Exercise and Cystic Fibrosis (CF) 2.0

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In 1989 we knew that exercise, including regular prescribed physical activity, could be safely performed and described some of the physiological responses to exercise in patients with cystic fibrosis (CF). Also in 1989, the genetic defect causing cystic fibrosis (CF) was identified leading to improvements in treatment that greatly extended the life span for these patients. Increased understanding of the factors limiting exercise capacity and of the important role of regular exercise in slowing the progression of CF and in modulating some of the effects of the genetic defect on airway function has led to the consensus that regular exercise should be part of the standard of care for this disease.

Exercise and Cystic Fibrosis Update

There are few diseases where the “exercise is medicine” theme has been advanced more than with cystic fibrosis (CF). Twenty-five years ago we knew that CF was a genetic disease that primarily affected exocrine gland secretion altering sweat content, pancreatic secretory processes and airway mucus formation. The loss of pancreatic secretions was largely overcome through the oral replacement of pancreatic enzymes. The primary cause of death was the progressive loss of lung function through mucus plugging, air trapping and increased lung bacterial infections. Treatment, consisting of attempts to control the infections and physical therapy to loosen and expectorate the thick, tenacious mucus, resulted in a prolongation of life to about 15 years of age.

The identification of the genetic defect in 1989 (cystic fibrosis transmembrane conductance regulator through the CFTR gene; the first disease for which this was done) resulted in our understanding that altered chloride transport across cellular epithelium was the basis for the disease prompting advances in treatment that have increased the average life span to over 40 years. This has been a remarkable era of discovery due to the tireless efforts of Cystic Fibrosis Foundations, government funding and thousands of scientists from around the world.

Thirty five years ago a handful of scientists with an interest in pediatric exercise and CF became convinced that the positive role of regular exercise in other diseases, also might play such a role in CF. The 1989 Pediatric Exercise Science article reported on a series of subsequent studies that established the low risk of
exercise in children with CF and began to describe the physiological responses to exercise (12,16,24). Disease-induced ventilation to perfusion mismatching, resulting in decreased ability to oxygenate the blood (reflected in arterial O₂ saturation, SaO₂) and eliminate CO₂ (reflected in end-tidal CO₂), was an important contributor to the exercise limitation, particularly as the lung dysfunction became severe (15,24).

Even in these early stages of investigation it was clear that these relationships were complex. Some patients with severe lung dysfunction were able to maintain exercise capacity and SaO₂ and others with almost normal lung function evidenced low exercise capacity with desaturation (30).

Orenstein and others (46) showed that regular exercise could be safely performed by these patients and that the expected benefits went beyond those for the cardiovascular system described in healthy children and adults to include improvements in lung function. The observation that exercise stimulated coughing and increased mucus expectoration in these patients led to studies exploring the use of exercise as a complementary form of airway clearance therapy (13).

The following review describes, with some broad strokes, new research findings that have extended our understanding of the important role of exercise testing, the physiologic responses to exercise in CF, and of the effects of regular exercise as part of the care for these patients. There have been several hundred scientific articles published on this topic since 1989 so the following reference list is not exhaustive—with apologies to those who have not been included.

**Exercise Testing**

**Now a Valuable Part of CF Care**

The wide use of exercise tests in the care of CF patients has been hampered by the fact that CF was considered a lung disease and therefore tests of lung function were the primary means of monitoring disease progression and response to treatment. This, in spite of the fact that pulmonary function testing is relatively insensitive as a predictor of death or lung transplantation (53), continues to be the prevailing view. Peak VO₂ on the other hand is a good predictor of mortality in CF patients including children and adults followed for 8–7 years (2,45,50) but not in adults followed over 5 years (40); it may be that 5 years is too short a time period to document the fitness mortality relationship. Neither lung function, exercise capacity, nor clinical scores predict those patients who are unable to work or attend school (23).

The response to exercise also is related to morbidity. The degree of desaturation during an exercise test is an independent predictor of lung function decline and days of hospitalization in the following 12 months (31) and the exercise response reflects changes in health status during a hospitalization (51). Finally, increased fitness, as measured by peak VO₂, is associated with a slower decline in lung function (25,29,35,41,56,59,68) further supporting the use of regular exercise testing to monitor fitness and disease status.

In spite of these relationships, exercise testing is underused in clinical practice for patients with CF (4,51). The International Working Group on Exercise and Cystic Fibrosis suggests that regular peak VO₂ exercise tests be performed to monitor patients’ physiological function over time.
New Insights Into Factors Limiting Exercise Capacity in CF

The relationship between exercise capacity and morbidity and mortality reinforced the idea that these tests were identifying disease-related exercise limitations beyond the pulmonary system (42). An analysis of the relationship between various CFTR mutations and exercise capacity indicated that specific genotypes affect different aspects of lung and muscle function (58) adding yet another level of complexity to disease and exercise interactions; conversely this also offers the potential for the development of individual exercise interventions based on mutation type.

Just how much these extrapulmonary factors contribute to exercise limitations must always be interpreted in light of the fact that the primary limitation still remains in the pulmonary system (1,39). In addition to gas exchange abnormalities we now understand that disease-related airway obstruction results in hyperinflation of the lungs, alters timing of the respiratory cycle and decreases inspiratory muscle function that may contribute to the inability to maintain SaO₂ and PETCO₂ in patients with moderate to severe lung dysfunction (33,34,39,64,66).

In spite of peripheral muscle weakness, respiratory muscle strength is maintained in moderate to severe CF; this is thought to be a response to chronic breathing against high airway resistances (19,37). Specific training of the inspiratory muscles results in improvements in lung function and exercise capacity (21) suggesting that “normal” inspiratory muscle strength may be insufficient to cope with the increased breathing demands of the disease. Absolute peripheral muscle function, either indirectly through malnutrition (26,33), drugs (5) or directly (6,7,17,44,60) is reduced in CF.

A CF specific peripheral muscle defect has been hypothesized to explain reduced muscle strength (36,44,60). Peripheral muscle weakness is related to reduced work capacity independent of reduced pulmonary or nutritional status (18) but when corrected for lean body mass, peripheral muscle strength is maintained, suggesting malnutrition as one cause of reduced strength. Noninvasive respiratory mass spectrometry during exercise (54) does not support a specific muscle defect hypothesis. It is likely that there is a small peripheral component to the CF exercise limitation that interacts with the pulmonary limitations (67).

Exercise as Treatment

The thick, tenacious mucus that collects in the airways of patients with CF is the primary cause of morbidity and mortality. By promoting coughing and expectoration of this mucus, regular exercise, in some patients, can be used to replace some of the standard time- and effort-consuming airway clearance treatments (3,9,22,52,55,65). The increased exercise-induced airflows, and related mechanical stress, result in greater ease of expectoration and reductions in sputum mechanical impedance (11,20) thus providing benefits similar to traditional airway clearance techniques.

Perhaps the most exciting recent finding is that exercise may reverse some of the disease related changes in ion transport, thus improving airway mucus characteristics (14,27,57,67). Exercise induced inhibition of epithelial sodium channels could account for some of the hypothesized increases in airway surface liquid and
consequent reductions in mucus viscosity (28). Further, changes in ion transport that mimic the effects of beta-agonists on lung function and diffusion (67) suggest that more research into exercise related alterations in ion transport will help to explain the relationship between peak VO2 and mortality.

The effects of exercise on immune function and inflammatory markers in CF are unclear. Suggestions that exercise may reduce markers of inflammation (14) are not supported by evidence (32) but how patients respond in the long term is also unknown. The possibility that regular exercise may enhance immune function (49), a potentially beneficial effect in CF, should be explored.

As the age of CF patients increases, the diagnosis of CF related diabetes (CFRD) has become more common; 17% of patients over the age of 13 are diagnosed with CFRD. CFRD is unique in that it shows characteristics of both Type 1 and Type 2 diabetes. While exercise likely is an important part of the treatment of CFRD (43) this has not been studied, making this an important area for research.

Patients who exercise regularly and increase their exercise capacity, improve lung function, bone health, habitual activity, quality of life and slow the decline in lung function (8,9,25,27,29,35,41,48,56,59,63,68). Patients respond to aerobic, anaerobic and strength training (47) and are able to tolerate repeated short high intensity bouts (62). Unfortunately, CF patients spend less time in moderate-intensity activity than healthy populations, with females being less active than males (61). In spite of the evidence supporting exercise as treatment for CF, there continues to be a need for large multicenter studies to help identify individual differences in response, genotype, and phenotype influences.

Again, there are few diseases where science has provided such overwhelming evidence that regular exercise should be considered part of the standard of care. The growing evidence indicates that for CF exercise is in fact good medicine (9,10).

References


