



Early Oxygen Uptake Recovery Following Exercise Testing in Children with Chronic Chest Diseases

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Complete List of Authors:	Stevens, Daniel; University of Exeter, Children's Health and Exercise Research Centre Oades, Patrick; Royal Devon and Exeter Healthcare Foundation NHS Trust, Paediatric Unit Armstrong, Neil; University of Exeter, Children's Health and Exercise Research Centre Williams, Craig; University of Exeter, Children's Health and Exercise Research Centre
Keywords:	chronic chest diseases, children, exercise testing, recovery, clinical measure



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3 **EARLY OXYGEN UPTAKE RECOVERY FOLLOWING EXERCISE**
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5 **TESTING IN CHILDREN WITH CHRONIC CHEST DISEASES**
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8 D. Stevens MSc,¹ P.J. Oades FRCPCH,² N. Armstrong D.Sc,¹ and C.A. Williams
9 Ph.D.¹
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12 ¹Children's Health and Exercise Research Centre, School of Sport and Health
13 Sciences, University of Exeter, Exeter, Devon, UK. ²Royal Devon and Exeter NHS
14 Foundation Trust Hospital, Exeter, Devon, UK.
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29 Correspondence to: Craig A. Williams, Ph.D., Children's Health and Exercise,
30 Research Centre, School of Sport and Health Sciences, University of Exeter, St.
31 Luke's Campus, Heavitree Road, Exeter, UK. EX1 2LU
32
33

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35
36 Tel: +44 (0) 1392 264890; Fax: +44 (0) 1392 264726
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38
39 Email: c.a.williams@exeter.ac.uk
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44 Running head: RECOVERY FOLLOWING EXERCISE IN CHRONIC CHEST
45 DISEASES
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3 **Summary.** The value of exercise testing as a prognostic measure of disease severity
4 in patients with chronic chest diseases (CCD) is becoming increasingly recognised.
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6 The aim of this study was to investigate changes in oxygen uptake ($\dot{V}O_2$) during
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8 early recovery following maximal cardiopulmonary exercise testing (CPXT) in
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10 relation to functional capacity and markers of disease severity. Twenty-seven children
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12 with CCD (age 12.7 ± 3.1 y; 17 female) [19 children with Cystic fibrosis (CF) (age
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14 13.4 ± 3.1 y; 10 female) and 8 with other stable non-CF chest diseases (NON-CF)
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16 (age 11.1 ± 2.2 y; 7 female)] and 27 healthy controls (age 13.2 ± 3.3 y; 17 female)
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18 underwent CPXT on a cycle ergometer. On-line respiratory gas analysis measured
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20 $\dot{V}O_2$ before and during CPXT to peak $\dot{V}O_2$ ($\dot{V}O_{2\text{ peak}}$), and during the first 10 min of
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22 recovery. Early $\dot{V}O_2$ recovery was quantified by the time (s) to reach 50 % of the
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24 $\dot{V}O_{2\text{ peak}}$ value. Early $\dot{V}O_2$ recovery was correlated against spirometry [forced
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26 expiratory volume in 1 s (FEV₁) and forced expiratory flow between 25 to 75 % of the
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28 forced vital capacity (FEF₂₅₋₇₅)] and aerobic fitness ($\dot{V}O_{2\text{ peak}}$) as a measure of
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30 functional capacity. Disease severity was graded in the CF patients by the
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32 Shwachman score (SS). Compared to controls, children with CCD demonstrated a
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34 significantly reduced $\dot{V}O_{2\text{ peak}}$ ($P = 0.011$), FEV₁ ($P = 0.000$), FEF₂₅₋₇₅ ($P = 0.000$),
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36 and a significantly prolonged early $\dot{V}O_2$ recovery ($P = 0.024$). In the CF patients the
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38 SS was significantly correlated with early $\dot{V}O_2$ recovery ($r = - 0.63$, $P = 0.004$),
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40 FEV₁ ($r = 0.72$, $P = 0.001$) and FEF₂₅₋₇₅ ($r = 0.57$, $P = 0.011$). In the children with
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42 CCD, FEV₁, FEF₂₅₋₇₅ and BMI were not significantly correlated with $\dot{V}O_{2\text{ peak}}$ or
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44 early $\dot{V}O_2$ recovery, indicating that lung function does not necessarily reflect aerobic
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46 fitness and the ability to recover from exercise in these patients. A significant
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48 relationship was found between $\dot{V}O_{2\text{ peak}}$ and early $\dot{V}O_2$ recovery ($r = - 0.39$, $P =$
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0.044) in the children with CCD, showing that a greater aerobic fitness corresponded with a faster recovery.

Key words: chronic chest diseases, children, exercise testing, recovery, clinical measure

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INTRODUCTION

Exercise testing is a valuable tool for monitoring the physiological impact of chronic chest diseases (CCD).¹ Exercise testing is incorporated in some paediatric respiratory centres as part of an annual assessment of children with Cystic fibrosis (CF),² based on evidence demonstrating that aerobic and anaerobic exercise are limited,³ and that this limitation is related to survival.⁴ Peak oxygen uptake ($\dot{V}O_{2\text{ peak}}$) during maximal cardiopulmonary exercise testing (CPXT) is considered the 'gold standard' measure for assessing aerobic fitness,¹ and is an important measure for well-being and prognosis in CF.^{4,5} Lung function measured by spirometry,⁶ and $\dot{V}O_{2\text{ peak}}$ measured during CPXT⁷ are commonly measured to assess functional capacity and disease severity in patients with CF. Limited data exists, however, regarding recovery parameters following exercise testing in children with CCD.

During early recovery from exercise, phosphocreatine (PCr) levels are inversely proportional to the rate of oxygen uptake ($\dot{V}O_2$), and dependent on the transport to and utilisation of oxygen (O_2) within contracting muscle.^{8,9} The importance of O_2 in the resynthesis of PCr has been previously reported.¹⁰⁻¹³ Anaerobic glycolysis ceases at the termination of peak exercise, and oxidative phosphorylation provides the ATP required for PCr recovery.¹⁴ In cardiac diseases where the transportation and utilisation of O_2 in the contracting muscle is adversely affected, PCr recovery time has been reported to be prolonged following exercise,¹⁵⁻¹⁸ whereas, a faster PCr recovery time has been demonstrated in healthy trained individuals.¹⁹ The rate of PCr resynthesis during recovery from exercise is, therefore, a reflection of oxidative capacity, and can be inferred from $\dot{V}O_2$ measurements in children.²⁰

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3 We hypothesised that PCr resynthesis, as reflected by the $\dot{V}O_2$ during early recovery
4 from CPXT, is an index of the efficiency of maximal oxidative rate, and 1) will be
5 prolonged in children with CCD compared to healthy controls, and 2) serve as an
6 index of disease severity. Therefore, the aims of the study are to assess the $\dot{V}O_2$
7 responses during early recovery from CPXT in children with CCD and healthy
8 controls, and explore the relationships with markers of functional capacity and disease
9 severity in children with CCD.
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MATERIALS AND METHODS

Participants

Twenty-seven children with CCD participated in the study (age 12.7 ± 3.1 y; 17 female). For further analysis the children with CCD were divided into two diagnostic groups. One group consisted of 19 children with CF (age 13.4 ± 3.1 y; 10 female), and the other group consisted of 8 children with other stable non-CF chest diseases (NON-CF) (age 11.1 ± 2.2 y; 7 female) [5 Non-CF bronchiectasis; 2 Primary ciliary dyskinesia; 1 Post-adenoviral obliterative bronchiolitis]. Twenty-seven healthy controls (age 13.2 ± 3.3 y; 17 female) free from any musculoskeletal, cardiovascular and pulmonary diseases that would compromise exercise performance were recruited from local schools and colleges in Devon, U.K. The controls were individually pair matched to the children with CCD for stature, body mass and pubertal maturity.

All participants volunteered for the study and written informed consent and assent was obtained from parents and participants, respectively. All children with CCD attended the outpatient clinic of the Royal Devon and Exeter NHS Foundation Trust Hospital. All children with CCD were clinically stable at the time of CPXT, with no symptomatic deterioration over the preceding month. None had musculoskeletal conditions that would compromise exercise performance. Diagnosis of CF was based on clinical features supported by an abnormal sweat test (sweat chloride > 60 mmol/L) and in 17/19 diagnostic genotyping. Pubertal staging was assessed during routine outpatient clinic assessment by a trained nurse and classified as pre-, peri- and post-pubertal.²¹ The study was approved by the NHS Local Research Ethics Committee.

Maximal Cardiopulmonary Exercise Testing (CPXT)

Infection control measures to prevent cross-infection were followed. Children with CCD were segregated in both waiting areas and testing places. Both equipment and the testing environment were cleaned using appropriate bacteriocidal wipes and solutions after each use.

Before CPXT all participants were instructed not to consume food or caffeine 2 hrs before and wear light comfortable clothes suitable for exercising on a cycle. All participants were also asked not to perform any strenuous exercise during 48 hrs prior to the test time. Maximal cardiopulmonary exercise testing was performed on a cycle ergometer (Excaliber Sport; Lode, Groningen, The Netherlands) using a ramp protocol, commencing with unloaded pedalling for 2 min and then 10 W increases were made incrementally every min. All participants pedalled at a cadence of 70 ± 5 rpm and encouraged to continue until voluntary exhaustion. Peak oxygen uptake was determined by satisfying the following criteria; a respiratory exchange ratio > 1.06 ; heart rate > 95 % age related predicted maximum; scores of 8 – 10 after exercise on a children's effort rating table (CERT); and clinically observed signs of facial flushing, sweating and tachypnoea.

An on-line metabolic gas analyser (Cortex Metalyzer; Cortex Medical, Leipzig, Germany) measured $\dot{V}O_2$ continuously. The system was calibrated with standard gas of known concentration before each test. Gas measurements were collected in the upright position before and during CPXT to $\dot{V}O_{2\text{ peak}}$, and during the first 10 min of recovery using a 10 s moving average. Peak oxygen uptake was calculated as the highest recorded 30 s stationary average value during the CPXT.

Assessment of Functional Capacity

Peak oxygen uptake and lung function were used as markers of functional capacity. Peak oxygen uptake was used as a measure of aerobic fitness and expressed relative to body mass ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Lung function was assessed by forced expiratory volume in 1 s (FEV_1), and forced expiratory flow between 25 to 75 % of the forced vital capacity (FEF_{25-75}). All lung function measurements were expressed as % predicted, using appropriate reference data.²² Each participant's lung function was measured before the start of the CPXT. The forced expiratory manoeuvre was performed as recommended by the British Thoracic Society (1994) guidelines for the measurement of respiratory function,²³ recording the best of three consistent exhalations, using an electronic spirometer (Microloop ML3535; Numed, Sheffield, UK).

Assessment of Early $\dot{V}\text{O}_2$ Recovery

Early $\dot{V}\text{O}_2$ recovery time was quantified by the time in seconds (s) from the cessation of exercise to reach 50 % of the $\dot{V}\text{O}_{2\text{ peak}}$ value. This method has been described in previous studies to assess early $\dot{V}\text{O}_2$ recovery in patients with cardiac diseases.²⁴⁻²⁶

Assessment of Disease Severity for the Cystic Fibrosis Patients

The Shwachman score (SS) was used to grade disease severity in the CF patients, and was recorded prior to CPXT by the patient's clinician. The SS scores four separate aspects of the disease profile, general activity, physical examination, nutritional status and chest radiographic findings, using the most recent routine annual review chest x-ray. Each disease profile is given an equal weighting of 25 points. A total of 100 points represents a perfect score of health.²⁷

Data Analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS; version 11.0, Chicago, IL). The independent *t*-test was used for the comparison of the anthropometric and physiological data between children with CCD and controls. The Pearson product moment correlation was used to assess the association between $\dot{V}O_2$ indexes and parameters of functional capacity and disease severity. Statistical significance was set *a priori* at $P < 0.05$.

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RESULTS

The anthropometric data in Table 1 shows no significant differences in stature, body mass, BMI and pubertal maturity between the children with CCD and controls. The lung function data (Table 1) showed when compared to controls, children with CCD demonstrated significantly reduced FEV₁ ($P = 0.000$), FVC ($P = 0.004$), PEF ($P = 0.003$), and FEF₂₅₋₇₅ ($P = 0.000$). Data from the CPXT (Table 2) showed that compared to controls the children with CCD had a significantly lower $\dot{V}O_{2\text{ peak}}$ ($P = 0.011$) and a significantly prolonged early $\dot{V}O_2$ recovery ($P = 0.024$). Other CPXT data such as maximum workload (W_{max}) was significantly lower ($P = 0.009$) in children with CCD compared to controls. Maximum heart rate (HR_{max}) did not differ significantly between children with CCD and controls during CPXT (Table 2).

The correlation data (Table 3a) showed in the children with CCD, FEV₁, FEF₂₅₋₇₅ and BMI were not significantly correlated with $\dot{V}O_{2\text{ peak}}$ or early $\dot{V}O_2$ recovery. A significant negative relationship between $\dot{V}O_{2\text{ peak}}$ and early $\dot{V}O_2$ recovery ($r = -0.39$, $P = 0.044$), however, was found in the children with CCD (Table 3a and Figure 1). Sub-group analysis within the children with CCD revealed, in the CF patients a significant negative correlation between the SS and early $\dot{V}O_2$ recovery ($r = -0.63$, $P = 0.004$) (Table 3a and Figure 2), and significant correlations were also shown between the SS and FEV₁ ($r = 0.72$, $P = 0.001$) (Table 3a and Figure 3), and FEF₂₅₋₇₅ ($r = 0.57$, $P = 0.011$) (Table 3a). No significant correlation, however, was found between the SS and $\dot{V}O_{2\text{ peak}}$ in the CF patients (Table 3a). Between the CF and NON-CF patients no significant differences in $\dot{V}O_{2\text{ peak}}$ ($P = 0.715$) and early $\dot{V}O_2$ recovery ($P = 0.755$) were shown, despite the NON-CF patients demonstrating a

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3 significantly reduced FEV₁ ($P = 0.044$) compared to the CF patients. Table 3b shows
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5 the correlational relationships for the healthy control group, only BMI was found to
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7 be significantly correlated to recovery ($r = 0.48, P = 0.011$).
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DISCUSSION

The present study found that compared to controls, children with CCD demonstrated a significantly reduced $\dot{V}O_{2\text{ peak}}$ and prolonged early $\dot{V}O_2$ recovery following CPXT.

The metabolic cost of exercise results from both the performance of external work, and the demands of the O_2 transportation system itself. This includes the work performed by the muscles of respiration and the enduring metabolic demand to restore homeostasis during recovery.²⁸ The rate of $\dot{V}O_2$ during early recovery from exercise in children with CCD will be influenced by many disease factors. For example, as disease progresses there is an increase in dead space,²⁹ that necessitates an increase in total ventilation in order to keep alveolar ventilation constant.^{30,31} Airway obstruction and air trapping would also reduce the rate of elimination of excess carbon dioxide formed during exercise, prolonging tachypnoea, which itself would increase the metabolic demand and which contributes to fatigue.³² Delayed elimination of carbon dioxide would also impair the ability to compensate for alterations in acid-based status.³³ Furthermore, in patients with CF the correlation between thin section computed tomographic (CT) findings of lung parenchymal damage and exercise limitation is stronger than that between spirometry results, or BMI and exercise limitation.³⁴ The CF genotype has also been reported to be related to exercise tolerance.³⁵

The lung function data from the present study showed that FEV₁, FVC, PEF and FEF₂₅₋₇₅ were all significantly reduced in children with CCD compared to controls. Forced expiratory volume in 1 s, FEF₂₅₋₇₅ and BMI in the children with CCD, however, were not significantly correlated with $\dot{V}O_{2\text{ peak}}$ or early $\dot{V}O_2$ recovery. Furthermore, the study showed that despite a significantly reduced FEV₁ in the NON-

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4 CF patients compared to the CF patients, $\dot{V}O_{2\text{ peak}}$ and early $\dot{V}O_2$ recovery were not
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6 significantly different between the two patient groups. These findings demonstrate,
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8 therefore, that exercise performance was similar between the NON-CF and CF
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10 patients, despite poorer lung function in the NON-CF patients. These finding may
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12 emphasise the physiological differences between the static nature of lung function
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14 testing and the dynamic nature of the cardiopulmonary system when exercising. It
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16 may also infer, however, the physiological differences between children with CF and
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18 other CCD, especially in regard to recent work which found that CF patients
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20 demonstrated reduced oxidative work efficiency in the skeletal muscle.³⁶
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28 Contrary to previous studies which have reported that reduced FEV₁ is associated
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30 with lower $\dot{V}O_{2\text{ peak}}$,^{29,37-41} a non-significant relationship between lung function and
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32 $\dot{V}O_{2\text{ peak}}$ in the children with CCD in the present study may provide further support to
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34 work which has reported that reduced aerobic performance is related to intrinsic
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36 abnormalities of skeletal muscle function.^{36,42-44} Furthermore, a recent study reported
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38 that $\dot{V}O_{2\text{ peak}}$ and exercise duration during CPXT was not affected in patients with
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40 mild CF using added dead space, suggesting the CPXT is not limited by respiratory
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42 factors.⁴⁵ Moser et al. (2000) also found no significant correlations between variables
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44 reflecting exercise performance (e.g., $\dot{V}O_{2\text{ peak}}$) and lung function measurements (e.g.,
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46 FEV₁) in children with CF.⁴³ This finding is also supported by Edwards et al. (2004),
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48 who reported no relationships between variables measured during exercise testing and
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50 lung function.⁴⁶ Peak oxygen uptake and early $\dot{V}O_2$ recovery, however, were
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52 significantly related; indicating the greater the aerobic fitness of the patient the faster
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54 the rate of recovery. This relationship although significant, however, is still quite
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3 weak ($r = -0.39$, $P = 0.044$), and therefore, may indicate that the $\dot{V}O_2$ recovery can
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6 not be explained predominantly by the $\dot{V}O_{2\text{ peak}}$. However, the finding that $\dot{V}O_{2\text{ peak}}$
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9 and early $\dot{V}O_2$ recovery were not significantly correlated for the healthy control
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12 group accentuates the relative importance of aerobic fitness and recovery and their
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14 impact on children with CCD.

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18 In children with CF a significant relationship between early $\dot{V}O_2$ recovery and the SS
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20 was found. Correlations between structural abnormalities of the lung scored on thin
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22 section CT images and exercise performance have been reported in patients with CF,
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24 and these relationships are stronger than that between spirometry results, or BMI and
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26 exercise limitation,³⁴ and may explain the relationship found in the present study.
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29 Forced expiratory volume in 1 s and FEF₂₅₋₇₅ in the children with CF were also
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31 significantly related to the SS, confirming previous reports that lung function is
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33 correlated with disease severity and survival in CF patients.^{6,47,48} No significant
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35 relationship between $\dot{V}O_{2\text{ peak}}$ and the SS in the CF patients was found in the present
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37 study. The $\dot{V}O_{2\text{ peak}}$ values for children with CF in this study are similar to published
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39 values of aerobic fitness for young CF patients of a similar age range.^{43,49,50} A
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41 significant correlation between $\dot{V}O_{2\text{ peak}}$ and SS has been previously reported in adults
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43 with CF,⁵¹ but not in children. The disease severity of the adult CF patients was
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45 greater than in the present study (71 ± 14 versus 80 ± 12 , respectively) and $\dot{V}O_{2\text{ peak}}$
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47 was lower (25 ± 7 versus 35 ± 8 mL·kg⁻¹·min⁻¹, respectively), which may have
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49 increased the likelihood of finding a significant relationship due to a greater
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51 heterogeneity of the correlated variables.
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3 In conclusion, children with CCD in the present study had mild to moderate disease as
4 interpreted by their lung function, and showed a reduced $\dot{V}O_{2\text{ peak}}$ and prolonged early
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6 $\dot{V}O_2$ recovery compared to a control group. The prolonged recovery may be an
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8 indication of reduced oxidative capacity for PCr resynthesis, attributed to impaired O_2
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10 transportation and utilisation in the contracting muscle. Indeed, the present study
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12 showed that early $\dot{V}O_2$ recovery was significantly related to the SS in children with
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14 CF, indicating that early $\dot{V}O_2$ recovery is prolonged with increased disease severity.
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16 Lung function was not significantly related to $\dot{V}O_{2\text{ peak}}$ and early $\dot{V}O_2$ recovery, and
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18 therefore may not accurately reflect the patient's ability to exercise and recover.
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20 Disease in CF can progress significantly, as shown on thoracic high resolution CT
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22 scanning, despite lung function stability.⁵² Exercise testing can therefore help to
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24 provide useful additional information about functional limitations and trends over
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26 time.⁵³ A recent study reported that higher aerobic fitness despite poor lung function
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28 is associated with a better prognosis.⁴⁹ The links between more detailed measures of
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30 exercise performance including recovery parameters, disease severity and quality of
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32 life deserve more attention and warrant further investigation.
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For Peer Review

TABLE 1 - Characteristics of the anthropometric and lung function data of the children with CCD (n = 27) and healthy controls (n = 27)

	Children with CCD (n = 27)	Healthy Controls (n = 27)	<i>P</i> value
Gender	17 females, 10 males	17 females, 10 males	<i>P</i> = 1.000
Age (y)	12.7 ± 3.1	13.2 ± 3.3	<i>P</i> = 0.610
Stature (m)	1.48 ± 0.15	1.55 ± 0.15	<i>P</i> = 0.133
Body mass (kg)	41.7 ± 12.6	45.9 ± 13.3	<i>P</i> = 0.233
BMI (kg m ⁻²)	18.4 ± 2.9	18.8 ± 2.8	<i>P</i> = 0.589
Pubertal maturity	2 ± 1	2 ± 1	<i>P</i> = 0.625
SS	80 ± 12	N/A ^ψ	
FEV ₁ (% predicted)	82 ± 23	103 ± 12	<i>P</i> = 0.000**
FVC (% predicted)	88 ± 19	102 ± 15	<i>P</i> = 0.004**
PEF (% predicted)	78 ± 22	93 ± 11	<i>P</i> = 0.003**
FEF ₂₅₋₇₅ (% predicted)	78 ± 31	105 ± 17	<i>P</i> = 0.000**

Values are means ± SD. ** *P* < 0.01. BMI, body mass index; SS, Shwachman score; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; FEF₂₅₋₇₅, forced expiratory flow between 25 to 75 % of the forced vital capacity. ^ψThe SS is a marker of disease severity for the CF patients only.

TABLE 2 - Characteristics of the maximal cardiopulmonary exercise testing data of the children with CCD (n = 27) and healthy controls (n = 27)

	Children with CCD (n = 27)	Healthy Controls (n = 27)	<i>P</i> value
$\dot{V}O_{2\text{ peak}}$ (mL·kg ⁻¹ ·min ⁻¹)	35 ± 8	42 ± 11	<i>P</i> = 0.011*
Early $\dot{V}O_{2}$ recovery (s)	58 ± 16	50 ± 7	<i>P</i> = 0.024*
HR _{max} (b·min ⁻¹)	173 ± 26	183 ± 16	<i>P</i> = 0.103
W _{max} (W)	121 ± 52	166 ± 67	<i>P</i> = 0.009**

Values are means ± SD. **P* < 0.05, ** *P* < 0.01. $\dot{V}O_{2\text{ peak}}$, peak oxygen uptake; Early $\dot{V}O_{2}$ recovery, early oxygen uptake recovery; HR_{max}, maximum heart rate; W_{max}, maximum workload.

TABLE 3a – Correlation data for the children with CCD (n = 27)

	BMI	FEV ₁ (% predicted)	FEF ₂₅₋₇₅ (% predicted)	$\dot{V}O_{2\text{ peak}}$ (mL·kg ⁻¹ ·min ⁻¹)	Early $\dot{V}O_2$ recovery (s)	SS ^ψ
BMI		<i>r</i> = 0.29 (<i>P</i> = 0.141)	<i>r</i> = 0.15 (<i>P</i> = 0.470)	<i>r</i> = 0.02 (<i>P</i> = 0.927)	<i>r</i> = - 0.02 (<i>P</i> = 0.904)	<i>r</i> = 0.00 (<i>P</i> = 0.989)
FEV ₁ (% predicted)			<i>r</i> = 0.89** (<i>P</i> = 0.000)	<i>r</i> = 0.18 (<i>P</i> = 0.363)	<i>r</i> = - 0.30 (<i>P</i> = 0.126)	<i>r</i> = 0.72** (<i>P</i> = 0.001)
FEF ₂₅₋₇₅ (% predicted)				<i>r</i> = 0.08 (<i>P</i> = 0.708)	<i>r</i> = - 0.20 (<i>P</i> = 0.328)	<i>r</i> = 0.57* (<i>P</i> = 0.011)
$\dot{V}O_{2\text{ peak}}$ (mL·kg ⁻¹ ·min ⁻¹)					<i>r</i> = - 0.39* (<i>P</i> = 0.044)	<i>r</i> = 0.39 (<i>P</i> = 0.095)
Early $\dot{V}O_2$ recovery (s)						<i>r</i> = -0.63** (<i>P</i> = 0.004)
SS ^ψ						

**P* < 0.05, ** *P* < 0.01. BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FEF₂₅₋₇₅, forced expiratory flow between 25 to 75 % of the forced vital capacity; $\dot{V}O_{2\text{ peak}}$, peak oxygen uptake; Early $\dot{V}O_2$ recovery, early oxygen uptake recovery; SS, Shwachman score. ^ψThe SS is a marker of disease severity for the CF patients only.

TABLE 3b – Correlation data for the healthy controls (n = 27)

	BMI	FEV ₁ (% predicted)	FEF ₂₅₋₇₅ (% predicted)	$\dot{V}O_{2\text{ peak}}$ (mL·kg ⁻¹ ·min ⁻¹)	Early $\dot{V}O_2$ recovery (s)
BMI		$r = 0.35$ ($P = 0.072$)	$r = -0.33$ ($P = 0.093$)	$r = -0.25$ ($P = 0.202$)	$r = 0.48^{**}$ ($P = 0.011$)
FEV ₁ (% predicted)			$r = 0.24$ ($P = 0.224$)	$r = -0.30$ ($P = 0.129$)	$r = 0.21$ ($P = 0.284$)
FEF ₂₅₋₇₅ (% predicted)				$r = -0.09$ ($P = 0.670$)	$r = -0.03$ ($P = 0.892$)
$\dot{V}O_{2\text{ peak}}$ (mL·kg ⁻¹ ·min ⁻¹)					$r = -0.24$ ($P = 0.219$)
Early $\dot{V}O_2$ recovery (s)					

** $P < 0.01$. BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FEF₂₅₋₇₅, forced expiratory flow between 25 to 75 % of the forced vital capacity; $\dot{V}O_{2\text{ peak}}$, peak oxygen uptake; Early $\dot{V}O_2$ recovery, early oxygen uptake recovery.

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4 **FIGURE 1 - The relationship between $\dot{V}O_{2\text{ peak}}$ and early $\dot{V}O_2$ recovery in the**
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6 **children with CCD (n = 27)**
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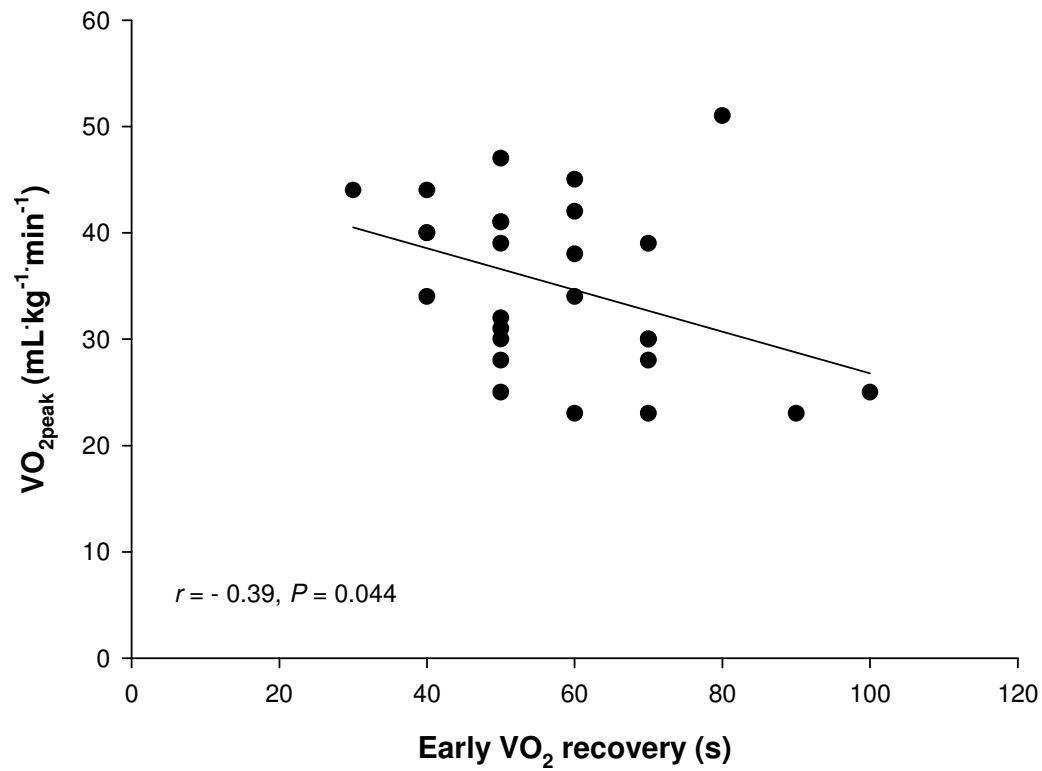
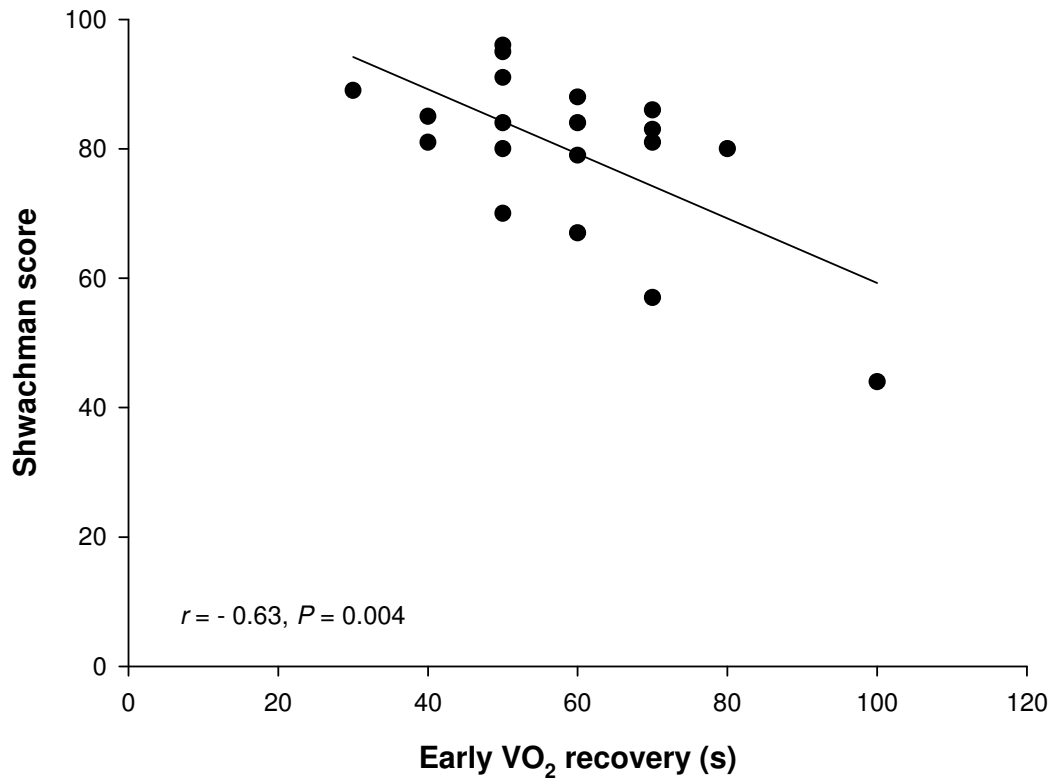
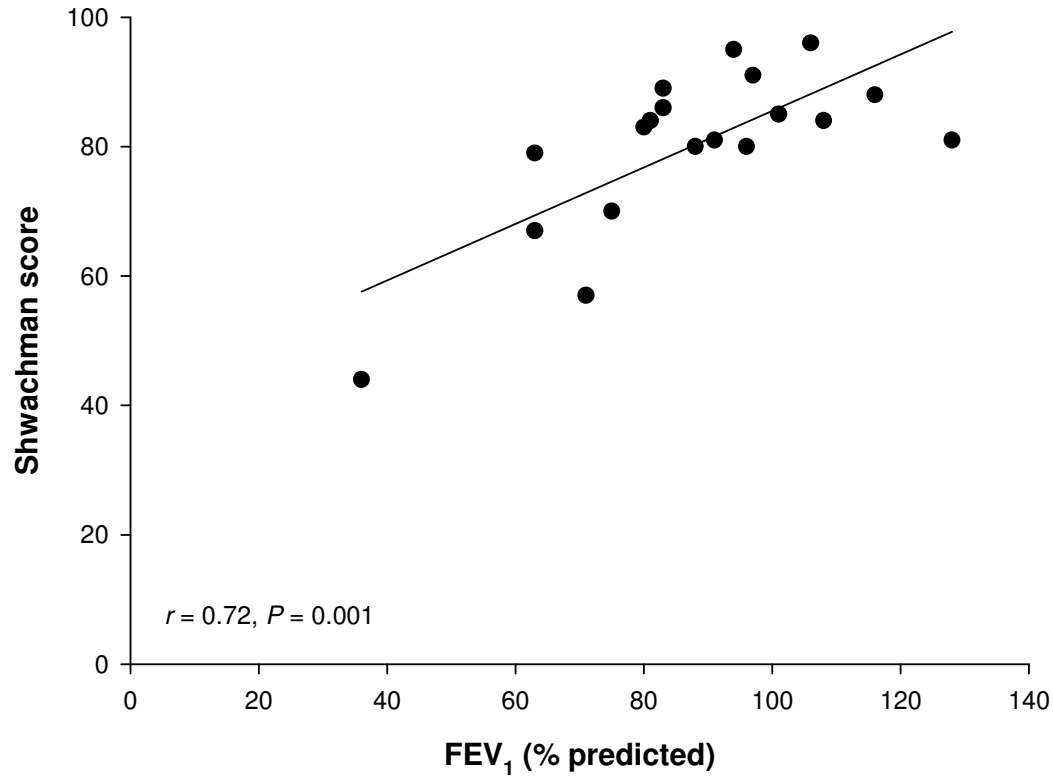


FIGURE 2 - The relationship between the Shwachman score and early $\dot{V}O_2$ recovery in the CF patients (n = 19)



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4 **FIGURE 3 - The relationship between the Shwachman score and FEV₁ in the CF**
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6 **patients (n = 19)**
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3 **EARLY OXYGEN UPTAKE RECOVERY FOLLOWING EXERCISE**
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5 **TESTING IN CHILDREN WITH CHRONIC CHEST DISEASES**
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8 D. Stevens MSc,¹ P.J. Oades FRCPCH,² N. Armstrong D.Sc,¹ and C.A. Williams
9 Ph.D.¹
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12 ¹Children's Health and Exercise Research Centre, School of Sport and Health
13 Sciences, University of Exeter, Exeter, Devon, UK. ²Royal Devon and Exeter NHS
14 Foundation Trust Hospital, Exeter, Devon, UK.
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23 Exeter, and the Royal Devon and Exeter NHS Foundation Trust Hospital.
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29 Correspondence to: Craig A. Williams, Ph.D., Children's Health and Exercise,
30 Research Centre, School of Sport and Health Sciences, University of Exeter, St.
31 Luke's Campus, Heavitree Road, Exeter, UK. EX1 2LU
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36 Tel: +44 (0) 1392 264890; Fax: +44 (0) 1392 264726
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39 Email: c.a.williams@exeter.ac.uk
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44 Running head: RECOVERY FOLLOWING EXERCISE IN CHRONIC CHEST
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Summary. The value of exercise testing as a prognostic measure of disease severity in patients with chronic chest diseases (CCD) is becoming increasingly recognised. The aim of this study was to investigate changes in oxygen uptake ($\dot{V}O_2$) during early recovery following maximal cardiopulmonary exercise testing (CPXT) in relation to functional capacity and markers of disease severity. **Twenty-seven children with CCD (age 12.7 ± 3.1 y; 17 female) [Nineteen 19 children with Cystic fibrosis (CF) (age 13.4 ± 3.1 y; 10 female) and 8 with other stable non-CF chest diseases (NON-CF) with other stable CCD (age 11.1 ± 2.2 y; 7 female)] and 27 healthy controls (age 13.2 ± 3.3 y; 17 female) underwent CPXT on a cycle ergometer. On-line respiratory gas analysis measured $\dot{V}O_2$ before and during CPXT to peak $\dot{V}O_2$ ($\dot{V}O_{2\text{ peak}}$), and during the first 10 min of recovery. Early $\dot{V}O_2$ recovery was quantified by the time (s) to reach 50 % of the $\dot{V}O_{2\text{ peak}}$ value. Early $\dot{V}O_2$ recovery was correlated against ~~lung function~~ **spirometry** [forced expiratory volume in 1 s (FEV_1) and forced expiratory flow between 25 to 75 % of the forced vital capacity (FEF_{25-75})] and aerobic fitness ($\dot{V}O_{2\text{ peak}}$) as a measure of functional capacity. Disease severity was graded in the CF ~~group~~ **patients** by the Shwachman score (SS). **Compared to controls, children with CCD demonstrated a significantly reduced $\dot{V}O_{2\text{ peak}}$ ($P = 0.011$), FEV_1 ($P = 0.000$), FEF_{25-75} ($P = 0.000$), and a significantly prolonged early $\dot{V}O_2$ recovery ($P = 0.024$).** In the CF ~~group~~ patients the SS was significantly correlated with early $\dot{V}O_2$ recovery ($r = -0.63$, $P = 0.004$), FEV_1 ($r = 0.72$, $P = 0.001$) and FEF_{25-75} ($r = 0.57$, $P = 0.011$). ~~The ratio $\dot{V}O_{2\text{ peak}}$ ($\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) / early $\dot{V}O_2$ recovery (s) ($r = 0.50$, $P = 0.028$) used in this study as a composite measure of exercise performance and recovery.~~ **In the children with CCD, FEV_1 , FEF_{25-75} and BMI were not significantly correlated with $\dot{V}O_{2\text{ peak}}$ or early $\dot{V}O_2$****

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3 recovery, indicating that lung function does not necessarily reflect aerobic fitness and
4 the ability to recover from exercise in these patients. A significant relationship was
5 found between $\dot{V}O_{2\text{ peak}}$ and early $\dot{V}O_2$ recovery ($r = -0.39$, $P = 0.044$) in the
6 children with CCD, showing that a greater aerobic fitness corresponded with a faster
7 recovery. In the CCD group FEV₁ was significantly lower compared to the CF group
8 (68 ± 21 vs 87 ± 21 % predicted, respectively; $P = 0.044$), however, no significant
9 differences were found between the groups for $\dot{V}O_{2\text{ peak}}$ (35.9 ± 8.4 vs 34.7 ± 8.0
10 mL·kg⁻¹·min⁻¹, respectively; $P = 0.715$) and early $\dot{V}O_2$ recovery (56 ± 16 vs 58 ± 16 s,
11 respectively; $P = 0.755$). In children with CF, early $\dot{V}O_2$ recovery following CPXT
12 and FEV₁ are significantly related to disease severity. In children with CF and other
13 CCD, however, FEV₁ does not fully reflect the ability to exercise and recover.
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30 **Key words:** chronic chest diseases, children, exercise testing, recovery, clinical
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INTRODUCTION

Exercise testing is a valuable tool for monitoring the physiological impact of chronic chest diseases (CCD).¹ Exercise testing is incorporated in some paediatric respiratory centres as part of an annual assessment of children with Cystic fibrosis (CF),² based on evidence demonstrating that aerobic and anaerobic exercise are limited,³ and that this limitation is related to survival.⁴ Peak oxygen uptake ($\dot{V}O_{2\text{ peak}}$) during maximal cardiopulmonary exercise testing (CPXT) is considered the 'gold standard' measure for assessing aerobic fitness,¹ and is an important measure for well-being and prognosis in CF.^{4,5} Lung function measured by spirometry,⁶ and $\dot{V}O_{2\text{ peak}}$ measured during CPXT⁷ are commonly measured to assess functional capacity and disease severity in patients with CF. Limited data exists, however, regarding recovery parameters following exercise testing in children with CCD.

During early recovery from exercise, phosphocreatine (PCr) levels are inversely proportional to the rate of oxygen uptake ($\dot{V}O_2$), and dependent on the transport to and utilisation of oxygen (O_2) within contracting muscle.^{8,9} The importance of O_2 in the resynthesis of PCr has been previously reported.¹⁰⁻¹³ Anaerobic glycolysis ceases at the termination of peak exercise, and oxidative phosphorylation provides the ATP required for PCr recovery.¹⁴ In cardiac diseases where the transportation and utilisation of O_2 in the contracting muscle is adversely affected, PCr recovery time has been reported to be prolonged following exercise,¹⁵⁻¹⁸ whereas, a faster PCr recovery time has been demonstrated in healthy trained individuals.¹⁹ The rate of PCr resynthesis during recovery from exercise is, therefore, a reflection of oxidative capacity, and can be inferred from $\dot{V}O_2$ measurements in children.²⁰

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4 We hypothesised that PCr resynthesis, as reflected by the $\dot{V}O_2$ during early recovery
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6 from CPXT, is an index of the efficiency of maximal oxidative rate, and 1) will be
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8 prolonged in children with CCD compared to healthy controls, and 2) serve as an
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10 index of disease severity. Therefore, the aims of the study are to assess the $\dot{V}O_2$
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12 responses during early recovery from CPXT in children with CCD and healthy
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14 controls, and explore the relationships with markers of functional capacity and disease
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16 severity in children with CCD.
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21 ~~Assessing exercise performance is a valuable tool in monitoring health status in~~
22 ~~cardiopulmonary disease.¹ In chronic chest diseases (CCD), especially Cystic fibrosis~~
23 ~~(CF), exercise limitation is a mark of disease progression.²¹ The measurement of~~
24 ~~peak oxygen uptake ($\dot{V}O_{2\text{ peak}}$) during exercise testing is a measure of aerobic~~
25 ~~functional capacity and may predict prognosis in patients with CF.^{4,22-24} Various~~
26 ~~exercise tests are incorporated into routine assessments of patients in CF centres.²⁵~~
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28 ~~Information regarding exercise performance in young patients with other CCD,~~
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30 ~~however, is limited.~~
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43 ~~Many studies in CF to date have concentrated on the measurement of $\dot{V}O_{2\text{ peak}}$~~
44 ~~without considering measures of recovery. In adults, however, with heart disease²⁶⁻³⁰~~
45 ~~and chronic obstructive pulmonary disease (COPD),³¹ the prognostic value of~~
46 ~~recovery measures following exercise testing have been investigated. Oxygen uptake~~
47 ~~($\dot{V}O_2$) recovery time increases as ischaemic heart disease progresses²⁸ and is~~
48 ~~prolonged in adults with heart failure²⁹ when compared to controls²⁷ and COPD.³¹~~
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50 ~~The metabolic cost of exercise results from both the performance of external work,~~
51 ~~and the demands of the oxygen transport system itself, including the work performed~~
52 ~~by the muscles for respiration and persistent hypermetabolism recognised during~~
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3 recovery.³² During early recovery, oxygen is primarily required for the re-
4 phosphorylation of creatine in skeletal muscles. The early rapid decline in $\dot{V}O_2$
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6 marks replenishment of muscle energy stores and the rate is an index of the efficiency
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8 of oxidative ATP resynthesis and this efficiency is reflected in an individual's
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10 functional capacity or ability to sustain repeated bouts of physical activity. Children
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12 with CF have less efficient oxidative ATP synthesis³³ which could prolong the early
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14 $\dot{V}O_2$ recovery period after exercise.
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23 Assessing the rate at which the patient recovers from exercise may provide additional
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25 information on current health status. Following exercise the rate of recovery from the
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27 increased oxygen requirements in children with lung disease will be influenced by
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29 many disease factors including the presence of chronic infection and numerous
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31 physiological abnormalities which impair gas exchange and increase the work of
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33 breathing. An increase in dead space as the disease progresses,³⁴ necessitates an
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35 increase in total ventilation in order to keep alveolar ventilation constant.^{35,36} Airway
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37 obstruction and air trapping reduces the rate of elimination of excess carbon dioxide
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39 formed during exercise, prolonging tachypnoea, which itself increases the metabolic
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41 demand for a given task and which contributes to fatigue.³⁷ Delayed elimination of
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43 carbon dioxide also impairs the ability to compensate for alterations in acid-based
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45 status.³⁸
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54 The aim of this study, therefore, was to explore the relationship of markers of
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56 functional capacity and disease severity with early $\dot{V}O_2$ recovery in children with CF
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58 and other CCD. We hypothesised that early $\dot{V}O_2$ recovery following maximal
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cardiopulmonary exercise testing (CPXT) is significantly related to other measures of disease severity and functional capacity in children with CF and other CCD.

MATERIALS AND METHODS

Participants

Twenty-seven children with CCD participated in the study (age 12.7 ± 3.1 y; 17 female). For further analysis the children with CCD were divided into two diagnostic groups. One group consisted of 19 children with CF (age 13.4 ± 3.1 y; 10 female), and the other group consisted of 8 children with other stable non-CF chest diseases (NON-CF) (age 11.1 ± 2.2 y; 7 female) CCD diagnostic groups. The CF group consisted of 19 children (age 13.4 ± 3.1 y; 10 female), and the CCD group consisted of eight children (age 11.1 ± 2.2 y; 7 female) [5 Non-CF bronchiectasis; 2 Primary ciliary dyskinesia; 1 Post-adenoviral obliterative bronchiolitis]. Twenty-seven healthy controls (age 13.2 ± 3.3 y; 17 female) free from any musculoskeletal, cardiovascular and pulmonary diseases that would compromise exercise performance were recruited from local schools and colleges in Devon, U.K. The controls were individually pair matched to the children with CCD for stature, body mass and pubertal maturity.

All participants volunteered for the study and written informed consent and assent was obtained from parents and participants, respectively. All children with CCD volunteered for the study and attended the outpatient clinic of the Royal Devon and Exeter NHS Foundation Trust Hospital. Written informed consent and assent was obtained from parents and children, respectively. All children with CCD were clinically stable at the time of CPXT, with no symptomatic deterioration over the preceding month. None had musculoskeletal conditions that would compromise

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3 exercise performance. Diagnosis of CF was based on clinical features supported by an
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5 abnormal sweat test (sweat chloride > 60 mmol/L) and in 17/19 diagnostic
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7 genotyping. Pubertal staging was assessed during routine outpatient clinic assessment
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9 by a trained nurse and classified as pre-, peri- and post- pubertal. ³⁹ The study was
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11 approved by the NHS Local Research Ethics Committee. ~~Table 1 shows the~~
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13 ~~anthropometric and physiological data of the CF and CCD.~~
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20 **Maximal Cardiopulmonary Exercise Testing (CPXT)**

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22 Infection control measures to prevent cross-infection were followed. Children **with**
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24 **CCD** were segregated in both waiting areas and testing places. Both equipment and
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26 the testing environment were cleaned using appropriate bacteriocidal wipes and
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28 solutions after each use.
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34 Before CPXT **all** participants were instructed not to consume food or caffeine 2 hrs
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36 before and wear light comfortable clothes suitable for exercising on a cycle. **All** The
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38 participants were also asked not to perform any strenuous exercise during 48 hrs prior
39
40 to the test time. Maximal cardiopulmonary exercise testing was performed on a cycle
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42 ergometer (Excaliber Sport; Lode, Groningen, The Netherlands) using a ramp
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44 protocol, commencing with unloaded pedalling for 2 min and then 10 W increases
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46 were made incrementally every min. All participants pedalled at a cadence of 70 ± 5
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48 rpm and encouraged to continue until voluntary exhaustion. Peak oxygen uptake was
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50 determined by satisfying the following criteria; a respiratory exchange ratio > 1.06;
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52 heart rate > 95 % age related predicted maximum; scores of 8 – 10 after exercise on a
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54 children's effort rating table (CERT); and clinically observed signs of facial flushing,
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3 sweating and tachypnoea. ~~Pulse oximetry, taken via the finger, recorded continuous~~
4 ~~oxygen saturation (Tuffsat; Datex Ohmeda, Colorado, USA).~~
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10 An on-line metabolic gas analyser (Cortex Metalyzer; Cortex Medical, Leipzig,
11 Germany) measured $\dot{V}O_2$ continuously. The system was calibrated with standard gas
12 of known concentration before each test. Gas measurements were collected in the
13 upright position before and during CPXT to $\dot{V}O_{2\text{ peak}}$, and during the first 10 min of
14 recovery **using a 10 s moving average**. Peak oxygen uptake was calculated as the
15 highest recorded 30 s stationary average value during the CPXT.
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28 **Assessment of Functional Capacity**

29 Peak oxygen uptake and lung function were used as markers of functional capacity.
30 Peak oxygen uptake was used as a measure of aerobic fitness and expressed relative to
31 body mass ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Lung function was assessed by forced expiratory volume
32 in 1 s (FEV_1), **and forced expiratory flow between 25 to 75 % of the forced vital**
33 **capacity (FEF_{25-75}).** **All lung function measurements were** and expressed as %
34 predicted, using appropriate reference data.⁴⁰ Each participant's lung function was
35 measured before the start of the CPXT. The forced expiratory manoeuvre was
36 performed as recommended by the British Thoracic Society (1994) guidelines for the
37 measurement of respiratory function,⁴¹ recording the best of three consistent
38 exhalations, using an electronic spirometer (Microloop ML3535; Numed, Sheffield,
39 UK).
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59 **Assessment of Early $\dot{V}O_2$ Recovery**

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4 Early $\dot{V}O_2$ recovery time was quantified by the time in seconds from the cessation
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6 of exercise to reach 50 % of the $\dot{V}O_{2\text{ peak}}$ value. This method has been described in
7
8 previous studies to assess early $\dot{V}O_2$ recovery in patients with cardiac diseases
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10 chronic heart failure.^{26,27,42}
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13 14 15 16 **Assessment of Disease Severity for the Cystic Fibrosis Patients**

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18 The Shwachman score (SS) was used to grade disease severity in the CF patients
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20 group, and was recorded prior to CPXT by the patient's clinician. The SS scores four
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22 separate aspects of the disease profile, general activity, physical examination,
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24 nutritional status and chest radiographic findings, using the most recent routine annual
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26 review chest x-ray. Each disease profile is given an equal weighting of 25 points. A
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28 total of 100 points represents a perfect score of health.⁴³
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34 35 ~~Assessment of Composite Measure of Exercise Performance for the Cystic~~ 36 37 ~~Fibrosis Group~~

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39 In this study a ratio of $\dot{V}O_{2\text{ peak}}$ ($\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) / early $\dot{V}O_2$ recovery (s) was also
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41 used as a composite measure of exercise performance and recovery in the CF group.
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47 48 **Data Analysis**

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50 Data were analysed using the Statistical Package for the Social Sciences (SPSS;
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52 version 11.0, Chicago, IL). The independent *t*-test was used for the comparison of the
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54 anthropometric and physiological data between children with CCD and controls the
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56 CF and groups. The Pearson product moment correlation was used to assess the
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58 association between $\dot{V}O_2$ indexes and parameters of functional capacity and disease
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60 severity. Statistical significance was set *a priori* at $P < 0.05$.

RESULTS

The anthropometric data in Table 1 shows no significant differences in stature, body mass, BMI and pubertal maturity between the children with CCD and controls. The lung function data (Table 1) showed when compared to controls, children with CCD demonstrated significantly reduced FEV₁ ($P = 0.000$), FVC ($P = 0.004$), PEF ($P = 0.003$), and FEF₂₅₋₇₅ ($P = 0.000$). Data from the CPXT (Table 2) showed that compared to controls the children with CCD had a significantly lower $\dot{V}O_{2\text{ peak}}$ ($P = 0.011$) and a significantly prolonged early $\dot{V}O_2$ recovery ($P = 0.024$). Other CPXT data such as maximum workload (W_{max}) was significantly lower ($P = 0.009$) in children with CCD compared to controls. Maximum heart rate (HR_{max}) did not differ significantly between children with CCD and controls during CPXT (Table 2).

The correlation data (Table 3a) showed in the children with CCD, FEV₁, FEF₂₅₋₇₅ and BMI were not significantly correlated with $\dot{V}O_{2\text{ peak}}$ or early $\dot{V}O_2$ recovery. A significant negative relationship between $\dot{V}O_{2\text{ peak}}$ and early $\dot{V}O_2$ recovery ($r = -0.39$, $P = 0.044$), however, was found in the children with CCD (Table 3a and Figure 1). Sub-group analysis within the children with CCD revealed, in the CF patients a significant negative correlation between the SS and early $\dot{V}O_2$ recovery ($r = -0.63$, $P = 0.004$) (Table 3a and Figure 2), and significant correlations were also shown was also present between the SS and FEV₁ ($r = 0.72$, $P = 0.001$) (Table 3a and Figure 3), and FEF₂₅₋₇₅ ($r = 0.57$, $P = 0.011$) (Table 3). No significant correlation, however, was found between the SS and $\dot{V}O_{2\text{ peak}}$ (Table 2) in the CF patients (Table 3a). Between the CF and NON-CF patients no significant differences in $\dot{V}O_{2\text{ peak}}$ ($P = 0.715$) and early $\dot{V}O_2$ recovery ($P = 0.755$) were shown, despite the NON-CF patients

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3 demonstrating a significantly reduced FEV₁ ($P = 0.044$) compared to the CF patients.
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5 Table 3b shows the correlational relationships for the healthy control group, only BMI
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7 was found to be significantly correlated to recovery ($r = 0.48$, $P = 0.011$).
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12 There were no significant differences between the CF and CCD groups in age, stature
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14 and pubertal maturity (Table 1). Body mass, body mass index and FEV₁ were
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16 significantly greater in the CF group than in the CCD group (Table 1). No significant
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18 differences were found between the CF group and CCD group in $\dot{V}O_{2\text{ peak}}$ and early
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20 $\dot{V}O_{2\text{ recovery}}$ (Table 1). No significant differences in the pulse oximetry data
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22 between the CF and CCD groups were found before or at the termination of CPXT
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24 (Table 1), but a significant fall in oxygen saturation before to the termination of
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26 CPXT was found in the CF group (97 ± 1 vs 94 ± 2 %, respectively; $P = 0.001$) and
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28 CCD group (97 ± 0.5 % vs 96 ± 1 %, respectively; $P = 0.015$).
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37 In the CF group a significant negative correlation was found between the SS and early
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39 $\dot{V}O_{2\text{ recovery}}$ (Table 2 and Figure 1), and a significant correlation was also present
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41 between the SS and FEV₁ (Table 2 and Figure 2). No significant correlation was
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43 found between the SS and $\dot{V}O_{2\text{ peak}}$ (Table 2). Furthermore, amongst the children with
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45 CF, the ratio of $\dot{V}O_{2\text{ peak}} / \text{early } \dot{V}O_{2\text{ recovery}}$ was significantly correlated with the
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47 SS (Table 2 and Figure 3), but not with FEV₁ (Table 2).
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55 In the CCD group early $\dot{V}O_{2\text{ recovery}}$ had a significant negative relationship with
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57 $\dot{V}O_{2\text{ peak}}$ (Table 3 and Figure 4), but not in the CF group (Table 2). No significant
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59 correlations were found between early $\dot{V}O_{2\text{ recovery}}$ and FEV₁ in either the CF
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3 group (Table 2) or the CCD group (Table 3). Similarly, FEV₁ and $\dot{V}O_{2\text{ peak}}$ were not
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6 found to be significantly related in either the CF group (Table 2) or CCD group
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9 (Table 3).

10 11 12 13 DISCUSSION

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15 The present study found that compared to controls, children with CCD demonstrated a
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17 significantly reduced $\dot{V}O_{2\text{ peak}}$ and prolonged early $\dot{V}O_{2}$ recovery following CPXT.
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19 The metabolic cost of exercise results from both the performance of external work,
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21 and the demands of the O₂ transportation system itself. This includes the work
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23 performed by the muscles of respiration and the enduring metabolic demand to restore
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25 homeostasis during recovery.³² The rate of $\dot{V}O_{2}$ during early recovery from exercise
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27 in children with CCD will be influenced by many disease factors. For example, as
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29 disease progresses there is an increase in dead space,³⁴ that necessitates an increase in
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31 total ventilation in order to keep alveolar ventilation constant.^{35,36} Airway obstruction
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33 and air trapping would also reduce the rate of elimination of excess carbon dioxide
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35 formed during exercise, prolonging tachypnoea, which itself would increase the
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37 metabolic demand and which contributes to fatigue.³⁷ Delayed elimination of carbon
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39 dioxide would also impair the ability to compensate for alterations in acid-based
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41 status.³⁸ Furthermore, in patients with CF the correlation between thin section
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43 computed tomographic (CT) findings of lung parenchymal damage and exercise
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45 limitation is stronger than that between spirometry results, or BMI and exercise
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47 limitation.⁴⁴ The CF genotype has also been reported to be related to exercise
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49 tolerance.⁴⁵ The aim of this study was to investigate if early $\dot{V}O_{2}$ recovery following
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51 CPXT was associated with disease severity and functional capacity in children with
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53 CF, and functional capacity in those with other CCD.
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6 The lung function data from the present study showed that FEV₁, FVC, PEF and
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8 FEF₂₅₋₇₅ were all significantly reduced in children with CCD compared to controls.
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10 Forced expiratory volume in 1 s, FEF₂₅₋₇₅ and BMI in the children with CCD,
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12 however, were not significantly correlated with $\dot{V}O_{2\text{ peak}}$ or early $\dot{V}O_2$ recovery.
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14 Furthermore, the study showed that despite a significantly reduced FEV₁ in the NON-
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16 CF patients compared to the CF patients, $\dot{V}O_{2\text{ peak}}$ and early $\dot{V}O_2$ recovery were not
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18 significantly different between the two patient groups. These findings demonstrate,
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20 therefore, that exercise performance was similar between the NON-CF and CF
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22 patients, despite poorer lung function in the NON-CF patients. These finding may
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24 emphasise the physiological differences between the static nature of lung function
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26 testing and the dynamic nature of the cardiopulmonary system when exercising. It
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28 may also infer, however, the physiological differences between children with CF and
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30 other CCD, especially in regard to recent work which found that CF patients
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32 demonstrated reduced oxidative work efficiency in the skeletal muscle.³³
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42 Contrary to previous studies which have reported that reduced FEV₁ is associated
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44 with lower $\dot{V}O_{2\text{ peak}}$,^{21,34,46-49} a non-significant relationship between lung function and
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46 $\dot{V}O_{2\text{ peak}}$ in the children with CCD in the present study may provide further support to
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48 work which has reported that reduced aerobic performance is related to intrinsic
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50 abnormalities of skeletal muscle function.^{33,50-52} Furthermore, a recent study reported
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52 that $\dot{V}O_{2\text{ peak}}$ and exercise duration during CPXT was not affected in patients with
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54 mild CF using added dead space, suggesting the CPXT is not limited by respiratory
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56 factors.⁵³ Moser et al. (2000) also found no significant correlations between variables
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3 reflecting exercise performance (e.g., $\dot{V}O_{2\text{ peak}}$) and lung function measurements (e.g.,
4 FEV₁) in children with CF.⁵¹ This finding is also supported by Edwards et al. (2004),
5 who reported no relationships between variables measured during exercise testing and
6 lung function.⁵⁴ Peak oxygen uptake and early $\dot{V}O_2$ recovery, however, were
7 significantly related; indicating the greater the aerobic fitness of the patient the faster
8 the rate of recovery. This relationship although significant, however, is still quite
9 weak ($r = -0.39$, $P = 0.044$), and therefore, may indicate that the $\dot{V}O_2$ recovery can
10 not be explained predominantly by the $\dot{V}O_{2\text{ peak}}$. However, the finding that $\dot{V}O_{2\text{ peak}}$
11 and early $\dot{V}O_2$ recovery were not significantly correlated for the healthy control
12 group accentuates the relative importance of aerobic fitness and recovery and their
13 impact on children with CCD.
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33 In children with CF a significant relationship between early $\dot{V}O_2$ recovery and the SS
34 was found. Correlations between structural abnormalities of the lung scored on thin
35 section CT images and exercise performance have been reported in patients with CF,
36 and these relationships are stronger than that between spirometry results, or BMI and
37 exercise limitation,⁴⁴ and may explain the relationship found in the present study.
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~~Based on the results of this study early $\dot{V}O_2$ recovery has value as an objective
measure of disease severity in children with CF. Forced expiratory volume in 1 s and
FEF₂₅₋₇₅ in the children with CF were also significantly related to the SS. A significant
relationship was also found in the CF group between FEV₁ and the SS, confirming
previous reports that lung function is correlated with disease severity and survival in
CF patients.^{6,55,56} This study found~~ No significant relationship between $\dot{V}O_{2\text{ peak}}$ and
the SS in the CF patients group was found in the present study. The $\dot{V}O_{2\text{ peak}}$ values

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3 for children with CF in this study are similar to published values of aerobic fitness for
4 young CF patients of a similar age range.^{23,24,51} A significant correlation between
5 $\dot{V}O_{2\text{ peak}}$ and SS has been previously reported in adults with CF,⁵⁷ but not in children.
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11 The disease severity of the adult CF patients was greater than in the present study (71
12 ± 14 versus 80 ± 12 , respectively) and $\dot{V}O_{2\text{ peak}}$ was lower (25 ± 7 versus 35 ± 8
13 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively), which may have increased the likelihood of finding a
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No significant differences in $\dot{V}O_{2\text{ peak}}$ or early $\dot{V}O_{2\text{ recovery}}$ between the CF and
CCD groups were found despite the children in the CCD group having a significantly
reduced FEV₁. This finding signifies that static airway obstruction as measured by
FEV₁ for the range of values in this study did not affect either group's ability to utilise
oxygen either during or immediately following CPXT. Furthermore, it emphasises the
physiological differences between the static nature of pulmonary function testing and
the dynamic nature of the pulmonary/respiratory system when exercising. This may
explain why FEV₁ was not significantly related to $\dot{V}O_{2\text{ peak}}$ and early $\dot{V}O_{2\text{ recovery}}$ in
either groups. Therefore, this study found that in children with CF and other CCD,
FEV₁ is a poor predictor of exercise performance and recovery.

A significant relationship was found between early $\dot{V}O_{2\text{ recovery}}$ and $\dot{V}O_{2\text{ peak}}$ in the
CCD group but not the CF group. Therefore, $\dot{V}O_{2\text{ peak}}$ is a good predictor of early
 $\dot{V}O_{2\text{ recovery}}$ in children with CCD but not in children with CF. This finding may
reflect more disease variables and physiological differences between the CF and CCD
groups. Published work has reported that impaired exercise performance in young CF

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3 patients is partly due to pathophysiological factors in skeletal muscle that cannot be
4 readily attributed to nutritional factors.^{51,58} Intrinsic metabolic abnormalities such as a
5 reduced metabolic efficiency (i.e., less oxidative ATP turnover for muscle mechanical
6 work) may exist in the muscle of young CF patients, which contribute to a reduced
7 exercise performance.⁵⁸
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17 Using the ratio of $\dot{V}O_{2\text{ peak}} / \text{early } \dot{V}O_{2\text{ recovery}}$ as a composite measure of exercise
18 performance, a significant correlation was found with the SS in the CF group and,
19 therefore, may be an objective measure of disease severity. Recovery time may refine
20 the $\dot{V}O_{2\text{ peak}}$ measure, and the ratio of the two measures may provide a comprehensive
21 exercise performance score. For example, where patients with higher aerobic capacity
22 and who recover more quickly have greater physical ability than those with high
23 aerobic capacity but slower recovery, or those with low aerobic capacity and slow
24 recovery. More research, however, is needed to verify this measure and the data in
25 this study is preliminary.
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42 Many studies of therapeutic interventions use lung function variables as the primary
43 outcome.⁵⁹⁻⁶³ Disease in CF can progress as shown on thoracic High Resolution
44 Computerised Tomography Scanning despite lung function stability.⁶⁴ Exercise
45 parameters may provide a more integrated outcome measure. Exercise involves the
46 amalgamation of respiratory, cardiovascular, metabolic, nutritional and psychological
47 systems and therefore measures of performance are more likely to reflect health status
48 than a single static test such as spirometric lung function. Exercise performance as
49 measured by $\dot{V}O_{2\text{ peak}}$ has been shown to have a closer correlation with prospective
50 mortality than resting lung function in CF.⁴ Exercise testing can provide useful
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3 additional information about functional limitations and trends over time.⁶⁵ The links
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5 between more detailed measures of exercise performance including recovery
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7 parameters, disease severity and quality of life deserve more attention. Objective
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9 measures may be more accurate in predicting prognosis and mapping progress and
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11 response to treatments than more subjective scoring systems of well-being. Peak
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13 oxygen uptake alone may have limitations and a more composite measure of exercise
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15 performance that includes the rate of recovery may be more meaningful.
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22 In conclusion, children with CCD in the present study had mild to moderate disease as
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24 interpreted by their lung function, and showed a reduced $\dot{V}O_{2\text{ peak}}$ and prolonged early
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26 $\dot{V}O_2$ recovery compared to a control group. The prolonged recovery may be an
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28 indication of reduced oxidative capacity for PCr resynthesis, attributed to impaired O_2
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30 transportation and utilisation in the contracting muscle. Indeed, the present study
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32 showed that early $\dot{V}O_2$ recovery was significantly related to the SS in children with
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34 CF, indicating that early $\dot{V}O_2$ recovery is prolonged with increased disease severity.
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36 Lung function was not significantly related to $\dot{V}O_{2\text{ peak}}$ and early $\dot{V}O_2$ recovery, and
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38 therefore may not accurately reflect the patient's ability to exercise and recover.
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40 Indeed, disease in CF can progress significantly, as shown on thoracic high resolution
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42 CT scanning, despite lung function stability.⁶⁴ Exercise testing can help to provide
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44 useful additional information about functional limitations and trends over time.⁶⁵ A
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46 recent study reported that higher aerobic fitness despite poor lung function is
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48 associated with a better prognosis.²³ The links between more detailed measures of
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50 exercise performance including recovery parameters, disease severity and quality of
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52 life deserve more attention and warrant further investigation. Furthermore, the present
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3 ~~study found that~~ early $\dot{V}O_2$ recovery and FEV₁ were both significantly related to
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6 disease severity, as assessed by the SS, in children with CF. Therefore, both early
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8 $\dot{V}O_2$ recovery and FEV₁ may be used to predict disease severity in children with CF.
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11 Furthermore, our data revealed that despite a significant reduction in FEV₁ in the
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13 CCD group compared to the CF group, there were no significant differences in
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15 $\dot{V}O_{2\text{ peak}}$ and early $\dot{V}O_2$ recovery between the two groups, indicating that spirometric
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17 pulmonary function does not necessarily reflect a CCD patient's exercise ability. A
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19 recent study reported that higher aerobic fitness despite poor lung function is
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21 associated with a better prognosis.²³ Therefore, measures of exercise performance
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23 and recovery should be considered as a routine test as they are likely to enhance the
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25 comprehensive assessment of patient well-being⁵.

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34
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44
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46
47 ~~Research and Development department, Royal Devon and Exeter NHS Foundation~~
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49 ~~Trust Hospital.~~ The authors declare that there are no conflicts of interest in this study.
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