Original Article

Submaximal exercise capacity in adolescent and adult patients with cystic fibrosis*

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Abstract

Objective: To determine the submaximal exercise capacity of patients with cystic fibrosis (CF) by means of the 6-minute walk test (6MWT), correlating the results with clinical score, nutritional status, radiographic score, and pulmonary function tests. **Methods:** This was a prospective, cross-sectional study involving patients aged 16 or older enrolled in a program for adults with CF. The patients were submitted to clinical evaluation, determination of maximal respiratory pressures, 6MWT, spirometry, and chest X-ray. **Results:** The study comprised 41 patients. The mean age was 23.7 ± 6.5 years, and the mean forced expiratory volume in one second (FEV_1) was 55.1 ± 27.8%. On the 6MWT, 30 (73.2%) of the patients covered a distance (mean, 556.7 ± 76.5 m) that was less than the predicted normal value. The distance walked did not correlate significantly with body mass index, clinical score, radiographic score, maximal respiratory pressures, peripheral oxygen saturation at rest, desaturation during the 6MWT, sensation of dyspnea, or fatigue, although it did so with age at diagnosis, FEV_1 in liters, and forced vital capacity in liters. Worsening of pulmonary function was associated with greater desaturation during the 6MWT. **Conclusion:** This study showed that most patients attending an adult CF program had reduced submaximal exercise capacity. The 6MWT can be valuable for identifying patients who might experience oxygen desaturation and physical impairment in daily activities.

Keywords: Cystic fibrosis; Respiratory function tests; Exercise tolerance.

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Introduction

Cystic fibrosis (CF) is a progressive hereditary disease associated with the deterioration of pulmonary function, malnutrition, and progressive exercise intolerance.[1] Studies have reported that patients with CF present decreased muscle strength,[2-4] which can contribute to fatigue during exercise and daily activities. In addition to the decreased muscle mass and nutritional depletion, the decline in pulmonary function can also accentuate exercise intolerance.[3,5-7]

Advances in the treatment and diagnosis of CF have led to a considerable increase in patient survival.[1,8] However, as patients with CF reach adulthood, which they are doing in ever-increasing numbers, limitations resulting from the progressive worsening of pulmonary function, from the exacerbation of exocrine pancreatic insufficiency, from the appearance of diabetes mellitus, from the progression of pulmonary arterial hypertension, and, consequently, from the decreased cardiorespiratory response, increase.[9-13]

The 6-minute walk test (6MWT) has been widely used in periodic evaluations of the submaximal exercise capacity of patients with lung disease and heart failure. This test has also been indicated for the measurement of the responses after therapeutic interventions and for the determination of functional exercise tolerance. The 6MWT, with its low operational cost, is reproducible and easily performed, functioning as a predictor of morbidity and mortality. The results obtained reflect the needs of the patients in their daily activities.[14]

Some studies have evaluated the submaximal capacity test in pediatric patients with CF.[15-17] However, the performance of adult patients with CF on the 6MWT, as well as their functional capacity, has yet to be well defined in the literature.

The objective of the present study was to evaluate the submaximal exercise capacity of patients enrolled in an adult CF program by analyzing how the submaximal exercise capacity relates to clinical score, nutritional status, radiographic score, and pulmonary function test results.

Methods

Study design

This was a prospective, cross-sectional study involving patients monitored by the Adolescent and Adult CF Treatment Team of the *Hospital de Clínicas de Porto Alegre* (HCPA, Porto Alegre *Hospital de Clínicas*).

The study protocol was approved by the Ethics and Research Committee of the HCPA, and all patients gave written informed consent.

Study sample

The study sample comprised patients with CF treated by the HCPA Adolescent and Adult CF Treatment Team. All patients who agreed to participate in the study and met the following criteria were sequentially included: being 16 years of age or older; having been diagnosed with CF in accordance with consensus criteria;[18] and being clinically stable, which was defined as presenting no changes in symptoms and no alterations in the maintenance treatment within the past 30 days. Exclusion criteria were as follows: having primary cardiovascular disease (congenital heart disease, rheumatic disease, or pericarditis) and being pregnant.

Measurements

The patients were submitted to a clinical evaluation, which was performed by the highest-ranking member of the team in order to define the clinical stability of the disease. Subsequently, patient nutritional status was assessed, as was their clinical score, and they were submitted to 6MWT, pulmonary function tests, determination of maximal static respiratory pressures, and chest X-ray.

Anthropometric parameters

The nutritional status was assessed by determining body mass index (BMI), triceps skinfold (TSF) thickness, mid-arm circumference, and mid-arm muscle circumference (MAMC). The patients with a BMI $\geq$20 kg.m^{-2} were classified as normal, whereas those with a BMI <20 kg.m^{-2} were classified as malnourished. The TSF thickness (in millimeters) using a caliper (Beta Technology Incorporated, Cambridge, MD, USA). The mid-arm circumference (in centimeters) was determined using a tape measure placed around the middle of the left arm. The MAMC was calculated using the following equation: mid-arm circumference (cm) $-$ (0.314 $\times$ TSF thickness). The TSF thickness and the MAMC are expressed as the percentage of

the predicted value, using the 50th percentile for age and gender.[19] All anthropometric parameters were measured by the same professional.

Clinical score

The clinical score of each patient was assessed by the highest-ranking member of the team using the Shwachman-Kulczycki (S-K) scoring system.[20]

Radiographic score

All chest X-rays of the patients with CF were scored by the same member of the research group using the Brasfield scoring system.[21] The researcher was blinded as to the clinical score, evaluation findings, and test results related to the patients.

Six-minute walk test

The functional capacity of the patients was quantitatively measured using the 6MWT. The distance that the patient was able to cover in 6 min was determined in a 30-m-long corridor following a standardized protocol. All patients received the same orientation prior to the test. The patients were instructed to walk as far as possible in 6 min, and each test was performed under the supervision of a physical therapist. The 6MWT was performed in accordance with the American Thoracic Society guidelines.[14] Peripheral oxygen saturation (SpO_2) was registered before and immediately after the 6MWT using a pulse oximeter (NPB-40, Nellcor Puritan Bennett, Pleasanton, CA, USA). One patient presented an SpO_2 at rest ≤90% and therefore required supplemental oxygen during the 6MWT. For each patient, the lower limit of normality for the distance covered was determined based on the equations devised by Enright and Sherrill.[22]

Pulmonary function tests

Pulmonary function tests were performed using a computerized spirometer (Jaeger-v4.31, Jaeger, Wuerzburg, Germany). Forced vital capacity (FVC) was registered, as were forced expiratory volume in one second (FEV_1) and the FEV_1/FVC ratio, each of these variables being expressed in liters as well as in % of predicted.[23] In accordance with the Brazilian guidelines for pulmonary function tests, the patients were classified into three categories based on the degree of obstructive respiratory disorder (ORD), expressed as % of predicted FEV_1: mild or no ORD (% of predicted FEV_1 > 60%); moderate ORD (% of predicted FEV_1 between 40-60%); and severe ORD (% of predicted FEV_1 < 40%).[24]

Maximal static respiratory pressures

A digital vacuum manometer (MVD, version 1.0, 500/+500 cmH_2O; Microhard, Porto Alegre, Brazil) was used to determine respiratory muscle strength. Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured. The maneuvers were performed five times, with a minimum of three acceptable measurements. The pressure value that was the most negative was registered. The values are expressed according to the equations mentioned above.[25]

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences, version 13.0, and the Number Cruncher Statistical System, version 2000. The data are expressed as number of cases, mean ± standard deviation, or median (and interquartile range). Pearson linear correlation test was used for variables with normal distribution, and Spearman correlation coefficient was used for variables without normal distribution. In order to analyze continuous variables, comparing the three functional severity groups, we used one-way analysis of variance for variables with normal distribution, followed by Tukey's post-hoc test, and the Kruskal-Wallis test for variables without normal distribution, followed by the Kruskal-Wallis post-hoc Z test. All tests were two-tailed. The level of statistical significance was set at $p < 0.05$.

Results

From September of 2004 to January of 2006, all patients with CF monitored by the HCPA Adolescent and Adult CF Treatment Team were studied. Table 1 shows the general characteristics of these patients. Of the 41 patients studied, 23 (56%) were female and 18 (44%) were male. The mean age was 23.7 ± 6.5 years (range, 16-47 years), and the median age at diagnosis was 10 years. All patients were Caucasian. The mean BMI was 20.2 ± 2.2 $kg.m^{-2}$ (range, 15.9-26.5 $kg.m^{-2}$). The mean % of predicted TSF thickness and the mean %

Table 1 - General characteristics.

Characteristic	(n = 41)
Age (years), mean ± SD	23.7 ± 6.5
Age at diagnosis (years), median (IR)	10 (18)
Gender (n), male/female	18/23
BMI (kg.m^{-2}), mean ± SD	20.2 ± 2.2
TSF (% of predicted), mean ± SD	98.8 ± 46.5
MAMC (% of predicted), mean ± SD	86.8 ± 9.5
Nutritional status (n), nourished/malnourished	16/25
S-K clinical score (points), median (IR)	75 (20)
Brasfield score (points), median (IR)	16 (6)
FEV_1 (L), mean ± SD	1.9 ± 1.1
FVC (L), mean ± SD	2.8 ± 1.1
FEV_1/FVC (%), mean ± SD	68.4 ± 14.6
FEV_1 (% of predicted), mean ± SD	55.1 ± 27.8
FVC (% of predicted), mean ± SD	67 ± 22.9
FEV_1/FVC (% of predicted), mean ± SD	79.4 ± 17.5
MIP (cmH_2O), mean ± SD	96 ± 33.6
MEP (cmH_2O), mean ± SD	102.1 ± 39.4
MIP (% of predicted), mean ± SD	84.5 ± 27.2
MEP (% of predicted), mean ± SD	84.4 ± 25.8

BMI = body mass index; TSF = triceps skinfold (thickness); MAMC = mid-arm muscle circumference; MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure; S-K = Shwachman-Kulczycki; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; SD = standard deviation; IR = interquartile range.

of predicted MAMC were, respectively, 98.8 ± 46.5% and 86.8 ± 9.5%. The median S-K clinical score was 75 points, and the median Brasfield radiographic score was 16 points. The mean % of predicted FEV_1 and the mean % of predicted FVC were, respectively, 55.1 ± 27.8% and 67 ± 22.9%. The mean % of predicted FEV_1/FVC ratio was 79.4 ± 17.5%. The mean % of predicted MIP and the mean % of predicted MEP were, respectively, 84.5 ± 27.2% and 84.4 ± 25.8%. A total of 10 patients (24.4%) were infected with *Burkholderia cepacia,* and 23 (56.1%) were infected with *Pseudomonas aeruginosa.*

No statistically significant correlation was found between the distance covered on the 6MWT and the following variables: age, BMI, %TSF thickness, %MAMC, clinical score, radiographic score, SpO_2 at rest, ΔSpO_2, pre-6MWT dyspnea, post-6MWT dyspnea, pre-6MWT fatigue of the lower limbs, post-6MWT fatigue of the lower limbs, MIP, or MEP. The distance covered on the 6MWT correlated significantly with age at diagnosis, FEV_1 in liters, FEV_1 in % of predicted, FVC in liters, and FVC in % of predicted (Figure 1).

The overall mean distance covered on the 6MWT was 556.7 ± 76.5 m, and no statistically significant difference was found among the three functional severity groups for this variable (p = 0.07). On the 6MWT, 30 (73.2%) of the patients covered a distance that was less than the predicted normal value. A significant difference was found among the groups for SpO_2 at rest (p = 0.006), SpO_2 being lower in the moderate ORD and severe ORD groups than in the mild or no ORD group. In addition, a significant difference was found among the groups for post-6MWT SpO_2 (p = 0.009), which was lower in the severe ORD group. The level of post-6MWT desaturation was significantly different among the groups (p = 0.039), being higher in the severe ORD group. There were no statistically significant differences among the groups for the following variables: heart rate at rest, post-6MWT heart rate, respiratory rate at rest, post-6MWT respiratory rate, pre-6MWT dyspnea, pre-6MWT fatigue of the lower limbs, and post-6MWT fatigue of the lower limbs. There was a difference among the groups for post-6MWT dyspnea (p = 0.018), the score being significantly higher in the severe ORD group.

Discussion

The present study evaluated patients aged 16 or older enrolled in an adult CF program at a referral center for CF. All 41 patients monitored through the adult CF program at the time of the study were included. We observed that 73.2% of the patients covered a distance that was less than the predicted normal value. The distance covered on the 6MWT inversely correlated with age at diagnosis of CF, and directly correlated with FEV_1 and with FVC. The patients with severe ORD presented greater post-6MWT desaturation and a greater degree of post-6MWT dyspnea.

In contrast to our results, Chetta *et al.*,[2] studying 25 adult patients (18-39 years) with CF, reported normal performance in terms of the distance covered on the 6MWT (629 ± 49 m). However, that study included only patients with mild to moderate lung disease, with a mean % of predicted FEV_1 of 69 ± 23% and a mean % of predicted FVC of

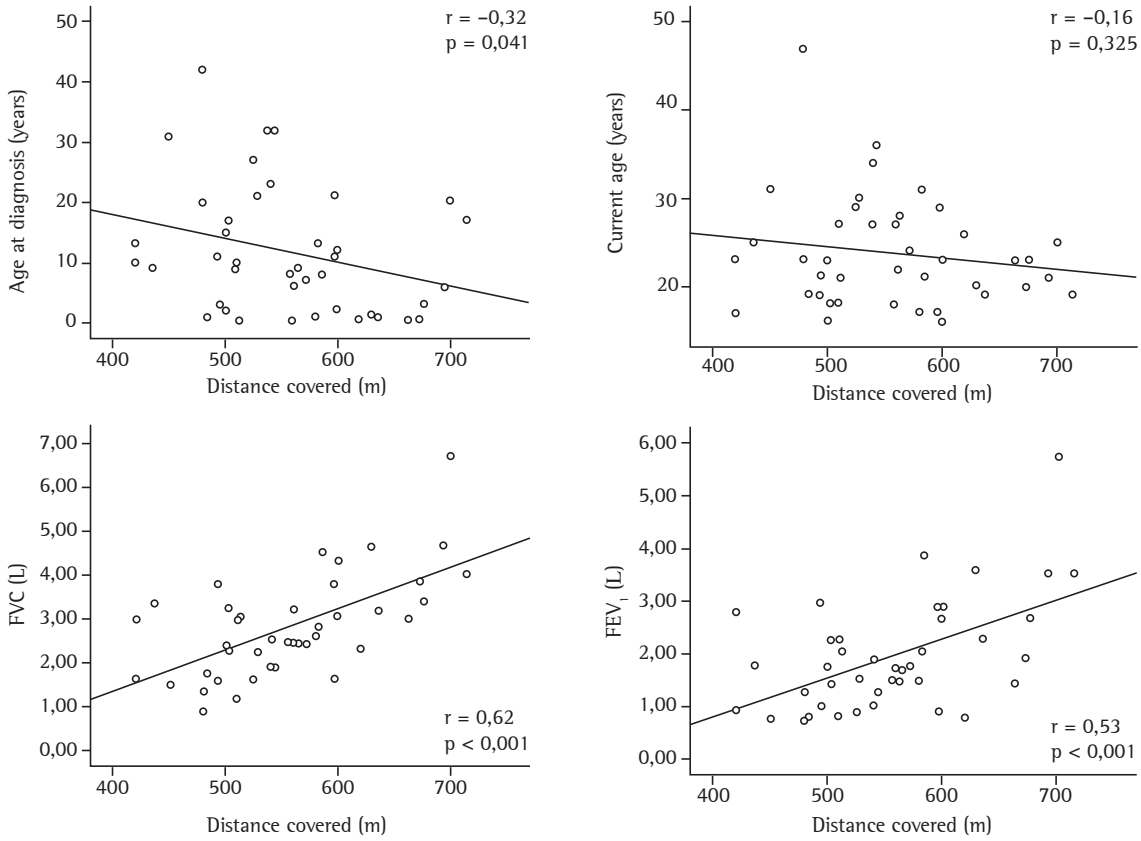

Figure 1 - Distance covered on the 6MWT: correlation with age at diagnosis, current age, and pulmonary function.

85 ± 20%. In our study, the mean distance covered (556.7 ± 76.5 m) was less than that found in the study mentioned above. However, we included all of the patients enrolled in the program, and this resulted in a group of patients with greater pulmonary function impairment. The mean % of predicted FEV1 and FVC in our study was 55.1 ± 27.8% and 67.0 ± 22.9%, respectively.

Gulmans *et al.* carried out a study with the objective of determining the validity and reproducibility of the 6MWT in children with CF.[16] The mean age of the patients studied was 11.1 ± 2.2 years, the % of predicted FEV_1 was 94.4 ± 16.5%, and the Z score was −0.81 ± 0.81. The distance covered by the patients evaluated in the Gulmans *et al.* study (737 ± 85 m) was greater than that reported in any of the other studies involving the 6MWT and CF.[2,15-17] However, it is important to emphasize that Gulmans *et al.* included only patients with mild to moderate lung disease.

Guillén *et al.* evaluated the reproducibility of the 6MWT in 29 pediatric and adolescent patients with CF.[17] The mean age of the patients studied was 15.9 ± 3.8 years, the mean FEV_1 was 83.0 ± 24.5%, the mean FVC was 91.2 ± 19.2%, and the mean BMI was 19.2 ± 3.2 $kg.m^{-2}$. In that study, the mean distance covered was 471 ± 47.7 m. Despite the fact that their patients were younger and had better pulmonary function, those authors found values regarding the distance covered on the 6MWT that were lower than those observed in the present study.

One group of authors carried out a study to determine the reproducibility of the 6MWT in 16 children with CF and found that the mean distance covered was 582.3 ± 60 m.[15] The mean age of the patients in that study was 11.0 ± 1.9 years, the mean FEV_1 was 63.1 ± 21.1%, and the mean FVC was 75.8 ± 16.7%. The patients studied presented significant nutritional impairment, with a

mean BMI of 15.8 ± 2.4 kg.m^{-2}. In addition to the pulmonary function impairment, malnutrition can also interfere with cardiorespiratory response and exercise performance.[22] In our study, the patients presented a better nutritional status (mean BMI, 20.2 ± 2.2 kg.m^{-2}), which indicates that the pulmonary function impairment is likely to have been the most important determining factor for exercise performance on the 6MWT.

It is important to emphasize that we found a significant correlation between the distance covered on the 6MWT to correlate significantly with FEV_1 and FVC (in liters and in % of predicted), whereas no such correlation was identified in the other, previously mentioned, studies involving submaximal exercise capacity in CF.[2,15,17] This might be related to the fact that those studies included patients with mild to moderate lung disease.

In our findings, the level of post-6MWT desaturation was significantly higher in the moderate ORD and severe ORD groups. However, no correlation was found between the level of post-6MWT desaturation and the distance covered on the test. The finding that desaturation did not constitute a determining factor for submaximal exercise capacity could be explained, in part, by the fact that the level of desaturation was not so intense in our patients (overall median desaturation of 1% versus 4% in the severe ORD group). However, the 6MWT is a tolerance test in which the patient defines the pace and the intensity of the exertion. More vigorous exercises generally cause greater desaturation, and this can limit physical performance.[26]

In the present study, neither the pre-6MWT sensation of dyspnea nor the post-6MWT sensation of dyspnea was found to correlate with the distance covered on the test. One group of authors showed that patients with CF reported a greater sensation of dyspnea during the submaximal exercise test than did patients in a control group, although, again, no correlation was found between the sensation of dyspnea and the distance covered.[2] Another group of authors did find a correlation between the distance covered on the 6MWT and the sensation of dyspnea in patients with CF.[15]

In the present study, age at diagnosis was found to be inversely correlated with the distance covered on the 6MWT. This could be explained by the functional impairment resulting from the delay in the institution of therapeutic measures that prevent disease progression. Although some authors have suggested that late diagnosis is associated with a less severe, atypical form of the disease,[26,27] our findings indicate that late diagnosis of CF is occasionally the result of less favorable health status and therefore related to typical cases with greater functional impairment.

The major limiting factor of the present study was the lack of a control group of healthy individuals matched for gender and age. In order to overcome this problem, we calculated the lower limit of normality for each patient based on the equations devised by Enright and Sherril.[22] In addition, the size of our sample was limited to the number of patients monitored in the adult CF program (41 patients).

In conclusion, this study showed that most patients enrolled in an adult CF program presented reduced submaximal exercise capacity. The 6MWT can be valuable for identifying patients who might experience oxygen desaturation and physical impairment during activities of daily living.

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