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Longitudinal Relationship between Physical Activity and Lung Health in Patients with Cystic Fibrosis

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Abstract

Objective: Exercise is beneficial for patients with Cystic Fibrosis (CF) but long term effects of physical activity on lung function evolution are unknown. We evaluated the longitudinal relationship between changes in habitual physical activity (HPA) and rate of decline in lung function in patients with CF.

Methods: We tracked HPA with the Habitual Activity Estimation Scale, FEV_1 and Stage I exercise tests in 212 patients with CF over a nine year period.

Results: Adjusting for gender, baseline age and FEV_1, mucoid *Pseudomonas aeruginosa* and CF related diabetes, FEV_1 % predicted *decreased* by -1.63%/year (SD=0.08 $p<0.0001$) while HPA *increased* by 0.28 hours/day/year (SD=0.03 $p<0.0001$), over the study period. A greater increase in HPA was associated with a slower rate of decline in FEV_1 ($r=0.19$, $p<0.0069$). Dividing into HIGH and LOW activity, (above or below the mean rate of change of activity respectively), a steeper rate of FEV_1 decline was observed for LOW (-1.90% /year) compared to HIGH (-1.39% /year; $p=0.002$).

Conclusion: Increases in HPA are feasible despite progression of lung disease and are associated with a slower rate of decline in FEV_1, highlighting the benefit of regular physical activity, and its positive impact on lung function in patients with CF.

INTRODUCTION

Advances in the treatment for cystic fibrosis (CF) have resulted in an increase in the median survival age for CF patients, however the disease continues to be life limiting [1]. Nutritional status, pulmonary function, genotype, age at diagnosis and infection with *Pseudomonas aeruginosa* have been identified as predictors of mortality in patients with CF [2;3]. A growing body of research has demonstrated that exercise training and physical activity contribute positively to outcome in patients with CF, with improvements in aerobic capacity, activity level, quality of life, weight gain, lung function and leg strength [4-6] and an association with a reduced rate of decline in lung function [7;8].

While physical activity has well documented benefits for healthy children [9], additional advantages for patients with CF include enhanced airway clearance [10] and improved ion channel function, possibly leading to better mucus hydration and enhanced mucus clearance [11]. Moreover, in patients with CF with severe lung disease, physical activity has been related to aerobic capacity [12], suggesting a direct relationship between aerobic capacity and survival.

Habitual physical activity (HPA) refers to activity which is incorporated into daily life, is less structured than traditional exercise training and can encompass a wide range of intensity levels. Thus far, a reduced HPA has been reported to be related to lung function decline in females with CF over a short observation period [8] and adults with CF have been shown to accumulate less HPA than their non CF peers [13]. While exercise training has been recommended for inclusion into CF routine therapy [14] issues such as the burden of disease [9] and inadequate adherence [15] have made it a challenge to incorporate into a treatment program. Knowing that focusing patients and parents on

the importance of regular activity could potentially change habitual levels over time, we sought to prospectively study the long term relationship between changes in habitual physical activity levels and lung function in patients with CF.

METHODS

Subject Selection

Patients 7-17 years of age were recruited from the Hospital for Sick Children (SK) and Montreal Children's Hospital (MCH) CF clinics. For those unwell, displaying symptoms such as an increased cough and sputum production, malaise, fever and/or inability to participate in regular habitual physical activity, recruitment was postponed to a later visit when they were well. The Research Ethics Boards of SK (1000009000), MCH (MCH003-28) and St. Michael's Hospital (05-06; site of follow up of patients > 18yrs) approved the study protocol and written informed consent was obtained from all participants.

Data Collection

Data were collected for all study patients at each quarterly clinic visit over the nine-year study period. Similar to recruitment, if a patient was not well enough to engage in their regular habitual physical activities, their data collection was postponed until the visit at which their typical HPA patterns had resumed, to control for potential losses in muscle force, and the documented reductions in HPA during exacerbation [16]. As a result, the number of data points varied among patients for the study period.

Anthropometric Measures

Height (standard Stadiometer with heel plate) and weight (SR Instruments; Model 555, Tonawanda, NY) were measured, and a z-score for body mass index percentiles (zBMI) was calculated according to CDC 2000 standards [17].

Pulmonary Function Testing

Spirometry was performed according to standard techniques [18] (SensorMedics VMax20 Pulmonary Spirometry Instrument, Yorba Linda, CA). Values were expressed as a percent of predicted value for height, gender and age for youth [19] and adults [20].

Habitual Activity Estimation Scale (HAES) [21]

At each quarterly clinic visit study patients completed the HAES for a typical weekday of the previous two weeks, as outlined in an earlier validation study in this population [22]. Total activity (sum of 'somewhat active' + 'very active') was calculated, as previously reported [8].

Aerobic Cycle Ergometer Test

Patients performed an annual Stage I exercise test (incremental, maximal) on an electrically braked cycle ergometer (Rodby Eectronik AB, Enhorna, Sweden), to determine peak oxygen consumption (VO_{2peak}) and work rate (WR_{peak}). One-minute work increments were chosen according to gender, height, and physical activity level [23] and a maximal test was performed, as reported previously [7].

Data Analysis

Descriptive statistics of means, medians, standard deviations and proportions were used to describe the variables measured. *T*-tests and/or chi-square were used to test for the difference between the two independent means or proportions respectively.

For the main analysis, weekday total activity (HPA) and pulmonary function (FEV_1) over time, mixed model analyses were used. To examine the association between activity level and pulmonary function, we obtained individualized slopes and intercepts, as well as the average slope and intercept, from the mixed model analyses of FEV_1 and HPA over time. Correlation analysis was used for those individual slopes and intercepts to examine the association of FEV_1 and HPA.

We then categorized individuals into above (if the individualized estimate was above – HIGH) or below (if the individualized estimate was below - LOW) the overall change in activity rate estimate. A mixed model analysis was performed to evaluate the effect of activity level on the primary outcome FEV_1, while controlling for the other potential confounders of baseline age and FEV_1, gender, mucoid *Pseudomonas aeruginosa* (mPA) and cystic fibrosis related diabetes (CFRD).

Finally, a mixed model analysis was performed to evaluate any effect of WR_{peak} (%pred) and VO_{2peak} ($ml.kg^{-1}.min^{-1}$) on the primary outcome, FEV_1, while controlling for baseline FEV_1.

SAS was used for all the analyses (version 9.1, SAS Institute Inc., Cary, NC). A p-value of 0.05 or less was considered statistically significant.

RESULTS

Two hundred twelve patients with Cystic Fibrosis (age 7-17yrs at baseline, females n=108; 50.9%) were recruited over a nine-year period. Baseline characteristics for the study population are shown in Table 1. Males had significantly higher pulmonary function, activity levels and VO_{2peak} values. Average HPA for the overall group at baseline was 5.47 (± 2.78) hours per day, with boys engaging in greater activity than girls (p=0.028).

Length of follow-up is presented in Table 2. The median length of follow-up was 5.21 years (range 0-9.7). A median of 9 (range 1-27) and 10 (range 1-29) measures were collected for HPA and FEV_1 respectively, over the study period.

Of 40 patients from MCH, 16 (40%) moved to adult care during the study period; these patients were not followed in the study after age 18. Of 172 patients from SK, 86 reached 18 years before the end of the study, of which 62 were followed after 18 years of age.

As the majority of patients (n=166) were recruited in the first year, we compared the baseline characteristics of recruited patients to the overall eligible clinic population in the major recruitment center (SickKids, Toronto). Patients participating in the study were younger (11.8 ± 2.9 vs 13.4 ± 3.3 years, $p<0.0005$) and had higher lung function (FEV_1 85.6 ±17.4 vs 67.2 ± 23.0 % predicted, $p<0.0001$) than patients not participating in the study (n=67). There was no significant difference in baseline FEV_1 (p=0.5048) or VO_2max (p=0.7126) between patients from the two paediatric centres (data not shown).

Adjusting for potential confounders of gender, baseline age and FEV_1, mucoid *Pseudomonas aeruginosa* and CFRD, overall FEV_1 decreased at a rate of -1.63

(SD=0.08) %/year ($p<0.0001$) and HPA increased at an rate of 0.28 (SD=0.03) hr/day/yr ($p<0.0001$), over the study period. There was a significant positive correlation between rates of change of activity level and change in FEV_1 decline, indicating that an increase in activity was associated with a slower rate of decline in lung function over the study period ($r=0.19$, $p<0.007$).

Participants were divided into HIGH (above the mean rate of change of activity) and LOW (below the mean rate of change of activity) groups. Table 3 indicates that all evaluated potential confounder variables were evenly distributed between the two groups. The HIGH group had a rate of *increase* in HPA of 0.59 hr/day/yr, while the LOW group had a rate of *decline* of activity of 0.15 hr/day/yr over the study period. Mixed model analysis results are presented in Table 4 and indicate that FEV_1 was significantly associated with baseline FEV_1 ($p=0.0001$), CFRD ($p=0.0452$) and change in activity level over time, such that the rate of decline of FEV_1, was less steep for the HIGH (-1.39% pred/yr) compared to the LOW group (-1.90% pred/yr) ($p=0.0001$).

One hundred eighty-nine patients performed Stage I exercise testing, with a total of 493 tests included for analysis (range 1 to 7 tests/patient). Adjusting for baseline FEV_1, there was a positive relationship between FEV_1 (%pred) and VO_{2peak} ($p=0.0194$) over the study period. Similarly, adjusting for baseline FEV_1, there was a positive relationship between FEV_1 (%pred) and peak work rate (%pred) ($p=0.0004$) over the study period. There was no significant association between VO_2peak and HPA ($p =0.7457$).

To confirm whether an increase in HPA was associated with a slower decline in FEV_1, we performed the following additional analysis. Between T1 (baseline) and T2 (2.5 yrs) we classified the patients into either increasing or reducing HPA over time. We

then used the data between T2 and T3 (6.6 yrs) to look at the rate of FEV_1 decline for the two groups. The results showed that the rate of decline in FEV_1 between T2 and T3 was significantly less steep for patients increasing their HPA (-0.58 % pred/yr) compared to those with reduced HPA (-2.15% pred/yr) ($p=0.0231$). Using the same method as above we found no differences in change of VO_2peak between the two groups ($p=0.7590$).

Using the definition of pulmonary exacerbation as hospitalization for respiratory symptoms requiring antibiotics [24], 57 (32.2%) of our study patients had at least one exacerbation with a median of 3 (range 1-16) over the study period. Hospital admissions were infrequent and there was no significant association between peak VO_2 and hospital admissions per year ($r=-0.07$, $p=0.35$).

DISCUSSION

In this prospective longitudinal study, after accounting for baseline characteristics known to affect clinical course, patients with CF with increasing activity levels had a reduced rate of decline of their FEV_1 compared to those that did not become more active over the study period. If the goal in the treatment of CF is to preserve lung function for as long as possible thus potentially extending survival [25], these results would suggest that enhancing physical activity should be an integral part of the management of the disease.

We found a significant overall increase in physical activity of 0.28 hr/day/yr over the study period, which translates into an increase of approximately 17 minutes per day. This contrasts with earlier reports of declining levels of habitual physical activity for the majority of youth, over a five-year period of growth from childhood to adolescence, regardless of gender or weight status [26] and the trend of decreasing activity levels of

children and youth in general [27]. It is possible that monitoring a patient's activity level while participating in a study may be a sufficient stimulus to effectively maintain what would otherwise be a predictable pattern of decreasing activity level with age [28]. This highlights the valuable opportunity to have a positive impact on lung function decline, by promoting a physically active lifestyle throughout childhood, to encourage the maintenance of activity and enhance the carryover into adulthood [29].

Previous reports of activity employing the HAES have indicated that children with CF engage in similar total amounts of habitual physical activity to their healthy peers [30]. Current values for HPA are similar to those reported in a small number of youth with CF [22] and somewhat lower than those reported by Ruf et al [31] of 7.4 (females) and 6.0 (males) hr/day for patients with CF (12-41 years). The latter may be explained by their inclusion of weekend activity, which was excluded in our analysis due to greater variability in preliminary analyses [8].

We investigated the relationship between lung function and habitual physical activity, as we were interested in documenting a 'lifestyle' variable in patients with CF, one that did not require an 'exercise prescription', which is generally difficult to maintain once the research study resources have ended [4;32]. Habitual physical activity refers to the level of activity that is inherent in daily life such as free play periods, climbing stairs, sporting activities, activities of daily living, and activities of lower intensity such as walking. Therefore changes in HPA represent a lifestyle modification which should result in longer lasting benefits. Enhancing habitual physical activity presents an interesting, widely feasible possibility for CF patients to improve their health and quality of life.

While multiple studies have highlighted factors that negatively affect the rate of decline of lung function, there are few that illustrate positive factors [25;33]. Likewise, most interventions in CF have been assessed regarding their short term efficacy in improving lung function rather than their long term effect on lung function decline, as the latter requires a much longer observation period to demonstrate an effect. This is the first prospective, longitudinal study to illustrate that increasing habitual physical activity has a positive effect in attenuating the rate of decline of lung function in patients with CF, possibly affecting survival.

There is evidence to suggest that physical activity affects lung function even in the absence of lung disease. Bernsten et al [34] reported that among a cross sectional group of 2,537 healthy children (9 to 10 years), FEV_1 was highest among those who were physically active 4 or more times per week, once adjusted for potential confounders ($p = 0.02$). The results of this study would suggest that any intervention assessing pulmonary function decline as an outcome should adjust for activity level, as it is a significant factor in addition to the traditional potential confounders.

Our findings of a positive longitudinal relationship between the rate of decline of both VO_{2peak} and WR_{peak} and FEV_1, agree with results of a two-year follow-up of children with CF [35] as well as support earlier reports of a relationship between VO_{2peak} and survival [36;37]. Thus it would suggest that both habitual physical activity and maximal aerobic fitness positively influence the outcome of patients with CF, reinforcing the association between physical activity and VO_{2peak} in patients with CF [38].

There are some inherent limitations to this study. Participants enrolled in the study were younger and had a higher FEV_1 than the remaining eligible clinic patients not

recruited that year. Self selection by those patients with mild disease is not uncommon in CF research studies [15], and in this case they would be healthier and less likely to have a chest exacerbation, and therefore eligible to participate in the activity study. On the other hand, the included population represented the majority of patients followed in our CF centre and demonstrating a positive effect of physical activity on lung function decline in patients having less severe lung function abnormalities highlights the opportunity to utilize enhancing physical activity as an early intervention strategy.

Given that HPA is an important adjunct to treatment for patients with CF, future research is needed to determine the most efficacious strategies to help patients increase their HPA and build a lifestyle conducive to lifelong involvement in physical activity.

In summary, we demonstrate that patients with CF with increasing activity levels have a reduced FEV_1 decline compared to those that did not become more active. This supports the hypothesis that even low intensity activity, such as that reported by our adolescents, is able to preserve lung function. This study highlights the importance of incorporating, facilitating and encouraging long-term habitual physical activity in the clinical management of cystic fibrosis.

Table 1. Baseline Characteristics (mean ± SD (n))				
Variable	*Combined*	*Male*	*Female*	*p-value*[1]
Age (yr)	12.00 ± 2.82 (212)	12.25 ± 2.79 (104)	11.76±2.84 (108)	0.21
Height (cm)	146.72±14.66 (212)	148.67±15.84 (104)	144.84±13.23 (108)	0.06
Weight (kg)	40.09±13.53 (212)	41.12±14.71 (104)	39.10±12.28 (108)	0.28
z-BMI	-0.17 ± 0.92 (212)	-0.24±0.84 (104)	-0.11±1.00 (108)	0.33
CFTR Genotype (%) F/- F/F Other	 97 (46.4) 95 (45.5) 17 (8.1)	 48 (47.0) 47 (46.1) 7 (6.9)	 49 (45.8) 48 (44.9) 10 (9.3)	 0.81[2]
CFRD (%) No Yes	 185 (87.3) 27 (12.7)	 94 (90.4) 10 (9.6)	 91 (84.3) 17 (15.7)	0.18[2]
PI (%) PS (%)	182 (88.4) 24 (11.6)	85 (85) 15 (15)	96 (90.6) 10 (9.4)	0.22[2]
ABPA No Yes	 199 (93.9) 13 (6.1)	 99 (95.2) 5 (4.8)	 100 (92.6) 8 (7.4)	0.43[2]
mPA No Yes	 101 (58.7) 71 (41.3)	 54 (64.3) 30 (35.7)	 47 (53.4) 41 (46.6)	0.14[2]
FVC (%pred)	94.40±13.92 (212)	96.30±13.19 (104)	92.57±14.41 (108)	0.05
FEV_1 (%pred)	85.53 ±17.27 (212)	88.07±16.14 (104)	83.08±18.04 (108)	0.04
FEF_{25-75} (%pred)	72.67±29.86 (205)	77.10±29.73 (101)	68.37±29.50 (104)	0.04
HPA (hr/d)	5.47 ± 2.80 (211)	5.90±2.87 (103)	5.06±2.69 (108)	0.028
VO_2peak ($ml.kg^{-1}.min^{-1}$)	40.03 ± 8.87 (n=188)	44.24 ± 8.48 (n=91)	36.08 ± 7.29 (n=97)	0.0001
WR_{peak} (%pred)	83.8± 17.5 (n=189)	85.2 ± 16.7 (n=90)	82.5 ± 18.2 (n=99)	0.298

1: Males compared to females; 2: χ^2 p-value. Abbreviations: z-BMI, Body Mass Index z-score; CFTR, cystic fibrosis transmembrane conductance regulator; CFRD, cystic fibrosis related diabetes; PI, pancreatic insufficient; PS, pancreatic sufficient; ABPA, Allergic bronchopulmonary aspergillosis; mPA, mucoid *Pseudomonas aeruginosa*; %pred, percent predicted; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; FEF_{25-75}, forced expiratory flow between 25-75% of FVC; HPA, habitual physical activity; VO_2peak, peak oxygen consumption; WRpeak, peak work rate.

Table 2. Number of Patients by Years of Follow-up										
Years	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Males	104	97	80	61	58	52	33	27	15	4
Females	108	102	82	69	67	63	45	41	25	9
Combined	212	199	162	130	125	115	78	68	40	13

Table 3. Comparison of High and Low Activity groups at Baseline				
Variable		*High Activity*	*Low Activity*	*p-value*
ABPA (yes)	n (% of group)	8 (7.5%)	5 (4.8%)	0.4101
mPA (yes)		37 (37.8%)	34 (45.9%)	0.2800
CFRD (yes)		15(14%)	12 (11.4%)	0.5717
PI/PS (PI)		83 (55%)	68 (45%)	0.1534
Gender (F)		58 (54.2%)	50 (47.6%)	0.3375
Age (yrs)	mean ($\pm$ SD)	11.9 (2.7)	12.1 (2.9)	0.5367
FVC (%)		95.6 (14.8)	93.2 (12.9)	0.2098
FEV_1 (%)		87.5 (18.2)	83.5 (16.1)	0.0967
FEF_{25-75} (%)		75.2 (29.4)	70.1 (30.3)	0.2192
zBMI		-0.08 (0.97)	-0.27 (0.87)	0.1397
ABPA, Allergic bronchopulmonary aspergillosis; mPA, mucoid *Pseudomonas aeruginosa*; CFRD, cystic fibrosis related diabetes; PI/PS, pancreatic insufficient/pancreatic sufficient; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; FEF_{25-75}, forced expiratory flow between 25-75% of FVC; zBMI, body mass index z-score				

Table 4. Mixed Model Analysis Results for Rate of Decline of FEV_1 on Activity

Variable		*Estimate*	*Standard Error*	*p-value*
Activity	High	-1.39	0.15	0.001
	Low	-1.90	0.11	
Baseline FEV_1		0.86	0.04	0.0001
Baseline Age		0.05	0.22	0.8175
Gender	F	-0.57	1.18	0.6306
RD	yes	-3.29	1.63	0.0452
mPA	yes	-2.26	1.27	0.0755

FEV_1, forced expiratory volume in one second; CFRD, cystic fibrosis related diabetes; mPA, mucoid *Pseudomonas aeruginosa*

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