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Clinical Exercise Testing in Children and Adolescents with Cystic Fibrosis

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Abstract: With advances in intensive supportive therapy and multi-disciplinary Cystic fibrosis (CF) care, life expectancy in CF has markedly increased over the last decade. Exercise testing has evolved as an integral part in CF patient management. Indeed, exercise testing includes the assessment of functional capacity and morbidity; however, it is also essential in demonstrating the effects of therapy and training programs. Moreover, regular exercise training can improve aerobic and anaerobic capacity, increase inspiratory muscle strength and enhance airway mucus clearance. Nevertheless, in spite of the beneficial effects of regular physical activity, standardized exercise testing followed by structured training is rather uncommon among CF clinicians. Reviewed in the present study are the most common field and laboratory exercise tests available in the healthcare of children and adolescents with CF.

Cover Letter

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Dear Editor

We submit two articles entitled “Clinical Exercise Testing in Children and Adolescents with Cystic Fibrosis” and “Exercise Training in Children and Adolescents with Cystic Fibrosis”, dividing our original article entitled “Clinical Exercise Testing and Training in Children and Adolescents with Cystic Fibrosis” in two parts as suggested by the reviewers. We believe both articles would be of interest to your readership and would fit very well as Part I and Part II. I can confirm that both articles are original and have not been published elsewhere nor are currently under consideration with another journal. I can confirm all four authors have been involved in the writing of the article and consent has been obtained to submit to your journal. I look forward to hearing from you in the near future.

Yours faithfully

Mr Thomas Radtke

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CLINICAL EXERCISE TESTING IN CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS

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Introduction

Exercise testing in Cystic fibrosis (CF) is gaining clinical interest as an important tool to assess disease severity and functional ability. Furthermore, exercise testing has been used as an outcome measure of therapy and exercise programmes, as well as for prognostic purposes (1-6). It has been established, that aerobic and anaerobic capacity is reduced in most patients with CF when compared to their healthy counterparts, with impaired respiratory function and malnutrition being likely contributing factors (7-10). It has also been documented that children with CF with higher activity levels have a better aerobic and anaerobic fitness and nutritional status, and a significantly lower disease severity (11). Moreover, higher aerobic fitness is associated with a higher health-related quality of life (11;12). Aerobic and anaerobic training has been shown to improve peak oxygen consumption (peak $\dot{V}O_2$), to enhance airway mucus clearance and to increase muscle mass, resulting in weight gain (3;13-16). In CF, aerobic capacity and training has received greater attention than anaerobic training. However, children's natural activity patterns are predominantly anaerobic, as opposed to aerobic.

Pulmonary function testing (PFT) at rest is widely used and an important tool to assess the severity of lung disease, although PFT cannot accurately predict a patient's exercise capacity (17;18). A combination of PFT, exercise testing and quality of life assessment may be better tools to evaluate a patient's overall health status (12).

Apart from laboratory exercise testing, simple field tests have been used to assess exercise tolerance and to determine the effects of therapeutic interventions in children with CF. In terms of validity, precision and objectivity, cardiopulmonary exercise testing (CPET) is considered the gold standard to assess a patient's exercise capacity and organ-specific function. As observed by Barker et al, exercise

testing is clinically important, even though clinicians do not generally use CPET as part of their routine examination. Field exercise testing may be the preferred choice, due to time constraints, lack of expertise, equipment and staff, and funding (19). Ideally, clinicians should encourage their patients to be physically active in their daily life as inactivity leads to further deconditioning. Therefore, exercise testing is vital in the provision of safe and effective training recommendations. The aim of the present study was to provide a review of field and laboratory exercise tests available to children and adolescents with CF.

Method of review

All relevant studies for this review were identified using electronic search of Medline® and PubMed® databases between the years 1958 and 2008. A bibliography search of all accessed publications was also performed. Key descriptors were Cystic fibrosis, exercise testing, aerobic fitness, children and adolescents. Two of the four authors (TR, DS) independently pre-selected relevant studies to be included in this article. The further selection of studies presented in the review was based upon the agreement of all four authors. We included studies of subjects with CF, independently of their disease severity, and type of physical training (aerobic training; anaerobic training; combination of aerobic and anaerobic training, as well as, inspiratory muscle training). As there is a lack of longitudinal studies on exercise training in children and adolescents with CF, the authors believe that there are too small a number of randomized controlled trials to allow a systematic Cochrane review. However, the authors propose that it is justified to include studies of shorter duration, different study designs and non-randomized controlled trials. We aim to provide a review on clinical exercise testing in children and adolescents with CF. This article is intended to be comprehensive, however, not exhaustive.

A. Field tests

1. Assessment of breathlessness

In CF patients, breathlessness is a common clinical symptom during physical exertion. Breathlessness is a subjective sensation, not necessarily associated with clinical symptoms such as wheezing or cough. However, breathlessness is often associated with fear and panic, resulting in reluctance to partake in physical activity. Depending on the pulmonary disease severity, dyspnoea can occur during exercise or even at rest. Several tools are available to quantify breathlessness during exercise testing; yet, measures of perceived breathlessness are not always well understood by children, and, therefore, need to be interpreted carefully. Both the modified Borg Scale of perceived breathlessness and the visual analogue score (VAS), are subjective measures to assess breathlessness. The original Borg Scale of perceived exertion was modified to assess perceived breathlessness during exercise (20). The patient is asked to rate his feeling regarding shortness of breath, using a rated scale (0 = no breathlessness at all; 10 = breathlessness at rest). The VAS consists of a 100 mm horizontal line anchored with word descriptors at each end. The patient is asked to mark horizontally through the line according to their actual perception of breathlessness, starting on the left (zero), labelled as ‘I am not at all short of breath’ to ‘The most short of breath I have ever been’ at the other end. The distance between the zero point and the mark is measured (mm). In contrast to subjective assessments of breathlessness, the fifteen-count breathlessness score aims to objectively evaluate breathlessness, a method that has also been tested in children with CF (21). The patient has to take a deep breath in while counting out loud to 15 in 8 seconds. The number of breaths required to complete the count, including the initial one, amount to the final score. The minimum score is, therefore, one. Most clinical

studies in children with CF use combinations of subjective and objective measures of breathlessness.

2. Six-Minute Walk Test

The 6-minute walk test (6-MWT) has been modified from the original 12-minute running test and the 12-minute walking test to assess the physical capacity of individuals (22;23). The 6-MWT is a practical and simple test, which primarily measures the distance a patient can quickly walk during six minutes. Walking is a daily activity; therefore, the 6-MWT is easy to perform. The test should be undertaken indoors, ideally along an enclosed corridor with a hard and flat surface. Most studies have used corridors with a length between 20 and 50 meters; however, there is no effect on the length of straight courses (24). The turnaround points as well as a starting line are marked with cones or coloured tape placed on the floor. A stopwatch is required to monitor testing time; turnarounds must be recorded to measure the covered walking distance. While the 6-MWT is self-paced, it is generally recommended not to walk alongside the patient. However, the practical use and application at individual centers seems to be different in daily clinical practice. According to our clinical experience, children might require verbal encouragement while performing the test to ensure maximum efforts. If the operator walks with the patient, it is required to stay behind him/her to avoid influencing the patients walking speed. Furthermore, in terms of standardization, we recommend that the test is ideally supervised and controlled by the same supervisor, particularly, if tests are performed longitudinally for comparison. If the patients walk alone, they can carry a portable pulse oximeter.

It has been documented that the 6-MWT is useful and reproducible in patients with respiratory disease, for whom a 12-minute walk test is too exhausting (25). In healthy

children, the 6-MWT has been shown to be highly acceptable and valid, with a significant correlation between the walking distance and peak $\dot{V}O_2$ during an incremental treadmill exercise test (26-28). Normative values for healthy children have been briefly published (27). However, normative values for children with CF are not available. Several investigators have described the 6-MWT as useful and valuable in assessing exercise tolerance in CF children and adults with mild to moderate lung disease (29-31). Gulmans et al found a high correlation between the walking distance for two walking tests in each individual (31). Furthermore, a significant correlation was determined between the walking distance and maximal power (watts) or peak $\dot{V}O_2$ obtained during incremental cycle ergometry testing. It is important to emphasize that the 6-MWT, as a self-paced test, is dependent on the patient's motivation and has a tendency for sub-maximal efforts. More studies are needed to obtain information about its validity, including larger numbers of children with CF at different stages of disease severity.

3. Shuttle tests

Shuttle walking tests are incrementally and externally paced exercise tests, which can be performed as a 12-level or the modified 15-level shuttle test. Bradley et al showed that the modified shuttle walking test (MSWT) is a reliable and sensitive measure of exercise capacity in adults with CF (32). Twelve patients performed two MSWT within two weeks, revealing a high correlation between distance walked, peak heart rate (peakHR), oxygen saturation (SaO_2) and perceived breathlessness. The MSWT incorporates a walk or run back and forth on a 10-m course marked with cones, with an increased speed every minute by a pre-recorded audio signal. The test ends when the patient is unable to keep the set pace or by the operator if the patient is no longer able to complete a shuttle in the given time (0.5-1.0 meter

distance away from the cone, depending on the set guidelines). In children with CF, the usefulness of the MSWT to measure exercise capacity and determine clinical improvement after hospitalization has been shown (33). Selvadurai et al compared two shuttle tests (10 m shuttle walk and 20 m shuttle run) with the results from treadmill exercise testing in CF patients with a wide range of disease severity, showing that both tests are reproducible and valid measures of exercise tolerance. Moreover, the authors reported a high correlation between the distance walked and measured peak $\dot{V}O_2$ values (34). Furthermore, the MSWT is useful in estimating peak aerobic capacity. In a recent study, Coelho et al demonstrated no differences in distance walked between healthy and CF children with normal lung function and mild to moderate symptoms, while healthy controls showed significantly higher ratings of perceived exertion (RPE) using the Borg Scale (35). The MSWT requires less space and is an inexpensive and appropriate alternative measure in comparison to CPET in children with CF.

4. Three-Minute Step Test

The 3-minute step test (3-MST), modified from the original 'master two-step exercise test' has been used in children with CF as an outcome measure of intravenous antibiotic treatment, to assess exercise capacity and symptomatic exercise tolerance, and to evaluate candidates for lung transplantation (36-39). The test is externally paced and thus not influenced by motivation. Subjects are instructed to step up and down on a commercially available step, set at a height of 15 cm. The step frequency is kept constant at a pace of 30 steps per minute for 3 minutes, controlled by a metronome and the testing time recorded by a stopwatch. Furthermore, to reduce localized muscle fatigue, patients should be instructed to change the leading leg during the test. In case of a prematurely terminated test due to muscle fatigue or

breathlessness, the number of steps taken must be added up. In terms of the test's validity, results of the 3-MST may be influenced by leg length of each individual. Thus to enhance validity, the bench height should be adjusted individually according to the subjects leg length (40). This issue is important if test results are interpreted; in particular, if longitudinal data of individuals are compared. As examined by Narang et al, the 3-MST is limited in its validity if applied to children with mild lung disease, due to its low intensity. Compared with an incremental exercise test to exhaustion, clinically relevant information such as exercise induced arterial oxygen desaturation may be missed using the 3-MST. However, compared to a 6-MWT, the 3-MST produces a significantly higher heart rate (HR) and breathlessness score, without any differences in SaO_2 (37;38). However, the 3-MST is easy to perform and requires little space. It does not, however, reflect a normal functional task and is also not able to measure aerobic capacity in patients with CF.

5. Modified Munich Fitness Test

The modified Munich Fitness Test (mMFT) has been adapted from the Munich Fitness Test (41). The original version is a well known and widely accepted test that was developed to assess physical fitness of school children at the age of 6 to 18 years. The mMFT includes the following four test-tasks:

1. **balancing and bouncing:** standing on a beam and bouncing a ball with both hands as fast as possible within 30s. The total number of correctly performed bounces is measured and implies the score.
2. **accurate throw:** a 500g bean bag has to be thrown to five target fields with a distance of 3m away from the throwing line. Each field has a certain

number (1-2-3-2-1). For the score, the number of five correctly performed attempts is summed.

3. **trunk flexibility:** standing on a beam, keeping feet one's together and reaching forward from the standing position with knees straight. The best of two attempts is scored (in cm).
4. **standing vertical jumping:** jumping as high as possible from the standing position with bended knees. The difference between standing reach-high and jump-and reach-high of two attempts is measured (in cm).

The individual testing results enable comparisons to a normative standard. Detailed instructions of the test are available at: "www.sportunterricht.de" (in German only). The only study, including the mMFT was performed in a large group of 286 children and adolescents with mild to moderate CF lung disease (6-18 years of age) during a 4-6 week inpatient rehabilitation. In comparison to healthy children, test scores of children with CF were lower, however within the normal range. Improvements were seen in all test tasks after an inpatient training regime. Gruber et al showed that the mMFT is a valid and useful tool to assessing several components of physical fitness including endurance capacity, flexibility, balance and motor skills in children with CF (42). Most other studies focus solely on increased aerobic fitness (peak $\dot{V}O_2$) or muscular strength of a certain muscle group, which are obviously clinically relevant parameters. However, the mMFT provides additional information regarding physical fitness as well as components of motor performance in children and adolescents with CF. Furthermore, individual limitations can be detected during testing and improved through a special training program. Thus, due to improved motor skills, activities of daily life could be implemented more easily. There is a need of more studies to obtain

more information regarding the validity and reliability of the mMFT, including patients with CF with a wider range of lung disease severity.

Summary

All field exercise tests discussed have shown to be useful when working with children and adolescents with CF. All the above field tests can be combined with different measurements, summarized in **Table 1**, solely the mMFT. This test is not appropriate to assessing aerobic fitness or provoking symptomatic exercise tolerance in CF. However, each test incorporates specific advantage and disadvantage. In comparison, the shuttle-walk test has a stronger correlation with oxygen consumption ($\dot{V}O_2$) than the 6-MWT. The 6-MWT is self-paced and has, therefore, been shown to be sub-maximal in its effort. In particular, compared to the step test, the 6-MWT relies more on patient motivation. In contrast, the step test may miss out important clinical information in patients with mild to moderate CF lung disease, due to its low intensity. The mMFT is easy to perform, provides important information for the clinician and is a useful tool to measure improvements of training programs. Further research is needed including patients with more advanced lung disease, while this test has only been established in children and adolescents with normal and mildly impaired lung function. In children with CF, the choice of each field test should be adapted for each individual subject according to the child's ability and disease severity.

B. Laboratory exercise tests

Laboratory exercise testing is usually performed on a cycle ergometer or treadmill in children and adolescents with CF. Depending on the disease severity, equipment and the clinical experience of the examiner, a choice of different tests is available.

Different tests measuring aerobic and anaerobic responses to exercise in children with CF are discussed below.

1. Sub-maximal exercise tests

Sub-maximal exercise testing may be a preferred method for patients who are not able to perform a maximal exercise task. Barry and Gallagher reported repeated sub-maximal exercise tests on the cycle ergometer (80 % of peak workload) as a suitable technique to assess therapeutic benefits in adults with CF (43). In a three-month supervised running program and a 12-month unsupervised exercise training program, HR at sub-maximal workloads significantly decreased as a result of improved cardio-respiratory fitness (3;44). Recently, $\dot{V}O_2$ kinetics in CF has been investigated. Hebestreit et al reported slower $\dot{V}O_2$ kinetics at the onset of exercise in children with CF compared to healthy children (45). However, kinetics protocols are not considered as practical in daily clinical care as they are laborious and require three to four repeated tests, and, therefore, regarded rather as a research tool. As shown, sub-maximal exercise testing is thus more valuable to determine benefits of training programs. However, to detect limiting factors, maximal exercise testing is a preferred method.

2. Maximal exercise tests

Maximal exercise testing can be performed on the cycle ergometer or treadmill combined with online analysis of expired air. In children, measurements of peak $\dot{V}O_2$, during an incremental exercise test to exhaustion, is widely recognized as the best single index of a child's cardiopulmonary fitness. The most frequently used protocols for children with CF are the 'Godfrey protocol for cycle tests' and the 'Bruce protocol

for treadmill testing' (46;47). Godfrey's cycle protocol starts with a workload of 0 watts for two minutes, with the work load being increased by 10, 15 or 20 watt increments, depending on the patient's height (<120 cm 10 watt; 120-150 cm 15 watt, >150 cm 20 watt). The choice of protocol also depends on the physical fitness, disease severity and an adequate testing time. Bruce's protocol for treadmill testing starts at a speed of 1.7mph and an incline of 10%. At three-minute intervals, the incline increases by 2% and the speed by 2.7 mph, 3.4 mph, 4.2 mph, 5.0 mph, 5.5 mph, 6.0 mph, 6.5 mph, 7.0 mph, and 7.5 mph, respectively, until exhaustion (46). Advantages of a cycle ergometer test are the reduced risk of injuries, an accurate and more comfortable record of additional parameters such as electrocardiogram, blood pressure, and SaO_2. Apart from financial implications and space requirements, the treadmill test is particularly applicable for younger patients. Furthermore, higher maximum values for oxygen consumption are obtained (up to 10 %) compared to cycle testing, due to the higher amount of muscle mass involved. In CF, there are many indications for CPET .

Studies have shown the usefulness of peak $\dot{V}O_2$ testing for prognostic purposes, and investigators have also documented high correlations between aerobic capacity and quality of life (1;2;4;12). Nixon et al also reported a positive association between aerobic capacity (peak $\dot{V}O_2$) and survival in CF over an extended period of eight years (2). In another longitudinal observation of 28 children with CF between 8 to 17 years of age, a correlation between forced expiratory volume in 1 sec (FEV_1) and peak $\dot{V}O_2$ was found. Furthermore, the decline in FEV_1 was correlated with the change in peak $\dot{V}O_2$ in individuals over a five year period (4).

Several training studies have shown improvements in aerobic fitness regardless of methodological differences in training parameters obtained (duration, intensity, frequency) and type of exercises (3;15;48;49). Unfortunately, fewer longitudinal data are available to support beneficial effects of regular physical activity (PA). In a recent study the relationship between PA and aerobic fitness (peak $\dot{V}O_2$) was investigated in CF patients (12-40 years of age) with a wide range of pulmonary disease severity (FEV_1 25–107% predicted) (50). The study revealed a significant relationship between PA and peak $\dot{V}O_2$, independently of other variables such as body size, sex, lung function and muscle power.

3. Wingate Test

The Wingate Anaerobic Test (WAnT) is the most thoroughly investigated and applied test to assess maximal anaerobic performance in healthy children, as well as children with CF and other chronic disease (11;51-56). The WAnT is a 30 s all-out sprint test against a pre-determined resistance on an electrically braked cycle ergometer set in a constant torque. The test measures the ability of a group of muscles to perform short supra-maximal tasks, measuring peak muscle power and muscle endurance (peak power, mean power, and fatigue index). Usually a warm-up (3-5 min) is performed including a few sprints (3-5 s) to get the subject familiarized with the test procedure. Detailed information regarding the test protocols is described elsewhere (51;57). When comparing CF and healthy children, their anaerobic capacity is reduced (7;52-54;58). Peak and mean power (watts) is lower in CF patients in correlation to percent fat-free mass, rather than body mass (7;10;56). Other factors which may affect anaerobic performance in CF are CF genotype and maturational status (7;59). Boas et al investigated energy metabolism during anaerobic exercise in

children with CF and proposed that lower percentages of peak $\dot{V}O_2$ and peak ventilation (peak $\dot{V}_E$) during the WAnT may be used compared to asthmatics and healthy controls. This is most likely mediated by a greater use of glycolytic metabolism in CF (52). Studies have also suggested that nutritional status is one of the main determinant affecting anaerobic performance (7;10;53). In contrast, Cabrera et al studied CF patients with a wide range of pulmonary disease severity and showed a negative relationship between impaired pulmonary function and anaerobic performance. The authors reported, anaerobic performance during the WAnT depends highly on anaerobic metabolism in the exercising muscle, and is thus largely independent on the oxygen transport system (53). However, this finding may not be significantly associated with the degree of lung function impairment and anaerobic capacity as measured by WAnT. Furthermore, the WAnT has also shown to be useful as an outcome measure for training studies. Klijn and colleagues showed significant improvements in both aerobic and anaerobic WAnT parameters following a 12-week individualized anaerobic training program (2 days per week, 30-45 min). After a 12-week follow-up period, most outcome parameters decreased compared to pre-training levels, except of anaerobic performance and quality of life (13). Moreover, CF children with higher levels of habitual activity have been found to possess increased anaerobic power during the WAnT and quality of life (11). More research is required in this field, in particular using training studies, to provide more detailed recommendations for exercise programs.

Safety instructions and contraindications

In general, specific safety guidelines have to be followed, particularly when children are involved. Therefore, resuscitation equipment and trained personnel have to be available. Compared to healthy children, CF children are at a higher risk of cardio-

respiratory compromise during exercise (e.g. hypoxemia, bronchoconstriction, and pneumothorax). During laboratory exercise testing, the continuous monitoring of HR and SaO_2 during the test is indicated. Any exercise stress test should be terminated if the SaO_2 drops below 75 % as previously recommended (37;38;60). If supplemental oxygen is required during an exercise test, clinical details need to be documented, and the amount of supplemental oxygen kept constant during and immediately after the exercise test. More detailed information regarding the absolute and relative risks as well as contraindications of exercise testing in children are described elsewhere (18;61).

Conclusion

Exercise testing is regarded an important prognostic tool in CF care. However, despite its beneficial effects, clinical exercise testing seems underused. Clinicians and their staff should encourage patients with CF to be physically active and recommend exercise testing to patients ideally once a year as it is already practiced in several countries. We conclude that, if no laboratory testing is available, field tests are an inexpensive and valid alternative. Nevertheless, field exercise testing is often crude and unable to detect exercised-induced limitations, which are common in patients with pulmonary disease. Furthermore, the measurement of peak $\dot{V}O_2$ is correlated with lung function and appears to be a valuable predictor of disease progression in CF. The use of laboratory exercise testing may be limited by cost and equipment, as well as time and personnel. In our experience, patients have to be well instructed regarding the test procedure, and the clinician and the CF team should be encouraged to create a positive environment, whenever possible.

Table

Table 1 Measurements obtained during field testing

Abbreviations

CF = Cystic fibrosis

peak $\dot{V}O_2$ = peak oxygen consumption

PFT = Pulmonary function testing

CPET = Cardiopulmonary exercise testing

VAS = Visual Analogue Score

6-MWT = Six-Minute Walk Test

MSWT = Modified Shuttle Walk Test

peak HR = peak Heart rate

SaO_2 = Oxygen saturation

RPE = Ratings of perceived exertion

3-MST = Three-Minute Step Test

HR = Heart rate

mMFT = modified Munich Fitness Test

FEV_1 = Forced expiratory volume in 1 s

PA = Physical activity

WAnT = Wingate Anaerobic Test

peak $\dot{V}_E$ = peak Ventilation

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Table

Table 1 Measurements obtained during field testing

Measurements	Three-Minute Step Test	Six-Minute Walk Test	Shuttle Test
Spirometry	pre and post	pre and post	pre and post
Heart rate	baseline and highest HR or continuous recording	baseline and highest HR or continuous recording	baseline and highest HR or continuous recording
Oxygen saturation	baseline and lowest SaO_2 or continuous recording	baseline and lowest SaO_2 or continuous recording	baseline and lowest SaO_2 or continuous recording
Breathlessness	Modified Borg Scale of Perceived Breathlessness; VAS; 15 Count Breathlessness Score	Modified Borg Scale of Perceived Breathlessness; VAS; 15 Count Breathlessness Score	Modified Borg Scale of Perceived Breathlessness; VAS; 15 Count Breathlessness Score
Muscle fatigue	Modified Borg Scale or Visual Analoque Score	Modified Borg Scale or Visual Analoque Score	Modified Borg Scale or Visual Analoque Score
Set length of test [min]	3	6	NA

Table 1 Measurements obtained during field testing « Continued »

Distance	NA	Distance walked	Distance walked

Abbreviations: HR, Heart rate; NA, not applicable; SaO_2, Oxygen saturation; VAS, Visual Analogue Score

RESPONSE TO REVIEWERS OF SUBMITTED MANUSCRIPT TO JOURNAL OF PEDIATRIC PHYSICAL THERAPY

CLINICAL EXERCISE TESTING AND TRAINING IN CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS

REVISED TITLE: CLINICAL EXERCISE TESTING IN CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS

Thank you very much for the careful review of our manuscript and comments and recommendations provided. We have revised our manuscript accordingly and made the appropriate amendments in response to the Reviewer's suggestions. We respond point-by-point to each comment of the reviewers. As suggested by both reviewers, we will submit a separate article focusing on exercise training in children and adolescent with cystic fibrosis and submit both articles simultaneously.

Response to Reviewer 1:

***Reviewer's comment*:** Maybe it is wise to make two manuscripts of this paper. The first one dealing with a review of field and laboratory tests; the second one dealing with an update of anaerobic and aerobic responses to exercise, including a case and general training recommendations

***Response*:** As suggested, we have split our manuscript into:

Part 1: "Clinical exercise testing in children and adolescents with cystic fibrosis" and

Part 2: “Exercise training in children and adolescents with cystic fibrosis”, which we will submit simultaneously.

***Reviewer’s comment*:** The methods section needs elaboration/clarification so that your literature study can be reproduced. With the current info it is not possible.

***Response*:** Further detailed information regarding the search strategy and selection process was added to our two manuscripts. *“We included studies of subjects with CF, independently of their disease severity, and type of physical training (aerobic training; anaerobic training; combination of aerobic and anaerobic training, as well as, inspiratory muscle training). As there is a lack of longitudinal studies on exercise training in children and adolescents with CF, the authors believe that there are too small a number of randomized controlled trials to allow a systematic Cochrane review. However, the authors propose that it is justified to include studies of shorter duration, different study designs and non-randomized controlled trials to present an overview of possible training effects in CF. This article is intended to be comprehensive, however, not exhaustive” (page 3).* According to your recommendation we included more detailed information on validity and reproducibility, as well as own experiences on each of the different field tests. The tests have been exactly described, that the clinician and physical therapist can make their choice of applying the tests. Normative values do not exist for each test, while this is mentioned in the revised manuscript. Furthermore, the modified Munich Fitness Test was added with a recently published paper focusing on physical fitness in a large number of children and adolescents with CF (Gruber et al, 2008).

Response to Reviewer 2:

***Reviewer's comment*:** The article needs to be reviewed for grammar, sentence structure, wording issues and content.

***Response*:** We have carefully corrected and revised our manuscript regarding issues, grammar and sentence structure. We believe our manuscripts read very well in its current format.

***Reviewer's comment*:** There needs to be consistent use of the terms "exercise testing", "field exercise testing", "formal exercise tests" ... etc.

***Response*:** We have made the appropriate change to the manuscript providing the necessary consistency.

***Reviewer's comment*:** There are errors in content (e.g. Line 60 to 61). Line 60 to 61 "As examined by Narang et al. the test is limited in its validity when working with children with moderate lung disease because of its low intensity." Narang et al discuss the limitation of using the 3MST in patients with mild, not moderate lung disease.

Response: The error was corrected accordingly (page 8).

***Reviewer's comment*:** Line 11, p. 4 - there is a discussion of the "modified Borg breathlessness Score." There are 2 distinct tests - the "15-Count Breathlessness Score" and the "Modified Borg Dyspnea Scale." In addition to the need to accurately identify these, there is a need to describe these.

Response: We have newly included a separate section on "Assessment of breathlessness" including a description of tools to assess breathlessness in children and adolescents with CF, which we believe shall satisfy the reviewer.

***Reviewer's comment*:** While the aim of the paper is to "review the most common field and laboratory tests,' all of the field tests should be described. In addition to the example of the Modified Borg or 15-Count Breathlessness Score, if the authors are to meet their aims, there should be descriptions of the field tests. An example involves

the shuttle tests which are only described as being 'incrementally and externally paced informal exercise tests." It does not describe what the test entails. In fact, the reader is informed that information about the testing can be found 'elsewhere.

Response: The tests included in the revised manuscript, have been described in more detail, providing clinicians and physical therapists a variety of choice of tests. A recent study applying the modified Munich Fitness Test was added to the revised manuscript, focusing on physical fitness in a large number of children and adolescents with CF (Gruber et al, 2008).

***Reviewer's comment*:** Some statements are vague. Line 57, p. 2 "Therefore, from a clinical point of view, a test must be able to answer the questions of the clinician." It would be helpful to address which questions the clinician would be looking to answer.

Response: In our revised manuscript, we have aimed to address aspects particularly interesting for the clinician.

***Reviewer's comment*:** The article often changes between the need for exercise, exercise protocols, and testing. It seems that it might be better organized if it dealt solely with exercise testing used for CF. While the information about training and sports recommendations is valuable, it might be better to include in a separate article so that the focus can be on assessment measures.

Response: We have split our manuscript accordingly and submit a second one providing an update on the aerobic and anaerobic response to exercise including a case report and general training recommendations for children and adolescents with CF.

Reviewer's comment: It is suggested that "people first" language be used throughout that the article would discuss individuals with CF instead of CF individuals.

Response: We have changed the wording of our revised manuscript accordingly.

Pediatric Physical Therapy

Copyright Transfer, Authorship Responsibility, and Financial Disclosure

Manuscript Title (the "Work"): Clinical Exercise Testing in Children and Adolescents with Cystic Fibrosis

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I would like to submit a research article to your journal for consideration as a publication. The article is entitled “Clinical Exercise Testing and Training in Children and Adolescents with Cystic Fibrosis” and I believe would be of interest to your readership. I can confirm that the article is original, has not been published elsewhere nor is currently under consideration with another journal. I can confirm all three authors have been involved in the writing of the article and consent has been obtained to submit to your journal. I look forward to hearing from you in the near future.

Yours faithfully

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Clinical Exercise Testing and Training in Children and Adolescents with Cystic Fibrosis

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Short Title: Exercise Testing and Training in Cystic Fibrosis

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Abstract

Life expectancy in Cystic Fibrosis (CF) has markedly increased over the last few decades. This increase is partially due to the multidisciplinary approach in CF therapy and exercise testing which has established an important role for prognosis. Exercise not only encompasses the assessment of functional capacity and morbidity, but is also central to demonstrating the benefits from therapy and training programmes. Regular exercise training can improve the aerobic and anaerobic capacity, increase inspiratory muscle strength, and enhance mucus clearance in the airways. Despite the growing interest and due to the beneficial effects of regular physical activity, standardised exercise testing followed by structured training is not common among clinicians. The aim of this article is to review the most common field and laboratory exercise tests, used in CF. Furthermore, it includes a clinical case report and provides training recommendations which should be an efficacious part of every patient's consultation.

Key words: pulmonary disease, exercise, aerobic fitness, training, physical activity

Introduction

Exercise Testing in Cystic Fibrosis (CF) is gaining clinical interest as an important tool to assess disease severity, functional ability and has been used as an outcome measure of therapy and exercise programmes (1;2), as well as a prognostic measure (3-6). There is little doubt that aerobic and anaerobic capacity is reduced in CF individuals, when compared to their healthy counterparts (7-10). This reduction may be explained by an impaired lung function and malnutrition. It has also been established that CF children with higher activity levels have a better aerobic and anaerobic fitness, nutritional status and significantly lower disease severity (11). It is known that higher aerobic fitness is associated with higher quality of life (11;12). Consequently, aerobic and anaerobic training has been shown to improve peak oxygen consumption (peak $\dot{V}O_2$), enhances sputum clearance in the airways, increases muscle mass and results in weight gain (1;13-16). Aerobic capacity and training has also been given more attention than anaerobic training in CF children. This is paradoxical as children's activity patterns are predominantly anaerobic in nature, as opposed to aerobic. Pulmonary function testing (PFT) at rest is widely used and an important tool to assess disease severity in patients with lung disease, but is not sufficient and accurate in predicting a patients exercise capacity (17;18). A combination of PFT, exercise testing and the assessment of quality of life may be a better outcome to assess the patient's overall health status (12). Apart from laboratory testing, exercise tests, such as the three minute step test, six-minute walking test and the modified shuttle test have been used to assess exercise tolerance, determine the suitability for undergoing lung transplantation, as well as, an outcome measure of treatment and therapy programmes in CF children. In terms of validity, precision and objectivity, formal laboratory testing with continuous respiratory gas analysis are the best method to assess a patient's exercise capacity. Therefore, from a clinical point of view, a test must be able to answer the questions of the clinician. As observed by Barker et al. (19) exercise testing is of clinical interest, even though clinicians do not use formal exercise tests as a routine

examination, because field tests are preferred. This may be explained by time constraints, a lack of equipment or expertise, staff and consumable costs. Clinicians should encourage their patients to be physically active in daily life because inactivity leads to further deconditioning in CF. Therefore, to provide safe and effective training and activity recommendations, exercise testing is necessary. The present paper aims to provide a review of field and laboratory exercise testing in CF children. Furthermore, an update on the aerobic and anaerobic response to exercise will be included and suggestions will be offered to the clinician with a special focus on peak $\dot{V}O_2$ testing, including practical training recommendations.

Method of Review

All relevant studies for review were located through computer searches of Medline and PubMed databases between the years 1958 and 2008. This procedure was enhanced with a search for bibliographies of accessed publications. Key descriptors were exercise testing, training, children, adolescents and cystic fibrosis (CF). One review article was found focusing on exercise testing in children with CF (20). The present review includes both, a summary of field exercise testing as well as laboratory exercise testing in CF, including a case report and recommendations for physical training.

Field Tests

Three Minute Step Test

The 3-minute step test (3MST), modified from the original Master two-step exercise test, is externally paced and has been used in CF children as an outcome measure of intravenous antibiotic treatment (21), to assess exercise capacity (22), symptomatic exercise tolerance (23), and as a suitability for lung transplantation (24). As examined by Narang et al. (22) the test is limited in its validity when working with children with moderate lung disease, because

of its low intensity. Compared with an incremental exercise test to exhaustion, clinically relevant information e.g. exercise induced arterial oxygen desaturation may be difficult to detect during the 3MST. The 3MST compared to a 6-minute walking test, produces a significantly higher heart rate and breathlessness score (modified Borg breathlessness Score), without any differences in oxygen saturation (23). However, the test is quick to perform, requires less space, but doesn't reflect a normal functional task and is not able to measure aerobic capacity.

Six Minute Walk Test

The six minute walk test (6MWT) has been modified from the original 12 minute running test (25) and the 12 minute walking test (26) to assess the physical capacity in individuals. As the 6MWT, it was shown to be useful and reproducible in patients with respiratory disease, for whom 12 minutes walking was too exhausting (27). In healthy children, the 6MWT has been revealed to be highly acceptable (28) and valid, as a significant correlation was established between the walking distance and $\dot{V}O_2$ max (r = 0.44) during an incremental treadmill exercise test (29). Several investigators found the test as useful and valuable in assessing exercise tolerance in CF children (30;31) and adults (32) with mild to moderate lung disease. Gulmans et al. (31) found a high correlation between the walking distance for two walking tests in each individual (r = 0.90). Furthermore, a significant correlation was determined between the walking distance and maximal power (watts) or $\dot{V}O_2$ max (r = 0.76) obtained in an incremental cycle ergometry test. The 6MWT as a self paced test is thus dependent on the patient's motivation with a tendency for submaximal effort. More studies are desirable to obtain information about its validity, including larger numbers of children with different stages of disease severity.

Shuttle Tests

Shuttle walking tests are incrementally and externally paced informal exercise tests. They can be performed as a 12-level or the modified 15-level test. Bradley et al. (33) found the modified shuttle test (MST) is a reliable and sensitive measure of exercise capacity in adults with CF. Twelve patients performed two shuttle walking tests within two weeks and a high correlation was found between walk distance, peak heart rates, oxygen saturation (SaO_2) and perceived breathlessness (r = 0.99). In children with CF the usefulness of the MST to measure exercise capacity and determine improvements after hospitalisation has been shown (34). Selvadurai et al. (35) compared two shuttle tests (10 m shuttle walk and 20 m shuttle run) with the results from treadmill exercise testing in CF patients with a wide range of disease severity and found both tests as reproducible and valid measures of exercise tolerance. Moreover, they reported a high correlation between the distance walked and measured peak $\dot{V}O_2$ values (r = 0.91). Furthermore, the test is useful in estimating peak aerobic capacity. In a recent study Coelho et al. (36) found no differences in walk distance between healthy and CF children (p = 0.20) with normal lung function and mild to moderate symptomatology, while the healthy controls showed higher ratings of perceived exertion (RPE) using the Borg Scale (p = 0.007). The modified shuttle test requires less space and is an inexpensive and alternative measure to formal laboratory testing in children with CF.

Summary

All the above mentioned exercise tests have shown to be useful when working with children and adolescents with CF. The tests can be combined with heart rate (HR) and oxygen saturation monitoring, RPE (Borg Scale) as well as breathlessness scores, e.g. the fifteen-count breathlessness score or the visual analogue score of perceived breathlessness (22;37). In comparison, the shuttle walk test has a stronger correlation with $\dot{V}O_2$ than the 6MWT. The 6MWT is self paced and has been shown to be submaximal in its effort. Compared to the step

test the 6MWT may rely more on patient motivation. In contrast as examined by Narang et al. (22) the step test may omit important and clinically essential information in patients with moderate lung disease, because of its low intensity. In CF children, the choice of each field test should be adapted for the individual according to the patient's ability and disease severity. More detailed information about the testing instruction for the 6MWT, the MSWT and the 3MST can be found elsewhere (23;38;39).

Anaerobic Exercise Tests

Anaerobic activities are characterized by very heavy intensities lasting typically up to 30 s and are characterised as being predominantly fuelled by non-oxidative sources for ATP resynthesis e.g. sprinting to a bus or doing a double back flip. The predominant energy is produced by the high energy phosphates; Adenosine triphosphate (ATP) and Phosphocreatine (PCr) or through anaerobic glycolysis. Glycolysis is the anaerobic degradation of glucose to two molecules of pyruvate, due to 10 enzymatically controlled chemical reactions, with lactate being formed as the end product of the anaerobic glycolysis. Further details can be found elsewhere (40;41).

Wingate Test

The Wingate Anaerobic Test (WAnT) is the most researched and applied test to assess maximal anaerobic performance in healthy children, as well as CF and other chronically diseased children (11;42-47). The WAnT is a 30 s all-out sprint test against a predetermined resistance on a cycle ergometer and is used to determine peak muscle power and muscle endurance measuring the peak power, mean power and the fatigue index. Interested readers seeking further information should consult Bar-Or (42) and Dotan and Bar-Or (48). When comparing children with CF and healthy children, their anaerobic capacity is reduced (7;43;44;49). The peak and mean power (watts) was found to be lower in CF patients when

correlated to percent fat free mass, rather than body mass (7;10;47). Other factors which may affect anaerobic performance in CF are genotype of mutation and maturational status (7;50). Boas et al. (43) investigated energy metabolism during anaerobic exercise in CF children and proposed that they may use lower percentages of their peak $\dot{V}O_2$ and peak ventilation ($\dot{V}_E$) during the WAnT, compared to asthmatics and healthy controls. This finding is thought to be mediated by a greater use of glycolytic metabolism in the CF children. Further studies have suggested that nutritional status is the main determinant affecting the anaerobic performance (7;10;44). In contrast Cabrera et al. (44) studied CF patients with a wide range of disease severity and found a negative relationship between impaired pulmonary function and anaerobic performance. As the authors noted themselves, the anaerobic performance in the WAnT depends to a high degree on anaerobic metabolism in the exercising muscle, and thus is largely independent from the oxygen transport system. This finding may not be significantly associated with the degree of lung impairment and anaerobic capacity as measured by WAnT. The WAnT also has shown to be useful as an outcome measure of training studies. Klijn and colleagues (13) found significant improvements in both aerobic and anaerobic (WAnT) parameters, after a 12 week individualised (2 days per week, 30-45 min) anaerobic training programme. After a 12 week follow up period, most outcome parameters decreased compared to the pre training level, except anaerobic performance and quality of life. Also, children with CF with higher levels of habitual activity have been found to have an increased anaerobic power in the WAnT and quality of life (11). More research would be beneficial in this field, especially in training studies, to provide more detailed recommendations during exercise programmes.

Aerobic Exercise Tests

Neither any physical activity nor exercise task can be considered as solely aerobic or anaerobic. However, aerobic activities refer to the predominant use of oxygen in the energy-

generating process. Typically, after ~90 s of maximal exercise, the oxidative contribution begins to dominant the resynthesis of ATP and exercise power or speed begins to decline. Oxidative metabolism begins with the entry of pyruvate in the mitochondria, a second stage of carbohydrate break down, namely the tricarboxylic acid cycle (TCA). This process is much slower, but possesses a greater capacity for energy generation than anaerobic pathways. Carbohydrates, free fatty acids (FFAs), amino acids and proteins all serve as energy releasers (40;41). Aerobic activities with moderate effort can be performed over hours without significant declines in exercise performance (although there is some variation on individual's physical fitness, energy intake during exercise, outside temperature etc). Aerobic capacity of CF children over a long period of time is not known.

Submaximal Exercise Tests

Submaximal exercise testing may be preferred for patients who are not able to perform a maximal exercise task. Barry and Gallagher (51) reported repeated submaximal exercise tests on the cycle ergometer (80 % of peak workload) as suitable to assess therapeutic benefits in adult CF patients. In a three month supervised running programme (1) and a 12 month unsupervised exercise training programme (52), heart rates at submaximal workloads significantly decreased as a result of improved cardiorespiratory fitness. Research has also been recently investigated into the oxygen uptake ($\dot{V}O_2$) kinetics in CF. Hebestreit et al. (53) found slower $\dot{V}O_2$ kinetics at the onset of exercise in CF children compared to healthy children. Although the kinetics protocols are laborious and require three to four repeat tests, which although interesting for further scientific related research are not considered practical in daily clinical practice. As shown, submaximal exercise testing is more valuable to determine benefits of training programmes. However, to detect limiting factors maximal exercise testing is necessary.

Maximal Exercise Tests

Maximal exercise tests can be performed on the cycle ergometer or treadmill combined with online analysis of expired air. The most often used protocols are the Godfrey (54) for cycle tests and the Bruce (55) protocol for treadmill testing. The choice of each protocol depends on the anthropometric variables, age and disease severity. An essential advantage of a cycle ergometer test is the reduced risk of injuries, an accurate and more comfortable record of additional parameters such as electrocardiogram, blood pressure, and oxygen saturation. Apart from the financial cost and space requirement, the treadmill test allows testing younger patients, a higher maximum values will be obtained (up to 10 %) compared to cycle testing, due to the higher amount of muscle mass moved during treadmill testing.

In CF, there are many reasons for maximal exercise testing. Studies have shown the usefulness of peak $\dot{V}O_2$ testing as a prognostic value (3-5) and investigators have found high correlations between aerobic capacity and quality of life (12). Nixon et al. (4) also reported positive associations between aerobic capacity ($\dot{V}O_2$ peak) and survival in CF patients over a period of eight years. Several training studies have shown improvements in aerobic fitness (1;15;56;57) despite methodological differences in the training parameters (duration, intensity, frequency) and type of exercises. Unfortunately, less longitudinal data are available to support beneficial effects of regularly physical activity on a long term basis. In a recent study Hebestreit et al. (58) investigated the relationship between physical activity (PA) and aerobic fitness ($\dot{V}O_2$ max) in CF patients (12-40 years) with a wide range of disease severity (FEV_1 25–107% predicted). The group report a significant relationship between PA and $\dot{V}O_2$ max, but independently for other variables such as body size, sex, lung function and muscle power.

Especially when testing children, safety guidelines have to be strictly followed. During formal laboratory exercise testing the continuous record of HR and SaO_2 during the test is useful not only for monitoring purposes but also in giving recommendations for training in CF. The exercise stress test should be terminated if SaO_2 drops below 75 % as recommended by Hebestreit et al. (59) and adopted in several studies (22;23). As an additional objective method, the gas-exchange threshold (GET) can be determined due to the continuous analysis of $\dot{V}O_2$ and $\dot{V}CO_2$ to estimate a threshold point (60). The following case report provides some practical applications for maximal exercise testing. These applications include the determination of baseline exercise capacity, to define exercise induced limitations, as well as to give safe and effective training recommendations.

Case Report

Clinical Findings

This 17-year-old boy with CF was referred to the hospital for routine intravenous antibiotic treatment and physiotherapy.

Measurements

Functional Capacity

The forced expiratory manoeuvre was performed according to the guidelines of the British Thoracic Society (61) using an electronic spirometer (Microloop ML3535; Numed, Sheffield, UK).

Maximal Exercise Testing

Maximal exercise testing was performed on an electronically braked cycle ergometer (Excalibur S port; Lode, Groningen, The Netherlands) using the Godfrey protocol (54). After a 2 minute warm up of unloaded pedalling, the work rate was increased by 10 W at 60 s

intervals until volitional exhaustion. The patient breathed through a mouthpiece from which ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}O_2$) and carbon dioxide ($\dot{V}CO_2$) production was analysed using a computerized breath-by-breath system (Cortex Metalyzer; Cortex Medical, Leipzig, Germany). Oxygen saturation (SaO_2) was monitored by a pulse oximeter (Tuffsat; Datex-Ohmeda, Colorado, USA). The ventilatory threshold was determined with the V-slope technique. Interpretation of aerobic fitness (peak $\dot{V}O_2$) was defined according to values described elsewhere (62).

Assessment of Disease Severity

The Shwachman score was used to assess disease severity and recorded prior to exercise testing (63). The score includes four separate parameters in the system (activity, physical examination, nutrition and chest radiographic findings). Each parameter has an assigned value of 25, while a hundred points represents a perfect score of health and reflects very accurately the patient's long-term prognosis.

Interpretation and Training Recommendations

This young patient has a severely impaired resting lung function (FEV_1 36%, Table 1). The peak $\dot{V}O_2$, maximum power as well as the threshold point are significantly reduced (Figure 1; Table 2;). The threshold point was determined at: a HR of 129 $b \cdot min^{-1}$; a work rate of 38 W and 42.7 % of peak $\dot{V}O_2$, while the maximum HR of 184 $b \cdot min^{-1}$ is reduced. During the incremental exercise test an arterial oxygen desaturation was determined, while SaO_2 dropped down to 87 % at maximal effort. At maximal effort the patient exceeded his predicted MVV (Figure 1), which is a limiting factor caused by the increased ventilatory demand and the decreased capacity. Moreover, the crossing of the MVV is a typical sign of an insufficient ventilatory reserve. In this case, the absolute maximum power workload reached at the end of

the test was 89 W (1.58 $W \cdot kg^{-1} \cdot min^{-1}$), but the physical capacity is significantly reduced due the pathological arterial oxygen saturation and the reduced ventilatory reserve. Unfortunately, in this case SaO_2 was not recorded continuously during the whole exercise test (only pre and post exercise SaO_2), which is an essential parameter to define exercise induced limitations and to give accurate training recommendations. For these reasons, cycle ergometer training for example should not exceed the work load and/or HR related to $SaO_2 \geq 90\%$, in order to prevent hypoxic conditions. The training parameters, such as HR (129 $b \cdot min^{-1}$) and power (38 W) obtained at the threshold point can be used for training sessions, with the request of a continuous record of SaO_2. In case of hypoxic conditions during training the power output has to be reduced, and/or resting periods increased. The low Shwachman score of 44 is congruent with the low functional capacity measured in this 17-y-old boy. Further training recommendations are discussed later in this article.

General Guidelines for Exercise and Training

Medical Check Up

Before commencing exercise the CF patient should consult a medical doctor and be carefully examined and advised about training. Therefore, pulmonary function testing at rest is important but not sufficient, while the examination should also include maximal exercise testing to provide objective data, as functional capacity and to detect pulmonary and cardial limitations. On that basis, fundamental criteria of physical training, such as the type of activity, training methods, frequency, duration, and intensity can be specified.

Exercise Training

The Clinical Guidelines for the Physiotherapy Management in the UK (64) support the fact that all patients with CF can exercise, while those with $FEV_1 > 55$ % predicted are able to

exercise at the same level as their healthy peers. Patients with severe disease and $FEV_1 < 55$ % predicted should be carefully tested and supervised during exercise.

Sports

When searching for sports the fun component should be the main consideration, but there are also some essential facts to be considered. We recommend performing different and varied activities, to improve endurance, strength, coordination and flexibility skills. As shown by Selvadurai et al. (15) exercise programmes including aerobic and anaerobic activities can be effective in improving muscle strength, lung function, quality of life and resulting in weight gain. Table 3 summarizes a selection of recommended exercises and activities with increased risk potential (e.g. pneumothorax) for the CF patient. Additional moderate strength training may include exercises for the whole body (arms, legs, back, and abdomen) with respect to the correct technical implementation and breathing work (expiration during contraction and inspiration during relaxation). The choice of each activity depends on the disease severity, social factors, time effort and the individual's interests. Whenever possible, we recommend participating in team sports, which may increase motivation in the long term and support more social integration. Before starting team sports, the therapist should be well informed about the typical characteristics of the disease (e.g. increased cough during exercise), whilst the patient should be able to rest whenever rest is needed. Next to exercise training, an active lifestyle in general may help to improve exercise capacity, for example using stairs instead of an elevator.

Training Components

Regarding training recommendations the general guidelines for healthy individuals are valid and can be used and transferred for the CF patient. Physical training can be characterised due to the components:

- intensity

- duration
- frequency
- type of activity

The proportion of training stimuli and recovery periods are essential to develop an individual's physical capacity, whereas permanent training at high intensities for example will lead to performance stagnancy or even cause physical damage in the CF patient. Particularly, CF patients may need longer resting times to recover after exercise than their healthy counterparts. Further prolonged $\dot{V}O_2$ kinetics after maximal exercise were found in CF adults, which could be explained by deconditioning and the oxygen cost of breathing, caused by an increased dead space and total ventilation (8). Whereas, improvements in aerobic capacity can be observed after a relatively short time, after terminating training the effects will rapidly decrease to pre training level. Training components can be found in Table 3. Conventional formulas to determine maximal HR according to age, and calculate training intensities are insufficient because maximum heart rates are reduced in CF. Therefore, training intensities should be individually determined during maximal exercise testing. While, the GET is relatively reliable to determine, there is no need to take blood lactate samples in pediatric populations. Furthermore, as a helpful tool and to supervise training, ratings of perceived exertion (65) and/or the fifteen-count breathlessness score (37) can be applied.

Precautions

Patients with advanced lung disease, and increased risk of arterial oxygen desaturation during exercise should continuously record their HR and SaO_2 with a portable pulse oximeter and HR monitor. During exercise, SaO_2 should be $\geq$ 90 % to prevent hypoxic conditions which may lead to a decrease in performance, increases pulmonary pressure and damages the heart function in long term. Additional oxygen supplementation during exercise at submaximal

work may avoid arterial oxygen desaturation as well as improve exercise performance in patients with advanced pulmonary disease (66-68). Patients with resting hypoxia (SaO_2 < 90 %) should generally exercise with additional oxygen supplementation. When suffering acute infections, patients should stop exercise and resume their training only after having consulted a medical doctor. Patients suffering CF related diabetes should be well trained about insulin dosages, the effects and risks of exercise (e.g. hypoglycaemia) and monitor their blood sugar levels in certain intervals. In order to prevent dehydration and excessive mineral loss (NaCl), sufficient fluids, ideally with higher salt contents, should be supplied during and after exercise, especially when exercising in hot environmental conditions (69;70). Moreover, children with CF may tend to underestimate their fluid loss during exercise and undergo the risk of excessive dehydration (69).

Table 4 summaries possible effects of exercise and training studied in CF. Unfortunately, few longitudinal data on the effects of exercise are available. Prolonged effects may also be complicated by the progressive character of the disease, less training possibilities during acute pulmonary exacerbations, motivation, as well as a certain sense of confidence to exercise with their healthy counterparts.

Conclusion

Exercise testing has shown to be valuable in the work with CF patients. Despite the beneficial effects of regularly exercise, clinical exercise testing is reported to be underused. Whenever possible, clinicians should include exercise testing as an additional diagnostic tool at least once a year as recommended in the UK. Moreover, it would be desirable to instruct patients about the beneficial effects of exercise and support them with effective training recommendations. Studies have shown that a combined training including aerobic and anaerobic activities may be most effective. Higher levels of habitual activity have been

associated with higher aerobic and anaerobic fitness, a better quality of life, as well as increased life expectancy. We conclude that, if no laboratory testing is available, field testing is an alternative, inexpensive and valid tool. Formal laboratory exercise testing may be limited by the cost and equipment, as well as the time and staff required in hospitals. Field exercise testing is more limited in detecting exercised induced limitations, which are essential in patients with pulmonary disease. With the experience of the authors, patients have to be well instructed about the testing procedure and the medical examiner needs to create a positive environment, whenever possible.

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Figure Title

Figure 1. Physiological responses during a maximal incremental cycle test to voluntary exhaustion (MVV = Maximal voluntary ventilation)

Abbreviations

CF = Cystic Fibrosis

$\dot{V}O_2$ = Oxygen Consumption

PFT = Pulmonary Function Testing

3MST = Three Minute Step Test

6MWT = Six Minute Walking Test

MST = Modified Shuttle Test

SaO_2 = Oxygen Saturation

RPE = Ratings of Perceived Exertion

HR = Heart Rate

MSWT = Modified Shuttle Walking Test

ATP = Adenosine Triphosphate

PCr = Phosphocreatine

WAnT = Wingate Anaerobic Test

$\dot{V}_E$ = Ventilation

TCA = Tricarboxylic Acid Cycle

FFAs = Fatty Free Acids

PA = Physical Activity

FEV_1 = Forced Expiratory Volume in 1 s

GET = Gas Exchange Threshold

$\dot{V}CO_2$ = Carbon Dioxide

MVV = Maximum Voluntary Ventilation

NACL = Sodium Chloride

Figure
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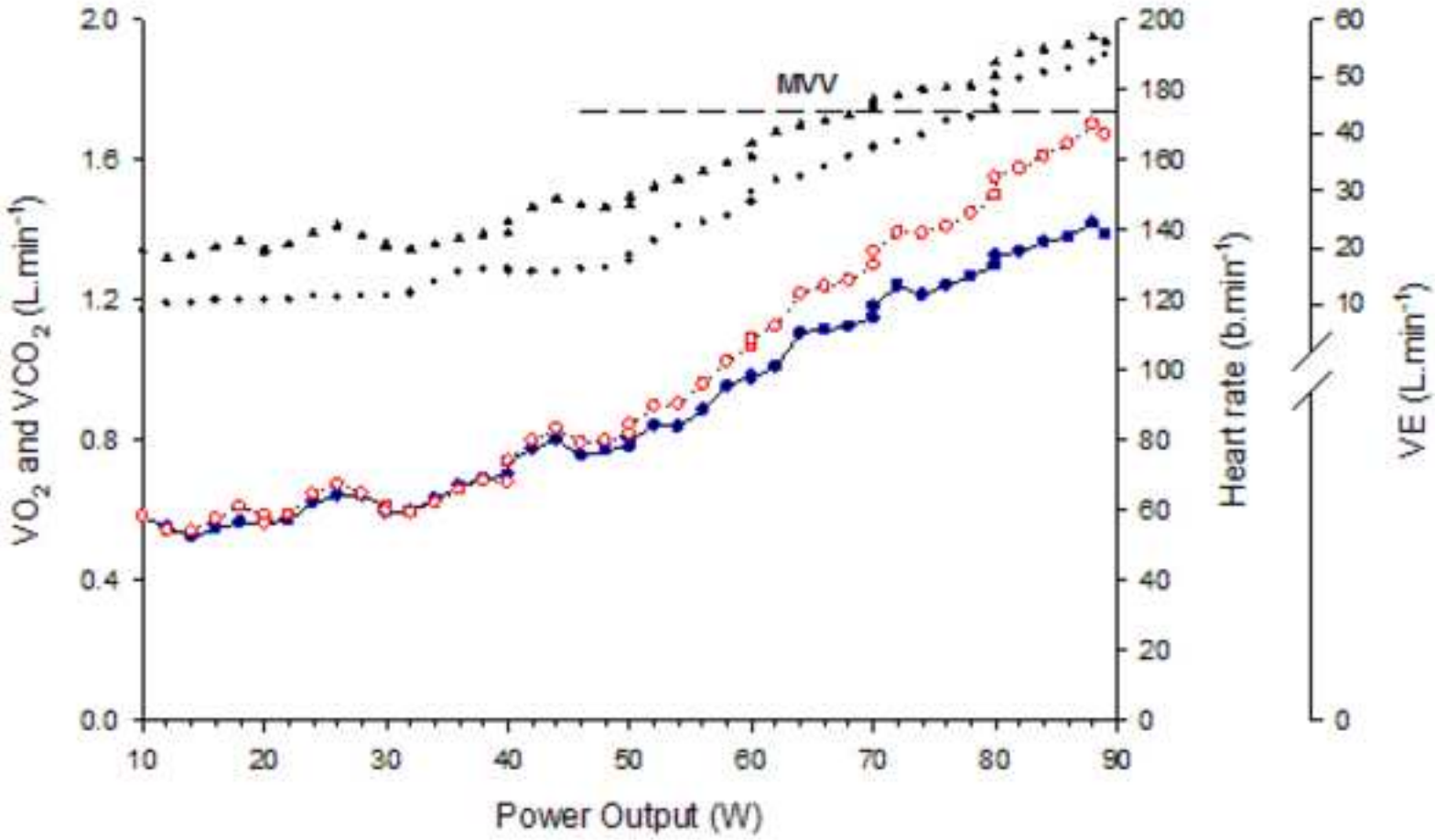

Figure 1. Physiological responses during a maximal incremental cycle test to voluntary exhaustion (MVV = Maximum voluntary ventilation)

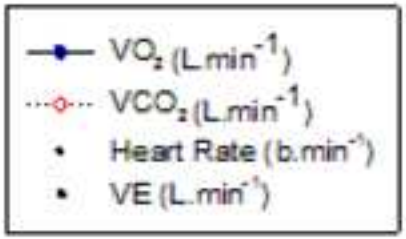

Table 1 Patient Characteristics of the Case Study

Variable	Measured	Predicted (%)
Age, yr	17	
Sex	male	
Height, cm	161	
Weight, kg	56.4	
BMI, kg/m^2	21.5	
Skinfold, mm	56.6	
VC, L	2.17	52
FEV_1, L	1.30	36
Resting SaO_2, %	95	
Shwachman Score	44	

BMI = body mass index; VC = vital capacity; FEV_1 = forced expiratory volume in 1s; SaO_2 = oxygen saturation.

Table 2 Peak Exercise Data

Variable	Measured	Predicted (%)
$\dot{V}_E$ peak, $L \cdot min^{-1}$	56.3	
$\dot{V}_E$ peak/predicted MVV, %	123.7	
$\dot{V}O_2$ peak, $L \cdot min^{-1}$	1.39	
$\dot{V}O_2$ peak, $mL \cdot kg^{-1} \cdot min^{-1}$	25.0	51%
AT/ $\dot{V}O_2$ peak, $L \cdot min^{-1}$	0.69	
$\dot{V}_E / \dot{V}O_2$	40.5	
$\dot{V}_E / \dot{V}CO_2$	33.6	
RER	1.20	
Wmax, W	89	
Wmax, W/kg/BW	1.58	
HRmax, $b \cdot min^{-1}$	190	
SaO_2, %	87	

$\dot{V}_E$ = minute ventilation; MVV= maximum voluntary ventilation; $\dot{V}O_2$ peak = peak oxygen consumption; AT = anaerobic threshold; $\dot{V}_E / \dot{V}O_2$ = ventilatory equivalent for oxygen; $\dot{V}_E / \dot{V}CO_2$ = ventilatory equivalent for carbon dioxide; RER = respiratory exchange ratio; Wmax = maximum work load; HRmax = maximum heart rate.

Table 3 General Exercise and Training Recommendations

	CF patients without pulmonary limitations and arterial oxygen desaturations	***Patients with (severe) arterial oxygen desaturations and/or transplanted patients***
Recommended activities	cycling, walking, hiking, running, rowing, tennis, swimming, climbing and roller-skating	ergometric cycling, walking, strength training and gymnastics
Method	Intermittent and steady-state	Intermittent
Duration	30-45 minutes	20 minutes
Intensity	70-85% HRmax; 60-80% peak $\dot{V}O_2$; LT; GET	60-80% HRmax; 50-70% peak $\dot{V}O_2$; LT; GET
Frequency	3-5 times per week	5 times per week
Oxygen supplementation	not necessary	permanent oxygen supplementation
Activities to avoid	bungee-jumping, high diving and scuba diving	bungee-jumping, high diving, scuba diving and hiking in high altitude

HRmax = maximum heart rate; LT = lactate threshold; GET = gas exchange threshold

Table 4 Possible Effects of Exercise in Cystic Fibrosis

	Effects	***Comments***	***References***
Cardio-Pulmonary System	Improved lung function and decelerate decline in lung function (FEV_1; FVC) over 3 years. Partially improved FVC and TLC.	Effects of exercise on lung function are only verifiably in some training studies in CF. Longitudinal and controlled studies would be desirable to confirm possible effects.	[15;67-69]
	Increased inspiratory muscle strength and endurance.		[70-72]
	Enhanced sputum clearance in the airways, improved $\dot{V}_E$ and lower breathlessness.	Exercise in combination with physiotherapy may have the best effects.	[14;53;69-71]
	Improved aerobic fitness ($\dot{V}O_2$ max) and reduced HR at rest and submaximal exercise levels.	After completion of training, improvements will drop back to baseline level.	[1;15;53;70]
Strength	Increased anaerobic power, muscle strength, and muscle size.	Strength was measured using different methods: Wingate Test; isokinetic dynamometer; manual muscle testing techniques and circumference measures or one repetition maximum weight lifts.	[13;15;16;52]
Body Composition	Increased FFM, weight gain respectively weight stabilization after training. Bone health?	Unfortunately, there have been no controlled intervention studies investigating the effects of training on bone mass and bone density, whereas studies have shown that children with CF are able to perform high intensity exercises. Investigators found higher levels of PA and energy expenditure associated with higher BMD in CF.	[73-75]
Quality of Life	Improved QoL and psychological status (less anxiety and depression scores). Higher degree of perceived confidence and self-esteem.	Higher habitual activity is correlated with higher QoL in CF.	[1;11;12;67;76]
Life Expectancy	Patients with higher $\dot{V}O_2$ max values may have a greater life expectancy and a more slowly progressive disease.	Higher levels of aerobic fitness have shown to be associated with a significantly lower risk of dying, whereas patients with high aerobic fitness were more than 3 times likely to survive.	[4]

FEV_1 = forced expiratory volume in 1s; FVC= forced vital capacity; TLC= total lung capacity; $\dot{V}_E$ = minute ventilation; $\dot{V}O_2$ max = maximal oxygen consumption; HR = heart rate; FFM = fat free mass; PA = physical activity; BMD = bone mineral density; QoL = quality of life.