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Cardiopulmonary exercise testing in children with Cystic Fibrosis: one centre’s experience

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ABSTRACT

Background
While exercise testing is increasingly used as a prognostic indicator in Cystic Fibrosis (CF), it is reported to be underused in UK CF centres, particularly in children. Here, we evaluated the cardiopulmonary exercise testing (CPET) results in children and young people with CF at CF annual review and its possible clinical value.

Method
An observational study comparing CPET results using a cycle ergometer ramp test (peak oxygen uptake ($VO_{2peak}$)) and pulmonary function (forced expiratory volume in 1 second ($FEV_1$)) was performed with body mass index (BMI) used as a disease severity marker. Data were identified from clinical case notes and our CF database.

Results
Thirty-eight children and young people (mean age 11±2.4; range 7-14 years; 17 males and 21 females) completed at least one CPET with 95 % achieving technically satisfactory tests allowing measurement of $VO_{2peak}$. Mean $VO_{2peak}$ was 107±17.6% predicted, range 74 - 150% predicted, with 8% having a reduced $VO_{2peak}$ of <85% of predicted. Mean $FEV_1$ z-score was -0.77±1.24, range -4.42 to 2.24. We did not demonstrate a significant correlation between $VO_{2peak}$ % predicted and $FEV_1$ z-score ($r=0.25$, $p=0.13$), or between $VO_{2peak}$ % predicted and BMI z-score ($r=-0.05$, $p=0.77$). Twenty-eight of 38 completed a second CPET the following year with 71% showing a decline in $VO_{2peak}$, (mean decline of 8% of predicted value, equivalent to 3.8 mL/kg/min).
Conclusion

CPET is feasible with 95% of children and young people achieving technically satisfactory assessments starting from age 7. In this group with relatively mild CF, mean VO$_{2peak}$ was normal with no significant correlation between VO$_{2peak}$ and FEV$_1$ or BMI, as markers of disease severity. The majority demonstrated a normal VO$_{2peak}$. However, 71% showed a downward trend on repeat testing 12-18 months later.

What is already known on this topic

- Exercise testing is not widely used in cystic fibrosis (CF) centres in the UK.
- Peak oxygen uptake (VO$_{2peak}$) and forced expiratory volume in 1 s (FEV$_1$) are independent predictors of mortality in CF.

What this study adds

- We demonstrate that it is feasible to include a cardiopulmonary exercise test (CPET) as part of annual review in children and young people aged 7 years and above.
- In mild disease, there is no significant correlation between VO$_{2peak}$ and FEV$_1$ or body mass index.
- A decline in fitness can be used as a trigger for more intensive physiotherapy intervention.
INTRODUCTION

Aerobic fitness has been found to be an independent predictor of mortality and morbidity in patients with cystic fibrosis (CF) [1,2,3]. At present, the UK CF trust guidelines recommend exercise testing at CF annual review when clinically indicated [4]. The European Cystic Fibrosis Exercise Working Group recommend that full cardiopulmonary exercise testing (CPET) should be performed routinely in children aged ≥10 years [5]. Exercise testing is reported to be underused in UK CF centres with field-based walking tests used most commonly [6]. To our knowledge, there are no studies assessing the prognostic value of the 6 min walk test (6MWT) in children with CF, and only limited reports in adults [7]. The prognostic value of an incremental shuttle test [8] in children with CF is also unknown. In contrast, peak oxygen uptake (VO_{2peak}) has been shown to predict mortality in children with CF [1,2].

VO_{2peak} represents the maximal amount of oxygen that can be delivered by the cardiovascular system and used at the muscles and defines functional aerobic capacity of a person [9,10]. In view of the potential usefulness of VO_{2peak} as a guide to understanding any exercise limitation and for guiding the prescription of exercise programmes [11], our centre replaced an annual 6MWT with an annual CPET for all children and young people aged >7 years from May 2013. Here, we review our experience of measuring VO_{2peak} using CPET and assess correlations with other more commonly used outcome measures such as pulmonary function test results and body mass index (BMI). We also investigated whether there was a difference in mean VO_{2peak} depending on sex, the presence of at least one DF508 mutation or a history of intravenous antibiotic treatment in the preceding year and whether there
were changes in aerobic capacity over time.

**MATERIALS AND METHODS**

**Study participants**

We retrospectively analysed data for children and young people regularly attending the CF clinic at the Royal Hospital for Sick Children, Glasgow, who were >7 years and who had completed at least one CPET between May 2013 and April 2016. Clinic treatment routines remained unchanged during the study period and the participants were clinically stable when tested.

**Anthropometry**

Height was recorded to the nearest 0.1 cm using a stadiometer (Holtan Limited, UK) [12]. Weight was measured with minimal clothing to the nearest 0.1 kg (Seca 704, Germany).

**Pulmonary function testing**

Before CPET, spirometry and lung volumes were measured using a Jaeger Masterscreen Body Plethysmograph (Jaeger V5.4, Germany). All pulmonary function measurements were carried out by an experienced paediatric physiologist according to American Thoracic Society/European Respiratory Society standards [13,14,15].

**Cardiopulmonary Exercise Testing**

A symptom-limited CPET was performed using an electronically braked cycle ergometer (Ergoline, Netherlands) with an incremental ramp protocol. Before each
test, the metabolic cart (Jaeger, CPX, Germany) was calibrated according to the instructions of the manufacturer. We used a Godfrey exercise protocol [16] modified to minimise large increments in power output. The cycle ergometer ramp ranged between 6.5 and 25 W/min. The ramp was increased every 10 s to minimise power output perception. To achieve an optimal test duration of 8-12 min, power output based on weight, predicted for each participant [17], was divided by 10 to give the rate of ramp increase. Participants received verbal encouragement to achieve as near to a maximal test as possible. The test was stopped when the participant could not maintain a cadence > 60 rpm even with verbal encouragement. \( \text{VO}_{2\text{peak}} \), peak oxygen pulse (\( \text{VO}_{2}/\text{HR}_{\text{peak}} \)) and peak minute ventilation (\( \text{VE}_{\text{peak}} \)) were averaged over the last 30 s of the test. The gas exchange threshold was non-invasively identified using a combination of the ‘V slope’ method and ventilatory equivalents [9].

We considered a CPET technically satisfactory if one of the following three criteria were achieved at the end of the test: (1) \( \text{HR}_{\text{peak}} \) within 15 bpm of predicted maximum based on age; (2) respiratory exchange ratio (RER) > 1.1; or (3) plateau in \( \text{VO}_{2} \).  

**Consent**

This study was a retrospective review of results from our standard clinical practice. As such, we did not seek informed consent for review of the data. All data of the patients were anonymised.

**Statistical Analysis**
Demographic data (age, sex, genotype and intravenous antibiotic use) were expressed as means and SDs. Forced expiratory volume in 1 s (FEV₁) was expressed in absolute terms and as z-scores using all age reference ranges [18]. Static lung volumes were expressed in absolute values and as z-scores using UK-derived paediatric reference ranges [19]. VO₂peak was expressed in L/min, mL/kg/min and as % predicted using a published paediatric reference range [17].

The relation between disease severity and VO₂peak was assessed in two ways: first, as the relation between VO₂peak and BMI since it is well recognised that poor nutritional status negatively affects pulmonary disease [20,21] and then, as the correlation between VO₂peak and intravenous antibiotic use in the preceding year. We included children and young people treated with intravenous antibiotics either for a CF exacerbation or routinely as part of their CF management.

To investigate relationships between VO₂peak % predicted and FEV₁ z-score, BMI z-score and age, we used Pearson’s correlation coefficient. For differences between mean VO₂peak % predicted with sex and intravenous antibiotics, we used a two-sample t-test. A one-way analysis of variance was conducted to compare the effect of genotype (DF508 homozygous, DF508 heterozygous and ‘other’ genotypes) on VO₂peak % predicted.

We used a paired t-test to check for statistically significant differences between initial and consecutive CPET parameters of aerobic fitness (absolute VO₂peak (L/min); relative VO₂peak (mL/kg/min); VO₂peak % predicted; and finally, allometrically scaled
VO₂peak (ml/kg²/³/min). Relationships between the change in VO₂peak % predicted and FEV₁ and BMI z-scores were studied using Pearson’s correlation coefficient.

RESULTS

Pulmonary function & anthropometry.

Anthropometry and pulmonary function are summarised for the 38 participants studied (17 males, 21 females) in tables 1 and 2. Seven participants had an FEV₁ consistently below the lower limit of normal [19].

Table 1

Table 2

We were able to perform technically satisfactory assessments on 36/38 (95 %) of children and adolescents (Table 3); in two of them (both aged 7 years), the CPET was technically unsatisfactory due to poor cooperation. Aerobic capacity in children with CF was within a range consistent with a normal, healthy population (VO₂peak of ≥85 % predicted [22]). Only five participants (13 %) had VO₂peak of <85 % predicted, none of whom had reduced FEV₁. Two participants desaturated to SpO₂ (oxygen saturation as measured by pulse oximetry) <95 % at peak exercise. No ECG arrhythmias were detected.

Table 3
We found no significant correlation between VO₂peak % predicted and FEV₁ z-score ($r = 0.25$, $p = 0.13$), VO₂peak % predicted and age ($r = -0.24$, $p = 0.15$) or between VO₂peak % predicted and BMI z-score ($r = -0.05$, $p = 0.77$). Using a two-sample t-test, we found no significant differences in mean VO₂peak between males (107.9±19.1% predicted) vs females (107.1±17.0% predicted), $p = 0.90$. Fourteen children and young people had received intravenous antibiotics in the preceding year with no significant differences in mean VO₂peak if they had intravenous antibiotics (103.0±18.5% predicted) vs did not have intravenous antibiotics (110.1±17.1% predicted), $p = 0.23$. Nineteen children and young people were DF508 homozygous, 16 were DF508 heterozygous and 3 had ‘other’ genotypes with no significant effect of genotype on VO₂peak ($p = 0.567$).

Figure 1. Change in VO₂peak % predicted in 28 children and adolescents with CF measured between 12-18 months apart.

Table 4

Consecutive annual CPET data were available for 28/38 (74%) children and young people (Figure 1), up to 18 months after the initial CPET due to CF annual review timings. The results for those who completed a second CPET are shown in table 4. Ten did not perform a repeat CPET: three transitioned to adult services; four did not attend; one had an intercurrent CF exacerbation; one CPET was unsatisfactory due to submaximal effort and there was insufficient staffing for one patient. Mean increase in body mass from test 1 to test 2 was 4.9 kg and height was 6.5 cm. There was no significant difference in mean change of absolute VO₂peak ($p = 0.74$). However,
there was a statistically significant decline in VO$_{2peak}$ when it was related to body weight ($p=0.001$), to % predicted VO$_{2peak}$ ($p=0.003$), which includes sex and body weight in the predicting equation, and when using allometric scaling (mL/kg$^{2/3}$/min) ($p=0.03$). Seventy-one per cent of patients had a decline in VO$_{2peak}$ relative to body weight. The mean decline relative to body weight was 3.8 mL/kg/min equivalent to an 8% decrease from baseline value. We found no significant correlation between the change in VO$_{2peak}$ % predicted and the change in FEV$_1$ z-score ($r=-0.07$, $p=0.72$) or between VO$_{2peak}$ % predicted and the change in BMI z-score ($r=0.10$, $p=0.61$).

**DISCUSSION**

In this study, the majority of our children and young people with CF had BMI and pulmonary function within the normal range, in keeping with UK CF registry data [23]. The majority also had VO$_{2peak}$ measurements within the normal range suggesting that they are an aerobically fit group.

We found no significant correlation between FEV$_1$ and VO$_{2peak}$, presumably explained by the majority having normal lung function and aerobic capacity. It is recognised that FEV$_1$ has to be significantly reduced to affect exercise capacity [24]. For example, McBride et al investigated 64 children with CF aged 8-11 years and found a statistically significant but weak correlation between FEV$_1$ % predicted and VO$_{2peak}$ % predicted with an $R^2$ value of 0.14[25]. The most likely explanation for the differences with our study is a combination of a larger sample and a wider range of lung function and fitness. As only seven of our participants had an FEV$_1$ below the lower limit of normal, it is perhaps not surprising that we did not see a relationship in a relatively
mildly affected population [26]. However, taken together, the low R² value in a study by McBride and the absence of any significant correlation in our data suggest no strong relationship between FEV₁ and VO₂peak. Additionally, we did not demonstrate a significant correlation between the change in VO₂peak % predicted and change in FEV₁ or BMI z-score in our CF group, highlighting that these measurements cannot be used as a surrogate marker for aerobic fitness. There is an ongoing debate about factors that limit aerobic function in CF with suggestions of both central (e.g. impaired stroke volume [27]) and/or peripheral mechanisms (e.g. impaired muscle metabolism) being involved, apart from changes in lung function [28].

There are varying reports in the literature on the aerobic fitness of CF children. Nixon et al investigated VO₂peak and its prognostic value in a group of 40 adults and 68 children and adolescents in whom 65 % had an FEV₁ of <65 % predicted. They found low aerobic capacity with a mean VO₂peak of 70% predicted (35 mL/kg/min) [1]. More recently, Hulzebos et al reported on 127 adolescents with CF who had a mean FEV₁ of 78 ±15.6 % predicted and a VO₂peak/kg 93±17.9% predicted [3]. Pianosi et al exclusively investigated children with CF and reported an initial VO₂peak of 41.2 mL/kg/min [2]. This would be classed as ‘fair’ aerobic fitness according to published paediatric reference values [24].

More recent studies have included control groups and showed that children and adolescents with CF had a significantly reduced VO₂peak when compared to healthy children. For example, Bongers et al in a group of 22 children with CF, found VO₂peak to be significantly lower than healthy controls [29] and Saynor et al found a
reduced aerobic capacity (mean VO$_{2\text{peak}}$ 36.3 mL/kg/min) in those with CF compared with controls [30].

Other studies have reported that nutritional status affects exercise capacity [31,32] but since very few of the children in our study had either an abnormal BMI or an abnormal VO$_{2\text{peak}}$ ($\leq$84 % predicted (range 64 – 84)) [22] we were unable to demonstrate a significant correlation. On reviewing the 3 participants with an abnormal VO$_{2\text{peak}}$, all had normal BMI $z$-scores (-0.57, 1.13, 1.83).

While the majority of our patients had normal CPET results, 71% demonstrated a decline in VO$_{2\text{peak}}$ relative to body weight on repeat testing 12-18 months later. We recognise that in the absence of a control group and more extensive longitudinal data, it is difficult to exclude normal variation and regression to the mean as a cause of this decline and indeed, we found some evidence of regression to the mean (Supplementary Figure).

There is little reported data about what constitutes a significant decline in VO$_{2\text{peak}}$ in patients with CF. It is also unclear how changes with growth in weight and height should be accounted for when reporting VO$_{2\text{peak}}$ data, both in healthy children and in those with CF, particularly around puberty. In a review by Krahenbuhl et al of data from healthy children, mean values of VO$_{2\text{peak}}$ relative to body weight were plotted against age in males and females over the age range 6-16 years [33]. Males had an unchanged VO$_{2\text{peak}}$ corrected for body weight over time, whereas females showed a decline from 52.0 to 40.5 mL/kg/min.
It is recognized that correcting VO$_{2\text{peak}}$ for body mass has limitations and does not normalise the data [34,35]. Ratio scaling of VO$_{2\text{peak}}$ by body mass (as opposed to fat-free mass) penalises females and those that are heavier than their aged match peers. Allometric scaling of VO$_{2\text{peak}}$ may be a more reliable method to interpret changes in VO$_{2\text{peak}}$ [36], particularly in the transition at puberty. In a cross-sectional study using allometric scaling, Armstrong and Welsman reviewed prepubertal, circumpubertal and adult males and females, and found significant increases in VO$_{2\text{peak}}$ when allometrically scaled relative to weight in males throughout the maturational range, whereas females increased till puberty then remained stable [37]. In contrast, the Amsterdam Growth and Health Longitudinal Study recently reported aerobic fitness for approximately 650 adolescents over a 25-year period. They found that from 12 to 17 years in both males and females, there was a downward trend in VO$_{2\text{peak}}$ relative to body weight. However, when allometrically scaled, VO$_{2\text{peak}}$ in males did not decrease while females declined [38]. We found a mean decline relative to body weight of 3.8 mL/kg/min equivalent to an 8% decrease from baseline value. This is greater than the normal coefficient of variation reported in the literature for VO$_{2\text{peak}}$ (4.8%) when looking at biological quality control subjects [39], although the variability for young patients with CF is likely to be greater [40]. In our data, aerobic fitness declined significantly, irrespective of whether VO$_{2\text{peak}}$ was related to body weight, % predicted values or using allometric scaling (table 4), although the decline was least using allometric scaling.
Pianosi et al reviewed annual CPET over a 5 year period in children with CF and found that VO$_{2\text{peak}}$ decreased in 70% of children with a mean annual decline of 2.1 mL/kg/min [2]. Although measured over a much shorter time period, our results are similar. We can only speculate on the reasons for the decline in some children. Although changes in lung function measured as FEV$_1$ were not correlated with changes in aerobic fitness, acute exacerbations as well as disease progression may have resulted in these patients participating in less physical activity with a consequent reduction in fitness. In others, an increase in fitness may result from the effects of planned exercise interventions. Pianosi also showed that initial VO$_{2\text{peak}}$ did not affect the rate of decline and that patients with VO$_{2\text{peak}}$ < 32 mL/kg/min exhibited a dramatic increase in mortality [2]. Further work will be required to investigate the value of repeated CPET tests in assessing exercise capacity in CF patients over time.

Whilst the capital initial cost of CPET equipment is significant, the cost of consumables is minimal. Performing an annual CPET added minimal time to the CF annual review visit with 95% of children and young people aged above 7 years achieving technically satisfactory assessments. Nevertheless, CPET is a more technically demanding test and can only be performed in a centre with the necessary equipment and appropriately trained staff. The majority of our patients engaged well with the test and participants reported that they enjoyed the challenge. Importantly, our respiratory physiotherapists found the results helpful in identifying children needing more targeted exercise advice. This emphasizes the value of CPET as a clinical tool to guide the prescription and monitoring of exercise programmes [41].
Study limitations

This was a retrospective review and we had no control group. Instead, we relied on published normal data for VO$_{2peak}$, data based on a limited number of North American children and published in 1984. Future research should focus on providing up-to-date reference data for UK children.

Only 74% (n = 28) completed a second CPET during the study period and the follow-up period was relatively short at 12-18 months. We continue to collect data in the expectation that longer follow up will give a more informed assessment of extent and value of changes in aerobic capacity over time.

In the context of a paediatric clinical population, it was not feasible to perform a supramaximal test on each patient to verify a ‘true’ VO$_{2peak}$ as demonstrated by a plateau in VO$_2$. The use of secondary criteria of HR$_{peak}$ and RER may, therefore, underestimate the ‘true’ VO$_{2peak}$ [42]. We also did not routinely take body fat measurements but recognise that this may affect the VO$_{2peak}$ % predicted which uses body weight in the predictive equation. Finally, we had no standardised recording of physical activity levels of the children and adolescents in the 12-18 month interval between the first and second tests, data that might have been informative in assessing the effect of regular activity and/or exercise on aerobic capacity.

CONCLUSION

CPET is a feasible test of aerobic function at CF annual review. In our population with relatively mild CF, most had normal VO$_{2peak}$. While most children and young people
showed a decline in VO$_{2\text{peak}}$ over time, it remains to be shown if these declines are clinically significant or are part of normal biological variation.

**Acknowledgements**

We would like to thank all the patients who performed PFT’s and CPET during the study period and our physiotherapy team who contribute to maintaining aerobic fitness in our patients with CF.

**Contributorship**

AD instigated, designed and supervised the study. EW and PB contributed to the design of the study, collected the data and analysed results with DY. EW and PB wrote the article. JYP reviewed and commented on the article.

**Funding**

No funding was obtained for this study.

**Competing interests**

None declared
REFERENCES

23. UK Cystic Fibrosis Registry 2014 Annual Data Report. Published August 2015
**Table 1**

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**Table 2**

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**Table 3**

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<td>Absolute VO₂peak (L·min⁻¹)</td>
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<td>Relative Peak power output W·kg⁻¹</td>
<td>2.5</td>
<td>0.56</td>
<td>1.6, 3.8</td>
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| **Submaximal Exercise**           |      |     |                |
| VO₂ at GET (ml·min⁻¹)             | 822  | 216.1| 415, 1455      |
| GET (% of VO₂peak)                | 53   | 7.3 | 38, 70         |
| VO₂/Work Rate (ml·W⁻¹·min⁻¹)      | 10.6 | 0.88| 9.1, 12.3      |
| VE/VO₂ Slope                      | 30.9 | 3.87| 22.4, 44.0     |

*GET - Gas exchange Threshold*
Table 4

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<td>VO_{2peak} Relative to bodyweight (ml·kg^{-1}·min^{-1})</td>
<td>42.7 ± 6.95</td>
<td>38.9 ± 8.19</td>
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<td>VO_{2peak} Allometrically scaled (ml·kg^{-2/3}·min^{-1})</td>
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<td>130 ± 21.9</td>
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<td>Body mass (kg)</td>
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<td>41.2 ± 13.51</td>
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<td>Height (cm)</td>
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