

Expert Review of Respiratory Medicine

Cystic Fibrosis and Physiological Responses to Exercise

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Abstract

Cardiopulmonary exercise testing (CPET) is underutilised within the clinical management of patients with cystic fibrosis (CF). But within the last five years there has been considerable interest in its implementation, which has included deliberations by the European Cystic Fibrosis Society about incorporating this method within the clinical assessment of patients. This review examines the current use of CPET in assessing the extent and cause(s) of exercise limitation from a paediatric perspective. Examples of the measured parameters and their interpretation are provided. Critical synthesis of recent work in the oxygen uptake (VO_2) kinetics response to and following exercise is also discussed, and although identified more as a research tool, its utilisation advances researchers understanding of the cardiovascular, respiratory and muscular limitations to exercise tolerance. Finally, exercise and its application in therapeutic interventions are highlighted and a number of recommendations made about the utility of exercise prescription.

Keywords: oxygen uptake kinetics, Ivacaftor, inspiratory muscle training, cardiopulmonary exercise testing, paediatrics, skeletal muscle

Introduction

Cystic fibrosis (CF) is the most common inherited, life-shortening disease amongst the Caucasian population. In 1985 the genetic defect in CF (located on chromosome 7) was discovered eventually leading to the gene defect identified by full-length gene sequencing in 1989 [1]. The defect is expressed as a disruption in the CF transmembrane conductance regulator protein (CFTR), which is found in membranes of cells that line airways of the lungs, liver, pancreas, intestines, reproductive tract, and skin. Abnormal CFTR function affects the ion transport necessary for functioning of epithelial structure. In the lungs, abnormal thick and dry mucus ensues, resulting in a vicious cycle of bronchial airway obstruction, bacterial infection, and inflammation. The resulting obstructive syndrome causes progressive disability and as this cycle continues, lung tissue is progressively destroyed, with eventual respiratory failure. Therefore, whilst this is a complex, multi-organ disease, lung disease accounts for more than 95% of the morbidity and mortality associated with CF.

Although the natural history of CF is progressive loss of lung function that leads to death, with early diagnosis and aggressive therapeutic intervention, survival into the third and fourth decade of life is now common. Indeed, a dramatic increase has been observed in the median survival of UK patients from 10.6 y in 1966 to 29.4 y in 1992 [2]. In 2010, for the ~ 9,385 patients registered in the UK, the predicted life expectancy had risen to 43.5 years [201]. Despite this improvement, largely resulting from earlier diagnosis and enhancement in the pharmacological treatment, there remains no cure for CF. Therefore, clinicians now face the challenge of fostering a normal quality of life (QoL) for this aging patient population. Developing and enhancing additional treatment and management strategies to facilitate this is therefore a clinical priority.

The initiative “Exercise is Medicine”™ by the American College of Sports Medicine (ACSM) is a timely reminder of the important role of exercise within medicine. Of course, this message is not new but the challenge still remains to elevate the utilisation of exercise *per se* into the clinical management of chronic diseases. However, there remains sparse information on the physiological responses to exercise of children and adolescents with CF. Increased exercise (structured and organised with a specific targeted fitness outcome) and/or physical activity (any bodily movement resulting in energy expenditure) is beneficial for healthy children and children with chronic diseases [3]. Bar-Or and Rowland’s [3] comment about children with chronic disease that “by prescribing exercise we are signalling to the child that he or she can, and should, act like his or her healthy peers” (p.112) is therefore pertinent. For example, a recent study reported an attenuate decline in lung function is attenuated in patients with CF aged 7-17 years who increased their levels of physical activity over a 7 year period [4]. Therefore, while it is intuitive to promote exercise in diseased children, the evidence base is currently sparse compared to healthy children.

The utilisation of exercise would include not only rehabilitative or training aspects for patients, but also a more regular and comprehensive use of exercise stress testing compared to current practice. Despite the acceptance by clinical and exercise physiologists that the cardiopulmonary exercise test (CPET) is the most objective test to determine the limits and/or mechanisms of exercise (in)tolerance, it remains significantly underutilised in clinical practice [5]. This is disappointing for several reasons. Firstly, a more standardised approach to CPET in all clinical patients [where applicable] would establish a normative data base upon which a determination of what is a ‘normal’ or abnormal’ physiological response. Secondly, establishing a patient’s ability to tolerate exercise and physiological response

profile will enhance the precision of exercise prescription, which is currently generalised, if at all utilised on an individual basis. This may be in the form of the prescription of exercise training intensities [6]. Lastly, routine CPET will allow for the prognostic value of the exercise parameters to be examined alongside more common clinical outcome measures i.e., lung function, quality of life, hospital admissions, drug administration. As noted above, there has been a marked increase in median survival age of patients with CF [7]. Therefore, the early publication of exercise testing in CF patients for prognostic purposes is largely redundant and urgently needs updating [8].

The recent promotion of CPET as a clinical outcome measure by the European Cystic Fibrosis Society (ECFS) [202] and the need for comprehensive and accurate outcomes to evaluate the rapidly advancing pharmacological treatment of CF are timely [9]. This is an exciting phase in the treatment and management of this complex condition; however, it is important that exercise testing should not be sidelined. As recommended by the British Thoracic Society and the Association of Chartered Physiotherapists in Respiratory Care [10], exercise should be an integral part of CF clinical care. The purpose of this review is to highlight the advances in the CPET method over recent years and outline current and future clinical application in paediatric CF patients.

Provision of Cardiopulmonary Exercise Testing in CF

Current provision of exercise testing in both clinical and research assessments remains limited [5,11,12]. As outlined by Stevens *et al.* [5], exercise testing is underused (53% uptake) within CF clinics across the UK, despite care teams recognising its value. Similar figures (44% and 63%, respectively) have been reported in CF centres in the US and Germany [11,12]. Furthermore, there is a notable lack of protocol standardisation.

Interestingly, however, as highlighted by Stevens *et al.* [5] the limited application of CPET within CF care is in contrast to the high importance given to its clinical utility by healthcare providers.

High aerobic fitness in CF has shown to be of clinical importance because of its positive association with patients' quality of life [13], prognosis [14,15,16] and risk of hospitalisation [17]. CPET, incorporating the measurement of pulmonary gas exchange, provides the most precise measure of aerobic fitness in patients with mild-to-moderate CF, and invariably focuses on the determination of maximal oxygen uptake ($\dot{V} O_{2\max}$). Not only does comprehensive CPET hold clinical utility, it also enables the factor(s) limiting patients' exercise capacity (e.g., motivation, poor fitness and/or disease pathophysiology) to be determined and is valuable for understanding the mechanism(s) by which aerobic fitness is reduced and by which new treatment strategies might be influenced. Currently, there is no consensus regarding whether aerobic fitness of CF patients is predominantly limited by respiratory, cardiovascular and/or muscular factors [18,19,20] as disease severity will be an important confounder.

Lung function and structural investigations and/or measures of nutritional status are traditionally relied upon to measure disease severity and progression in CF, but they cannot accurately predict exercise capacity and are often not sensitive to change in mild-to-moderate disease. Appropriate exercise testing provides an integrated, objective assessment of cardiovascular, respiratory, muscular and metabolic function of patients. This information therefore provides a more comprehensive clinical assessment which can inform medication and therapy strategies and assist with pre-transplant stratification. Furthermore, thorough exercise testing enables individualised exercise prescription plans. Therefore, current clinical

standards for CF management recommend exercise testing on at least an annual basis (Cystic Fibrosis Trust)[202] .

Besides $\dot{V}O_{2\max}$, additional submaximal gas exchange measurements, such as the $\dot{V}_E/\dot{V}CO_2$ -slope and the oxygen uptake efficiency slope (OUES) have yielded superior prognostic utility in other clinical populations [21,22] and thus, warrant investigation in CF. Furthermore, despite the wealth of knowledge it provides, exercise testing as an outcome in therapeutic trials remains in its infancy [23]. To objectively quantify physical functional changes under different pharmacological treatments, CPET should be included within future, long-term research.

CPET protocols

Although CPET has been established for many decades, the ECFS Exercise Working Group has only recently promoted CPET as the exercise testing method of choice for this patient group [202]. Moreover, the ECFS Clinical Trials Network Standardisation Committee called for assessment of the validity, reproducibility and feasibility of outcome measures utilised in the assessment of CF patients and advocated research into the most appropriate test for paediatric patients [24].

Consequently, there has been much debate regarding what are the most appropriate testing protocol and guidelines to implement for these patients. This uncertainty is likely to be a factor in the current poor clinical uptake of CPET [5]. With regard to treadmill versus cycling exercise, the consensus appears to be cycle based protocols. Not only do these prevent falls and facilitate measurements such as electrocardiography during exercise, they are also more paediatric friendly and can enable testing of patients as young as 7 years of age [25,26].

The Godfrey protocol [27] consists of a 3-min warm up followed by increases in work rate each minute until exhaustion. In children with chronic conditions, however, it has been suggested that a ramp incremental protocol, whereby exercise intensity is increased linearly rather than each minute, is more appropriate [28]. The consensus by exercise physiologists is that a linear increase in work rate is important to depict the progressive response to exercise. Additional protocols, such as the Steep Ramp Test (SRT) have also recently been introduced [28]. One key consideration in the choice of testing protocol is how accurate is the derived aerobic fitness measurement.

Accuracy considerations

Obtaining a valid $\dot{V}O_{2\max}$ measurement is critical and a particularly important issue in paediatric groups. $\dot{V}O_{2\max}$ represents the integrated capacity of the pulmonary, cardiovascular and muscular systems to transport and utilise oxygen during intense exercise, and is traditionally identified by a $\dot{V}O_2$ plateau upon exhaustion despite an increasing work rate. However, young people rarely exhibit this response [29,30] and the use of the term $VO_{2\text{peak}}$ is often used. Reliance has, therefore, traditionally fallen upon secondary verification criteria, encompassing subjective indicators of effort (sweating, facial flushing and hyperpnoea) and objective physiological secondary criteria (heart rate, respiratory exchange ratio and/or blood lactate concentration). But, adherence to these criteria has been shown to drastically under measure $\dot{V}O_{2\max}$ in patients with CF [25].

A procedure termed the ‘verification phase’, whereby CPET is followed by an individualised supramaximal ‘step’ test to exhaustion (S_{\max}), can ensure that a valid $\dot{V}O_{2\max}$ is measured. The verification phase is completed after 15 minutes recovery from the CPET test and

requires the patient to cycle at 110% of the peak power attained at the end of the CPET for as long as possible until the required cadence cannot be maintained. If $\dot{V}O_2$ is lower or equal to the CPET oxygen uptake values, then the clinician can be assured it is a maximal effort. Although this requires another 20 minutes onto the length of a CPET it is the only way (apart from asking the patient to return to the laboratory a few days later to repeat the CPET) that the VO_2 values can be verified as a 'true' maximum. A recent study by Saynor *et al.* (Figure 1) demonstrated that S_{max} can verify $\dot{V}O_{2max}$ in most cases and, importantly, identify those patients who have provided a submaximal effort [25]. Not only can the combination of a traditional ramp incremental and S_{max} test permit measurement of a valid $\dot{V}O_{2max}$, this protocol can be safely and effectively administered within a single visit, confirming that maximal CPET is safe for patients with mild-to-moderate CF [10].

Recommendations and considerations

Whilst the importance of calibration of metabolic carts is widely acknowledged with regard to accuracy of CPET derived data [32,33], thorough familiarisation and the choice of testing protocol are also vital. From a practical point of view, patients' familiarisation with the expectations of the protocol and what it feels like to maintain a steady cadence at various work rates is important. This is very relevant when testing young and/or nervous patients. The choices of protocol and verification criteria are also essential to obtaining a 'true' representation of patients' maximal aerobic fitness. However, at a time when the ECFS have recognised CPET as *the* exercise testing method of choice when assessing aerobic fitness in mild-to-moderate CF patients, only a S_{max} verification protocol, as outlined by Saynor *et al.* [25] can confirm a 'true' $\dot{V}O_{2max}$ measurement obtained during a progressive exercise test in young CF patients. Furthermore, a key benefit of ramp incremental exercise compared with a

shorter SRT is that ramp testing spans the range of exercise intensities and therefore derives both important maximal and submaximal fitness parameters [34].

These recommendations have significant implications for the assessment and interpretation of CPET in young CF patients in clinical and research settings. To utilise $\dot{V}O_{2\max}$ in prognostic stratification and assessment of clinical or research interventions, it is essential that 'true' measurements are obtained. Accepting submaximal efforts will significantly distort the clinical interpretation of patients' aerobic fitness. From a practical viewpoint, S_{\max} verification is straightforward to implement as the imposed power is calculated on an individual basis from the peak power output achieved during the ramp test and, clinically, may minimise the costs associated with re-tests when the validity of a test is questionable. Whilst it is important that these new concepts and advances within exercise physiology are incorporated within clinical practice, the authors [25] did caution that the safety of S_{\max} exercise in older patients with more severe CF has yet to be confirmed.

Interpretation of CPET data

Several excellent reviews, books and position stands have been published regarding interpretation of CPET outcomes [6,32,35,36,37,38]. A CPET provides a large number of important parameters, including but not limited to, gas exchange and metabolic data [$\dot{V}O_2$, carbon dioxide output ($\dot{V}CO_2$), gas exchange threshold (GET), minute ventilation (\dot{V}_E), ventilatory equivalents for O_2 ($\dot{V}_E/\dot{V}O_2$) and CO_2 ($\dot{V}_E/\dot{V}CO_2$), O_2 pulse, oxygen saturation via pulse oximetry (SaO_2), end tidal O_2 and CO_2], in conjunction with test duration and work rate. These additional parameters are often overlooked in favour of the final maximal values. However, submaximal data should assist with diagnostic and prognostic evaluations and need to be incorporated more fully in patient reports [6]. No one single parameter should be used

exclusively, rather it is the integration of the exercise responses as a whole which add value when utilising CPET combined to other tests.

Parameters of aerobic function

Maximal oxygen uptake ($\dot{V}O_{2\max}$) represents the gold standard measure of aerobic fitness and provides an indication of how well patients' lungs, pulmonary and cardio circulation (large and small vessels) and muscles function in an integrated system during exercise. This allows researchers, clinicians and other health care professionals to assess the entire cardiopulmonary pathway from mouth to the exercising muscle in one simple measurement (i.e., the rate of oxygen flowing through the various subsystems). Unlike other chronic conditions, CF appreciably affects the gas exchange response to exercise.

$\dot{V}O_{2\max}$ is currently the principal outcome measure from a CPET, as it has been shown to be an independent predictor of mortality in CF (14). However, a more comprehensive evaluation of patients' cardiorespiratory fitness may be gained through quantification of submaximal parameters of aerobic function [i.e., lactate threshold (or its non-invasive equivalent the gas exchange threshold (GET)), the kinetics of $\dot{V}O_2$ and work efficiency ($\Delta\dot{V}O_2/\Delta WR$)]. These three parameters combined with $\dot{V}O_{2\max}$ represent the key parameters of aerobic function [39]. Despite suggestions that it may be difficult to non-invasively identify the lactate threshold (via the GET and ventilatory threshold) in patients with chronic respiratory disease and airflow limitation [40], it has been demonstrated that these parameters are reproducible using a cluster of measures and two independent observers [21].

Ventilatory function is best examined by relating $\dot{V}O_2$ and $\dot{V}CO_2$ dynamics to \dot{V}_E [41], through the slope of ventilatory equivalent for CO_2 response ($\dot{V}_E/\dot{V}CO_2$ -slope) and the

oxygen uptake efficiency slope (OUES). The OUES is useful since it is, theoretically, resistant to early test termination and intra- and inter-observer variability [41]. Although these parameters possess documented utility to identify the presence and severity of ventilatory inefficiency of the heart/lung organs and/or response to intervention in heart failure patients, their uptake within the assessment of respiratory conditions has been scarce [42].

Systemically, the greater the ventilation (\dot{V}_E) required for a given amount of gas exchange ($\dot{V}CO_2$), the less efficient is the cardiopulmonary system. This has been documented as irregular in CF patients. Consideration of altered ventilatory equivalents for CO_2 have featured in heart failure CPET over recent years, however less so in CF, but the reduced elimination of carbon dioxide as a central mechanism may also reduce aerobic fitness. However, use of the OUES and $\dot{V}O_2$ gain have been advocated and reported [28,43] but there is still debate to its reliability and validity [42]. From a practical point of view, outcome measures which can assess patients' function at submaximal intensities, similar to activities of daily living, are also important. Furthermore, submaximal parameters may be especially useful in the clinic environment when patients may be unwilling to provide a maximal effort and/or are limited by ventilatory capacity. In addition, the GET can improve independently of any changes in $\dot{V}O_{2max}$ [44,45] and is often used in the prescription of individualised exercise intensities within specific exercise intensity domains (i.e., at a %GET), as recently demonstrated by Stevens and colleagues [46]. Additional common parameters of interest attained during CPET include peak power output, arterial oxygen saturation, time to exhaustion, subjective ratings of perceived exertion and dyspnoea which aid interpretation of limiting factors as either more respiratory or muscular.

Indices of cardiac function and muscle oxygenation

In addition to reported $\dot{V}O_{2\max}$ measurements, parameters such as O_2 delivery and estimations of SV can be calculated. The Fick cardiac output equation can be used to estimate stroke volume whilst arterial oxygen saturation can also be estimated when examining oxygen delivery during exercise. There is growing support for the contribution from inadequate delivery of oxygen to the tissue resulting in suppressed aerobic fitness in CF patients [47]. It is therefore advantageous that measures of cardiac function and O_2 delivery are included in the CPET of these patients, although this might not be convenient and does require more technical support.

Key to exploring the effectiveness and adequacy of oxygen delivery to the exercising muscles during exercise is having some measurements of cardiac function and provision from the cardiorespiratory unit. Due to ethical constraints, non-invasive devices such as thoracic bioelectrical impedance analysis have been validated in CF patients. Such tools provide non-invasive estimations of stroke volume and cardiac output. It may well, depending on equipment available, be important to investigate ventricular function, as this may result in impaired oxygen delivery during exercise in these patients [19].

Minimal important clinical changes

Interpreting data in relation to normative values and typical error enables researchers and clinicians to determine meaningful change. Reproducibility over time is critical when evaluating the efficacy of CF treatments (e.g., antimicrobials, mucolytics and gene mutation targeted therapies) which may accrue over weeks or months, as well as monitoring exercise training interventions. One study previously reported the reproducibility of CPET in children with CF [50], however this study was limited since an intermittent sprint cycle test preceded the ramp test, resulting in insufficient test durations (~4 min). A recent study [26] examined

the reproducibility of CPET derived maximal and submaximal outcomes measures using a valid protocol in young patients with mild-to-moderate CF. Using a solitary traditional ramp test, coefficient of variation of 6.9% [49] and 8.5% [50] in $\dot{V}O_{2\text{peak}}$ have been reported over 4 weeks in CF adults, demonstrating CPET is a reliable tool.

Whilst the typical error reported in paediatric patients [26] is comparable to earlier studies, the improved validity should be considered in future studies. Whilst the compromised validity of traditional tests to ascertain $\dot{V}O_{2\text{peak}}$, e.g., the Godfrey protocol, has previously been documented [25,26], it has also been demonstrated that there is a larger within-subject variation in $\dot{V}O_{2\text{max}}$ over both the short- (13.5 vs. 9.3%) and medium-term (15.2 vs. 13.3%) compared with the combined ramp and S_{max} approach to testing. Determining the extent to which changes in outcome measures relate to a given reference measure is essential to the utility of CPET. So too is the establishment of national normative data, but currently limited normative data exists [50]. Establishing robust normative data for both CF patients and their healthy counterparts represents an important next step.

CPET and limiting factors to exercise

Due to limited scientific evidence, it remains unclear what are the relative contributions and interactions of the central (reduced oxygen delivery) and peripheral (altered muscle mass and function) mechanisms that result in the reduced aerobic fitness of patients with CF compared to healthy controls. Although dysfunction at the skeletal muscle level have been proposed [18,51], this may not be specific to CF *per se* and, rather, presents as a consequence of chronic respiratory sepsis[52]. A review by Rand and Prasad[53] recently outlined a number of the factors which likely contribute to the reduced exercise performance in patients with CF; including lung function, nutrition, muscle (dys)function, genotype, habitual physical

activity levels (and gender), and psychosocial influences. However, little attention was focused on the possible contribution from altered oxygen delivery (i.e., hypoxemia, reduced stroke volume and cardiac output) during exercise.

Evidence to support a contribution from an inadequate O₂ delivery to reduced $\dot{V}O_2$ max [52] and slow $\dot{V}O_2$ kinetics [54] in CF patients has been presented. These suggestions are supported by previous reports demonstrating altered cardiac function [16,19,55] and an inability to augment stroke volume during exercise in this patient group[52]. Rosenthal and colleagues [52] presented an important investigation with regard to the mechanistic bases of exercise limitation in CF.

The body's upper limit for O₂ utilisation during exercise is determined by the maximal cardiac output (Q), arterial oxygen content, fractional distribution of Q to the exercising muscles, and the ability of the skeletal muscle to extract this O₂. Simultaneous measurements at both the central (cardiorespiratory unit) and peripheral (skeletal muscle) levels are essential to understand the dynamic matching of O₂ delivery-to-O₂ utilisation. Since previous studies in CF have largely neglected to investigate this complex interaction and have based their inferences on investigations of isolated organ systems [17,18,19], knowledge of integrated function is limited.

Other non-invasive techniques are available to provide further evidence on how CF disease pathophysiology alters the oxygen delivery-to-oxygen utilisation relationship during exercise. Near-infrared spectroscopy (NIRS) is one such instrument, whereby the signal of muscle deoxygenated haemoglobin/myoglobin may be used to provide a non-invasive insight into microvascular O₂ extraction dynamics at the muscle level. Using this device, Saynor and

colleagues [56] have recently shown children with CF to have comparable muscle O₂ extraction dynamics compared to healthy controls, despite an impaired aerobic fitness. The latter was likely caused by an impairment in muscle O₂ delivery, as evidence through a reduction in arterial blood O₂ saturation.

The oxygen uptake kinetics response to exercise

As mentioned above, the measurement of $\dot{V}O_{2\max}$ in patients with CF has been associated with mortality [16], quality of life [13] and risk of hospitalisation [17]. However, patients with CF rarely exercise at their maximal metabolic rate meaning the measurement of $\dot{V}O_{2\max}$ lacks external validity with regard to the ‘real-world’ challenges faced by the O₂ transport and utilisation pathways. Rather, activities of daily living require repeated transitions to and from a range of sub-maximal metabolic rates. The adequacy of a patient to undertake these activities can be captured in the $\dot{V}O_2$ kinetic response during exercise, which reflects the integration of the pulmonary, cardiovascular and muscular systems to meet the increasing and decreasing energy demands within the muscle. Dysfunction at any step of the O₂ transport and utilisation pathway, as typically found in disease, leads to a slowed $\dot{V}O_2$ kinetic response during exercise (Figure 2). This increases the O₂ deficit, the requirement for substrate level phosphorylation (e.g. muscle phosphocreatine [PCr] breakdown, anaerobic glycolysis) and the accumulation of fatigue inducing metabolites (e.g. inorganic phosphate, hydrogen ions), which impairs exercise tolerance [57]. Consequently, the measurement of the $\dot{V}O_2$ kinetic response to and from exercise in patients with CF provides valuable insight into the limiting factors of oxidative phosphorylation and exercise tolerance.

Methodological considerations

To understand how the $\dot{V}O_2$ kinetic response to exercise is altered by CF a brief overview of the different phases of the $\dot{V}O_2$ response to exercise with respect to exercise intensity is required [reviewed in Refs. 57,58, and see Figure 3]. At the onset of constant work-rate moderate-intensity exercise, that is work-rates below the GET, $\dot{V}O_2$ increases almost immediately (phase I, termed cardiodynamic) due to a rise in cardiac output (\dot{Q}) and pulmonary blood flow [59]. Subsequently, the arrival of the reduced mixed venous O_2 content reaches the lungs, and, with the increasing \dot{Q} response, drives the exponential rise (phase II) in $\dot{V}O_2$ towards a new steady-state (phase III). The kinetics of phase II have been shown to reflect the kinetics of muscle O_2 consumption [60] and muscle PCr in humans [61]. The time constant (τ , time to reach 63% of the response amplitude) of the phase II response during upright cycling is $\sim 20\text{-}30$ s in healthy children and young adults and reaches a steady state (phase III) with an O_2 cost of exercise ($\Delta \dot{V}O_2 / \Delta W$) of $\sim 10 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$ [62,63]. For work rates above the GET, the $\dot{V}O_2$ response is characterised by a delayed increase in the O_2 cost of exercise that either attains a delayed steady state (heavy intensity exercise) or increases with time until $\dot{V}O_{2\text{max}}$ is achieved (very heavy exercise) [64]. The heavy and very heavy exercise intensity domains are demarcated by the critical power (CP), which represents the asymptote of the hyperbolic relationship between work rate and time to exhaustion [64,65]. The development of the so-called $\dot{V}O_2$ slow component during supra GET work-rates increases the O_2 cost of exercise to $\sim 12\text{-}14 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$ (impaired efficiency) and reflects the fatigue processes occurring within the contracting myocytes. The higher the work-rate is above CP, the lower the magnitude of the $\dot{V}O_2$ slow component, such that at work-rates close to $\dot{V}O_{2\text{max}}$, the $\dot{V}O_2$ kinetic follows a single-exponential function until exhaustion occurs with the participant achieving $\dot{V}O_{2\text{max}}$ [63].

The impact of exercise intensity on the $\dot{V}O_2$ kinetic response to exercise requires careful consideration. For example, the prescription of a single absolute work rate (e.g. 150 W or 1.5 W·kg⁻¹ of body mass) is likely to render the CF patient exercising at a higher percentage of their aerobic capacity compared to a healthy control, given the well documented reduced $\dot{V}O_{2\max}$ in this group [66]. Equally, the prescription of a work rate relative to $\dot{V}O_{2\max}$ (e.g. 60% $\dot{V}O_{2\max}$) is flawed, as although the GET appears to be preserved in CF when normalised to $\dot{V}O_{2\max}$ [54,66], there is a large variability in the position of the GET relative to $\dot{V}O_{2\max}$ across CF patients and healthy controls. Consequently, the use of an absolute work rate or a work rate in relation to $\dot{V}O_{2\max}$ will result in participants exercising across the moderate or heavy intensity domains, which will mask our understanding of the effect of CF on the $\dot{V}O_2$ kinetic response.

Are $\dot{V}O_2$ kinetics altered in CF patients?

Unfortunately, our understanding of the effect of CF on the $\dot{V}O_2$ kinetic response to exercise is limited as this has been applied more to clinical research than practice. In the first study to address this topic, Braggion and colleagues [67] reported no differences in the $\dot{V}O_2$ kinetic response between CF patients (FEV₁ 77 ± 22% predicted, age 11.1-15.3 y) and age-matched controls (age 12.2-15.2 y) during 6 min of submaximal exercise equivalent to 1.7 W·kg⁻¹ of body mass. However, it should be noted that in this study, only a single exercise transition was employed to quantify the $\dot{V}O_2$ response, and the modelling procedure employed did not isolate the phase II kinetic response, which is crucial to reflect muscle O₂ consumption [60]. Furthermore, no consideration was given to standardising the exercise intensity domain within and between the groups. In contrast, using pseudo-random binary sequence exercise,

slowed $\dot{V}O_2$ kinetics have been observed in CF patients (FEV₁ 42-88% predicted, age 13-31 y) compared to controls (age 9-29 y), although this analysis was also unable to differentiate between the phase I and II of the kinetic response [68].

To extend this work, Hebestreit et al. [54] examined $\dot{V}O_2$ kinetics in CF patients (FEV₁ 37-98% predicted, age 9.8-33.8 y) compared to healthy controls (age 9.9-30.8 y) during a two stage protocol consisting of semi-supine cycling at 20 W for 2 min and a further 3 min at a work rate calculated as 1.4 W·kg⁻¹ for males and 1.3 W·kg⁻¹ for females. This protocol was repeated 2-4 times to improve the signal to noise ratio of the $\dot{V}O_2$ kinetic response [69]. After analysis of the $\dot{V}O_2$ kinetic response, the authors found a slower phase II $\dot{V}O_2$ τ in CF compared to the control group (36.8 ± 13.6 vs. 26.4 ± 9.1 s) with no difference in the O₂ cost of exercise (10.9 ± 1.8 vs. 10.2 ± 1.6 mL·min⁻¹·W⁻¹), respectively. Although this study suggests CF patients are characterised by sluggish $\dot{V}O_2$ kinetics and thus an increased O₂ deficit, a number of methodological issues confound interpretation of this study. Firstly, the work-rate was not prescribed to a particular exercise intensity domain, increasing the possibility that participants within and between groups were exercising across the moderate or heavy intensity domains. Secondly, 2-4 repetitions of the exercise protocol were undertaken on the same day with only 10 min recovery. This raises the possibility that a ‘priming’ effect may have occurred on the $\dot{V}O_2$ kinetic response [70], which is likely to be more influential on those with slower $\dot{V}O_2$ kinetics (i.e. CF patients) [71]. Finally, the exercise involved semi-supine rather than upright cycling, which may have reduced muscle O₂ delivery due to the absence of the gravitational assist to muscle blood flow, and slowed the $\dot{V}O_2$ kinetic response [72].

$\dot{V}O_2$ kinetics and limiting factors to exercise

Despite the aforementioned limitations, it is important to consider the mechanisms that may cause a slowing of the $\dot{V}O_2$ kinetic response in patients with CF. In the context of CF, dysfunction may be present at the pulmonary (e.g. arterial hypoxemia, increased cost of breathing), cardiovascular (reduced stroke volume and cardiac output) and muscular (reduced oxidative capacity, reduced muscle mass) systems [reviewed in Ref. 73] which ultimately may impact $\dot{V}O_2$ kinetics in this patient group. Debate continues as to whether phase II $\dot{V}O_2$ kinetics are limited by the ability of the contracting myocytes to deliver or utilise O_2 [74]. While an interaction of these factors are likely to be important [75], it has been proposed that in disease a ‘tipping point’ may be passed whereby the phase II $\dot{V}O_2$ kinetics become O_2 delivery dependent [76]. In support of this hypothesis, Hebestreit and colleagues [55] observed an inverse correlation ($r=-0.69$, $P=0.002$) between the phase II $\dot{V}O_2 \tau$ and arterial O_2 saturation (SaO_2) measured at the end of the exercise bout in CF patients only, suggesting the slower $\dot{V}O_2$ kinetics are mechanistically linked to a reduction in muscle O_2 availability. However, correlations was also found between the phase II $\dot{V}O_2 \tau$ and FEV_1 ($r=-0.53$, $P=0.029$) and $\dot{V}O_2 \max$ ($r=-0.59$, $P=0.013$), suggesting respiratory factors and aerobic conditioning may be equally important. Finally, although Kusenbach and colleagues [68] observed CF patients to have slower $\dot{V}O_2$ kinetics during normoxia (21% O_2), when the CF patients were exposed to hyperoxia (40% O_2), their $\dot{V}O_2$ kinetic repose was unchanged despite an increase in SaO_2 . Thus, these findings suggest that the ability of the muscle to utilise O_2 may be the limiting factor of $\dot{V}O_2$ kinetics in CF patients. Indeed, the expression of CFTR in human skeletal muscle raises the possibility of a CF specific muscle defect than may impair muscle metabolism and exercise tolerance [77], which is supported by ^{31}P -

magnetic resonance spectroscopy based measures of an impaired muscle oxidative capacity in CF [51].

Recovery of $\dot{V}O_2$ following exercise

Besides the $\dot{V}O_2$ kinetic response to exercise, the recovery kinetics of $\dot{V}O_2$ have been studied, as it may provide an index of the muscle oxidative capacity [78] and is independent of effort. Pouliou et al. [78] found the recovery of $\dot{V}O_2$, as quantified using a linear slope function to characterise the rapid exponential-like phase during the first minute of recovery following a $\dot{V}O_2$ max test, to be slower in CF (FEV₁ 23-128% predicted, age 14-61 y) compared to healthy controls (age 22-36 y). Interestingly, the recovery of $\dot{V}O_2$ was correlated with the Schwachman Score ($r=0.81$, $P<0.001$), a clinical index of disease severity, which remained the only significant predictor after accounting for confounding variables ($\dot{V}O_2$ max, FEV₁) in a multivariate analysis. Similar results have also been reported in a more homogenous sample of patients with chronic chest diseases (70% CF, FEV₁ $82 \pm 23\%$ predicted, age 12.7 ± 3.1 y) against healthy controls (age 13.2 ± 3.3 y) [79]. Patients were characterised by a slower recovery of $\dot{V}O_2$ following a $\dot{V}O_2$ max test, which was correlated with $\dot{V}O_2$ max ($r=-0.39$, $P=0.044$). In CF patients only, $\dot{V}O_2$ recovery was correlated with the Schwachman Score ($r=-0.63$, $P=0.004$), which supports previous work by Pouliou and colleagues [78]. Therefore, although the slower recovery kinetics of $\dot{V}O_2$, at least following maximal exercise to exhaustion, are prolonged in CF, and appear to be related to disease prognosis independent of $\dot{V}O_2$ max, further studies are needed to establish the clinical utility of this measurement independent of more established clinical outcomes.

Exercise Interventions and the CF patient

A number of strategies (e.g., nutritional supplementation, antibiotics, assisted breathing and exercise) are employed by healthcare professionals to increase functional aerobic fitness, whilst simultaneously attempting to reduce the decline of clinical status and the costs associated with the treatment of the disease. Supervised aerobic and strength training programmes have shown some effect in improving $\dot{V}O_{2\max}$ and FEV₁ in patients with CF. The Cochrane review by Bradley and Moran [80] concludes that there is some evidence of short and long term benefits of physical training in people with CF. However, this was concluded on only seven trials with a total of 231 participants, inclusive of children and adults. As it has been shown that both aerobic capacity [81] and lung function decline upon the cessation of training, it may be suggested that regular, long-term, sustainable programmes must be promoted as part of CF management [82]. Within a paediatric population, aerobic training has been demonstrated to improve pulmonary function over the short term (3 weeks [83]), and a three-year home-based intervention slowed the rate of decline in children with CF with mild-to-moderate disease, compared to patients undertaking normal physical activity [84].

Inspiratory muscle training (IMT)

Regular aerobic exercise has been suggested to hold a significant benefit upon respiratory muscle function, with increased maximal inspiratory and expiratory pressures in patients that undertake regular aerobic exercise, despite similar FEV₁ and FVC with a non-exercising control group. Thus, Dassios and colleagues suggested that regular exercise can decrease the possibility of respiratory fatigue in CF patients when they are exposed to increased respiratory loads [85]. This causal relationship could be of benefit to health practitioners in order to encourage aerobic exercise amongst CF patients; however it is also worth considering how well respiratory muscles may be conditioned independently of traditional exercise programmes in order to benefit patients that may be clinically unstable, or

unaccustomed to intense exercise. A recent review of IMT within the CF population revealed insufficient evidence to either support or refute the use of this technique [86]. Although IMT has been shown to improve inspiratory muscle endurance in an adult CF group, no increase in FEV₁, FVC or $\dot{V}O_{2\max}$ was observed [87]. However, increases in lung volume and exercise performance have been observed in a paediatric CF group (7-14 y) [88]. This discrepancy observed between adult and paediatric CF patients may be due to the progressive and life-limiting nature of the disease, with the beneficial pulmonary effects of IMT being masked in adults (>18 y) as they can effectively be classified as ‘middle age’ once they reach adulthood, a point whereby irreversible lung damage may have already occurred [86].

High intensity interval training

High intensity interval training (HIIT) has been proposed as a time-efficient alternative to traditional programmes and may be of particular benefit to unstable, or de-conditioned, patients due to the intermittent nature of the exercise; providing patients with regular breaks between exercise bouts [89]. A recent HIIT study in adults with CF has shown this exercise modality (continuous walking speed, between 3 and 4 km/h lasting 16 min, 5 times weekly and comprised ten intervals of 20 or 30 s high intensity bouts at 50% of maximal grade achieved during the steep ramp test, followed by 60 s active recovery phases at 0% grade treadmill inclination) to be equally effective at improving $VO_{2\max}$ as a traditional aerobic exercise programme, with benefits seen at both maximal ($\dot{V}O_2 \max$) and submaximal exercise intensities (ventilatory threshold) [90]. The efficacy of HIIT has been further supported by a recent case study in an adolescent female with CF, whereby $VO_{2\text{peak}}$ improved by 18% following a 6-week HIIT programme. In addition, pulmonary parameters were improved (FEV₁, 49%; V_E, 50%) when compared to baseline [91]. HIIT therefore warrants further investigation in paediatric CF patients, especially as the intermittent nature of the

exercise closely mimics physical activity patterns of children and may subsequently promote sustainable engagement in physical activity.

Multi-modal interventions

Whilst it is informative to note what effect independent interventions strategies have upon pulmonary factors, it is imperative to understand how these strategies combined might improve aerobic fitness in the CF child. Furthermore, multi-modal interventions have been identified as reducing the reliance on antibiotics and associated healthcare costs, whilst simultaneously improving aerobic function and reducing the rate of decline of lung function [92].

Pharmacological intervention

Whilst exercise appears to be a highly beneficial mode for improving pulmonary function and quality of life, not all patients will be well enough to undertake intense exercise. As a short-term measure, intravenous antibiotics (IVABs) can be utilised to improve clinical status and restore exercise performance. In an adult population, FEV₁ was restored to baseline within seven days following the initiation of a course of antibiotics [92]. Lung function has also been shown to increase (FEV₁; +9.5 %) in a paediatric population following a 14-day course of IVABs. In addition to improvements in pulmonary function, exercise performance (stepping exercise) was also improved with significantly reduced heart rate and dyspnoea, alongside increased SaO₂ following a 3-minute step test [93]. However, to the best of our knowledge no IVAB study has utilised CPET. Whilst IVABs may provide an intermediary improvement in function, and that patients report feeling well, whether lung function is sensitive to detect enough of an improvement to send the patient home or stop treatment at home remains to be investigated.

To combat reliance on IVABs as a treatment option, long-term pharmacological treatments are continually being developed, with the most promising of recent developments being an orally administered CFTR potentiator, VX-770, otherwise known as Ivacaftor, and most recently marketed under the name Kalydeco[®]. Ivacaftor has been shown to be effective in moderately ill patients (40-90% predicted FEV₁) that are heterozygous for the G551D mutation, with a significant treatment effect identified in children (<18 y) through increases in predicted FEV₁, weight and quality of life (CFQ-R [14,106]), alongside reductions in pulmonary exacerbations [95]. Furthermore, administration of Ivacaftor has revealed improvements in the pulmonary function of severely ill patients (<40% predicted FEV₁[107]) and young children aged 6-11[96]. Exercise performance has also been shown to improve within two weeks, with distance in the 6-minute walking distance increasing by over 200% in a case-study of a woman that is homozygous for the G551D mutation. The majority of this improvement was observed within two-weeks of the initiation of Ivacaftor therapy, and continued to increase for the following 50-weeks. This is in contrast to the plateau observed in functional capacity for heterozygous individuals [97]. However, the subjective nature of the 6-minute walk test provides little insight into the mechanistic explanations of the improvement of aerobic function. Despite the promising results shown by the administration of Ivacaftor, no studies have yet fully assessed its impact upon the aerobic capacity of patients through a rigorous exercise protocol. Furthermore, as only 5.6% of the UK population are identified as having the G551D allele [98], the development of new treatments to target the Δ F508 mutation is essential. Assessment of aerobic function should be a key clinical outcome within these future trials.

Conclusion

Previous studies indicate the impact of aerobic fitness upon survival rates upon patients with CF [14,16] and therefore it is appropriate that valid and reliable exercise tests are utilised within this population to determine $\dot{V}O_{2\max}$ where possible. However, as the increased life expectancy of patients today is considerably greater than observed in the 1980s, this association between prognosis and fitness needs urgent re-evaluation. Importantly, measures of $\dot{V}O_{2\max}$ should only be determined via valid and reproducible tests as it is possible that fitness levels of CF paediatric patients may have been under-estimated [28]. Currently, the cost-effectiveness data for CPET needs to be established to assist with its incorporation as a standard clinical tool. Considering the inexpensive cost and greater availability of the equipment and professional groups being educated to run these tests (e.g., physiotherapists, clinical exercise physiologists), once tests are established, their implementation is not as impractical as once envisaged. Finally, there remains debate on the factors limiting exercise tolerance in CF patients, with suggestions this could reside at the respiratory, cardiovascular and muscular levels. Further research in this area is crucial to optimise interventions to enhance exercise tolerance, and thus quality of life.

Expert commentary

CPET is an underutilised tool for those working with CF patients in both clinical and research settings but the barriers to implementation are being removed. Its key strength is the ability to identify, in an integrated fashion, the factor(s) primarily responsible for exercise limitation in this patient group. A more frequent uptake of CPET parameters as an essential outcome measures within CF clinical trials will also help to expand upon the mechanisms of functional improvement above standard markers e.g., BMI, sweat chloride and pulmonary function. By thorough familiarisation and an appropriate choice of testing protocol, accurate CPET data can be established and clinicians can therefore have greater confidence in its utility. CPET

should become a component within (at least) the annual review of all CF paediatric patients with mild-to-moderate disease status. The potential of $\dot{V}O_2$ kinetics to investigate mechanistic limitations holds much promise, but the lack of methodologically robust studies in CF is preventing the area from moving forward. In particular, studies are needed across the exercise intensity domains, and including recovery kinetics, to document the effect of CF on $\dot{V}O_2$ kinetics, in conjunction with simultaneous measures of muscle O_2 delivery and utilization. Once the factors limiting exercise intolerance are identified, these research findings can be translated into clinical practice.

Five-year view

Where indicated, routine uptake of CPET within clinical assessment of young CF patients will become established. The importance of normative values cannot be underestimated and will become established for both CF patients and their healthy counterparts using valid protocols. The increased uptake of exercise testing as an outcome measure within clinical research investigating pharmacological or physiotherapy based interventions in paediatric patients will lead to significant advancements in the management care of CF patients. We speculate that the topical ‘systems medicine’ based approach will benefit research in exercise *per se*, as the integrated approach is fundamental biologically to what occurs in everyday life. CPET for translating healthcare research and exercise has significant potential to be recognised as a potent and inexpensive medicine.

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FIGURES

Figure 1

Schematic of the exercise test protocol. A: 3-min warm-up at 20 W. B: Incremental ramp exercise at a rate of 10-30 W/min (individualized to patients' anthropometric data). C: 5-min active recovery (unloaded pedalling). D: 10-min seated recovery off the cycle ergometer. E: 3-min warm-up at 20 W. F: Supramaximal confirmation bout of exercise to volitional exhaustion at 110% of the peak power output produced in the prior ramp exercise test B. G: 3-min recovery (unloaded pedalling).

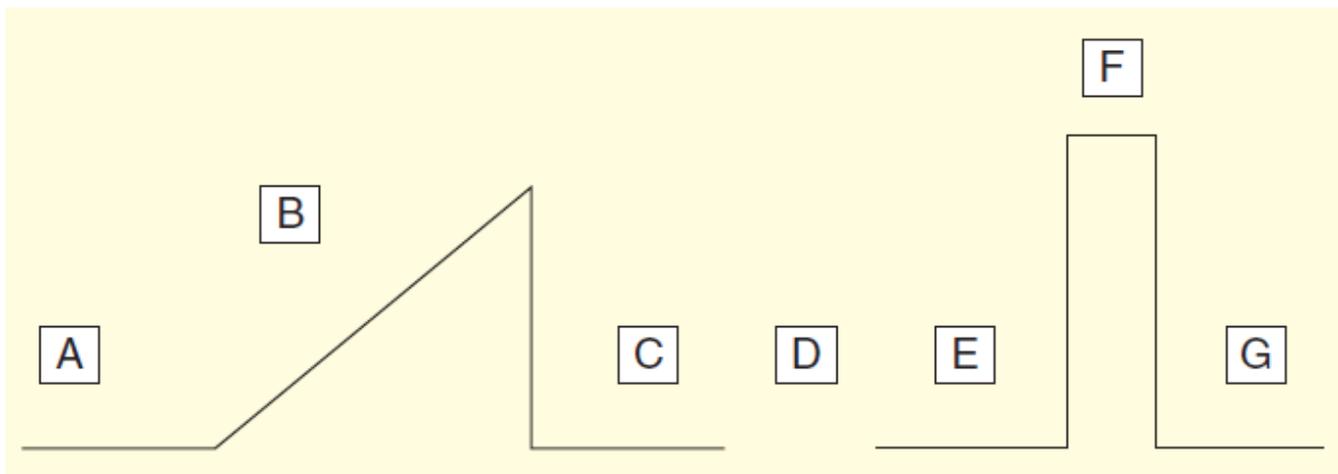


Figure 2

Example VO_2 kinetics profile in a pediatric patient with cystic fibrosis during moderate (● black circles) and very heavy (○ white circles) intensity cycling exercise. The vertical dotted lines represent the different phases (I, II and III) of the VO_2 kinetic response. Notice that during moderate-intensity exercise, after Phase II (~120 s), the VO_2 response has attained a steady state. In contrast, for very heavy exercise, after Phase II (~120 s), a steady-state VO_2 response is not achieved due to the emergence of the VO_2 slow component which increases the O_2 cost of exercise toward $\text{VO}_{2\text{max}}$, which in this patient was 1.68 l/min. VO_2 : Oxygen uptake.

