patients with GOLD stage I COPD (post-bronchodilator $FEV_1$ ≥80 %predicted and $FEV_1$/forced vital capacity (FVC) ratio <0.7)[10] who were referred to the COPD Centre at our institution. Patients were excluded if they had: *1)* other medical conditions which could cause or contribute to breathlessness, i.e., metabolic, cardiovascular, asthma or other respiratory diseases, or *2)* other disorders which could interfere with exercise testing such as neuromuscular diseases or musculoskeletal problems.

### Study Design

This randomized, double-blind, placebo-controlled, crossover study was approved by the Queen's University and Affiliated Hospitals Research Ethics Board. After informed consent and screening of medical history, completed four visits conducted approximately 7 days apart. At

Visit 1, subjects completed pulmonary function tests and a symptom-limited incremental cycle exercise test, followed after 60 min of rest by a familiarization constant-load cycle endurance test at 80-85% of their maximal achieved work rate ($W_{max}$). At Visit 2, the constant-load cycle test was repeated and, after 60 min of recovery, subjects performed pulmonary function tests pre- and 20 minutes post-salbutamol (400µg). At Visits 3 and 4, subjects were randomized (sequence) to receive either nebulized ipratropium bromide 500µg (IB) or a placebo (PL). Subjects performed pulmonary function tests before and 60 min after nebulization, followed by a constant-load exercise test. All series of pulmonary function tests included spirometry, body plethysmography, diffusing capacity, and respiratory muscle strength measurements. All symptom-limited constant-load exercise tests were conducted at the same work rate for each subject. Withdrawal of bronchodilators before each visit included: short-acting $\beta_2$-agonists (8 hours), short-acting anticholinergics (8 hours), long-acting $\beta_2$-agonists (48 hours), and long-acting anticholinergics (72 hours). Subjects avoided caffeine, alcohol, and heavy meals for 4 hours before visits and avoided major physical exertion entirely on visit days.

**Interventions**

A 3.5 mL solution containing either 500µg IB or sterile 0.9% saline (PL) was administered by nebulizer (Parimaster compressor with Pari LC Jet+ nebuliser; PARI Respiratory Equipment Inc, Richmond, VA, USA) over a 15-20 minute period in a double-blind fashion.

**Procedures**

Routine spirometry, body plethysmography (i.e., functional residual capacity (FRC) and specific airway resistance (sRaw)), diffusing capacity for carbon monoxide ($D_{LCO}$), and maximum inspiratory and expiratory mouth pressures (MIP and MEP; measured at FRC and total lung capacity (TLC), respectively) were performed using an automated system (6200 Autobox DL or Vmax229d; SensorMedics, Yorba Linda, CA) in accordance with recommended techniques.[11-16] Measurements were expressed as percentages of predicted normal values;[17-19] predicted normal inspiratory capacity (IC) was calculated as predicted TLC minus predicted FRC.

Symptom-limited exercise tests were conducted on an electronically-braked cycle ergometer as previously described.[5,20,21] The incremental test consisted of 2-min increments of 20 W to the point of symptom limitation; $W_{max}$ was defined as the greatest work rate that the subject could maintain for at least 30 seconds. Constant-load tests at 80-85% $W_{max}$ were performed during all four visits; endurance time was defined as the duration of loaded pedaling. At end-exercise, subjects were asked why they needed to stop exercising. *Rest* was the steady-state period after at least 3 minutes of breathing on the mouthpiece before exercise began; *peak* was the last 30 seconds of loaded pedaling; and *isotime* was the duration of the shortest post-treatment test rounded down to the nearest full minute, i.e., highest equivalent isotime.

Cardiopulmonary and breathing pattern measurements were collected in a breath-by-breath fashion while subjects breathed through a mouthpiece with nasal passages occluded by a nose-clip using a cardiopulmonary exercise testing system (SensorMedics Vmax229d). Pulse oximetry, electrocardiography and blood pressure measurements were also performed. Subjects rated the intensity of their "breathing discomfort" and "leg discomfort" at rest, every minute during exercise and at end-exercise using the modified 10-point Borg scale.[22] Operating lung volumes were derived from IC measurements performed at rest, every second minute during exercise and end-exercise as previously described.[5] Maximal flow-volume loops were obtained at rest and at end-exercise. Tidal flow-volume curves at rest, every 2 minutes during

exercise and at peak exercise were placed within their respective maximal flow-volume loops using coinciding IC measurements; expiratory flow-limitation was estimated as the percent of tidal volume ($V_T$) encroaching on the maximal flow envelope.[23] In 6 subjects, esophageal pressure (Pes) was recorded continuously during constant-load exercise tests using an integrated data acquisition set-up as described elsewhere.[20](***see online supplement***) Inspiratory sniff manoeuvres were performed pre-exercise at rest and immediately at end-exercise to obtain maximum values for Pes ($PI_{max}$).

**Statistical Analysis**

A sample size of 16 was used to provide the power (80%) to detect a significant difference in dyspnoea intensity (Borg Scale) measured at a standardized work-rate during incremental cycle exercise based on a relevant difference in Borg ratings of ±1, a SD of 1 for Borg ratings changes found at our laboratory, $\alpha$=0.05. Results were expressed as means ± SD. A $p<0.05$ level of statistical significance was used for all analyses.

Although unlikely in this single-dose study, the possibility of a carry-over effect was tested using paired *t* tests to evaluate pre-dose (pre-treatment) pulmonary function measurements. Period effects were evaluated using the two-sample *t* test approach.[24] Treatment comparisons were made using paired t-tests with appropriate Bonferroni adjustments for multiple comparisons. Responses at rest and at different time points and/or intensities during exercise were also compared. Repeated measures ANOVA (with treatment, time and interaction as fixed effects and subject as a random effect) was applied to compare the overall treatment effects. Dyspnoea descriptors were analysed as frequency statistics and compared using the Fisher's exact test. Physiological contributors to exertional dyspnoea intensity were determined by multiple regression analysis: Borg dyspnoea ratings at a standardized exercise work rate (dependent variable) were analyzed against concurrent relevant independent variables, i.e., exercise measurements of ventilation, breathing pattern, operating lung volumes, cardiovascular and metabolic parameters, and baseline pulmonary function measurements.

## RESULTS

**Subjects**

Subject characteristics are summarized in Table 1. All subjects were symptomatic and had a diagnosis of COPD; the majority (11/16) had a diagnosis made within the previous 5 years. Seven subjects did not use any respiratory medications, 2 subjects only used a short-acting $\beta_2$-agonist bronchodilator on an "as needed" basis, and 7 subjects used inhalers on a regular basis. Of these latter 7 subjects: all used short-acting $\beta_2$-agonists, 5 used a long-acting $\beta_2$-agonist, 5 used an anticholinergic (1 short-acting, 4 long-acting), and 6 used an inhaled corticosteroid (5 in combination with a long-acting $\beta_2$-agonist). Comorbidities included: stable coronary artery disease (n=2), well controlled diabetes mellitus type 2 (n=1), treated hypertension (n=1), and varying degrees of osteoarthritis (n=4). All subjects had a smoking history ≥15 pack-years (range 15-63 pack-years)(Table 1): 4 subjects were current smokers and 12 subjects were ex-smokers who had stopped smoking at least two years prior to the study.

Chronic activity-related dyspnoea was assessed with the Baseline Dyspnoea Index (BDI)[25] and the Medical Research Council (MRC) dyspnoea scale.[26] BDI focal scores ranged from 5 to 12; 9 subjects reported a BDI ≤8 and 7 subjects reported a BDI ≥9. The majority (11 out of 16) of subjects had a rating ≥2 on the MRC dyspnoea scale.

All subjects had a normal post-bronchodilator $FEV_1$ and a $FEV_1$/FVC ratio <70%. Lung volumes indicated mild static lung hyperinflation (mean FRC and RV >120 %predicted) with a preserved vital capacity and IC (Table 1). Symptom-limited incremental exercise testing showed a reduced peak $VO_2$ and work rate. The subgroup of subjects with Pes-derived measurements had comparable baseline characteristics to the group as a whole (Table 1). There were also no significant differences in the baseline characteristics or in the magnitude of the treatment responses between patients who were using respiratory medication versus those who were not.

**TABLE 1. Subjects characteristics**

| | **Enrolled subjects (n = 16)** | **Subjects (n=6) with complete mechanical measurements** |
|---|---|---|
| Gender | 63% male | 83% male |
| Age, yr | 63 ± 8 | 67 ± 8 |
| Body mass index, $kg/m^2$ | 27.8 ± 4.6 | 26.4 ± 3.8 |
| Cigarette smoking history, pack-years | 44 ± 16 | 43 ± 18 |
| BDI focal score (0 -12) | 8.3 ± 2.0 | 8.3 ± 1.9 |
| MRC dyspnoea scale (1-5) | 1.8 ± 0.7 | 1.5 ± 0.5 |
| CHAMPS, kcal/week consumed at moderate activities | 2123 ± 2221 | 1736 ± 1974 |
| **Symptom-limited peak exercise (% predicted maximum):** | | |
| Work rate, W | 121 ± 39 (72) | 119 ± 30 (74) |
| $VO_2$, L/min | 1.84 ± 0.58 (79) | 1.79 ± 0.58 (79) |
| **Pulmonary function (%predicted):** | | |
| $FEV_1$ post-bronchodilator, L | 2.50 ± 0.58 (90) | 2.44 ± 0.64 (86) |
| FVC post-bronchodilator, L | 4.25 ± 1.08 (108) | 4.39 ± 1.18 (108) |
| $FEV_1$/FVC post-bronchodilator, % | 59 ± 7 (84) | 56 ± 8 (80) |
| IC, L | 3.01 ± 0.97 (103) | 3.34 ± 1.13 (106) |
| FRC, L | 4.10 ± 0.91 (122) | 4.45 ± 0.71 (126) |
| TLC,L | 7.11 ± 1.50 (113) | 7.79 ± 1.32 (117) |
| RV, L | 2.83 ± 0.48 (129) | 3.08 ± 0.32 (131) |
| MIP, $cmH_2O$ | 95 ± 32 (115) | 87 ± 23 (95) |
| MEP, $cmH_2O$ | 149 ± 59 (83) | 139 ± 44 (100) |
| $D_LCO$, ml/min/mmHg | 21.2 ± 5.9 (95) | 22.4 ± 4.5 (106) |
| sRaw, $cmH_2O \cdot s$ | 12.3 ± 4.0 (294) | 13.3 ± 2.9 (303) |

Values are means ± SD (% of predicted normal values in parentheses).

*Abbreviations*: BDI, Baseline Dyspnoea Index; MRC, Medical Research Council; CHAMPS, Community Healthy Activities Model Program for Seniors; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; FRC, functional reserve capacity; TLC, total lung capacity; RV, residual volume; MIP, maximal inspiratory mouth pressure; MEP, maximal expiratory mouth pressure; sRaw, specific airway resistance.

There were no significant differences between pre-dose measurements of pulmonary function on treatment days, i.e., no significant carry-over effect. No significant period effects were found when examining pulmonary function or exercise test outcomes.

**Pulmonary Function Responses**

Differences in pulmonary function after IB compared with PL are shown in Table 2. Subjects with the worst baseline pre-bronchodilator sRaw had the greatest IB-induced improvements in sRaw (r=-0.595, p=0.015) and IC (r=0.594, p=0.015); improvements in sRaw and IC were also strongly inter-related (r=-0.680, p=0.004). Maximal expiratory flows measured at FRC after PL were compared with the maximal flow at the same absolute volume after IB within each individual: these isovolume flows improved from 0.27±0.18 to 0.43±0.30 L/s after PL and IB, respectively (p=0.006).

**TABLE 2. The effect of placebo (PL) and ipratropium bromide (IB) on pulmonary function tests in GOLD stage I COPD**

| | Post-PL | Post-IB |
|---|---|---|
| $FEV_1$, L<br>Δ $FEV_1$, L | 2.30 ± 0.60 (83)<br>0.07 ± 0.09 (3)† | 2.46 ± 0.59 (88)*<br>0.26 ± 0.19 (9)† ‡ |
| FVC, L<br>Δ FVC, L | 4.07 ± 1.13 (103)<br>0.02 ± 0.18 (1) | 4.20 ± 1.17 (106)*<br>0.23 ± 0.21 (6)† ‡ |
| $FEV_1$/FVC, %<br>Δ $FEV_1$/FVC, % | 57 ± 7 (81)<br>1.3 ± 2.0 (2)† | 59 ± 7 (83)<br>2.9 ± 3.2 (4) † |
| $D_LCO$, ml/min/mmHg<br>Δ $D_LCO$ | 21.0 ± 6.2 (94)<br>-0.1 ± 1.4 (-1) | 20.2 ± 6.5 (90)<br>-1.1 ± 2.3 (-5) |
| MIP, $cmH_2O$<br>Δ MIP, $cmH_2O$ | 96 ± 20 (120)<br>-1 ± 11 (-2) | 98 ± 21 (121)<br>1.6 ± 7.7 (1) |
| MEP, $cmH_2O$<br>Δ MEP, $cmH_2O$ | 148 ± 54 (82)<br>1 ± 12 (1) | 148 ± 48 (83)<br>-6 ± 13 (-10) |
| TLC, L<br>Δ TLC, L | 7.16 ± 1.49 (114)<br>-0.03 ± 0.26 (-1) | 7.04 ± 1.42 (112)<br>-0.15 ± 0.20 (-3) † |
| RV, L<br>Δ RV, L | 2.73 ± 0.34 (125)<br>-0.14 ± 0.19 (-6)† | 2.49 ± 0.47 (113)*<br>-0.38 ± 0.22 (-19) † ‡ |
| FRC, L<br>Δ FRC, L | 4.05 ± 0.71 (121)<br>-0.07 ± 0.17 (-2) | 3.90 ± 0.82 (115)*<br>-0.27 ± 0.29 (-9) † ‡ |
| IC, L<br>Δ IC, L | 3.10 ± 1.01 (106)<br>0.04 ± 0.19 (1) | 3.15 ± 0.86 (109)<br>0.12 ± 0.32 (4) |
| sRaw, $cmH_2O$·s<br>Δ sRaw, $cmH_2O$·s | 12.7 ± 4.3 (301)<br>-0.6 ± 1.7 (-15) | 9.3 ± 4.6 (220)*<br>-4.7 ± 3.5 (-111) † ‡ |

Values are means ± SD (% of predicted normal values in parentheses).

*p<0.05 post-IB *versus* post-PL, †p<0.05 post-dose *versus* pre-dose within treatment, ‡p<0.05 IB *versus* PL post-minus pre-dose differences.

*Abbreviations*: Δ, post-dose minus pre-dose difference; $FEV_1$, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; $DL_{CO}$, diffusing capacity of the lung for carbon monoxide; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; SVC, slow vital capacity; RV, residual volume; IC, inspiratory capacity; sRaw, specific airway resistance.

**Responses to Constant-Load Exercise**

Post-dose exercise endurance time at 99±32 W (60±11 % predicted maximum; 82±9 %Wmax) did not change significantly after IB compared with PL (Table 3): six subjects improved endurance time by ≥30 sec, three subjects decreased endurance time by ≥30 sec, and the rest had less than a 30 sec difference in endurance time. The distribution of reasons for stopping exercise was not different between treatments. In both visits, leg discomfort was reported as the primary reason for stopping exercise, 2- to 3-fold more than breathing discomfort (Table 3).

**TABLE 3. Postdose peak of symptom-limited constant-load exercise at 80-85%$W_{max}$ (99±32 W)**

| | Placebo | Ipratropium bromide |
|---|---|---|
| Exercise time, min | 8.2 ± 5.3 | 8.2 ± 4.8 |
| Dyspnoea, Borg scale | 7.8 ± 2.9 | 7.7 ± 2.5 |
| Leg discomfort, Borg scale | 8.6 ± 1.9 | 8.4 ± 2.2 |
| Reason for stopping, n (%): | | |
| Breathing | 3 (19) | 2 (13) |
| Legs | 6 (37) | 9 (56) |
| Both breathing and legs | 7 (44) | 5 (31) |
| $V'O_2$, L/min | 1.88 ± 0.64 | 1.81 ± 0.56 |
| $V'CO_2$, l/min | 1.73 ± 0.55 | 1.75 ± 0.58 |
| $V'_E$, l/min | 69.4 ± 18.2 | 73.5 ± 23.9 |
| *F*, breaths/min | 39.6 ± 7.9 | 39.1 ± 7.3 |
| $V_T$, liters | 1.81 ± 0.56 | 1.91 ± 0.58 * |
| IC, liters | 2.46 ± 0.70 | 2.59 ± 0.70 |
| IRV, liters | 0.65 ± 0.26 | 0.67 ± 0.32 |
| $V_T/T_E$, l/sec | 2.10 ± 0.59 | 2.24 ± 0.80 |
| $V_T/T_I$, l/sec | 2.56 ± 0.63 | 2.68 ± 0.80 |
| $T_I/T_{TOT}$ | 0.45 ± 0.03 | 0.45 ± 0.03 |
| $P_{ET}CO_2$, mmHg | 34.4 ± 4.7 | 33.0 ± 5.4 |
| Heart rate, beats/min | 142 ± 16 | 140 ± 17 |
| $SpO_2$, % | 95 ± 3 | 95 ± 2 |

Values are means ± SD.

*p<0.05 ipratropium bromide versus placebo.

*Abbreviations*: $V'O_2$, oxygen uptake; $V'CO_2$, carbon dioxide production; $V'_E$, minute ventilation; *F*, breathing frequency; $V_T$, tidal volume; IC, inspiratory capacity; IRV, inspiratory reserve volume; $V_T/T_E$ and $V_T/T_I$, mean inspiratory and expiratory tidal flows; $T_I/T_{TOT}$, inspiratory duty cycle, inspiratory time over total breath time; $P_{ET}CO_2$, partial pressure of end-tidal $CO_2$; $SpO_2$, oxygen saturation.

Exertional symptoms. After IB compared with PL there was no change in peak Borg ratings of breathing or leg discomfort (Table 3); however, ratings of breathing and leg discomfort

at the highest equivalent isotime (6.8±4.5 min) during exercise were lower after IB compared with PL by 0.88±1.83 (p=0.073) and 0.81±1.28 (p<0.05) Borg units, respectively (Table 4, Figure 1). Ten out of sixteen patients decreased the intensity of their breathing discomfort at isotime by at least 1 Borg unit, while the remaining subjects increased (n=4) or did not change (n=2) ratings of breathing discomfort after IB compared with PL. Dyspnoea/$V'_E$ ratios were evaluated to account for the potential effects of IB-induced alterations in $V'_E$ on exertional dyspnoea intensity: dyspnoea/$V'_E$ ratios were significantly lower (p<0.05) at isotime after IB compared with PL (Table 4, Figure 1). By repeated measures ANOVA, there were no significant interactions between treatment and time during exercise for exertional symptom ratings (i.e., the treatment effect did not vary at different times); however, a significant treatment effect was found for dyspnoea/$V'_E$ ratios (p=0.075) and leg discomfort ratings (p=0.021).

Ventilatory responses. Ventilatory responses to exercise after IB and PL are shown in Figure 2. Tidal volume ($V_T$) was greater after IB compared with PL from minute 4 in exercise to peak exercise by between 0.10 and 0.16 L (p<0.05); increases in $V_T$ were accommodated by concurrent increases in IC of between 0.12 and 0.15 L (p<0.05). Inspiratory reserve volume (IRV) was not different at rest or throughout exercise across treatments. Estimates of expiratory flow limitation were reduced at isotime and at peak exercise by 10 and 17% (p<0.05), respectively, after IB compared with PL. Repeated measures ANOVA also showed a significant treatment effect for $V_T$ (p=0.012), IC (p=0.001) and expiratory flow limitation (p=0.014); with no significant interactions between treatment and exercise time.

**TABLE 4. Post-dose values at isotime (6.8 ± 4.5 min) during constant-load exercise**

| | **Placebo** | **Ipratropium bromide** |
|---|---|---|
| Dyspnoea, Borg | 7.4 ± 2.4 | 6.6 ± 2.4 (p=0.07) |
| Dyspnoea/$V'_E$, Borg/L/min | 0.12 ± 0.05 | 0.10 ± 0.05 * |
| Leg discomfort, Borg | 8.3 ± 1.7 | 7.5 ± 2.1 * |
| $V'O_2$, L/min | 1.72 ± 0.54 | 1.82 ± 0.66 |
| $V'CO_2$, L/min | 1.67 ± 0.56 | 1.71 ± 0.62 |
| Heart rate, beats/min | 137 ± 19 | 136 ± 19 |
| $SpO_2$, % | 96 ± 3 | 96 ± 2 |
| $V'_E$, L/min | 65.7 ± 19.6 | 69.0 ± 24.9 |
| *F*, breaths/min | 36.7 ± 8.3 | 35.3 ± 8.2 |
| $V_T$, L | 1.83 ± 0.57 | 1.99 ± 0.65 * |
| IC, L | 2.51 ± 0.70 | 2.63 ± 0.66 * |
| ΔIC isotime-rest, L | -0.55 ± 0.40 | -0.49 ± 0.33 |
| IRV, L | 0.68 ± 0.31 | 0.64 ± 0.30 |
| $T_I$, sec | 0.77 ± 0.20 | 0.81 ± 0.21 |
| $T_E$, sec | 0.93 ± 0.20 | 0.98 ± 0.23 (p=0.06) |
| $T_I/T_{TOT}$ | 0.45 ± 0.03 | 0.45 ± 0.03 |
| $V_D/V_T$ estimated, % | 30 ± 7 | 29 ± 8 * |
| $P_{ET}CO_2$, mmHg | 35.4 ± 5.1 | 34.3 ± 5.5 |
| EFL, % of $V_T$ overlapping maximal flow-volume curve | 78 ± 13 | 62 ± 20 * |

Values are means ± SD.

* p<0.05 ipratropium bromide versus placebo.
*Abbreviations*: V'$O_2$, oxygen uptake; V'$CO_2$, carbon dioxide production; $SpO_2$, oxygen saturation; V'$_E$, minute ventilation; $V_T$, tidal volume; VC, vital capacity; *F*, breathing frequency; $V_D$, estimated dead space; IC, inspiratory capacity; IRV, inspiratory reserve volume; $T_E$, expiratory time; $T_I$, inspiratory time; $T_I/T_{TOT}$, inspiratory duty cycle, inspiratory time over total breath time; $P_{ET}CO_2$, partial pressure of end-tidal $CO_2$; EFL, expiratory flow limitation.

Ventilatory mechanics (Figure 3). The pressure-time integral and its surrogate, the calculated tension-time index ($Pes/PI_{max} \times T_I/T_{TOT}$), were not different in response to treatment. However, lung resistance was reduced after IB compared to PL in the order of 0.7 to 0.8 $cmH_2O/L/s$ at standardized timepoints throughout exercise, i.e., a reduction of ~20% ($p<0.05$). Total work of breathing expressed as J/L fell significantly ($p<0.05$) during exercise but not at rest after IB compared with PL; primarily due to significant ($p<0.05$) decreases in the inspiratory threshold load and the elastic work performed against this load. Repeated measures ANOVA showed a significant treatment effect for resistance (p=0.0007), the inspiratory threshold load (p<0.0001), total work of breathing (p=0.002) and elastic work of breathing (p=0.001); with no significant interactions between treatment and exercise time. Work of breathing measurements were not different when expressed as J/min, thus differences were offset by increases in V'$_E$.

**Correlates of Dyspnoea**

The best predictors of the IB-induced decrease in dyspnoea ratings at isotime were the baseline (pre-bronchodilator) pre-exercise resting IC expressed as %predicted (r=0.637, p=0.008), the EILV/TLC ratio (r= -0.561, p=0.024) and the IRV expressed as %predicted TLC (r=541, p=0.030); no other baseline pulmonary function parameters correlated. The best correlates of the IB-induced decrease in dyspnoea/V'$_E$ ratios at isotime were also the pre-bronchodilator pre-exercise resting IC expressed as %predicted (r=0.714, p=0.002), the EILV/TLC ratio (r= -0.637, p=0.008) and the IRV expressed as %predicted TLC (r=0.549, p=0.028). When dyspnoea was expressed as a ratio against V'$_E$ (Borg/(L/min)), the strongest correlate of this treatment difference at isotime was the concurrent difference in EELV/TLC (r=0.585 p<0.05).

## DISCUSSION

The novel findings of this study are as follows: first, treatment with IB was associated with consistent improvements in forced expiratory flow rates, specific airway resistance and residual volume in symptomatic patients with GOLD stage I COPD; second, during exercise IB treatment was associated with significant increases in dynamic IC and tidal volume in the absence of an increase in cycle exercise endurance time, and; third, improvement in dynamic EELV was linked to a reduction in ratings of exertional dyspnoea intensity at higher levels of ventilation.

**Changes in Resting Pulmonary Function**

Our patients had extensive physiological impairment and long-term activity-related dyspnoea as measured by validated questionnaires. More than half of the group was already receiving empiric bronchodilator therapy. Our results confirm that release of cholinergic smooth muscle tone improved airway function both at rest and during exercise in these patients. In general, changes in resting spirometry and lung volumes were in the same direction but more modest than those previously reported following a similar dosage of IB in moderate to severe COPD.[7-9] Airway resistance, corrected for the lower resting operating volume, decreased after IB by 33% of baseline values while isovolume maximal flow rates in the effort-independent range also consistently improved.

In contrast to previous studies of the acute effects of IB in more advanced disease, resting IC did not increase significantly in our milder COPD cohort. Thus, FRC and TLC fell in tandem and to a similar extent such that change in IC underestimated the extent of IB-induced lung deflation. Small but consistent bronchodilator-associated decreases in TLC have previously been reported in COPD but the precise mechanisms are unknown.[27,28] Decreases in the plethysmographically-determined TLC may reflect measurement artifact since mouth pressure during panting could potentially underestimate true alveolar pressure in patients with airflow limitation. A reduction in this disparity after a bronchodilator may result in an artifactual reduction in TLC. We tried to minimize this effect by controlling panting frequency at ~1 Hz. It is unlikely that changes in (regional) lung compliance can explain the observed reductions in TLC: lung compliance curves were superimposed before and after IB in our small subsample with mechanical measurements.

The lack of increase in resting IC in our patients is not surprising. Based on the study of Tantucci et al.,[29] bronchodilator-induced increases in IC are only expected in patients with COPD who have more extensive expiratory flow-limitation and lung hyperinflation (i.e., IC<80 % predicted) at rest.

**Altered Ventilatory Responses to Exercise after Bronchodilator**

Exercise endurance time did not increase after bronchodilator compared with placebo. Possible explanations for this include: *1*) the study was powered to detect an improvement in dyspnoea at a standardized work rate and not a change in exercise endurance time; and *2*) intolerable leg discomfort and not dyspnoea was the dominant exercise-limiting symptom in the majority of this group.

From rest to peak exercise, IC diminished by 0.55 L confirming the presence air trapping due to expiratory flow limitation and high ventilatory demand in patients with mild COPD. Compared with placebo, IB treatment was associated with a significant increase in IC by ~0.12 to 0.15 L throughout exercise despite slightly greater levels of ventilation (~3 L/min); however, the magnitude of acute change in IC from pre-exercise resting levels at each time-point and at peak exercise remained similar (Figure 2). We also found consistent reductions in our estimate of expiratory flow limitation at higher exercise levels after IB. Moreover, pulmonary resistance and conductance were significantly improved during exercise in the subsample who consented to esophageal balloon measurements. Therefore, the likeliest explanation for lung deflation is improvement in the time constant for lung emptying as a result of reduced airway resistance rather than minimal changes in expiratory time (prolongation) and static lung recoil pressure. The improved dynamic IC allowed greater $V_T$ expansion throughout exercise without further encroachment on the dynamic IRV.

**Mechanisms of Dyspnoea Relief**

Standardized ratings of exertional dyspnoea intensity as measured by the Borg scale were not statistically different (p=0.07) after IB compared with placebo, likely due to small concomitant increases in $V'_E$ with IB. However, when IB-induced alterations in $V'_E$ were taken into account by examining dyspnoea/$V'_E$ ratios, these changes reached statistical significance (p<0.05). After IB compared with placebo, the decrease in the dyspnoea/$V'_E$ ratio correlated best with the concurrent decrease in the dynamic EELV/TLC ratio. In a small subset of patients, the measured work of breathing and the pressure-time product (reflecting the oxygen cost of breathing) was not increased after IB despite significantly greater $V_T$ expansion. The work associated with

overcoming the inspiratory threshold load (the intrinsic PEEP effect) was significantly reduced at standardized times during exercise. We have argued that increased threshold loading of the inspiratory muscles as a result of dynamic pulmonary hyperinflation plays an important role in dyspnoea causation in asthma during bronchoconstriction and in more advanced COPD during exercise.[30-32] Reduction of the inspiratory threshold load by lung deflation should relieve dyspnoea by reducing the disparity between efferent motor output (sensed by increased corollary discharge) and afferent inputs from mechanosensors in the respiratory muscles, chest wall and lungs (i.e., neuromechanical coupling).[33] Thus, dyspnoea relief was related to improved inspiratory muscle function as a result of a reduced dynamic EELV as well as the recruitment of an increased dynamic IC which allowed greater $V_T$ displacement for the same inspiratory effort.

It is noteworthy that patients who derived the greatest reduction in exertional dyspnoea with IB treatment were those with the most severe lung hyperinflation at baseline. In fact, of all the resting physiological parameters that we measured, only the resting pre-bronchodilator IC and IRV (expressed %predicted) correlated with improved dyspnoea intensity ratings during exercise. Previous studies have shown that when the normal spontaneous $V_T$ response to increasing central respiratory drive is constrained (either volitionally or by imposition), dyspnoea quickly escalates to intolerable levels.[34,35] It follows that release of $V_T$ restriction (i.e., IC recruitment) should improve dyspnoea.[21,36]

In summary, traditional spirometric measurements reliably detected modest but consistent improvements in airway function after bronchodilator treatment in symptomatic mild COPD. Bronchodilator administration was associated with improved dynamic IC and a deeper breathing pattern throughout exercise. Dyspnoea intensity ratings fell only at the higher levels of ventilation with IB treatment, in association with reduced dynamic EELV. Mechanical and subjective improvements during exercise after IB treatment were most pronounced in those with the smallest resting IC (and IRV) and therefore the greatest mechanical constraints on tidal volume expansion.

This study highlights the challenges involved in the assessment of bronchodilator efficacy in milder COPD where no evidence-based guidelines for pharmacotherapy currently exist. Our results provide a sound physiological rationale for consideration of a trial of bronchodilator therapy in selected patients with GOLD stage I COPD who experience troublesome activity-related dyspnoea.

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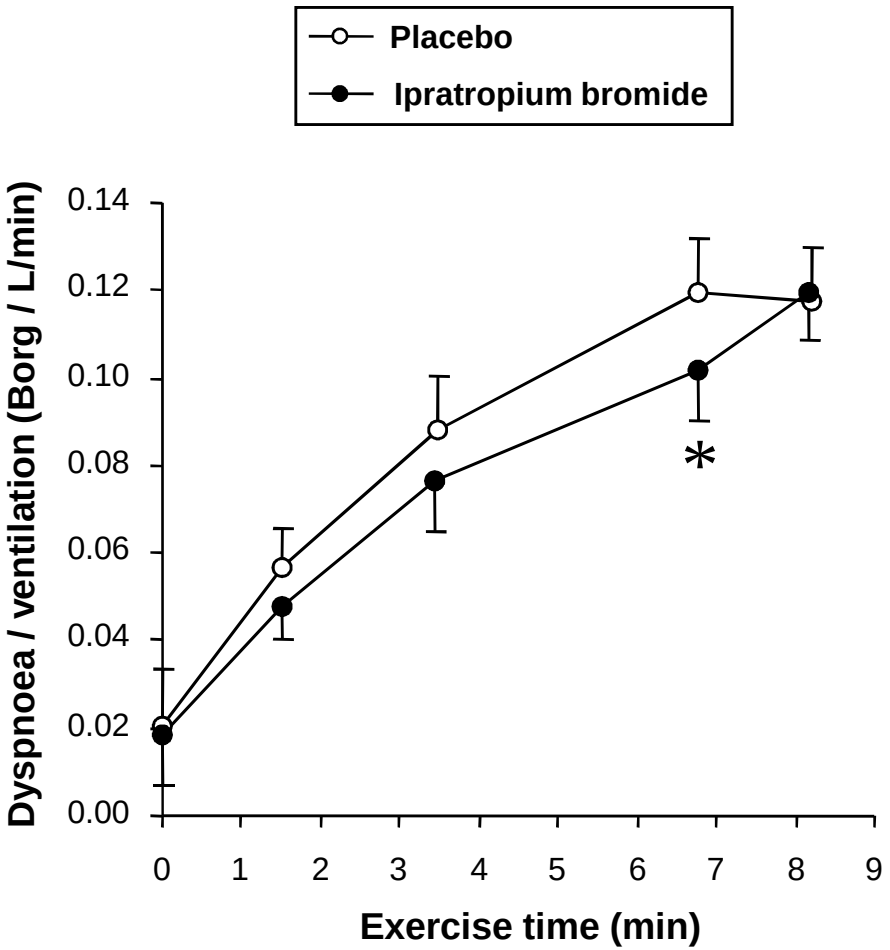
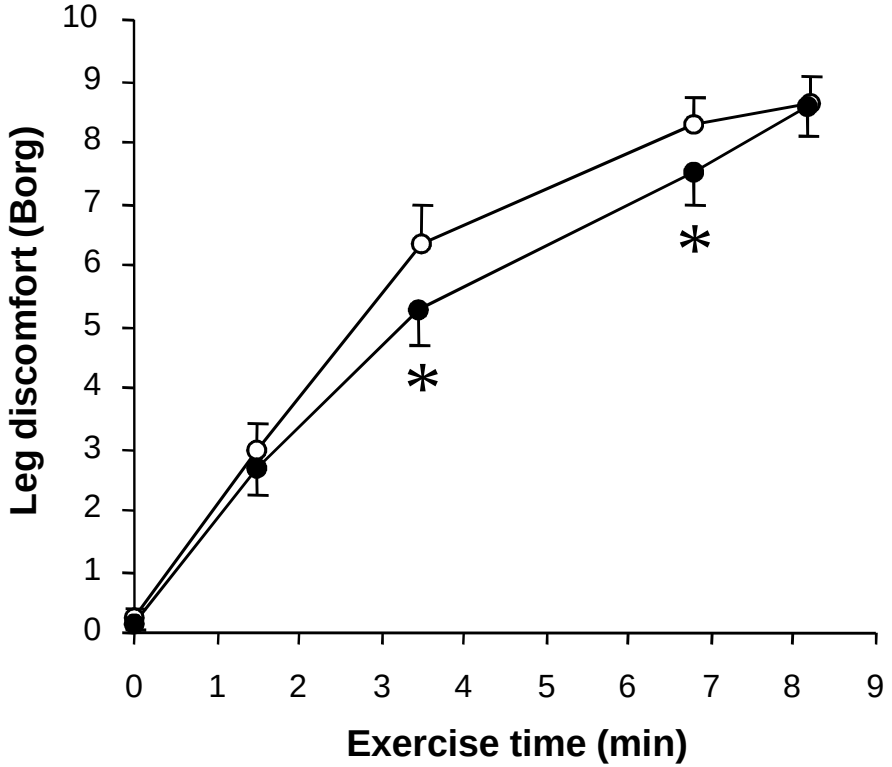
## FIGURE LEGENDS

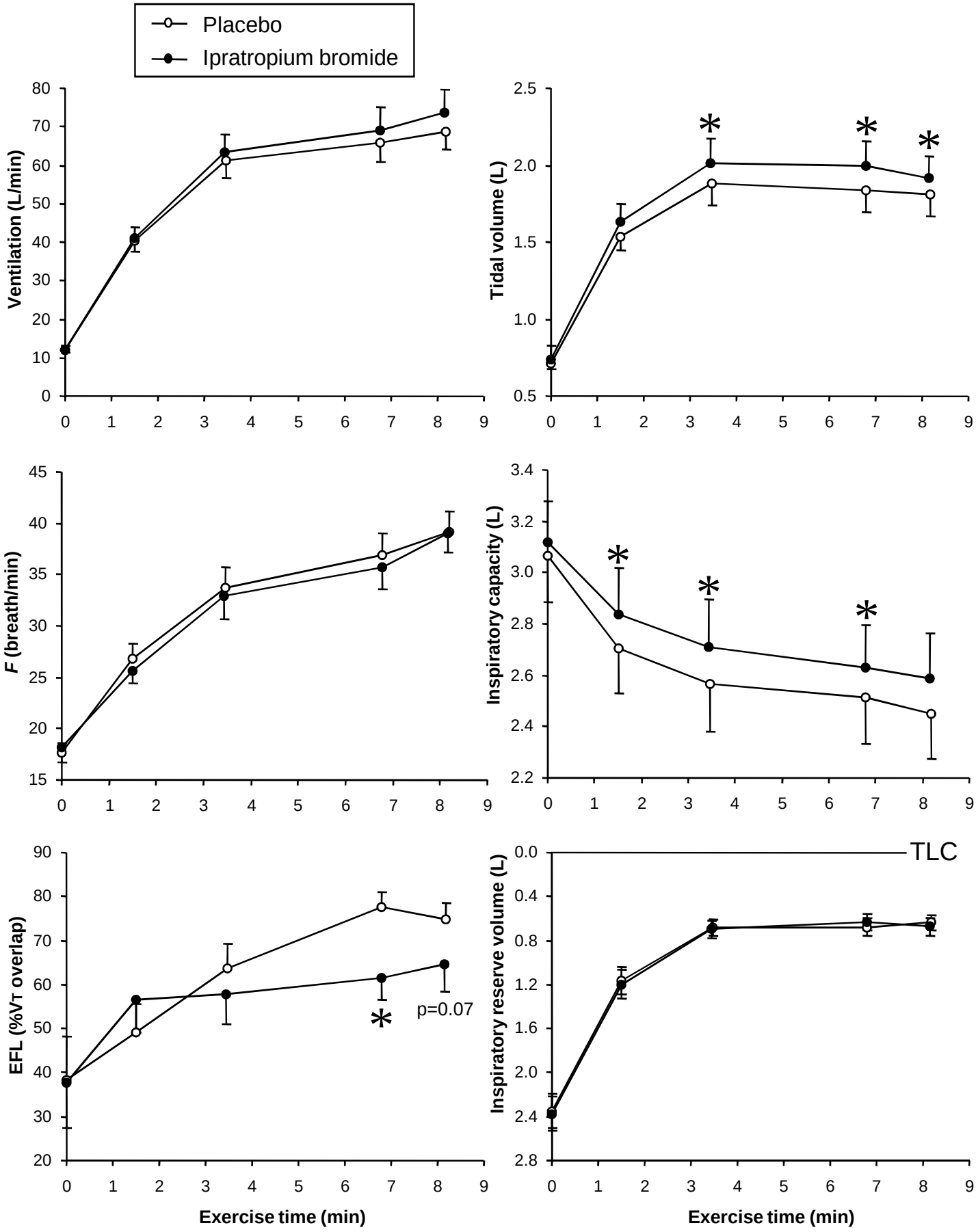
**Figure 1.** Ratings of dyspnoea intensity expressed relative to ventilation and ratings of intensity of leg discomfort are shown against exercise time during constant-load cycle testing at 80-85% of the maximum work rate achieved during incremental testing. *p<0.05 ipratropium bromide versus placebo at a given time-point. Values are means ± SEM.

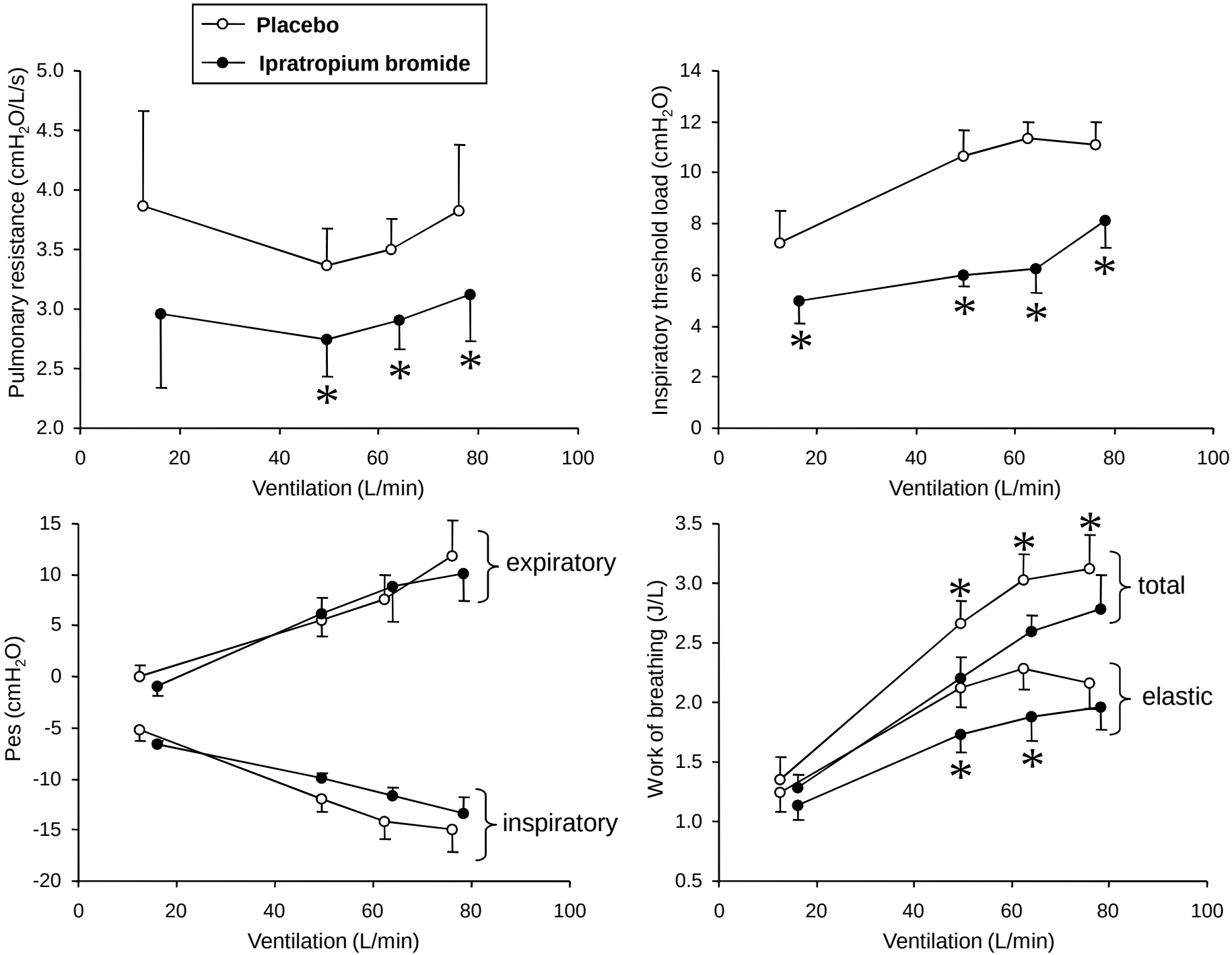
**Figure 2.** Ventilatory responses to constant-load exercise are shown against constant-load exercise time after ipratropium bromide (IB) compared with placebo (PL) in 16 subjects with mild COPD. Tidal volume ($V_T$), inspiratory capacity, and estimates of expiratory flow limitation (EFL) were lower after IB compared with PL; minute ventilation, breathing frequency (*f*) and inspiratory reserve volume were not different between treatments. TLC, total lung capacity. *p<0.05 ipratropium bromide versus placebo at a given time-point or at peak exercise. Values are means ± SEM.

**Figure 3.** Respiratory mechanical measurements are shown in 6 subjects during constant-load exercise after ipratropium bromide compared with placebo. Pulmonary resistance, the inspiratory threshold load, total work of breathing and the elastic work of breathing component all decreased during exercise after ipratropium bromide compared with placebo. However, peak tidal inspiratory and expiratory esophageal pressure (Pes) did not change in response to treatment. *p<0.05 (one-tailed) ipratropium bromide versus placebo at a given time-point or at peak exercise. Values are means ± SEM.







# Evaluation of Acute Bronchodilator Reversibility in Symptomatic GOLD Stage I COPD

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## ONLINE DATA SUPPLEMENT

### Measurement of Respiratory Mechanics

In a subgroup of consenting subjects, esophageal pressure (Pes) was recorded continuously during the post-treatment constant-load exercise tests using an integrated data acquisition set-up as described elsewhere.[1] An adult balloon-tipped catheter (Ackrad Laboratories, Cranford, NJ) was placed according to an accepted technique.[2] Pes was sampled continuously at a rate of 100 Hz by using a differential pressure transducer (MP45; Validyne Engineering, Northridge, CA), a signal conditioner (Carrier amplifier; Gould Electronics, Chandler, AZ), and computer data-acquisition software (CODAS; Dataq Instruments, Akron, OH). The continuous flow signal from the Vmax229d system was simultaneously input into this system for further analysis. Maximum inspiratory sniff maneuvers were performed pre-exercise at rest and immediately at end-exercise to obtain maximum values for Pes ($PI_{max}$). The inspiratory threshold load was calculated as the difference between Pes at the onset of inspiratory flow and at isovolume on the predicted chest-wall compliance curve.[3] The resistance to flow across the lung was calculated based on the differences in pressure and flow between two isovolume (mid-tidal) points.[4] Campbell diagrams were constructed to calculate work of breathing measurements.[5]

### Pulmonary Function Reversibility

Post-salbutamol $FEV_1$ and FVC were similar to post-IB measurements; significant improvements in response to salbutamol were also found in RV (-0.14 ±0.25 L, p=0.031), FRC (-0.13±0.17 L, p=0.007) and sRaw (-2.9±2.9 $cmH_2O \cdot s$, p=0.001) with no change in TLC (-0.01 ±0.16 L, p=0.568) (values are reported as means±SD). It is noteworthy that the airway reversibility effect size (for flow and lung volume change) with nebulized ipratropium bromide 500µg (IB) was broadly similar to that measured in response to inhaled salbutamol (400 µg), the latter was tested originally to identify patients fitting the GOLD stage I entry criteria.

### Exercise Endurance in Response to Bronchodilator

Exercise endurance time did not increase after bronchodilator compared with placebo in this group of patients with GOLD stage I COPD. It is clear that among our patients there was significant variability in the baseline endurance time at a constant work rate of 80-85 % maximum (placebo visit: range 4-24 min; average: 8.1±5.0 min). It follows that cycle exercise endurance protocols which have been shown to be sufficiently responsive for the purpose of evaluation of bronchodilator efficacy in more advanced COPD[6-9] may not be appropriate for patient populations with mild COPD.

### Reduced Leg Discomfort

We were surprised to find that, in contrast to several previous studies on the effects of bronchodilators in more advanced COPD, perceived leg discomfort was reduced during IB

compared to placebo in mild COPD. However, this subjective benefit was not sufficient to improve exercise endurance, even in patients who reported leg discomfort as the primary exercise limiting symptom. The mechanisms for this benefit, in so far as it pertains to acutely improved peripheral muscle function, are unknown. Thus, we were unable to demonstrate consistent improvements in indirect indices of cardiac function (heart rate, blood pressure, ventilatory threshold) or in pulmonary gas exchange (arterial oxygen saturation, $P_{ET}CO_2$ or $V_E/VCO_2$) which might have indicated improved blood perfusion or oxygen delivery to the active locomotor muscles. Similarly, work of breathing when corrected for minute ventilation or indirect assessment of the oxygen cost of breathing (pressure-time product) were not reduced during IB treatment in our small subgroup. Our results therefore did not support (or refute) the recently advanced hypothesis that increased competition between the ventilatory muscles and the active peripheral muscles for a finite oxygen delivery is a key factor limiting exercise performance in early COPD.[10]

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