

Effectiveness of salmeterol versus ipratropium bromide on exertional dyspnoea in COPD

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Effectiveness of salmeterol versus ipratropium bromide on exertional dyspnoea in COPD. M.L. Ayers, R. Mejia, J. Ward, T. Lentine, D.A. Mahler. ©ERS Journals Ltd 2001.

ABSTRACT: The hypothesis of the study was that salmeterol and ipratropium would have similar dyspnoea ratings during steady-state cycle ergometry at 1 h, but that salmeterol would reduce dyspnoea at 6 h after administration in patients with chronic obstructive pulmonary disease (COPD).

The study design was a randomized, double-blind trial in 16 patients (aged 63 ± 11 yrs) with symptomatic COPD. Two days after familiarization with testing procedures, patients were randomly assigned to receive either two puffs (42 µg) of salmeterol and two puffs of placebo inhaler, or two puffs (36 µg) of ipratropium from each of two inhalers (total, 72 µg). Two days later, patients received the alternative medication. During exercise at 60% of peak oxygen consumption patients rated dyspnoea and performed inspiratory capacity manoeuvres each minute.

Forced expiratory volume in one second was 1.13 ± 0.48 L ($37 \pm 13\%$ predicted). Dyspnoea ratings were similar for salmeterol and ipratropium at 1 and 6 h. Inspiratory capacity was similar for salmeterol and ipratropium at 1 h, but significantly higher for salmeterol at 6 h ($\Delta = 120$ mL; $p = 0.03$).

It is concluded that with the doses used, salmeterol and ipratropium provided similar dyspnoea ratings during exercise at 1 and 6 h after administration.

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Bronchodilator medications are prescribed to improve expiratory airflow and to reduce symptoms in patients with chronic obstructive pulmonary disease (COPD). The traditional approach to evaluate the response to bronchodilator therapy has been to examine the improvement in lung function, particularly forced expiratory volume in one second (FEV₁), as the most comprehensive physiological test [1–4]. Over the past decade, investigators have shown that patients with COPD develop dynamic hyperinflation (DH) during exertion, which can contribute to dyspnoea [5–7].

At the present time, only two studies have examined the effects of bronchodilator therapy on DH and its possible role in the relief of exertional dyspnoea. In 1996, BELMAN *et al.* [8] found that three puffs of inhaled salbutamol reduced exercise DH and improved neuroventilatory coupling (the relationship of inspiratory effort and the resultant mechanical response) as well as exertional breathlessness in 13 patients with COPD. In 1998, O'DONNELL *et al.* [9] showed that 500 µg of nebulized ipratropium bromide improved exercise endurance time and inspiratory capacity (IC), as well as reduced the slope of dyspnoea ratings over time, compared with placebo.

Although comparison of a bronchodilator medication with placebo can demonstrate efficacy, a more relevant consideration is direct head-to-head

comparison with another bronchodilator in order to examine effectiveness. The purpose of the present study was to compare the acute effects of salmeterol (S), an inhaled long-acting β_2 -adrenergic bronchodilator, with ipratropium bromide (IB), an inhaled anticholinergic bronchodilator, on exertional breathlessness. Both medications have been recommended as maintenance therapy in the treatment of symptomatic COPD [1, 10, 11]. The hypothesis of the study was that S and IB would similarly reduce dyspnoea during steady-state cycle ergometry at 1 h, but that S would provide a greater reduction at 6 h after administration. To investigate the effects of these medications on DH and its impact on the sensation of dyspnoea, the patients performed IC manoeuvres during exercise after both S and IB therapy.

Materials and methods

Study subjects

Patients were recruited from the outpatient clinics at the authors institution (Dartmouth Medical School, Lebanon). The following inclusion criteria were used: 40–80 yrs of age; a diagnosis of COPD as defined by the American Thoracic Society [1]; an FEV₁/forced vital capacity (FVC) ratio of $\leq 70\%$; and dyspnoea on

exertion. Exclusion criteria were: inability to tolerate temporary discontinuation of bronchodilator medications prior to each visit; inability to exercise on the cycle ergometer; an unstable respiratory status within the previous 4 weeks; any clinically significant comorbid disease; presence of an active infection; $> 10 \text{ mg}\cdot\text{day}^{-1}$ of prednisone; and a change in the dose of inhaled corticosteroid in the past month. The study was approved by the Institution Review Board and each patient provided written consent.

Study design

The study was a randomized, double-blind trial. At visit 1, patients were familiarized with the testing procedures. At visit 2 (2–3 days later), each patient was randomly assigned by alternating order to receive either inhaled S or inhaled IB prior to testing. At visit 3 (2–3 days later), the patients received the alternative medication. Prior to any testing at all three visits, patients were instructed not to use short-acting inhaled bronchodilators for 8 h, and long-acting bronchodilators for 24 h. All testing was started by 08:00–08:30 h at all three visits. At visits 2 and 3 the sequence of testing was spirometry, measurement of IC and lung volumes before and 1 h after inhalation of the study bronchodilator, and then exercise testing. The same sequence was used at 6 h after inhalation of the study medication.

Methods

Visit 1. The purpose of visit 1 was for practice and familiarization with the technique. Spirometry, IC, and single-breath carbon monoxide diffusing capacity (DL_{CO}) were measured using the SensorMedics 2200 testing system (Yorba Linda, CA, USA). Lung volumes were then measured by body plethysmography (SensorMedics). Patients were seated on an electronically-braked cycle ergometer (ErgoMetrics 800S, ErgoLine, Bitz, Germany) and practiced performing IC manoeuvres while cycling at no work load. The following written and verbal instructions were given: "At the end of a normal breath out, take a full, deep inspiration". The practice sessions took about 5–10 min until each subject was able to produce consistent IC values. During a 10-min rest period, each patient read the following instructions regarding the 0–10 category-ratio (CR-10) scale [12]: "This is a scale for rating breathlessness. The number 0 represents no breathlessness. The number 10 represents the strongest or greatest breathlessness that you have ever experienced. Each minute during the exercise test you will be asked to point to a number with your finger which represents your perceived level of breathlessness at that time. Use the written description to the right of the number to help guide your selection. I will say the number out loud to confirm your choice. During the exercise test you may have an even stronger or greater intensity of breathlessness than you have ever experienced. You should then point to the word 'maximal' if the severity is greater than 10. You can

tell us the number after the mouthpiece has been removed".

While seated on the cycle ergometer, each subject breathed ambient air through a mouthpiece and a hot wire pneumotachygraph. Expired gas was analysed for minute ventilation ($V'E$), oxygen consumption ($V'O_2$), and carbon dioxide production ($V'CO_2$) using breath-by-breath analysis from the (V_{max}) system (SensorMedics). After a 5-min equilibration period, the patients started exercise at zero load at a pedal speed of 50 revolutions per minute (rpm). After 1 min, a load of $12.5 \text{ W}\cdot\text{min}^{-1}$ was applied, and thereafter increased by $12.5 \text{ W}\cdot\text{min}^{-1}$ every minute until the patient reached exhaustion or stopped because of symptom limitation. At each minute the patient was asked to rate the intensity of dyspnoea on the CR-10 scale. There was continuous monitoring of 12-lead electrocardiography (ECG) and oxygen saturation by pulse oximetry (Oxyshuttle; SensorMedics).

After a 30 min rest each participant performed steady-state exercise at $\sim 60\%$ of peak $V'O_2$ for 10 min. Expired gases, ECG, and oximetry were measured continuously as described for the incremental exercise test. After steady-state was achieved (first 5 min of exercise) the patient gave a rating of breathlessness at 40 s after the start of each minute (min 6–10) and was then instructed to perform an IC manoeuvre. The flow/volume loop was visualized by one of the investigators to verify that the start of each IC manoeuvre occurred at a consistent end-expiratory lung volume (EELV) and reached the expected end-inspiratory lung volume (EILV) as previously determined on a maximal flow/volume loop at rest which was displayed on the monitor. Prior to and upon completion of the study, the accuracy of the IC values using the V_{max} system during steady-state exercise was confirmed with measurements using a pneumotachygraph system.

Visit 2 (2–3 days later). After initial measurements each patient was randomly assigned to receive two puffs (42 μg) of salmeterol and two puffs of an identical appearing placebo inhaler or two puffs (36 μg) of ipratropium bromide from each of two inhalers (total, 72 μg). All patients were familiar with use of a metered-dose inhaler (MDI) and had demonstrated an appropriate technique at visit 1. The following instructions were provided: "breathe out normally; put your mouth around the end of the inhaler; as you start to breathe in, actuate the inhaler and breathe in the spray with a slow, deep breath; hold your breath for up to 10 s; wait one minute and repeat the process".

One of the investigators observed each patient inhale the study medication. At both 1 and 6 h after inhalation of the study medication each patient performed the following tests: spirometry, IC, lung volumes, and then steady-state exercise on the cycle ergometer for 10 min. The same instructions and testing procedures were used as described at visit 1.

Visit 3 (2–3 days later). Baseline FEV₁ was required to be within $\pm 5\%$ of the value at visit 2. Patients returned for similar testing as described for visit 2

Table 1. – Baseline characteristics of the subjects

Subjects n	16
Sex M:F	9:7
Age yrs	63 ± 11
Weight kg	81 ± 18
Height cm	170 ± 9
Lung function	
FEV ₁ L	1.13 ± 0.48 (37 ± 13)
FVC L	3.01 ± 0.92 (77 ± 14)
FEV ₁ /FVC %	37 ± 9
TLC L	7.50 ± 1.80 (124 ± 22)
FRC L	5.71 ± 1.43 (175 ± 38)
RV L	4.48 ± 1.35 (210 ± 66)
IC L	2.00 ± 0.74
Oxygenation	
Sa _a O ₂ %	95 ± 2
Exercise performance	
Peak $\dot{V}O_2$ l·min ⁻¹	1.13 ± 0.50 (48 ± 15)
Peak power watts	76.4 ± 29.0
Peak $\dot{V}E$ l·min ⁻¹	40.4 ± 21.1 (88 ± 19)
Peak heart rate beats·min ⁻¹	128 ± 24 (76 ± 14)
Peak ratings (0–10)	
Dyspnoea	6.3 ± 2.5
Leg discomfort	5.3 ± 2.7

Values are presented as mean ± SD; values in parenthesis represent per cent of the predicted value. FEV₁: forced expiratory volume in one second; FVC: force vital capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; IC: inspiratory capacity; Sa_aO₂: arterial oxygen saturation; $\dot{V}O_2$: oxygen consumption; $\dot{V}E$: minute ventilation.

except they received the alternative medication. Predicted values for lung function were taken from CRAPO *et al.* [13].

Calculations

STUBBING *et al.* [14] have shown that total lung capacity (TLC) does not change during exercise in patients with COPD. Accordingly, EELV was calculated by subtracting IC from TLC. EILV was determined by adding exercise tidal volume to EELV.

Statistical analysis

The major outcome of the study was ratings of dyspnoea during exercise. Values at visits 2 and 3 at

respective time periods were compared using the paired t-test for FEV₁ and lung volumes and analysis of variance for multiple comparisons (MANOVA) for selected variables during steady-state exercise. Correlations among various physiological variables and dyspnoea ratings were made using the Spearman rank order correlation test.

It was calculated that 16 patients were required to have 80% power to detect a mean difference between subjects of 1 unit on the CR-10 scale at an alpha of 0.05 (two-sided) based on a standard deviation of 1 unit. A p-value < 0.05 was considered as significant.

Results

Subjects

Of the 17 patients recruited for the study, 16 completed testing. One subject withdrew from the study after visit 1 because of an acute respiratory infection. Baseline characteristics of the subjects are listed in table 1.

Lung function

There were no significant differences for spirometry, IC, and lung volumes at baseline testing at visits 1, 2, and 3. Values for these physiological variables at 1 and 6 h after inhalation of the study medication are shown in table 2. For both S and IB there were significant increases in FEV₁, FVC, and IC at 1 and 6 h and significant decreases in FRC and residual volume (RV) at 1 and 6 h. Direct comparisons between the two medications showed no significant differences in any of these measures.

Exercise responses

Values for dyspnoea ratings and for selected physiological variables during min 6–10 of steady-state exercise are shown in table 3. These data indicate that the exercise intensity and the major cardiorespiratory responses were nearly identical during exercise with bronchodilator therapies. Of note, heart rate (HR)

Table 2. – Values for forced expiratory volume in one second (FEV₁) and lung volumes at rest after bronchodilator therapy

	1 hour				6 hour			
	S	IB	Mean (95% CI) diff.*	-value	S	IB	Mean (95% CI) diff.*	-value
FEV ₁	1.36 ± 0.50 (20)	1.33 ± 0.47 (18)	0.03 (-0.07–0.13)	0.53	1.36 ± 0.58 (20)	1.25 ± 0.48 (11)	0.11 (-0.06–0.30)	0.19
FVC	3.48 ± 1.01 (16)	3.55 ± 0.91 (18)	-0.07 (-0.17–0.05)	0.24	3.46 ± 1.09 (15)	3.23 ± 0.88 (7)	0.23 (-0.02–0.47)	0.07
TLC	7.34 ± 1.63 (-2)	7.27 ± 1.62 (-4)	0.07 (-0.05–0.20)	0.24	7.48 ± 1.59 (0)	7.38 ± 1.66 (-2)	0.10 (-0.05–0.25)	0.17
FRC	5.22 ± 1.20 (-9)	5.04 ± 1.35 (-12)	0.18 (-0.01–0.38)	0.07	5.11 ± 1.21 (-11)	5.20 ± 1.45 (-9)	-0.09 (-0.38–0.21)	0.54
RV	3.81 ± 1.07 (-15)	3.73 ± 1.16 (-17)	0.08 (-0.08–0.24)	0.31	3.92 ± 1.02 (-13)	4.07 ± 1.17 (-9)	-0.15 (-0.40–0.12)	0.27
IC	2.12 ± 0.56 (6)	2.23 ± 0.51 (12)	-0.11 (-0.37–0.14)	0.11	2.37 ± 0.55 (19)	2.18 ± 0.63 (9)	0.19 (-0.21–0.28)	0.77

Data are presented as mean ± SD (% change from premedication values). S: salmeterol; IB: ipratropium bromide; CI: confidence interval. FVC: force vital capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; IC: inspiratory capacity; *: mean differences between S and IB. The paired t-test was used to compare S and IB at 1 and 6 h.

Table 3. – Values for selected variables during steady-state exercise

Parameter	1 hour			6 hour		
	S	IB	Mean (95% CI) & the difference between S and IB	S	IB	Mean (95% CI) & the difference between S and IB
Work watts	25±15	25±15	0.0 (0.0–0.0)	25±15	25±15	0.0 (-0.9–0.4)
$\dot{V}O_2$ L·min ⁻¹	0.65±0.23	0.65±0.24	0.00 (-0.05–0.05)	0.67±0.23	0.64±0.20	0.03 (-0.01–0.06)
HR beats·min ⁻¹	101±18	95±17 [#]	6.0 (1.1–10.9)	101±14	101±15	0.0 (-4.8–4.8)
$\dot{V}E$ L·min ⁻¹	26±8	26±8	0.0 (-2.3–3.2)	26±8	24±6	2.0 (-0.5–3.1)
Tidal volume L	1.18±0.35	1.18±0.32	0.0 (-0.09–0.08)	1.12±0.33	1.08±0.26	0.04 (-0.10–0.09)
IC L	2.03±0.65	1.99±0.56	0.04 (-0.04–0.15)	1.88±0.71	1.76±0.55 [†]	0.12 (0.00–0.24)
EILV L	6.49±1.56	6.47±1.56	0.02 (-0.08–0.17)	6.57±1.45	6.68±1.62	-0.11 (-0.16–0.26)
EELV L	5.31±1.38	5.28±1.42	0.03 (-0.08–0.18)	5.60±1.35	5.62±1.53	-0.02 (-0.24–0.21)
Dyspnoea (0–10)	2.0±1.3	1.9±1.4	0.1 (-0.6–0.8)	2.1±1.2	2.2±1.2 ⁺	-0.1 (-0.5–0.2)

Values are presented as mean±SD during 5 min of steady-state exercise; $\dot{V}O_2$: oxygen consumption; HR: heart rate; $\dot{V}E$: minute ventilation; IC: inspiratory capacity; EILV: end-inspiratory lung volume; EELV: end-expiratory lung volume; CI: confidence interval; S: salmeterol; IB: ipratropium bromide. Analysis of variance for multiple comparisons used to compare S and IB at 1 and 6 h. [#]: $p=0.02$ for $S>IB$ at 1 h; [†]: $p=0.03$ for $S>IB$ at 6 h; ⁺: $p=0.05$ for $S<IB$ at 6 h; For all other comparisons between S versus IB, $p>0.05$.

response was higher with S (101 ± 18 beats·min⁻¹) compared with IB (95 ± 17 beats·min⁻¹) at 1 h ($p=0.02$).

At both 1 and 6 h, dyspnoea ratings were similar with the two medications, although statistical comparison showed borderline significance for $S<IB$ at 6 h ($p=0.05$) (fig. 1a). Values for IC were similar with S and IB at 1 h; at 6 h IC was significantly higher with S compared with IB ($\Delta=120$ mL; $p=0.03$) (fig. 1b).

Correlation analyses

When considering data at 1 and 6 h with both medications at visits 2 and 3 ($n=64$), dyspnoea ratings during steady-state exercise were significantly correlated with IC values ($r_s=-0.28$; $p=0.03$). However, there were no significant correlations between dyspnoea ratings during exercise and resting lung function or other exercise variables.

Discussion

The present results showed that two puffs (42 µg) of S and four puffs (72 µg) of IB provided similar dyspnoea ratings during steady-state exercise at both 1 and 6 h after administration. Furthermore, physiological variables during exercise were also comparable between the two bronchodilator medications, except for a higher IC with S than with IB at 6 h ($\Delta=120$ mL). However, the difference in the IC did not contribute to a corresponding reduction in breathlessness with S.

Several factors in the design of the study were considered. In comparing a long-acting β_2 -adrenergic agonist and an anticholinergic agent, generally accepted doses as used commonly in clinical practice were selected. For S, 42 µg (two puffs) were used. Studies have shown no additional bronchodilator benefit with higher doses [15, 16]. For IB, bromide 72 µg (four

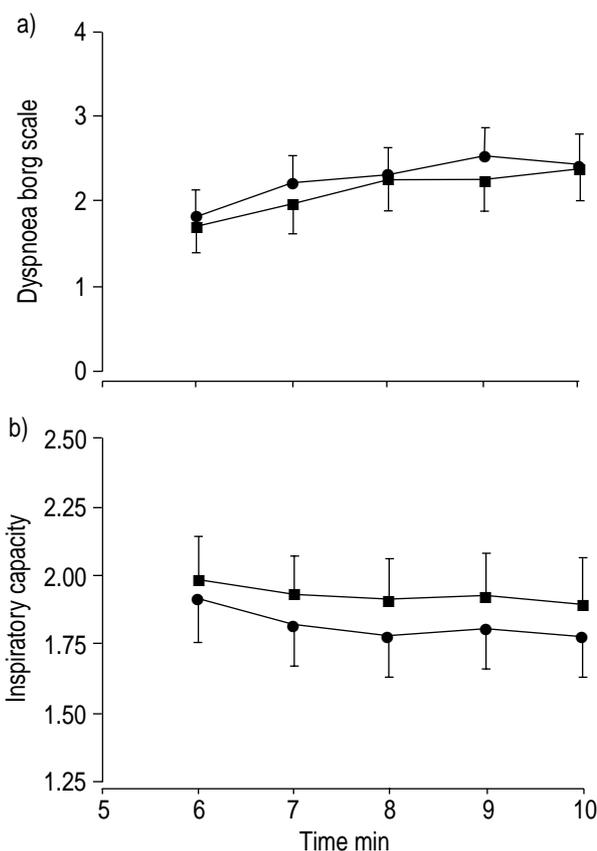


Fig. 1. – a) Dyspnoea ratings (mean±SD) at 6 h during min 6–10 of steady-state exercise with salmeterol (■) and ipratropium bromide (●) for the 16 patients. Dyspnoea ratings were similar with the two medications, although statistical comparison showed borderline significance for salmeterol (S) less than ipratropium bromide (IB) ($p=0.05$). b) Values for inspiratory capacity (IC) in Litres at 6 h during min 6–10 of steady-state exercise with S (■) and IB (●) for the 16 patients. IC was significantly higher with S compared with IB ($p=0.03$).

puffs) were used. Although two puffs is considered the starting dose, higher doses are used frequently [1, 10]. Thus, it was considered that four puffs of IB and two puffs of S would be a clinically relevant comparison. In fact, the changes in resting lung function were similar after S and for IB (table 2). Exertional breathlessness was chosen as the major outcome of the study because it is the most frequent complaint of patients with COPD. Furthermore, a preliminary report describing the objectives of the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) emphasized a "symptom-driven approach" for treatment of this condition [17]. In addition to evaluation of dyspnoea in this study, the development of exercise DH as a potential factor contributing to exertional dyspnoea was also examined [6, 8, 9]. Thus, both dyspnoea ratings and IC were measured during exercise and the responses of these two bronchodilator medications compared.

However, a placebo arm was not included in the study design for two major reasons. Firstly, the hypothesis of the study addressed a head-to-head comparison of these maintenance bronchodilators at doses used in clinical practice in the treatment of COPD (*i.e.* effectiveness). Secondly, previous studies have shown that both S and IB reduce dyspnoea relative to placebo therapy [9, 11, 18]. For example, O'DONNELL *et al.* [9] showed that nebulized IB decreased dyspnoea ratings and increased IC compared with placebo during submaximal exercise on the cycle ergometer. Therefore, inclusion of a placebo trial was considered not to be either necessary or important.

An additional consideration was the time period for examining the effects of the agents. BELMAN *et al.* [8] studied the immediate (~ 2 h) effects of albuterol therapy and O'DONNELL *et al.* [9] performed testing before and 1 h after patients received nebulized IB or placebo, both at the beginning and at the end of an 8-week study. However, S has a 12-h duration of action, whereas IB lasts ~ 4 –6 h. Thus, in order to complete testing for each medication in a single day, these agents were compared at two time periods, at 1 h, when the benefits might be similar, and at 6 h when S might provide greater effectiveness because of a longer duration of action.

As expected, both medications improved expiratory airflow (increased FEV₁) and lung volumes (increased FVC and IC; decreased FRC and RV) at both time periods. The acute improvements in FEV₁ and FVC observed with S and IB were similar to those observed by investigators in other studies [11, 18, 19]. Furthermore, the reductions in resting lung volumes (FRC and RV) with S were comparable in magnitude to the changes observed by RAMIREZ-VENEGAS *et al.* [18] with S over a 4-h time period. Any decreases in lung hyperinflation with inhaled bronchodilator therapy should enable the patient to breathe with improved ventilatory mechanics [8, 9]. As such, the benefits should include reductions in: mechanical restriction; elastic threshold loading; and inspiratory pleural pressure swings [20, 21].

To investigate the possible role of DH as a mechanism contributing to the sensation of exertional

breathlessness, the patients performed IC manoeuvres during steady-state exercise. At the initial visit, each patient practiced the IC manoeuvre firstly at rest and then during cycle ergometry. Steady-state exercise rather than incremental exercise was selected for three reasons. Firstly, the authors experience has been that patients with COPD can perform IC manoeuvres more consistently during submaximal, steady-state exercise as opposed to incremental exercise. Patients and healthy individuals may experience difficulty doing IC manoeuvres at high intensities of exercise due to the excessive physiological and subjective demands. Secondly, submaximal exercise is clearly more relevant to daily activities experienced by patients with COPD as opposed to incremental exercise to exhaustion. Thirdly, studies have demonstrated that steady-state exercise is more responsive to change with anticholinergic therapy in patients with severe COPD [9, 22].

Except for the slightly higher IC during exercise with S at 6 h ($p=0.03$ versus IB), both bronchodilator agents otherwise provided comparable physiological and perceptual exercise responses. The actual values for IC during exercise in the present study were similar in magnitude to those observed after nebulized IB by O'DONNELL *et al.* [9], who had subjects exercise at 50–60% of the maximum work rate. Unfortunately, neither BELMAN *et al.* [8] or YAN *et al.* [7] reported actual IC values during exercise in patients with COPD.

Previous investigators have demonstrated the validity and utility of measuring IC during exercise to evaluate the development of DH in patients with COPD [5–9, 23]. In brief, DH can be determined noninvasively by having the subject perform successive IC manoeuvres during exercise. Based on the finding by STUBBING *et al.* [14] that TLC does not change during exertion in patients with COPD, an observed decrease in IC reflects an increase in EELV (*i.e.* DH) [5, 7, 20]. Although DH allows patients to generate greater expiratory flow, the consequences include shortening of the vertical muscle fibres of the diaphragm and an elastic load on the muscles during inspiration [20, 21]. Previous studies of inhaled bronchodilator therapy in patients with COPD have shown that even a modest reduction in DH may contribute to an improvement in dyspnoea [8, 9, 24].

Although a significant relationship between dyspnoea ratings and IC was observed during exercise, the correlation coefficient was low ($r_S=-0.28$). O'DONNELL *et al.* [9] observed a slightly higher, albeit modest correlation coefficient (-0.35) among changes in the same parameters. These results suggest that although DH can contribute to exertional breathlessness in patients with COPD, additional physiological and/or sensory factors are also important to the perception of dyspnoea during exercise.

To the best of the authors' knowledge, only one previous study has compared the effects of S and IB on exertional dyspnoea and exercise responses in patients with COPD. In a previous study, PATAKAS *et al.* [25] compared 50 μg (two puffs) of S and 120 μg (six puffs) IB on breathlessness during treadmill exercise in 15 patients with COPD. The authors

found that the distance walked increased significantly with both S and with IB, but the distance walked on the treadmill when patients had no breathlessness was increased with S ($p < 0.05$), but not with IB. PATAKAS *et al.* [25] concluded that the overall effects of these two medications were similar as related to the dyspnoea sensation during exercise. Thus, the present results both confirm and extend these observations on the effectiveness of S and IB.

In summary, at the doses used, salmeterol and ipratropium bromide had similar effects on both physiological and perceptual outcomes at 1 and 6 h after administration, at rest as well as during steady-state exercise. Previous studies have demonstrated the efficacy of salmeterol and ipratropium bromide on similar outcomes compared to placebo medication [9, 11, 18]. Although dynamic hyperinflation contributed, at least in part, to the severity of exertional dyspnoea in this study, other factors appear to be important in explaining the sensation of breathlessness in patients with chronic obstructive pulmonary disease.

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