Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis

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ABSTRACT 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.

We tracked HPA using the Habitual Activity Estimation Scale, forced expiratory volume in 1 s (FEV_1) and Stage I exercise tests in 212 patients with CF over a 9-year period.

Adjusting for sex, baseline age and FEV_1, mucoid *Pseudomonas aeruginosa* and CF-related diabetes, mean$\pm$SD FEV_1 % predicted decreased by 1.63$\pm$0.08% per year ($p<0.0001$) while mean$\pm$SD HPA increased by 0.28$\pm$0.03 $h \cdot day^{-1}$ per year ($p<0.0001$) 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 subjects 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% per year) compared to high (-1.39% per year) ($p=0.002$).

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.

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For editorial comments see page 675.

Received: March 27 2013 | Accepted after revision: Sept 04 2013 | First published online: Oct 31 2013

Support statement: This study was supported by Cystic Fibrosis Canada (2000–2003: #708; 2003–2006: #278; and 2006–2008: #990), The Irwin Foundation at the Hospital for Sick Children (G.D. Wells) and the Hospital for Sick Children Research Training Fellowship (J.E. Schneiderman).

Conflict of interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

Introduction

Advances in the treatment of 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 that is incorporated into daily life, is less structured than traditional exercise training and can encompass a wide range of intensity levels. Thus far, 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 programme. Knowing that focusing patients and parents on the importance of regular activity could potentially change habitual levels over time, we sought to study prospectively the long-term relationship between changes in HPA levels and lung function in patients with CF.

Methods

Subject selection

Patients aged 7–17 years were recruited from the Hospital for Sick Children (Toronto, Canada) and Montreal Children's Hospital (Montreal, Canada) CF clinics. For those who were 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 the Hospital for Sick Children (1000009000), Montreal Children's Hospital (MCH003-28) and St Michael's Hospital (Toronto; 05–06) (site of follow-up of patients aged >18 years) 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 9-year study period. Similarly to the recruitment process, if a patient was not well enough to engage in their regular HPA, their data collection was postponed until a 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 (Model 555; SR Instruments, Tonawanda, NY, USA) were measured, and a z-score for body mass index percentiles was calculated according to Centers for Disease Control and Prevention 2000 standards [17].

Pulmonary function testing

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

Habitual Activity Estimation Scale

At each quarterly clinic visit study patients completed the Habitual Activity Estimation Scale (HAES) [21] for a typical weekday of the previous 2 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 and maximal) on an electrically braked cycle ergometer (Rodby Electronik AB, Enhörna, Sweden), to determine peak oxygen consumption ($V'O_{2peak}$)

DOI: 10.1183/09031936.00055513

and work rate (WR_{peak}). 1-min work increments were chosen according to sex, 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-squared tests were used to test for the difference between two independent means or proportions.

For the main analysis, weekday total activity (HPA) and pulmonary function (forced expiratory volume in 1 s (FEV_1)) over time, mixed model analyses were used. To examine the association between activity level and pulmonary function, we obtained individualised 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 categorised individuals into those above (if the individualised estimate was above (''high'')) or below (if the individualised 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, sex, mucoid *P. aeruginosa* and CF-related diabetes (CFRD).

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

SAS (version 9.1; SAS Institute Inc., Cary, NC, USA) was used for all the analyses. $p \leqslant 0.05$ was considered statistically significant.

Results

212 patients with CF (aged 7–17 years at baseline, 108 (50.9%) females) were recruited over a 9-year period. Baseline characteristics for the study population are shown in table 1. Males had significantly higher pulmonary function, activity levels and $V'O_{2peak}$ values. Mean$\pm$SD HPA for the overall group at baseline was 5.47 ± 2.78 $h \cdot day^{-1}$, with males engaging in greater activity than females ($p=0.028$).

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

Of 40 patients from Montreal Children's Hospital, 16 (40%) moved to adult care during the study period; these patients were not followed in the study after the age of 18 years. Of 172 patients from the Hospital for Sick Children, 86 (50%) reached 18 years of age before the end of the study, of which 62 (72%) were followed after the age of 18 years.

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 centre (the Hospital for Sick Children). Patients participating in the study were younger (11.8 ± 2.9 years *versus* 13.4 ± 3.3 years, $p<0.0005$) and had higher lung function (FEV_1 85.6 ± 17.4% pred *versus* 67.2 ± 23.0% pred, $p<0.0001$) than patients not participating in the study ($n=67$). There was no significant difference in baseline FEV_1 ($p=0.5048$) or $V'O_{2max}$ ($p=0.7126$) between patients from the two paediatric centres (data not shown).

Adjusting for the potential confounders of sex, baseline age and FEV_1, mucoid *P. aeruginosa* and CFRD, overall FEV_1 decreased at a mean$\pm$SD rate of 1.63 ± 0.08% per year ($p<0.0001$) and HPA increased at a mean$\pm$SD rate of 0.28 ± 0.03 $h \cdot day^{-1}$ per year ($p<0.0001$) 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 $h \cdot day^{-1}$ per year, while the low group had a rate of decline of activity of 0.15 $h \cdot day^{-1}$ per year 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 group (-1.39% pred per year) compared to the low group (-1.90% pred per year) ($p=0.0001$).

189 patients performed Stage I exercise testing, with a total of 493 tests included for analysis (range 1–7 tests per patient). Adjusting for baseline FEV_1, there was a positive relationship between FEV_1 (% pred) and $V'O_{2peak}$ (p=0.0194) over the study period. Similarly, adjusting for baseline FEV_1, there was a positive relationship between FEV_1 (% pred) and WR_{peak} (% pred) (p=0.0004) over the study period. There was no significant association between $V'O_{2peak}$ 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 years) 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 who incresed their HPA (-0.58% pred per year) compared to those with reduced HPA (-2.15% pred per year) (p=0.0231). Using the same method, we found no differences in change of $V'O_{2peak}$ between the two groups (p=0.7590).

Defining pulmonary exacerbation as hospitalisation for respiratory symptoms requiring antibiotics [24], 57 (32.2%) of our study patients had at least one exacerbation with a median (range) of three (1–16) over the study period. Hospital admissions were infrequent and there was no significant association between $V'O_{2peak}$ 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.

TABLE 1 Baseline characteristics

	Combined	Male	Female	p-value[#]
Age years	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/-	97 (46.4)	48 (47.0)	49 (45.8)	0.81[¶]
F/F	95 (45.5)	47 (46.1)	48 (44.9)	
Other	17 (8.1)	7 (6.9)	10 (9.3)	
CFRD				0.18[¶]
No	185 (87.3)	94 (90.4)	91 (84.3)	
Yes	27 (12.7)	10 (9.6)	17 (15.7)	
Pancreatic sufficiency				
Insufficient	182 (88.4)	85 (85)	96 (90.6)	0.22[¶]
Sufficient	24 (11.6)	15 (15)	10 (9.4)	
ABPA				0.43[¶]
No	199 (93.9)	99 (95.2)	100 (92.6)	
Yes	13 (6.1)	5 (4.8)	8 (7.4)	
mPA				0.14[¶]
No	101 (58.7)	54 (64.3)	47 (53.4)	
Yes	71 (41.3)	30 (35.7)	41 (46.6)	
FVC % predicted	94.40±13.92 (212)	96.30±13.19 (104)	92.57±14.41 (108)	0.05
FEV_1 % predicted	85.53±17.27 (212)	88.07±16.14 (104)	83.08±18.04 (108)	0.04
$FEF_{25–75\%}$ % predicted	72.67±29.86 (205)	77.10±29.73 (101)	68.37±29.50 (104)	0.04
HPA h·day^{-1}	5.47±2.80 (211)	5.90±2.87 (103)	5.06±2.69 (108)	0.028
$V'O_{2peak}$ mL·kg^{-1}·min^{-1}	40.03±8.87 (188)	44.24±8.48 (91)	36.08±7.29 (97)	0.0001
WR_{peak} % pred	83.8±17.5 (189)	85.2±16.7 (90)	82.5±18.2 (99)	0.298

Data are presented as mean±SD (n) or n (%), unless otherwise stated. z-BMI: body mass index z-score; *CFTR*: cystic fibrosis transmembrane conductance regulator; F: ΔF508; CFRD: cystic fibrosis-related diabetes; ABPA: allergic bronchopulmonary aspergillosis; mPA: mucoid *Pseudomonas aeruginosa*; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC; HPA: habitual physical activity; $V'O_{2peak}$: peak oxygen consumption; WR_{peak}: peak work rate. [#]: males compared with females; [¶]: Chi-squared p-value.

DOI: 10.1183/09031936.00055513

TABLE 2 Number of patients by years of follow-up

	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
Total	212	199	162	130	125	115	78	68	40	13

Data are presented as n.

We found a significant overall increase in physical activity of 0.28 h·day^{-1} per year over the study period, which translates into an increase of ~17 min·day^{-1}. This contrasts with earlier reports of declining levels of HPA for the majority of youth over a 5-year period of growth from childhood to adolescence, regardless of sex 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 a 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 carry-over into adulthood [29].

Previous reports of activity employing the HAES have indicated that children with CF engage in similar total amounts of HPA to their healthy peers [30]. Current values for HPA are similar to those reported in a small number of youths with CF [22] and somewhat lower than those reported by RUF *et al.* [31] of 7.4 h·day^{-1} (females) and 6.0 h·day^{-1} (males) for patients with CF (aged 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 HPA, 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]. HPA 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 that should result in longer lasting benefits. Enhancing HPA 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

TABLE 3 Comparison of "high"- and "low"-activity groups at baseline

	High activity	Low activity	p-value
ABPA	8 (7.5)	5 (4.8)	0.4101
mPA	37 (37.8)	34 (45.9)	0.2800
CFRD	15 (14)	12 (11.4)	0.5717
Pancreatic insufficiency	83 (55)	68 (45)	0.1534
Female sex	58 (54.2)	50 (47.6)	0.3375
Age years	11.9±2.7	12.1±2.9	0.5367
FVC % predicted	95.6±14.8	93.2±12.9	0.2098
FEV_1 % predicted	87.5±18.2	83.5±16.1	0.0967
$FEF_{25–75\%}$ %	75.2±29.4	70.1±30.3	0.2192
z-BMI	-0.08±0.97	-0.27±0.87	0.1397

Data are presented as n (%) or mean± SD, unless otherwise stated. ABPA: allergic bronchopulmonary aspergillosis; mPA: mucoid *Pseudomonas aeruginosa*; CFRD: cystic fibrosis-related diabetes; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC; z-BMI: body mass index z-score.

TABLE 4 Mixed model analysis results for rate of decline of forced expiratory volume in 1 s (FEV_1) on activity

	Estimate ± SE	p-value
Activity		0.001
High	-1.39 ± 0.15	
Low	-1.90 ± 0.11	
Baseline FEV_1	0.86 ± 0.04	0.0001
Baseline age	0.05 ± 0.22	0.8175
Female	-0.57 ± 1.18	0.6306
CFRD	-3.29 ± 1.63	0.0452
mPA	-2.26 ± 1.27	0.0755

CFRD: cystic fibrosis-related diabetes; mPA: mucoid *Pseudomonas aeruginosa*.

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. BERNTSEN *et al.* [34] reported that among a cross-sectional group of 2537 healthy children (aged 9–10 years), FEV_1 was highest among those who were physically active four 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 FEV_1 and both $V'O_2peak$ and WR_{peak} agree with results of a 2-year follow-up of children with CF [35] and support earlier reports of a relationship between $V'O_2peak$ and survival [36, 37]. Thus, it would suggest that both HPA and maximal aerobic fitness positively influence the outcome of patients with CF, reinforcing the association between physical activity and $V'O_2peak$ 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. Conversely, 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 utilise 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 with those who 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 CF.

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DOI: 10.1183/09031936.00055513

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