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ALTERATIONS OF MUSCLE FATIGABILITY AND EXERCISE CAPACITY AFTER MAXIMAL EXERCISE IN YOUNG ADULTS WITH CYSTIC FIBROSIS

Walid Kamal Abdelbasset[1,2]*

[1]Department of Physical Therapy and Health Rehabilitation, College of Applied Medical Sciences, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia.

[2]Department of Physical Therapy, Kasr Al-Aini Hospital, Cairo University, Giza, Egypt.

***Corresponding Author: Dr. Walid Kamal Abdelbasset**
Department of Physical Therapy and Health Rehabilitation, College of Applied Medical Sciences, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia.

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ABSTRACT

Background: Cystic fibrosis is a genetic disorder affecting many physiological systems that may cause alterations of skeletal muscle strength, such as lowering of exercise capacity and impairment of physical activity. **Objectives:** The aim of this study was to investigate the effects of maximal exercise training on exercise capacity and muscle fatigability in cystic fibrosis young adults with moderate respiratory disease. **Methods:** Twenty eight young adults (18 ♂ and 10 ♀) were enrolled in the study. The study included two groups of young adults; the group of CF comprised of fourteen young adults with cystic fibrosis (9 ♂ and 5 ♀) and the group of healthy subjects comprised of fourteen age-matched healthy subjects (9 ♂ and 5 ♀). All participants have performed a maximal exercise test, muscle fatigue assessment, and cross-section area imaging. All measures were recorded and analyzed. **Results:** This study outcome demonstrated that there were lower FEV1, FVC, exercise capacity and had more oxygen desaturation with more breathing reserve index in young adults with CF than healthy subjects with $p<0.05$. Whereas, the two groups of this study had nonsignificant differences in cross section area, muscle fatigability, and maximal contraction of the quadriceps muscle with $p>0.05$. **Conclusions:** This study suggests that young adults with cystic fibrosis who had moderate pulmonary disorder and healthy subjects have similar effects in cross section area, muscle fatigability, and maximal contraction of the quadriceps muscle. Whereas maximal exercise has negative effects on exercise capacity in young adults with CF.

KEYWORDS: Cystic fibrosis; Young adults; Maximal exercise; Exercise capacity; Fatigability.

INTRODUCTION

Cystic fibrosis (CF) is a genetic disorder affecting many body systems due to dysfunction in the cystic fibrosis transmembrane conductance regulator protein (CFTR). The CF disease has many complications such as pancreatic enzyme dysfunction and progressive airway impairments with chronic pulmonary infections.[1]

Previous studies approved that the main cause of mortality in the disease end stages is respiratory failure, but deteriorations of pulmonary function don't illustrate all disability aspects fledged by CF patients. Recent studies and many secondary problems of the disease indicate the main function of peripheral muscles as a vital systemic outcome of CF disease. The mass of large muscles is directly associated with high rates of CF disease.[2] Deterioration of skeletal muscle strength is associated directly with clinical problems in CF disease, including lowering of exercise capacity and impairment of quality of life.[3]

Recent evidences explained that the weakness of peripheral muscles was observed in CF patients. There is a reduction of skeletal muscle strength and endurance in patients with cystic fibrosis when comparing with the healthy subjects, indicated impairment of skeletal muscles function.[4,5] The quadriceps muscle strength is related to pulmonary functions and exercise capacity. It was observed that many patients with cystic fibrosis have airway obstruction and cannot complete exercise training as they feel muscle fatigue of the lower limbs.[6]

Endurance is extensively considered as the individual ability to perform a physical function and can be classified to 2 ingredients; total body endurance and specific muscle endurance. In respiratory diseases particularly patients with CF, performance of total body endurance can be restricted through many causes, such as impairment of oxygen delivery (muscle perfusion, hypoxemia, and cardiac output impairment), skeletal muscle dysfunction and ventilatory impairments.[7,9] Total body assessment is thus required to provide an integrated picture of why exercise is limited[10], providing compensation to all body systems possibly included.

The causes affecting exercise capacity in patients with CF are usually uncharted. Assessments that result in exercise performance limitations is particularly noticeable in CF patients. Clinically, exercise capacity is associated with mortality rate and quality of life in CF patients and can be applied to evaluate the responses of treatment.[11] Hence, treatment programs planned to increase exercise capacity are influential and entirely rehabilitation should appoint to appropriate contribute agents.

Early study explained deteriorations of neuromuscular activity in the skeletal muscles after maximal exercise training in COPD patients.[12] Although the pathophysiology of skeletal muscle is reasonably not definitely similar, the present study may predict that same impairments continue in another pulmonary disease including cystic fibrosis.

Physical activity and aerobic exercise have many advantageous impacts on several measurements of health in patients with CF and high exercise capacity are associated with high quality of life[13] and high endurance in these patients.[11, 14]

Although impairment of exercise capacity is a usual manifestation of cystic fibrosis, the precise mechanical physiology continues to be explained, especially to enhance the exercise of pulmonary rehabilitation. Not only, respiratory factors are appropriate to indicate the disturbance of exercise capacity in patients with cystic fibrosis, certainly in patients with moderate pulmonary disease, for instance, bronchodilators improve respiratory functions and don't improve exercise capacity in CF patients.

The present study hypothesis suggested that young adults with CF may lead to decrease exercise capacity and increase muscle fatigability of the trained muscles after maximum exercise training together with ventilatory impairments. So that, the purpose of this study was to investigate the effects of maximal exercise training on exercise capacity and muscle fatigability in cystic fibrosis young adults with moderate respiratory disease.

MATERIALS AND METHODS

Subjects

Fourteen CF young adults (9 ♂ and 5 ♀) with moderate respiratory disease were recruited from Cairo University hospitals. The young adults with CF had moderate respiratory dysfunction with FEV1 ranged from forty to fifty nine percent of the predicted value. These young adults aged 18-25 years and were clinically stable for three months before participating in this study, had pancreatic medication and multivitamins. Fourteen age-matched healthy young adults (9 ♂ and 5 ♀) were recruited in this study as a control group with FEV1 more than eighty percent of predicted value. All participants had no cardiopulmonary limitations and had no physical activity before assessment. Participants were excluded from this study if they have severe medical disease such as cancer, cardiac disease, musculoskeletal limitations and endocrine diseases that could influence exercise performance. Baseline characteristics of the participating young adults in the study are demonstrated in table 1. This study was approved by the ethical committee of the department of physical therapy, Cairo University Hospitals in accordance with the guidelines in the Declaration of Helsinki. All participants were instructed about the principles, methods and measurement of the study and signed a consent form before enrolled in the study.

Instrumentations

Digital spirometer (CONTEC:SP10, China) was used to measure pulmonary functions (FEV1 and FVC) for each participant, Bicycle Ergometer (Monark, 939 Novo, Electronically Braked Cycle Ergometer, USA) was used to perform cardiopulmonary exercise test and to measure exercise capacity, magnetic resonance imaging (MRI) with a 3T scanner (General electric, WI, Philips, USA) was used to measure the cross-section area (CSA) of the quadriceps muscle. Electromyography (Cloud EMG, Florida, USA) was used to assess neuromuscular, muscle fatigability and maximal voluntary contraction (MVC) of the quadriceps muscle.

Procedures

All The steps of the procedure were explained to each participant. All young adults were appointed to perform exercise to a symptom-limited maximum. Oxygen uptake (VO_2) and pulmonary functions were measured at the beginning of the study. Maximum heart rate and gas exchange were measured to provide the maximal characteristics of the cycling exercise. All participants carried out a cardiopulmonary exercise test (CPET) and assessment of the quadriceps muscle, including neuromuscular fatigue assessment and definition of the muscle cross-sectional area (quadriceps muscle) in random request throughout 48 hours. CPET was performed by measurement of gas exchange breath by breath gas.

All participating young adults obtained for assessment with magnetic resonance imaging with a 3.0 T whole-body system to determine CSA of the quadriceps muscle. All evaluations were applied during isometric contractions on the right side. Briefly, participants laid in supine position with knee flexion at 90° and 130° hip flexion. The strength of the quadriceps was assessed under voluntary contractions through a transducer adjusted force. After quadriceps warm-up, participants carried out 3 voluntary contractions at maximum exercise. Pre- and post-test neuromuscular investigation was applied.

At the end of the study all measures were obtained and the pre and post records of the two groups were compared.

Statistical Analysis

Descriptive statistical analysis in the form of means and standard deviations was calculated for all measures. The *t*-tests (paired and unpaired) were applied to assess the mean differences of the outcome variables within and between the CF and control groups. The significance level was assigned at $p<0.05$ for all statistics. Data analysis was performed using SPSS, version 19 (SPSS, Chicago, IL).

RESULTS

From August to October 2017, Twenty eight young adults (18 ♂ and 10 ♀) aged 18-25 years were enrolled in the study. The study included two groups of young adults; the group of CF comprised of fourteen young adults with cystic fibrosis (9 ♂ and 5 ♀) and the group of healthy subjects comprised of fourteen age-matched healthy subjects (9 ♂ and 5 ♀). According to this study criteria, there was no statistical significant difference between the two groups of the study (CF and healthy groups) in baseline characteristics, including (ages, heights, weights, BMI) with $p>0.05$ whereas there were statistical significant differences between the CF and healthy groups in their pulmonary functions including FEV1) and FVC. The baseline characteristics of all the participating young adults in this study are shown in table 1.

Table 1: Baseline characteristics of the participating young adults in the study.

Items	CF group (n=14)	Healthy group (n=14)	*p*-value
Sex (♂/♀)	9/5	9/5	1.000[b]
Age (yrs)	20.4±3.5	21.2±2.4	0.486[a]
Height (cm)	173±6.6	171±7.3	0.454[a]
Weight (kg)	71.6±4.7	70.2±5.2	0.462[a]
BMI (kg/m^2)	23.6±3.2	23.3±3.5	0.814[a]
Pulmonary functions			
FEV1 (L)	2.7±0.8	4.5±1.3	0.002[a]
FVC (L)	4.3±1.1	5.6±1.3	0.008[a]
Data was applied in form of mean±SD; [a] p-value of independent t-test; [b] p-value of Mann-Whitney U test; CF, cystic fibrosis; ♂/♀, male/female; BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.			

In accordance with the criteria of the participating young adults in this study, the two groups (CF and healthy groups) have executed a maximal incremental cycling exercise (cardiopulmonary exercise test). The young adults with CF had lower peak power output, lower VO_{2peak}, lower MMV and lower HR_{max} when comparing with the healthy group ($p<0.05$). In contrast, the young adults with CF had more breathing reserve index (BRI) after maximal exercise and more oxygen desaturation when comparing with the healthy group ($p<0.05$) whereas, there was a statistically nonsignificant difference in measure of muscle fatigue, CSA and MVC between the CF and healthy groups as shown in table 2.

Table 2: The changes during cycling exercise test and maximal voluntary contractions in the CF and healthy young adults.

CPET variables	CF group (n=14) Mean± SD	Healthy group (n=14) Mean± SD	*P*-value
Peak power output (W)	178±47	284±66	0.001
VO_{2peak} (L)	2.5±0.8	3.5±1.1	0.010
MMV (L)	95.7±24.3	142.2±29.5	0.001
BRI_{max}	0.97±0.11	0.84±0.17	0.023
HR_{max} (bpm)	175±13	192±11	0.009
Oxygen desaturation (%)	2.9±1.6	0.8±0.3	0.001
Muscle fatigue	89±17	85±12	0.478
CSA (cm^2)	65.4±11.2	74.7±15.6	0.082
MVC (Nm)	188±69	234±98	0.163
SD, standard Deviation; P, probability; CF, cystic fibrosis; VO_{2peak}, peak oxygen uptake; MMV, maximum minute ventilation; BRI_{max}, maximum breathing reserve index; HR_{max}, maximum heart rate; CSA, cross-section area; MVC, maximal voluntary contraction.			

DISCUSSION

The outcomes of this study approved when compared between the CF young adults with moderate respiratory disorders and healthy that the young adults with CF had lower peak power output, lower VO_{2peak}, lower MMV, and lower HR_{max} when comparing with the healthy group ($p<0.05$). In contrast, the young adults with CF had more breathing reserve index (BRI) after maximal exercise and more oxygen desaturation when comparing with the healthy group ($p<0.05$) whereas, there was a

statistically nonsignificant difference in measure of muscle fatigue, CSA, and MVC between the CF and healthy groups. These outcomes don't uphold the present study hypothesis of skeletal muscle dysfunction in patients with cystic fibrosis. Number of researches assessed muscle strength in patients with CF, these researches have commonly examined the quadriceps muscle because this muscle has an arrogant functional role. Many studies explained influential lowering in MVC of the quadriceps muscle[5,15] while other studies didn't explain that.[16] When comparing between the CF and healthy groups with similar levels of physical activity using neuromuscular evaluations, the findings of this study explained some differences noticed in the last studies and can approve substantial thoughts reflecting the mechanical physiology of muscle weakness in patients with cystic fibrosis. The results of this study included nonsignificant lowering of the strength of the quadriceps muscle in patients with cystic fibrosis. This lowering of the strength of quadriceps muscle may due to decrease of voluntary activation and contractile function of the muscle in young adults with CF. Anyway, these nonsignificant small changes were not found with observed relative to CSA regarding that lowering of the muscle strength illustrated in last researches can be resulted from a muscle mass decrease rather than changes of muscle excitation-contraction. Some agents can cause lowered the CSA of the muscle in young adults with CF including medication causes[17], inflammation causes[18] and a reduction in Ca2+ factors.[19] Therefore, the results of this study propose that the alterations of muscle excitation–contraction, commonly presented through the muscle myofibrils, was actually the principle cause engaged in peripheral muscle fatigue in the two groups. Like mentioned before in the control group with healthy populations[20], the maximal exercise in this study only caused slight nonsignificant muscle fatigue. Recently, cerebral deteriorations were approved in patients with COPD and associated with other causes as hypoxemia and inflammation.[21,22] Unlikely, these causes play an important part in the young adults with CF, that suggest certainly the similar results in the CF and healthy groups, explaining the central alterations in young adults with CF who had moderate respiratory disorder. The nonsignificant results of muscle fatigue in the two groups are in agreement with the nonsignificant differences in quadriceps endurance as suggested by the similar sub-maximal contractions number applied in the CF and healthy groups. Together interpreted and regarding parallel neuromuscular fatigue in the CF and healthy young adults, this study results reflect the lack of inherent changes of the skeletal muscle in CF group. Therefore, skeletal muscle of CF patients had to show a suitable exercise in reaction to allot excitation, as exhibited recently.[22] Lately, the muscle mass is identified with mortality in patients with CF, the present study results had to support the systematic unification of assigned improvement rehabilitation to enhance muscle mass, that may have a better quality of life and exercise capacity.

A recent study found lowering of the concentration of adenosine triphosphate (ATP) and the intramuscular acidosis of the end-exercise in the quadriceps muscle in children suffering from cystic fibrosis as compared to the healthy subjects with similar age and level of physical activity. Although, Patients with cystic fibrosis performed the identical work rates within a 30-s, 90-s compared to both healthy children and patients with ciliary dyskinesia.[23] Therefore, the possible inherent changes in the skeletal muscles in CF young adults may be occurring, if they still, don't get functional repercussions. As an alternative, it could be that the CFTR mutation type influence the function of the skeletal muscle which may increase muscle fatigue.[24]

Limitations

This study used isometric contraction to assess muscle fatigue which is not enough to illustrate daily living activities of the young adults with cystic fibrosis. This study recruited only CF with moderate pulmonary disease and further studies have to include mild and severe pulmonary disease. The lowering of BRI at maximum exercise training in CF young adults suggests that, not only muscle strength, has a role in exercise restriction of total body but also, pulmonary causes have a vital role to restrict total body exercise in CF young adults. Finally, this study provided that the identified VO_{2peak} by cardiopulmonary exercise test resulted mainly from the quadriceps muscle endurance and strength. So that, the peripheral muscle role may clarify the lowering exercise capacity in part in CF young adults with moderate pulmonary disease.

CONCLUSIONS

This study concluded that young adults with cystic fibrosis who had moderate pulmonary disorder and healthy subjects have similar effects in cross section area, muscle fatigability, and maximal contraction of the quadriceps muscle. Whereas maximal exercise has negative effects on exercise capacity in young adults with CF.

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Conflict of interests

No competing of interests.

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