ORIGINAL ARTICLES

Changes in Exercise Tolerance, Health Related Quality of Life, and Peripheral Muscle Characteristics of Chronic Obstructive Pulmonary Disease Patients After 6 Weeks' Training

M. Montes de Oca,[a] S.H. Torres,[b] Y. González,[a] E. Romero,[c] N. Hernández,[b] and C. Tálamo[a]

[a]Servicio de Neumonología, Hospital Universitario de Caracas, Universidad Central de Venezuela, Caracas, Venezuela.
[b]Sección de Adaptación Muscular, Instituto de Medicina Experimental, Universidad Central de Venezuela, Caracas, Venezuela.
[c]Instituto Nacional de Enfermedades Respiratorias, Universidad Nacional Autónoma de México, México DF, Mexico.

OBJECTIVE: This study was designed to assess changes in skeletal muscle characteristics after 6 weeks' high-intensity physical training of patients with moderate to severe chronic obstructive pulmonary disease (COPD) and to determine how the changes were related to improvements in exercise tolerance and health related quality of life (HRQL).

PATIENTS AND METHODS: Ten patients with a mean (SD) age of 60 (10) years and a forced expiratory volume in 1 second of 32% (9%) were enrolled. The effect of training on the 6-minute walk test, HRQL questionnaires, and skeletal muscles was examined for the 8 patients who completed the program. The structural and chemical characteristics of skeletal muscles before and after training were studied in vastus lateralis muscle biopsies.

RESULTS: Training significantly modified the 6-minute walk test (*P*<.01), HRQL (*P*<.05), and citrate synthetase activity (*P*<.05). Changes in distances walked during the 6-minute walk test were significantly related to changes in the mean area of fibers (r=0.81).

CONCLUSIONS: The results of this study indicate that 6 weeks of high-intensity physical training of COPD patients produces moderate changes in skeletal muscles which could partly explain improvements observed in exercise tolerance after respiratory rehabilitation.

Key words: *Chronic obstructive pulmonary disease (COPD). Respiratory rehabilitation. Skeletal muscles.*

Cambios en la tolerancia al ejercicio, calidad de vida relacionada con la salud y características de los músculos periféricos después de 6 semanas de entrenamiento en pacientes con EPOC

OBJETIVO: Este estudio se diseñó para evaluar los cambios en las características de los músculos esqueléticos después de 6 semanas de entrenamiento físico de alta intensidad, en pacientes con enfermedad pulmonar obstructiva crónica (EPOC) moderada-grave, y para determinar cómo se relacionan con la mejoría de la tolerancia al esfuerzo y la calidad de vida relacionada con la salud (CVRS).

PACIENTES Y MÉTODOS: Se estudió a 10 pacientes (edad media ± desviación estándar: 60 ± 10 años) con un volumen espiratorio forzado en el primer segundo del 32 ± 9%. Se analizaron el efecto del entrenamiento sobre la marcha de 6 min (M6M), cuestionarios de CVRS y músculos esqueléticos en los 8 pacientes que completaron el programa. Se estudiaron las características histoquímicas y morfológicas de los músculos esqueléticos antes y después del entrenamiento en biopsias del *vastus lateralis*.

RESULTADOS: La intervención de estos pacientes modificó significativamente la M6M (p < 0,01), la CVRS (p < 0,05) y la actividad de la citrato sintetasa (p < 0,05). El cambio en la distancia recorrida durante la M6M se relacionó significativamente con el cambio en el área promedio de las fibras (r = 0,81).

CONCLUSIONES: Los resultados de este trabajo indican que la intervención con 6 semanas de entrenamiento físico de alta intensidad en pacientes con EPOC induce cambios modestos en los músculos esqueléticos, que podrían explicar en parte los beneficios observados en la tolerancia al esfuerzo tras la rehabilitación respiratoria.

Palabras clave: *Enfermedad pulmonar obstructiva crónica (EPOC). Rehabilitación respiratoria. Músculos esqueléticos.*

Introduction

Chronic obstructive pulmonary disease (COPD) patients frequently develop progressive dyspnea on effort, which affects their health related quality of life (HRQL) and limits their capacity to perform activities

Correspondence: Dra M. Montes de Oca.
CCS 5150, PO Box 025323, Miami, FL 33102-5323, USA.
E-mail: mmdeoca@cantv.net

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of daily living. They consequently feel forced to adopt a sedentary lifestyle and thus start a vicious circle which leads to severe deterioration of their physical condition.

Reduced tolerance to exercise is a common problem in COPD patients. Several studies have shown that intolerance in these patients does not depend only on ventilatory limitation or gas interchange abnormalities.[1-3] Other factors such as skeletal muscle dysfunction can contribute to intolerance.

In recent years, our understanding of structural and functional anomalies in the skeletal muscles of COPD patients has been increasing.[4-6] Histochemical and biochemical findings indicate a change from oxidative aerobic to glycolytic anaerobic metabolism.[4-6] Some studies have shown that these anomalies can be corrected, at least in part, with physical exercise.[4,7-10]

Despite the widespread incorporation of physical exercise in the clinical management of COPD patients, there is disagreement over the optimal type, intensity, and duration of these programs. Some authors claim that high-intensity and prolonged exercise can produce central and peripheral muscle adaptation in COPD patients.[8,9] Two studies on the same group of patients showed that high-intensity exercise over 12 weeks increased the activity of mitochondrial oxidative enzymes, the size of the type I fibers, and the number of capillaries in contact with type I and IIa fibers in COPD patients.[4,9] Only 2 studies have assessed skeletal muscle changes following a 6-week exercise program. Belman and Kendregan[11] observed that COPD patients were incapable of exercising with sufficient intensity to produce either the classical responses to exercise or changes in muscular enzymes. Puente-Maestu et al,[12] however, found that skeletal muscles had increased oxidative capacity correlating with duration of effort.

To date, no study has assessed the histochemical modifications of skeletal muscles in COPD patients following a high-intensity exercise program of less than 12 weeks duration. Nor has the relation to changes in HRQL and exercise tolerance after such a regimen been explored.

The objective of this study was to study the characteristics of skeletal muscles following a 6-week (18-session) high-intensity physical exercise program in patients with moderate to severe COPD, and the association between the characteristics and changes in the 6-minute walk test (6MWT) and St George's Respiratory Questionnaire on HRQL.

Patients and Methods

Patients

Ten patients from the pneumology department of the Hospital Universitario de Caracas, Venezuela, who had been diagnosed with moderate to severe COPD were included in the study after giving their informed consent to participate. Diagnosis of COPD was made according to the American Thoracic Society guidelines.[13] At the start of the study, patients were clinically stable, were receiving appropriate bronchodilatory treatment (β_2 agonists, anticholinergics, theophylline, and inhaled corticosteroids), and were not regularly using systemic corticosteroids. The study was approved by the bioethics committee of the hospital.

The following patients were excluded from the study: patients with significant response following bronchodilation defined as an increase in forced expiratory volume in 1 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.

During the exercise program, 2 patients presented acute exacerbations and withdrew from the program. Eight patients completed the program and were reassessed.

Lung Function and HRQL

Lung function at rest was measured with a spirometer (CardiO2 System MedGraphics, St Paul, Minnesota, USA). Forced vital capacity (FVC), FEV_1, and FVE_1/FVC values were calculated according to the American Thoracic Society guidelines.[14] Normal reference values were taken from the literature.[15]

HRQL was assessed before and after the exercise program, using the Spanish version of the St George's Respiratory Questionnaire.[16]

6MWT

The 6MWT was conducted in a quiet, 22-meter-long corridor. The test was standardized using international guidelines.[17] Two tests were performed with a 30-minute interval between them. Patients were instructed and encouraged to walk quickly for 6 minutes and then rest for the interval period if they needed to. The distance walked in the established time was recorded. Oxygen saturation (pulse oximeter Model 950, Respironics, Kennesaw, GA, USA) was also measured during the test. Heart rate and degree of dyspnea were assessed both at rest and during peak effort using the Borg scale.[18] Distance walked was measured in meters and the greater distance walked during the 2 tests was used in the analysis.

Skeletal Muscle Measurement

Muscular biopsies were taken from all patients on enrollment to measure the chemical and metabolic characteristics of skeletal muscles. A second assessment of these muscles was performed on patients who completed the physical training program. The biopsies were taken from the vastus lateralis (quadriceps muscle) with the necessary antiseptic precautions and under local anesthetic with 2% lidocaine. The needle described by Bergström[19] was used and the sample was divided into 2 parts. One part was embedded in optimal cutting temperature medium (Tissue-Tek, Sakura Finetek, USA) and frozen in liquid nitrogen-cooled isopentane. Cross sections 10 µm thick were cut in a cryostat at –20ºC. Muscle fibers were classified according to the reaction of myofibrillar adenosine triphosphatase (ATP-asa) with alkaline (pH 10.3) and acid (pH 4.37 and 4.6) preincubation.[20] Capillaries were visualized by the alpha-amylase method with periodic acid-Schiff staining.[21] Microphotographs magnified by 200 were taken of the sections and the fibers were identified by comparison with the

ATP-asa section. An area of the photograph was traced and measured with a planimeter, and the fibers and capillaries were counted to calculate capillary density (mm^2) and the capillary/fiber relation. The capillaries around each fiber were counted, the mean of each type of fiber was calculated, and the results were expressed as contact capillaries. Fibers were grouped in types and a planimeter was used to measure the mean area of each type of fiber.

The second part of the sample was snap frozen with liquid nitrogen and used to analyze the citrate synthetase (CS), β-hydroxyacylcoenzyme A dehydrogenase (HAD), and lactate dehydrogenase (LDH) enzymes, using fluorometric techniques.[22] The results of the enzyme activity were expressed in µmol/min·g of tissue wet weight.

Physical Training Program

All patients began a respiratory rehabilitation program which emphasized exercising the lower limbs. Patients attended a rehabilitation center 3 times a week for 6 weeks. Lower-limb training was performed on a calibrated cycle ergometer, in 30-minute sessions.

Physical training sessions were supervised by a rehabilitation doctor who encouraged patients to reach the pre-established training intensity. Load corresponded to 70% to 80% of the peak oxygen consumption reached in a maximum effort test performed prior to the rehabilitation program to establish intensity. The test was performed on a cycle ergometer (CardiO2 System, MedGraphics, St Paul, Minnesota, USA) using slope to increase the load. Physical training sessions started with 2 minutes' rest followed by 3 minutes' pedaling without load and finally a gradual increase in load (slope) of 10 W/min. The end of the session was determined by symptoms such as exhaustion, dyspnea, or lower-limb tiredness. Patients were able to complete 30 minutes' training from the start of the program but at lower loads than the pre-established maximum. In subsequent sessions the load was gradually increased according to tolerance. Once patients reached the pre-established intensity, it was maintained until the end of the program.

Sessions also included upper-limb exercises, warm up, and relaxation. Supplementary oxygen was administered to patients who presented significant desaturation.

Statistical Analysis

Anthropometric characteristics, lung function, 6MWT, HRQL, and skeletal muscle parameters were expressed as means (SD). Changes in 6MWT, HRQL, and skeletal muscle following physical training were determined using the Student *t* test for dependent variables. Pearson correlation (r) was used to assess the relation between changes in the 6MWT and HRQL with the modifications observed in the muscle. The statistical program StatSoft Statistica was used for the analysis. A *P* value of less than .05 was considered statistically significant.

Results

Mean (SD) values of patients' physical characteristics and lung function at rest are shown in Table 1. Patients' lung function values show severe airflow obstruction (FEV_1% and FEV_1/FVC% of 32 [9] and 42 [10] respectively). As expected, spirometric values did not change following physical training.

TABLE 1
Physical Characteristics and Basal Lung Functions*

Variables	Mean (SD)
Age, years	60 (10)
Height, cm	165 (15)
Weight, kg	63 (15)
BMI	23 (4)
FVC, %	60 (9)
FEV_1, %	32 (9)
FEV_1/FVC, %	42 (10)
MVV, L/min	38 (6)

*BMI indicates body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; MVV, maximal voluntary ventilation.

TABLE 2
Six-Minute Walk Test and Health Related Quality of Life Before and After Training*

Variables	Before	After
6MWT, m	402 (88)	495 (48)†
MHR, beats/min	122 (16)	118 (15)
Dyspnea		
Rest	1.2 (1.2)	0.6 (1)‡
Peak	3.6 (2.2)	3.8 (2.9)
SaO_2		
Rest (%)	92 (2)	93 (2)
Peak (%)	82 (6)	82 (8)
SGRQ		
Symptoms	44 (26)	26 (18)‡
Activity	74 (30)	52 (20)‡
Impact	49 (21)	34 (6)
Total	50 (11)	38 (10)‡

*6MWT indicates 6-minute walk test; MHR, maximum heart rate; SaO_2, arterial oxygen saturation; SGRQ, St. George's Respiratory Questionnaire.
†P<.01.
‡P<.05.

Results of 6MWT and HRQL before and after respiratory rehabilitation are shown in Table 2. Low baseline scores were observed for the various aspects of HRQL measured (symptoms, daily living activities, and disease impact) with a significant reduction in St George's Respiratory Questionnaire scores following physical training, from 403 (88) m to 495 (48) m (P<.01). Oxygen saturation, heart rate, and dyspnea intensity did not change with training.

Chemical characteristics of skeletal muscles before and after training are shown in Table 3. Patients presented an altered fiber distribution characterized by a lower percentage of oxidative fibers (type I) and a greater percentage of type II fibers, compared with normal controls in our laboratory (type I, 48% [10%]; type IIa, 38% [11%]; type IIb, 15% [6%]).

The percentages of the types of fibers, the area of each type of fiber, and the capillary parameters did not change with physical training. However, the mean area of fibers showed a tendency to increase after respiratory rehabilitation although the difference was not significant (P=.08).

Oxidative enzyme (CS and HAD) and glucolytic enzyme (LDH) activity before and after physical

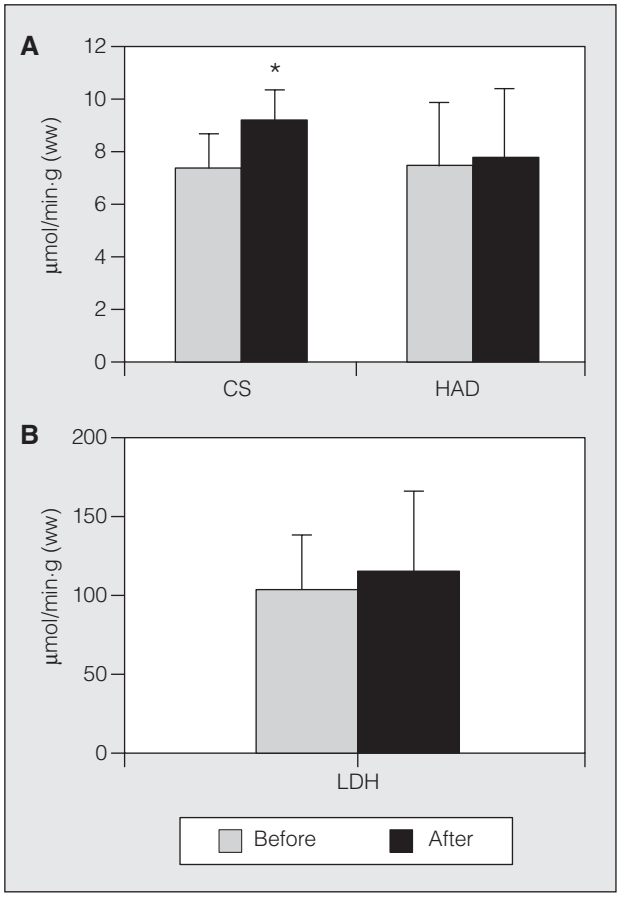

Figure 1. Citrate synthetase (CS), β-hydroxyacylcoenzyme A dehydrogenase (HAD), and lactate dehydrogenase (LDH) enzyme concentrations in skeletal muscles of COPD patients before and after training. ww indicates wet weight. *P<.05.

training is shown in Figure 1. CS activity significantly increased after training, from 7.4 (1.3) to 9.2 (1.2) µmol/g·min (P<.05). HAD and LDH enzymes did not show significant changes, activity increasing from 7.58 (2.27) to 7.74 (2.70) and from 106 (35.6) to 118.7 (60.48) µmol/g·min respectively.

TABLE 3
Characteristics of Skeletal Muscles Before and After Training

Variables	Before	After
Fiber type, %		
Type I	34 (7)	28 (11)
Type IIa	41 (9)	41 (10)
Type IIb	24 (10)	30 (12)
Mean area, µm^2	5119 (1225)	5908 (1213)
Type I area, µm^2	5859 (1555)	6043 (1640)
Type IIa area, µm^2	5365 (1632)	6211 (2691)
Type IIb area, µm^2	4116 (1718)	4119 (1575)
Capillary/fiber	1.42 (0.20)	1.51 (0.30)
Capillary density, mm^2	287 (50)	261 (50)
Contact capillaries		
Type I	4.2 (0.9)	4.3 (0.5)
Type IIa	3.7 (0.7)	3.8 (0.8)
Type IIb	3.5 (0.7)	3.2 (0.6)

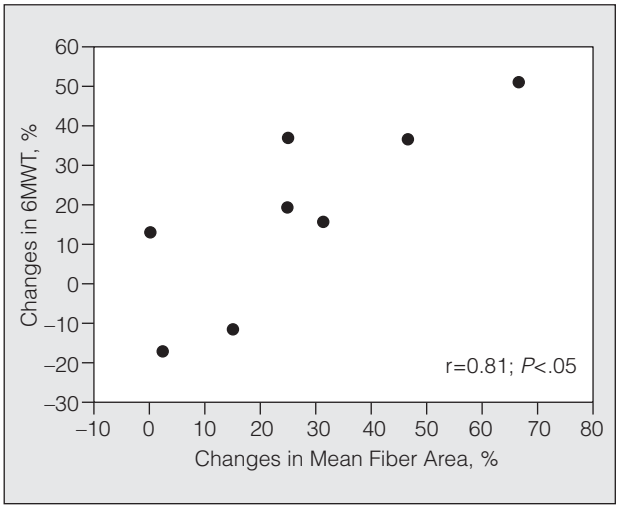

Figure 2. Correlation between percentage changes in the duration of the 6-minute walk test (6MWT) and changes in the mean fiber area (r^2=0.66). P<.01.

Figure 2 shows the significant correlation observed between the percentage of increased distance covered in the 6MWT and the percentage of increase in the mean area of fibers (r^2=0.66; P<.05). No relation was found between the 6MWT and changes in CS, in St George's Respiratory Questionnaire scores, or skeletal muscle (CS or mean area of fibers).

Discussion

The most important findings in this study on the characteristics of skeletal muscle in COPD patients following 6 weeks of physical training were *a)* that the muscle response to training was reflected by an increase in CS oxidative enzyme activity, and *b)* that the increase in mean area of fibers, although not significant, showed a significant correlation with the increase in distance walked in the 6MWT.

Belman and Kendregan[11] did not find an increase in CS in COPD patients who underwent 6 weeks of training while Puente-Maestu et al[12] reported a 33% increase in concentrations of the enzyme in patients who underwent high-intensity training. The results of our study show a 20% increase in CS activity. The difference between our results and those of Belman and Kendregan[11] can probably be explained by the low-intensity physical training used in their study (approximately 50% of the peak work rate). The difference between our findings and those of Puente-Maestu et al[12] could be related to the length of the training sessions, which were 45 minutes long in their study and 30 minutes in ours. However, an increase in CS concentrations of barely 12% was reported from a study of the same 30-minute sessions but with training prolonged to 12 weeks.[9] That study showed an increase in HAD, which may need longer training to be detected. It must be noted that very few severe COPD patients can undertake training at 70% to 80% of peak oxygen

consumption and the time needed to reach this level varied from patient to patient; it could therefore be useful to prolong training to 12 weeks in order to improve both HAD and CS activity.

Some studies have found a significant relation between distance walked in the 6MWT and the oxidative capacity of the peripheral muscles in COPD patients.[12,23] However, a close relation has also been reported between the capacity of the quadriceps muscles and the 6MWT (r=63)[24]; in the cited study, multiple regression analysis revealed that the isometric strength of the quadriceps and the peak inspiratory pressure (inspiratory muscle strength) were the best determinants of the total variance in 6MWT. In COPD, peripheral myopathy involves mainly anaerobic metabolism in the muscle, characterized by a predominance of type II fibers,[4-6] a reduction in oxidative enzymes, and a sharper rise in lactic acid concentrations during exercise.[25] Atrophy of the muscle fibers has also been observed,[4,26] due to lack of training and/or to the presence of inflammation.[27] Atrophy is apparent in the reduction of fiber area, which is directly related to the loss of fat-free mass and with the body mass index in COPD patients.[26] Distance walked in the 12-minute walk test has been shown to be closely related to patient fat-free mass and body weight[28] so fiber area might be relevant in 6MWT results. All these findings help explain the relation observed between the increase in the 6MWT and the changes in mean fiber area following our patients' physical training.

Our findings, consistent with those of other studies,[8,9,12] support the theory that lack of exercise is a reversible factor involved in skeletal muscle dysfunction in COPD patients and helps explain, partially at least, the improvements in tolerance to effort observed in these patients after physical training.

Unlike results reported in other studies,[4,9] we did not observe changes in capillarity or in the area of the various fiber types. The difference between the findings could be due to differences in the length of training and in the baseline condition of the patients' skeletal muscles. A 6-week training program (18 sessions) is probably insufficient to modify the muscular deficiencies related to the lack of exercise common in COPD patients. Moreover, the mean area of fibers and the capillary parameters in our patients before training were similar to those reported by Whittom et al[4] after 12 weeks of rehabilitation. The muscular deterioration of our patients may not have been as severe as they generally had low socioeconomic status and were therefore used to walking and using public transport and were less negatively affected than are patients with greater economic resources. The results of the 6MWT before training in our patients (Table 2) support this argument. We venture to speculate that it is probably difficult to improve skeletal muscle deficiencies caused by lack of exercise when these are slight or nearly normal.

The results of our study show that the St George's Respiratory Questionnaire values decreased significantly after physical training. No relation, however, was found between the muscular response and changes in HRQL. These findings are more difficult to attribute to muscular weakness and other factors probably contribute to this process. The small number of patients included in the study may have prevented detection of a relation. Further studies are needed to determine the contribution of skeletal muscle dysfunction to changes in HRQL in COPD patients.

Our study was somewhat limited by the relatively small sample size and therefore the results cannot be generalized to all COPD patients. However, most studies that assess chemical characteristics of skeletal muscle enroll small numbers of patients when they involve invasive tests like muscle biopsies, especially when 2 samples (before and after training) are needed.

In conclusion, the results of the present study show that 6 weeks of high-intensity physical training in COPD patients significantly modify tolerance to effort as well as HRQL and produce slight changes in skeletal muscle which are related to the increases observed in the 6MWT results. These findings indicate that changes in muscular deficiencies related to lack of exercise probably improve with physical training and could partly explain the improvements observed in tolerance to effort following respiratory rehabilitation.

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