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Six-Minute Walking Versus Shuttle Walking: Responsiveness to Bronchodilation in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Rationale: The responsiveness of the endurance shuttle walk to functional changes following bronchodilation was recently demonstrated, while the current literature suggests that the six-minute walking test is less responsive in that setting. **Objective:** To compare bronchodilator-induced changes in exercise performance between the 6-minute walking test and the endurance shuttle walk. **Methods:** In a randomised, double-blind, placebo-controlled and crossover trial, 14 patients with chronic obstructive pulmonary disease (FEV_1: 50 (8)% predicted) completed two 6-minute walking tests and two endurance shuttle walks, each preceded by the nebulization of either a placebo or 500 µg of ipratropium bromide. Cardiorespiratory parameters were monitored during each walking test with a portable telemetric gas analyser. Quadriceps twitch force was measured with magnetic stimulation of the femoral nerve before and after each walking test. **Results:** Six-minute walking distance did not change significantly following bronchodilation despite a significant increase in FEV_1 (0.18 (0.09)L, $p < 0.001$). A similar change in FEV_1 (0.18 (0.12)L, $p < 0.001$) was associated with a significant improvement in the distance walked on the endurance shuttle walk (Δdistance ipratropium bromide-placebo: 144 (219) meters, $p = 0.03$). Quadriceps muscle fatigue was infrequent (<15% of patients) after both walking tests. **Conclusion:** The endurance shuttle walk is more responsive than the 6-minute walking test to detect changes in exercise performance following bronchodilation.

INTRODUCTION

Recent management guidelines recommend that treatments for chronic obstructive pulmonary disease (COPD) be evaluated not only for their effects on lung function, but also for their impact on exercise capacity[1]. In that regard, exercise testing is a useful evaluative tool allowing for standardised measurement of exertional dyspnea and exercise tolerance[1]. However, little is known about the responsiveness of the different exercise testing protocols to pharmacological treatments in COPD.

We recently conducted a trial comparing two exercise tests, the constant-workrate cycling test and the endurance shuttle walk, with respect to their ability to detect changes in functional status following acute bronchodilation in patients with COPD[2]. Our results demonstrated that the endurance shuttle walk was able to capture larger and more consistent improvements in exercise performance than the constant-workrate cycling test following bronchodilation. Our findings also indicated that the cardiorespiratory response was similar between the two testing modalities, while the presence of quadriceps muscle fatigue was more frequent and more pronounced after cycling than after walking. Given that leg fatigue may prevent bronchodilation from translating into further improvement in exercise tolerance[3], we concluded that the endurance shuttle walk was a particularly well-designed evaluative tool to detect changes in functional status following bronchodilation in COPD.

The current literature suggests that the six-minute walking test (6MWT) may not be as responsive to bronchodilation as the endurance shuttle walk[4-11]. In general, only modest changes in six-minute walking distance (6MWD) of little clinical significance have been reported following acute bronchodilation in COPD[4-11]. The underlying physiological mechanisms for the apparent lack of sensitivity of the 6MWT to acute bronchodilation have yet to be fully explained. It is therefore currently unclear why the 6MWT and the endurance shuttle walk would not share the same responsiveness to bronchodilation.

One fact worth highlighting is that these two functional walks have different designs. The 6MWT is a self-paced test (i.e. patients determine their own walking speed) with a fixed duration. In contrast, the endurance shuttle walk is an externally-paced test (i.e. walking speed is dictated to patients) with an indefinite duration. Accordingly, improvements in performance are achieved differently for the two tests. Patients have to increase walking speed to cover more distance on the 6MWT, while they have to increase endurance time to achieve the same outcome on the endurance shuttle walk. We hypothesised that these differences in test design, and their associated physiological consequences, were responsible for the differences in responsiveness to bronchodilation between the 6MWT and the endurance shuttle walk.

We therefore undertook the present study *i*) to directly compare, in patients with COPD, the changes in exercise performance detected by the 6MWT against those detected by the endurance shuttle walk in response to the administration of a bronchodilator, and *ii*) to provide a physiological understanding for the tests' responsiveness to change by examining the cardiorespiratory response and the degree of quadriceps muscle fatigue elicited by each test.

METHODS (word count: 983)

Subjects

Sixteen patients volunteered to participate in the study. Two patients were excluded after the first visit, one because of a respiratory exacerbation and the other because of an inability to comply with the exercise testing procedure. Thus, fourteen patients completed the study protocol. Four of these patients had participated to a previous investigation comparing the constant-workrate cycling test and the endurance shuttle walk[2]. This sample size was based on a previous investigation completed in our laboratory in which a statistically significant improvement in endurance shuttle walking distance was obtained in response to bronchodilation in a similar number of patients[2].

Inclusion criteria were as follows: (1) moderate to severe COPD according to the GOLD guidelines (class II and III)[1]; (2) age > 50 years; (3) smoking history > 10 pack-years; (4) no COPD exacerbation within the preceding 4 weeks; (5) no history of asthma; (6) no need for supplemental oxygen during exercise; and (7) no other active condition that could influence exercise tolerance. Patients on tiotropium bromide were excluded from the study. 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 five visits at the research facility. The first visit included pulmonary function testing, incremental shuttle walking, and familiarization to both functional walks (6MWT and endurance shuttle walk). The familiarisation consisted of completing two full tests for the 6MWT and several minutes at the target speed for the endurance shuttle walk. On the following four visits, subjects completed two 6MWT and two endurance shuttle walks in a random order, at the rate of one test per visit. Each test was preceded by the nebulization of either a placebo or 500 μg of ipratropium bromide, administered in a randomised and double-blind fashion. Subjects were asked to withdraw from short-acting β2-agonists (6 hours), short-acting anticholinergics (6 hours), long-acting β2-agonists (12 hours), and theophyllines (24 hours) before these visits. Study visits were separated by at least 48 hours and no more than a week. Subjects were scheduled at the same time of day throughout the study. More details about the experimental design are provided in the online data supplement.

Pulmonary Function Testing

Spirometry was obtained according to recommended techniques[12]. Results were compared to predicted normal values from the European Community for Coal and Steel/European Respiratory Society[13].

Incremental Shuttle Walk

Peak walking capacity was first determined with incremental shuttle walking[14]. More details about this test can be found in the online data supplement.

Endurance Shuttle Walk

The endurance shuttle walk was performed in an enclosed corridor on a flat 10-meter-long course, as previously described by Revill and colleagues[15]. After a two-minute warm-up, walking speed was set at the speed corresponding to 80% of $\dot{V}O_2$ peak, as predicted from the incremental shuttle walk. Before each test, patients were instructed to walk for as long as possible at the speed dictated by the auditory signal. Patients were notified that no further encouragement would be provided to them during the test. This was done to avoid any potential confounding effect on their performance[16].

Six-Minute Walking Test

The 6MWT was completed in an enclosed corridor on a flat 30-meter-long course according to the procedures recommended by the American Thoracic Society (ATS)[17]. More details about this test can be found in the online data supplement.

Physiological Measures

Cardiorespiratory parameters ($\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, respiratory rate and heart rate) were monitored breath-by-breath with a portable telemetric system (K4b^2, Cosmed, Rome, Italy). More details about this system are available in the online data supplement. Oxygen saturation (SpO_2) was measured at rest, every 60 meters during the tests, and at end-exercise by pulse oximetry (OSM2 Hemoximeter; Radiometer, Copenhagen, Denmark).

Quadriceps twitch force was measured before and immediately after each test using magnetic stimulation of the femoral nerve as previously described by Saey and colleagues[3]. Contractile muscle fatigue was defined as a post-exercise reduction in quadriceps twitch force of more than 15% from the resting value[3]. Further details on this methodology are available in the online data supplement.

Subjective Measures

Dyspnea was evaluated at rest, every 60 meters during the tests, and at end-exercise with the modified 10-point Borg scale[18]. Perception of leg fatigue was evaluated at rest and at end-exercise with the same scale. Patients were asked to identify the main limiting factor that precluded them from walking faster (6MWT) or longer (endurance shuttle walk).

Statistical Analyses

Results are reported as mean (SD). The distance walked on the endurance shuttle walk excluded the two-minute warm-up period. The extent to which the two walking tests (6MWT and endurance shuttle walk) were able to detect changes in exercise performance (walking distance) between the two conditions (placebo and ipratropium bromide) was evaluated with repeated-measures ANOVA, where both treatment and carryover effects were examined. In addition, a standardised response mean (mean change in distance walked from placebo to ipratropium bromide/standard deviation of change) was computed for each walking test. The degree of association between baseline FEV_1, bronchodilator-induced change in FEV_1, average walking distance (placebo and ipratropium bromide), and bronchodilator-induced changes in walking distance was examined with Pearson correlations. Cardiorespiratory kinetics were compared between both walking tests and both testing conditions using a crossover ANOVA with repeated measurements within treatment periods[19]. When a statistically significant interaction with time was obtained (e.g., test*time), post-hoc tests were performed using Fisher's protected LSD with Bonferroni corrections to identify at which time points the differences occurred. Peak cardiorespiratory values were compared across the four testing conditions with repeated-measures ANOVA. The difference between resting and post-exercise quadriceps twitch force was evaluated for each walking test with paired *t*-tests. The degree of quadriceps muscle fatigue was compared between both walking tests and both testing conditions with repeated-measures ANOVA. The locus of symptom limitation was compared between the two walking tests using a Wilcoxon signed-rank test. The level of statistical significance was set at $p < 0.05$.

RESULTS

Subjects

Baseline characteristics of the study group are presented in Table 1. Patients had stage II to stage III COPD, according to GOLD classification, and variable exercise capacities, as indicated by the wide range of performances on the incremental shuttle walk.

TABLE 1. BASELINE SAMPLE CHARACTERISTICS (N = 14)

	Mean (SD)	Range
Age, yrs	64 (6)	51–73
Height, m	1.65 (0.10)	1.47–1.81
Weight, kg	73 (20)	46–106
BMI, kg/m^2	27 (5)	18–34
FEV_1, L	1.31 (0.39)	0.78–2.00
FEV_1, % predicted	50 (7)	39–64
FVC, L	2.83 (0.61)	1.66–3.82
FEV_1/FVC, %	46 (7)	34–55
ISW distance, m	514 (135)	340–790
$\dot{V}O_{2\ peak}$, L/min	1.81 (0.65)	0.89–3.48
$\dot{V}O_{2\ peak}$, ml/kg/min	25 (6)	16–33

Definition of abbreviations: BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ISW: incremental shuttle walk; $\dot{V}O_2$: oxygen uptake.

Pulmonary Function

Pre- and post-nebulization FEV_1 values obtained prior to the two 6MWT and the two endurance shuttle walks are presented in Figure 1. As illustrated, pre-nebulization values were similar across the four testing conditions. FEV_1 remained unchanged after both placebo nebulizations, while a similar and significant increase was observed with ipratropium bromide on both occasions (post-ipratropium bromide increase in FEV_1: 0.18 (0.09)L for the 6MWT vs. 0.18 (0.12)L for the endurance shuttle walk).

Walking distance

Individual data and group mean for the distance walked across the four walking tests are depicted in Figure 2. Baseline walking distance and test duration (i.e. under placebo) were significantly greater for the 6MWT than for the endurance shuttle walk (walking distance: 553 (68) vs. 420 (183) meters, $p < 0.05$; walking time: 360 (0) sec vs. 253 (112) sec, $p < 0.01$, for the 6MWT and the endurance shuttle walk, respectively). Estimated walking speed was similar between the two walking tests. Patients achieved 88 (8)% of their predicted 6MWD[20]. On average, the distance walked on the endurance shuttle walk increased significantly with bronchodilation (Δdistance walked ipratropium bromide-placebo: 144 (219) meters, 95% CI 30 to 259 meters). In contrast, 6MWD did not increase significantly with ipratropium bromide (Δdistance walked ipratropium bromide-placebo: 7 (17) meters, 95% CI –1 to 16 meters). There was no carryover effect for either walking test. The individual data indicates that 9 out of the 14 patients (64%) improved their performance on the endurance shuttle walk with bronchodilation, whereas performances on the 6MWT remained remarkably constant between the two conditions. The standardised response mean (magnitude of change/standard deviation of change) was larger for the endurance shuttle walk than for the 6MWT (0.66 and 0.42, respectively).

The average walking distances (placebo and ipratropium bromide) and the changes in walking distance with bronchodilation did not correlate significantly; this was true both for the 6MWT ($r = 0.14$, $p = 0.63$) and the endurance shuttle walk ($r = 0.41$, $p = 0.15$). Finally, improvement in 6MWD and shuttle walking distance after bronchodilation did not correlate with changes in FEV_1.

Physiological Response

Figure 3 illustrates time course and end-exercise values for $\dot{V}O_2$, $\dot{V}_E$, $\dot{V}_E$/maximal voluntary ventilation (MVV), respiratory rate, dyspnea and heart rate during the 6MWT and the endurance shuttle walk under placebo. The initial rise was significantly faster for the endurance shuttle walk than for the 6MWT. During the endurance shuttle walk, $\dot{V}_E$, respiratory rate and heart rate quickly approached values achieved on the maximal incremental shuttle walk, while these parameters remained at submaximal levels throughout the 6MWT.

The cardiorespiratory response to six-minute walking under placebo and ipratropium bromide is depicted in Figure 4. $\dot{V}O_2$ showed a steady-state profile after the third minute of both 6MWT, as previously reported[21 22]. Cardiorespiratory kinetics were remarkably similar for the two tests, suggesting that both 6MWT were performed at similar paces. This physiological observation was supported by the data related to the estimated walking speed, which indicated that patients replicated the same walking pattern during the two 6MWT. The cardiorespiratory response to endurance shuttle walking was also similar between the placebo and ipratropium bromide conditions, but patients were able to sustain the workload for a longer duration under ipratropium bromide (Figure 5). Interestingly, end-exercise dyspnea was similar between the two endurance shuttle walks despite the fact that a higher $\dot{V}_E$ was reached under ipratropium bromide than under placebo. Finally, neither test elicited a significant fall in quadriceps twitch force. Quadriceps muscle fatigue occurred in less than 15% of patients after both walking tests.

Subjective Response

The perception of dyspnea was significantly higher for the endurance shuttle walk than for the 6MWT from the fourth measurement (180 meters) up until the end of the tests. The locus of symptom limitation was similar between the two walking tests. Dyspnea was cited as the main limiting factor by 9 and 11 patients for the 6MWT and the endurance shuttle walk, respectively. Finally, 11 out of the 14 patients reported the endurance shuttle walk to be more difficult than the 6MWT.

DISCUSSION

The objective of the present study was to compare two field walking tests, the 6MWT and the endurance shuttle walk, with respect to their ability to detect functional changes after bronchodilation in COPD patients. Our results demonstrate that the endurance shuttle walk is more responsive to the acute effects of bronchodilation than the 6MWT in that patient population. Given the wide use of field walking tests as evaluative tools, this finding has important implications for future clinical trials assessing the functional impact of bronchodilation in COPD patients.

In the present study, 6MWD did not improve significantly with ipratropium bromide. Previous investigations of the impact of anticholinergic agents on 6MWD have yielded inconsistent results[4,5,23-26]. In one large multicenter clinical trial, no significant change in 6MWD was observed after 12 weeks of treatment with ipratropium bromide[5]. In contrast, other smaller investigations obtained statistically significant improvements in 6MWD in response to single doses of oxitropium bromide[4,24,25], ipratropium bromide[23] and a combination of salbutamol and ipratropium bromide[26]. In these studies, improvements in 6MWD have ranged from 6 to 39 meters after bronchodilation with anticholinergic agents, which is consistent in magnitude with the change obtained in the present study (7 (17) meters). Considering that the minimal clinically important difference in 6MWD is 54 meters (95% CI 37 to 71 meters)[27], the clinical significance of the improvement in 6MWD with acute bronchodilation is questionable.

Studies reporting significant improvements in 6MWD in response to bronchodilation were conducted among patients with baseline 6MWD ranging from 237 to 490 meters [4,23-26]. This may suggest that the lack of responsiveness observed with the 6MWT in the present study could be related to the presence of a ceiling effect because of a relatively high baseline 6MWD (553 (68) meters). This possibility was considered, but was not supported by our data. First, although 6MWD was relatively well preserved in our patients, it represented 88% of normal predicted values, indicating that room was available for further improvement. In addition, there was no correlation between average 6MWD and improvement in 6MWD with bronchodilation, indicating that there was no systematic bias in the magnitude of bronchodilator-induced improvement in 6MWD according to average performance. Thus, patients with high performances on the 6MWT did not show lesser gains in 6MWD than patients with lower performances.

Little is known regarding the sensitivity of the endurance shuttle walk to bronchodilation. To our knowledge, the present study is only the second one to report its responsiveness to bronchodilation. In a prior investigation[2], we demonstrated that the distance walked on the endurance shuttle walk significantly improved with ipratropium bromide, that the test was able to detect an improvement in exercise performance in 82% of the patients, and that its standardised response mean (signal to noise ratio) was greater than that of the constant-workrate cycling test. Similarly, in the present study, the distance walked on the endurance shuttle walk significantly increased in response to ipratropium bromide. The test captured an improvement in exercise performance in 64% of the patients and its standardised response mean was greater than that of the 6MWT. The test's standardised response mean was somewhat lower in the present study than in our previous investigation (0.66 versus 0.94, respectively). The reasons underlying this observation remain unclear. Subjects had slightly less severe airflow obstruction and higher baseline functional capacity in our previous investigation, supporting the notion that the lower responsiveness to bronchodilation in the present study was not due to the relatively well preserved lung function and functional status. Nevertheless, when the data from both studies are combined, the resulting standardised response mean for the endurance shuttle walk is 0.82, which is considered large[28].

Two physiological mechanisms were explored in order to explain differences in sensitivity to bronchodilation between the 6MWT and the endurance shuttle walk: the cardiorespiratory response and the degree of quadriceps muscle fatigue elicited by each test. Previous investigations have demonstrated that the occurrence of contractile fatigue of the quadriceps is much less common after walking tests than after cycling tests[2,29]. In the present study, average quadriceps twitch force was maintained after both walking tests and quadriceps muscle fatigue (post-exercise fall in twitch force ≥ 15%) was observed in less than 15% of patients. These findings support the concept that the relative contribution of quadriceps muscle fatigue to walking capacity is minor.

Several important observations were made with regards to the cardiorespiratory response to both walking tests. First, the initial response was faster during the endurance shuttle walk than during the 6MWT. Minute ventilation, respiratory rate, and heart rate quickly approached maximal values during endurance shuttle walking, while the same three parameters remained at submaximal levels throughout the 6MWT. This likely explains, at least partly, the shorter duration (and walking distance) of the endurance shuttle walk under placebo. Second, cardiorespiratory kinetics and walking speeds were remarkably similar for both 6MWT, suggesting that patients tend to reproduce the same walking pattern during six-minute walking, whether on placebo or ipratropium bromide. In a previous investigation, Casas and colleagues[22] demonstrated that the average walking speed achieved during a 6MWT was highly predictive of critical walking speed, a surrogate of critical power, in patients with COPD. They reported a high concordance between the critical walking speed and the walking speed during the 6MWT suggesting that patients naturally set their walking speed at the maximal sustainable level. Critical walking speed cannot be estimated from our set of data. However, the average walking speed during the 6MWT in our patients, which ranged between 1.25 and 1.90 m/s, was very similar to that achieved by the patients studied by Casas and colleagues, suggesting that our patients were actually walking at their maximum sustainable walking speed. If we accept the idea that critical walking speed is a surrogate of critical power, our study would imply that critical power does not change with bronchodilation. Third, the cardiorespiratory response to endurance shuttle walking was also similar between the two testing conditions but, unlike for the 6MWT, this was expected since the workload was imposed and was identical for both conditions. A potential explanation for the improvement in endurance shuttle walking distance with bronchodilation is that, despite higher peak $\dot{V}_E$ reached during the ipratropium shuttle walk compared to the placebo walk, dyspnea at the end of the walk was similar between the two conditions. Reduction in dyspnea for a given $\dot{V}_E$ could be explained by reduced work of breathing or lesser dynamic hyperinflation under the ipratropium bromide condition[30]. This physiological exploration was however beyond the scope of the present study. Irrespectively of the mechanisms, patients were able to tolerate the same load for a longer time, which translated into improvements in the endurance shuttle walking distance.

Subjective information obtained from patients supported our physiological observations. A majority of patients cited dyspnea as the main limiting factor for both walking tests (as opposed to leg fatigue or to a combination of dyspnea and leg fatigue), which supports the notion that leg fatigue is not a prevalent finding after walking test, whether evaluated objectively or subjectively. Patients rated their dyspnea higher for the endurance shuttle walk than for the 6MWT and perceived the endurance shuttle walk to be more demanding than the 6MWT.

Together, our findings pertaining to test duration, cardiorespiratory response and perceived degree of difficulty suggest that the endurance shuttle walk is more physiologically demanding than the 6MWT. Surprisingly, the average walking speed was similar between both tests. However, the endurance shuttle walk was performed on a 10-meter course while the 6MWT was performed on a 30-meter course. This was done to comply with each test's respective guidelines[15,17]. The endurance shuttle walk therefore required that patients change direction much more frequently than the 6MWT. Although a recent multicenter study showed no effect of course length on 6MWD for straight courses ranging from 15 to 50 meters[31], our physiological and subjective data suggest that the numerous accelerations and decelerations required during the endurance shuttle walk made it more difficult for patients to maintain the same average walking speed than during the 6MWT.

Although patients perceived the endurance shuttle walk to be demanding, they were able to increase their endurance time with ipratropium bromide and therefore covered more distance. In contrast, patients replicated the same walking pattern for the 6MWT, regardless of the testing condition, and consequently did not increase 6MWD in response to bronchodilation. These findings suggest that it is easier for patients to increase endurance time than it is to increase walking speed, thereby suggesting that the tests' different designs had an impact on their respective response to bronchodilation. The situation appears to be different in pulmonary rehabilitation, since the 6MWT has been shown to be somewhat responsive in that setting[32]. One potential explanation is that patients may learn how to walk faster during pulmonary rehabilitation, an effect unlikely to be achieved by acute bronchodilation alone. Nonetheless, improvements in 6MWD after pulmonary rehabilitation have not consistently reached the minimal clinical important difference[32]. In addition, recent evidence suggests that the endurance shuttle walk is more responsive to the effects of pulmonary rehabilitation than the 6MWT[33]. The endurance shuttle walk has also been recently shown to discriminate between treatments in short-term studies using altered gas mixtures[34]. Together, these findings provide growing support for the use of the endurance shuttle walk as an evaluative tool to monitor response to treatment in COPD.

CONCLUSIONS

In summary, the results from this study indicate that the endurance shuttle walk is more responsive to the acute effects of bronchodilation than the 6MWT. Clinical, physiological and subjective findings suggest that differences in test designs may explain, at least partly, these differences in responsiveness to bronchodilation. This may be especially true when evaluating COPD patients with a wide range of disease severity and with a relatively well-preserved functional status. Overall, these findings have important implications for future clinical trials evaluating the functional impact of bronchodilation in patients with COPD.

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