Clinical Exercise Testing in Children and Adolescents with Cystic Fibrosis

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Purpose: To review the most common field and laboratory exercise tests available for children and adolescents with cystic fibrosis (CF). Methods: Relevant studies for this review were identified by electronic search of Medline and PubMed databases between the years 1958 and 2008. The bibliographies of all accessed publications were also searched. Key descriptors were cystic fibrosis, exercise testing, aerobic fitness, children, and adolescents. Results: Five field tests were selected for presentation, including discussion of their strengths and weaknesses. Laboratory tests measuring aerobic and anaerobic responses to exercise in children with CF were also selected for presentation and discussed along with a summary of safety considerations for exercise testing of children with CF. 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 annually. (Pediatr Phys Ther 2009;21:275–281) Key words: aerobic fitness, children, cystic fibrosis, exercise, physical activity

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 programs, as well as for prognostic purposes.1–6 It has been established that aerobic and anaerobic capacities are reduced in most patients with CF when compared with that of 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 \( \text{VO}_2 \)), to enhance airway mucous clearance, and to increase muscle mass, resulting in weight gain.3,13–16 In CF, aerobic capacity and training have 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,19 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 and the lack of expertise,
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 4 authors (T.R., D.S.) independently preselected relevant studies to be included in this article. The further selection of studies presented in the review was based on the agreement of all 4 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). Because there is a lack of longitudinal studies on exercise training in children and adolescents with CF, the authors believe that there are too few 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 nonrandomized, 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 but not exhaustive.

Field Tests

Assessment of Breathlessness. In patients with CF, breathlessness is a common clinical symptom during physical exertion. Breathlessness is a subjective sensation, not necessarily associated with clinical symptoms such as wheezing and coughing. However, breathlessness is often associated with fear and panic, resulting in reluctance to participate in physical activity (PA). Depending on the pulmonary disease severity, dyspnea can occur during exercise or even at rest. Several tools are available to quantify breathlessness during exercise testing; however, 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 analog score are subjective measures to assess breathlessness. The original Borg Scale of perceived exertion was modified to assess perceived breathlessness during exercise. The patient is asked to rate his or her feeling regarding shortness of breath (0 = no breathlessness at all; 10 = breathlessness at rest). The visual analog score 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 his or her actual perception of breathlessness, starting on the left (zero), labeled 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 (in millimeters). In contrast to subjective assessments of breathlessness, the 15-count breathlessness score aims to objectively evaluate breathlessness, a method that has also been tested in children with CF. 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, amounts to the final score. The minimum score is, therefore, 1. Most clinical studies in children with CF use combinations of subjective and objective measures of breathlessness.

6-Minute Walk Test (MWT). The 6-MWT has been modified from the original 12-minute running test and the 12-MWT to assess the physical capacity of individuals. The 6-MWT is a practical and simple test that primarily measures the distance a patient can quickly walk in 6 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 m; however, there is no effect on the length of straight courses. The turnaround points and a starting line are marked with cones or colored tape placed on the floor. A stopwatch is required to monitor testing time; turnarounds must be recorded to measure the covered walking distance. Although 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 seem 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, he or she is required to stay behind the patient to avoid influencing the patient’s walking speed. Furthermore, in terms of standardization, we recommend that ideally the test be supervised and controlled by the same person, 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-MWT is too exhausting. In children who are healthy, the 6-MWT has been shown to be highly acceptable and valid, with a significant correlation between the walking distance and peak VO₂ during an incremental treadmill exercise test. Normative values for children who are healthy have been published. Normative values for children with CF, however, are not available. Several investigators have described the 6-MWT as useful and valuable in assessing exercise tolerance in children and adults with CF with mild to moderate lung disease. Gulmans et al found a high correlation between the walking distance for 2 walking tests in each individual. Furthermore, a significant correlation was determined between the walking distance and maximal power (watts) or peak VO₂ 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 may represent...
submaximal effort. More studies are needed to obtain information about its validity, including larger numbers of children with CF at different stages of disease severity.

**Shuttle Tests.** Shuttle walking tests are incrementally and externally paced exercise tests that can be performed as a 12-level shuttle test or the modified 15-level shuttle test. Bradley et al\(^a\) showed that the modified shuttle walking test (MSWT) is a reliable and sensitive measure of exercise capacity in adults with CF. Twelve patients performed 2 MSWTs within 2 weeks, revealing a high correlation between distance walked, peak heart rate (HR), 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 prerecorded 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 m 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\(^a\) compared 2 shuttle tests (10-m shuttle walk and 20-m shuttle run) with the results from treadmill exercise testing in patients with CF 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 Vo\(_2\) values.\(^{34}\) Furthermore, the MSWT is useful in estimating peak aerobic capacity. In a recent study, Coelho et al\(^a\) demonstrated no differences in distance walked between children who are healthy and children with CF with normal lung function and mild to moderate symptoms, whereas healthy controls showed significantly higher ratings of perceived exertion using the Borg Scale. The MSWT requires less space and is an inexpensive and appropriate alternative measure compared with CPET in children with CF.

**3-Minute Step Test (MST).** The 3-MST, modified from the original “master 2-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, particularly if longitudinal data of individuals are compared. As examined by Narang et al,\(^{38}\) the 3-MST is limited in its validity if applied to children with mild lung disease because of its low intensity. Compared with an incremental exercise test with exhaustion, clinically relevant information such as exercise-induced arterial oxygen desaturation may be missed using the 3-MST. However, compared with a 6-MWT, the 3-MST produces a significantly higher 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.

**Modified Munich Fitness Test (mMFT).** The mMFT has been adapted from the MFT.\(^{41}\) The original version is a well-known and widely accepted test that was developed to assess the physical fitness of school children 6–18 years of age. The mMFT includes the following 4 tasks.

1. **Balancing and bouncing:** standing on a beam and bouncing a ball with both hands as fast as possible for 30 seconds. The total number of correctly performed bounces is the score.
2. **Accurate throw:** a 500-g bean bag has to be thrown to 5 target fields at a distance of 3 m away from the throwing line. Each field has a certain number (1–2–3–2–1). The number of 5 correctly performed attempts is summed to create the score.
3. **Trunk flexibility:** standing on a beam, keeping one’s feet together and reaching forward from the standing position with knees straight. The better of 2 attempts is scored (in centimeters).
4. **Standing vertical jumping:** jumping as high as possible from the standing position with bent knees. The difference between the highest standing reach and highest jumping reach in 2 attempts is calculated (in centimeters).

The individual testing results enable comparisons with a normative standard. Detailed instructions for the test (in German only) are available at www.sportunterricht.de. The only study including the mMFT was performed in a large group of 286 children and adolescents with mild to moderate CF (6–18 years of age) during 4- to 6-week inpatient rehabilitation. Compared with children who are healthy, test scores of children with CF were lower but within normal range. Improvements were seen on all test tasks after an inpatient training regimen. Gruber et al\(^a\) showed that the mMFT is a valid and useful tool to assess several components of physical fitness, including endurance capacity, flexibility, and balance and motor skills in children with CF. Most other studies focus solely on increased aerobic fitness (peak Vo\(_2\)) 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, because of improved motor skills, activities of daily living could be implemented more easily. More studies need to be performed 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 been 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, except the mMFT. The latter test is not appropriate to assess aerobic fitness or provoking symptomatic exercise tolerance in CF. However, each test discussed incorporates specific advantages and disadvantages. For example, the shuttle walk test has a stronger correlation with oxygen consumption (VO₂) than the 6-MWT. The 6-MWT is self-paced and has, therefore, been shown to be submaximal in its effort. In particular, compared with the step test, the 6-MWT relies more on patient motivation. In contrast, the step test may miss important clinical information in patients with mild to moderate CF lung disease because of 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, because the mMFT 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.

**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 later.

**Submaximal Exercise Tests.** Submaximal exercise testing may be a preferred method for patients who are not able to perform a maximal exercise task. Barry and Gallagher reported repeated submaximal exercise tests on the cycle ergometer (80% of peak workload) as a suitable technique to assess therapeutic benefits in adults with CF. In a 3-month supervised running program and a 12-month unsupervised exercise training program, HR at submaximal workloads significantly decreased as a result of improved cardiopulmonary fitness. Recently, VO₂ kinetics in CF was investigated. Hebestreit et al reported slower VO₂ kinetics at the onset of exercise in children with CF compared with that of children who are healthy. However, kinetics protocols are not considered practical in daily clinical care because they are laborious and require 3 to 4 repeated tests. They are, therefore, regarded as a research tool. Submaximal exercise testing is, thus, more valuable to determine benefits of training programs. However, to detect limiting factors, maximal exercise testing is a preferred method.

**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 VO₂, during an incremental exercise test to exhaustion, are 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. Godfrey's cycle protocol starts with a workload of 0 W for 2 minutes, with the workload being increased in 10-, 15-, or 20-W increments, depending on the patient's height (<120 cm, 10 W; 120–150 cm, 15 W; and >150 cm, 20 W). 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 1.7 mph and an incline of 10%. At 3-minute intervals, the incline increases by 2% and the speed by 2.7, 3.4, 4.2, 5.0, 5.5, 6.0, 6.5, 7.0, and 7.5 mph, respectively, until exhaustion. Advantages of a cycle ergometer test are

**TABLE 1**

Measurements Obtained During Field Testing

| Measurements         | 3-Minute Step Test                          | 6-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 Sao2 or continuous recording | Baseline and lowest Sao2 or continuous recording | Baseline and lowest Sao2 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 analog score  | Modified Borg Scale or visual analog score  | Modified Borg Scale or visual analog score |
| Set length of test, min | 3                                            | 6                                            | NA                                        |
| Distance             | NA                                          | Distance walked                              | Distance walked                           |

HR, heart rate; NA, not applicable; Sao2, oxygen saturation; VAS, visual analog score.
the reduced risk of injuries and an accurate and more comfortable record of additional parameters such as electrocardiogram, blood pressure, and SaO2. Apart from financial implications and space requirements, the treadmill test is particularly applicable for younger patients. Furthermore, higher maximum values for VO2 are obtained (up to 10%) compared with cycle testing because of the higher amount of muscle mass involved. In CF, there are many indications for CPET.

Studies have shown the usefulness of peak VO2 testing for prognostic purposes, and investigators have also documented high correlations between aerobic capacity and quality of life.1,2,4,12 Nixon et al2 also reported a positive association between aerobic capacity (peak VO2) and survival in CF over an extended period of 8 years. In another longitudinal observation of 28 children with CF between 8 and 17 years of age, a correlation between forced expiratory volume in 1 second (FEV1) and peak VO2 was found.4 Furthermore, the decline in FEV1 was correlated with the change in peak VO2 in individuals over a 5-year period.

Several training studies have shown improvements in aerobic fitness regardless of methodological differences in training parameters obtained (duration, intensity, frequency) and type of exercises.3,13,48,49 Unfortunately, fewer longitudinal data are available to support beneficial effects of regular PA. In a recent study, the relationship between PA and aerobic fitness (peak VO2) was investigated in patients with CF (12–40 years of age) with a wide range of pulmonary disease severity (FEV1 25%–107% predicted).50 The study revealed a significant relationship between PA and peak VO2, independent of other variables such as body size, sex, lung function, and muscle power.

Wingate Test. The Wingate Anaerobic Test (WAnT) is the most thoroughly investigated and applied test to assess maximal anaerobic performance in children who are healthy, as well as children with CF and other chronic diseases.11,51–56 The WAnT is a 30-second all-out sprint test against a predetermined 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 supramaximal tasks, measuring peak muscle power and muscle endurance (peak power, mean power, and fatigue index). Usually, a warm-up (3–5 minutes) is performed including a few sprints (3–5 seconds) to get the subject familiarized with the test procedure. Detailed information regarding the test protocols is described elsewhere.31,57 When comparing children with CF and children who are healthy, their anaerobic capacity is reduced.7,52–54,58 Peak and mean power (watts) is lower in patients with CF in correlation to the percentage of fat-free mass rather than body mass.7,10,56 Other factors that may affect anaerobic performance in CF are CF genotype and maturational status.7,59 Boas et al12 investigated energy metabolism during anaerobic exercise in children with CF and proposed that lower percentages of peak VO2 and peak ventilation (peak VE) during the WAnT may be used compared with asthmatics and healthy controls. This is most likely mediated by a greater use of glycolytic metabolism in CF. Studies have also suggested that nutritional status is one of the main determinants affecting anaerobic performance.7,10,53 In contrast, Cabrera et al53 studied patients with CF with a wide range of pulmonary disease severity and showed a negative relationship between impaired pulmonary function and anaerobic performance. The authors reported that anaerobic performance during the WAnT depends highly on anaerobic metabolism in the exercising muscle and is thus largely independent of the oxygen transport system. This finding, however, 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 et al13 showed significant improvements in both aerobic and anaerobic WAnT parameters after a 12-week individualized anaerobic training program (2 days per week, 30–45 minutes). After a 12-week follow-up period, most outcome parameters decreased compared with those of pretraining levels, except anaerobic performance and quality of life. Moreover, children with CF with higher levels of habitual activity have been found to possess increased anaerobic power during the WAnT and in the 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 must be followed during exercise testing, particularly when children are involved. Therefore, resuscitation equipment and trained personnel must be available. Compared with children who are healthy, children with CF are at a higher risk of cardiorespiratory compromise during exercise (eg, hypoxemia, bronchoconstriction, and pneumothorax). During laboratory exercise testing, the continuous monitoring of HR and SaO2 during the test is indicated. Any exercise stress test should be terminated if the SaO2 drops below 75%.37,60,61 If supplemental oxygen is required during an exercise test, clinical details need to be documented and the amount of supplemental oxygen should be 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 as 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 yearly because 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 VO₂ is correlated with lung function and seems 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 must be well instructed regarding the test procedure, and the clinician and the CF team should be encouraged to create a positive environment whenever possible.

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