1. Implications of an exercise test

While the determination of exercise capacity is viewed as clinical best practice in cystic fibrosis (CF), its measurement using a cardiopulmonary exercise test (CPET) remains as somewhat of a mystery for many CF clinicians. Two studies [1,2] in the current issue (of the Journal of Cystic Fibrosis) highlight the use of exercise testing in CF clinical practice. The role of retained exercise capacity (VO2max) and levels of physical activity in CF in maintaining health status is compelling. Using an accelerometer to determine levels of physical activity, Hebestreit et al. [3] found that more physically active CF patients had best preserved VO2max, FEV1 and nutritional status. These results are supported by a more recent review by Wilkes and colleagues [4] who reported that children with CF with increased activity demonstrated a reduced decline in pulmonary function.

To date we know that there is a clear relationship between pulmonary dysfunction and exercise capacity in patients with CF i.e. those with more severe pulmonary disease have lower exercise capacity [5]. Interestingly the relationship between VO2max and the extent of radiological damage (modified Bhalla score on thin section chest HRCT) was stronger than with spirometry or body mass index [6] which suggests that the simple physiological measures used in the clinic setting may not be sufficiently sensitive to detect subtle changes in the lungs and in particular the airway. It has been suggested that in patients with mild pulmonary disease, parameters of exercise at peak or maximal performance may detect disease not identified by routine lung function testing [7]. Additional parameters obtained during formal exercise testing can therefore be useful in patients with CF. An example in children with CF; was the finding that the retention of CO2 during exercise was associated with more rapid decline in pulmonary function [8].

The study by GRUET et al. [1] highlights the usefulness of using CPET in CF and in particular the robustness of the oxygen uptake efficiency slope (OUES). The OUES, first described by Baba et al. [9] in the Journal of American College of Cardiology in 1996, has proven to be a useful measure in a number of clinical populations. In heart failure patients followed for 2 years, Arena et al. [12] developed a prognostic indicator for VE/VCO2. Individuals with the steepest VE/VCO2 had the highest risk of mortality. As a result, a clinical algorithm was developed to determine the appropriate program of clinical management for chronic heart failure based on CPET outcomes.

While much of the focus on CPET in clinical populations has been the determination of maximal (VO2max) or peak oxygen consumption, the results of GRUET et al. [1] highlight the importance of obtaining other important exercise related measures during CPET and that the OUES can be assessed during a sub-maximal exercise test. Measures such as the anaerobic threshold (also known as the lactate or gas exchange threshold—GET) can also be determined during an incremental CPET. Similarly the relationship between ventilation (VE) and carbon dioxide production (VCO2) (VE/VCO2 slope) can also be simply extracted from incremental exercise tests. Indeed, chronic heart and lung disease patients, VE/VCO2 has proven to be a useful prognostic indicator. In over 450 chronic heart failure patients followed for 2 years, Arena et al. [12] developed a prognostic indicator for VE/VCO2. Individuals with the steepest VE/VCO2 had the highest risk of mortality. As a result, a clinical algorithm was developed to determine the appropriate program of clinical management for chronic heart failure based on CPET outcomes.

The OUES represents the rate of increase in oxygen uptake (VO2) in response to given ventilation (VE) or in other words it indicates how efficiently oxygen is extracted across the range of ventilations achieved during incremental exercise. Physiologically, the OUES is based two factors (i) on the development of metabolic acidosis, which is determined by the distribution of blood flow to the skeletal muscles and (ii) the change in physiological dead space which is affected by perfusion to the lungs [9]. Hence for CF patients the OUES represents an ideal index for changes in oxygen transport from the lungs to the exercising muscle. Gruet and colleagues [1] found the OUES more easily detectable than the GET, confirming the results of earlier studies [9]. Therefore there is strong potential for the OUES to be used in a more widespread manner in the clinical setting for CF. While normative data are still be established for OUES, it appears a simple and robust measure, which does not need to be determined under maximal exercise conditions.

Several studies have examined the relationship between measures of exercise capacity and prognosis in CF. Higher levels of aerobic fitness in patients with CF was associated with a significantly lower risk of dying [13]. Aerobic fitness may be a marker for less severe illness; however the authors suggested that measurement of VO2max appeared to be valuable for predicting prognosis. In a five year observational study
Moorecroft and colleagues [5], reported that VO$_{2\text{max}}$, Work$_{\text{max}}$ and the ventilatory equivalent for oxygen (V$E$/VO$_2$) were related to survival, however, these indices were not overall better than FEV$_1$ in predicting survival. In contrast, parameters derived from six minute walk tests in adults with severe CF lung disease listed for lung transplantation, did not predict mortality in a multiple regression analysis [14]. Resting heart rate was the only predictor of the risk of death in this cohort of adult patients.

Further studies in patients with CF are needed to understand the relationship between exercise parameters and clinical outcomes, particularly in the utilisation of parameters derived from sub-maximal exercise tests. Such studies could evaluate the utility in detecting mild pulmonary disease in younger children with CF, the sensitivity of exercise as a method of detecting disease progression and its role as a method of monitoring treatment response.

2. Exercise testing in the CF clinic

In CF, CPET remains an underutilised clinical measure. The study by STEVENS et al. [2] highlights that despite the UK CF Standards of Care Guidelines, which recommends annual assessment, the use of exercise is limited both in terms of assessing or intervening with patients. This study suggests that many CF centres in the UK do not have access to formal exercise testing facilities. This is likely to be compounded by the logistic limitations of available space and need for coordination of large numbers of patients who often have tremendous pressures placed upon them when attending the outpatient clinic. The relative importance placed on the assessment of exercise capacity varies considerably between CF centres even when facilities are readily available.

The reasons for limited utilisation of CPET in CF populations include factors such as the requirement for specialised exercise testing equipment and physical space to perform the tests, inadequate health care rebate, lack of facilities and resources including trained staff and inconclusive evidence to date of the clinical usefulness of performing CPET in CF. The burden of health maintenance therapies, frequent visits to the hospital and the need to extensive investigations are also likely to limit uptake of formal CPET. This has contributed to studies of the validation of various alternative measures to determine exercise capacity in CF populations and include: incremental and endurance exercise testing, timed walking tests, shuttle tests, step tests, etc.

3. Exercise testing and its relationship to exercise prescription for patients with CF

Physical training is thought to be an important component of the health maintenance for people with CF. A recent systematic review of exercise training in CF examined the role of aerobic, strength and anaerobic interventions in children and adults [15]. In summary, these trials demonstrate that both aerobic and strength training increase pulmonary function, strength and aerobic capacity [15]. Other benefits may include a positive impact diabetes control, body image and levels of anxiety.

Whilst studies are limited in both size and duration and include a range of physical training interventions, there is no evidence to discourage exercise as a part of a long term strategy for maintaining health in persons with CF. There is some evidence to suggest increased habitual activity slow the rate in decline of lung function and regular exercise may lead to greater treatment adherence in the longer term [16].

An important study finding by STEVENS et al. is the limited utilisation of exercise training for patients with CF in the UK. Whilst, exercise activity is commonly discussed in paediatric and adult CF clinics at routine appointments the prescription of formal exercise recommendations is limited (10.0–12.5% of specialist clinics). It far more common for clinics to generally encourage exercise activity than provide formal programs.

An assessment of exercise capacity can be useful to inform the the safe prescription of exercise programs in patients with CF, particularly in those with advanced lung disease. Additionally, information about requirement for oxygen supplementation during exercise can be provided. In some health care settings, exercise capacity can provide an objective assessment of level of disability which can be useful for decisions about the timing of lung transplantation and government disability support applications. In these situations, field assessments of exercise capacity may be suitable substitutes for the more formal laboratory-based exercise testing.

4. Exercise test: what to perform?

The use of formal CPET remains useful for determining mechanisms of the limitation of oxygen transportation and its impact on exercise capacity in patients with CF, however, its uptake in the clinic is limited. Field tests, such as shuttle tests, timed walking and step tests, which are logistically easier to perform and require less formalised equipment, are reasonable surrogates for incremental CPET and can determine changes in exercise capacity such as in response to a therapeutic intervention. In the future, new technologies such as the LifeShirt®, may be useful to allow cardiopulmonary assessments to be made in the field, though the role in clinical practice is yet to be established [17].

In conclusion, more study is required to understand the mechanisms of exercise limitation in CF and the optimal prescription of exercise which accounts for the varying degrees of severity of pulmonary disease and nutritional status. The role of formal exercise assessments as an outcome measure for the many new therapies currently being studied in late phase clinical trials remains in its infancy.

References


