Cystic Fibrosis

CHAPTER 18

Cystic Fibrosis

Cystic fibrosis (CF) is an extremely complicated disorder of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Over 1000 unique mutations have been described and linked to CFTR, which affects the lungs and digestive tracts. Impaired function of CFTR affects the secretion of chloride and bicarbonate, which results in the secretion of thick viscous mucus. The thickened mucus subsequently causes tissue and organ damage to the lungs and digestive tract. In the lungs, this thick mucus increases the risk of chronic inflammation and infection of the airways. An inflammatory response often results in tissue destruction of the lungs and deteriorating lung function. Because of this, CF is classified as a chronic lung disease, even though it affects other organs such as the pancreas.

Pancreatic involvement in CF mainly affects digestive enzymes, but also vulnerable to CF are the islets of Langerhans, and damage to islet cells leads to insulin deficiency and development of diabetes. Although the majority of people with CF develop exocrine pancreas insufficiency, only some in this group develop CF-related diabetes.

Management and Medications

Because of the complexity of the disease, CF is a difficult disorder to treat. The following principles are the pillars of CF treatment:

- Improving poor nutritional status (in particular in relation to fat-free body mass) with the use of oral pancreatic enzyme supplements to enhance digestion of dietary fats and proteins
- Improving general physical fitness
- Airway clearance techniques to facilitate removal of mucus
- Antibiotic therapy to fight pulmonary infection, colonization, and inflammation
- Influenza vaccination before every flu season

To treat and improve symptoms of CF, many people require multiple medications to achieve the goals of these pillars (table 18.1). Pancreatic enzyme supplements are used to aid nutritional status because CF impairs secretion of digestive enzymes and thus can lead to protein–calorie malnutrition. In individuals who lose pancreatic islet cell function, insulin is necessary to manage the resulting diabetes. The pulmonary aspects of CF are primarily a form of chronic bronchitis, requiring anti-inflammatory treatment (inhaled and oral corticosteroids), inhaled and oral bronchodilators, and mucolytic medications to help mobilize and expel airway secretions. This is commonly monitored at home with inexpensive peak expiratory flow meters, and in the clinic by measurement of the forced expiratory volume in 1 second (FEV_1). Supplemental oxygen is necessary for some people during exercise (sometimes at rest as well).

Effects on the Exercise Response

Effects of CF on exercise are highly dependent on the severity of the disease. Pulmonary, cardiac, and peripheral skeletal muscle function, along with physical inactivity, all contribute to exercise limitation. Logically, CF has detrimental effects on the exercise response under these circumstances:

- If ventilation is impaired
- If central circulation is secondarily impaired
- If nutritional deficiency and inactivity lead to low muscle mass

Table 18.1 Medications Used in Cystic Fibrosis

Medications	Mechanism of action	Adverse effects
Prednisone (see chapter 17 on asthma)	Glucocorticoid for reducing inflammation Often prescribed for airway obstruction exacerbations with the hope of improving pulmonary function and speeding recovery	• Skin atrophy and fragility • Osteoporosis • Muscle atrophy • Myopathy (including ventilatory muscles) • Obesity (increases work of breathing)
Albuterol Metaproterenol Salmeterol Formoterol Indacaterol	Selective β_2-adrenoceptor sympathomimetic agonists that produce bronchodilation	• Tachycardia, palpitations, and tremulousness • Nonselective sympathomimetic drugs (e.g., epinephrine and isoprenaline) should not be used
Theophylline Aminophylline	Methylxanthines have potent bronchodilator activity	• Tachycardia, cardiac dysrhythmias • Central nervous system stimulation • Increased respiratory drive • Risk of seizures
Cromolyn sodium Nedocromil	Mast cell stabilizers decrease mediator release from mast cells, eosinophils, neutrophils, monocytes, alveolar macrophages, and lymphocytes	• Stinging transiently on use
Guaifenesin Potassium iodide	Mucolytic therapy reduces viscosity of mucus to promote clearance of secretions	• Negligible side effects
Recombinant human deoxyribonuclease	Hydrolyzes deoxyribonucleic acid content in sputum, reducing mucus viscosity	• Pharyngitis, laryngitis • Upper respiratory symptoms, congestion
Ivacaftor	Facilitates chloride transport in patients who have the G551-CFTR genetic variant	• Headache • Abdominal pain, diarrhea • Upper respiratory symptoms, congestion

See also chapter 7 on chronic obstructive pulmonary disease and chapter 17 on asthma.

Individuals who have few pulmonary limitations and are able to obtain adequate protein and calories while remaining active are much less affected than someone who has severe pulmonary disease and malnourishment and is frequently hospitalized with respiratory infections. Exercise capacity thus has important prognostic value in CF and is a major determinant of quality of life in CF.

In healthier individuals, symptoms are muted and the exercise response is essentially normal. But in many cases, particularly noted in adolescents, CF is often associated with a low exercise capacity from multifactorial causes. The aerobic capacity (as indicated by peak oxygen uptake [$\dot{V}O_2$peak]) of adolescents with CF at the age of 12 years is comparable to that of age-matched healthy controls; however, it declines 20% during adolescence. This longitudinal decline in exercise capacity is independent of age, pulmonary function, and body mass.

An early clinical feature of lung disease is the development of hyperinflation, which increases with further lung injury. Progressive hyperinflation changes the shape of the thorax, putting the inspiratory muscles (and particularly the diaphragm) at a mechanical disadvantage. Additionally, decreased chest wall compliance increases the energy and oxygen costs of breathing. Progressive airflow obstruction (caused by chronic mucus hypersecretion) involves an increase in airflow resistance, intrapulmonary gas trapping, and ventilation–perfusion mismatching. These changes may compromise respiratory muscle function, and individuals with CF are thus more susceptible to respiratory failure or ventilation limitation during exercise, resulting in oxyhemoglobin desaturation and carbon dioxide retention during exercise.

Effects of Exercise Training

The research evidence for exercise training in people with CF is limited. However, the research that currently exists suggests that aerobic exercise training can improve or enhance the following:

- Exercise capacity
- Muscular endurance and strength
- Mucus clearance
- Skeletal development and bone mineral density
- Posture
- Mobility of the chest wall
- Self-esteem

Exercise training in CF can positively affect pulmonary function, aerobic fitness, and muscle strength, but conclusions about the efficacy of exercise programs in CF are limited by small sample sizes, short duration, and incomplete reporting. Research is needed to comprehensively assess the benefits of exercise programs in persons with CF, particularly in children using a combination of modalities and respiratory muscle training.

Recommendations for Exercise Testing

The Basic *CDD4* Recommendations are not appropriate for most people with CF, who need a more specialized set of measurements. In part, this is because of the unique effects of CF on physiology and in part because the Basic *CDD4* Recommendations are geared more toward adults with chronic disease, not children, adolescents, and young adults.

The standard progressive exercise test used to assess fitness in adults is not sufficient for children and adolescents with CF. Children with CF, who typically have very different physical activity profiles than normal adults, typically require more extensive testing to enable full understanding of their limitations in physical functioning. Guidelines to perform exercise testing in CF are being developed by an international study group and will likely specify measures of muscle function, cardiopulmonary function, and habitual physical activity. This will provide better identification of the impact of limiting factors and help tailor advice to patients or clients.

Pending these guidelines, an incremental cardiopulmonary exercise test to measure $\dot{V}O_2$peak using either a treadmill or cycle ergometer is recommended. Respired gas analysis accurately measures $\dot{V}O_2$peak and assesses the integrated physiological response of the pulmonary, cardiovascular, and metabolic systems. Only through use of this analysis can one see how the respiratory and nutritional functioning affect the physical functioning of the individual. In addition to the standard measurements of heart rate, blood pressure, and perceived exertion, the following measures should also be monitored for all people with CF:

- Pulse oximetry (if the system has breath-by-breath mode, also end-tidal gases)
- Breathing strategy (minute ventilation, tidal volume, and respiratory rate)
- Electrocardiogram preferred, but heart rate monitoring acceptable (low risk of cardiac ischemia)
- Perceived dyspnea ratings

The strength and flexibility measures in the Basic *CDD4* Recommendations are not ideally suited for persons with CF but could be used in those who are most severely affected. A high-quality accelerometer might be a good tool to measure habitual physical activity in children, since many of their activities are likely to be activities other than walking (an inexpensive pedometer might provide misleading data).

Recommendations for Exercise Programming

The Basic *CDD4* Recommendations for exercise programming can be used, but in general they are not adequate for children, adolescents, and young adults with CF.

No "one size fits all" principle should apply to persons with CF, and exercise programs, habitual physical activity, or both must be individualized as an integral part of the particular treatment regimen. Maintaining physical functioning, vitality, and

as normal a childhood as possible are essential elements of optimizing the prognosis. Exercise specialists should thus consider factors that help or hinder long-term adherence to the program, including these:

- Social support
- Perceptions of competency and self-esteem
- Enjoyment of the activities (play)
- Availability of a variety of activities

All persons with CF have their own unique combination of physiological factors that limit their exercise capacity. The data from exercise testing should be used to focus on various goals and indications that best suit the individual. These indications depend not only on the individual, but also on the person's own disease progression and exacerbations. These inter- and intraindividual characteristics may require repeated exercise testing in order to give persons with CF safe training recommendations. In general, programs should be configured as listed next.

Mild to Moderate Disease (FEV_1 65% to 50% Predicted)

Nonpulmonary factors usually limit exercise capacity, so exercise training should

- prevent lung function deterioration,
- optimize chest mobility and airway clearance techniques, and
- generally focus on peripheral muscle function (strength and power).

Severe Disease (FEV_1 <50% Predicted)

Pulmonary factors usually limit exercise capacity, so exercise training should

- continue the efforts just listed for those with mild to moderate disease,
- include inspiratory muscle training to improve ventilatory efficiency and work of breathing, and
- include high-intensity interval training to train muscles with a low ventilatory burden.

In individuals with CF, building and maintaining muscle mass is important, because the work of breathing is hard and intercurrent illnesses are likely to cause atrophy. Having a reserve of strength and muscle mass defends against these vulnerabilities.

The following are contradictions to exercise for children with CF:

- Fever >38 °C
- Exercise-induced desaturation (SpO_2 < 90%)
- Cardiac dysfunction
- Scuba diving
- Avoidance of contact or collision sports in persons with an enlarged spleen or liver disease

Integration Into a Medical Home Model

Persons with CF will have multiple specialists, likely a pulmonologist, a gastroenterologist, and an infectious-disease doctor. One of these physicians is likely to be the main care provider, and office staff need to coordinate with the other providers and make sure that physical functioning remains a key goal for all. It is important to monitor physical activity level, muscle atrophy, and obesity and osteoporosis side effects of medications. For a person who has long-standing CF leading to multiple complications and diminished respiratory function, during an intercurrent illness it may be necessary to do low-intensity activities or even eliminate exercise entirely until her health status improves.

Special Considerations

- Bronchodilator premedication may benefit persons who respond to bronchodilators.
- SpO_2 should be monitored at the beginning to determine the level of O_2 supplement.
- Supplemental O_2 may help people obtain a training effect.
- Prolonged oral corticosteroid therapy may cause myopathy, obesity, elevated blood glucose, and high blood pressure.
- Severe disease with hypertrophic pulmonary osteoarthropathy can cause bone pain.
- End-stage lung disease may severely limit training intensity due to the development of cor pulmonale.

Take-Home Message

Individuals with CF greatly benefit from exercise training, and most people with CF do not require supervision or monitoring while performing exercise. Comprehensive exercise testing, including graded exercise with respired gas analysis, is extremely helpful for individualizing an exercise program to suit the unique physiological needs of each patient or client.

- Building skeletal muscle function (strength, mass, and power) is a key defensive strategy.
- Pulmonary hygiene (including nebulizer) is central to avoiding respiratory complications.
- For children, especially, exercise must be fun—play—and not a health chore or workout.
- Oxyhemoglobin saturation should be monitored in persons who exhibit hypoxemia.
- Bronchodilators or cromolyn will help people with exercise-induced bronchoconstriction.
- Long exercise sessions increase need for fluid and salt intake.
- People with severe lung disease may experience bone or joint pain in the legs.

Suggested Readings

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Additional Resources

Cystic Fibrosis Foundation, www.cff.org [Accessed November 4, 2015].

Cystic Fibrosis Worldwide, www.cfww.org [Accessed November 4, 2015].

European Cystic Fibrosis Society, www.ecfs.eu [Accessed November 4, 2015].