International Journal of Chronic Obstructive Pulmonary Disease
Dovepress
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ORIGINAL RESEARCH

Changes in six-minute walking distance during pulmonary rehabilitation in patients with COPD and in healthy subjects

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease
29 June 2010

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Background: The six-minute walking distance (6MWD) test has demonstrated validity and reliability to assess changes in functional capacity following pulmonary rehabilitation in patients with chronic obstructive lung disease. However, no attempt has been made to establish an iterative measurement of 6MWD during the overall period of pulmonary rehabilitation. Therefore, the aim of this study was to evaluate the impact of a twelve-week rehabilitation program on the iterative weekly measurement of 6MWD in chronic obstructive pulmonary disease (COPD) patients and healthy subjects.

Methods: Twenty-six patients with COPD and nine age-matched healthy subjects were studied. Measurements were taken at baseline and after twelve weeks except for the 6MWD. The exercise measurements included a six-minute walking test (6MWT) and an incremental exercise test. Oxygen saturation, heart rate, and dyspnea will be monitored during all these tests.

Results: At baseline there were significant differences between groups, except in age, body mass index, and oxygen saturation. After 12 weeks, there was no significant change in lung function in patients with COPD and healthy subjects. The 6MWD, peak oxygen uptake $\dot{V}O_{2peak}$ and anaerobic threshold increased significantly after training in both groups ($P < 0.01$). The averaged trace of the 6MWD of patients with COPD and healthy subjects was followed-up respectively by a logarithmic and linear fitting. 6MWD showed a plateau after eight weeks in patients with COPD, however, it increased continually overall in healthy subjects.

Conclusion: Both patients with COPD and healthy subjects demonstrated functional responses to training but with somewhat different patterns in quality of the improvement of the 6MWD.

Keywords: six-minute walking distance (6MWD), chronic obstructive pulmonary disease (COPD), healthy subjects, pulmonary rehabilitation

Chronic obstructive pulmonary disease (COPD), characterized by chronic inflammation with irreversible airflow limitation, causes chronic morbidity and disability. COPD is predicted to be the fifth most frequent cause of death in the world.[1] Dyspnea, decrease of exercise capacity, and impairment of quality of life are common in patients with COPD.[2] Recently, it has been demonstrated that the decrease in exercise capacity is associated with mortality of these patients.[1,2] Patients with COPD often report walking slower than people of the same age, having to stop walking to breathe, or not leaving the house because of breathlessness.[3]

Pulmonary rehabilitation is strongly endorsed as an evidence-based intervention for the management of patients with COPD.[2] It is the recommended standard of care for patients with COPD as it has been shown to decrease the perception of dyspnea,[4] to enhance exercise capacity,[5] to reduce health care resource utilization[5,6] and to improve health status.[4] Reduction of lactic acidosis,[7] reduction in minute ventilation and heart

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rate for a given work rate and enhanced activity of mitochondrial enzymes and improved capillary density in the trained muscles,[8,9] are among the underlying physiological changes that contribute to these improvements.

Timed walking tests such as the six-minute walking test (6MWT) have gained popularity for use in clinical practice and research setting[10–12] to assess changes in functional capacity following pulmonary rehabilitation intervention.[11] Previous studies using the 6MWT were conducted in patients with COPD, but did not include healthy subjects.[13,14]

The aim of this study was to evaluate the impact of a twelve-week rehabilitation program on the iterative measurement of six-minute walking distance (6MWD) in COPD patients and healthy subjects.

Methods

Study subject

The study has been approved by the Ethical Committee of the University Hospital of Sousse. Thirty-two patients from the department of physiology of the Academic Hospital of Sousse, Tunisia, who had been diagnosed with moderate to severe COPD and twelve healthy subjects, were included in the study after giving their informed consent to participate. Diagnosis of COPD was made according to international recommendations.[1] At the start of the study, patients were clinically stable; they received regular treatment with inhaled bronchodilators and inhaled steroids according to current guideline for their disease stage. Patients with a significant response following bronchodilator use, defined as an increase in forced expiratory volume in one second (FEV_1) of more than 12% and 200 mL, patients with congestive heart failure, ischemic heart disease, or neuromuscular problems; and patients who had participated in an earlier training program, were excluded from the study.

The healthy subjects were all nonsmokers and free of significant cardiovascular, metabolic, and musculoskeletal disorders that could limit exercise capacity.

Study design

Subjects were evaluated on three consecutive days at baseline and at the end of the three months training program. On the first day of the study, patients were informed of the purpose of the study and had agreed to participate. Pulmonary function test was performed using a body plethysmograph. On the second day a 6MWT test was performed. On the third day, the exercise capacity was assessed by using a cycle ergometer.

Methods

Pulmonary function test

All participants underwent spirometry with determination of FEV_1 and forced vital capacity (FVC). Spirometry was performed using the pneumotachograph of a constant volume plethysmograph (ZAN 500 Body II; ZAN Meßgreräte GmbH, Germany) according to European Respiratory Society recommendations.[15]

Exercise testing

Subjects were evaluated before and after rehabilitation program. An exercise test was performed on a calibrated cycle ergometer (Ergoline, Bitz, Germany) according to the individualized and standardized exercise test protocol reported by the American Thoracic Society and American College of Chest Physicians.[16] The maximal predicted work load was calculated and adapted to the patient by multiplication of the percentage fall in FEV_1 by comparison to the predicted value.

Prior to each experiment, the volume and the gas analysers were calibrated. The theoretical maximal oxygen uptake ($\dot{V}O_{2max\ Th}$) was calculated.[16] Subject wore a mask for gas exchange analysis using a breath-by-breath automated exercise metabolic system (ZAN 600 Ergotest; ZAN Meßgeräte GmbH). The three-minute warm-up was conducted at 20% of this maximal estimated workload. The workload was then increased every minute. The rate of increase was defined as 8% of maximal estimated workload, in order to obtain the maximal workload in about 10 minutes.

Oxygen saturation (SO_2) was continuously monitored via a finger pulse oxymeter (Model 9847 Nonin Medical, Inc.; Minneapolis, MN, USA). Systolic blood pressure and dyspnea (Borg CR-10 scale) were recorded before and after exercise. The heart rate was continuously monitored using a 12-lead ECG (ZAN ECG, 800; ZAN Meßgeräte GmbH).

To ensure that peak oxygen uptake ($\dot{V}O_{2peak}$) was attained, at least three of the following criteria had to be met: an increase in $\dot{V}O_2 < 5$ mL with the last increase in work rate; attainment of age predicted maximal cardiac frequency; a respiratory exchange ratio >1.10 and an inability to maintain the required pedaling frequency (60 rev min^{-1}) despite maximal effort and verbal encouragement. $\dot{V}O_{2peak}$ was accepted as maximum $\dot{V}O_2$. The anaerobic threshold was determined by the V-slope method and confirmed by the traditional gas exchange.[17]

Six-minute walking test

The 6MWT was performed before and every week during the three months of the rehabilitation program. The 6MWT was conducted according to international recommendations.[10] Reference values were calculated by Tunisian equations.[18] Subjects were instructed to walk at their own maximal pace along a 40 m long hospital corridor. They were asked to cover as much distance as they could within six minutes. Subjects were given feedback on time progression at each minute. Subjects were allowed to stop and rest during the test, but were instructed to resume walking as soon as they felt able to do so. Before the test, patients rested in a chair, located near the starting position, for ≥10 minutes. Heart rate and SO_2 were measured for one minute at baseline, and during the first minute of recovery by a pulse oxymeter. Pre- and post-walk dyspnea was recorded using the Borg scale. At the end of the 6MWT, the participant was told to stop, and ambulatory distance was recorded.

Training program

The subjects were required to participate in the rehabilitation program three days/week during the three months. They received the same exercise training and education program. This consisted of two sessions of 30 minutes/week of seminars and discussions covering the following topics: relaxation, disease education, benefits advice, energy conversation, medication advice, chest clearance, and breathing control techniques. The training schedule was the same in the two groups, consisting of a five minute warm-up followed by 10 minutes of work and five minutes of active recovery, repeated over a 45 minute session. The exercise program was individualized according to the initial physical fitness assessment before intervention. Each subject was trained to its target heart rate corresponding to the gas exchange threshold. Subjects were instructed to perform a stationary bicycle exercise and the warm-up, cool-down, and upper extremity exercises. During training, heart rate was continuously monitored by means of a cardiofrequency meter (Polar, S810). The cardiofrequency meter was set in such a way that subject could exercise within ± 5 beats/minute of prescribed intensity. An alarm insured that the subject trained within the preselected range.

Analysis

The results of the study are presented as mean ± standard deviation (SD). The nonparametric Mann–Whitney U test was used to compare baseline characteristics and training-related changes in patients with COPD and healthy subjects, Wilcoxon's matched pairs test was used to assess training-induced changes within the group. Repeated measures ANOVA was used to assess weekly changes of 6MWD overall of pulmonary rehabilitation. When the ANOVA F ratio was significant, the means were compared by using the post-hoc contrast test. The statistical program Statistica was used for the analysis (Statistica Kernel Version 6; Stat Soft, France). The level of significance was set as $P < 0.05$.

Results

Six patients and three healthy subjects were dropped out of the rehabilitation group due to an acute exacerbation of respiratory symptoms and lack of motivation or transport problems.

Anthropometric characteristics and pulmonary function parameters of patients with COPD and healthy subjects before and after the rehabilitation program are provided in Table 1. Age and body mass index (BMI) were similar in both groups. The main differences were observed in pulmonary function where the patients with COPD showed moderate to very severe airflow obstruction. There was no significant change in FEV_1 and FVC in the two groups after rehabilitation program.

Table 2 shows exercise characteristics of patients with COPD and healthy subjects before and after the rehabilitation program. There are significant changes in $\dot{V}O_{2peak}$, the anaerobic threshold, dyspnea, and heart rate ($P < 0.01$). The SO_2 did not change significantly after rehabilitation program in both groups.

The 6MWD increased significantly after the rehabilitation program in both groups ($P < 0.01$), as shown in Table 3. The dyspnea and heart rate at the peak of 6MWT decreased significantly after the rehabilitation program ($P < 0.05$). Any change in SO_2% was marked at the peak of 6MWT in both groups compared with values before rehabilitation program.

Figure 1 shows the averaged trace and the corresponding logarithmic and linear fitting of the dependant variables of 6MWD for patients with COPD and healthy subjects.

The average walking distance of both groups increased significantly during the first week of training ($P < 0.05$), and within two weeks all the subjects showed an increase in 6MWD. The mean walking distance in COPD patients increased according to a logarithmic curve (r = 0.98). The walking distance in healthy subjects increased linearly during the overall period of training (r = 0.98). However, in patients with COPD, it continued to improve and reaching 613.91 ± 56.06 m after eight weeks, after that the mean distance showed little change which presented as a plateau.

Table 1 Anthropometric characteristics and pulmonary function parameters of healthy subjects and patients with chronic obstructive pulmonary disease before and after rehabilitation program

	Healthy subjects (n = 9)		Patients with COPD (n = 26)	
	Before RP	**After RP**	**Before RP**	**After RP**
Age, Yr	58 ± 7	–	61 ± 4	–
BMI; kg/m^2	26,52 ± 1.78	25.19 ± 2.13	24.01 ± 5.16	25.18 ± 4.61
FEV_1, L	2.94 ± 0.45	2.97 ± 0.56	1.42 ± 0.52***	1.57 ± 0.75†††
FEV_1, % Predicted	88.66 ± 9.1	92.50 ± 5.17	48.86 ± 11.31***	51.31 ± 9.73†††
FVC, L	3.16 ± 0.57	3.27 ± 0.51	2.21 ± 0.86***	2.36 ± 0.71†††
FVC, % Predicted	82.75 ± 13.29	85.49 ± 9.41	58.82 ± 9.8***	65.43 ± 7.42†††
FEV_1/FVC ratio	82.81 ± 9.5	84.27 ± 10.75	55.64 ± 8.91***	57.91 ± 9.91†††

Unit: Mean ± SD; n, number of subjects.

Notes: Comparisons between patients with COPD and healthy subjects before rehabilitation program: ***$P < 0.001$; Comparisons between patients with COPD and healthy subjects after rehabilitation program: †††$P < 0.001$.

Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; RP, rehabilitation program.

Table 2 Exercise characteristics of healthy subjects and patients with chronic obstructive pulmonary disease before and after rehabilitation program

	Healthy subjects (n = 9)		Patients with COPD (n = 26)	
	Before RP	**After RP**	**Before RP**	**After RP**
$\dot{V}O_{2peak}$, mL min^{-1} Kg^{-1}	29.03 ± 6.15	32.6 ± 4.32**	26,27 ± 3.23‡‡	27.54 ± 5.7†† §§§
Anaerobic threshold, l min^{-1}	1.18 ± 0.22	1.38 ± 0.24**	0.84 ± 0.09‡‡‡	1.12 ± 0.05†† §§
Dyspnea				
Rest	0.2 ± 0.3	0.14 ± 0.23	2.4 ± 1.7‡‡‡	1.4 ± 0.6†††
Peak	3.45 ± 1.12	1.02 ± 1.18**	6.6 ± 1.9‡‡‡	3.3 ± 2.7†††
SO_2, %				
Rest	96.2 ± 0.2	96 ± 1.3	94 ± 1.24‡‡	93 ± 2.5§§
Peak	95 ± 1.8	96.21 ± 1.5	91 ± 3‡‡‡	92.27 ± 1.3§§§
HR, bat min^{-1}	156.72 ± 18.9	149.27 ± 18.4**	136 ± 7‡‡‡	137 ± 5††

Unit: mean ± SD; $\dot{V}O_{2peak}$ l/min.

Notes: Comparison in healthy subjects with values before and after rehabilitation program: **$P \leq 0.01$; Comparison in patients with COPD with values before and after rehabilitation program: ††$P \leq 0.01$, †††$P \leq 0.001$; Comparison between patients with COPD and healthy subjects before rehabilitation program: ‡‡$P \leq 0.01$, ‡‡‡$P \leq 0.001$; Comparison between patients with COPD and healthy subjects after rehabilitation program: §§$P \leq 0.01$, §§§$P \leq 0.01$.

Abbreviations: HR, heart rate; SO_2, oxygen saturation; VO_{2peak}, peak oxygen uptake; COPD, chronic obstructive pulmonary disease; RP, rehabilitation program.

Table 3 Six-minute walking test parameters of healthy subjects and patients with chronic obstructive pulmonary disease before and after rehabilitation program

	Healthy subjects (n = 9)		Patients with COPD (n = 26)	
	Before RP	**After RP**	**Before RP**	**After RP**
6MWD, m	600 ± 28.28	789 ± 19.07**	504 ± 55.46‡‡‡	620 ± 69.71††,§§§
6MWD, %	86 ± 4	113 ± 3**	72 ± 8‡‡‡	89 ± 10††,§§§
SO_2, %				
Rest	96.9 ± 1.13	96.72 ± 1.1	96 ± 2.4	95 ± 2.7
Peak	96.27 ± 1.1	95.45 ± 1.8	91.82 ± 4.5‡‡‡	89 ± 6.5§§§
Dyspnea				
Rest	0.18 ± 0.4	0.91 ± 0.3*	0.72 ± 1.27‡‡	0.45 ± 0.47†,§§
Peak	1.72 ± 1.48	0.36 ± 0.5*	4.5 ± 3.033‡‡‡	2.59 ± 2.13† §
HR				
Rest	73.72 ± 8.9	65 ± 4.07	75.63 ± 13.87‡‡	76.45 ± 14.03§§
Peak	87.8 ± 12.1	82.27 ± 27.7*	111.09 ± 11.2‡‡	104.81 ± 22.7†,§§§

Unit: Mean ± SD.

Notes: Comparison in healthy subjects with values before and after rehabilitation program, *$P \leq 0.05$, **$P \leq 0.01$; Comparison in patients with COPD with values before and after rehabilitation program, †$P \leq 0.05$, ††$P \leq 0.01$; Comparison between patients with COPD and healthy subjects before rehabilitation program; ‡‡$P \leq 0.01$, ‡‡‡$P \leq 0.001$; Comparison between patients with COPD and healthy subjects after rehabilitation program, §$P \leq 0.05$, §§$P \leq 0.01$, §§§$P \leq 0.001$.

Abbreviations: 6MWD, six-minute walking distance; HR, heart rate; SO_2, oxygen saturation; RP, rehabilitation program.

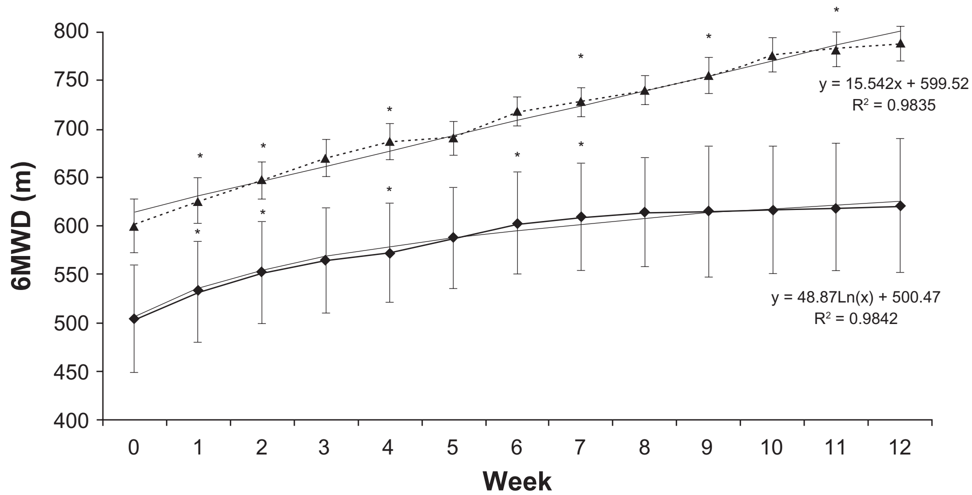

Figure 1 Logarithmic and linear fitting of the dependant variables for patients with COPD (–♦–) and healthy subjects (---▲---).

On the last evaluation, the mean walking distance was 620.73 ± 69.71 m. However, the walking distance of healthy subjects increased continually overall period of the rehabilitation program.

Discussion

The aim of this study was to evaluate the impact of 12 weeks, rehabilitation program on the iterative measurement of 6MWD in COPD patients and healthy subjects.

The major finding of this study was that, for comparable training conditions and duration, while patients with COPD and healthy subjects presented a distinct 6MWD response during endurance training, these responses differed quantitatively and qualitatively.

Quantitatively, the increase of 6MWD was significantly higher in controls than patients with COPD. From a qualitative point of view, physical training induces, in COPD patients, a logarithmic increase of 6MWD. Whereas, healthy controls showed a linear increase in the same period of training.

Assessment of cardiopulmonary function and $\dot{V}O_{2peak}$ during exercise stress reveals valuable insights with respect to the disease process and limitations imposed.[17] Exercise training programs were individualized. They were adapted to the individual limitations of the patient, taking cardiovascular, pulmonary, and skeletal muscle limitations into account and can be demonstrated to show overall benefit for each patient.[19]

As demonstrated in other studies,[7] no significant modification of pulmonary function was marked after a training program. Indeed, respiratory muscles are affected by multiple factors related to both the presence and severity of COPD which may impair their structure and function.[20] Pulmonary rehabilitation causes modification in peripheral myopathy but not ventilator limitation. The airflow limitation in most cases is both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[19]

The effect of individualized training on dyspnea peak and the maximal heart rate after 6MWT and exercise test, after rehabilitation program, was significantly important in both groups. This could be explained, firstly by improved physical conditions and a very good response to exercise, which supports a decreased sensation of dyspnea.[21] Secondly, by some physiological changes, like better cardiac adaptation, decrease in lactic acid production and reduction in metabolic cost of exercise.[7] This also explains the significant improvement of $\dot{V}O_{2peak}$ (13%) for patients with COPD. This result was similar to some studies which showed 10% improvement of $\dot{V}O_{2peak}$[20] and differs from other studies which showed 20% improvement.[22] This difference could be due to the variation in the length of training periods or to the intensity of training.

Compared to the healthy controls, COPD patients had significantly less walking distance during 6MWT. The magnitude of the overall increase in walking distance is in agreement with previous findings.[23] In our study, patients showed a mean increase in the 6MWT of 117 m or 23% in COPD patients and of 189 m in healthy subjects or 32% after 12 weeks. The percentage of walking distance improvement in patients with COPD was similar to those reported by Troosters et al.[24] In this study, patients with moderate to severe COPD, who tolerate exercise, presented an increase of 25% in their 6MWD.

Quantitatively, the largest difference in 6MWD between COPD patients and healthy subjects can be explained by the more fatigability of the quadriceps in patients with COPD than in healthy subject. Indeed, as shown in another study,[25] which compared patients with COPD to normal subjects, peripheral muscle strength was not completely corrected after training in COPD patients,[26,27] suggesting that factors others than chronic inactivity are involved in explaining muscle atrophy and weakness in patients with COPD.[22] In young and older normal subjects, muscle hypertrophy and improved neural recruitment patterns account for the increase in muscle strength following program training.[24,28] Both mechanisms could play an important role in the improvement of walking distance after training the participants.

Qualitatively, the progress of 6MWD presented a linear and a logarithmic improvement respectively for patients with COPD and healthy subjects during program training. The above linear increase could be explained by a linear rise of $\dot{V}O_{2peak}$ after program training.[28,29] In contrast, COPD patients reached a plateau after eight weeks which may be due to many factors such as baseline structure and biochemical status in COPD muscles[6,8] or oxidative stress induced by exercise.[23] Evidence show that the exercise intolerance in patients with COPD is related to muscular dysfunction, that includes low muscle mass and strength,[5] low muscle aerobic enzymes and capillarity,[6] early onset of lactic acidosis,[7] among other effects.[24]

Oxidative stress have also been suggested as a potential mechanism in the pathogenesis of COPD and can explain a plateau observed after eight weeks in patients with COPD.[30] Evidence for increased oxidative stress in obstructive airway diseases is emerging and several studies have suggested that it can play an important role in their evolution and pathogenesis.[23]

Opposed to the benefits of the physical exercise on patient with COPD, evidences indicate that physical exercise, especially aerobic, generate reactive oxygen species such as superoxide anion and hydrogen peroxide, capable of causing muscular damage and inflammation.[30] This process is known as oxidative damage and could limit the 6MWD progress in patients with COPD.[31]

These qualitative changes could also be explained by the effect of training on muscle gene expression in COPD and healthy subjects. Indeed, different patterns in muscle gene expression were described, potentially reflecting the specific molecular response of the muscle to exercise in patients with COPD and suggesting additional mechanisms for exercise limitation in COPD.[24]

In conclusion, the findings of this study demonstrate that an individualized training is more likely to produce optimal benefit for patients with COPD like healthy subjects but with some differences. Rehabilitation program, over 12 weeks, induces a linear improvement of 6MWD in healthy subjects, and a logarithmic improvement for patients with COPD.

Acknowledgments

The authors thank Professor Mohamed Shamssain and Bechir Jarrar for correction of the English. They also wish to thank the participants for their co-operative attitude and dedicated performance.

Disclosure

The authors report no conflicts of interest in this work.

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