Physical Fitness and Quality of Life in Children with Cystic Fibrosis

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Physical Fitness and Quality of Life in Children with Cystic Fibrosis

Determinants and Training Effects

Proefschrift

met nederlandse samenvatting

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Petrus Hendrikus Cornelis Klijn

geboren op 29 april 1964 te Mijdrecht

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Proloog

'Hij twijfelde nog steeds over zijn beslissing.
Maar hij begreep wel één belangrijk iets: beslissingen zijn niet meer dan het begin.
Wanneer je er een neemt, duik je in feite in een machtige stroom, die je meevoert naar een plek waar je nog niet van gedroomd hebt op het moment van de beslissing.'

Paulo Coelho | De Alchemist | 1988

Voor Sanja, Anika en Milena

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Contents

General Introduction

Peter Klijn

Cystic Fibrosis

Incidence and mortality

Cystic fibrosis (CF) is the most common life-shortening genetic disease in the Caucasian population. It is inherited as an autosomal recessive disease. CF has an incidence of 1 in every 2500 Caucasians life births, 1 in 17000 blacks and 1 in 90000 Orientals [1].

The first accurate description of CF was published in 1938 when more than 80% of CF patients died within 1 year of birth [2]. Since then, our understanding of the basic pathophysiologal mechanisms and significant improvements in diagnosis and treatment have increased. These developments improved prognosis and median survival age from 18 yr. in 1976 to 29 yr. in the early 1990s [1]. Recent estimates have projected a median survival of 40 years for children born in 1990 who are receiving current standard therapy for CF [3,4]. With further progress, the outlook may even be more optimistic. Frederiksen and colleagues stated that the survival probability for a CF child born after 1989 to reach his or hers 45th birthday was 80.4% (95% confidence interval 76.5-84.6%) [5].

Pathogenesis and diagnosis.

A range of different mutations at the DNA level can cause CF. The most common CF gene mutation [ΔF508] is the absence of three sequential nucleotides

(one cytosine, two thymines), which leads to the deletion [Δ] of a phenylaline residue (F) at partition 508 on the cystic fibrosis transmenbrane conductance regulator (CFTR) [6]. CFTR is important in the flow of electrolytes and fluid across cellular membranes. The resultant of the basic defect is sweat that is high in sodium and chloride levels, and mucus that is abnormally thick and vicous [7]. In the lungs this leads to impaired mucocilliary clearance, infection with bacteria, and inflammatory response, and ultimately to fibrosis, and progressive lung destruction [8] (figure 1). Loss of functional lung tissue leads to respiratory compromise and is responsible for more than 90% of the morbidity and mortality in CF [9].

Mucus and inflammation in the pancreas and gastrointestinal tract result in insufficient secretion of digestive enzymes and malabsorption of nutrients [10]. Nutritional deficiencies lead to decreased fat stores and, as a result of protein malnutrition, may even lead to muscle wasting [11,12]. Pancreas insufficiency occurs in 90% of patients with CF [11,12].

Recent advances in CF genetics have major implications for earlier and more accurate diagnosis of the disease and for identification of CF gene carriers (genotyping). At present, CF is clinically diagnosed with the classic 'diagnostic triad': abnormal sweat chloride concentration (> 60mEq/L), chronic pulmonary disease, pancreatic insufficiency [1]. Pulmonary disease and/or pancreatic insufficiency may be clinically inapparent early in life.

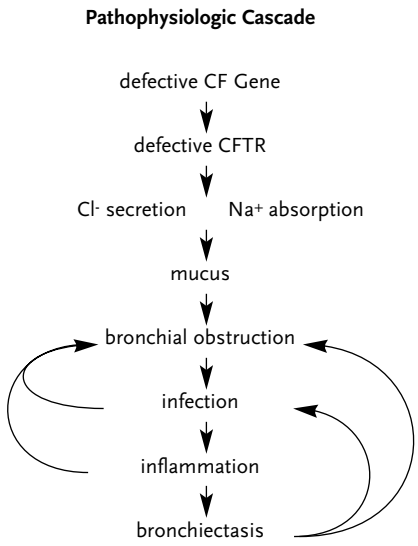

Figure 1
Pathophysiologic cascade for CF pulmonairy disease from Davis [1]

Patients with CF differ greatly in the expression of pulmonary symptoms, but the natural history of the disease shows progressive lung disease during life. In general, early impairment in lung function results primarily from obstruction and inflammation of the small airways by obstructive viscous secretions, leading to increased airway resistance and hyperinflation with increased residual volume (RV) [13,14]. These events are accompanied by a decrease in maximal midexpiratory flow ($FEF_{25-75\%}$), followed by reductions in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC). Progressive peripheral bronchial obstruction, leads to a mismatch of ventilation/perfusion, a decreased oxygenation, and an impaired gas exchange.

Current treatment strategies are generally aimed at control of pulmonary infection through antibiotic treatments, improvement of mucociliary clearance with chest physiotherapy and nebulisation, and improvement of nutritional status through hyperalimentation and enzyme replacement. In addition, physical activity is an essential element in the care for patients with CF and patients should be encouraged to exercise regularly.

Exercise and cystic fibrosis

The benefits of exercise in CF have been recognized as early as in1969 [15]. Survival and favorable prognosis in patients with CF have been associated with higher aerobic fitness and better nutritional status [16-18]. Important determinants of aerobic exercise performance are pulmonary function and nutritional status [12,13,19-22].

The majority of scientific research in patients with CF has focussed on aerobic exercise capacity. With aerobic training, skeletal muscle undergoes structural and biochemical changes, which permits a greater extraction and more efficient usage of oxygen delivered by the cardiorespiratory system. The ability to sustain exercise comfortably, or in other words exercise tolerance, is thought to influence the degree of daily activities and the feeling of well-being in everyday life [23-25].

The role of exercise training in the treatment of CF has received increasing attention over the past 15 to 20 years. Table 1 summarizes published exercise studies that included children with CF. All studies used an aerobic training program, while one study used resistance-training [26]. These studies will be briefly discussed with respect to pulmonary function, functional status and quality of life. However, a remark should be made on the methodological quality of some of these studies, since they did not use a control group [27-29] or randomized design [30-35]. Only three studies used a randomized controlled design [26,36,37].

Table 1 Training studies in children with cystic fibrosis

	Subjects		Exercise protocol		
Study	Exercise	Control	Frequency, time, intensity, lenght	Program	Results
Orenstein [33]	EX n=21 10-30 yrs	CN n=10 10-30 yrs	3 sessions|wk, 60min, 70-85% HR_{max}, 12 wks	walk-run | games	EX: VO_{2peak}↑, HR_{submax} ↑, FEV_1↔, RME↑ CN: FEV_1↓, other variables↔
Zach [29]	EX n=12 6-17 yrs 6f | 6m		5 sessions|wk, 17 days	swimming | jogging | hiking | games	FEV_1 FVC FEF_{25-75}↑, peak flow↑,
Blomquist [28]	EX n=14 13-23 yrs 8f | 6m		2 sessions|day, ≥75% HR_{max}, ≥15 min, 6 months	individual choice [e.g. jogging | dancing | gymnastics]	FEV_1 FVC↔, W_{max}↔
Edlund [31]	EX n=12 7-14 yrs 3f | 7m	CN n=11 7-14 yrs 5f | 5m	2 sessions|wk, 60 min, 60-85% HR_{max}, 12 wks	swimming	EX: FEV_1 FVC↔, VO_{2peak}↑, exercise time↑ CN: FEV_1 FVC↔, VO_{2peak}↑, exercise time↔
Andreasson [27]	EX n=7 6-20 yrs 3f | 4m		7 sessions|wk, ≥30 min, HR ≥160|min, 30 months	circle training | jogging | swimming | games	FEV_1↔, W_{max}↑
Stanghelle [34]	EG1 n=8 9-17 yrs, 6f | 7m EX2 n=10 10-21 yrs, 8f | 11m	19 CG 11-14 yrs [healthy]	7 sessions|wk, ≥30 min, 2 wks	gymnastics | outdoor activities | swimming | ball games	EX1: FEV_1 FVC↔, W_{max}↑ EX2: FEV_1 FVC↑, W_{max}↑ CN: NA
Stanghelle [35]	4 EX n=4 10-13.5 yrs 6f | 2m	4 CN n=4 10-13.5 yrs	3 times|day, 7 sessions|wk, 2-6 min, 70% HR_{max}, 8 wks	trampoline	EX: FVC↑, FEV_1↔, VO_{2peak}↑ CN: NA [cross over design]

Study	Exercise	Control	Frequency, time, intensity, lenght	Program	Results
Braggion [30]	EX n=10 11-15 yrs 3f | 7m	CN n=10 12-15 yrs 2f | 8m [healthy]	3 sessions|wk, 60 min, HR<150|min and HR 165-175|min, 8 wks	jogging | circuit training [e.g. sprint-run | motor skill games]	EX: FEV_1 FVC↔, VO_{2peak}↔, W_{max}↑ CN: FEV_1↔, FVC↓, VO_{2peak} W_{max}↔
Cerny [36]	EX n=9 15.4 ± 4.9 yrs	8CN 15.9 ± 4.9 yrs [bronchial drainage]	daily, 5-10 min to 15-20 min, 25-40% HRR to 45-65% HRR 13 days	cycle ergometer	EX: FEV_1 FVC↑, FEF_{25-75}↔, W_{max}↑ CN: FEV1 FVC FEF_{25-75}↑, W_{max}↑
Gulmans [32]	EX n=14 10-16 yrs 5f | 9m		5 sessions|wk, 20 min, 70% W_{max}, 6 months	cycle ergometer	FEV_1 FVC↔, VO_{2peak}↑, isometric muscle force↑, perceived competence↑
Schneiderman [37]	EX n=30 13.4 ± 3.9 yrs	CN n=35 13.3 ±3.6 yrs	3 sessions|wk, ≥20 min, HR 150|min, 3 years	favorite aerobic exercise	EX: FEV_1↔, FVC↓, VO_{2peak}↔, well-being↑ CN: FEV_1↔, FVC↓, VO_{2peak}↔
Selvadurai [26]	EX1 n=22 13.2 ± 2.0 yrs 13f | 9m [aerobic]	CN n=22 13.2 ± 2.0 yrs 13f | 9m	EX1:5 sessions|wk, 30 min, 70% HR_{max}, 18.6 ± 3.9 days	EX1: treadmill | cycle ergometer	EX1: FEV_1↑, FVC↔, VO_{2peak}↑, QOL↑, FFM↑, strength↔
	EX2 n=22 13.1 ± 2.1 yrs 12f | 10m [resistance]		EX2: 5 sessions|wk, 5 sets, 10 repetitions, 70% 1RM, 18.8 ± 4.1 days CN: 18.6 ± 3.8 days	EX2: resistance machine upper|lower limbs	EX2: FEV_1↑, FVC↔, VO_{2peak}↔, QOL↔, FFM↑, strength↑ CN: FEV_1↑, FVC↔, VO_{2peak}↔, QOL↔, FFM↑, strength↔

EX = exercise group; CN = control group; f = female; m = male; HR_{max} = maximum heart rate; HR = heart rate ; HRR = heart rate reserve; VO_{2peak} = peak oxygen uptake; HR_{submax} = submaximum heart rate; RME = respiratory muscle endurance; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; FEF_{25-75} = forced expiratory flow between 25 and 75% of expiratory vital capacity; Wmax = maximum work load; QOL = quality of life; FFM = fat-free mass; NA = not available; ↑ = improvement; ↔ = no change; ↓ = worsening

After aerobic training, a significant increase in exercise tolerance was found in several controlled [30-35] and randomized controlled [26] trials, whereas uncontrolled studies [27,28] did not find improvements in exercise capacity. Schneiderman-Walker and colleagues reported no aerobic training effect after a three-year unsupervised home exercise program [37]. This raises the question if unsupervised programs are effective in improving aerobic capacity.

The only published resistance-training study in children with CF, reported significant larger improvements in leg muscle-strength in the resistance-training group than either the aerobic training group or the control group [26].

With respect to pulmonary function, significant improvements were found in several short-term studies after aerobic training [27,29], while in other studies [30,31] these positive effects were not seen. Changes in pulmonary function were reported in two randomized controlled studies [26,37]. Schneiderman and coworkers reported a significant greater mean rate of annual decrease in FVC percentage predicted in the control group compared to the exercise group at three year follow-up [37]. The resistance-training group in a study by Selvadurai and colleagues showed greater mean increase in FEV_1 percentage predicted compared to the aerobic training group or the control group [26].

Improvement in quality of life after aerobic training, as measured with perceived competence scales or generic questionnaires, was reported in three studies [26,32,37]. Disease-specific questionnaires are thought to be more sensitive for specific problems associated with CF than generic questionnaires [38].

Measures of health-related quality of life (HRQL) are multidimensional constructs that include the core dimensions of physical, psychological, social and occupational functioning [38]. HRQL summarizes the subjective judgements patients make to describe their experiences of health and illness. Traditional clinical measures do not capture the impact of the disease on physical, social and psychological functioning [38-40]. Thus, HRQL measures can make a significant contribution to a comprehensive assessment of functioning in CF. In addition, HRQL measures are useful in detecting transient changes in health status or functioning due to an intervention (e.g. drug therapy, exercise training, psychosocial).

Therefor, a reliable and valid CF-specific health-related measure was developed: the Cystic Fibrosis Questionnaire (CFQ) [41,42]. However, a Dutch disease-specific questionnaire is not yet available. Cross-validation of the CFQ will be an important part of this thesis.

In summary, with short-term aerobic training children with CF are able to improve their aerobic fitness but not their pulmonary status. However, long-term participation in exercise programs seems important in slowing the decline in pulmonary function, which ultimately may improve prognosis. Moreover, resistance-training seems to be of clinical value next to aerobic training. Gulmans and colleagues showed that acceptability of single activity programs is very poor [32]. In order to increase long-term compliance to exercise, programs should consist of a variety of activities, which are enjoyable for the participants.

Simultaneously, exercise should be beneficial in terms of health status, functional status and quality of life, since it is included into the already demanding regimen of (daily) care of patients with CF.

In the next part, a framework will be presented to incorporate anaerobic activities in exercise programs for children with CF.

Concept of anaerobic training

Aerobic and anaerobic energy metabolism

During any muscular work, anaerobic and aerobic metabolism is inextricably linked [43]. The relative contribution of both systems depends on the preferential use of the systems (e.g. type of training). Within the first seconds of muscle contraction, the anaerobic alactic pathway provides a high level of mechanical output at a very fast rate through the split of creatine phosphate (PCr) and adenosine triphosphate (ATP) stored in the resting muscle cells [44]. The capacity of this pathway is limited in humans. It has been calculated that this energy reserve is almost totally depleted after about 25 seconds of maximal exercise [45,46]. The next pathway, the anaerobic glycolysis, generates lactate. Its maximal rate of energy supply is only about half that of the ATP-PCr pathway, but its capacity is twice as great [44]. The aerobic pathway demonstrates the slowest rate of energy supply, but its capacity is immense, allowing exercise for hours at submaximal levels.

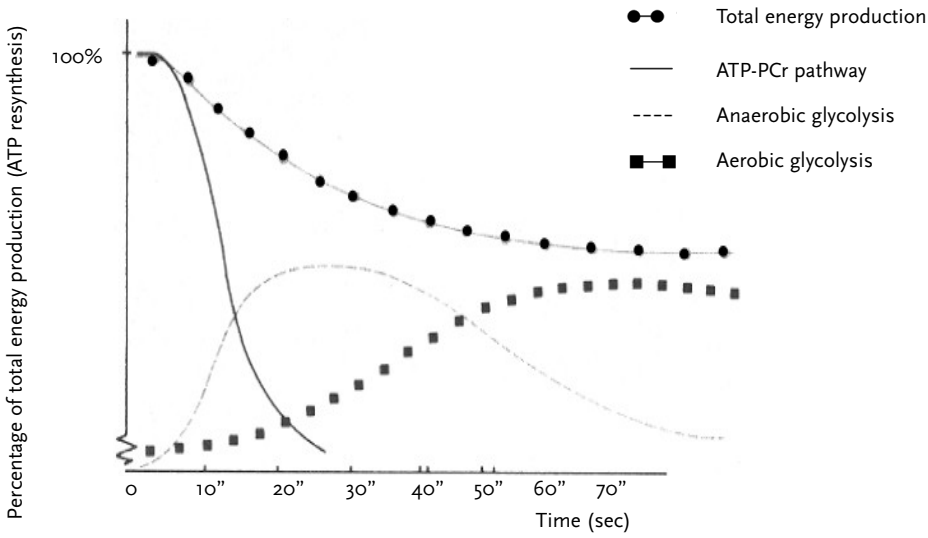

Figure 2
Total and relative energy production: Adenosine triphosphate (ATP) resynthesis (see text for explanation)

It is important to understand that all three pathways operate at the same time even in short-term exercise lasting for a few seconds. Moreover, energy pathways are not recruited in a mutually exclusive sequence, but a particular energy source may dominate during a certain phase without exclusion of the other energy pathways [44].

Characterization of pediatric physical activity

Assessment of physical activity has become increasingly important with the growing awareness of the association between physical activity, health, growth and development.

Many techniques to assess habitual physical activity have been developed and the advantages and disadvantages have been extensively reviewed [47,48]. Direct observational methods are especially useful in order to make an accurate characterization and quantification of energy expenditure. Bailey and coworkers used this method to capture the patterning of activities by frequency, duration and intensity [49]. They showed that the pattern of children's physical activity under free living conditions could be characterized as 'short bursts of vigorous physical activity interspersed with varying intervals of low and moderate intensity'. The median duration of low and medium intensity activities being 6 seconds, and of high intensity activities only 3 seconds with 95% lasting less than 15 seconds (figure 3). This implies that children's physical activity pattern is predominately anaerobic in nature.

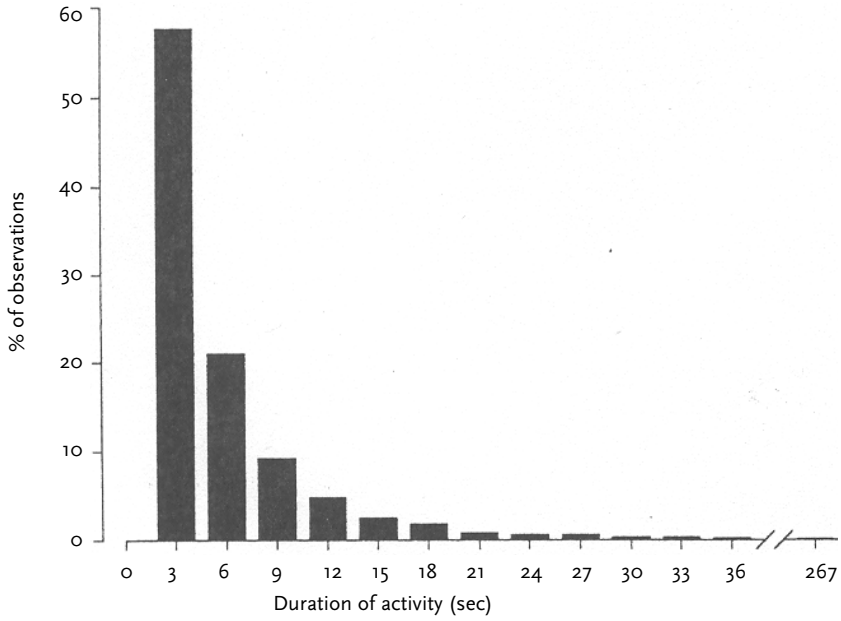

Figure 3
Characterization of physical activity in Children. From Bailey [49]

Habitual physical activity

Despite the proven benefits of aerobic exercise, the evidence of relating habitual physical activity to children's aerobic capacity is not strong [50]. The periods of habitual activity may not be sustained for periods of sufficient length associated with a cardiovascular training response [51]. In children with CF as well as in healthy children, levels of activity tend to decrease in the mid to late adolescence [52]. In addition, it has been shown that the amount of daily physical activity is clinically related to a diminished nutritional status in children with CF with significant airflow limitation [53].

Daily activities as well as sporting activities frequently require repeated bouts of intense anaerobic exercise – for example climbing a flight of stairs, short sprints to catch a bus, playing football or basketball, playing chase on the school play ground – rather than performance of sustained, aerobic efforts. In children with CF, less time spend in vigorous physical activities is associated with lower aerobic fitness, despite a good pulmonary function [54]. Data on the relationship between daily physical activity and anaerobic fitness in children are lacking.

CF and anaerobic exercise

In some pediatric diseases, anaerobic muscle power and muscle endurance is deficient. In CF, malnutrition may influence muscle performance and decrease anaerobic exercise capacity. However, data are limited regarding anaerobic performance in children with CF. Only four studies have compared anaerobic performance in children with CF with healthy children. In all studies anaerobic performance was related to some measure of nutritional status, percentage of ideal body weight [55], body mass index [11], lean body mass [56] and fat-free mass [57]. With respect to pulmonary function, only Cabrera and colleagues reported an association between anaerobic performance and increased severity of lung disease [55]. The other three studies concluded that anaerobic performance was not related to pulmonary function [11,56,57].

Boas and colleagues reported a marked increase in glycolytic energy contributions during an anaerobic exercise test in children with CF, which was related to reduced pulmonary function or aerobic capacity [57]. They suggested a compensatory increase in ATP-phosphocreatine or glycolytic pathways (in a disorder associated with chronic hypoxia). This was also suggested in a study in children with asthma [58]. Counil and colleagues observed an altered maximal anaerobic power in children with asthma, which might have originated from qualitative modifications in anaerobic metabolic pathways [58].

In summary, it would appear that the transitory nature of children's physical activity patterns might be well suited for a high intensity intermittent training program. Short, high intensive activities simulate conditions that replicate many daily activities as well as play and sport activities. Since children with

CF have lower anaerobic capacity and do not participate as much in high intensity activities as their healthy peers, anaerobic training may not only improve anaerobic exercise performance but also health-related quality of life. In addition, anaerobic training may support the proposed physiological adaptation process seen in CF due to chronic pulmonary disease.

Scope and outline of this thesis

Our primary aim was to develop an anaerobic training program for children with CF, and to investigate the effects of this program on several components of physical fitness, pulmonary function, nutritional status and health-related quality of life. Incorporating anaerobic activities in exercise programs contributes to greater variation of exercise and are thought to increase adherence and acceptability of exercise in treatment of CF.

As shown in the introduction, in cross-sectional studies aerobic capacity is related to the severity of pulmonary function and nutritional status. In chapter 2 the longitudinal relationship between aerobic performance, lung function and nutritional status in children with CF is described. Since little is known about the anaerobic performance in children with CF, chapter 3 describes the determinants of anaerobic exercise performance, with special reference to disease severity. Chapter 4 describes the process of validation of the Dutch version of the Cystic Fibrosis Questionnaire, for school age children (CFQ-C) and their parents (CFQ-P). In chapter 5 the validation of the Dutch version of the Cystic Fibrosis Questionnaire for adolescents and adults (CFQ-14+) is described. The effects of our anaerobic training program on aerobic and anaerobic exercise performance, pulmonary function, body composition, peripheral muscle strength and health-related quality of life (HRQL) of children with CF are provided in chapter 6. Chapter 7 contains a general discussion and suggestions for further research.

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Longitudinal Determinants of Peak Aerobic Performance in Children with Cystic Fibrosis

2

Chest: Accepted for publication

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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_{2peak}). 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 VO2peak in children with CF.

Design and methods: Fat-free mass (FFM), lung function and VO_{2peak} 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_{2peak} 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_{2peak} (240 ml, $p<0.001$), while a decrease was found for predicted values of FEV1 (–8.9%, $p<0.001$) and VO_{2peak} (–4.4%, $p<0.05$). Changes in VO_{2peak} (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_{2peak} over the two-year period.

Conclusions: Our results show that longitudinal changes in VO_{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 aero-bic 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 (FEV_1) 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/height^2 (kg/m^2). 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 (VO_2), carbon

dioxide production (VCO_2), ventilation (VE) and respiratory exchange ratio (RER). The highest VO_2 achieved during the last 30 seconds of exercise was taken as VO_{2peak} [17]. Heart rate was monitored by 3-lead electrocardiogram (Hewlett-Packard, Amstelveen, The Netherlands) and oxygen saturation (SpO_2) 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. VCO_2/VO_2) above 1.0 [5,10].

Predicted VO_{2peak} ($VO_{2peak\%}$) 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), FEV_1 ($dFEV_1$) and VO_{2peak} (dVO_{2peak}) were calculated between T1 and T2 (T12). Correlation analyses (Pearson's r) and stepwise linear regression were made for dFFM, $dFEV_1$ and dVO_{2peak} 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 VO_{2peak} 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

Subjects (n=65)	T1	T2
Age, yr	10.5 (2.9)	12.5 (2.9)
Body weight, kg	33.6 (11.3)	40.6 (12.7)
Height, cm	140.8 (17.0)	151.6 (16.4)
BMI, kg/m²	16.5 (2.0)	17.2 (2.5)
FFM, kg	27.6 (9.3)	33.6 (10.4)
FEV_1, ml	1828 (630)	2055 (713)
FEV_1, % pred	92.6 (20.5)	83.6 (21.5)
FVC, ml	2260 (732)	2694 (828)
FVC , % pred	94,8 (15,4)	92.3 (14.9)
VO_{2peak}, ml/min	1435 (475)	1678 (524)
VO_{2peak}, %pred	91.4 (21.7)	87.1 (20.3)

Values are mean ± SD. BMI = body mass index; FFM = fat free mass;
FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity;
VO_{2peak} = peak oxygen uptake.

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

	T12
FFM (kg)	6.1 (5.3 to 6.9) ‡
FEV_1 (ml)	229 (134 to 325) ‡
FEV_1, % pred	-8.9 (-12.8 to -4.8) ‡
VO_{2peak} (ml/min)	240 (162 to 318) ‡
VO_{2peak} % pred	-4.4 (-8.52 to -0.29) *

FFM = fat free mass; FEV_1 = forced expiratory volume in one second;
VO_{2peak} = peak oxygen uptake. * p<0.05; † p<0.01; ‡ p<0.001

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

	dFEV1	dVO2peak
dFFM	0.506‡	0.564‡
$dFEV_1$		0.619‡

dFFM = change in fat free mass; $dFEV_1$ = change in forced expiratory volume in one second;
dVO_2 = change in peak oxygen uptake. † p<0.01; ‡ p<0.001

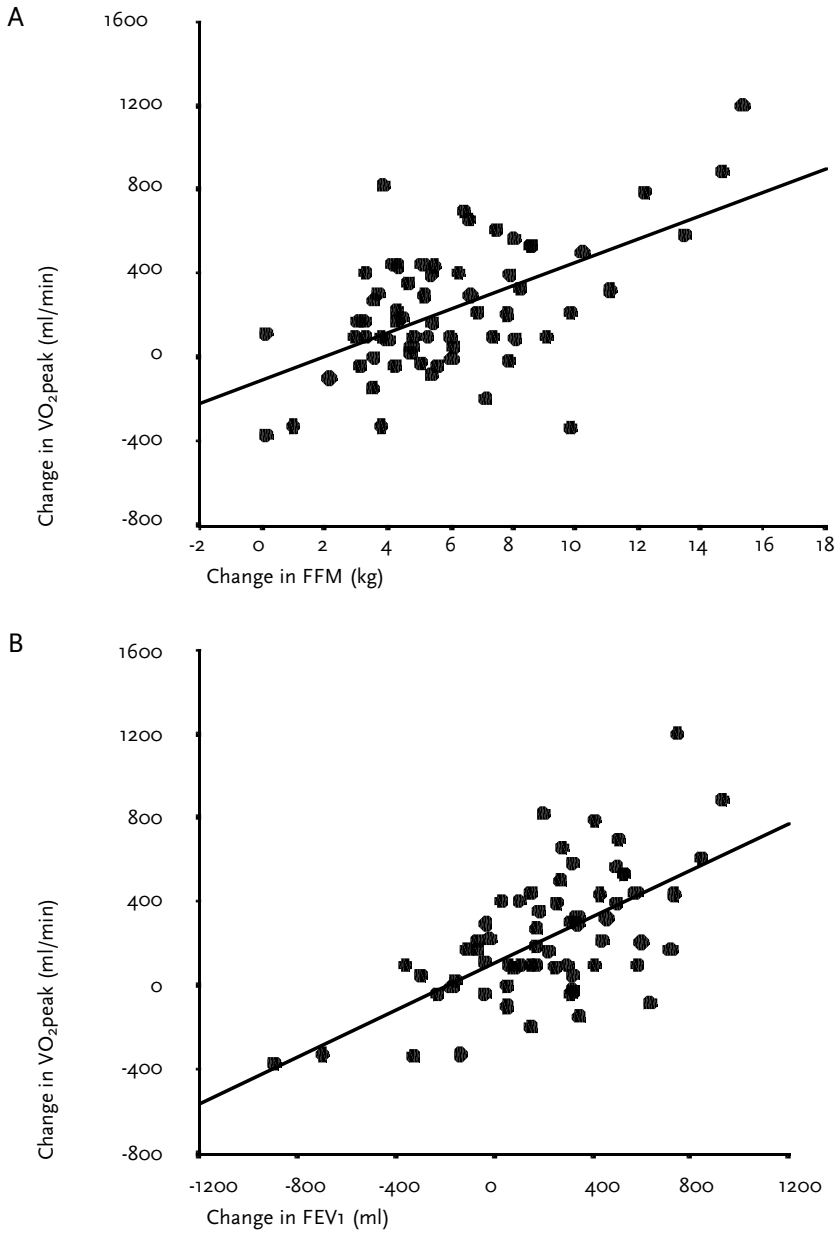

Figure 1
The individual change in peak oxygen uptake (VO_{2peak}) related to
A) the change in fat-free mass (FFM) [$r = 0.564$; $p < 0.001$] and B) the change in forced expiratory volume in one-second (FEV_1) [$r = 0.619$; $p < 0.001$] over a two-year period (T12).

Comparisons between T1 and T2 are presented in table 2. Absolute values of FFM, FEV_1 and VO_{2peak} increased during the two-year period. With respect to predicted values, FEV_1% and VO_{2peak}% 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 VO_{2peak} correlated best with changes in FEV_1 and to a lesser degree with changes in FFM. The relationship between these variables and dVO_{2peak} for T12 are demonstrated in figure 1.

Changes in FEV_1, FFM, height, weight and BMI were entered in a stepwise regression model, with dVO_{2peak} as the dependent variable. Analysis revealed that $dFEV_1$ ($p<0.001$) explained 38% of the variation in dVO_{2peak}. dFFM ($p<0.001$) was also included in the model, whereas changes in height, weight and BMI were excluded. Together $dFEV_1$ and dFFM accounted for 47% of the variability in dVO_{2peak} (regression equation: $dVO_{2peak} = -60.4 + 0.40 \cdot dFEV_1 + 33.40 \cdot dFFM$).

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 VO_{2peak}.

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 FEV_1 in adult patients with CF over a mean period of 6.3 years [13]. VO_{2peak} remained stable in this study and an association between lung function and aerobic capacity was not found. In our study, the increase in absolute VO_{2peak} was mainly related to an increase in FEV_1. Lung growth typically occurs in healthy subjects under the age of 20 years and may account for the increase in FEV_1 [25]. In young patients with CF the growth-related increase in absolute values of FEV_1 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 FEV_1 (% 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 VO_{2peak}. 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 FEV_1 and VO2peak in young children with CF, can only be judged when predicted normal values of FEV_1 and VO_{2peak} 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 ($r^2 = 0.25$) is in agreement with the cross-sectional relationship between lung function and nutritional status found for children ($r^2 = 0.06$ to 0.25) [34] and adults ($r^2 = 0.19$) [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, VO_{2peak} 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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Anaerobic Exercise in Pediatric Cystic Fibrosis

3

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Abstract

Anaerobic fitness is important for daily functioning of children with cystic fibrosis (CF). The aim of this study was to assess the determinants of anaerobic performance in CF. Anaerobic performance was measured in thirty-nine children with CF (mean age 13.2 ± 1.8 [SD] yr, FEV_1 81.6 ± 22.1% predicted) using a Wingate anaerobic Test. Significant associations were found for peak power (PP) and mean power (MP) with fat-free mass (FFM) body weight, body mass index, maximal isometric muscle force and aerobic capacity. Pulmonary function was correlated with anaerobic indices when controlled for FFM. Multiple regression analysis indicated that FFM and FEV_1 accounted for 82% and 86% of the variability in PP and MP, respectively. Patients with moderate CF (FEV_1 < 80 %), as compared to mild CF (FEV_1 ≥ 80 %), had higher PP (difference = 85 W [95% CI = 27 to 144 W] and MP (difference = 53 W [95% CI = 42 to 63 W]) at equivalent FFM. Our results indicate that FFM and pulmonary function are important determinants of anaerobic exercise performance in children with CF. With progression of pulmonary disease, anaerobic performance may be enhanced.

Introduction

Many studies have shown that aerobic fitness is important for well being and prognosis in patients with cystic fibrosis (CF)[1,1,2]. More recently, several authors have

addressed the important role of anaerobic fitness in daily functioning[3-5]. Many activities in daily life as well as sport activities have considerable anaerobic components [4,6]. Especially in children physical activity patterns are characterized by short intense activities which predominantly depend on anaerobic characteristics of the exercising muscle.[7] Several studies have shown reduced anaerobic performance in children and adolescents with CF[3-5,8-10] predominantly due to poor nutritional status.[3-5] In children with CF reduced pulmonary function may lead to hypoxic conditions in exercising muscles and to increase in muscle glycolytic metabolism during short-term exercise, both impairing muscle function [3]. Although poor muscle strength and airflow limitation are related to a decrease of aerobic fitness,[11] the direct effects of pulmonary function and muscle force on anaerobic performance are not clear yet.

With respect to the importance for daily functioning, we studied the determinants of anaerobic exercise performance in children with CF. Insight into these determinants might direct future intervention strategies for improvement of anaerobic performance and well being of these patients.

Methods

Subjects

Thirty-nine children with CF, who were able to perform the study protocol, were recruited from the CF-Center of the Wilhelmina Children's Hospital, University Medical Center Utrecht. Children aged 9-17 year with a stable clinical condition, no active musculo-skeletal disorders and a forced expiratory volume in 1 sec (FEV_1) > 30% predicted were included. Our institutional Ethics Committee approved the study protocol. Informed consent was obtained from each participant or from his or her parents.

Nutritional assessment

Anthropometric measurements were made prior to exercise testing. Body weight was measured using a platform beam balance (Mettler, Greifensee, Switzerland) with an accuracy of 0,02 kg. Height was measured with a stadiometer (Holtain, Crymich, UK) with an accuracy of 0,1 cm. Fat-free mass (FFM) was determined in fasting condition using bioelectrical impedance techniques [3,12]. Body mass index (BMI) was calculated (weight/height^2).

Peripheral muscle strength

Isometric muscle force measurements were performed for six muscle groups on the nondominant side of the patient, using a hand-held dynamometer (Penny and Giles, Christchurch, UK). Measurement of maximal voluntary force of the shoulder

abductors, elbow flexors, hip-extensors and knee extensors were made, as described by Bäckman [13]. Each muscle group was tested three times and the highest value obtained was reported.

Pulmonary function tests

Pulmonary function tests were performed after administration of 800 µg of salbutamol, in order to rule out important bronchial hyperreactivity. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were obtained from maximal expiratory flow-volume curves (Masterscreen; Jaeger, Wuerzburg, Germany). Residual volume (RV) and total lung capacity (TLC) were measured in a volume-constant body plethysmograph (Masterlab; Jaeger, Wuerzburg, Germany) and the RV/TLC ratios were calculated from the actual values. Valus are expressed as the percent of predicted values [14].

Exercise testing

Subsequent anaerobic and aerobic exercise tests were performed on an electronically braked cycle ergometer (Lode Examiner; Lode, Groningen, The Netherlands). The seat height was adjusted to the patient's leg length. Each subject performed a Wingate test (WanT) to assess anaerobic performance. The subjects rested for at least 45 minutes before aerobic fitness was assessed. During the tests heart rate was monitored continuously by 3-leads electrocardiogram (Hewlett-Packard, Amstelveen, The Netherlands) and oxygen saturation (SaO_2) by pulse oximetry (Nellcor 200 E, Breda, The Netherlands). All subjects were familiar with the test equipment. Verbal encouragement was given throughout the tests to stimulate maximal performance.

Anaerobic testing

The WanT consists of a 30-second all-out sprint on a cycle ergometer against a fixed resistance [15]. The WanT is a valid and reliable test to evaluate short-term anaerobic power in healty children, children with CF and other chronic illnesses [3,9,15-17]. The resistance was set relative to body weight, age and gender, according to the manufactures instructions (boys 9-14 yr: 0,55 · body weight, boys 15-19 yr: 0,7 · body weight, girls 9-14 yr: 0,53 · body weight, girls 15-19 yr: 0,67 · body weight). Before starting the WanT the subjects were allowed a 1-min warm-up at 60 rpm against a 15 W resistance. The subjects were instructed to start pedalling as fast as possible after the 1-min warm-up, while at the same time the full breaking force was applied through a integrated computer program (Wingate 3.1, Lode, Groningen, The Netherlands). Anaerobic performance indices were reported as peak power (PP; highest power during the test) and mean power (MP; power averaged over 30-sec).

Aerobic testing

Aerobic fitness was assessed by a standard progressive incremental exercise test. After assessment of baseline cardiorespiratory values during a 3-min rest period, the test started with pedalling at 60 rpm against a 15 W load. Thereafter, the workload was increased by the constant increment of 15 W at 1-min intervals. Subjects exercised to the limit of their tolerance. The maximal workload (W_{max}) was defined as the highest workload maintained during 30 seconds.

Continuous breath by breath respiratory gas analysis and volume measurements were performed with a triple V valveless mouthpiece and stored in a computerized exercise system (Oxycon Champion, Jaeger, Breda, The Netherlands). Internal gas and volume calibrations were performed before each measurement. Eight-breath averages of oxygen uptake (VO_2), ventilation (VE) and CO_2 exhalation (VCO_2) were measured during rest and exercise.

The average of measurements made for the last 30 seconds of exercise was taken as the individual's VO_{2peak}.

Efforts were considered to be at a maximum level if subjects showed clinical signs of intense effort and were unable to maintain speed above 50 rpm [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. VCO_2/VO_2) above 1.0 [19,20]. Predicted values of VO_{2peak} (VO_{2peak}%) were obtained from an age and gender matched Dutch reference population [21].

To allow ventilation at peak exercise (VE_{peak}) to be viewed in relation to ventilatory capacity, it was examined as a percentage of predicted maximum voluntary ventilation (VE_{peak}/MVV). MVV was estimated from the maximal expiratory flow-volume curves as 40 times FEV_1 [11].

Data analysis

All data were tested for normality with the Shapiro-Wilks test. Pearson correlation analyses and stepwise multiple regression analyses were performed for anaerobic indices with nutritional status, muscle force, aerobic indices and pulmonary function.

As the CF group represents subjects with a wide range of pulmonary function, subjects were also categorized according to the level of pulmonary impairment. Comparisons between subgroups were made with t tests for unrelated samples. Data were analyzed using the Statistical Package for the Social Science (SPSS, version 9.0, Chicago. IL, USA). Comparisons were made for between-group differences in slopes and intercepts between regression lines with appropriate analyses of covariance (ANCOVAS), according to the procedure outlined by Altman and Gardner[22]. Differences were considered significant if $p < 0.05$ (two-tailed). Data are presented as mean ± SD unless otherwise indicated.

Results

Subject characteristics are presented in table 1. Both exercise tests were well tolerated by all patients. Correlations of nutritional status, muscle force and aerobic exercise with anaerobic performance are presented in table 2. The best correlations were found between anaerobic performance and FFM, and to a lesser degree with other indices of nutritional status. Significant correlations were found for anaerobic performance with peripheral muscle force. Knee extensor force revealed the highest correlations with PP and MP. With respect to aerobic performance, PP and MP

Table 1 Patient characteristics

	Subjects (n=39)
Age (years)	13.2 ± 1.8
Length (cm)	155.9 ± 10.1
Weight (kg)	43.5 ± 9.8
BMI (kg/m2)	17.7 ± 2.3
FFM (kg)	31.0 ± 6.7
FEV_1 (mL/min)	2139 ± 654
FEV_1 (% predicted)	81.6 ± 22.1
FVC (mL/min)	2763 ± 707
VC (% predicted)	87.4 ± 16.8
RV/TLC (%)	34.0 ± 11.6

Data are means ± SD. BMI = body mass index; FFM = fat-free mass;
FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity;
VC = vital capacity; RV = residual volume; TLC = total lung capacity.

Table 2 Correlation analysis for anaerobic performance with nutritional status, muscle strength and aerobic performance

	PP	MP
FFM (kg)	0.893‡	0.914‡
BMI (kg/m2)	0.589‡	0.614‡
Body weight (kg)	0.880‡	0.870‡
Elbow flexors (N)	0.680‡	0.720‡
Shoulder abductors (N)	0.692‡	0.724‡
Hip extensors (N)	0.543‡	0.582‡
Knee extensors (N)	0.752‡	0.778‡
VO_{2peak} (mL/min)	0.761‡	0.756‡
W (W)	0.724‡	0.781‡

PP = peak power; MP = mean power; FFM = fat-free mass; BMI = body mass index;
VO_{2peak} = peak oxygen uptake; Wmax = maximum workload. ‡$p < 0.001$.

correlated significantly with VO2peak and Wmax. Pulmonary function was not correlated with anaerobic indices. When FFM was controlled for in the multiple regression analysis significant correlations were found for anaerobic performance with FEV_1 (PP: $r = -0.493$; $p < 0.01$ and MP: $r = -0.472$; $p < 0.01$). Multiple regression analysis revealed that FFM and FEV_1% accounted for 82% of the variability in PP and 86% of variability in MP (compared to 77% and 82%, respectively, for FFM alone). Body weight, BMI, muscle force and VO2peak were excluded from the regression model.

CF-subgroups

The patients were also subdivided based on the degree of airway obstruction: a mild group ($N = 20$, $FEV_1 \geq 80$ %) and a moderate group ($N = 19$, $FEV_1 < 80$ %) (table 3). No differences were found in age between both groups (mild: 12.8 ± 2.1, moderate: 13.5 ± 1.2). Subjects in the moderate group had significantly more airway obstruction (FEV_1: 99.2 ± 10.6% vs 62.9 ± 14.2%, $p<0.001$) and showed marked air trapping (RV/TLC: 25.9 ± 8.0 vs 42.5 ± 8.1, $p < 0.001$).

No significant differences were found for body weight (mild: 44.6 ± 11.6, moderate: 42.4 ± 7.5) and FFM (mild: 31.1 ± 6.7, moderate: 28.9 ± 6.9), but BMI was significantly lower in the moderate group (18.6 ± 2.8 vs 16.8 ± 1.3, $p<0.05$).

As shown in table 3, muscle force of the upper extremity muscle groups was significantly lower in the moderate group while no differences were found for the lower extremity muscle groups. Patients with mild or moderate lung dysfunction had no significant different PP, MP, VO_{2peak} and W_{max}, but significantly different VO2peak%. The moderate group used a significant larger part of their ventilatory reserve and showed lower oxygen saturation at peak aerobic exercise. Pulmonary limitation to aerobic exercise may involve an increase in $EqVO_{2peak}$ [4]. In our study the moderate group had higher EqVO2peak compared to the mild group, but the difference did not reach significance ($p = 0.10$).

Regression analyses of PP and MP (Y, given in W units) as a function of FFM (X, given in kg) are shown in figures 1 and 2, respectively. Significant differences in fitted PP and MP between the two CF subgroups were found (PP: difference in vertical distance = 85 W [95% CI = 27 to 144 W], MP: difference in vertical distance = 53 W [95% CI = 42 to 64 W]). When the slopes of the relationships for PP and for MP were compared, no differences were found.

Table 3 Physical performance compared between groups of patients with different pulmonary function

	Mild (n=20)	Moderate (n=19)
Elbow flexors (N)	177 ± 33	154 ± 33 *
Shoulder abductors (N)	144 ± 32	112 ± 30 †
Hip extensors (N)	238 ± 66	205 ± 57
Knee extensors (N)	221 ± 62	211 ± 56
PP (W)	548 ± 187	576 ± 217
MP (W)	309 ± 97	321 ± 112
VO2peak (mL/min)	1666 ± 365	1605 ± 474
VO2peak (% of predicted)	87.0 ± 14.7	73.7 ± 12.5‡
Wmax (W)	137 ± 31	129 ± 38
VCO_{2peak} (mL/min)	1905 ± 425	1734 ± 555
Eq VO_{2peak}	41.9 ± 6.2	38.3 ± 7.0
Eq VCO_{2peak}	36.5 ± 3.9	35.7 ± 6.2
VEpeak/MVV (%)	69.7 ± 10.2	88.3 ± 15.0 ‡
ΔSaO_2 (%)	-1.6 ± 1.5	-4.4 ± 3.1 †

Values are presented as mean ± SD. PP = peak power; MP = mean power; VO_{2peak} = peak oxygen uptake; Wmax = maximum workload; VCO_{2peak} = carbon dioxide production; Eq VO_{2peak} = ventilatory equivalent for oxygen; Eq VCO_{2peak} = ventilatory equivalent for carbon dioxide; VE_{peak}/MVV = peak ventilation as a percentage of predicted maximal voluntary ventilation; ΔSaO2 = percentage change in oxygen saturation;
* p < 0.05, † p<0.01, ‡p < 0.001.

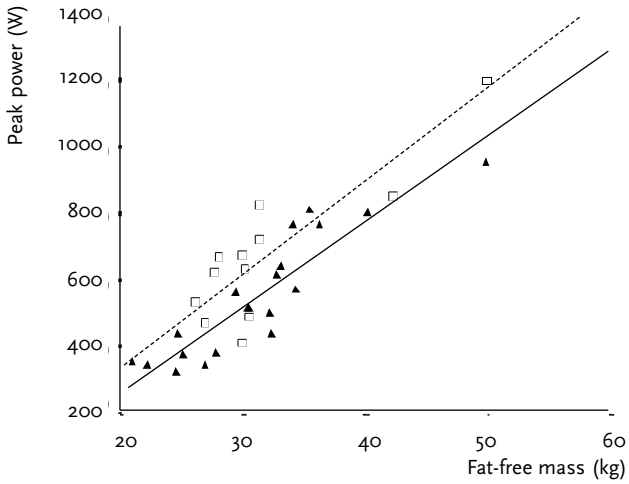

Figure 1
Fat-free mass and peak power in CF patients with FEV_1 < 80% (open squares; dashed line) and with FEV_1 ≥ 80% (closed triangles; solid line). Regression equations (X = FFM [kg]; Y = peak power [W]): FEV_1 < 80: Y = -242.7 + 28.4 · X (r = 0.90, p < 0.001); FEV1 ≥ 80: Y = -243.7 + 25.8 · X (r = 0.90, p < 0.001)

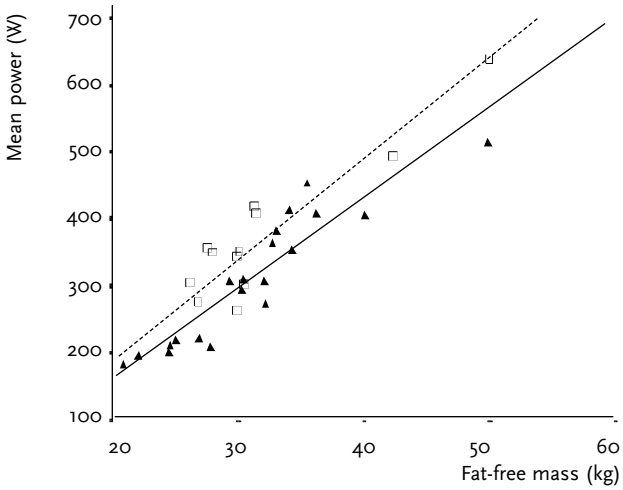

Figure 2

Fat-free mass and mean power in CF patients with $FEV_1 < 80\%$ (open squares; dashed line) and with $FEV_1 \geq 80\%$ (closed triangles; solid line). Regression equations (X = FFM [kg]; Y = mean power [W]): $FEV_1 < 80$: $Y = -120.4 + 15.3 \cdot X$ ($r = 0.94$, $p < 0.001$); $FEV_1 \geq 80$: $Y = -110.5 + 13.5 \cdot X$ ($r = 0.92$, $p < 0.001$).

Discussion

In recent years more research has focused on the physiological aspects of short-term maximal exercise in patients with CF [10,23,24]. We studied the direct effects of nutritional status, muscle force, aerobic capacity and pulmonary function on anaerobic performance in children and adolescents with CF. Our results indicate that FFM and pulmonary function are important determinants of anaerobic performance in CF patients. Patients with moderate pulmonary dysfunction showed a marked decrease in SaO_2 during aerobic exercise testing. However, our results also suggest that this patient group may have better anaerobic performance at equivalent FFM compared to patients with mild or normal pulmonary function.

We showed that 77 – 82% of the variance in anaerobic exercise was explained by FFM. This is consistent with the results of other studies in which FFM has been found to be the most important determinant of anaerobic exercise performance in patients with CF [3-5,25]. Although body weight and BMI were significantly correlated with PP and MP, they were not independent predictors of anaerobic performance. Since body weight of patients with CF consists of a higher proportion of FFM, due to fat depletion, correction for body weight is likely to overestimate the power output of CF patients [19]. These results are in agreement with data of Boas et al. who showed that differences in anaerobic performance

between children with CF and controls persisted after correction for FFM but not when corrected for body weight [5]. These results suggest that FFM should be used in favor of body weight or BMI to analyze anaerobic performance in relation to nutritional status.

Some remarks should be made on the use of bioelectrical impedance to assess FFM in patients with CF. Impedance is affected by the intra- and extracellular water distribution. Abnormal electrolyte transport in CF may potentially affect fluid and electrolyte distribution [26] and thereby affecting the bioelectrical impedance measurements. Despite the potential inaccuracies of using this method, several studies have shown that bioelectrical impedance techniques can be used in patients with CF by comparing this technique with other measures of body composition [12,27-31]. However, specific predictive equations for patients with CF will need to be developed.

A general reduction in skeletal muscle function is common in patients with CF [11,32,33]. Therefore, skeletal muscle dysfunction should also be considered when evaluating anaerobic exercise capacity in children with CF. To our knowledge, this is the first study to document the relationship between peripheral muscle force and anaerobic exercise. Our results demonstrate that not all muscle groups are equally important in evaluating anaerobic performance. Knee extensors are the most important muscle group during sprint work on a cycle ergometer. However, muscle force was not a determinant of anaerobic performance when we accounted for FFM. These findings are inconsistent with findings regarding aerobic performance. De Meer et al. found a reduced aerobic performance in children with CF, which was associated with a diminished peripheral muscle force, even in the absence of decreased FFM [11]. It is not clear whether strength training can improve anaerobic performance in children with CF. Selvadurai et al. reported an increase in leg strength after resistance training, but no significant change was found in VO_{2peak} [34]. Anaerobic performance however, was not assessed.

Patients with CF suffer from progressive airway obstruction and hyperinflation, resulting in limited maximal oxygen uptake and hypoxemia. Until now, the influence of pulmonary function on anaerobic performance has not been clearly established. We demonstrated that PP and MP at equivalent FFM was higher in a group of CF patients with moderate pulmonary dysfunction compared to a group with mild pulmonary dysfunction. In contrast, Cabrera et al. showed an association between a reduced anaerobic performance and worse pulmonary function. [9] Other studies did not find a relationship between pulmonary function and anaerobic indices [4,5,8]. Diversity in anaerobic exercise tests and subjects might account for these differences. However, Boas et al. and Cabrera et al. also used the WanT [5,9]. Cabrera et al. evaluated nutritional status based on body weight and percentage ideal body weight. As shown in the present study and the study of Boas et al. FFM instead of body weight should be used in order to normalize indices of anaerobic performance. True effects may be obscured by the use of body weight. Ideally, the resistance used for the WanT

should be based on FFM and not total body weight[15]. Boas et al. used FFM to account for differences in PP and MP but severity of pulmonary disease was not an independent determinant of anaerobic performance[5]. An explanation for these opposite results is not readily apparent. Differences in the composition of the CF-subgroups might be important. However, more research is needed in order to clarify the different findings.

The higher anaerobic power output per FFM in our subjects with worse pulmonary function was an interesting outcome. These findings suggest that during progression of disease there is a shift from aerobic to anaerobic metabolism possibly induced by recurrent hypoxemia. In most activities, energy for the exercising muscle is supplied by both anaerobic and aerobic metabolism[35]. The relative contribution of both systems depends on the preferential use of the systems (e.g. type of training). In children up to 40% of energy production in the WanT test comes from aerobic processes [36]. In our group of patients, $VO_{2peak\%}$ was lower in the moderate group while their anaerobic performance was higher compared to the mild group. This suggests a lower relative contribution of aerobic energy production during the WanT in the moderate group. In children with asthma it has been suggested that a reduced aerobic capacity might be compensated for by an increase in anaerobic performance [37]. Varray et al. suggested that due to earlier dependence on anaerobic metabolism during aerobic exercise, anaerobic capacity in children with asthma might be maintained or enhanced [37]. Similar findings have been described in children with CF with a reduced pulmonary function, in whom glycolytic metabolism was markedly increased during anaerobic exercise, which was related to reduced pulmonary function [3].

The better anaerobic performance in the patients with worse pulmonary function may originate from several factors. Type II fibers with an anaerobic metabolic profile have been shown to be positively correlated with anaerobic exercise performance [38] and greater proportions of type II fibers could help explain our results. In addition, a reduced metabolic efficiency has been reported in CF patients [39,40]. Clinical factors, such as genotype may influence maximal anaerobic power in children with CF as well. The results of Selvadurai et al. indicate that a relationship might exist between some measures of physical fitness (peak aerobic capacity and PP) and CF genotype [41]. 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 [42] and the amount of time spend in vigorous physical activities is associated with lower aerobic fitness [43]. However, it is not clear whether anaerobic performance is influenced by daily physical activity. Therefor, no clear inferences can be made on the cause of the differences seen in PP and MP between patients with different pulmonary dysfunction. Further studies in patients with different clinical conditions and in more homogenous age groups are needed to address the observation of increased anaerobic performance in relation to pulmonary function.

In conclusion, our study has shown that FFM and pulmonary function are important determinants of anaerobic exercise performance in children with CF. With progression of pulmonary disease, anaerobic performance may be enhanced in children with CF. The underlying mechanisms need to be clarified.

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Validation of the Dutch Pediatric Cystic Fibrosis Quality of Life Questionnaire

4

Disability and Rehabilitation:
Accepted for publication

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Abstract

The aim of this study was to validate the Dutch version of the Cystic Fibrosis Questionnaire, which measures health-related quality of life, in school age children (CFQ-C) and their parents (CFQ-P). The 35 item CFQ-C covers six domains and two symptom scales. The CFQ-P consists of 43 items covering seven domains, three symptom scales and one health perception scale.

Cross-sectional and test-retest designs were used to assess psychometric characteristics of the CFQ. Sixty-eight children with CF (11.3 ± 1.9 years) and their parents completed the questionnaires during a routine visit.

Internal consistency was acceptable for most domains of the CFQ-C (α=0.43-0.78) and the CFQ-P (α=0.47-0.93). Test-retest reliability was high for all domains: CFQ-C (0.76 – 0.96) and CFQ-P (0.74 – 0.98). Construct validity of both CFQ questionnaires was good, with moderate to strong correlations between physically oriented CFQ-domains and pulmonary function (rs=0.35-0.57), nutritional status (rs=0.46-0.51), inflammation (rs=0.40-0.53) and physical performance (rs=0.36-0.61). Both measures were able to differentiate between two levels of disease severity. The convergence between the CFQ-C and the CFQ-P was confirmed by strong correlations on observable domains (rs=0.50-0.60).

The CFQ questionnaires are reliable and valid measures of health-related quality of life for use in children with CF and their parents.

Introduction

Cystic fibrosis (CF) is a progressive disease, which eventually leads to reduction in exercise capacity due to impaired pulmonary function and diminished nutritional status. Physical limitations and disruptions of daily life activities have serious implications for the social and psychological well being of children [1]. It is important to monitor the impact of disease progression and to assess the effect of interventions on the health-related quality of life (HRQL) of children with CF. Traditional clinical measures like pulmonary function and nutritional status are important, but they do not capture the impact of the disease on physical, social and psychological functioning [2-4]. As in other chronic pulmonary diseases, somatic factors such as pulmonary function are poor predictors of the degree of disability [5-7].

Studies on HRQL in children with CF have used generic questionnaires [8]. Generic health measures allow for comparisons between a variety of diseases, but are not sensitive to the specific problems associated with CF [2] and they may not be sufficiently responsive to the effects of clinical interventions [4]. Recently a CF-specific health-related measure was developed and validated in France, the Cystic Fibrosis Questionnaire (CFQ) [9], with a linguistically valid translation of the measure completed in the United States [2]. In addition, the CFQ has been validated in Germany [10] and is presently being validated in Spain. The CFQ consists of three quality of life measures: a teen/adult version (14 years of age or older), a child version (6-13 years of age) and a parent version (used in conjunction with the child version). The CFQ takes into account the different developmental stages and makes it possible to monitor the health status and quality of life of patients with CF from the age of 6 years throughout adulthood [2,11].

Cross-cultural validation of an existing measure has the advantage of avoiding the initial stages of development of a new questionnaire, which is a long process [12,13]. In addition, translation into different languages makes it possible to use the CFQ questionnaires in comparative international multi-center studies [10].

The aim of the present study was: 1) to develop a conceptually equivalent Dutch version of the CFQ for school-age children 6 to 13 years, and for parents of school-age children; 2) to evaluate the following characteristics: homogeneity, reproducibility (10-14 days test-retest reliability), construct, discriminative and convergent validity. The Dutch CFQ for teens and adults is presently being validated.

Methods

Patients and procedure

Sixty-eight patients were recruited from the CF-Center of the Wilhelmina Children's Hospital, University Medical Center Utrecht. Patients and their parents

were approached during routine visits and asked for consent to complete the CFQ. Patients and parents who had problems understanding the Dutch language were excluded from the study. In a subset of parents and clinically stable patients the questionnaire was administered twice within 10-14 days. The study was approved by the appropriate Ethics Committee.

Translation

Backward and forward translations were made. The American version of the child and parent CFQ developed by Quitener and colleagues was translated into Dutch and translated back in English by a second independent translator [14,15]. The original American questionnaires for children and parents were compared to their respective back translated versions. Apart from checking how literal the back translated versions were in comparison to the original versions, discussions were held to resolve semantic and conceptual discrepancies, in collaboration with the developers of the original American questionnaires.

Cystic Fibrosis Questionnaire

The CFQ child version (CFQ-C) consists of 35 items divided into six domains: physical functioning (six items), emotional state (nine), social limitations (six), body image (three), eating disturbances (three) and treatment constraints (three). Two symptom scales are included: respiratory (four) and digestive (one). Seven-teen items require a frequency response, ranging from "all the time" to "never" on a 4-point scale, and eighteen items require a true-false rating on a 4-point scale. For children between 6-11 years, the questionnaire was administered by the researcher; children who were 12-13 years old completed the questionnaire themselves. Parents were not present when the CFQ was filled out. Completing the questionnaire took approximately 10-15 minutes.

Parents' report of their child's disease-specific quality of life was measured using the CFQ parent version (CFQ-P). The CFQ-P consists of 43 items which measure physical functioning (9 items), vitality (5), emotional state (5), body image (3), performance at school (3), eating disturbances (2) and treatment constraints (3). Three symptom scales, weight (1), respiratory (6) and digestive (3), and a health perception scale (3) are included. Items require either a frequency response on a 4-point scale ("all the time" to "never"), a difficulty rating on a 4-point scale ("a lot of difficulty" to "no difficulty"), a true-false rating on a 4-point scale, or the selection of a statement that describes the child (on a 4- or 5-point scale) [2]. Parents completed the questionnaire without the child being present. Completing the questionnaire took approximately 10-15 minutes.

Scores are standardized by adding the ratings of all items within a domain to facilitate comparison of scores across domains. The scores range from 0 to 100 with higher scores corresponding to higher quality of life. Scores

for each domain are calculated if at least two-thirds of the items are completed. There is no total score.

Appendix A and B outline the distribution of the questions by domain for CFQ-C and CFQ-P, respectively.

Homogeneity

Internal consistency of each domain was assessed using Cronbach alpha coefficients. Generally the internal consistency is considered acceptable with a Cronbach alpha coefficient of 0.7 or above [16]. However, slightly lower coefficients (0.6 or higher) are acceptable for newly developed scales [17]. Furthermore, item to domain correlations were calculated. Psychometric guidelines suggest that item to domain correlations should be 0.40 or greater [17].

Reproducibility

Test-retest reliability measures the stability of the scores on the CFQ questionnaires over time. Eighteen patients with a stable clinical condition and their parents completed the CFQ 10-14 days apart. The questionnaire was mailed home and patients and parents were asked to complete the questionnaire independently. Children 6 to 11 years were interviewed by telephone and parents were requested to leave the room.

Construct, discriminative and convergent validity

Construct validity was calculated by correlating CFQ scores with nutritional status, pulmonary functioning, inflammation rate (the level of serum immunoglobolin G (Ig-G)) and physical performance. Furthermore, we investigated if other factors, related to the treatment and managing of CF (tube feeding and aerosol therapy), were associated with HRQL.

To assess whether the measure could discriminate between patients with varying degrees of disease severity, patients were categorized according to the level of pulmonary impairment: mildly impaired group (FEV1 $\geq$ 80%pred) and moderately impaired group (FEV1 < 80%pred) [18,19]. Since there was a limited range of illness severity in our study group, a severely impaired subgroup could not be included.

In addition, comparisons were made between younger (6-9 years) and older (10-13 years) and between boys and girls. Convergent validity was obtained by calculating correlation coefficients between CFQ scores for parent and child dyads.

Nutritional assessment

Body weight was measured using a platform beam balance (Mettler, Greifensee, Switzerland) with an accuracy of 0,02 kg. Height was measured with a

stadiometer (Holtain,Crymich, UK) with an accuracy of 0,1 cm. Body mass index (BMI) was determined (weight.height^{-2}). Standard deviation scores (z-scores, expressed in sd units) were calculated for height, body weight and BMI from a Dutch reference population [20].

Pulmonary function and inflammation

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) were obtained from maximal expiratory flow-volume curves (Masterscreen; Jaeger, Wuerzburg, Germany). Residual volume (RV) and total lung capacity (TLC) were measured in a constant-volume body plethysmograph (Masterlab; Jaeger, Wuerzburg, Germany) and the RV/TLC ratios were calculated from the actual values. Values are expressed as the percent of predicted values [21].

Serum immunoglobulin-G (IgG) was determined by enzyme-linked immunosorbent assay (ELISA). IgG levels were used as an indicator of the severity of chronic lung infection and inflammation [22].

Physical performance

The standard exercise protocol for annual check-up measurements was used. Until the age of 12 years, children perform a treadmill test according to the Bruce protocol [23]. Children aged 12 years and older used an electronically braked cycle ergometer (Lode Examiner; Lode, Groningen, The Netherlands). Workload was increased by 15 W at 1-min intervals.

The highest VO_2 achieved during the last 30 seconds of exercise was taken as VO_{2peak} [24]. Predicted VO2peak (VO_{2peak} %) values were obtained from an age and gender matched Dutch reference population in which the same modes of exercise were used [25].

Isometric muscle force measurements were performed for four muscle groups (shoulder abductors, elbow flexors, hip-extensors and knee extensors) as previously described [26]. Results for peripheral muscle force are presented as total maximal muscle force (i.e. summed maximal force in four muscle groups, since factor analyses showed a single-factor solution [Eigenvalue = 3.2; 81% of total variance]).

Data analysis

The Statistical Package for the Social Sciences (SPSS for Windows version 10.1) was used for data management and analyses. The internal consistency reliability was evaluated using Cronbach's α. Spearman (rs) correlation coefficients were used to describe relationships between outcome measures. Strength of the correlations was interpreted using criteria described by Guyatt and colleagues: less than 0.2 as very weak, from 0.2 to 0.35 as weak, from 0.35 to 0.5 as moderate,

and 0.5 or greater as strong [27]. Intraclass correlation coefficients were used to estimate the reproducibility (test-retest reliability) [28]. Domain comparisons between groups (disease severity, treatment issues, gender, age) were calculated using t tests for unrelated samples. Differences were considered significant if $p < 0.05$ (two-tailed). Data are presented as mean ± SD unless otherwise indicated.

Results

The majority of patients had mild pulmonary disaese and compared to age- and gender-corrected values, had lower height, weight and BMI scores (table 1). Most of the parents who completed the questionnaire were mothers (69%). Table 2 shows mean (sd) values of the different domains. The lowest score on the CFQ-Child version (CFQ-C) was found for Eating Disturbances while on the CFQ-Parent version (CFQ-P) Health Perceptions, Body Image and Vitality showed the lowest scores.

Internal consistency

Internal consistency coefficients (Cronbach alpha) for the domains of the CFQ-C and CFQ-P are shown in table 2. Most domains in both questionnaires had acceptable Cronbach alpha coefficients (0.60 or above). The exceptions to this were Emotional and Social Functioning in the CFQ-C, and School Performance in the CFQ-P. Overall, items in the CFQ-C and CFQ-P loaded conceptually on their respective domains, with the majority of the loadings above 0.40. However, in CFQ-C one item in the social functioning domain ("you felt comfortable sleep-

Table 1 Patient characteristics

	Subjects (n=68)
Age year	11.3 ± 1.9
height cm / SDSheight	144.9 ± 11.9 / -0.78 ± 0.91
weight kg / SDSweight	35.8 ± 9.5 / -0.58 ± 1.17
BMI kg•m2 / SDSBMI	16.7 ± 2.1 / -0.21 ± 1.12
FEV1 % pred	87.8 ± 20.8
FVC % pred	92.6 ± 16.9
RV/TLC %	32.8 ± 10.1
VO_{2peak} % pred	85.6 ± 20.8
Total muscle force N	626.5 ± 174

Data are means ± SD. SDS: standard deviation score; BMI: body mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; $VO_{2peak:}$ peak oxygen uptake.

Table 2 CFQ scores and Cronbach alpha for each domain on the CFQ-C and the CFQ-P

	CFQ-C		CFQ-P	
	CFQ score	alpha coefficient	CFQ score	alpha coefficient
Physical Functioning	73.9 ± 23.2	0.78	82.4 ± 21.7	0.93
Emotional Functioning	81.1 ± 9.9	0.52	80.2 ± 17.7	0.80
Vitality	-	-	69.3 ± 12.5	0.65
Eating Disturbances	69.4 ± 23.1	0.60	74.4 ± 30.3	0.84
Body Image	84.4 ± 19.7	0.63	69.2 ± 25.6	0.64
Health Perception	-	-	67.2 ± 24.5	0.72
Social Functioning	81.1 ± 14.0	0.29	-	-
Weight	-	-	76.1 ± 33.7	#
School Performance	-	-	76.2 ± 22.2	0.47
Treatment Burden	84.0 ± 15.8	0.68	73.8 ± 18.3	0.70
Respiratory Symptoms	77.1 ± 13.7	0.61	82.4 ± 16.5	0.80
Digestion	77.5 ± 21.1	#	71.5 ± 15.9	0.61

is single item scale

ing away from home") was allocated to the emotional state domain since the item domain correlation was far higher for the Emotional Functioning domain (0.62 vs 0.26). The allocation of the item was considered justified, based on the fact that Cronbach alpha of the Emotional Functioning domain increased from 0.52 to 0.70 after re-allocation. The Cronbach alpha for the Social Functioning domain was only raised to 0.43.

Reproducibility

Eighteen patients (11.3 ± 2.4 years) and their parents (40.5 ± 4.3 years) participated in the test-retest reliability phase. The intraclass correlation coefficients were high for all domains, ranging from 0.76 to 0.96 for the CFQ-C and from 0.74 to 0.98 for the CFQ-P.

Construct, discriminative and convergent validity

Moderate correlations were found between CFQ-C scores and pulmonary function, inflammation (IgG), nutritional status or physical performance (table 3). With respect to CFQ-P scores, the relationships with pulmonary function, inflammation, nutritional status or physical performance were moderate to strong (table 4). The results indicate that children with worse pulmonary functioning, higher levels of inflammation, lower nutritional status, aerobic capacity or muscle force, report poorer quality of life on several domains. In addition,

patients who used tube feeding (yes: n=14; FEV_1 71.6%, SDSBMI –1.0; no: n=54, FEV_1 90.9 %, SDSBMI –0.1) or aerosol therapy (yes: n=38, FEV_1 82.3%; no: n=30, FEV_1 94.9%) reported lower quality of life scores (table 3); their parents also reported lower quality of life scores on several domains (table 4).

To assess whether the measure could differentiate between patients with varying degrees of disease severity, patients were categorized according to the level of pulmonary impairment. Two groups were formed: a mildly impaired (N=43, FEV1 99.0 ± 12.2%) and moderately impaired group (N=25, FEV_1 65.1 ± 15.4%). The moderate group had significantly lower scores on the Treatment Burden domain (77.8 ± 11.1 vs 88.1 ± 15.8, p<0.01) and tended to be lower on the Physical Function (66.1 ± 28.4 vs 77.9 ± 20.0, p=0.06) and Body Image domains (80.0 ± 24.2 vs 89.9 ± 16.4, p=0.06). The CFQ-P scores for the patients with moderate pulmonary impaiment were significantly lower for Physical Functioning (71.6 ± 29.1 vs 86.6 ± 16.5, p<0.05), Vitality (64.0 ± 13.9 vs 71.6 ± 11.8, p<0.05), Body Image (55.0 ± 27.6 vs 74.9 ± 21.8, p<0.01) and Treatment Burden (64.4 ± 19.6 vs 77.5 ± 16.5, p<0.01).

Comparisons between younger (6 to 9 year) and older children (10 to13 year), and between boys and girls revealed no differences in CFQ domain scores on the child and parent versions.

Paired correlations were obtained on the CFQ-C and CFQ-P scores. Strongest convergence was found for Physical Functioning (rs=0.60, p<0.001), Body Image (rs=0.55, p<0.001) and Eating Disturbances (rs=0.50, p<0.001). Moderate correlations were found for Respiratory Symptoms (rs=0.49, p<0.001) and Emotional Functioning (rs =0.40, 0.01) and weak correlations for Digestion (rs=0.32, p<0.05) and Treatment Burden (rs=0.29, p<0.05).

Table 3 Correlation between CFQ Child scores and respiratory, nutritional or physical variables.*

	PF	ED	BI	TB	RS
FEV_1 %pred	0.42	-	0.41	0.34	0.35
FVC % pred	0.53	-	0.44	0.40	-
RVTLC %	-0.34	-0.34	-0.47	-	-0.43
Aerosol therapy	-0.31	-	-	-0.33	-
IgG	-0.45	-	-0.53	-	-
SDSBMI	-	-	0.46	-	-
Tube feeding	-0.32	-	-0.40	-	-
VO_{2peak} %pred	0.42	-	0.54	-	-
Muscle force N	0.37	-	0.45	-	-

* Only the correlations with $p < 0.01$ and $r > 0.3$ are reported. PF: Physical Functioning; ED: Eating Disturbances; BI: body image; TB: Treatment Burden; RC: Respiratory Symptoms; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; IgG: imunoglobulin G; SDS: standard deviation score; VO_{2peak}: peak oxygen uptake.

Table 4 Correlation between CFQ Parent scores and respiratory, nutritional or physical variables.*

	PF	ED	BI	HP	TB	W	RS
FEV_1 %pred	0.57	-	0.47	0.37	0.45	0.32	0.41
FVC % pred	0.57	0.35	-	-	0.49	0.39	0.40
RVTLC %	-0.49	-0.39	-0.47	-	-0.51	-0.34	-0.47
Aerosol therapy	-0.31	-	-	-	-0.34	-	-
IgG	-0.41	-	-0.40	-	-	-	-
SDSBMI	-	-	0.51	-		0.53	-
Tube feeding	-0.44	-	-0.33	-0.33	-	-0.50	-
VO_{2peak} %pred	0.55	0.36	0.61	-	0.45	0.44	0.38
Muscle force N	-	-	-	-	0.37	-	-

* Only the correlations with $p < 0.01$ and $r > 0.3$ are reported. PF: Physical Functioning; ED: Eating Disturbances; BI: Body Image; HP: Health Perception; TB: Treatment Burden; W: Weight; RS: Respiratory Symptoms; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; IgG: imunoglobulin G; SDS: standard deviation score; VO_{2peak}: peak oxygen uptake.

Discussion

This study showed that the Dutch versions of the CFQ-C and CFQ-P are reliable and valid disease-specific measures of HRQL for children with CF and their parents. The internal consistency was acceptable for most domains of both CFQ-C and CFQ-P, while the test-retest reliability was high. Several aspects of validity were assessed. The construct validity with clinically relevant parameters was good. Furthermore, the CFQ was able to discriminate between levels of severity. The association between patients' and parents' reports on observable domains was high.

The internal consistency estimates of the CFQ-C and CFQ-P were adequate, exceeding Ware's criteria for newly developed scales [17]. Overall, the parent version showed higher internal reliability than the child version. Three domains evidenced a low Cronbach alpha coefficient [17]. However, Emotional Functioning (CFQ-C) improved to an acceptable level (0.7) after re-allocation of one item from the Social Functioning domain. The Social Functioning domain in the CFQ-C improved as well but remained low. An explanation for this low alpha value is not readily apparent. The item to domain correlations in the Social Functioning domain were all equal to or above 0.40 and the items had no concurrent domains. Possibly, items in this domain (e.g. "you stayed at home more than you wanted to") are more associated with a social preference (e.g. playing computer games) rather than a consequence of having CF [2]. In addition, it is not yet clear whether HRQL questionnaires and response scales measure the same concepts in different cultures [12]. Based on these analyses, minor revisions should be made to capture specific patient problems in the Social

Functioning domain. Recently Gee and colleagues developed and validated a disease-specific quality of life measure for adolescents and adults with CF, which showed better psychometric properties than the CFQ [29]. However, the advantage of the CFQ is that it takes into account the different development stages and makes it possible to monitor the health status and quality of life of CF patients from the age of 6 years throughout adulthood [2,11].

School Performance in the CFQ-P showed low internal consistency. This may be explained by the large number of missing items in this domain (25%), causing a statistical power problem. In other domains, the number of missing items was negligible (results not shown). This finding suggests that parents are not sufficiently informed about the functioning of their children at school. More research is needed to confirm this clinically relevant assumption.

The analysis of test-retest reliability showed high intraclass correlations, indicating that the assessment of HRQL using the CFQs is stable over a 10 to 14 day period. This length of time was chosen to preclude participants from remembering their prior responses, but short enough to prevent deterioration in disease status [29].

Confirmation of the construct validity of the CFQ depends on significant associations between CF-specific characteristics and relevant domains [30]. CF is characterized by deterioration of nutritional status and irreversible loss of lung function, both of which impair functional performance. In addition, inflammation has been associated with the systemic effect of CF, possibly leading to changes in body composition (i.e. muscle wasting) [31]. The association between CFQ scores on child and parent version and the clinical variables used for construct validity, showed moderate to strong correlations. The discriminative value of the CFQ questionnaires offered further evidence of validity. Although our study group consisted of patients with a relatively low levels of pulmonary dysfunction, both questionnaires differentiated between two levels of disease severity, as measured by FEV1. Furthermore, specific treatment regimes like tube feeding or the use of aerosol therapy affected quality of life on several domains.

No differences were found between younger and older children. Since illness severity is related to older age (adolescents, adults) differences between children in our age group were not expected. Gender differences were also not statistically significant. Gender or age differences on certain domains (e.g. Body Image) may become apparent when children reach puberty.

The CFQ showed strong associations between parent and patient reports on observable domains (Physical Functioning, Body Image and Eating Disturbances), confirming the convergent validity of the measure. The weak to moderate correlations found for other domains are probably caused by the fact that these domains are less observable. Parents are less aware of social behavior of their children, have a limited understanding of children's internal state [32], and children are reluctant to inform their parents about digestive difficulties. In addition, parents may rate their children's HRQL based on their own concerns about the disease. It is important to note that not only is convergence

between parents and children important, but parent's HRQL scores may provide complementary information about how the child and family is functioning. Differences in scores might alert the health care team to potential problems in either child or parent's ability to cope with various aspects of the illness which might be clinically detrimental [33].

Some issues of the present study need further comment. Although the construct validity of the CFQ with clinical variables is good, assessment of its relation with generic health status and psychological wellbeing should be done. Data are needed on the responsiveness of the CFQ, which measures whether a questionnaire is able to detect changes brought about by an intervention. However, a prerequisite of sensitivity testing is establishment of the test-retest reliability of the measure, which in this study, appears to be very good. Additional testing of the discriminant validity of the CFQ-C and CFQ-P is needed in order to evaluate the CFQ's performance in the full range of illness severity of young patients with CF.

In summary, the Cystic Fibrosis Questionnaire is a reliable and valid measure of health-related quality of life for school-aged children with CF and their parents. The CFQ questionnaires (child and parent forms) are valuable instruments for measuring the multidimensional impact of the disease in clinical practice. Cross-cultural comparisons are possible for all domains with the exception of social functioning in CFQ child version. A study is presently underway to improve the consistency of this domain.

Appendix A CFQ child version

Domain	Question	Content of questions
Physical	1	Able to walk as fast as others
	2	Able to climb stairs as fast as others
	3	Able to run, jump, and climb as you wanted
	4	Able to run as quickly and as long as others
	5	Able to participate in all the sports that you enjoy
	6	Difficulty carrying or lifting heavy things such as books
Emotional state	7	Had trouble listening in the class
	8	Felt tired
	9	Felt mad
	10	Felt grouchy
	11	Felt worried
	12	Felt sad
	13	Had trouble falling asleep
	14	Had bad dreams or nightmares
	15	Felt good about yourself
Social	21	Got together with friends
	22	Stayed at home more than you wanted
	23	Felt comfortable sleeping away from home...
	24	Felt left out
	25	Often invited friends to your house
	26	Were teased by other children
Body image	27	Think you are too short
	28	Think you are too thin
	29	Think you are physically different from others your age
Eating	16	Trouble eating
	18	Pushed to eat
	20	Enjoyed eating
Treatment burden	17	Had to stop playing because of your treatments
	19	Were able to do all of your treatments
	30	Doing your treatments bothers you
Respiratory	31	Coughing during the day
	32	Woke up during the night because of coughing
	33	Cough up mucus
	34	Trouble breathing
Digestion	35	Stomach hurt

Appendix B CFQ parent version

Domain	Question	Content of questions
Physical	1	Difficulty performing vigorous activities such as running
	2	Difficulty walking as fast as others
	3	Difficulty climbing stairs as fast as others
	4	Difficulty carrying or lifting heavy objects
	5	Difficulty climbing several flights of stairs
	13	Difficulty walking a long time
	14	Child absent or late for school
	15	Participation in sports at school
	16	Child has trouble recovering after physical effort
Vitality	8	Seemed tired
	9	Seemed short-tempered
	10	Seemed well
	11	Seemed grouchy
	12	Seemed energetic
Emotional state	6	Seemed happy
	7	Seemed worried
	23	Child tends to be withdrawn
	25	Child has less fun than usual
	26	Child has trouble getting along with others
Body image	19	Child feels small compared to other kids the same age
	20	Child feels physically different from other children the same age
	21	Child thinks he/she is too thin
School functioning	27	Child has trouble concentrating
	28	Child is able to keep up with his/her school work
	29	Child is not doing as well as usual in school
Eating disturbances	17	Mealtimes are a struggle
	44	Child has eating problems
Treatment burden	18	Treatment gets in the way of activities
	30	Difficult to do treatments each day
	31	Time spent on treatments
Health	22	Child feels healthy
	24	Child leads a normal life
	32	How do you think child's health is now?
Weight	33	Trouble gaining weight

Appendix B [cont.]

Domain	Question	Content of questions
Respiratory	34	Congested
	35	Coughing during the day
	36	Cough up mucus
	37	Description of child's mucus
	38	Wheezing
	39	Trouble breathing
	40	Woke up during the night because of coughing
Digestion	41	Gas
	42	Diarrhea
	43	Abdominal pain

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Validation of the Dutch Cystic Fibrosis Questionnaire in Adolescents and Adults

5

Submitted for publication

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Abstract

Background: This study assesses the reliability and validity of the Dutch version of a disease-specific measure of health-related quality of life (HRQOL) for adolescents and adults with CF (CFQ-14+). The 47 item CFQ-14+ covers nine domains, three symptom scales and one health perception scale.

Methods: To assess psychometric characteristics of the CFQ-14+, cross-sectional (homogeneity, discriminative and construct validity) and test-retest designs were used. Eighty-four adolescents and adults with CF (mean age: 21.4 years, range 14.0 to 46.5 years) and moderate to severe airway obstruction (mean FEV1: 59,9% predicted, range 15 to 121%) completed the questionnaire during a routine visit.

Results: Internal consistency was acceptable for most domains of the CFQ-14+ (α=0.43-0.92) and test-retest reliability was high for all domain scores (0.72 – 0.98). Several domains of the CFQ-14+ were able to differentiate between individuals with varying disease severity and between nourished and malnourished patients. Construct validity of the questionnaire was fair, with moderate to strong correlation between physically orientated domains and pulmonary function (rs=0.36-0.62).

Conclusion: The results demonstrate that the CFQ-14+ questionnaire is a well validated measure of HRQOL assessment in adolescents and adults with CF.

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Introduction

Advances in therapy and treatment of cystic fibrosis (CF) have led to improved patient survival into adulthood [1]. However, therapy and treatment of CF, coupled with the progressive nature of the disease, which can require hospitalization, makes management of CF time-consuming and difficult [1,2]. Traditional clinical measures are important but they do not capture the broader impact of the disease [3-5]. The measurement of health-related quality of life (HRQL) in CF provides additional information about the impact of the disease on physical, social and psychological functioning [2,5,6]. Studies on HRQL in patients with CF have typically used generic or specific respiratory questionnaires which were not specifically developed for CF [7-12]. Generic health measures allow for comparisons between a variety of diseases, but are not sensitive for specific problems associated with CF [6] and may not be sufficiently responsive to the effects of clinical interventions. Recently a reliable and valid CF-specific health-related measure was developed and validated in France, the Cystic Fibrosis Questionnaire (CFQ) [13]. In addition, the CFQ has been validated in Germany [14] and is presently being validated in the United States and Spain. The CFQ consists of three quality of life measures: a adolescent/adult version (14 years of age or older), a child version (6-13 years of age) and a parent version (used in conjunction with the child measure). The advantage of the CFQ is that it takes into account differences in developmental stages and makes it possible to monitor the health status and quality of life in CF patients from the age of 6 years throughout adulthood [6,15]. This allows health care professionals to analyze long-term outcome and efficacy of early intervention.

Cross-cultural validation of an existing measure has the advantage of avoiding the initial stages of development of a new questionnaire, which is a long process [16,17]. Furthermore, translation into different languages makes it possible to use the CFQ questionnaires in comparative international multicenter studies [14].

The aims of the present study were: 1) to develop a conceptually equivalent Dutch version of the CFQ for adolescents and adults with CF and 2) to evaluate the following characteristics: homogeneity, reproducibility (10-14 days test-retest reliability), discriminative and construct validity.

The Dutch CFQ for children with CF and their parents is presently being validated.

Methods

Patients and procedure

Eighty-four patients were recruited from the children and adult CF-Center of the University Medical Center Utrecht. All patients were approached during routine

visits between 2001 and 2002 and asked for consent to complete the CFQ. Patients who had problems understanding the Dutch language were excluded from the study. In a subset of clinically stable patients, as determined by a pulmonologist, the questionnaire was administered twice within 10-14 days. The study was approved by the institutional Medical Ethics Committee.

Translation

Backward and forward translations were completed. The French CFQ was translated into Dutch and a second independent translator made a backward translation into French. A third expert compared the original French list to the backward translated French list. Discussions were held between the translators to resolve semantic and conceptual discrepancies and to develop a consensus forward translation.

Cystic Fibrosis Questionnaire

The CFQ for adolescents and adults (CFQ-14+) consists of 47 items divided into nine domains: physical functioning (8 items), energy and well-being (4), emotional state (5), social limitations (4), role limitations (2), body image (3), eating disturbances (2), treatment burden (2), and embarrassment (3). Three symptom scales are included, respiratory (7), digestive (2), and weight (1), and overall health perception (4). Items require either a frequency response on a 4-point scale ("all the time" to "never"), a difficulty rating on a 4-point scale ("a lot of difficulty" to "no difficulty"), a true-false rating on a 4-point scale, or the selection of a statement that describes the patient (on a 3- or 4-point scale) [6]. Completing the questionnaire took approximately 15-20 minutes.

Scores are standardized by adding the ratings of all items within a domain to facilitate comparison of scores across domains. The scores range from 0 to 100 with higher scores corresponding to higher quality of life. Scores for each domain are calculated if at least two-thirds of the items are completed. There is no total score.

Appendix A outlines the distribution of the questions by domain for CFQ-14+.

Homogeneity

Internal consistency of each domain was assessed using Cronbach alpha coefficients (i.e. the strength of the associations between items and their respective domains). Generally the internal reliability is acceptable with a Cronbach alpha coefficient of 0.7 or above [18]. However, slightly lower coefficients (0.6 or higher) are acceptable for newly developed scales [19]. Furthermore, item to domain correlations were calculated. These correlations assess whether items are more strongly associated with their hypothesized versus competing scale.

Psychometric guidelines suggest that item to domain correlations should be 0.40 or greater [19].

Reproducibility

Test-retest reliability measures the stability of the scores on the CFQ questionnaires over time. Twenty-one patients with a stable clinical condition (i.e. no need for oral or intravenous antibiotic treatment in three months prior to testing) completed the CFQ 10-14 days apart.

Discriminative and construct validity

To assess whether the measure could discriminate between patients with varying levels of disease severity, patients were categorized according to their level of pulmonary impairment: mildly impaired group ($FEV_1 \geq 71$ %pred), mode-rately impaired group ($FEV_1 = 41 - 70$ %pred) and severely impaired group ($FEV_1 \leq 40$ %pred) [20]. In addition, patients were categorized according to their nutritional status: nourished group (BMI ≥ 19) and malnourished group (BMI < 19).

Since disease severity is related to older age comparisons were made between age groups: adolescents (14-17 years), young adults (18-25 years) and adults (26 years of age and older). Comparisons were also made between males and females.

Construct validity was assessed by correlating CFQ scores with pulmonary functioning.

Pulmonary function.

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were obtained from maximal expiratory flow-volume curves (Masterscreen; Jaeger, Wuerzburg, Germany). Values are expressed as the percent of predicted values [21,22].

Data analysis

The Statistical Package for the Social Sciences (SPSS for Windows version 10.1) was used for data management and analyses. The internal consistency reliability was evaluated using Cronbach's α. Spearman (rs) correlation coefficients were used to describe relationships between outcome measures. Correlations were interpreted as described by Guyatt and colleagues: less than 0.2 as very weak, from 0.2 to 0.35 as weak, from 0.35 to 0.5 as moderate, and 0.5 or greater as strong.[23] Intraclass correlation coefficients were used to estimate the reproducibility (test-retest reliability) [24]. Domain comparisons between groups were made using t-tests for unrelated samples and one way analysis of variance

(ANOVA). Post hoc testing was done with Tukey's honest significant difference, which corrects for multiple comparisons. Differences were considered significant if $p < 0.05$ (two-tailed). Data are presented as mean ± SD unless otherwise indicated.

Results

Eighty-four patients with CF (mean age: 21.4 years, range 14.0 to 46.5 years) who had moderate to severe airway obstruction (mean FEV_1: 58.5%, range 15 to 121%; mean FVC: 74.1%, range 26 to 121%) completed the CFQ-14+. Table 1 shows mean values of the different domains. The lowest scores on the CFQ-14+ were found for Vitality and Respiratory Symptoms, while the highest scores were found for Digestion and Embarrassment.

Internal consistency

The internal consistency reliability levels (Cronbach alpha) for the domains of the CFQ-14+ are shown in table 1. Most domains had an acceptable Cronbach alpha coefficient (0.60 or above). The exceptions to this were Body Image, Treatment Burden and Embarrassment. Overall, items in the CFQ-14+ loaded conceptually on their respective domains with all of the loadings above 0.40.

Table 1 CFQ-14+ scores, Cronbach alpha and test-retest reliability for each domain

	CFQ score (mean ± SD)	Alpha coefficient	Test-retest reliability
Physical functioning	64.4 ± 25.7	0.92	0.98
Vitality	56.3 ± 17.6	0.81	0.90
Emotional state	77.7 ± 15.6	0.69	0.84
Social functioning	63.1 ± 24.8	0.64	0.97
Role limitations	60.6 ± 27.2	0.74	0.98
Body image	68.7 ± 21.2	0.45	0.89
Eating disturbances	78.0 ± 22.9	0.66	0.87
Treatment burden	61.7 ± 22.3	0.53	0.83
Embarrassment	80.1 ± 18.6	0.53	0.90
Respiratory constraints	53.0 ± 13.4	0.79	0.92
Digestion	84.1 ± 18.5	0.69	0.68
Weight	72.6 ± 32.8	#	#
Health problems	70.6 ± 23.6	0.73	0.98

is single item scale.

Reproducibility

Twenty-one patients (22.8 ± 8.9 years; range 13.9 – 36.4 years) agreed to participate in the test-retest reliability phase. The intraclass correlation coefficient werehigh for all domains, ranging from 0.72 to 0.98 (table 1). This means that the domain scores of the CFQ-14+ are highly reproducible.

Discriminative and construct validity

To assess whether the measure could differentiate between patients with varying degrees of disease severity, patients were categorized according to the level of pulmonary impairment. Three groups were formed: mildly impaired group (N=28, FEV_1 89.1% ± 14.0%), moderately impaired group (N=36, FEV_1 56.0% ± 8.6%) and severely impaired group (N=20, FEV_1 26.4% ± 7.1%). ANOVA tests indicated significant main effects for Physical Functioning ($F=27.34$, $p<0.001$), Body Image ($F=13.43$, $p<0.001$), Eat Disturbances ($F=5.17$, $p<0.01$), Respiratory Symptoms ($F=5.78$, $P<0.01$), Health Perceptions ($F=4.16$, $p<0.015$) and Weight ($F=5.57$, $p<0.01$). Table 2 shows significant post-hoc comparisons between CFQ domains and disease severity.

With respect to nutritional status, comparisons between the nourished and malnourished group demonstrated that the nourished group had hi-gher scores for Body Image (72.2 ± 16.8 vs 65.1 ± 18.3, $p<0.05$), Eating Disturbances (83.3 ± 20.1 vs 72.4 ± 21.3, $p<0.05$) and Weight (77.5 ± 21.3 vs 67.1 ± 22.1, $p<0.05$).

Comparisons were made between adolescents (N=35; 15.4 ± 1.1 years), young adults (N=31; 20.5 ± 1.4 years) and adults (N=18; 34.5 ± 6.3 years). ANOVA tests indicated significant main effects for Physical Functioning ($F=13.56$, $p<0.001$), Vitality ($F=4.44$, $p<0.05$), Body Image ($F=6.29$, $p<0.01$), Treatment Burden ($F=3.58$, $p<0.05$), Respiratory Symptoms ($F=9.87$, $P<0.01$), Health Perceptions ($F=10.17$, $p<0.01$). Post hoc analyses revealed the following differences between age groups: (1) adolescents reported higher quality of life than young adults for the Body Image domain; (2) adolescents reported higher quality of life than adults for the domains of Physical Functioning, Vitality, Body Image, Treatment Burden, Respiratory Symptoms, Digestion and Health Perception; (3) young adults reported higher quality of life than adults for the domains of Physical Functioning, Vitality, Respiratory Symptoms and Health Perception. Comparisons between male (N=44) and female (N=40) patients demonstrated that males had higher scores for the Emotional Functioning domain (80.9 ± 12.2 vs 74.2 ± 18.1, $p<0.05$) and lower scores for the Body Image domain (62.9 ± 24.3 vs 75.0 ± 15.0, $p<0.01$).

Table 3 shows weak to moderate correlations for pulmonary function with Treatment Burden, Health Perceptions, Eating Disturbances, Weight, Respiratory Symptoms, and strong correlations with Physical Functioning and Body Image. The results indicated that patients with worse pulmonary function reported poorer quality of life on these domains.

Table 2 Comparison between CFQ-14+scores and disease severity

	mild CF (mean±SD)	moderate CF (mean±SD)	severe CF (mean±SD)	mild CF vs moderate CF d_i (95%CI)	mild CF vs severe CF d_i (95%CI)	moderate CF vs severe CF d_i (95%CI)
Physical functioning Vitality	78.5 ± 20.5	69.0 ± 19.4	36.3 ± 21.1	9.6 (-2.5 to 21.7)	42.3 (28.3 to 56.4)*	32.7 (19.3 to 46.2)*
Vitality	58.9 ± 19.4	55.2 ± 16.2	54.6 ± 17.6	3.8 (-6.9 to 14.4)	4.3 (-0.8 to 16.7)	0.6 (-11.2 to 12.4)
Emotional state	79.8 ± 19.7	77.2 ± 12.1	75.7 ± 15.3	2.5 (-6.9 to 12.0)	4.1 (-6.9 to 15.1)	1.6 (-8.9 to 12.0)
Social functioning	66.4 ± 24.3	60.6 ± 26.7	62.9 ± 22.5	5.7 (-9.3 to 20.8)	3.5 (-14.0 to 20.9)	-2.3 (-18.9 to 14.4)
Role limitations	66.0 ± 27.4	54.9 ± 26.8	65.3 ± 27.0	11.1 (-6.0 to 28.2)	0.7 (-22.0 to 23.5)	-10.4 (-32.1 to 11.4)
Body image	81.0 ± 19.1	67.9 ± 17.6	52.8 ± 19.7	13.1 (1.9 to 24.2)*	28.2 (15.2 to 41.2)*	15.1 (2.7 to 27.5)*
Eating disturbances	88.7 ± 19.8	73.6 ± 22.3	70.8 ± 23.4	15.1 (2.0 to 28.2)*	17.9 (2.6 to 33.1)*	2.7 (-11.7 to 17.3)
Treatment constraints	67.9 ± 26.0	60.6 ± 19.1	55.0 ± 21.0	7.2 (-6.1 to 20.5)	12.9 (-2.6 to 28.3)	5.6 (-9.1 to 20.4)
Embarrassment	83.3 ± 17.5	71.0 ± 20.7	80.8 ± 18.3	6.2 (-5.1 to 17.4)	2.5 (-10.5 to 15.5)	-3.7 (-16.1 to 8.8)
Respiratory constraints	58.5 ± 11.7	52.7 ± 12.2	45.8 ± 14.7	6.8 (-1.1 to 14.7)	13.1 (4.0 to 22.2)*	6.3 (-2.3 to 14.9)
Digestion	81.5 ± 18.3	81.9 ± 21.2	91.7 ± 10.1	-0.4 (-11.3 to 10.9)	-10.1 (-22.8 to 2.6)	-9.7 (-21.8 to 2.4)
Weight	88.1 ± 22.6	67.6 ± 33.3	60.0 ± 36.8	20.5 (1.8 to 39.2)*	28.1 (6.3 to 49.8)*	7.6 (-13.1 to 28.3)
Health problems	78.2 ± 22.7	71.0 ± 20.7	59.1 ± 26.0	7.3 (-6.3 to 20.9	19.2 (3.3 to 35.0)*	11.9 (-3.3 to 27.0

di (95%) = difference between means with 95% confidence interval. *Significant interaction effects

Table 3 Correlation between CFQ-14+ scores and pulmonary function.#

	PF	BI	ED	TC	RC	W	HP
FEV1 %pred	0.62***	0.52***	0.33**	0.26*	0.36**	0.40***	0.34**
FVC % pred	0.58***	0.41***	0.24*	-	0.23*	0.40***	0.27*

PF: physical functioning; BI: body image; ED: eating disturbances; TC: treatment constraints; RC: respiratory constraints; W: weight; HP: health problems; FEV1: forced expiratory volume in one second; FVC: forced vital capacity.
#Only significant correlations are reported. *p<0.05, **p<0.01, ***p<0.001.

Discussion

This study assesses the reliability and validity of the Dutch version of a disease-specific measure of HRQL for adolescents and adults with CF (CFQ-14+). The conceptual model of the CFQ was confirmed and the internal consistency was acceptable for most domains. Strong test-retest reliability was obtained and discriminative validity with pulmonary function, nutritional status and age was demonstrated.

The homogeneity of the CFQ was sufficient since all of the items showed higher correlations with the intended scale than with a competing scale. The internal consistency reliability estimates of the CFQ-14+ were adequate, exceeding Ware's criteria for newly developed scales[19]. However, three domains showed a low Cronbach alpha coefficient. Internal consistency coefficients of the Treatment Constraints domain have found to be even lower in previous studies [25]. One possible reason for this is that early detection leads the initiation of treatment regimens at a very young age. Patients may slowly accommodate to deterioration in their health status and a concomitant increase in the treatment regimen. Therefore, they may not perceive this as limiting their daily functioning. Internal consistency on the Body Image domain was also poor. The low alpha coefficient was, in part, caused by a gender effect. The Cronbach alpha for males and females was 0.56 and 0.10, respectively. However, deleting gender-based items or scales could lead to losing important information related to males and females with CF. For example, there is a significant gender difference in morbidity and mortality among males and females with CF which may be better understood in relation to their HRQL scores [26]. Calculations of internal consistency are strongly determined by the number of items on each scale [27]. Possibly, Body Image, Treatment Burden and Embarrassment have not enough items to highlight specific patient problems. Based on these analyses, revisions should be made. Recently, we added new items to these domains to solve this problem. These items will be tested in subsequent studies with the CFQ.

Currently there is only one other validated CF-specific HRQL measure for adolescents and adults (CFQoL) [20]. The authors reported high Cronbach

alpha coefficients on all domains. However, this measure does not have a version for children with CF and their parents. The CFQ questionnaires make it possible to follow individual patients throughout their life span and to capture the impact of the disease on the patient's ability to cope with various aspects of the illness. Furthermore, there was no effort to counterbalance positively and negatively worded items on the CFQoL, which can skew the wording of the items in a negative direction ("CF makes it difficult for me to....").

The analysis of test-retest reliability showed high intraclass correlations, indicating that the assessment of HRQL is stable over a 10 to 14 day period. This period is long enough not to introduce memory as a confounding factor while being short enough to prevent deterioration in disease status [20].

Generic quality of life measures do not capture the symptoms and areas of functioning that are relevant for majority of patients with a particular disease [5,27]. Confirmation of the discriminative and construct validity of the CFQ depends on the significant associations found between specific measures of disease impairment and relevant domains. CF is characterized by deterioration of nutritional status and irreversible loss of lung function, which impairs functional performance. The CFQ-14+ differentiated between three levels of disease severity (as measured by FEV_1) and between nourished and malnourished patients

Important differences were also found between younger and older patients. In addition, gender differences were found for Body Image and Emotional Functioning. These findings converge with the results of other studies, showing that gender differences exist in morbidity and mortality with CF [26,28]. Thinness and low body weight are perceived by women as less of a problem than males [6], although this condition is unfavarouble for their health [29-31]. Furthermore, it is well-documented that woman report more emotional problems due to poor health than men [20].

The construct validity of the CFQ-14+ offered further evidence of validity. The CFQ-14+ domains Physical Functioning, Body Image, Respiratory Symptoms and Weight showed moderate to strong correlations with pulmonary function parameters. Weak correlations were found for Treatment Burden and Health Perceptions.

Some issues in the present study need further comment. The sample size for this study was relatively small. Possibly stronger evidence of reliability might have been found in the Treatment Constraints, Body Image and Embarrassment domains with a larger sample size. Although the construct validity of the CFQ-14+ with pulmonary function is good, assessment of its relationship to generic health status and psychological well-being should be conducted. Data are also needed on the responsiveness of the CFQ-14+, which measures whether a questionnaire is able to detect changes brought about by an intervention. However, a prerequisite of sensitivity testing is the establishment of the reliability and stability of the measure, which in this study, appears to be

very good. Evaluation of the child and parent versions of the CFQ is presently underway.

In summary, although revisions are needed to improve the psychometric performance of the Cystic Fibrosis Questionnaire, this measure holds promise for assessing health-related quality of life in adolescents and adults with CF.

Appendix A List of items of the Dutch CFQ-14+

Domain	Question	Content of questions
Physical	1	Difficulty performing vigorous activities such as running or sports
	2	Difficulty to walk as fast as others
	3	Difficulty carrying or lifting heavy things such as books
	4	Difficulty climbing one flight of stairs
	5	Difficulty to climb stairs as fast as others
	13	Difficulty walking
	19	Trouble recovering after physical effort
	20	Limit vigorous activities such as running or sports
Vitality	6	Felt happy
	9	Felt tired
	10	Felt energetic
	11	Felt exhausted
Emotional state	7	Felt worried
	8	Felt useless
	12	Felt sad
	28	Difficult to make plans for the future
	33	Feel lonely
Social	22	Stayed at home more than you wanted
	26	Feel comfortable sleeping away from home...
	30	To get together with friends a lot
	32	Feel comfortable going out at night
Role	37	Absent from school or work because of illness or treatments
	39	Trouble keeping up with school, work or daily activities
Body image	23	Think you are too thin
	24	Think you are physically different from others your age
	25	Feel bad about physical appearance
Eating	14	Feel about eating
	21	Force myself to eat
Treatment constraints	15	Treatment makes daily life more difficult
	16	Time spend on treatment each day compared to one year ago
Embarrassment	27	People ask uncomfortable questions
	29	People are afraid that my illness may be contagious
	31	Think coughing bothers others
Health	17	Health at this moment
	18	Health compared to three months ago
	34	Feel healthy
	35	Lead a normal life
Weight	40	Trouble gaining weight

Appendix A [cont.]

Domain	Question	Content of questions
Respiratory	41	Felt congested
	42	Coughing during the day
	43	Cough up mucus
	44	Color mucus
	45	Wheezing
	46	Trouble breathing
	47	Woke up during the night because of coughing
Digestion	48	Diarrhea
	49	Abdominal pain

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Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study

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Abstract

Children's physical activity pattern is characterized by short-term anaerobic activities. Anaerobic exercise performance in children with cystic fibrosis (CF) has received little attention compared to aerobic performance. This study investigated the effects of anaerobic training in children with CF.

Twenty patients were randomly assigned to the training group (TG) (n=11; age 13.6 ± 1.3 yrs, FEV_1%predicted 75.2 ± 20.7%) or control group (CG) (n=9; age 14.2 ± 2.1 yrs, FEV_1%predicted 82.1 ± 19.1%). The TG trained two days per week for 12 weeks with each session lasting 30-45 minutes. The training program consists of anaerobic activities, lasting 20 to 30 seconds. Body composition, pulmonary function, peripheral muscle force, habitual physical activity, aerobic and anaerobic exercise performance, and quality of life were re-evaluated at the end of the training program and again after a 12-week follow-up period.

TG significantly improved their anaerobic performance, aerobic performance and quality of life. No significant changes were seen other parameters and no improvements were found in CG. After the follow-up period only anaerobic performance and quality of life in TG were significantly higher compared to pretraining values.

Anaerobic training has positive effects on aerobic and anaerobic performance and health-related quality of life in children with CF. Therefor, anaerobic training could be an important component of training programs for CF patients.

Introduction

Regular aerobic exercise has positive effects on the aerobic capacity of patients with cystic fibrosis (CF) [1-3]. In addition, higher aerobic fitness has been associated with prolonged survival and quality of life [4,5]. Compared to aerobic studies little attention has been given to anaerobic fitness. Especially controlled studies on the effect of anaerobic training in children and adolescents with CF are lacking. This is somewhat surprising since children's natural activity patterns are characterized by very short vigorous bouts of physical activity, interspersed with varying levels of low to moderate intensity [6]. Therefore, physical activity patterns in children may be more suited for a high intensity, anaerobic training program.

Several studies showed reduced anaerobic performance in children with CF [7-12]. In addition, children with CF do not participate as much in activities with high intensity compared to healthy controls [13].

It has been shown that healthy children's anaerobic performance can be enhanced through participation in structured exercise programs [14,15]. Besides an increase in anaerobic performance, Rotstein and colleagues reported an increase in aerobic performance as well after an anaerobic training program [14]. It is not clear whether anaerobic training can improve anaerobic and aerobic fitness in children with CF.

With respect to the importance for daily functioning, the aim of this study was therefore to investigate the effects of an anaerobic training program on anaerobic and aerobic performance, lung function, body composition, peripheral muscle strength and health-related quality of life (HRQL) of children with CF.

Methods

Subjects

Children with CF were recruited from the CF-Center, University Medical Center at Utrecht. Inclusion criteria were: children aged 9 -18 years with a stable clinical condition (no need for oral or intravenous antibiotic treatment in three months prior to testing), absence of musculo-skeletal disorders and a forced expiratory volume in 1 sec (FEV_1) > 30% predicted. Twenty-three patients agreed to participate. Our institutional Ethics Committee approved the study protocol. Informed consent was obtained from each participant and from his or her parent.

Study protocol

After the baseline measurements the tests were repeated within seven days after the training program was finished, and again 12 weeks later. The study was designed as a randomized controlled trial. After the pretraining tests the children

were randomly assigned by concealed opaque envelopes to either the training group (TG) or the control group (CG). The control subjects were asked to continue their normal daily activities as well as their physiotherapy regime. The primary researcher was blinded for the experimental condition.

Nutritional assessment

Anthropometric measurements were made prior to exercise testing. Fat free mass (FFM) was determined in fasting condition using bioelectrical impedance techniques. Body weight was measured using a platform beam balance (Mettler, Greifensee, Switzerland) with an accuracy of 0,02 kg. Height was measured with a stadiometer (Holtain,Crymich, UK) with an accuracy of 0,1 cm. Body mass index (BMI) was determined (weight.height^{-2}).

Pulmonary function tests

Pulmonary function tests were performed after inhalation of 800 µg of salbutamol via metered dose inhaler with a spacer, in order to rule out important bronchial hyperreactivity. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and forced expiratory flow between 25 and 75% of expiratory vital capacity (FEF_{25-75}) were obtained from maximal expiratory flow-volume curves (Masterscreen; Jaeger, Wuerzburg, Germany). Residual volume (RV) and total lung capacity (TLC) were measured in a volume-constant body plethysmograph (Masterlab; Jaeger, Wuerzburg, Germany) and the RV/TLC ratios were calculated from the actual values. Values are expressed as the percent of predicted values [16].

Peripheral muscle strength

Isometric muscle force measurements were performed for four muscle groups (shoulder abductors, elbow flexors, hip-extensors and knee extensors) according to the description of Backman [17]. Results for peripheral muscle force are presented as total maximal muscle force (i.e. summed maximal force in four muscle groups, since factor analyses showed a single-factor solution [Eigenvalue = 2.7; 68% of total variance]).

Exercise testing

Subsequent anaerobic and aerobic exercise tests were performed on an electronically braked cycle ergometer (Lode Examiner, Groningen, The Netherlands). All subjects were familiar with the different tests and equipment used. During the tests heart rate was monitored continuously by 3-leads electrocardiogram (Hewlett-Packard, Amstelveen, The Netherlands) and oxygen saturation (SaO2)

by pulse oximetry (Nellcor 200 E, Breda, The Netherlands). Verbal encouragement was given throughout the tests to stimulate maximal performance.

Each subject performed a Wingate anaerobic Test (WanT) to assess anaerobic performance.[18] The WanT is a valid and reliable test to evaluate short-term anaerobic power in healthy children, children with CF and other chronic illnesses [7,11,18,19]. The subjects were instructed to start pedaling as fast as possible after a 1-minute warming-up against 15 W resistance, while at the same time the full breaking force was applied through an integrated computer program. Anaerobic performance indices were reported as mean power (MP; power averaged over 30 seconds) and peak power (PP; highest power during the test).

After the WanT the subjects rested for at least 45 minutes before aerobic fitness was assessed by a standard progressive incremental exercise test. Workload was increased by 15 W at 1-min intervals. The maximal workload (Wmax) was defined as the highest workload maintained during 30 seconds. 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). Internal gas and volume calibrations were made before each test. Measurements taken included oxygen uptake (VO_2), carbon dioxide production (VCO_2), ventilation (VE) and respiratory exchange ratio (RER= VCO_2/VO_2). The highest VO_2 achieved during the last 30 seconds of exercise was taken as VO2peak [8].

Efforts were considered to be at a maximum level if subjects showed clinical signs of intense effort and were unable to maintain speed above 50 rpm [20], and if at least one out of two criteria were met: 1) cardiac frequency above 180 beats/min; 2) maximal RER above 1.0 [21,22]. Predicted VO2peak (VO_{2peak}%) values were obtained from an age and gender matched Dutch reference population [23].

Lactate

Blood samples were drawn three minutes after peak aerobic exercise, from an antecubital vein and collected in Vacutainer tubes and subsequently analyzed (Vitros 250 analyzer, Johnson & Johnson, Clinical Diagnostics, Rochester, USA).

Daily physical activity

Physical activity was assessed with the Habitual Activity Estimation Scale (HAES) [24]. This scale reviews the subject's activity level for two weekdays during the last two weeks. The total percentage of time being active is presented. The HAES has been used in children with CF [25,26] and in other studies of children with chronic disease [27].

Quality of life

Quality of life was measured with a disease-specific health-related quality of life questionnaire, the Cystic Fibrosis Questionnaire (CFQ). The CFQ consists of a 47 item teen/adult version (CFQ-14+) and a 35 item child version (CFQ-C) [28,29]. The CFQ takes into account the different developmental stages and makes it possible to monitor the health status and quality of life of patients with CF from the age of 6 years throughout adulthood [28,29].

Anaerobic training program

The subjects in the training group (TG) trained on a individual basis and the standardized training sessions were led by the children's own physiotherapist. Specific written instructions in the form of a booklet were given to the physiotherapists. The TG trained two days per week for 12 weeks. Each session lasted 30-45 minutes. Guidelines based on a review of anaerobic training studies in children were used [30]. The training program consists of eight basic training sessions (running lanes and movement games, lasting 20 to 30 seconds) which were repeated every four weeks. Individual scores and changes in training overload were carefully recorded in a logbook. The children were constantly encouraged to exercise at maximal speed.

Data analysis

Data are presented as mean ± SD. All data were tested for normality with the Shapiro-Wilks test. The analysis of variance for repeated measures was used for within- and between group comparisons. Between-group comparisons were made with an unpaired t-test. Changes within the two groups were analysed with a two-tailed paired t-test. Pearson correlation analyses and linear regression analyses were performed for HRQL with aerobic and anaerobic indices. Data were analysed using the Statistical Package for the Social Science (SPSS, version 9.0, Chicago. IL, USA).

To achieve a difference in peak power per kg body weight of 10% with a SD of 0.8 W/kg and a statistical power of 80%, it was calculated that eight patients had to be included in each study group.

Results

Twenty-three patients were initially enrolled. Two patients (FEV_1: 37,5 ± 7,8%) in the control group failed to complete the study because of pulmonary exacerbation and one patient (FEV_1: 105%) in the training group withdrew from the study for practical reasons. The baseline characteristics of the remaining twenty

patients are shown in table 1 and the baseline results for anaerobic and aerobic performance are shown in table 2. Both exercise tests were well tolerated by all patients and all patients fulfilled the criteria for a maximal aerobic exercise test. Comparisons between groups revealed no significant differences at baseline.

The adherence of the training group to the exercise training was excellent. The attendance rate at the exercise sessions was 98.1 ± 4.3%. Reasons for absence were holidays and sickness.

Effects of exercise training

Body composition, pulmonary function, muscle force and habitual physical activity

At the end of the 12-week training period, a significant within group increase was found for height (TG 1.5 ± 0.9 cm, $p<0.001$; CG 1.1 ± 1.0 cm, $p<0.05$) and weight (TG 0.4 ± 0.6 kg, $p<0.05$; CG 0.8 ± 1.0, $p<0.05$). With-in and between-group comparisons revealed no significant differences for body composition, pulmonary function, peripheral muscle force and habitual physical activity at the end of the training period.

Anaerobic and aerobic performance

The changes observed after the 12-week training period for anaerobic and aerobic performance are shown in table 3. TG showed significant improvements in absolute PP (11.7%) and MP (12.4%), in PP and MP per kg body weight (BW) (10.9% and 10.1%, respectively) and PP and MP per kg FFM (11.8% and 11.9%,

Table 1 Baseline characteristics of the training group and the control group

	Training group (n=11)	Control group (n=9)
Age years	13.6 ± 1.3	14.2 ± 2.1
Height cm	155.5 ± 8.2	159.8 ± 8.5
Weight kg	41.9 ± 5.9	47.7 ± 8.7
BMI kg/m²	17.2 ± 1.0	18.5 ± 2.3
FFM kg	27.9 ± 3.4	31.4 ± 4.6
FEV_1 % pred	75.2 ± 20.7	82.1 ± 19.1
VC % pred	85.0 ± 14.0	93.2 ± 15.8
FEF_{25-75} % pred	54.1 ± 45.3	51.0 ± 30.6
RV/TLC %	37.2 ± 11.2	32.6 ± 8.7
Isometric muscle force Nm	648 ± 118	668 ± 78
Activity level %	25.6 ± 13.7	25.9 ± 19.1

Data are means ± SD. BMI: body mass index; FFM: fat-free mass, FEV_1: forced expiratory volume in one second; VC: vital capacity; FEF_{25-75}: forced expiratory flow at 25-75% of VC, RV: residual volume; TLC: total lung capacity. p = NS for all between-group comparisons.

Table 2 Baseline results for anaerobic and aerobic performance

		Training group (n=11)	Control group (n=9)
Anaerobic performance			
Peak power	W	547 ± 178	647 ± 179
	W/kg BW	12.8 ± 2.5	13.4 ± 1.6
	W/kg FFM	18.7 ± 3.7	20.3 ± 3.2
Mean Power	W	296 ± 92	365 ± 104
	W/kg BW	6.9 ± 1.3	7.7 ± 0.9
	W/kg FFM	10.1 ± 1.8	11.4 ±1.8
Aerobic performance			
VO2peak	mL/min	1677 ± 242	1904 ± 330
	mL/kg·min	40.2 ± 4.2	40.7 ± 8.3
	mL/kg·FFM	60.1 ± 5.4	60.8 ± 8.4
	%predicted	83.1 ± 9.1	84.2 ± 10.4
Wmax	W	140 ± 20	156 ± 26
Lactate	mmol/L	6.9 ± 1.9	9.6 ± 4.0

VO_{2peak} = peak oxygen uptake; BW = body weight; FFM = fat-free mass; Wmax = maximal workload p = NS for all between-group comparisons.

respectively). With respect to aerobic measurements, TG showed significant improvements in VO_{2peak} (mL/min: 5.2% and %predicted: 5.7%), W_{max} (7.9%) and serum lactate (26.1%) while the increase in VO_{2peak} per kg FFM (5.2%) was not significant. In CG a significant decrease was found for VO_{2peak} per kg BW (-1.5%) and per kg FFM (-5.6%), while other parameters were unchanged.

Quality of life

At the end of the 12-week training period, a significant higher score was found in the domain of Physical Functioning in TG (70.3 ± 13.8 versus 88.4 ± 9.0, $p<0.001$) but no change was found in CG (83.2 ± 18.5 versus 87.1 ± 17.9, $p=0.20$) or in other quality of life domains.

Regression analysis in TG indicated that the change in PP accounted for 41% of the variance in the Physical Functioning domain ($p<0.05$). Changes in MP or VO2peak were not independent correlates of changes in quality of life scores.

Effects of follow-up period

Comparing pretraining and end of the follow-up period, a significant increase was found for height (TG 2.8 ± 1.0 cm, $p<0.001$; CG 2.1 ± 1.2 cm, $p<0.01$), weight (TG 1.7 ± 1.5 kg, $p<0.01$; CG 1.7 ± 1.3 kg, $p<0.01$) and FFM (TG 2.0 ± 2.3 kg,

p<0.05; CG 1.7 ± 1.2 kg, p<0.05) but no changes were found for habitual physical activity. However, between-group comparisons of changes observed at the pretraining assessment as compared with end of the follow-up period were not significant. BMI, pulmonary function, peripheral muscle force and habitual physical activity did not change significantly in both groups.

TG showed significant higher follow-up levels of absolute PP (54.6 ± 47.7 W, p<0.001) and MP (24.9 ± 73.5 W, p<0.01) when compared with pretraining levels The increase in CG was not significant compared to baseline values (PP 21.7 ± 15.6, p=0.34; MP 12.7 ± 34.4, p=0.31). All other anaerobic indices decreased to baseline values.

With respect to aerobic performance, no significant differences were found in the TG between baseline and end of follow-up period. CG showed significant lower VO_{2peak} (kg BW -1.5 ± 1.7 mL/kg·min, p<0.05; kg FFM –3.0 ± 1.9 mL/kg·min) and serum lactate (-1.2 ± 1.2 mmol/L, p<0.05) when pretraining and end of follow-up period were compared.

At the end of the follow up period, the domain of Physical Functioning in TG (8.3 ± 8.4, p<0.01) was still significantly higher compared to pretraining values.

Table 3 Effect of training program on anaerobic and aerobic performance

		Training group (n=11)	Control group (n=9)
Anaerobic performance			
Peak power	W	66.9 ± 23.8***	-3.4 ± 53.7
	W/kg BW	1.4 ± 0.6***	-0.3 ± 1.1
	W/kg FFM	2.2 ± 1.2***	-0.6 ± 2.0
Mean Power	W	36.6 ± 11.8***	-6.7 ± 29.9
	W/kg BW	0.7 ± 0.3***	-0.3 ± 0.8
	W/kg FFM	1.2 ± 0.6***	-0.4 ± 1.1
Aerobic performance			
VO2peak	mL/min	88 ± 106*	-48 ± 63
	mL/kg·min	1.5 ± 2.6	-0.6 ± 1.9*
	mL/kg·FFM	1.3 ± 4.6	-3.2 ± 2.5**
	%predicted	4.7 ± 5.6*	-2.1 ± 2.8
Wmax	W	11 ± 14*	-2 ± 5
Lactate	mmol/L	1.8 ± 1.4**	-1.6 ± 2.9

Values are mean ± SD. Significant differences from baseline values are indicated. BW = body weight; FFM = fat-free mass; VO_{2peak} = peak oxygen uptake; W_{max} = maximal workload. *p<0.05, ** p<0.01, *** p<0.001; p = NS for all other within- and between-group comparisons.

Discussion

The aim of this study was to investigate the effects of an anaerobic training program in children with CF. In this single blind, randomized controlled study, after a 12-week training period, improvements were observed in anaerobic and aerobic outcome parameters and in HRQL. In addition, at the end of a 12-week follow-up period most outcome parameters decreased to pretraining values with the exception of anaerobic performance and HRQL.

To our knowledge, this is the first study to document that children with CF are able to improve their anaerobic exercise capability through a high-intensity training program. These results are in agreement with anaerobic training studies in healthy children [14,31]. TG increased their PP with 12.2%, which compares favorably with the results of McManus and colleagues after a three-times a week, 8-week sprint-running training program in healthy girls (PP: 9.7%) [32]. Rotstein and colleagues reported an increase in PP and MP per kg BW (14% and 10%, respectively) after a 9-week, 3 times per week training program [14]. These results are consistent with the increase found in our study (PP/kg BW 11% and MP/kg BW 10%). Grodjinovsky and colleagues reported much lower improvements in MP per kg BW (3-4%) and PP per kg BW (4%) after a 6-week 3-times per week anaerobic training program in 11-13 year old healthy children [15]. Although guidelines for anaerobic training in children are not yet clearly established [30], the outcome of these findings suggest that a minimal time-period of approximately 8 weeks would be likely to induce a substantial improvement in pediatric anaerobic fitness.

Changes in aerobic exercise capacity are usually associated with specific training programs involving several hours per week at submaximal intensity [33]. Although the intensity of our training program may be considered as very stressful and the duration of the exercises very brief, anaerobic training resulted in an increase in VO2peak (5%). This result is in accordance with studies in healthy children that show an increase of aerobic capacity of 4-7% after anaerobic training [14,34]. These results may be explained by the fact that resynthesis of adenosine triphosphate (ATP) during high-intensity exercise depends on both aerobic and anaerobic processes [35]. Moreover, in children approximately 40% of energy production in the WanT test comes from aerobic metabolism [30]. In addition, although an incremental exercise test explores aerobic capacity and is not a valid tool for assessing anaerobic performance [36], the increase in serum lactate values seen in TG suggests a larger contribution of anaerobic glycolysis during peak aerobic exercise. In other words, improved anaerobic energy metabolism possibly enhanced aerobic power output. This is supported by the finding that during specific aerobic training a decrease is seen in serum lactate concentration [37].

Increased anaerobic performance has been linked to biochemical changes in muscle of children [31]. Fournier and colleagues reported a 21% increase in anaerobic enzyme activity after sprint training [31]. Subsequently,

higher serum lactate values in our study provides indirect evidence in support of improvements in biochemical processes associated with anaerobic metabolism as a result of the training program.

Improvements in HRQL, as measured by the disease-specific Cystic Fibrosis Questionnaire, were seen in TG. This is consistent with the results other studies who found improvements in quality of life scores after aerobic training as measured with a generic measure (Quality of Well-Being Scale) [5,38]. Furthermore, as shown in our study and in other studies [5,38], changes in HRQL are related to changes in exercise performance. This emphasizes the need to further assess both HRQL and exercise performance which provides valuable information on the multidimensional impact of the disease on patient's quality of life and can make an important contribution to decision making in clinical practice [38,39].

In our study no positive or adverse effects were seen in pulmonary function, FFM and peripheral muscle strength due to the training program. As could be expected, no change was found in the amount of habitual physical activity, since we asked the participants not to change their activity level during the study period. Until now, the influence of physical training on pulmonary function has not been clearly established. Several studies showed improvements in pulmonary function after aerobic training [40-42]. In contrast, other studies failed to detect improvements in pulmonary function [1,2,38,43]. Eventually, all studies show that training is safe for the patients' respiratory condition.

Effects of follow-up period

The increases found in the study parameters in TG decreased to baseline value after the 12-week follow-up period with the exception of anaerobic performance and HRQL. Generally, benefits of exercise disappear if physical activity is discontinued. However, as shown in our study and studies of others [38,41] benefits due to training seem to continue for some time in patients with CF, regardless of follow-up training sessions.

Clinical implications of anaerobic training

Up to now, anaerobic exercise has received little attention compared to aerobic exercise, although many activities in daily life as well as sport activities are both aerobic and anaerobic in nature [8,9]. Regular exercise is an important part of treatment in CF. Adherence to exercise programs depends on individual motivation and variation in activities. The children enjoyed our training program, which motivated them to attend 98% of the training sessions. Our anaerobic training program offered the necessary variation to enhance its adherence. The increase in anaerobic and aerobic performance and in HRQL after anaerobic training indicates that this type of training can be included in the overall physical rehabilitation of children with mild to moderate CF. Ideally, an exercise program for children with CF could be made of aerobic, anaerobic and strength-

training activities. This makes it possible to individual tailor the program according to the preference of the participants, thereby improving levels of exercise adherence [44].

In conclusion, our results suggest that children with mild to moderate CF can enhance their anaerobic and aerobic performance and HRQL through participation in a structured anaerobic exercise training program. In addition, aerobic performance increases as well. The improvements in anaerobic performance and HRQL are maintained through a 12-week follow-up period. Therefore, anaerobic training could be an important component of the rehabilitation program of children with CF.

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7

General Discussion

Peter Klijn

Introduction

In this chapter, a general discussion is presented based on the studies reported in this thesis. In addition, some issues that have not been addressed in the previous chapters, and might give more insight in the direction of future studies, will be discussed.

Aerobic and anaerobic metabolism

An important aim of this thesis was to investigate the influence of CF on anaerobic exercise performance of children. So far, research has focussed on aerobic exercise performance. As stated in the introduction, this is somewhat surprising since children's natural activity pattern is characterized by anaerobic activities (figure 3). However, aerobic fitness is associated with prolonged survival and quality of life, and regular aerobic exercise has positive effects on the aerobic exercise capacity of patients with CF [1-5]. Until now, the effects of CF on aerobic fitness in children have only been described in cross sectional studies. In chapter 2 we demonstrated that longitudinal changes in pulmonary function are associated with changes in aerobic exercise capacity in children with CF and mild pulmonary disease. Over a two-year period a decrease was found in age and gender predicted values of pulmonary function and VO_{2peak}. In the introduction, a description was given on the close relationship between aerobic and anaerobic

energy metabolism. In CF, as in other pulmonary diseases like chronic obstructive pulmonary disease (COPD) and asthma, a shift from aerobic to anaerobic energy production as a resultant of disease progression, is thought to be an important factor in maintaining exercise performance [6-8]. Generally, anaerobic energy production does not depend on the lung's ability to exchange gas but on the amount of fat-free mass (FFM; i.e. muscle mass). Therefor, anaerobic exercise performance should be independent of pulmonary dysfunction. However, until now the relationship between pulmonary function and anaerobic performance has not been clearly established in children with CF. In chapter 3 we showed that children with CF and moderate pulmonary dysfunction had better anaerobic exercise capacity at equivalent FFM, but lower predicted aerobic exercise capacity compared to children with mild pulmonary dysfunction.

Decrease in aerobic capacity is already seen in young children with mild pulmonary disease, which on the long-term might lead to enhanced anaerobic energy metabolism with progression of pulmonary disease. So, from these studies we hypothesise that in children with CF and progressive lung disease, the decline of aerobic exercise performance is compensated by increase of anaerobic exercise performance. This can be a mechanism to maintain physical fitness for a prolonged period (see Figure 1).

More evidence that is direct and possible explanations for a compensatory mechanism needs to be studied. In children, non-invasive methods like phosphorus-31 nuclear magnetic resonance (^{31}P-NMR) measurements are to be preferred. It would be interesting to study whether intrinsic abnormalities of skeletal muscle and defects in the synthesis of ATP are present in pediatric CF muscle during high intensity anaerobic work using a NMR spectrometer as has been shown for aerobic work in children with CF. In addition, further studies are indicated to investigate the combined long-term changes in aerobic and anaerobic exercise performance of children with CF in the full range of illness severity.

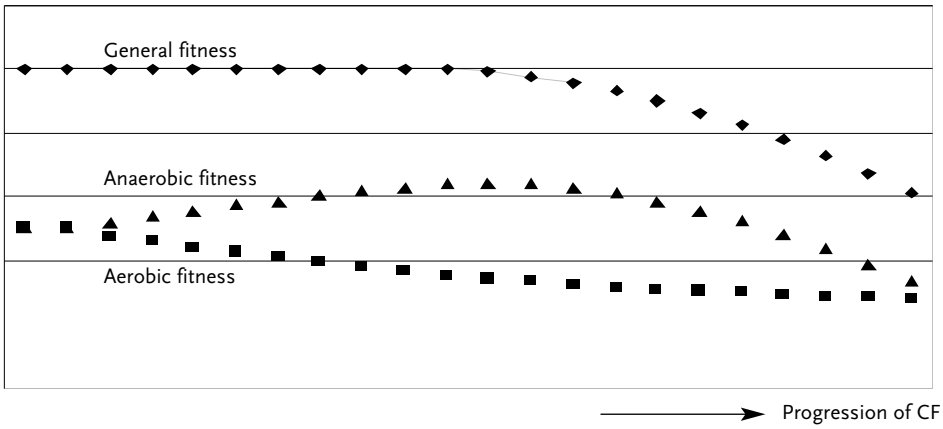

Figure 1
Hypothesised change in aerobic and anaerobic fitness with disease progression

Body composition

Another matter that needs further comment is the use of indices of nutritional status and body composition in relation to exercise performance and disease severity. Nutritional status and body composition are often used together and sometimes considered as synonymous. BMI is widely used in pediatric research for evaluating nutritional status or body composition, owing to the relative ease with which the measurements can be done. However, BMI is highly correlated with FM and FFM but can not distinguish either of them. Therefore, BMI is at best seen as an abstract index of nutritional status rather than as a measure of body composition [9]. The studies described in chapter 2 and 3 demonstrated that FFM was an important predictor of aerobic and anaerobic exercise capacity. However, as stated in chapter 2, age and gender predicted values for pediatric FFM proportions are missing. These are especially important since CF has adverse effects on fat mass and fat-free mass, causing changes in body composition. A complicating factor is that due to growth and maturation FFM increases with age. However, the statural growth and the increase in FFM and FM are slower in young children with CF compared to healthy controls [10]. In addition, the adolescent growth spurt, which is an important phase in the deposition of FM and FFM, is delayed by about a year in CF [11]. These are all sources of variation in the evaluation of body composition in relation to exercise performance in children with CF. Therefore, reference values for pediatric FFM proportions should not only be based on gender and chronological age, but also on biological age (biological maturity).

Biometric modeling

The separation and quantification of the independent contribution of disease severity to aerobic and anaerobic exercise performance lies upon the appropriate removal of the effects of FFM. Traditionally, ratio standards are used to facilitate comparisons between individuals of different body-size (e.g. PP per kg FFM; VO_2 per kg body weight). The resulting scaled physiological performance variables are assumed to be independent of the individuals body-size dimension [12]. However, ratio standards are theoretically not correct as was already shown by Tanner in 1949 [13]. Ratio standards imply that every kilogram FFM or body weight is associated with a specific amount of power (W) or oxygen uptake. In recent years more research has focussed on the use of allometric or power function models in the healthy population. The power function assumes the following model between the physiological variable (Y) and the body size variable (X) [14]:

$$Y = a \cdot X^b$$

When scaling or normalizing physiological measurements for differences in body size, Nevill and colleagues proposed the power function ratio (Y/X^b), derived from the allometric model that would render the subject's physiological performance variable (Y) independent of their body size variable (X) [12].

The power function model was applied to the anaerobic and FFM data from chapter 3. No differences were found between the power function of the mild group ($FEV_1 \geq 80\ \%$) and the moderate group ($FEV_1 < 80\ \%$). Hence, a common power function was derived:

$$PP = 4.18 \cdot FFM^{1.44}$$ (figure 2)

The appropriate method of scaling should be the power function ratio standard:

$$PP/FFM^{1.44}$$

The correlation between the simple ratio standard, PP (W/kg FFM), and FFM (kg) was $r = 0.47$ ($p<0.01$), i.e. the simple ratio standard failed to produce a size independent physiological performance variable. In contrast, when PP was scaled according to the power function method ($PP/FFM^{1.44}$) and correlated with FFM (kg) the correlation was found to be zero ($r = 0.01$, $p=0.906$). Hence, the scaled physiological variable was independent of the body size dimension.

With respect to disease severity, table 1 shows correlations between absolute PP, PP adjusted for FFM and BW (simple ratio standard) and PP adjusted for FFM (power function ratio standard). The results indicate that when the appropriately scaling method is used, PP adjusted for FFM is significantly correlated with all pulmonary function measures. This result strongly underlines the results found in chapter 3.

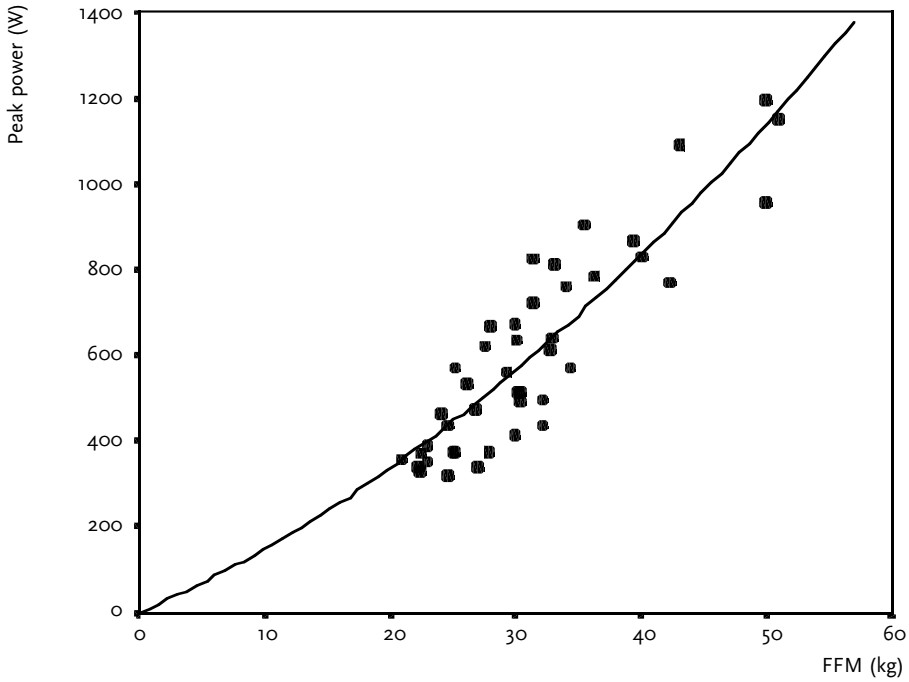

Figure 2
The power functional relationship between peak power and fat-free mass

Table 1 Correlation between pulmonary function and absolute and relative peak power

	FEV_1 %pred	VC %pred	RV/TLC %	FEF25-75 %pred
PP (W)	-0.05	0.07	-0.02	-0.14
PP (W/kg BW)	-0.08	-0.03	0.04	-0.16
PP (W/kg FFM)	-0.32*	-0.16	0.27	-0.40**
PP (W/ kg $FFM^{1.44}$)	-0.49**	-0.33*	0.48**	-0.53***

PP = peak power; BW = body weight; FFM = fat-free mass; FEV_1 = forced expiratory volume in one second; VC = vital capacity; RV = residual volume; TLC = total lung capacity; FEF25-75: forced expiratory flow at 25-75% of VC. *p<0.05, ** p<0.01, *** p<0.001

Multi-level modeling is a another comparatively new and complex biometric method, but it provides a valuable adjustment to existing analytical techniques used in physiology of exercise and to longitudinal studies that investigate the physiological development from childhood through adolescence to adulthood [15]. Multi-level modeling is a form of multiple regression that can analyze hierarchically structured data. In longitudinal data, a hierarchy is set at two levels: level 1 and level 2. Level 1 comprises the repeated measurement occasions and level 2 comprises the individual [16]. For example, individuals have their own rates of growth that might vary randomly in comparison with the mean response of the group (level 1). Similarly, each individual's measurement might vary around their growth trajectory (level 2). An advantage of multi-level modeling compared to traditional methods is that data sets do not have to be complete from occasion to occasion and the time intervals between measurements do not have to be equal for each individual. The interested reader is referred to the work of Goldstein [17,18].

Multi-level modeling has only recently been applied to sport and exercise science. It is promising to see that published studies have demonstrated the utility of the technique, especially where the effects of growth, development, gender and exercise training have to be disentangled [19-24]. The group of Neil Armstrong and Joanne Welsman in Exeter, United Kingdom have done a lot of interesting research in this area [19,25-30]. It is important to note that increasingly more books on exercise physiology include chapters or paragraphs on the use of scaling factors and multi-level modeling [31-33].

Quality of life

With respect to quality of life, we validated the three CFQ questionnaires (i.e. CFQ-C, CFQ-P, CFQ-14+). In chapter 4 and 5 it was stated that data are needed on the responsiveness of the CFQ. In chapter 6 it was shown that the CFQ-C and CFQ-14+ were able to detect changes brought about by the training intervention. Although numbers are small and the study was not designed to test the responsiveness of the CFQ-C and CFQ-14+, this result adds to the validation of the CFQ questionnaires.

The standardized response mean (SRM i.e. the ratio of change in mean scores to the standard deviation of the change) was calculated to assess the relative magnitude of observed changes. SRM is interpreted using criteria described by Cohen: 0.2 represents a small change; 0.5 a moderate change and changes of 0.8 or higher are interpreted as a large change. Over the training period a large change of 1.10 was found for the Physical Functioning domain. However, the minimal important clinical difference should be determined in order to define the meaning of the HRQL changes found in chapter 6.

This was the first study to document an improvement in the subjective judgement of children with CF about their physical functioning after an anaerobic training intervention. So far, changes in quality of life have only been related to changes in aerobic capacity [34]. However, this emphasizes the need to perform aerobic and/or anaerobic exercise tests in children with CF, since it reflects the overall impact of the disease on the patient's quality of life.

Anaerobic exercise testing

Some remarks should also be made on the use of the anaerobic exercise test, the Wingate test (WanT). The WanT is by far the most popular anaerobic test [35]. However, no objective criteria have been established to judge whether a 'true' maximal workload has been reached. In order to obtain maximal power output it is essential to match the external load to the capability of the active muscles. Optimization of resistance setting is a disadvantage of the WanT. The main problem of using body weight to predict anaerobic performance, is that the relationship between body weight and leg function varies due to growth and maturation [36]. In addition, because of the test duration, the WanT has a considerable aerobic component [7].

An alternative test, which is thought to be a more specific anaerobic test is the force-velocity test (F-V test). The test consists of several (5 to 8) "all-out" 5 – 7 seconds cycling bouts, each performed against a different, but constant, braking force. Force-velocity and power-velocity functions are established and the resulting parabola enables calculation, by interpolation, of PP for each subject, as well as the force that is needed to achieve PP [36]. PP achieved by the F-V test is thought to be closer to a person's 'true' peak cycling power than measured by the WanT [37]. However, Van Praagh and colleagues showed a high correlation ($r = 0.93$) between PP obtained by the F-V test and PP obtained by the WanT, suggesting that both tests measure the same factor [38]. A disadvantage of the F-V test is the total time required (30 to 40 minutes) to complete the test protocol. In comparison, the WanT takes about 15 minutes to complete. Since aerobic and anaerobic energy metabolism are inextricably linked during exercise, and the WanT covers a larger range of the anaerobic metabolism, the WanT seems relatively favored in determining the effects of anaerobic training.

Anaerobic training

To our knowledge, this was the first intervention study in children with CF that used anaerobic training. We showed that children with CF are able to improve their anaerobic and aerobic exercise performance, and HRQL due to a specific anaerobic training program. In addition, the anaerobic training effect and the effect on HRQL was, in part, maintained after a 12-week follow-up period. Moreover, VO_{2peak} remained stable in the training group over the 6-month study period. Selvadurai and colleagues showed that benefits due to aerobic training continue for some time in patients with CF, regardless of follow-up training sessions [34]. Including anaerobic training is likely to improve adherence to exercise training due to larger variation in training activities. Therefore, further studies are indicated to investigate the long-term effects of combined aerobic and anaerobic training studies. Training sessions of approximately 8 weeks, every six months might effectively improve long-term clinical outcome in children with CF. Moreover, these "booster" sessions are possibly an attractive alternative for patients who have poor adherence to life-long exercise regimes. Selvadurai and colleagues showed that resistance-training is safe and clinically effective for children with CF, thereby increasing the possibilities of composing exercise programs for children with CF [34]. In order to create a coherent and motivating training network for children with CF, physical education teachers could, next to physical therapy, organize extracurricular sport and exercise classes.

Main conclusions

Exercise benefits in CF can be obtained from a wide variety of activities and from different training modalities (e.g. aerobic, anaerobic and strength). Training guidelines should be followed, but most importantly, exercise programs should be primarily based on the preference of the individual child! Including specialists, like physical education teachers and exercise physiologists, could be of great value in designing exercise programs in clinical practice.

Moreover, more work needs to be done before we fully understand the optimal training guidelines and the role of physical exercise in the life of healthy children and in those suffering from chronic diseases like CF.

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Summary

In chapter 1 an introduction on general characteristics of cystic fibrosis (CF) is provided, followed by an overview of literature on exercise studies in children with CF. This literature review showed that children with CF are able to improve their aerobic capacity with short-term training programs. While their pulmonary function did not improve. Furthermore, an outline for anaerobic training in children with CF is presented. Improvement of anaerobic performance is thought to positively influence participation in daily activities as well as sport activities, which may eventually lead to improvements of health-related quality of life.

Chapter 2 describes the longitudinal relationship between changes in peak aerobic performance (VO_{2peak}), pulmonary function and fat-free mass (FFM) in sixty-five children with mild to moderate CF. It was concluded that changes in VO2peak are associated with changes in pulmonary function and to a lesser degree with changes in fat-free mass.

In chapter 3 the determinants of anaerobic performance are described in thirty-nine children with mild to moderate CF. FFM was found the most important determinant of anaerobic performance. In addition, pulmonary function also contributed significantly to anaerobic performance when FFM was controlled for. An interesting outcome was that subjects with moderate pulmonary dysfunction had higher anaerobic power output per FFM than subjects with mild pulmonary dysfunction. It was suggested that anaerobic energy metabolism may be enhanced with progression of pulmonary disease.

Chapter 4 describes the validation process of the Cystic Fibrosis Questionnaire (CFQ) for children with CF in the age from 6 to 13 years (CFQ-C) and their parents (CFQ-P), and chapter 5 describes the validation process of the CFQ for adolescents and adults (CFQ-14+). Although minor revisions are needed, all three questionnaires showed adequate validity and reliability. It was concluded that, the CFQ questionnaires can be used to monitor the health status and quality of life of patients with CF from the age of 6 years throughout adulthood.

Chapter 6 describes the effects of our anaerobic training program on aerobic and anaerobic exercise performance, pulmonary function, fat-free mass, peripheral muscle force and health-related quality of life. In the training group significant positive effects were found for aerobic and anaerobic performance and for health-related quality of life. It was concluded that anaerobic training could be an important component of the physical rehabilitation program of children with CF.

Samenvatting

In hoofdstuk 1 wordt een inleiding gegeven over de aandoening cystic fibrosis (CF, taaislijmziekte). Achtereenvolgens worden besproken de incidentie en mortaliteit, pathogenese en diagnose, en de pathofysiologie bij CF.

Daarnaast wordt aan de hand van een literatuuroverzicht aandacht besteed aan de rol van fysieke training bij kinderen met CF. De geselecteerde trainingsstudies worden kort besproken wat betreft effecten op longfunctie, functionele status (aëroob uithoudingsvermogen en spierkracht) en kwaliteit van leven. Uit dit deel kan worden geconcludeerd dat kinderen met CF in staat zijn om hun aërobe fitheid te vergroten door deelname aan een kortdurend aëroob trainingsprogramma. De longfunctie verbeterd niet ten gevolge van een trainingsprogramma, daarentegen lijkt lichamelijke inspanning wel van invloed op het vertragen van de achteruitgang van de longfunctie. Daarnaast lijkt krachttraining een goede aanvulling op de bestaande trainingsprogramma's.

In het resterende deel van hoofdstuk 1 wordt een onderbouwing gegeven voor het inzetten van anaërobe training bij kinderen met CF. Activiteiten in het dagelijks leven, evenals veel sport- en spelactiviteiten zijn niet alleen aëroob van aard, maar hebben ook een grote anaërobe component. In het dagelijks leven komt het regelmatig voor dat kinderen een anaërobe inspanning moeten leveren (bijvoorbeeld traplopen, een sprintje trekken). Het anaëroob metabolisme zou meer gerelateerd zijn aan de activiteiten in het dagelijks leven dan het aëroob metabolisme. Diverse studies hebben aangetoond dat het anaërobe prestatievermogen van kinderen met CF lager is in vergelijking met gezonde leeftijdgenoten. Bovendien nemen kinderen met CF minder deel aan activiteiten met een hoge intensiteit (grote anaërobe component). Door gerichte anaërobe training zou de kwaliteit van leven van kinderen met CF kunnen verbeteren doordat zij makkelijker kunnen deelnemen aan allerlei bewegingsactiviteiten.

In hoofdstuk 2 van dit proefschrift worden de resultaten beschreven van een twee-jarige longitudinale studie. Doel was om de lange termijn relatie tussen veranderingen in de aërobe fitheid, longfunctie en lichaamssamenstelling te bepalen bij 65 kinderen met CF in de leeftijd van 4 tot 18 jaar. Het aëroob inspanningsvermogen werd gemeten met een maximale inspanningstest op de

loopband door kinderen tot 12 jaar en op fietsergometer door kinderen vanaf 12 jaar. Geconcludeerd wordt dat longitudinale veranderingen in de piek zuurstofopname geassocieerd zijn met veranderingen in de longfunctie en in mindere mate met veranderingen in de vetvrije massa. Fysieke training en voedingsinterventies lijken belangrijk bij de klinische prognose op lange termijn.

In hoofdstuk 3 is gekeken naar determinanten van het anaërobe inspanningsvermogen bij 39 kinderen met mild tot matig CF in de leeftijd van 9 tot 17 jaar. Vetvrije massa, longfunctie, perifere spierkracht, en aëroob en anaëroob inspanningsvermogen werden bepaald. De perifere spierkracht werd gemeten met een 'handheld' dynamometer. Het aëroob en anaëroob inspanningsvermogen werden bepaald op een fietsergometer respectievelijk met een maximale inspanningstest en de Wingate test. De Wingate test is een maximale anaërobe sprinttest met een duur van 30 seconden. De resultaten laten zien dat de vetvrije massa de belangrijkste determinant is van het anaëroob inspanningsvermogen. Een opvallende bevinding is dat bij een gelijke hoeveelheid vetvrije massa, kinderen met een milde longfunctiestoornis een lagere score behalen op de Winagte test dan kinderen met een matige longfunctiestoornis. Daarentegen heeft laatst genoemde groep een significant grotere daling van de zuurstofsaturatie tijdens de maximale aërobe inspanningstest. Deze resulaten suggereren dat met een toename van de ernst van de longfunctiestoornis de achteruitgang van de aërobe fitheid mogelijk gecompenseerd wordt door het anaërobe energiemetabolisme.

In hoofdstuk 4 wordt de validatie en het bepalen van de betrouwbaarheid beschreven van een ziekte-specifieke kwaliteit van leven vragenlijst, de Cystic Fibrosis Questionnaire voor kinderen met CF (CFQ-C) en hun ouders (CFQ-P). De CFQ-C bestaat uit 35 items verdeeld over 6 domeinen en 2 symptoomschalen. De CFQ-C wordt gebruikt bij kinderen in de leeftijd van 6 tot en met 13 jaar. De CFQ-P bestaat uit 43 items verdeeld over zeven domeinen, drie symptoomschalen en één gezondheidsschaal. Bij 68 kinderen en hun ouders werden de CFQ lijsten afgenomen. De resultaten laten zien dat de CFQ-C en de CFQ-P valide en betrouwbare lijsten zijn voor het meten van gezondheidsgerelateerde kwaliteit van leven bij kinderen met CF en hun ouders.

In hoofdstuk 5 wordt de validatie van de CFQ voor adolescenten en volwassenen (CFQ-14+) uit een gezet. De CFQ-14+ wordt gebruikt voor patienten met CF vanaf 14 jaar. De CFQ-14+ bestaat uit 47 items verdeeld over negen domeinen, drie symptoomschalen en één gezondheidsschaal. Uit het onderzoek kan geconcludeerd worden dat de CFQ-14+ een valide instrument is voor het meten van gezondheigsgerelateerde kwaliteit van leven bij adolescenten en volwassenen met CF. Tezamen maken de CFQ-C en de CFQ-14+ het mogelijk om de kwaliteit van leven en de gezondheidstoestand van patienten met CF vanaf 6 jaar te vervolgen.

In hoofdstuk 6 zijn de effecten van een anaëroob trainingsprogramma voor kinderen met CF beschreven. Twintig kinderen met CF in de leeftijd tussen 10 en 17 jaar werden gerandomiseerd in een trainingsgroep (n=11) en in een

controle groep (n=9). De kinderen in de trainingsgroep trainden tweemaal per week, gedurende twaalf weken onder begeleiding van een geïnstrueerde (kinder)fysiotherapeut of oefentherapeut. De trainingen vonden plaats in de eigen woonplaats van de kinderen.

In de trainingsgroep zijn significant positieve effecten gevonden op het aëroob en anaëroob inspanningsvermogen. Bovendien is een significante toename gevonden op het domein van Fysiek Functioneren van de CFQ-C en CFQ-14+. Bij de controle groep zijn geen veranderingen gevonden op deze parameters. Ook de longfunctie, de spierkracht en de vetvrije massa bleven onveranderd in beide groepen.

Na een follow-up periode van twaalf weken bleek dat in de trainingsgroep het anaëroob inspanningsvermogen en de kwaliteit van leven nog steeds significant hoger waren dan bij aanvang van het trainingsprogramma.

Uit dit onderzoek kan geconcludeerd worden dat anaërobe training bij kinderen met CF leidt tot een verbetering van de aërobe en anaërobe fitheid en van de gezondheidsgerelateerde kwaliteit van leven. Daarnaast is het van belang om vast te stellen dat de effecten van dit anaëroob trainingsprogramma deels behouden blijven na een periode van twaalf weken, waarin geen formele training heeft plaatsgevonden.

Een twee, een twee, daar kwam Haas aangerend.
Hij was aan het joggen in de sneeuw.
'Hoi,' riep hij vrolijk, 'sport is gezond!
Doe mee, Kikkertje, beweging is goed voor je.'

Max Velthuis | Kikker in de kou | *1999*

Dankwoord

Ruim 2,5 jaar geleden ben ik begonnen aan het avontuur dat nu ten einde is. Velen hebben bijgedragen aan de tot standkoming van dit proefschrift. Dank daarvoor.

Ik wil een aantal mensen in het bijzonder noemen.
Allereerst wil ik alle kinderen en hun ouders bedanken voor het deelnemen aan de vele onderzoeken die nodig waren om dit proefschrift te vullen!

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op jullie te mogen doen. Dank voor jullie vriendschap. Rink, ik vind het geweldig dat je mijn paranimf wilt zijn.

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Curriculum Vitae

Peter Klijn werd geboren op 29 april 1964 te Mijdrecht. Nadat hij mavo, havo en vwo achter zich had gelaten begon hij in 1984 zijn studie tot leraar lichamelijke opvoeding aan de Academie voor Lichamelijke Opvoeding te Amsterdam. Na het behalen van zijn akte L.O. studeerde hij vanaf 1988 studeerde aan de Faculteit Bewegingswetenschappen van de Vrije Universiteit van Amsterdam. In 1992 studeerde hij af met als specialisaties inspanningsfysiologie en biochemie, en als nevenspecialisatie psychologie met betrekking tot het menselijk bewegen.

In 1993 heeft hij met zijn huidige vrouw Sanja een reis door Azie gemaakt, waarna hij in 1994 neerstreek als bewegingstherapeut op astmacentrum Heideheuvel te Hilversum.

Hij is als co-auteur betrokken geweest bij het 'Bewegingsprogramma voor kinderen met astma'. In mei 2000 is hij begonnen aan het promotieproject 'anaerobe training en kwaliteit van leven bij kinderen met Cystic Fibrosis' op de afdeling kinderfysiotherapie (hoofd: Prof Dr PJM Helders) en de afdeling kinderlongziekten (hoofd: Dr CK van der Ent) van het Wilhelmina Kinderziekenhuis te Utrecht. Naast zijn promotietraject heeft hij op astmacentrum Heideheuvel onderzoek gedaan naar een bewegingsprogramma voor kinderen met obesitas en een trainingsprogramma voor kinderen met astma. Vanaf februari 2003 werkt hij als onderzoeker en bewegingstherapeut op astmacentrum Heideheuvel.

Peter is getrouwd met Sanja Zivojnovic. Samen hebben zij twee kinderen, Anika (1996) en Milena (1999).

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Epiloog

‘Als je iets wilt, spant het hele universum samen
om ervoor te zorgen dat je je droom verwezenlijkt.’

Paulo Coelho | De Alchemist | 1988