Inflammatory process modulation in children with cystic fibrosis submitted to aerobic training

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Abstract

Introduction: Systemic inflammatory response in cystic fibrosis (CF) alters exercise capacity. The aim of the present study was to assess the systemic inflammatory process through C-reactive protein levels and the capacity for aerobic exercise in patients with cystic fibrosis submitted to physical training.
Material and methods: A controlled, prospective clinical trial was carried out on a consecutive sample were twenty Caucasian children, with a mean age of 13.21 years. Two groups of patients with CF were formed: one group submitted to physical training (G1) and one group without physical training (G2). The experimental protocol was made up of medical history, lung function test, step test, cardiopulmonary exercise test and collection of blood samples.
Results: Prior to the experiment, lung function and systemic C-reactive protein in the patients with CF underwent correlation analysis. A moderately significant = –0.62, pρ relationship was found between FEV_1 and CRP (< 0.01). Pre-training and post-training values were compared at the end of the six-week period. There was a significant increase in the number of steps in G1 alone, with a reduction in dyspnea, HR and leg fatigue.
Conclusions: We may infer that aerobic exercise training maintained the inflammatory process stable and increased exercise capacity in patients with CF. Thus, the measurement of systemic inflammatory response may be a variable to determine whether a proposed training program will trigger greater inflammation.

Key words: cystic fibrosis; aerobic training, C-reactive protein.

Introduction

Cystic fibrosis (CF) is an inherited, monogenic, autosomal, recessive disease that results in abnormalities of the cystic fibrosis transmembrane conductance regulator gene (CFTR) [1]. Defects in the CFTR gene (7q31.2) contribute toward an accentuated increase in the viscoelasticity of pulmonary secretions, thereby causing obstruction of the airways with viscous mucus [2]. More than 1100 mutations of the CF gene have been described since 1989. The different degrees of the severity of clinical manifestations depend on the genotype as well as the result of obstructive phenomena in the pulmonary exocrine glands stemming from viscous secretions. It is calculated that approximately 90% of patients die as a result of the progression of lung disease [3, 4].

The severity of CF leads to a reduced capacity for aerobic exercise, which is likely related to pulmonary injury [5]. According to Klijn *et al*., the deterioration in lung function leads to a significant decrease in exercise capacity and is associated to a reduction in quality of life and a compromised life expectancy [6, 7]. These conditions are directly correlated to the severity of the disease, lung function [7, 8], nutritional state [9, 10] and peripheral muscle strength [11].

Regular aerobic exercise has been demonstrated to have a positive effect on aerobic capacity in patients with CF [12, 13]. An increase in aerobic activity has also been associated to an increase in quality of living and life expectancy [6, 7]. A number of studies [14-20] have demonstrated positive effects on lung function, peak VO_2, increased strength [15], increased expectoration of secretions [16], reduced shortness of breath [17] and improved performance in activities of daily life [18, 19] following aerobic training. Changes in aerobic capacity are often associated to specific training programs involving several hours per weak at submaximal intensity [20, 21].

C-reactive protein (CRP) is an important and sensitive indicator of inflammation. An increase or reduction in its concentration in the blood closely follows inflammatory processes of either an infectious or non-infectious nature. C-reactive protein levels are higher in patients with bacterial respiratory infections. According to Bradley *et al*., the systemic inflammatory response in CF (demonstrated by CRP) affects exercise capacity. Thus, treatment strategies should not focus merely on direct approaches to obstructive pulmonary disease, but also on interventions that modulate the inflammatory response to infection and increase tolerance to exercise, thereby improving quality of life [22].

No direct, controlled correlations were found in the literature involving physical training and systemic inflammatory response assessed through CRP levels. Thus, there an evident need for establishing new clinical parameters that allow the follow up of clinical manifestations in these patients throughout any type of intervention in the rehabilitation process. The aim of the present study was to assess the systemic inflammatory process through C-reactive protein levels and the capacity for aerobic exercise in patients with cystic fibrosis submitted to physical training.

Material and methods

A controlled, clinical trial was carried out on a consecutive sample from the Physiotherapy Clinic of Nove de Julho University (UNINOVE, São Paulo, Brazil). CF was confirmed for all patients by the positive sweat test and measuring fecal fat. The participants were twenty Caucasian children, with a mean age of 13.21 years (range: 6 to 16 years). The study received approval from the UNINOVE Research Ethics Committee (process n°. 154202/2007). Informed consent was obtained after the parents/guardians were made aware of the study protocol. Ten healthy children were also evaluated and made up the control group.

The inclusion criteria were a clinical diagnosis of cystic fibrosis (confirmed by a pediatric pneumologist), age between 6 and 16 years, and no clinical exacerbations in the two months prior to the study (based on the evaluation of chief physician). Exclusion criteria were an inability to walk due to orthopaedic impairment, respiratory infection prior to or during physical training and severe associated heart disease.

Procedures

The experiment included the patient's medical history (personal identification, summary of clinical history, previous diseases and current medication use), a lung function test, step test, cardiopulmonary exercise test and collection of blood samples, which were carried out during both the evaluation and re-evaluation.

The lung function test was carried out using a spirometer (Spirobank®, RDSM, USA). The following parameters were measured: forced expiratory volume in the first second (FEV_1), vital capacity (VC), forced vital capacity (FVC), 25-75% forced expiratory flow (FEF_{25-75}), and maximal voluntary ventilation (MVV). All determinations were performed in compliance with the technical guidelines recommended by the European Respiratory Society and Brazilian Respiratory Society.

The three-minute step test (3MST) was performed on a step with a height of 15 cm for 3 min, assessing heart rate (HR), blood pressure (BP), Borg scale, oxygen saturation (SaO_2) at the beginning and end of the test. Reasons for interrupting the test were a reduction in SaO_2 (< 75%), excessive shortness of breath or leg fatigue [23].

The cardiopulmonary exercise test (CPT) (limited by symptoms) was performed on a treadmill (TRG Fitness, Progress 3.4, RS, Brazil), using the modified Bruce protocol [24]. The following aspects were measured: duration of treadmill exercise, expressed in minutes; maximum HR, expressed in beats per minute (bpm), peripheral SaO_2, continuously monitored; and maximal systolic pressure (SP), manually measured in mm Hg. Reasons for interrupting the test were muscle fatigue, reduced patient cooperation, significant respiratory symptoms or significant heart symptoms [25].

Blood samples

Collection of CRP samples was carried out at a clinical analysis laboratory with the assistance of trained professionals. C-reactive protein plasma

levels were determined using a highly sensitive enzyme linked immunosorbent assay (ELISA).

Protocol

Two groups of patients with CF were formed aleatory randomly: one group submitted to physical training (G1, $n = 10$) and one group without physical training (G2, $n = 10$). A third group was the control (CG), made up healthy children who were not submitted to physical training.

G1 trained on the treadmill for 30 min three times a week, using 60 to 80% maximal velocity and maximal slope achieved during the CPT. PA, HR, SaO_2 and Borg scale were determined before, during and after the activity. The patients in G1 and G2 maintained their normal bronchial hygiene routine.

Statistical analysis

Results are expressed in mean ± SD. All data were tested for normality using the Kolmogorov-Smirnov test. Spearman's ρ was used in the correlation analysis to investigate the relationship between variables of interest. Analysis of variance (ANOVA) for repeated measurements was used for intra-group and inter-group comparisons. Inter-group comparisons were performed using ANOVA with Tukey's *post hoc* test. The paired Student's *t*-test was used for intra-group comparisons (pre and post), with the level of significance set at $p \leq 0.05$. Data were analysed using the SPSS statistical software package, version 10 (SPSS, Chicago, IL). The sample power considered was 80%.

Results

Twenty patients were initially enrolled in the study. Two patients from G1 and four from G2 failed to complete the study due to exacerbations during the experiment. Baseline characteristics of the remaining 14 patients are displayed in Table I, which summarises the physical characteristics and physiological data. Inter-group analysis revealed significant differences ($p < 0.05$) between the CG and CF groups. Intra-group analysis revealed homogeneity among the patients with CF. Prior to the experiment, lung function and systemic CRP in the patients with CF underwent correlation analysis. A significant relationship was found between FEV_1 and CRP ($\rho = -0.62$, $p < 0.01$).

Pre-training and post-training values were compared at the end of the 6-week period. There was a significant increase in the number of steps in G1 alone, with a reduction in dyspnea, HR and leg fatigue. CRP was also reduced, but this reduction did not achieve statistical significance (Table II). Inter-group delta analysis (Table III) revealed a significant difference in the number of steps, but no significant difference for the other variables analysed.

The patients had mild-to-moderate pulmonary disease, as demonstrated by the baseline mean vital capacity and expiratory flow rates (Table I). Following the program, there was no significant change in resting vital capacity and forced expiratory flow (25-75%) rates in either the large and small airways. Similarly, the resting cardiopulmonary parameters were unchanged following the program (Table II). However, there was a significant reduction in HR following training.

Discussion

The aim of the present study was to investigate the inflammatory process and capacity for exercise among patients with cystic fibrosis submitted to aerobic physical training in a controlled, prospective clinical trial. Improvements were observed in the group submitted to the 6-week training period. The results suggest that gains in performance are related to improvement in airway obstruction, which is the limiting factor to exercise capacity. However, dynamic maximal flow parameters, as measured by FEV_1, FEV_{25-75} and FVC, did not improve significantly.

Table I. Baseline characteristics of CF group with physical training (intervention), CF group without physical training (non-intervention) and control group

Characteristics	Intervention group ($n = 8$)	Non-intervention group ($n = 6$)	Control group ($n = 10$)
Age [years]	13.88 ±2.01	12.33 ±4.6	12.33 ±2.58
Height [cm]	149.2 ±0.14	146.7 ±0.21	155.5 ±0.09
Weight [kg]	37.95 ±8.68	34.67 ±9.18	42.95 ±10.74*
BMI [kg/m^2]	16.92 ±1.25	16.82 ±1.24	17.48 ±2.58
FEV_1, % predicted	62.31 ±30.24	51.21 ±24.42	102.9 ±8.8*
FVC, % predicted	54.20 ±36.32	79.70 ±42.9	91 ±10.34*
FEF_{25-75}	49.57 ±43.31	62.41 ±66.23	117.4 ±27.8*
CRP	0.58 ±0.35	0.39 ±0.75	0.23 ±0.26

*BMI – body mass index, FEV_1 – forced expiratory volume in the first second, VC – vital capacity, FEF_{25-75} – 25-75% forced expiratory flow, CRP – C-reactive protein, cm – centimeters, kg – kilograms, *p < 0.05*

Table II. Baseline and post-intervention variables in CF group with physical training (intervention) and CF group without physical training (non-intervention)

Variables	Intervention group		Non-intervention group	
	pre	post	pre	post
N°ş of steps	79.5 ±9.8	89.6 ±6.1*	77.2 ±14.2	77.4 ±15.2
Resting SaO_2	90.5 ±4.3	93.7 ±3.4	90.3 ±4.5	92.3 ±4.8
Final SaO_2	89.8 ±4.4	92.8 ±3.3	89.3 ±9	91.7 ±5.3
Resting HR	100.75 ±14.2	94.12 ±12.8	101 ±15.8	130 ±40
Final HR	126.25 ±25.5	124.12 ±19.03	120 ±15.4	134 ±25.3
CRP	0.586 ±0.43	0.439 ±0.35	0.396 ±0.75	0.483 ±0.07

*SaO_2 – peripheral saturation of oxygen, HR – heart rate, CRP – C-reactive protein, *p < 0.05*

There were no improvements in SaO_2 either at rest or during peak effort, thereby indicating no change in gas exchange properties. This result is in agreement with other programs in which patients exhibited improved work tolerance, but no change in resting pulmonary function [26-29], but contrasts with studies in which patients exhibited transient improvement in the results of lung function tests [30, 31]. The reasons for these discrepancies may be attributed, at least in part, to the complexity of the pathophysiology of lung disease. We found a moderate correlation between FEV_1 and CRP, suggesting that the analysis of systemic inflammation can be used as an inflammatory marker of this pathology [28]. Several of studies have analysed CRP in this population using sputum [23, 29], but in this study we were analysed based in systemic blood sample that we think was more accurate.

Systemic inflammatory response to infection, as determined by CRP levels, may have a direct impact on changes in CF induced by treatment using exercise. In the present study, the group of patients with CF submitted to physical exercise exhibited a considerable decrease in CRP. This suggests that physical exercise was beneficial to these patients, as there was decrease in the systemic inflammatory process. Regardless of the exact mechanisms involved, these findings highlight the importance of directly measuring the outcome of treatment, which should focus on interventions that improve sputum production, modulate the inflammatory response to infection and improve tolerance to exercise [22].

Studies had confirmed that circulating CRP levels are higher in stable CF patients and may therefore be regarded as a valid biomarker of low-grade systemic inflammation. Ours results showed that CRP is significantly higher in CF patients with a low FEV_1, evidence a negative correlation.

The 6-week physical training program led to an increase in cardiopulmonary conditioning among ours patients, as shown in Tables II and III. These findings corroborate those described by Moorcroft *et al*. in a study involving one year of physical training in adults. Our program lead to performance improvements in patients with CF within a much shorter period of time and promoted cardiopulmonary improvements, as revealed by the tests employed. Our exercise protocol were able to reduce CRP levels during training, which is similar to the findings described by Bradley *et al*.

Table III. Delta variables of intervention and non-intervention group

Variables	Intervention group	Non-intervention group
ΔN° of steps	13.75 ±11.13	–0.001 ±3.78*
ΔCRP	130.07 ±450.8	682.14 ±497.5

*CRP – C-reactive protein, Δ = (post – pre) x 100/pre, *p < 0.05*

In our studies the sub-maximal assessment was performed using the step test. Compared to the 6-min walk test, the step test has been shown to produce significantly greater changes in heart rate and shortness of breath as well as a comparable drop in SaO_2 [23]. In children with severe lung disease undergoing assessment for heart-lung transplant, the 3-min step test has been shown to produce a significantly greater drop in SaO_2 than the 6-min walk. This test was able to discriminate between children with normal resting PaO_2 and good exercise tolerance from those with lower resting PaO_2 and poor exercise tolerance [24]. Although this test may be a useful tool as a prognostic indicator in the assessment of children for heart-lung transplant.

Following our training, there were reductions in HR and Borg scale scores as well as an increase in the number of steps in the 3 min step test, thereby demonstrating greater tolerance to exercise (Tables II, III) and an improvement in the aerobic conditioning of the patients. This was confirmed by the cardiopulmonary test, which revealed a reduction in HR and improved SaO_2, with an increase in time performing the test. These findings corroborate those described by Moorcroft *et al*. and Marcotte *et al*., who found a reduction in lactate levels and heart rate in adult patients with CF.

Patients with CF range from being asymptomatic, with few signs of ill health, to having chronic

cough, large amounts of sputum, wheezing, dyspnea and limited exercise tolerance. Some of this variability may be attributed to specific gene mutations, but environmental factors and treatment strategies also play a significant role [32, 33]. Moreover, the physical, social and emotional effects of these clinical manifestations are specific to each individual. For example, disability incurred by a patient with moderate disease impairment will be less in a patient who leads a sedentary lifestyle than one who is very active.

In conclusion, from the results of the present study, we may infer that aerobic exercise training the reduced inflammatory process stable and increased exercise capacity in stables patients with cystic fibrosis. Thus, the measurement of systemic inflammatory response, by CRP levels in blood sample, may be a variable to determine whether a proposed training program will trigger greater inflammation.

Acknowledgments

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