Abstract

Background: Several cross-sectional studies in patients with cystic fibrosis (CF) have shown that nutritional status and lung function are important determinants of peak aerobic capacity (VO$_{2\text{peak}}$). In order to account for individual changes the aim of this study was to determine the longitudinal relationship of changes in nutritional status, lung function and VO$_{2\text{peak}}$ in children with CF.

Design and methods: Fat-free mass (FFM), lung function and VO$_{2\text{peak}}$ were assessed in sixty-five children with CF at baseline (age 10.5 ± 2.9 year and FEV$_1$ 92.6 ± 20.5%) and again two years later. FFM was calculated using skin fold thickness and VO$_{2\text{peak}}$ was measured using an incremental treadmill test for children until the age of 12 or an incremental cycle ergometry test for children of 12 years and older. Lung function was measured before the exercise test.

Results: Over the two-year study period an increase was found for absolute values of FFM (6.1 kg, p<0.001), forced expiratory volume in one second (FEV$_1$: 229 ml, p<0.001) and VO$_{2\text{peak}}$ (240 ml, p<0.001), while a decrease was found for predicted values of FEV$_1$ (–8.9%, p<0.001) and VO$_{2\text{peak}}$ (–4.4%, p<0.05). Changes in VO$_{2\text{peak}}$ (dVO$_2$) over the two-year period were best correlated with changes in FEV$_1$ (dFEV$_1$; r=0.619, p<0.001) and to a lesser degree with the changes in FFM (dFFM; r=0.506, p<0.001). Multiple regression analysis demonstrated that dFEV$_1$ and dFFM explained 47% of the variation of the change in VO$_{2\text{peak}}$ over the two-year period.
Conclusions: Our results show that longitudinal changes in VO\textsubscript{2peak} are associated with changes in lung function and to a lesser extent with changes in nutritional status in children with CF. Special consideration should be given to exercise training and nutritional intervention which might improve long-term clinical outcome in children with CF.

Introduction

Cystic Fibrosis (CF) is characterized by deterioration of nutritional status and irreversible loss of lung function. Favorable prognosis and survival in this patient group have been associated with higher aerobic fitness and better nutritional status while mortality of most patients is determined by the rate of deterioration of respiratory function [1,2]. Several cross-sectional studies have shown that aerobic performance in patients with CF is associated with nutritional status [3-6]. In these studies, patients with a diminished body weight have a lower aerobic capacity compared to age-matched healthy controls. Furthermore, CF has adverse effects on fat mass and fat-free mass (FFM). Nutritional deficiencies may lead to decreased fat stores and, as a result of protein malnutrition, may even lead to muscle wasting [4,7]. Muscle mass, which is the largest constituent of fat-free mass (FFM), is found to be a critical determinant of peak aerobic performance [8,9].

Another major determinant of aerobic capacity is the lung’s ability to exchange gas [10]. Cross-sectional sectional data in patients with CF show that poor lung function is associated with reduced aerobic performance [11,12].

From cross-sectional studies it can be speculated that individual changes in aerobic performance are caused by changes in lung function and nutritional status. However, with cross-sectional sectional investigations individual changes cannot be detected. Longitudinal data may enable clinicians to design interventions that are relevant and effective in improving outcome in children with CF. The longitudinal relationship between aerobic performance, lung function and nutritional status has been described for adults with CF [13] but has not been studied previously in children with CF. The aim of this study was to determine the longitudinal relationship between changes in aerobic performance, lung function and body composition in children with CF.

Methods

Subjects

Measurement of nutritional status, lung function and exercise performance is part of the annual medical check-up of the Cystic Fibrosis Center of the Wilhelmina Children’s Hospital and University Medical Center at Utrecht.
Patients who met the following criteria were approached for the study: age between 4 and 18 years, stable clinical condition, i.e. no need for oral or intravenous antibiotic treatment in three months prior to testing and the children should be able to perform the tests. One hundred and sixty three children with CF were eligible for inclusion in the study. Seventy-nine children and their parents agreed to participate. Children completed the measurements of nutritional status, lung function and exercise performance (T1) and again two years later (T2). The treatment regime for the study subjects was consistent with current standards of care for CF. The study was approved by the institutional review board. Assent was obtained from each participant and informed consent from their parents.

Lung function testing

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁) were obtained from maximal expiratory flow-volume curves (Masterscreen; Jaeger, Wuerzburg, Germany). Values are expressed as the percentage of predicted values [14].

Assessment of nutritional status

Weight and height were measured with an electronic scale (Mettler, Greifensee, Switzerland) and a stadiometer (Holtain, Crymich, UK), respectively. Body mass index (BMI) was calculated from the ratio weight/height² (kg/m²). Left-sided biceps, triceps, subscapular and supra iliac skinfolds were measured with an accuracy of 0,1 mm (Holtain caliper, Crymich, UK). The mean of three readings was recorded for each site. Total body fat percentage was estimated by the use of age- and gender-dependent equations on the relation between body fat percentage and body density [15]. FFM was then calculated as the difference between body weight and fat mass (FM).

Exercise testing

The standard exercise protocol for annual check-up measurements was used. Until the age of 12 years, the children performed a treadmill test according to the Bruce protocol [16]. Children aged 12 years and older used an electronically braked cycle ergometer (Lode Examiner; Lode, Groningen, The Netherlands). Workload increased 15 W each minute. Subjects were asked to maintain a pedaling rate at 60 rpm. During the tests patients were encouraged to perform to the best of their abilities. Both tests were continued to voluntary exhaustion.

Continuous respiratory gas analysis and volume measurements were performed breath-by-breath with a triple V valveless mouthpiece and stored in a computerized exercise system (Oxycon Champion, Jaeger, Breda, The Netherlands). Measurements taken included oxygen uptake (VO₂), carbon
dioxide production (VCO₂), ventilation (VE) and respiratory exchange ratio (RER). The highest VO₂ achieved during the last 30 seconds of exercise was taken as VO₂peak [17]. Heart rate was monitored by 3-lead electrocardiogram (Hewlett-Packard, Amstelveen, The Netherlands) and oxygen saturation (SpO₂) by pulse oximetry (Nellcor 200 E, Breda, The Netherlands). Internal gas and volume calibrations were made before each test.

Efforts were considered to be at a maximum level if subjects showed clinical signs of intense effort and were unable to maintain speed [18], and if at least one out of two criteria were met: 1) cardiac frequency above 180 beats/min; 2) maximal respiratory exchange ratio (i.e. VCO₂/VO₂) above 1.0 [5,10].

Predicted VO₂peak (VO₂peak%) values were obtained from an age and gender matched Dutch reference population, which used the same modes of exercise [19].

Data analysis

Data are presented as mean value ± standard deviation unless otherwise indicated. Comparisons of group characteristics between T1 and T2 were made with paired t tests. Individual differences in FFM (dFFM), FEV₁ (dFEV₁) and VO₂peak (dVO₂peak) were calculated between T1 and T2 (T₁₂). Correlation analyses (Pearson's r) and stepwise linear regression were made for dFFM, dFEV₁ and dVO₂peak for the two measurements. Differences were considered significant if p < 0.05 (two-tailed). Data were analyzed using the Statistical Package for the Social Science (SPSS, version 9.0, Chicago, IL, USA).

Results

Eight out of the 79 children were excluded from the analysis because they did not fulfill the criteria for a maximum exercise test. Six children reached the age of twelve during the study period and therefore changed from treadmill to cycle ergometer. Several studies have shown higher VO₂peak on a treadmill compared to a cycle ergometer [20-22]. Consecutive annual changes in VO₂peak could be the result of different exercise modes and therefore these six children were also excluded.

Table 1 summarizes the characteristics of the study group at T1 and T2 (N=65). The group had mild to moderate airflow obstruction while their ages were normally distributed. There were no differences between the patients that collaborated in the study and the group of CF patients (N=163) that was eligible for participation. Comparisons between boys and girls showed no differences in baseline characteristics or in changes of the study parameters during the study period.
### Table 1 Patient characteristics at baseline and at repeat testing two years later

<table>
<thead>
<tr>
<th>Subject (n=65)</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>10.5 (2.9)</td>
<td>12.5 (2.9)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>33.6 (11.3)</td>
<td>40.6 (12.7)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>140.8 (17.0)</td>
<td>151.6 (16.4)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>16.5 (2.0)</td>
<td>17.2 (2.5)</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>27.6 (9.3)</td>
<td>33.6 (10.4)</td>
</tr>
<tr>
<td>FEV₁, ml</td>
<td>1828 (630)</td>
<td>2055 (713)</td>
</tr>
<tr>
<td>FEV₁, % pred</td>
<td>92.6 (20.5)</td>
<td>83.6 (21.5)</td>
</tr>
<tr>
<td>FVC, ml</td>
<td>2260 (732)</td>
<td>2694 (828)</td>
</tr>
<tr>
<td>FVC, % pred</td>
<td>94.8 (15.4)</td>
<td>92.3 (14.9)</td>
</tr>
<tr>
<td>VO₂peak, ml/min</td>
<td>1435 (475)</td>
<td>1678 (524)</td>
</tr>
<tr>
<td>VO₂peak, % pred</td>
<td>91.4 (21.7)</td>
<td>87.1 (20.3)</td>
</tr>
</tbody>
</table>

Values are mean ± SD. BMI = body mass index; FFM = fat free mass; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; VO₂peak = peak oxygen uptake.

### Table 2 Comparisons of differences between means for fat-free mass, lung function and aerobic capacity

<table>
<thead>
<tr>
<th></th>
<th>T12</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFM (kg)</td>
<td>6.1 (5.3 to 6.9)‡</td>
</tr>
<tr>
<td>FEV₁ (ml)</td>
<td>229 (134 to 325)‡</td>
</tr>
<tr>
<td>FEV₁, % pred</td>
<td>-8.9 (-12.8 to -4.8)‡</td>
</tr>
<tr>
<td>VO₂peak (ml/min)</td>
<td>240 (162 to 318)‡</td>
</tr>
<tr>
<td>VO₂peak % pred</td>
<td>-4.4 (-8.52 to -0.29) *</td>
</tr>
</tbody>
</table>

FFM = fat free mass; FEV₁ = forced expiratory volume in one second; VO₂peak = peak oxygen uptake. * p<0.05; † p<0.01; ‡ p<0.001

### Table 3 Correlation between changes in body composition, lung function and peak aerobic capacity over two-year period

<table>
<thead>
<tr>
<th></th>
<th>dFEV₁</th>
<th>dVO₂peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>dFFM</td>
<td>0.506‡</td>
<td>0.564‡</td>
</tr>
<tr>
<td>dFEV₁</td>
<td>0.619‡</td>
<td></td>
</tr>
</tbody>
</table>

dFFM = change in fat free mass; dFEV₁ = change in forced expiratory volume in one second; dVO₂ = change in peak oxygen uptake. † p<0.01; ‡ p<0.001
Figure 1
The individual change in peak oxygen uptake (VO_{2peak}) related to A) the change in fat-free mass (FFM) \([r = 0.564; p < 0.001]\) and B) the change in forced expiratory volume in one-second (FEV₁) \([r = 0.619; p < 0.001]\) over a two-year period (T12).
Comparisons between T1 and T2 are presented in table 2. Absolute values of FFM, FEV₁ and VO₂peak increased during the two-year period. With respect to predicted values, FEV₁% and VO₂peak% decreased over the two-year period. Correlations between individual changes in body composition, lung function and aerobic performance are shown in table 3. The changes in VO₂peak correlated best with changes in FEV₁ and to a lesser degree with changes in FFM. The relationship between these variables and dVO₂peak for T12 are demonstrated in figure 1.

Changes in FEV₁, FFM, height, weight and BMI were entered in a step-wise regression model, with dVO₂peak as the dependent variable. Analysis revealed that dFEV₁ (p<0.001) explained 38% of the variation in dVO₂peak. dFFM (p<0.001) was also included in the model, whereas changes in height, weight and BMI were excluded. Together dFEV₁ and dFFM accounted for 47% of the variability in dVO₂peak (regression equation: dVO₂peak = -60.4 + 0.40 · dFEV₁ + 33.40 · dFFM).

Discussion

We longitudinally studied the effect of changes in FFM and lung function on peak aerobic capacity in children with CF. Our longitudinal data indicate that changes of peak aerobic capacity in children with CF can be ascribed, to a great extent, to changes in lung function. The additional effect of changes in FFM may increase up to 9% of the explained variance of the changes in VO₂peak.

The results of this longitudinal study are in agreement with results from cross-sectional sectional studies showing that lung function [3,4,6,23,24] and nutritional status [3,4,6] are important predictors of aerobic performance in patients with CF. Long-term data describing the relationship between these variables in children are not available. Moorcroft and colleagues reported a decline in absolute and predicted values of FEV₁ in adult patients with CF over a mean period of 6.3 years [13]. VO₂peak remained stable in this study and an association between lung function and aerobic capacity was not found. In our study, the increase in absolute VO₂peak was mainly related to an increase in FEV₁. Lung growth typically occurs in healthy subjects under the age of 20 years and may account for the increase in FEV₁ [25]. In young patients with CF the growth-related increase in absolute values of FEV₁ might compensate for the disease-related loss of pulmonary function. In addition, the amount of FFM seems a potential factor in offsetting losses in pulmonary function [13]. In the study of Moorcroft and coworkers potential lung growth was not to be expected. This could explain the absence of an association between change in lung function and aerobic capacity in their study. Our patients clinically deteriorated over the two-year period as FEV₁ (% of predicted) decreased, which is in agreement with the study results of Moorcroft and colleagues [13]. However, in addition we found a concomitant decrease in age- and gender predicted values of VO₂peak. Absolute
values of lung function show lung growth in children with CF but may underestimate progression of lung disease [13]. The clinical relevance of absolute changes in FEV₁ and VO₂peak in young children with CF, can only be judged when predicted normal values of FEV₁ and VO₂peak are taken into account.

FFM is a critical determinant of aerobic exercise capacity in conditions of health and disease [5,9,26]. Long-term decline in nutritional status with a reduction in total body weight occurs in many patients with CF. When patients with CF reach adulthood, the main impact of weight loss is likely a decrease in FFM since there usually is a preexisting reduced fat mass [26]. FFM increased significantly during the study period, which was to be expected due to the young age of our patients. During the normal process of growth, FFM increases but different periods of FFM deposition can be discriminated [27]. Tempo and timing of progression in VO₂peak may depend on age- and gender related changes in fat-free mass. Since reference values for FFM are not available, it is not clear how large the increase in muscle mass should be, based on gender and age. In order to detect clinically relevant changes in FFM of individual patients, more research is warranted to develop age- and gender specific values for pediatric FFM proportions.

Measuring FFM by measurement of skinfolds is based on the assumption that measuring fatness reflects lean body mass as well. Besides that, it assumes that subcutaneous distribution of fat is a constant proportion of total body fat. Both might be questioned. However, significant correlations between FFM estimated with skinfold measurements as compared to water isotope dilution techniques, which is considered to be the gold standard, have been published [28]. Furthermore, de Meer and colleagues showed that skinfold measurements can be used to monitor FFM irrespective of clinical severity of CF [29].

Results of cross-sectional sectional studies in chronic airway obstruction have shown a relationship between lung disease and nutritional status, which acts by a catabolic intermediary metabolism secondary to pulmonary infection and inflammation [30,31]. In general, chronic catabolic influence of inflammatory mediators (cytokines) may induce protein breakdown and inhibit muscle development in patients with CF [32,33]. To our knowledge there are no studies available in which the long-term association between lung function and body composition in children with CF have been described. The relationship between dFFM and dFEV₁ over our study period (r² = 0.25) is in agreement with the cross-sectional relationship between lung function and nutritional status found for children (r² = 0.06 to 0.25) [34] and adults (r² = 0.19) [13] with CF.

Other factors, like habitual physical activity, muscle function and peripheral muscle strength are also important for maintaining exercise tolerance. A limitation of our study is that we did not assess daily physical activity. It has been shown that the amount of daily physical activity is related to a diminished nutritional status [35] and that the amount of time spend in vigorous physical activities is associated with lower aerobic fitness [36]. In addition, Lands and colleagues found that muscle function assessed with an anaerobic exercise test,
was a more sensitive determinant of maximal aerobic capacity than lean body mass in adults with CF [3]. In children with CF peripheral muscle force is related to maximal work load, even in the absence of diminished pulmonary function and nutritional status [34].

Our results suggest that deterioration in lung function in children with CF might also point to a significant decrease in peak exercise capacity. The latter is associated with quality of life [37] and survival [1]. Special consideration should be given to exercise training, since several studies have shown positive effects on lung function, $\text{VO}_{2}\text{peak}$ and quality of life after a period of exercise training [38-40]. Since FFM has an additional effect on aerobic performance, emphasis should also be given to nutritional management [13].

We conclude that longitudinal changes in lung function are associated with functional changes in the aerobic capacity of children with CF. On the long-term, FFM may be important for maintaining functional exercise capacity. We speculate that regular exercise training and nutritional intervention might effectively improve long-term clinical outcome in patients with CF.
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