Endurance Shuttle Walking Test: Responsiveness to Salmeterol in COPD

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ABSTRACT

Background: Few studies have shown that the endurance shuttle walking test (ESWT) is responsive to treatment in patients with chronic obstructive pulmonary disease (COPD). This exercise test needs to be further investigated because of its relevance for activity of daily living.

Objective: To evaluate, in patients with COPD, the responsiveness of the endurance shuttle walk to detect improvement in walking performance after single dose of salmeterol.

Methods: In a randomised, double-blind, placebo-controlled, crossover trial, 20 patients with COPD performed two ESWT at 80% of peak capacity 2.5 hours after inhaling either a placebo or 50µg of salmeterol. Cardiorespiratory parameters were monitored during each walking test. Inspiratory capacities and Borg ratings for dyspnea were obtained every other minute throughout the tests.

Results: Compared to placebo, salmeterol produced a significant change in lung function and a significant improvement in walking performance (Δ time: 117 (96) seconds, p = 0.02; Δ distance: 160 (125) meters, p = 0.02). At isotime, a significant reduction in dyspnea was observed after bronchodilation.

Conclusion: Bronchodilation with salmeterol reduced dyspnea during walking and improved walking capacity in patients with COPD. These findings provide further support for the use of the ESWT as an evaluative tool in COPD.

Word count: 199
**Keywords:** bronchodilators; chronic obstructive pulmonary disease; endurance; exercise capacity; exercise testing; salmeterol.
INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) complain of premature exertional dyspnea and leg fatigue[1] and exercise intolerance mainly due to a reduced ventilatory capacity, impaired gas exchange and peripheral muscle dysfunction. While short-acting bronchodilators may be sufficient to handle symptoms in the early phases of the disease process, long-acting bronchodilators are typically better suited to treat patients with more advanced disease[2, 3].

Long-acting bronchodilators, such as salmeterol and tiotropium, have been shown to improve dyspnea and quality of life and to reduce exacerbations in patients with COPD [4-6]. In well-designed, randomized, placebo-controlled clinical trials, these two bronchodilators have also been convincingly shown to improve the endurance time to submaximal cycling exercise in this patient population[7-9]. This benefit can be shown in the few hours following the administration of the first dose of the medication[7, 8]. For a given exercise stimulus, long-acting β2-agonists and anticholinergics also reduce the perception of dyspnea[8, 9].

Although the symptomatic and functional benefit associated with these drugs is felt to be clinically relevant, we do not know whether the observed improvement in cycling capacity would translate into better performances in different activities of daily living, such as walking.-To date, clinical trials assessing the impact of salmeterol on walking performance in COPD patients have led to disappointing results[6, 10, 11]. However, these trials used the six-minute walking test (6MWT), a test recently shown to lack sensitivity to bronchodilation[12, 13]. Thus, it is possible that the impact of salmeterol on walking performance was underestimated by these clinical trials.
Recently, the endurance shuttle walking test (ESWT), an externally-paced field walking test, was found to be responsive to bronchodilation and to rehabilitation [13-15]. The present investigation was therefore undertaken to test, in patients with COPD, the hypothesis that the ESWT is responsive to detect improvement in walking capacity following a single dose of salmeterol. More specifically, the objectives of the study were to i) measure the acute changes in walking performance induced by a single dose of salmeterol against those induced by a placebo, and ii) evaluate the physiological (\( \dot{V}E \), \( \dot{V}O_2 \), \( \dot{V}CO_2 \), heart rate and inspiratory capacity) and symptomatic (dyspnea) responses during each walking test to provide a mechanistic explanation to our findings.
METHODS

Subjects
Twenty Patients with clinically stable COPD participated in this study. Inclusion criteria were as follows: (1) age ≥ 50 yrs (2) current or past smoking history of ≥ 10 pack-yrs (3) a forced expiratory volume in one second (FEV₁) ≤ 70% of the predicted value (4) FEV₁/forced vital capacity (FVC) ≤ 70% (5) no acute COPD exacerbation within the preceding 2 months (6) no history of asthma (7) no significant O₂ desaturation (SaO₂ < 85%) at rest or during exercise, and (8) no other active condition that could influence exercise tolerance. Patients on long-acting anticholinergics were excluded from the study due to the long wash out period required for this medication. No participant was involved in pulmonary rehabilitation in the previous year. The research protocol was approved by the institutional ethics committee, and a signed, informed consent was obtained from each subject.

Study design
The study required 5 visits at the research facility. Each visit was separated by at least 48h and no more than 4 days. The first visit included a baseline assessment of pulmonary function and an incremental shuttle walking test (ISWT). The following two visits (visits 2 and 3) were used to familiarize participants to the ESWT. The goal of the familiarization was to reduce the learning effect that typically occurs when an individual completes the same endurance test several times⁸. We also excluded patients whose ESWT at visit 2 and 3 were not reproducible (when the difference in endurance time between visit 2 and 3 was greater than 2 minutes) or longer than 20 minutes. For the remaining two visits (visits 4 and 5), subjects entered a cross-over design where
they completed one ESWT at each visit, 150 ± 15 minutes after the inhalation of 50 µg of salmeterol (Serevent®) or the inhalation of a placebo. Pulmonary function tests were performed before (pre-dose) and 120 ± 20 minutes after (post-dose) the inhalation of the placebo or salmeterol. The medication was administered in a randomized and double-blind fashion using the Diskus® device, which was identical in appearance between placebo and active medication. Treatment sequence was determined using a random number table.

All visits were conducted at the same time of the day for each subject. Subjects remained on their usual medication between visits. Short-acting β2-agonists and short-acting anticholinergics were stopped 6 hrs preceding visits 2 to 5, while theophyllines and long-acting β2-agonists were stopped 48 hrs before visits 4 and 5. Inhaled salbutamol (short-acting β2-agonists) was used as rescue medication when subjects had to stop their medication for 48 hrs. Finally, subjects were asked to avoid smoking, caffeine, dark chocolate, cola beverages, heavy meals, alcohol and major physical exertion prior to visits because these factors can influence exercise performance.

The sponsor (GSK) was not involved in the study design, data collection, analysis and interpretation. The sponsor had the opportunity to read and comment the manuscript with no obligation for the authors to incorporate any suggestion into the final version.

**Pulmonary function testing**

Standard pulmonary function tests, including spirometry, lung volumes and diffusing capacity (DLco) were measured according to previously described guidelines[16]. Results were compared with predicted normal values from the European Community for Coal and Steel/European
Respiratory Society[17]. Maximum voluntary ventilation (MVV) was estimated by multiplying FEV₁ by 35[18].

**Incremental walking exercise test**

Peak walking capacity was determined with the ISWT[19] that was performed in an enclosed corridor on a flat 10-meter-long course. The course was identified by two cones, each positioned 0.5m from either end to allow patients to walk in circle and thereby avoid the need for abrupt changes in direction. Patients had to follow the rhythm dictated by the audio signal. Walking speed was initially set at 0.5 meters/second and subsequently increased by 0.17 meters/second every minute until the patient reached a symptom-limited maximum. Encouragement was provided during the test and patients received standardized instructions to walk for as long as possible.

**Endurance walking exercise test**

Endurance walking capacity was determined with the ESWT. The ESWT was performed on the same course than the ISWT in accordance with published guidelines[20]. After 1.5 minutes of warm-up, walking speed was set at the speed corresponding to 80% of VO₂ peak, as predicted from the ISWT[20]. Before each ESWT, patients received standardized instructions to walk for as long as possible although there was a predetermined 20-minutes maximum. No encouragement was provided during these tests to avoid any potential confounding effect on exercise performance[21]. Reproducibility criteria were set at $\leq 2$ minutes or 10% between consecutive ESWT.

**Physiological measures**
Cardiopulmonary measures. During each exercise test, gas exchange parameters ($\text{VO}_2$, $\text{VCO}_2$, $\text{VE}$, oxygen saturation (SpO$_2$), respiratory rate (RR), tidal volume (V$_T$) and heart rate (HR)) were monitored breath by breath with a portable telemetric system (Oxycon Mobile, Jaeger, Viasys Healthcare GmbH, Germany). This system, both light (950g including belt, battery and mask) and compact, consisted of a facemask, heart rate monitor, battery, transmitting unit (containing the O$_2$ and CO$_2$ gas analyzers) and receiving unit. The volume sensor and gas analyzers were calibrated before each test. Patients were asked to perform inspiratory capacity manoeuvres at two-minute interval during the exercise period. This was done to follow changes in operational lung volumes occurring during exercise as previously described[22]. When end-expiratory volume was stable, as indicated by real time flow/volume loops, subjects were asked, at the end of a normal expiration, to take a deep inspiration to total lung capacity.

Subjective measures
Dyspnea and perception of leg fatigue were evaluated at rest and at end-exercise using the modified 10-point Borg scale[23]. Dyspnea was also evaluated at two-minute intervals during the exercise tests. At the end of each test, patients were asked to identify the main reason for which they stopped the test.

Statistical analysis
Results are reported as mean (standard deviation, SD), unless otherwise reported. The level of significance of $\alpha=0.05$ was used for all analyses. The endurance time was defined as the duration of walking at 80% maximum capacity, excluding the 1.5-minute warm-up period. Comparisons of the values observed with salmeterol and placebo were made using a 2 x 2 cross-over design in
which the period, sequence and treatment effects were considered. In order to study possible
determinants of the improved walking capacity after bronchodilation, multiple regression analysis
was performed using the changes in walking endurance time as the dependant variable and the
post-bronchodilator changes in FEV\textsubscript{1}, FVC, FRC, inspiratory capacity, and dyspnea at isotime
during exercise as independant variables. Isotime was defined as the latest exercise time that was
reached on both ESWT. The sample size calculation was based on the assumption that the
improvement in the walking endurance time with salmeterol should be at least of similar
magnitude than that of ipratropium bromide (164 ± 177s)[14]. We computed that 20 patients
would be needed to complete the study with a power of 0.85 and a type I error of 0.05.
RESULTS

Subjects
The study flow chart is presented in figure 1. Twenty-eight patients initially volunteered to participate to the study and 20 patients were actually randomized at visit 4 and received the study medication. These patients all completed the study. The following results pertain to this population. Subject characteristics are presented in Table 1. Thirty percent of the study group was composed of women. Patients had on average moderate to severe airflow obstruction with mild hyperinflation and gas trapping at rest.

Pulmonary function
Pre and post dose pulmonary function measurements are shown in Table 2. Significant drug effects were found after treatment with salmeterol compared to placebo. The pre and post bronchodilator improvements in FEV\textsubscript{1} and FVC and reduction in RV were significantly larger for salmeterol compared to placebo (Table 2).

Endurance time and walking distance
No sequence or carry-over effect was observed in this investigation. There was a significant improvement in walking performance ($\Delta$ endurance time salmeterol-placebo: 117 ± 208 seconds, $p = 0.02$) and walking distance ($\Delta$ walking distance salmeterol-placebo: 160 ± 277 meters, $p = 0.02$) with salmeterol inhalation. Individual data for changes in endurance time from the placebo to the salmeterol condition for the ESWT are shown in Figure 2. In multiple regression analysis, the change in Borg at isotime and post-bronchodilator increase in FVC explained 71\% of the variance in the endurance time with bronchodilation. The post-bronchodilator changes in FEV\textsubscript{1} or IC did not improve the ability to predict the changes in endurance time in the multiple regression analysis.
Physiological response

Time course and end-exercise values for dyspnea under the placebo and salmeterol conditions are shown in Figure 3. Salmeterol significantly reduced dyspnea at isotime (Δ dyspnea salmeterol-placebo: -0.60 ± 1.10, p = 0.006), as shown in Table 3 and figure 3. The cardiorespiratory response to ESWT was similar between the placebo and salmeterol conditions. Interestingly, patients were able to reach greater $V_t$ (+ 0.04 ± 0.08 l, p = 0.005) at end-exercise after salmeterol. End-exercise dyspnea was similar between the two conditions. Inspiratory capacity measurement while walking was challenging and some patients were unable to perform the maneuvers. In others, a drift in the end-expiratory lung volume was observed preventing reliable estimation of inspiratory capacity. In the 8/20 patients in whom this procedure was completed, inspiratory capacity at isotime was 220 ml greater with salmeterol compared to placebo (p = 0.07).

Locus of symptom limitation

The perception of dyspnea and leg fatigue at end-exercise was not significantly altered by salmeterol. During the salmeterol condition, twelve patients (60%) cited dyspnea as the main limiting factor, whereas four (20%) cited leg fatigue, four (20%) cited the combination of both symptoms. For the placebo condition, fourteen patients (70%) cited dyspnea, two (10%) cited leg fatigue, four (20%) cited the combination of both symptoms.
DISCUSSION

The major finding of this study was that the ESWT allowed to detect functional changes after bronchodilation in patients with COPD. In addition to the improvement in walking endurance time with salmeterol, a reduction in dyspnea at a given exercise time and a tendency toward reduced dynamic hyperinflation during walking were also observed.

There are growing interest in demonstrating the efficacy of bronchodilation on functional status in patients with COPD[7-9]. To this end, the utility and responsiveness of constant workrate cycling exercise to pharmacotherapy have been confirmed in large clinical trials[7-9]. Despite providing convincing physiological evidence of the efficacy of bronchodilation in patients with COPD, the clinical relevance of these findings may be questioned since cycling is not a typical activity of daily living in patients with COPD[24]. Walking would appear as one obvious alternative to cycling to address this limitation of cycling-based indices of exercise capacity. Although the initial experience with the 6-minute walking test to evaluate the effects of bronchodilation was disappointing[12], Pepin and colleagues have reported more encouraging results using the ESWT[13, 14]. In these investigations, the ESWT was proven sensitive to acute bronchodilation and more responsive to this intervention than the 6-minute walking test[13, 14]. The current state of knowledge about the efficacy of salmeterol to improve walking capacity is consistent with these notions. Three previous investigations reported that salmeterol did not improve 6-minute walking distance, casting doubt about the efficacy of this medication to improve functional status[6, 10, 11]. In contrast, by using a walking protocol with better evaluative properties than the 6-minute walking test, the present investigation confirms that a long-acting β2 agonist may improve walking capacity in patients with COPD. This indicates that
the evaluative properties of a given exercise test have to be considered when designing clinical trials.

The ESWT was initially developed as a simple field exercise test to measure response to therapy in patients with COPD[20]. The use of portable technology, now allowing a detailed physiological evaluation during walking and the assessment of dyspnea perception, makes it possible to explore possible mechanisms of improvement in walking capacity as it is often done during cycling[7-9]. The changes in breathing pattern with slower respiratory rate and larger tidal volume were small but consistent in magnitude with previous reports[7-9]. An interesting novelty of the present investigation was the possibility to perform, in a subset of patients, repeated measurements of inspiratory capacity while they were actually walking in the corridor and to monitor the degree of dynamic hyperinflation occurring during walking exercise. The magnitude of improvement in inspiratory capacity with bronchodilation was consistent with previous clinical trials[7-9]. Reduced perception of dyspnea at isotime with bronchodilation together with the improvement in FVC, a reflection of more complete lung emptying and reduced gas trapping, were important determinant of the improvement in endurance time as indicated by the multiple regression analysis.

The present study confirms that the ESWT in conjunction with a portable exercise circuit is an appropriate exercise modality to assess the functional and physiological responses to bronchodilation. One interesting feature of walking is that it induces less leg fatigue compared other exercise modalities such as cycling[14, 25]. This may be important given that the occurrence of leg fatigue during exercise may prevent bronchodilation to fully translate into better exercise capacity[26]. Indeed, in patients predominantly limited by quadriceps muscle fatigue during cycling exercise, the administration of a bronchodilator has been shown not to
translate into improvements in exercise tolerance[26]. Other advantages of the ESWT include the fact that it may show more consistently than cycling the functional gain associated with bronchodilation[14] and that it is relevant for daily living.

It is nevertheless important to appreciate the potential shortcomings of walking as an evaluating exercise modality. Inspiratory capacity and dyspnea are more difficult to assess during free walking as compared to stationary cycling. The pattern of lower limb muscles recruitment is also not as well controlled during walking than cycling. For instance, stride length and strategies during turning, which may influence the metabolic requirements, cannot be easily controlled from one walking test to the other. Despite this, walking appears as a promising strategy for future clinical trials aiming at evaluating the impact of pharmacotherapy on functional status in patients with COPD. In the absence of a minimal clinically important difference for the ESWT, the significance of changes observed with treatment is difficult to interpret. Preliminary results from our laboratory indicate that an 85-sec improvement in ESWT is likely to be perceived positively by patients[27]. As such, it is possible that the averaged gain in walking endurance obtained with salmeterol was not only statistically significant but also clinically meaningful. Further investigation will be necessary to better appreciate the clinical significance of the gain in walking capacity reported in the present investigation.

In conclusion, the present investigation demonstrates the ability of salmeterol to improve walking capacity in patients with COPD. This study extends the results of previous investigations about the evaluative properties of the ESWT in patients with COPD. This exercise modality can be used to assess endurance to constant workrate walking exercise. Detailed physiological evaluation can also be obtained during free walking when coupled with a portable exercise circuit.
ACKNOWLEDGEMENT

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REFERENCES


**LEGENDS FOR FIGURES**

**Figure 1.** Study flow chart.

**Figure 1.** Individual data for changes in endurance time from the placebo to the salmeterol condition for the ESWT. The group mean for each experimental condition is represented by the horizontal bars. * p = 0.02.

**Figure 2.** Time course (circles) and end-exercise values (squares) for dyspnea under the placebo (closed symbols) and salmeterol (open symbols) conditions for the ESWT. At minute four, dyspnea scores were available for 19/20 patients. There was a significant reduction in dyspnea at isotime (p = 0.006). Values are mean ± SEM.
Table 1. Subject characteristics and data at peak exercise*

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>% pred</th>
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<tbody>
<tr>
<td>Subjects, n</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>6 (30%)</td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>65 ± 6</td>
<td></td>
</tr>
<tr>
<td>BMI, kg⋅m⁻²</td>
<td>26.9 ± 4.7</td>
<td></td>
</tr>
<tr>
<td>FEV₁, l</td>
<td>1.38 ± 0.55</td>
<td>52 ± 15</td>
</tr>
<tr>
<td>FVC, l</td>
<td>3.27 ± 1.23</td>
<td>95 ± 19</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>43 ± 10</td>
<td></td>
</tr>
<tr>
<td>TLC, l</td>
<td>6.42 ± 1.79</td>
<td>108 ± 15</td>
</tr>
<tr>
<td>IC, l</td>
<td>2.34 ± 0.77</td>
<td>88 ± 20</td>
</tr>
<tr>
<td>FRC, l</td>
<td>4.07 ± 1.33</td>
<td>125 ± 30</td>
</tr>
<tr>
<td>RV, l</td>
<td>3.02 ± 0.86</td>
<td>134 ± 33</td>
</tr>
<tr>
<td>SpO₂ %, rest</td>
<td>94.8 ± 4.1</td>
<td></td>
</tr>
<tr>
<td>DLco, % pred</td>
<td></td>
<td>61 ± 15</td>
</tr>
<tr>
<td>VO₂ peak, ml·kg⁻¹·min⁻¹</td>
<td>18.5 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>VO₂ peak, l·min⁻¹</td>
<td>1.4 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>VE peak, l·min⁻¹</td>
<td>49.4 ± 16.8</td>
<td></td>
</tr>
<tr>
<td>VE/MVV peak, %</td>
<td>97.7 ± 15.0</td>
<td></td>
</tr>
<tr>
<td>HR peak, beats·min⁻¹</td>
<td>133 ± 15</td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean ± SD. Definition of abbreviations: BMI: body mass index; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity;
TLC: total lung capacity; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume; SpO$_2$: pulse oxygen saturation; DLco: single-breath diffusing capacity of the lung for carbon monoxide; $\dot{V}O_2$: oxygen uptake; $\dot{V}CO_2$: carbon dioxide output; $\dot{V}E$: minute ventilation; MVV: maximum voluntary ventilation; HR: heart rate.
Table 2. Pre-post dose pulmonary function measurements*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Salmeterol</th>
<th>Δ Salmeterol (post-pre) - Δ Placebo (post-pre)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre, l</td>
<td>Post, l</td>
<td>Pre, l</td>
</tr>
<tr>
<td>FEV(_1), l</td>
<td>1.24 ± 0.49</td>
<td>1.19 ± 0.50</td>
<td>1.21 ± 0.45</td>
</tr>
<tr>
<td>FVC, l</td>
<td>3.10 ± 1.06</td>
<td>3.02 ± 1.14</td>
<td>3.07 ± 1.04</td>
</tr>
<tr>
<td>FRC, l</td>
<td>4.31 ± 1.19</td>
<td>4.22 ± 1.24</td>
<td>4.21 ± 1.09</td>
</tr>
<tr>
<td>TLC, l</td>
<td>6.46 ± 1.59</td>
<td>6.37 ± 1.67</td>
<td>6.43 ± 1.48</td>
</tr>
<tr>
<td>RV, l</td>
<td>3.28 ± 0.92</td>
<td>3.22 ± 0.95</td>
<td>3.23 ± 0.82</td>
</tr>
<tr>
<td>IC, l</td>
<td>2.14 ± 0.68</td>
<td>2.13 ± 0.74</td>
<td>2.21 ± 0.73</td>
</tr>
</tbody>
</table>

*Values are mean ± SD. Definition of abbreviations: FEV\(_1\): forced expiratory volume in 1 second; FVC: forced vital capacity; FRC: functional residual capacity; TLC: total lung capacity; RV: residual volume; IC: inspiratory capacity. †: p < 0.0001, ‡: p < 0.05
### Table 3. End-exercise and isotime measurements during the ESWT*

<table>
<thead>
<tr>
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<th>Salmeterol</th>
<th>Placebo</th>
<th>Salmeterol</th>
</tr>
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<tbody>
<tr>
<td><strong>Exercise time, sec</strong></td>
<td>373 ± 216</td>
<td>490 ± 312†</td>
<td>358 ± 221</td>
<td>358 ± 221</td>
</tr>
<tr>
<td><strong>Distance, m</strong></td>
<td>512 ± 353</td>
<td>672 ± 478†</td>
<td>---</td>
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</tr>
<tr>
<td><strong>Dyspnea, Borg</strong></td>
<td>8.1 ± 2.2</td>
<td>7.9 ± 2.0</td>
<td>6.2 ± 2.6</td>
<td>5.6 ± 2.5‡</td>
</tr>
<tr>
<td><strong>Leg discomfort, Borg</strong></td>
<td>5.6 ± 2.6</td>
<td>5.6 ± 3.1</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>( \dot{V}O_2 ), ml·kg(^{-1})·min(^{-1} )</td>
<td>18.2 ± 3.1</td>
<td>18.0 ± 3.3</td>
<td>18.1 ± 3.2</td>
<td>17.7 ± 3.0</td>
</tr>
<tr>
<td>( \dot{V}O_2 ), l·min(^{-1} )</td>
<td>1.4 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>( \dot{V}CO_2 ), l·min(^{-1} )</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>( \dot{V}E ), l·min(^{-1} )</td>
<td>45.6 ± 15.7</td>
<td>47.2 ± 16.2</td>
<td>45.3 ± 15.8</td>
<td>45.7 ± 13.9</td>
</tr>
<tr>
<td>( \dot{V}E /MVV ), %</td>
<td>103.6 ± 16.0</td>
<td>107.1 ± 18.5</td>
<td>---</td>
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</tr>
<tr>
<td><strong>RER</strong></td>
<td>0.98 ± 0.13</td>
<td>0.98 ± 0.11</td>
<td>0.97 ± 0.12</td>
<td>0.97 ± 0.11</td>
</tr>
<tr>
<td>**RR, breaths·min(^{-1} )</td>
<td>35.8 ± 5.9</td>
<td>36.1 ± 6.3</td>
<td>35.6 ± 6.2</td>
<td>34.8 ± 5.5</td>
</tr>
<tr>
<td><strong>V(_T), l</strong></td>
<td>1.27 ± 0.37</td>
<td>1.31 ± 0.39**</td>
<td>1.27 ± 0.36</td>
<td>1.32 ± 0.39</td>
</tr>
<tr>
<td><strong>IC, l</strong></td>
<td>1.86 ± 0.58</td>
<td>1.83 ± 0.63</td>
<td>1.93 ± 0.60</td>
<td>2.15 ± 0.75***</td>
</tr>
<tr>
<td>**HR, beats·min(^{-1} )</td>
<td>129 ± 12</td>
<td>131 ± 11</td>
<td>128 ± 13</td>
<td>127 ± 11</td>
</tr>
<tr>
<td><strong>SpO(_2), %</strong></td>
<td>89.5 ± 7.4</td>
<td>90.2 ± 6.2</td>
<td>90.1 ± 6.5</td>
<td>90.8 ± 5.9</td>
</tr>
</tbody>
</table>

*Values are mean ± SD.

Definition of abbreviations: \( \dot{V}O_2 \): oxygen uptake; \( \dot{V}CO_2 \): carbon dioxide output; \( \dot{V}E \): minute ventilation; MVV: maximum voluntary ventilation; RER: respiratory exchange ratio; RR: respiratory rate; \( V_T \): tidal volume; IC: inspiratory capacity; HR: heart rate; SpO\(_2\): pulse oxygen saturation. †: p=0.02; ‡: p=0.006; §: MVV was calculated from the post-bronchodilator FEV\(_1\) value obtained at the placebo visit; **: p=0.005; ***: due to technical reasons, data about IC are available only for 8 of 20 patients p = 0.07.
Figure 1. Study flow chart

56 screened

28 patients not evaluated
- recent exacerbation 6
- could not be reached 3
- refusal 13
- use of tiotropium 1
- contraindication to exercise 5

28 evaluated at visit 1-3

8 patients excluded
- refusal 3
- FEV₁ > 70% predicted 2
- Exercise duration > 20 minutes 2
- Exercise not reproducible 1

20 randomized at visit 4

20 completed the study
Figure 2. End-exercise endurance time *p=0.02
Figure 3. Time course and end-exercise values for dyspnea under the placebo and salmeterol conditions for the ESWT Values are mean ± SEM. *: Borg at isotime, p=0.006.