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Longitudinal changes in exercise capacity among adult cystic fibrosis patients

Abstract

Introduction: Longitudinal data regarding changes in exercise capacity among adult cystic fibrosis (CF) patients are currently scarce. The aim of this brief report was to assess changes in exercise capacity among adult CF patients with stable and mild-to-moderate disease eight years after their initial evaluation.

Material and methods: Maximum cardiopulmonary exercise testing (CPET) was utilized. Other assessments included Doppler echocardiography, the 6-minute walking test, spirometry, and lung volume evaluation.

Results: Eleven (6 male, 5 female) patients completed both evaluations (initial and after eight years). During follow-up, indices of ventilatory impairment (such as ventilatory reserve; $p=0.019$, and ventilatory equivalent for carbon dioxide; $p=0.047$) deteriorated significantly following a decline in respiratory function measurements. Peak oxygen uptake (VO_2), both as an absolute (26.6 ± 8.46 vs 23.89 ± 6.16 mL/kg/min; $p=0.098$) and as a % of predicted value (71.21 ± 16.54 vs 70.60 ± 15.45 ; $p=0.872$), did not deteriorate. This is also true for oxygen pulse ($p=0.743$), left heart ejection fraction ($p=0.574$), and pulmonary artery systolic pressure ($p=0.441$). However, the anaerobic threshold, both as an absolute ($p=0.009$) and as a % of predicted value ($p=0.047$), was significantly lower during follow-up.

Conclusion: In adult CF patients with stable, mild-to-moderate disease, a peak VO_2 may be preserved for several years. However, even in these patients, deconditioning is present.

Adv Respir Med. 2020; 88: 420–423

Key words: cardiopulmonary exercise testing, peak oxygen uptake, anaerobic threshold, longitudinal study, adult cystic fibrosis patients

Introduction

Exercise impairment in patients with cystic fibrosis (CF) is well established and has been attributed to a variety of pulmonary and non-pulmonary factors [1]. Although several tests have been previously adopted to assess exercise capacity in this patient population, cardiopulmonary exercise testing (CPET) offers an integrative assessment of the pulmonary, cardiovascular, and skeletal muscle system responses during exercise [2]. Moreover, peak oxygen uptake (VO_2), which is assessed during maximum CPET, is related to

quality of life and is a strong predictor of hospitalization and mortality in adult CF patients [3–6].

As CF is a progressive disease, exercise capacity may deteriorate in time following pulmonary and extra-pulmonary manifestations. However, data on longitudinal changes of peak VO_2 and other CPET variables in adult CF patients are currently scarce. In the few available studies, changes in CPET variables were followed up for 12–18 months [7, 8], a period probably not long enough for disease deterioration to manifest. Moreover, all available studies were conducted in children or adolescents [7, 8]. However, several

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DOI: 10.5603/ARM.a2020.0145

Received: 25.02.2020

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ISSN 2451–4934

different, non-specific factors may complicate the pathophysiology of exercise limitation of the adolescent versus adult CF patient population (e.g. age of first CF presentation, effects of aging on cardiovascular function, different CPET approach, cautious caregiver that limits exercise participation, etc.) [3, 9]. Therefore, findings cannot be generalized. Under this scope, we conducted a pilot longitudinal study to assess the changes in peak VO_2 , anaerobic threshold (AT), and other CPET variables eight years after initial evaluation in a population of adult CF patients with mild-to-moderate disease.

Materials and methods

Between September 2010 and June 2011, 17 adult CF patients prospectively underwent maximum CPET and Doppler echocardiogram; the details are published elsewhere [1]. From this initial population, all surviving adult CF patients who had not undergone lung transplantation, were not lost to follow-up, and gave informed consent for participation were re-assessed between October 2018 and September 2019. All participating patients were regularly attending the adult CF unit of a major chest hospital in Greece, were life-long non-smokers, and were in a stable condition. In case of an exacerbation during the baseline assessment, the patient was properly treated and re-entered the protocol after at least 3 months of disease stabilization. Patients who received long-term oxygen treatment or presented with any contraindications for CPET were excluded. Ethical approval for the study protocol was received from the G Papanikolaou Hospital Scientific Committee.

The study protocol consisted of two visits conducted within a frame of one week. During the first visit, all patients underwent spirometry, lung volume measurement, and a 6-minute walking distance (6MWD) test. During the second visit, all patients underwent a transthoracic echocardiographic study (Philips medical system, Andover, MA, USA). Pulmonary artery systolic pressure (PASP), ejection fraction, and left and right heart dimensions were obtained by previously recommended techniques (10,11). Following this, all patients conducted a maximum CPET on a cycle ergometer. The exercise protocol required 2 minutes of unloaded pedaling with a ramp increase of work rate by 10-15 watts/minute until exhaustion followed by 3 minutes of recovery. The Borg dyspnea scale and the Borg Rate of Perceived exertion (RPE) were also recorded. Statistical analysis was

conducted utilizing the SPSS, version 20 for Windows XP. The Shapiro-Wilk test was applied to assess whether the distribution of data was normal or not. The paired samples t-test or the Wilcoxon rank test were utilized for group comparisons based on the normality of distribution of values with a level of $p < 0.05$ considered significant.

Results

Eleven patients (6 male, 5 female) who suffered from mild-to-moderate disease completed both assessments (initial, and after eight years). Seven patients had a Medical Research Council (MRC) dyspnea scale rating of 0–1, 3 patients had a rating of 2, and only one patient had a rating of 3. Moreover, the number of annual CF exacerbations which required hospitalization and intravenous antibiotic treatment was also limited in most of the cases. Specifically, 9 patients had 0-1 such exacerbations annually and only two had ≥ 3 . Compared to the initial assessment, respiratory function, evaluated by forced expiratory volume in 1 second (FEV_1), and total lung capacity (TLC) deteriorated. However, forced vital capacity (FVC) was similar during follow up (Table 1). The body mass index (BMI) of patients did not change longitudinally, while left heart function (as assessed by ejection fraction, $p = 0.574$) and systolic pulmonary artery pressure ($p = 0.441$) was also similar during follow-up.

Changes in the exercise capacity of these patients are also presented in Table 1. The follow-up 6MWD was significantly lower when compared with the initial one (605 ± 58.5 vs 513 ± 73.45 ; $p = 0.001$) and patients presented with more severe desaturation during the test. Maximum exercise capacity, as assessed by absolute peak VO_2 (26.6 ± 8.46 vs 23.89 ± 6.16 ; $p = 0.098$), % of predicted peak VO_2 (71.21 ± 16.54 vs 70.60 ± 15.45 ; $p = 0.872$), and % of predicted peak work rate (WR) (65.2 ± 13.63 vs 63.7 ± 15.09 ; $p = 0.559$) was below normal, but similar between the two evaluations. On the contrary, AT (both as an absolute and as a % of predicted values) was significantly lower during the second evaluation ($p = 0.009$ and $p = 0.048$, correspondingly). As for the rest of CPET parameters, the ventilatory equivalent for carbon dioxide at AT ($\text{VE}/\text{VCO}_2@$ AT) was higher ($p = 0.047$) and the ventilatory reserve by the end of the exercise was lower ($p = 0.019$) during follow-up, although it should be noted that peak minute ventilation (VE) did not differ between the two time periods. The oxygen pulse (peak VO_2 /peak heart rate), Borg dyspnea,

Table 1. Longitudinal changes of anthropometrics, lung function, echocardiographic parameters and exercise capacity variables among adult CF patients

Parameters	Initial evaluation	Follow-up evaluation	p
Age [years]	27.2 (4.15)	34.63 (3.98)	<0.001
Body mass index [kg/m ²]	22.2 (2.65)	23.1 (3.65)	0.231
Forced expiratory volume in 1 second (FEV ₁)	2.62 (1.17)	1.99 (0.81)	0.012
% predicted	66.72 (21.7)	56.41 (19.14)	0.028
Forced vital capacity (FVC)	3.33 (1.1)	3.15 (1.06)	0.294
% predicted	76.96 (18.17)	76.53 (21.1)	0.914
FEV ₁ /FVC	77.42 (18.87)	62.33 (13)	0.005
Total lung capacity [%predicted]	81.69 (14.71)	69.83 (14.25)	0.005
Ejection fraction [%]	66.6 (4.3)	66.4 (3.9)	0.574
Pulmonary artery systolic pressure [mm Hg]	24.18 (6.57)	24.72 (5.87)	0.441
6 minute walking distance [m]	605 (58.5)	513 (73.45)	0.001
SpO ₂ rest* [%]	95 (4)*	95 (5)*	0.726**
SpO ₂ nadir* (during 6 minute walking test) [%]	94 (15)*	92 (15)*	0.005**
Peak oxygen uptake			
mL/kg/min	26.6 (8.46)	23.89 (6.16)	0.098
% predicted	71.21 (16.54)	70.60 (15.45)	0.872
Anaerobic threshold			
mL/kg/min	17.95 (5.09)	14.12 (4.47)	0.009
% predicted	47.63 (10.58)	41 (12.51)	0.048
Peak work rate			
watts	117.6 (40.2)	101.1 (36)	0.013
% predicted	65.2 (13.63)	63.7 (15.09)	0.559
Borg dyspnea* (at peak VO ₂)	3 (6)*	5 (8)*	0.347**
Borg RPE* (at peakVO ₂)	4 (6)*	5 (5)*	0.354**
Peak VO ₂ /peak heart rate [% predicted]	83.94 (15.61)	82.13 (13.86)	0.743
VE/VCO ₂ @AT	31.2 (3.73)	33.6 (3.78)	0.047
Peak minute ventilation [lit]	60.89 (23.61)	63.19 (23.1)	0.483
Ventilatory reserve (MVV-peak VE) [lit]	40 (30.98)	16.7 (17.8)	0.019

All data are presented as mean (SD), unless otherwise indicated. *Median (range). **Wilcoxon rank test was utilised for group comparisons.

MVV — maximum voluntary ventilation; RPE — rate of perceived excursion; SpO₂ — pulse oxymeter oxygen saturation; VE/VCO₂@AT — ventilatory equivalent for carbon dioxide at anaerobic threshold; VE — minute ventilation; VO₂ — oxygen uptake

and Borg RPE scores were also similar during the two evaluations.

Discussion

Pulmonary, cardiac, metabolic, or peripheral muscle disorders may all negatively impact peak VO₂ [2]. Previous literature indicated that a peak VO₂ may be largely preserved in children and adolescents with mild CF [8, 9, 12]. In our study, VE/VCO₂ increased (indicating an increase in dead space ventilation) as was expected, and breathing reserve decreased during follow up. These abnormalities are frequently present among patients with CF even when peak VO₂ is preserved [7, 9] because they follow the pattern of typical

respiratory function decline. Respiratory limitation is an important pathophysiological factor of dyspnea and exercise limitation in chronic respiratory diseases [13]. Nevertheless, correlations between exercise outcome parameters and FEV₁ and/or FVC are often weak or absent in CF patients [3, 8], which suggests that respiratory restriction might not always be the major cause of exercise limitation. Moreover, cardiac index is a strong predictor of exercise outcome during CPET in CF patients [14]. The fact that oxygen pulse (an index of cardiac output) along with echocardiographic indices of left heart function and pulmonary circulation did not deteriorate in our study may partially explain why peak VO₂ did not further decrease after eight years.

Contrary to peak VO_2 , both the 6MWD and AT declined with time. The 6MWD test is considered a submaximal exercise test [15] so its decline cannot accurately reflect the maximal exercise capacity of the patients, but it associates well with most activities of daily living [15]. Moreover, the reduced AT, without signs of cardiovascular involvement, probably reflects the physical inactivity and deconditioning that has been frequently observed among CF patients [16, 17]. Exertional dyspnea, or the fear of it, combined with malnutrition, muscle cachexia, and disease exacerbations are only some of the causes [18].

Conclusion

In conclusion, in a population of CF patients with mild-to-moderate disease, the maximum exercise capacity did not decline further over 8 years. This is contrary to AT and 6MWD, which did decline. To our knowledge, no other study has yet provided data of such a long-term follow-up regarding CPET variables in this patient population. This study's findings are somewhat limited by the small number of participants and by the fact that only patients with mild-to-moderate disease, which remained relatively stable over the years, were analyzed. However, our study does make the point that, even in CF patients with long-term preserved peak VO_2 , physical deconditioning may be present. As CF patients with higher aerobic fitness present with better quality of life and higher survival [17], one could hypothesize that comprehensive exercise programs with continuous training in the long-term might be an important adjunct to regular treatment, even for CF patients with milder disease.

Conflict of interest

None to declare for any of the authors.

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