

Exercise capacity and muscle fatiguability alterations following a progressive maximal exercise of lower extremities in children with cystic fibrosis

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Abstract

Background: Impairment of peripheral skeletal muscle function is a common phenomenon in patients with cystic fibrosis (CF) in addition to great clinical connotations, such as lack of exercise tolerance and decrease of health-related quality of life. There is very limited data on the effects of maximal exercise on muscle fatiguability and exercise capacity in children with cystic fibrosis.

Objectives: The aim of this study was to evaluate the effect of progressive maximal exercise training of the lower extremities on exercise capacity and muscle fatiguability in children with cystic fibrosis.

Study design: Between June and September 2017, eighteen children aged 8-12 years were recruited in this study. This study had two groups of children; the CF group consisted of nine children (6 males and 3 females) with cystic fibrosis and the control group consisted of nine healthy age matched children (6 males and 3 females). The children underwent a progressive maximal cardiopulmonary exercise cycling test (CPET), muscle fatigue test, and magnetic resonance imaging (MRI) to measure a muscle cross-section area (CSA). Also, pulmonary functions were assessed.

Results: The findings of this study showed that the CF children had less pulmonary functions, had a less exercise capacity, and had a higher breathing reserve index and oxygen desaturation when compared with healthy children ($p < 0.05$). On the other hand, there was a non-significant difference in muscle fatiguability, muscle cross-section area, and maximal voluntary contraction between the CF and healthy children ($p > 0.05$).

Conclusion: This study indicates that progressive maximal exercise doesn't affect muscle fatiguability, muscle cross-section area, and maximal voluntary contraction in CF children with moderate respiratory diseases but includes lower exercise capacity. CF children and healthy age matched children have similar responses to maximal exercise in muscle fatiguability, muscle cross-section area, and maximal voluntary contractions but lower exercise capacity in the CF group.

Keywords: Cystic fibrosis, children, lower extremities, exercise capacity, muscle fatiguability.

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Introduction

Cystic fibrosis (CF) is an inherited lung disease character-

ized by the accumulation of abnormal sticky, thick mucus that lead to damage of many body's organs including respiratory system damage and chronic complications in digestive system.¹ CF is one of the most common inherited genetic disorder that causes progressive abnormalities in the respiratory and digestive systems, leading to pancreatic dysfunction and chronic airway infection with extreme loss of lung function and physical capacity. Although chronic airway infection is considered as a main cause of mortality in the disease end stages, pulmonary

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function deteriorations didn't clarify all characteristics of the disability accomplished in cystic fibrosis disease.^{1,2}

Recently, many manifestations of the cystic fibrosis disease indicate impairment of peripheral muscle function as a main systemic manifestation of CF disease.² Also, the weakness of skeletal muscles is related to consequential clinical complications such as decrease of exercise capacity³, decrease of quality of life (QOL).⁴

Previous studies approved that peripheral muscle weakness was reported in patients with cystic fibrosis. Strength and endurance of skeletal muscle are reduced in CF patients compared with the control group, indicating dysfunction of skeletal muscles.^{3,5} In addition, the strength of the quadriceps muscle is associated with aerobic capacity and lung function. A considerable number of CF patients with airway obstruction cannot do continuous exercise as they suffer from lower extremity fatigue, using a visual analogue scale.⁶

Factors which affect exercise capacity in CF patients is generally unknown. Examining which causes conduce to the limitation of exercise performance is especially prominent in patients with CF. Actually, aerobic capacity is related to quality of life and mortality in CF and can be used to investigate the treatment responses.⁷ Therefore, therapeutic plans intended to enhance aerobic capacity are important and pure rehabilitation has to direct towards proper conducting factors.

Jeffery et al., early observed neuromuscular activity deteriorations in the quadriceps muscle after high-intensity aerobic exercise in patients with chronic obstructive pulmonary disease.⁸ In spite the pathophysiology of skeletal muscle is plausibly not precisely alike, the current study could anticipate that similar deteriorations exist in other respiratory disease such as CF.

Exercise training has several beneficial effects on many health measurements in CF and high scores of exercise capacity are related to high QOL 4 and more endurance in this population.^{7,9} Despite the fact that impaired exercise tolerance is a common characteristic of CF disease, the accurate physiological mechanism abide to be clarified, in special to improve pulmonary rehabilitation exercise. It has been identified that respiratory reasons alone are not enough to clarify the lack of exercise tolerance in patients with CF, particularly in subjects characterized by moderate respiratory disorder such as, bronchial dilations increase pulmonary function but do not increase aerobic tolerance in patients with cystic fibrosis.

Many studies illustrated the effect of maximal exercise training on muscle fatigue and exercise capacity in adults with CF but very limited studies explained the changes of exercise capacity and muscle fatiguability after maximal exercise training in children with CF.^{2,6,9,10} The hypothesis of this study suggested that children with cystic fibrosis could lead to fatiguability of the muscles exercised after maximum symptom-restricted exercise test in addition to their ventilatory limitations. Hence, this study aimed to evaluate the effect of progressive maximal exercise training of the lower extremities on exercise capacity and muscle fatiguability in children with cystic fibrosis.

Methods

Participants

This experimental controlled study was approved by the department of physical therapy, Cairo University Hospitals, according to the ethical standards of human research. The protocol of this study proceeded according to the guidelines in the Declaration of Helsinki. A written consent form was signed by caregivers or parents of children before enrollment in the study. Each parent or caregiver was informed about the aim, procedures, and expected risks of this study. Nine children (6 males and 3 females) aged 8-12 years with CF were obtained from Cairo University pediatric hospital. The CF children had moderate pulmonary disease [FEV1= 40-59% of predicted value]. The children were stable clinically for two months before starting the study, received pancreatic enzymes supplements and vitamins. Nine healthy age matched children were obtained for this study to constitute the control group (FEV1 > 80-100% of predicted values, no cardiopulmonary restrictions, and no exercise training before examination). Children with severe medical illness such as cardiovascular disease, orthopedic problems and endocrine disorders that could affect physical exercise were excluded from the study. Demographic and clinical characteristics of the participated children in this study are shown in table 1.

Sample size

Power analysis was initially performed to calculate the sample size. The current study required a sample size of 9 children for each group which was calculated by assuming 80% power with 10% changes in muscle fatiguability with standard deviation of 2 and significance level of 5% (two-sided test; $\alpha=0.05$; power desired, 80%).

Procedures

Assessment and measures

Cardiopulmonary exercise cycling test (CPET) was performed using an electronic ergometer (Monark, 939 Novo, Electronically Braked Cycle Ergometer, USA) and maximum oxygen uptake ($\text{VO}_{2\text{peak}}$) was assessed. Quadriceps cross-section area (CSA) in random request within 2 days was measured by magnetic resonance imaging (MRI) using (Centauri MPF 3000 0.3T, XBO medical systems Ltd., Baotou, China). Muscle fatiguability and maximal voluntary contraction (MVC) of the quadriceps muscle was assessed by digital Electromyography (EMG) using (Dantec Keypoint Focus - 6 channels, Natus medical incorporated, Pleasanton, USA).

Intervention (CPET Protocol)

CPET was performed on a cycle ergometer as previously described¹¹ and according to the international standards of the American thoracic society.¹² Each child was instructed for warming up for 2-3 minutes of constant-state riding a bicycle (60-70 rpm) to calculate the child's ability to cycling and to prepare the child to the cycle test program. During the warming up, the maximum heart rate (HR_{max}) was 100 to 115 bpm. After warm up, each child was yielded to sub-maximal constant-state pedaling for 5 minutes with steady cycling speed (60-70 rpm), providing more reinforcement. The sub-maximal workload ($1.75 \times$ warm-up load) had a HR_{max} of 60%-70% of the maximal calculated HR.¹³ During CPET, if the heart rate was not (60%-70%) of the HR_{max}, the resistance (5-10 W) was increased or decreased. In between the progressive maximal cycling exercise test, there was one minute rest. The examiner determined the workload of the sub-maximal test according to the initial load, and increased the load every minute gradually from 3 to 10 W, based

on child's ability. The needed cycle pedaling was 60 to 70 rpm. All children were instructed to execute exercise training to a symptom-restricted maximum. Oxygen uptake (VO_2) and carbon dioxide production (VCO_2) were recorded breath by breath. Respiratory exchange ratio and predicted maximum heart rate were measured to approve the maximal feature of the cycling exercise. Muscle fatigability was assessed following CPET through isometric contraction of the quadriceps muscle.

Data analysis

Statistical analysis was applied in the form of means and standard deviations. Inferential statistics analyzed all measurement changes using unpaired t-test between CF and control groups and paired t-test to assess the changes within the group. Mann-Whitney U test was used to analyze the gender's difference between the two groups. Analysis was done using SPSS version 19.0 (SPSS, Chicago, IL) with statistical significance at $p\text{-value} \leq 0.05$.

Results

Between June and September 2017, eighteen children aged 8-12 years were recruited in this study. This study had two groups of children; the CF group consisted of nine children (6 males and 3 females) with cystic fibrosis and the control group consisted of nine healthy age matched children (6 males and 3 females). In demographic data, there were no statistically significant differences between the CF and control groups in their ages, heights, weights, BMI ($p > 0.05$) while in pulmonary function, there were statistically significant differences between the two groups in their forced expiratory volume in one second (FEV1) and forced vital capacity (FVC). The demographic and pulmonary function of the participating children are demonstrated in table 1.

Items	CF group (n=9)	Control group (n=9)	p-value
Sex (M/F)	6/3	6/3	1.000 ^b
Age (yrs)	11±0.3	12±0.4	0.557 ^a
Height (cm)	144±5.3	146±4.7	0.409 ^a
Weight (kg)	43.4±3.7	45.7±3.5	0.194 ^a
BMI (kg/m ²)	20.9±2.3	21.4±2.8	0.684 ^a
Pulmonary functions			
FEV1 (L/ % pred)	2.3±0.7 (56.4)	4.1±0.8 (102.7)	0.001 ^a
FVC (L/ % pred)	4.0±0.8 (67.5)	5.2±1.2 (103.4)	0.023 ^a
Abbreviations: 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; M/F, male/female; BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.			

According to the children criteria in this study, the CF and control groups performed the cardiopulmonary exercise test (CPET) through a maximal incremental cycling exercise. The CF children had less value of peak power output, VO₂ peak, maximum minute ventilation, and maximum heart rate when compared with the control

group (p<0.05). Moreover the CF children had higher values of the breathing reserve index at maximal exercise and oxygen desaturation when compared with the control group (p<0.05) but there was a non-significant difference in muscle fatigue measure, cross-section area, and maximal voluntary contraction between the two groups as demonstrated in table 2.

CPET variables	CF group (n=9) Mean± SD	Control group (n=9) Mean± SD	P-value
Peak power output (W)	139.4±21.5	237.2±42.3	0.001
VO _{2peak} (L)	1.8±0.6	2.9±0.8	0.004
MMV (L)	87.4±18.2	117.5±25.3	0.011
BRI _{max}	0.97±0.11	0.88±0.06	0.045
HR _{max} (bpm)	161±11	178±12	0.006
Oxygen desaturation (%)	2.7±1.2	0.7±0.3	0.002
Muscle fatigue	82±13	79±11	0.604
CSA (cm ²)	35.2±8.3	42.3±9.7	0.114
MVC (Nm)	112±37	141±45	0.154
Abbreviations: SD, standard Deviation; P, probability; CF, cystic fibrosis; VO _{2peak} , peak oxygen uptake; MMV, maximum minute ventilation; BRI _{max} , breathing reserve index; HR _{max} , maximum heart rate; CSA, cross-section area; MVC, maximal voluntary contraction.			

Discussion

The main findings of this study, the stable CF children had less pulmonary functions (FEV1, FVC), had a less exercise capacity (peak power output, peak oxygen uptake, maximum minute ventilation, maximum heart rate), and had a higher breathing reserve index and oxygen desaturation when compared with healthy children. On the other hand, there was a non-significant difference in muscle fatiguability, cross-section area, and maximal voluntary contraction between the CF and healthy children. These findings didn't conduct the hypothesis of this study, which supposed that CF children could suffer from extreme fatiguability of the muscles exercised after maximum symptom-restricted exercise test. Many studies have evaluated muscle endurance in patients with CF including adults and children. The most studied muscle was the quadriceps muscle, as it has a consequential functional activity. Previous studies documented considerable reduction in maximal voluntary contraction of the quadriceps muscle^{3,14} whereas the other studies did not approve these reports.¹⁵

The present study results may clarify some of the differences reported in the previous studies and can give significant perceptions respecting the underlying mechanisms of muscle dysfunction in children with CF. This study found a non-significant decrease of quadriceps muscle fatigue in children with CF. This inclination may be associated with decreases in contractile function and voluntary activation of the muscle also inclined to be decreased in children with CF. Though, all of these delicate non-significant discrepancies extinct when related to muscle cross-section area indicating that the decrease of muscle strength reported in earlier studies may be associated with decrease of muscle mass more than changes of stimulation contraction connection. Several causes may possibly lead to decrease in CSA the muscle in children with CF, like alterations of the nutrition status¹⁴, expressed exacerbations¹⁶, medication¹⁷, physical inactivity³, or inflammation.¹⁸

According to this study results, it was reported that a delicate inclination for decreased CSA of the quadriceps muscle in children with CF exists, which is coherent with the results of previous studies in more severe children.¹⁸ The CF children in the present study characterized by good conditions, such as stable clinically, proper nutrition, and no corticosteroids therapy. Also, the level of systemic in-

flammation is associated with the level of airway impediment¹⁹, the role of inflammation was apparently restricted in the children of this study as they had a moderate pulmonary disease, moreover illustrating the disappearing of the considerable decrease of CSA in CF children in this study. Early study explained that children with CF are less included in moderate to high-intensity exercise in spite of same commitment in low-intensity exercise.³ Therefore, in spite of similar worldwide physical activity level, it may believe that the possible delicate decreases of CSA of the quadriceps muscle and contractile variables are in apportion result from lower obligation of this study children in maximal intensity or strengthening exercise than healthy children. Muscle fatigue and endurance assessment were very restricted in children with CF. Previous studies assessed the endurance of the quadriceps muscle in adults with CF.^{5,20} It was documented that the time of endurance was decreased during isometric contraction in adults with CF at 50% maximum voluntary contraction maintained up to fatigue²⁰, and another study documented fewer number in women knee flexions, not in men, when compared with age-matched healthy adults.⁵ These studies had many limitations; adults were not subjected to a similar level of physical activity which cannot be ignored that low level of usual physical activity could result in decreased muscle endurance in patients with CF. Also, these assessments of muscle endurance were completely dependent on physical exertion and therefore greatly affected by collaboration and inspiration of the subject. This limitation can illustrate the cause of higher changes of endurance time in adults with CF than healthy adults.²⁰

The present study established similar decreases in maximum voluntary contraction during the task of muscle fatigue in CF and healthy subjects, indicating non-significant differences in muscle fatigue in the two groups. This similarity may be related to similarity of muscle fatigue development.

Therefore, the skeletal muscle in patients with cystic fibrosis should exhibit sufficient capability for training in response to proper excitation, as recently reported.²¹ Because muscle mass is associated with a mortality rate in patients with CF², the findings of this study may support the systematic integration of allot effectiveness rehabilitation methods aspiration to improve muscle mass, as it may have a beneficial impact on aerobic capacity, quality of life, morbidity, mortality.

Recently, one study established reduced intramuscular acidosis and concentrations of ATP in the thigh muscles of children with CF when compared with matching-age healthy subjects and ciliary dyskinesia patients.²² Even so, patients with CF accomplished similar work rates throughout a 30-s, 90-s with 5-min CPET compared with matching-age healthy subjects and ciliary dyskinesia patients. So, it is suitable that the intrinsic changes in muscles of children with CF, if these changes survive, haven't functional outcomes such as decrease of muscle strength and increase of muscle fatigue. On the other hand, Selvadurai et al²³ reported an association between genotype and exercise capacity, pulmonary functions. This report would necessitate more assessments joining evaluations at the levels of the cell with muscle fatigue measurement to find out, whether a presented alteration or particular mutation such as decrease of genotype manifestation in the myocytes that could result in muscle fatigue.²⁴

Limitations

The test of muscle fatiguability through isometric contraction is not necessary to demonstrate the activity daily life of the children. By contrast, the present study approved that VO₂ peak demonstrated throughout cycling exercise test was related significantly to the strength and endurance of the quadriceps muscle. Therefore, the function of the peripheral muscle may illustrate particularly the decreased exercise capacity in children with CF. Although, the smaller the difference of VO₂ peak between the two groups was decreased when standardized to CSA of the quadriceps muscle in children with CF. The decrease of the breathing reserve index at maximum cycling exercise test in children with CF reflects that, beside muscle strength, pulmonary agents have an important role concerning exercise restriction of whole body in children with moderate pulmonary disease.

Conclusion

The findings of this study indicate that progressive maximal exercise doesn't affect muscle fatiguability, muscle cross section area, and maximal voluntary contraction in CF children with moderate respiratory diseases but includes lower exercise capacity. CF children and healthy age matched children have similar responses to maximal exercise in muscle fatiguability, muscle cross-section area, and maximal voluntary contractions but lower exercise capacity in the CF group.

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Competing interests

No conflict of interests regarding the publication of this study.

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