# Exercise Testing in Cystic Fibrosis

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**Abstract**

Cystic fibrosis (CF) is the most frequent genetic disease in the Caucasian population. It is characterized by absent or incorrect function of the channel that regulates the chloride exchange at cell surface (CTRF). The lungs are particularly involved as the very thick and tenacious mucus leads to progressive airflow limitation, respiratory infections, bronchiectasis, lung destruction, and ultimately respiratory failure. Dyspnea and exercise intolerance are the hallmarks of the diseases. Patients, however, should be encouraged to exercise regularly since early childhood because it promotes expectoration and contributes to good nutritional status and overall level of fitness. In addition, there are no contraindications to agonist sports. It follows that a growing number of CF patients will be referred to exercise-based evaluations in the forthcoming years. Cardiopulmonary exercise testing (CPET), in particular, is useful to determine the mechanisms of exercise intolerance in individual patients which may have treatment and prognostic implications.

## 6.1 Introduction

Cystic fibrosis (CF) is the most frequent genetic disease in the Caucasian population due to the absent or incorrect function of the channel that regulates the chloride exchange at cell surface (CTRF). Because of the systemic nature of

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the disease, many organs are involved; the lungs, however, are mainly affected because of progressive chronic obstructive disease, secondary to the very thick and tenacious mucus that leads to respiratory infections, bronchiectasis, lung destruction, and ultimately respiratory failure. Exercise tolerance is a very well-known prognostic index in CF [1], as it is in many chronic pulmonary and cardiac disorders. Patients with CF should be encouraged to exercise regularly and to have a very active lifestyle from a physical activity point of view, together in keeping a good nutritional state. In CF patients several studies have demonstrated that regular exercise and physical activity together with a good nutritional state are capable to reduce the rate of decline in lung function. Exercise training programs and pulmonary physiotherapy are fundamental therapeutic strategies aimed at improving mucus clearance and at reducing rates of pulmonary exacerbations.

### 6.1.1 Indications to CPET in CF Patients

It is well known that measurements of lung function, such as $FEV_1$, obtained at rest provide only a rough estimation of exercise tolerance in patients with CF [2, 3]. Therefore, particularly in the mild and moderate phases of the disease, the evaluation of exercise tolerance should be obtained by using the most appropriate tool and exercise protocol. Cardiopulmonary exercise testing is considered the "gold standard" for the assessment of exercise tolerance [2] in many diseases states. CPET, in addition to clearly define maximal power output ($W_{max}$) and peak $O_2$ uptake ($V'O_{2peak}$), provides information of the ventilator response/efficiency ($V'_E/V'CO_2$), of the cardiovascular and metabolic responses to exercise. CF patients with $V'O_{2peak} > 82\%$ predicted normal have more than three times as likely to survive for 8 years than those with low $V'O_{2peak} < 58\%$ predicted [1] (Fig. 6.1). Also, CF patients with a $V'O_{2peak} < 32$ mL/min/kg had an increase in mortality compared to those with $V'O_{2peak} > 45$ mL/min/kg [4]. The following are the indications to CPET in CF (Table 6.1).

### 6.1.2 CPET Protocols

During CPET measurement of lung gases ($O_2$ and $CO_2$), minute ventilation ($V'_E$), heart rate (HR), arterial blood pressure (BP), and peripheral arterial $O_2$ saturation ($SpO_2$) are obtained. Calculated variables include $V'O_2$, carbon dioxide output ($V'CO_2$), breathing reserve (i.e., $V'_{Epeak}$/maximal voluntary ventilation or MMV), HR reserve (HRR = (220 − age) − $HR_{peak}$), and $O_2$ pulse ($O_2$ pulse = $V'O_2$/HR). Important additional information is provided with measurements of symptoms (dyspnea and leg fatigue), inspiratory capacity (IC), arterial blood gases ($PaO_2$ and $PaCO_2$), and blood lactate (La-) obtained at rest, during and at peak of exercise. In adult subjects the maximal incremental ramp test on a cycle ergometer is the protocol recommended by the ERS [2]; the test is expected to last 10–12 min during

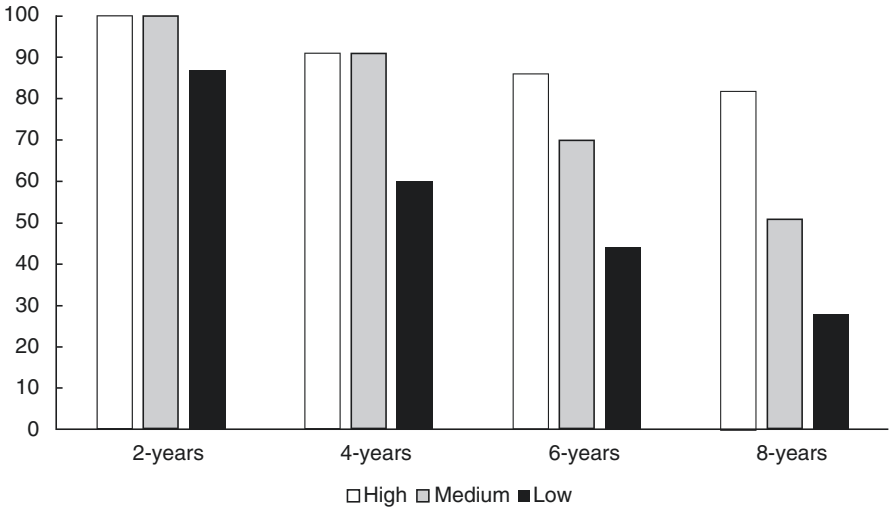


**Fig. 6.1** Rate of survival (%) among CF patients according to aerobic fitness (i.e., maximal aerobic capacity). Level of fitness according to maximal aerobic capacity ($V'O_{2peak}$) measured during cardiopulmonary exercise testing (CPET). High, $V'O_{2peak} \geq 82\%$ predicted; medium, $V'O_{2peak} = 81 - 59\%$ predicted; low, $V'O_{2peak} \leq 58\%$ predicted (According to data from Ref. [1])

**Table 6.1** Indications to CPET in CF

| |
|---|
| 1. Functional and prognostic evaluation. |
| 2. Evaluation of the causes of exercise intolerance. |
| 3. Detection of exercise-induced bronchoconstriction. |
| 4. Detection of exercise-induced arterial oxygen desaturation. |
| 5. Preoperative evaluation, e.g., lung transplantation. |
| 6. Exercise prescription before exercise-based rehabilitation. |
| 7. Evaluation of therapeutic interventions, e.g., drugs, rehabilitation. |

which subject is pushed to his/her limit of tolerance. In CF children, the maximal incremental Godfrey cycle ergometer protocol [4] has been utilized extensively. It requires the subject to maintain a rate of 60 revolutions per minute while the load is increased every minute until volitional fatigue. Treadmill exercise protocols have been widely used in clinical assessment of myocardial ischemia in adult subjects, being the Bruce protocol [5] the most utilized; this protocol has been utilized to detect changes with interventions in children with CF [6]. The Bruce protocol requires the subject to walk initially and run subsequently on a treadmill, where both the speed and the gradient of incline are increased every 3 min. It should be kept in mind that power output during a treadmill test is estimated, while with cycle ergometer exercise, a precise measurement of power output is obtained if the ergometer is calibrated routinely; if measurement of work efficiency (i.e., $V'O_2/W$) is required, the cycle ergometer or another calibrated ergometer (e.g., arm ergometer) should be used.

### 6.1.3 Factors Limiting Exercise Tolerance in CF Detected at CPET

In the advanced phase of the disease, CF patients are usually exercise limited by ventilatory constraints (e.g., low $FEV_1$). However, "peripheral factors" related to deconditioning and/or to poor nutritional state may play a very important role. Dyspnea and leg fatigue are usually the symptoms limiting exercise tolerance in CF. Interestingly, as shown in a recent published study, the frequency of these two symptoms in stopping exercise does not differ, CF versus control [7]. Poor skeletal muscle condition, with reduced muscle mass and force, is associated with low aerobic capacity and early lactate production; this may lead to increase ventilatory requirement during exercise (i.e., higher $V'_E/W$).

As in other chronic respiratory diseases such as chronic obstructive pulmonary diseases (COPD), patients with CF may experience lung dynamic hyperinflation (DH) during exercise [8]. Since DH highly correlates with dyspnea sensation and is susceptible to treatment with bronchodilators, this negative mechanism should be ruled out during exercise testing through measurements of IC and end expiratory lung volume (EELV). Arterial oxygen desaturation may be observed during exercise. In other diseases such as COPD and lung fibrosis, arterial oxygen desaturation usually occurs when diffusion lung CO (DLco) is < 50% of predicted; also, arterial oxygen desaturation is more evident during walking compared to cycling exercise [9]. In some CF patients, due to the deconditioning of peripheral muscles and poor muscle energy, anaerobic metabolism with lactate production occurs at the beginning of the exercise. The anaerobic contribution to exercise metabolism (in addition to the aerobic one) can be detected noninvasively by the use of the lactate threshold (LT). The recommended graphical method to detect LT is the "V-slope" originally described by Beaver et al. [10]; by plotting exercise $V'CO_2$ and $V'O_2$, data is possible to detect a change in the slope of the relationship that indicates LT. In normal subjects, LT occurs at 40–50% of the predicted $VO_{2max}$. Ultimately CPET helps in determining not only the degree of exercise limitation (i.e., $V'O_{2peak}$) that predicts prognosis in CF [1] but also gives a better insight on the causes of the reduced exercise tolerance. The possible causes of exercise intolerance (i.e., low $V'O_{2peak}$) detectable at CPET in CF are illustrated in Table 6.2.

**Table 6.2** Possible causes of exercise intolerance in CF

| Cause | CPET finding |
|---|---|
| 1. Reduced ventilatory capacity. | Low breathing reserve; high $V'_E/V'O_2$ |
| 2. Deconditioning, poor nutritional state. | Early LT, high $HR/V'O_2$ |
| 3. Exercise-induced bronchoconstriction. | >10% drop in baseline $FEV_1$ |
| 4. Exercise-induced arterial oxygen desaturation. | >4% drop in baseline $SpO_2$ |
| 5. Pulmonary hypertension (rare). | $V'O_2/W$ slope < 8 |
| | High $V'_E/V'CO_2$ (slope and nadir) |
| | Low $O_2$ pulse; high $HR/V'O_2$ |

### 6.1.4 Field Tests

When exercise lung gas exchange equipment are not available, field tests can be utilized. These tests are however less sensitive than CPET in assessing the degree of exercise intolerance and the responses to treatment, compared to the constant work exercise protocols at CPET [11]. The distance covered at the 6-min walking test (6 MWT) or the number of steps climbed during a 3-min step test [12] has been utilized in CF studies to evaluate the response to therapeutic intervention. It is recommended to measure HR and $SpO_2$ at baseline and at peak exercise. While the 6 MWT is a self-paced walking test that roughly correlates with $V'O_{2peak}$ measured at CPET, the "shuttle test" is an incremental externally paced audio signal. The highest speed measured at shuttle test better correlates, compared to 6 MWT, with $V'O_{2peak}$ measured at CPET [13].

### 6.1.5 Pulmonary Exercise-Based Rehabilitation in CF

Patients with CF should be encouraged to exercise regularly since the early years of life. It has been demonstrated that even moderate exercise promotes sputum expectoration by increasing airway lining fluid [14, 15]. Exercise-based rehabilitation programs clearly demonstrated beneficial effects in CF patients [16–18]. In addition, exercise-based rehabilitation programs have demonstrated to reduce the rate of pulmonary exacerbations [19]. A Cochrane review is available that demonstrates definitive benefit of exercise programs in subjects with CF [20].

### 6.1.6 Daily Physical Activity in CF

In normal individuals, the levels of daily physical activity (PA) and maximal exercise tolerance are somewhat related. Recent studies from our laboratory have demonstrated that in CF levels of PA are better evaluated by the use of accelerometers compared to questionnaires [21]. In addition, we were able to demonstrate that daily PA positively correlated with maximal aerobic fitness (i.e., $V'O_{2peak}$) [22]. Perhaps more importantly, adult CF patients with more pulmonary exacerbations in the preceding year have more advanced disease and are less active than their peers; in this study PA was independently associated with gender and airflow obstruction, being the females less active than males [23].

**Key Points**

- Cystic fibrosis (CF) is a genetic disease due to the absent or incorrect function of the channel that regulates the chloride exchange at cell surface (CTRF). Lungs are mainly affected because of progressive chronic obstructive disease, secondary to the very thick and tenacious mucus that

leads to respiratory infections, bronchiectasis, lung destruction, and ultimately respiratory failure.

- Exercise intolerance is a hallmark of the disease. Measurements of lung function, such as $FEV_1$, obtained at rest provide a rough estimation of exercise tolerance in CF patients. Particularly in the mild and moderate phases of the disease, the evaluation of exercise tolerance should be obtained by using the most appropriate tool and exercise protocol, such as cardiopulmonary exercise testing (CPET).
- In the advanced phase of the disease, CF patients are usually exercise limited by ventilatory constraints. Also peripheral factors related to deconditioning and poor nutritional state may play a very important role. Dyspnea and leg fatigue are usually the symptoms limiting exercise tolerance in CF.
- In CF regular exercise since early childhood promotes expectoration and contributes to good nutritional status and overall level of fitness, which, in turn, are capable to reduce the rate of decline in lung function.
- Cardiopulmonary exercise testing (CPET), in particular, is useful to determine the mechanisms of exercise intolerance in individual patients which may have treatment and prognostic implications.

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