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Endurance shuttle walking test: responsiveness to salmeterol in COPD

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ABSTRACT: 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. The aim of the present study was to evaluate, in patients with COPD, the responsiveness of the ESWT in detecting improvement in walking performance after a single dose of salmeterol.

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

Compared with placebo, salmeterol produced a significant change in lung function and a significant improvement in walking performance (mean±SD difference in time: 117±20 s; difference in distance: 160±277 m). At isotime (the latest exercise time that was reached on both ESWT), a significant reduction in dyspnoea was observed after bronchodilation.

Bronchodilation with salmeterol reduced dyspnoea during walking and improved walking capacity in patients with chronic obstructive pulmonary disease. These findings provide further support for the use of the endurance shuttle walking test as an evaluative tool in chronic obstructive pulmonary disease.

KEYWORDS: Bronchodilators, chronic obstructive pulmonary disease, endurance, exercise capacity, exercise testing, salmeterol

Patients with chronic obstructive pulmonary disease (COPD) complain of premature exertional dyspnoea 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 for handling symptoms in the early phases of the disease process, long-acting bronchodilators are typically better suited to treating patients with more advanced disease [2, 3].

Long-acting bronchodilators, such as salmeterol and tiotropium, have been shown to improve dyspnoea and quality of life and to reduce exacerbations in patients with COPD [4–6]. In well-designed, randomised, 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 β_2-agonists and anticholinergics also reduce the perception of dyspnoea [8, 9].

Although the symptomatic and functional benefit associated with these drugs is felt to be clinically relevant, it is not known 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 6-min 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 rehabilitation [13–15]. The present investigation was therefore undertaken to test, in patients with COPD, the hypothesis that the ESWT is responsive in detecting improvement in walking capacity following a single dose of salmeterol. More specifically, the objectives of the study were: 1) to measure the acute changes in walking performance induced by a single dose of

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salmeterol against those induced by a placebo; and 2) to evaluate the physiological (minute ventilation (V'_E), oxygen uptake (V'_{O_2}), carbon dioxide production (V'_{CO_2}), cardiac frequency (f_C) and inspiratory capacity) and symptomatic (dyspnoea) responses during each walking test to provide a mechanistic explanation of the findings.

METHODS

Subjects

Patients with clinically stable COPD participated in the study. Inclusion criteria were as follows: 1) age $\geq$50 yrs; 2) current or past smoking history of $\geq$10 pack-yrs; 3) forced expiratory volume in one second (FEV1) $\leq$70% of the predicted value; 4) FEV1/forced vital capacity (FVC) $\leq$70%; 5) no acute COPD exacerbation within the preceding 2 months; 6) no history of asthma; 7) no significant arterial oxygen desaturation (<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 (Hôpital Laval, Quebec City, QC, Canada) and a signed, informed consent was obtained from each subject.

Study design

The study required five visits to the research facility. Each visit was separated by $\geq$48 h and $\leq$4 days. The first visit included a baseline assessment of pulmonary function and an incremental shuttle walking test (ISWT). The following two visits (visits 2 and 3) were used to familiarise participants to the ESWT. The goal of the familiarisation was to reduce the learning effect that typically occurs when an individual completes the same endurance test several times [8]. Patients whose ESWT at visit 2 and 3 were not reproducible (when the difference in endurance time between visit 2 and 3 was >2 min) or longer than 20 min were excluded. For the remaining two visits (visits 4 and 5), subjects entered a cross-over design where they completed one ESWT at each visit, 150$\pm$15 min after the inhalation of 50 μg of salmeterol or the inhalation of a placebo. Pulmonary function tests were performed before (pre-dose) and 120$\pm$20 min after (post-dose) the inhalation of the placebo or salmeterol. The medication was administered in a randomised and double-blind fashion using the Diskus® (GlaxoSmithKline, Ware, UK) 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 β_2-agonists and short-acting anticholinergics were stopped 6 h preceding visits 2–5, while theophyllines and long-acting β_2-agonists were stopped 48 h before visits 4 and 5. Inhaled salbutamol (short-acting β_2-agonist) was used as rescue medication when subjects had to stop their medication for 48 h. 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.

Pulmonary function testing

Standard pulmonary function tests, including spirometry, lung volumes and diffusing capacity of the lung for carbon monoxide 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 was estimated by multiplying FEV1 by 35 [18].

Incremental walking exercise test

Peak walking capacity was determined with the ISWT [19], which was performed in an enclosed corridor on a flat 10 m-long course. The course was identified by two cones, each positioned 0.5 m from either end to allow patients to walk in a 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 $m \cdot s^{-1}$ and subsequently increased by 0.17 $m \cdot s^{-1}$ every minute until the patient reached a symptom-limited maximum. Encouragement was provided during the test and patients received standardised 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 as the ISWT in accordance with published guidelines [20]. After 1.5 min of warm up, walking speed was set at the speed corresponding to 80% of peak V'_{O_2}, as predicted from the ISWT [20]. Before each ESWT, patients received standardised instructions to walk for as long as possible, although there was a predetermined 20-min 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 min or 10% between consecutive ESWT.

Physiological measures

During each exercise test, gas exchange parameters (V'_{O_2}, V'_{CO_2}, V'_E and arterial oxygen saturation measured by pulse oximetry), respiratory frequency (f_R), tidal volume (V_T) and f_C were monitored breath by breath with a portable telemetric system (Oxycon Mobile; Viasys Healthcare GmbH, Hoechberg, Germany). This system is both light (950 g including belt, battery and mask) and compact, and consists of a facemask, f_C monitor, battery, transmitting unit (containing the O_2 and CO_2 gas analysers) and receiving unit. The volume sensor and gas analysers were calibrated before each test. Patients were asked to perform inspiratory capacity manoeuvres at 2-min intervals during the exercise period. This was carried out to follow changes in operational lung volumes occurring during exercise, as described previously [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

Dyspnoea and perception of leg fatigue were evaluated at rest and at end exercise using the modified 10-point Borg scale [23]. Dyspnoea was also evaluated at 2-min 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±SD, unless otherwise stated. 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-min warm-up period. Comparisons of the values observed with salmeterol and placebo were made using a 2×2 crossover 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 FEV1, FVC, functional residual capacity, inspiratory capacity and dyspnoea 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 to that of ipratropium bromide (164±177 s) [14]. It was calculated 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. In total, 28 patients initially volunteered to participate in the study but only 20 patients were actually randomised 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. Of the study group, 30% were females. Patients had, on average, moderate-to-severe airflow obstruction with mild hyperinflation and gas trapping at rest.

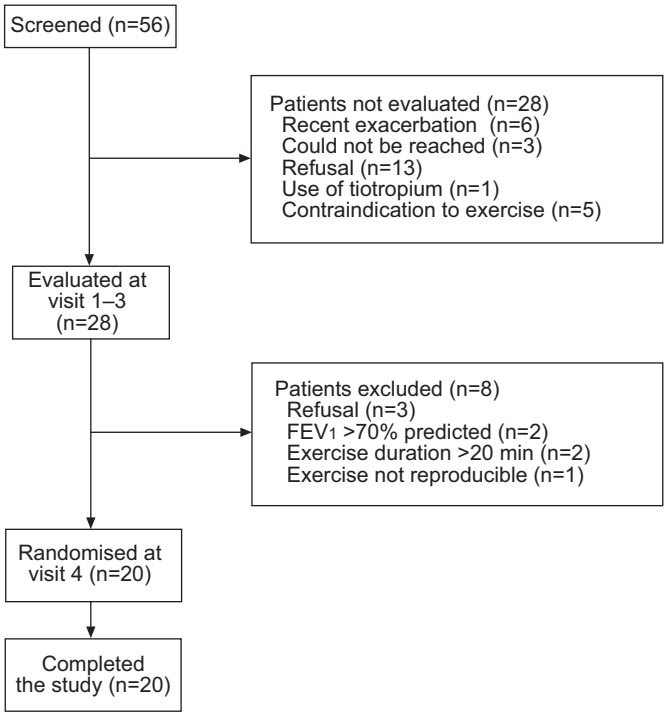

FIGURE 1. Flow chart of the study. FEV1: forced expiratory volume in one second.

Pulmonary function

Pre- and post-dose pulmonary function measurements are shown in table 2. Significant drug effects were found after treatment with salmeterol compared with placebo. The pre- and post-bronchodilator improvements in FEV1 and FVC and reduction in residual volume were significantly larger for salmeterol compared with placebo (table 2).

Endurance time and walking distance

No sequence or carry-over effect was observed in the present investigation. There was a significant improvement in walking performance (difference in endurance time salmeterol-placebo: 117±208 s; $p=0.02$) and walking distance (difference in walking distance salmeterol-placebo: 160±277 m; $p=0.02$) 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 FEV1 or inspiratory capacity 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 dyspnoea under the placebo and salmeterol conditions are shown in figure 3. Salmeterol significantly reduced dyspnoea at isotime (difference in dyspnoea salmeterol-placebo: -0.60±1.10; $p=0.006$), as

TABLE 1 Subject characteristics and data at peak exercise

	Value	% predicted
Subjects	20	
Females	6 (30)	
Age yrs	65±6	
BMI kg·m^{-2}	26.9±4.7	
FEV1 L	1.38±0.55	52±15
FVC L	3.27±1.23	95±19
FEV1/FVC %	43±10	
TLC L	6.42±1.79	108±15
IC L	2.34±0.77	88±20
FRC L	4.07±1.33	125±30
RV L	3.02±0.86	134±33
S_{P,O_2} % rest	94.8±4.1	
$D_{L,CO}$ % pred		61±15
Peak V'_{O_2} mL·kg^{-1}·min^{-1}	18.5±3.6	
Peak V'_{O_2} L·min^{-1}	1.4±0.4	
Peak V'_E L·min^{-1}	49.4±16.8	
V'_E/MVV peak %	97.7±15.0	
Peak f_C beats·min^{-1}	133±15	

Data are presented as n, n (%) and mean±SD. BMI: body mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume; S_{P,O_2}: pulse oxygen saturation; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; V'_{O_2}: oxygen uptake; V'_E: minute ventilation; MVV: maximum voluntary ventilation; f_C: cardiac frequency.

TABLE 2 Pre- and post-dose pulmonary function measurements

	Placebo		Salmeterol		ΔSalmeterol (post-pre)–Δplacebo (post-pre)
	Pre	Post	Pre	Post	
FEV_1 L	1.24±0.49	1.19±0.50	1.21±0.45	1.31±0.51	0.15±0.08#
FVC L	3.10±1.06	3.02±1.14	3.07±1.04	3.22±1.08	0.23±0.18#
FRC L	4.31±1.19	4.22±1.24	4.21±1.09	4.04±1.15	-0.07±0.33
TLC L	6.46±1.59	6.37±1.67	6.43±1.48	6.32±1.46	-0.03±0.31
RV L	3.28±0.92	3.22±0.95	3.23±0.82	2.98±0.91	-0.19±0.38*
IC L	2.14±0.68	2.13±0.74	2.21±0.73	2.27±0.76	0.07±0.27

Data are presented as mean±SD. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; FRC: functional residual capacity; TLC: total lung capacity; RV: residual volume; IC: inspiratory capacity. *: $p<0.05$; #: $p<0.0001$.

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 dyspnoea was similar between the two conditions. Inspiratory capacity measurement while walking was challenging and some patients were unable to perform the manoeuvres. In others, a drift in the end expiratory lung volume was observed, preventing reliable estimation of inspiratory capacity. In the eight out of 20 patients in whom this procedure was completed, inspiratory capacity at isotime was 220 mL greater with salmeterol compared with placebo ($p=0.07$).

Locus of symptom limitation

The perception of dyspnoea and leg fatigue at end exercise was not significantly altered by salmeterol. During the salmeterol condition, 12 patients (60%) cited dyspnoea as the main limiting factor, whereas four (20%) cited leg fatigue and four (20%) the combination of both symptoms. For the placebo condition, 14 patients (70%) cited dyspnoea, two (10%) leg fatigue and four (20%) the combination of both symptoms.

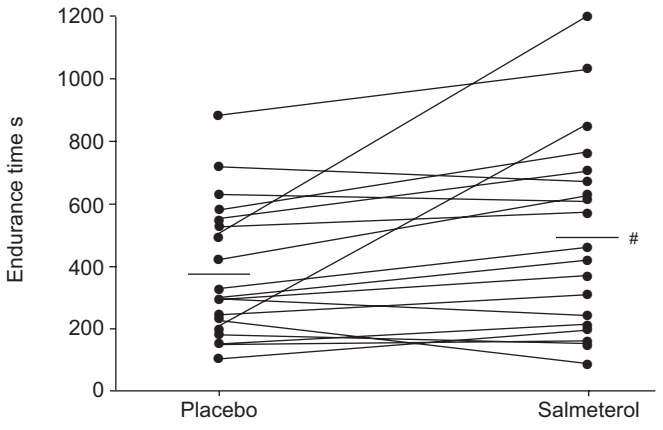

FIGURE 2. Individual data for changes in endurance time from the placebo to the salmeterol condition for the endurance shuttle walking test. The group mean for each experimental condition is represented by the horizontal bars. #: end exercise endurance time $p=0.02$.

DISCUSSION

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

There is 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 work-rate 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 an obvious alternative to cycling in order to address the limitation of cycling-based indices of exercise capacity. Although the initial experience with the 6MWT to evaluate the effects of bronchodilation was disappointing [12], PEPIN and co-workers [13, 14] have reported more encouraging results using the ESWT. In these investigations, the ESWT has proved to be sensitive to acute bronchodilation and more responsive to this intervention than the 6MWT [13, 14]. The current state of knowledge about the efficacy of salmeterol in improving walking capacity is consistent with these notions. Three previous investigations reported that salmeterol did not improve 6-min walking distance, casting doubt on the efficacy of this medication in improving functional status [6, 10, 11]. In contrast, by using a walking protocol with better evaluative properties than the 6MWT, the present investigation confirms that a long-acting β_2-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 for the measurement of 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 dyspnoea perception, makes it possible to explore possible mechanisms of improvement in walking

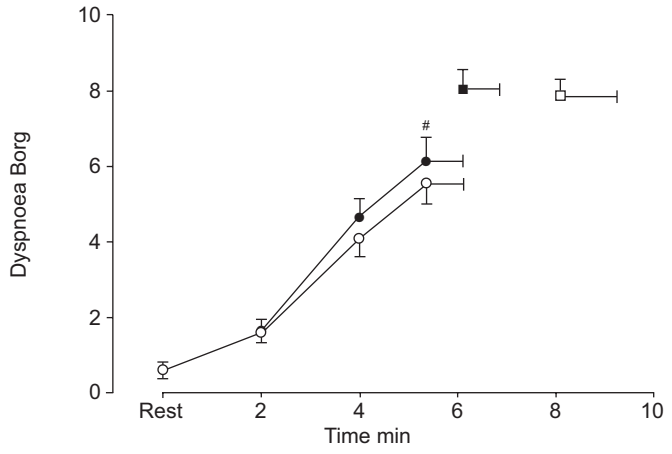

FIGURE 3. Time course (● and ○) and peak end exercise values (■ and □) for dyspnoea under the placebo (● and ■) and salmeterol (○ and □) conditions for the endurance shuttle walking test. At 4 min, dyspnoea scores were available for 19 out of 20 patients. There was a significant reduction in dyspnoea at isotime. Data are presented as mean±SD. #: p=0.006.

TABLE 3 End exercise and isotime measurements during the endurance shuttle walking test

	End exercise		Isotime	
	Placebo	Salmeterol	Placebo	Salmeterol
Exercise time s	373±216	490±312¶	358±221	358±221
Distance m	512±353	672±478¶		
Dyspnoea Borg	8.1±2.2	7.9±2.0	6.2±2.6	5.6±2.5+
Leg discomfort Borg	5.6±2.6	5.6±3.1		
V'_{O_2} m·kg^{-1}·min^{-1}	18.2±3.1	18.0±3.3	18.1±3.2	17.7±3.0
V'_{O_2} L·min^{-1}	1.4±0.3	1.4±0.3	1.4±0.3	1.3±0.3
V'_{CO_2} L·min^{-1}	1.3±0.4	1.3±0.4	1.3±0.4	1.3±0.4
V'_E L·min^{-1}	45.6±15.7	47.2±16.2	45.3±15.8	45.7±13.9
V'_E/MVV# %	103.6±16.0	107.1±18.5		
RER	0.98±0.13	0.98±0.11	0.97±0.12	0.97±0.11
f_R breaths·min^{-1}	35.8±5.9	36.1±6.3	35.6±6.2	34.8±5.5
V_T L	1.27±0.37	1.31±0.39§	1.27±0.36	1.32±0.39
IC L	1.86±0.58	1.83±0.63	1.93±0.60	2.15±0.75ƒ
f_C beats·min^{-1}	129±12	131±11	128±13	127±11
S_{p,O_2} %	89.5±7.4	90.2±6.2	90.1±6.5	90.8±5.9

Data are presented as mean±SD. V'_{O_2}: oxygen uptake; V'_{CO_2}: carbon dioxide output; V'_E: minute ventilation; MVV: maximum voluntary ventilation; RER: respiratory exchange ratio; f_R: respiratory frequency; V_T: tidal volume; IC: inspiratory capacity; f_C: cardiac frequency; S_{p,O_2}: pulse oxygen saturation. #: MVV was calculated from the post-bronchodilator forced expiratory volume in one second value obtained at the placebo visit; ¶: p=0.02; +: p=0.006; §: p=0.005; ƒ: due to technical reasons, IC data are only available for eight out of 20 patients (p=0.07).

capacity as it is often carried out during cycling [7–9]. The changes in breathing pattern with slower f_R and larger V_T were small but consistent in magnitude with previous reports [7–9]. An interesting novelty of the present investigation was the possibility of performing, in a subset of patients, repeated measurements of inspiratory capacity while they were actually walking in the corridor and of monitoring 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 dyspnoea at isotime with bronchodilation together with the improvement in FVC, a reflection of more complete lung emptying and reduced gas trapping, were important determinants 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 for the assessment of the functional and physiological responses to bronchodilation. An interesting feature of walking is that it induces less leg fatigue compared with other exercise modalities, such as cycling [14, 25]. This could be important given that the occurrence of leg fatigue during exercise may prevent bronchodilation from fully translating into better exercise capacity [26]. Indeed, in patients predominantly limited by quadriceps muscle fatigue during cycling, 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.

Nevertheless, it is important to appreciate the potential shortcomings of walking as an evaluating exercise modality. Inspiratory capacity and dyspnoea are more difficult to assess during free walking compared with during stationary cycling. Also, the pattern of lower limb muscles recruitment is 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 to be a promising strategy for future clinical trials aiming to evaluate 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 the current authors' laboratory indicate that an 85-s improvement in ESWT is likely to be perceived positively by patients [27]. As such, it is possible that the average gain in walking endurance obtained with salmeterol was not only statistically significant but also clinically meaningful. Further investigation is necessary to better appreciate the clinical significance of the gain in walking capacity reported in the present study.

In conclusion, the present study demonstrates the ability of salmeterol to improve walking capacity in patients with chronic obstructive pulmonary disease. The study extends the results of previous investigations about the evaluative properties of the endurance shuttle walking test in patients with chronic obstructive pulmonary disease. This exercise modality can be used to assess endurance to constant work rate walking exercise. Detailed physiological evaluation can also be obtained during free walking when coupled with a portable exercise circuit.

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