Impaired Aerobic Function in Young Cystic Fibrosis Patients During Ramp Exercise

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Running Title: NIRS ramp exercise response in paediatric CF
ABSTRACT

Purpose: To document the matching of muscle O$_2$ delivery-to-O$_2$ utilisation in young cystic fibrosis (CF) patients from muscle deoxygenation (HHb) dynamics during ramp exercise.

Methods: Ten patients with stable, mild-to-moderate CF (12.7 ± 2.8 y) and 10 healthy controls (CON; 12.8 ± 2.8 y) completed a combined ramp and supramaximal cycling test to determine maximal O$_2$ uptake (VO$_{2\text{max}}$). Changes in gas exchange and ventilation, heart rate and m. vastus lateralis HHb (near-infrared spectroscopy) were assessed. ∆[HHb]-work rate and ∆[HHb]-VO$_2$ profiles were normalised and fit using a sigmoid function. Results: Aerobic function was impaired in CF, indicated by very likely reduced fat-free mass normalised VO$_{2\text{max}}$ (mean difference, ±90% CI: -7.9 mL·kg$^{-1}$·min$^{-1}$, ±6.1), very likely lower VO$_2$ gain (-1.44 mL·min$^{-1}$·W$^{-1}$, ±1.12) and a likely slower VO$_2$ mean response time (11 s, ±13). An unclear effect was found upon the absolute and relative WR (-14 W, ±44 and -0.7 %PPO, ±12.0, respectively) and the absolute and percentage (-0.10 L·min$^{-1}$, ±0.43 and 3.3 %VO$_{2\text{max}}$, ±6.0) VO$_2$ corresponding to 50% ∆[HHb] amplitude, respectively, between groups. However, arterial hypoxemia was very likely lower in CF (-1%, ±1) and demonstrated moderate-very large relationships with parameters of aerobic function. Conclusion: Young patients with mild-to-moderate CF present with impaired aerobic function during ramp incremental cycling exercise. Since the rate of fractional O$_2$ extraction during ramp cycling exercise was not altered by CF, yet arterial hypoxaemia was greater, the present findings support the notion of centrally mediated oxygen delivery principally limiting the aerobic function of paediatric CF patients during ramp incremental cycling exercise.

Keywords: Near-infrared spectroscopy, aerobic function, exercise testing, exercise limitation, lung disease, paediatrics.
INTRODUCTION

Cystic fibrosis (CF) is a complex, multiorgan genetic disease, expressed as a disruption in the CF transmembrane conductance regulator (CFTR) protein. In conjunction with its clinical presentation, reduced aerobic fitness [typically determined as maximal oxygen uptake (\(\dot{V}O_{2\text{max}}\))], is commonly observed in both adult (10) and paediatric patients (18). Reduced aerobic fitness is of clinical relevance in patients with CF given its association with longevity (26,29), quality of life (6) and risk of hospitalisation (27). Key parameters of aerobic function (\(\dot{V}O_{2\text{max}}, \dot{V}O_2\text{ gain, gas exchange threshold (GET) and \(\dot{V}O_2\text{ mean response time}\)}\) (38) have not, however, been comprehensively documented in CF. Moreover, no previous studies have used a valid protocol (31) to obtain a ‘true’ measure of \(\dot{V}O_{2\text{max}}\) in this population. Identifying the limiting factor(s) impairing aerobic function in CF will facilitate the development of more effective strategies to improve longevity and quality of life in this aging patient population.

Since the body’s upper limit for \(O_2\) utilisation is determined by the maximal cardiac output (\(\dot{Q}\)), arterial \(O_2\) content, fractional distribution of \(\dot{Q}\) to the exercising muscles, and the ability of the skeletal muscle to extract \(O_2\) (36), simultaneous measurements at the central (cardiorespiratory) and peripheral (skeletal muscle) levels are required to understand the dynamic matching of \(O_2\) delivery-to-\(O_2\) utilisation during exercise. Previous studies in CF have, however, largely neglected this complex interaction and based inferences on investigations of isolated organ systems (8,17,21).

As a result, debate remains regarding the relative importance of central and peripheral mechanisms to explain the reduced \(\dot{V}O_{2\text{max}}\) in patients with mild-to-moderate CF. Expression of CFTR in human skeletal muscle (20) suggests an intrinsic myocyte metabolic abnormality,
which may be specific to CF (7,8) or a consequence of chronic respiratory disease (30,37). In addition, there is evidence to support a central limitation to exercise through a reduction in stroke volume (SV) (28) and, presumably, muscle O_2 delivery (30), in paediatric CF patients. Although a compensatory increase in muscle O_2 extraction may be expected to occur in the presence of reduced muscle O_2 delivery, this was not observed in a previous study (30). However, further confirmation of this response is warranted since inferences at the skeletal muscle level were based upon indirect, interlinked mathematical calculations.

To further understand how disease pathophysiology alters the O_2 delivery-to-O_2 utilisation relationship during exercise, near-infrared spectroscopy (NIRS) can provide valuable, non-invasive insight into peripheral O_2 extraction. Specifically, the profile of the deoxyhaemoglobin ([HHb]) signal has been used to describe O_2 extraction dynamics during ramp exercise, which in turn permit inferences regarding blood flow within the microcirculation of exercising muscle (4,9,25). Although the HHb profile during ramp exercise has been used to describe the effect of trained status (4,22) and ageing (11,22), there are no data documenting the influence of disease on the [HHb] response to incremental exercise. If the supply of blood to the active muscle during exercise is impaired in CF, as would be indirectly inferred from previous reports of a reduced SV (28), an increased rate of fractional O_2 extraction for a given $\dot{V}O_2$ would be expected (9).

The purpose of the present study was twofold: 1) to characterise the four key parameters of aerobic function in stable mild-to-moderate paediatric CF patients and 2) to characterise the dynamic adjustment of NIRS-derived leg muscle [HHb] during ramp exercise. It was hypothesised that: 1) aerobic function would be impaired in CF, as evidenced by a reduced $\dot{V}O_2_{max}$, slower $\dot{V}O_2$ MRT, earlier occurrence of the GET and shallower $\dot{V}O_2$ gain. Furthermore,
that 2) CF patients would be characterised by reduced \( O_2 \) delivery through a reduced arterial \( O_2 \) saturation and more rapid [HHb] dynamics during ramp exercise (i.e. left-ward shift), which will correlate with impaired parameters of aerobic function.

**MATERIALS and METHODS**

**Study participants.** Ten young patients [9 males (Table 1)] with stable mild-to-moderate CF disease (CF) regularly partaking in school and/or extracurricular physical activity were recruited from outpatient clinics at the Royal Devon and Exeter NHS Foundation Trust Hospital. CF inclusion and exclusion criteria are detailed elsewhere (31). Ten healthy age- and gender-matched control participants (CON) were recruited from the local area (Table 1). Neither group presented with any contraindications to exhaustive exercise and CON were free from any pulmonary conditions. Ethics approval was granted by the South West NHS Research Ethics Committee. Informed written consent and assent were obtained from parents/guardians and patients, respectively. Details concerning the CF patients’ disease severity and clinical profile were obtained by their clinician (Table 2). All CF maintenance medications were continued as usual throughout the study.

**Anthropometry and pulmonary function.** Body mass (Seca 220; Vogel & Halke, Hamburg, Germany) and stature (Seca 220; Vogel & Halke, Hamburg, Germany) were measured to the nearest 0.01 kg and 0.01 m, respectively. Pubertal maturity was determined using Tanner staging (35). Skin folds measured to the nearest 1 mm on the right-hand side of the body at the tricep and subscapula regions (Harpenden; British Indicators, Burgess Hill, UK) were used to estimate fat-free mass (FFM) (33). Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV\(_1\))
were assessed using flow-volume loop spirometry (MicroMedical MicroLoop 3535, Numed, Sheffield, UK). The best of three consistent (< 5% variability) exhalations was documented and expressed as a percentage of predicted reference data (34).

**Exercise testing.** Participants arrived to the laboratory in a rested state, ≥ 2 h postprandial and having refrained from caffeine for ≥ 2 h. A maximal cardiopulmonary exercise test (CPET) was performed on a cycle ergometer (Lode Excalibur or Lode Corival, Groningen, The Netherlands) using a single session, combined ramp incremental and supra-maximal CPET protocol which has been validated in healthy children (1) and children with CF (31). This protocol involved an exhaustive ramp incremental (10-25 W·min\(^{-1}\)) cycling test with a subsequent supramaximal [110% peak power output (PPO)] test to exhaustion to verify \(\dot{V}O_{2\text{max}}\). Following a 3-min warm-up period (20 W cycling), participants completed the incremental ramp test whilst cycling at a cadence of ~70-80 rpm until volitional exhaustion, defined as a drop in cadence ≥ 10 rpm for 5 consecutive seconds, despite strong verbal encouragement. Five minutes active recovery (20 W cycling) and 10-min passive seated recovery preceded the \(S_{\text{max}}\) verification test, which involved 3-min warm-up (20 W cycling) before a ‘step’ transition to a constant work rate equivalent to 110% PPO. Upon voluntary exhaustion, 5-min active recovery (20 W cycling) completed the CPET assessment.

**Experimental measures**

Prior to each test, the metabolic cart (Metalyzer 3B Cortex, Biophysik, Leipzig, Germany) was calibrated using gases of known concentration and a 3 L calibration syringe (Hans Rudolph, Kansas City, MO) was used to calibrate the turbine volume transducer. Breath-by-breath changes
in pulmonary gas exchange and ventilation were measured and averaged to 15-s time bins, with the highest 15-s stationary average from the ramp or \( S_{\text{max}} \) representing \( \dot{V}O_{2\text{max}} \) (11). The gas exchange threshold (GET) in absolute terms and expressed as a percentage of \( \dot{V}O_{2\text{max}} \) was non-invasively identified (2) and confirmed through visual identification of the ventilatory equivalents for \( \dot{V}O_2 \) and carbon dioxide output (\( \dot{V}CO_2 \)). The \( \dot{V}O_2 \) mean response time (MRT) was determined using the time from the onset of ramp exercise to the intersection point between baseline \( \dot{V}O_2 \) and a backward extrapolation of the slope of \( \dot{V}O_2 \) as a function of time (38). Regression of the linear portion of the \( \dot{V}O_2 \) response versus power output was used to determine the functional \( \dot{V}O_2 \) gain (\( \Delta \dot{V}O_2 / \Delta \text{WR} \)). Equation 1 was used to determine oxygen pulse (\( \dot{V}O_2 / \text{HR}_{\text{peak}} \)).

\[
\dot{V}O_2 / \text{HR}_{\text{peak}} \,(\text{mL} \cdot \text{beat}^{-1}) = \dot{V}O_2 \,(\text{L} \cdot \text{min}^{-1}) \, x \, 1000 \, \text{mL} / \text{HR} \,(\text{beats} \cdot \text{min}^{-1})
\]

**Equation 1.**

*Near-infrared spectroscopy.* HHb dynamics from the *m. vastus lateralis* were non-invasively measured using NIRS (Portamon, Artinis Medical Systems). This system has previously been used in children (22) and consists of an emission probe, with three light sources emitting two wavelengths of light (760 and 850 nm) and a photon detector. The intensity of incident and transmitted light was recorded continuously at 10 Hz and used to estimate [HHb]. Since the NIRS-derived [HHb] signal does encompass contribution from intramyocyte myoglobin and does not solely reflect the microcirculatory compartment [vascular (Hb) deoxygenation] (19), the changes in muscle HHb should be considered to represent [Hb+Mb]. The wireless emitter-detector unit was placed over the *m. vastus lateralis*, midway between the greater trochanter and lateral epicondyle of the femur. The area of interrogation was initially cleaned and shaved and,
following marking of the placement area, the device was secured with tape (KinesioTex®) and a dark elastic bandage, to minimise extraneous light interference with the near-infrared signal.

**Additional measures:** Heart rate (HR) was measured on a beat-by-beat basis using the ECG-derived R-R interval (PhysioFlow, PF-05, Manatec Biomedical, Paris, France). Fingertip arterial oxygen saturation (SpO₂%) was recorded via pulse oximetry (NONIN, Avant 4000, NONIN Medical Inc., USA). Subjective ratings of perceived exertion (RPE) and dyspnoea (RPD) were determined upon exhaustion using the pictorial children’s effort rating table (P-CERT) and the 0-10 category ratio (CR-10) scale, respectively, the methodology for which is described elsewhere (31).

**HHb modelling procedures**

Muscle [HHb] data were interpolated to 1 s intervals and averaged data (15 s) for the entire test were subsequently normalised to the total amplitude of the response (%Δ[HHb]), such that 0% represented steady-state values observed during the period of baseline (20 W) cycling and 100% represented the highest average (i.e., Δ[HHb]_{peak}) (4,11). The response was then expressed as a function of absolute and relative PPO and $\dot{V}O_{2\text{max}}$. Preliminary statistical analyses (GraphPad Prism, GraphPad Software, San Diego, CA) revealed that a sigmoid function provided a superior fit to the HHb response when compared to a bi-linear or hyperbolic curve fitting procedure (data not reported). The Δ[HHb] response to incremental ramp cycling exercise was therefore described using a sigmoidal model (Equation 3) in line with previous studies (22, 9, 4):

$$y = f_0 + A / (1 + e^{-(c+dx)}) \quad \text{Equation 3.}$$
Where \( f_0 \) represents baseline [HHb], \( A \) the amplitude of the response, \( d \) the slope of the sigmoid, \( c \) the constant that is dependent on \( d \) and \( c/d \) the value corresponding to 50% of the total amplitude, respectively.

**Statistical Analyses.** Log-linear allometric models were used to adjust \( \dot{V}O_{2\text{max}} \) for body size. The log-linear allometric model yielded a scaling exponent close to unity for FFM \( (b = 1.03) \), meaning the ratio standard method for normalising \( \dot{V}O_{2\text{max}} \) was deemed appropriate.

Data are expressed as means and standard deviations unless otherwise stated. Independent samples \( t \)-tests (SPSS v19.0, Chicago, USA) derived \( p \)-values for subsequent inferential analyses. Inferential statistics, using 90% confidence intervals (CI) and the effect size (ES), were employed to derive magnitude-based inferences regarding the true value of the observed effect statistic (16). Facilitated by a published Microsoft Excel® spreadsheet (15), any influence of CF on parameters of the [HHb] response and maximal and submaximal CPET parameters was calculated, using a 90% CI and the ES. Using a smallest worthwhile ES change of 0.2 (5) and the 90% CI, the likelihood that the observed effect was beneficial (e.g. higher \( \dot{V}O_{2\text{max}} \), faster MRT), trivial or harmful (e.g. lower \( \dot{V}O_{2\text{max}} \), slower MRT) was reported. The qualitative terms used to inform these decisions were: < 0.5%, ‘most unlikely’; 0.5-5%, ‘very unlikely’; 5-25%, ‘unlikely’; 25-75%, ‘possibly’; 75-95%, ‘likely’; 95-99.5%, ‘very likely’; > 99.5%, ‘most likely’. An effect was deemed trivial when the majority (> 50%) of the 90% CI resided between beneficial and harmful. Conversely, an effect was deemed unclear when the likelihood of a beneficial and harmful effect was > 5%.
Hopkins’ published spreadsheet (15) was also used to determine the 90% CI for Pearson’s correlation coefficients to explore the relationship between key parameters of aerobic function (i.e., $\dot{V}O_{2\text{max}}$, $V_{O_2}$ gain, MRT and the GET) and mechanistically linked parameters of muscle $O_2$ extraction (e.g., $d$ and $c/d$ of the [HHb] response) and $O_2$ delivery (e.g., end-exercise $SpO_2\%$ and $O_2$ pulse) in CF. Cohen’s thresholds (5) for small (0.1), moderate (0.3), large (0.5) and very large (0.7) relationships describe the magnitude of correlations.

RESULTS

Table 1 presents participants’ baseline physical characteristics, with Table 2 detailing the CF clinical profile. BMI was likely higher whilst FEV$_1$ (% predicted) was likely lower in CF than CON. Pubertal maturity of both groups were as follows; pre-pubertal ($n = CF, 3$; $CON, 1$), circum-pubertal ($n = CF, 7$; $CON, 8$) and post-pubertal ($n = CF, 0$; $CON, 1$).

Maximal and submaximal CPET parameters are presented in Table 3. All participants completed CPET without any adverse events. Ramp PPO was possibly lower in CF and likely lower when expressed relative to body mass. As expected, CF presented with very likely reduced $\dot{V}O_{2\text{max}}$, when normalised for both body mass and FFM. Furthermore, the $\dot{V}O_2$ gain was very likely lower and the $\dot{V}O_2$ MRT was likely slowed in CF. The RPD upon exhaustion were also most likely higher in CF.

Parameter estimates for normalised muscle [HHb] as a function of absolute and percentage PPO (%PPO) and $\dot{V}O_{2\text{max}}$ (%$\dot{V}O_{2\text{max}}$) are compared in Table 4 and the $\Delta[HHb]$-WR profile for two representative CF and CON matched pairs are shown in Figure 1. Any effect of the reduced aerobic fitness in CF patients upon the slope ($d$) of the $\Delta[HHb]$-WR response was mechanistically unclear, when expressed as either a function of absolute and percentage PPO and
absolute and percentage \( \dot{VO}_{2\text{max}} \). Furthermore, the effect of CF upon the absolute and relative WR and \( \dot{VO}_2 \) corresponding to 50% amplitude (c/d) was mechanistically unclear.

Correlational analyses within the CF group revealed small relationships between patients’ \( \dot{VO}_{2\text{max}} \) and their [HHb] c/d, expressed as a function of %PPO (\( r = 0.14, \pm 0.58 \)) and %\( \dot{VO}_{2\text{max}} \) (\( r = -0.21, \pm 0.57 \)), respectively. With the exception of the very large relationship between \( \dot{VO}_2 \) gain and [HHb] c/d %PPO (\( r = 0.70, \pm 0.36 \)), relationships between \( \dot{VO}_2 \) gain and [HHb] c/d %\( \dot{VO}_{2\text{max}} \) and the GET and MRT with [HHb] c/d %PPO and %\( \dot{VO}_{2\text{max}} \) were all small. A moderate relationship was observed between \( \dot{VO}_{2\text{max}} \) and end-exercise \( \text{SpO}_2\% \) (\( r = 0.33, \pm 0.51 \)) in CF (Figure 2), however this was small (\( r = 0.20, \pm 0.54 \)) in the healthy control group. The relationship between \( \dot{VO}_{2\text{max}} \) and \( \text{O}_2 \) pulse was large in CF (\( r = 0.58, \pm 0.41 \); Figure 2) and CON (\( r = 0.98, \pm 0.00 \)). Similarly, the relationships between \( \dot{VO}_2 \) gain and end-exercise \( \text{SpO}_2\% \) and \( \text{O}_2 \) pulse were moderate (\( r = 0.40, \pm 0.49 \)) and large (\( r = 0.65, \pm 0.37 \)), respectively in CF, however these were small in CON (\( r = -0.15, \pm 0.54 \) and \( r = 0.1, \pm 0.58 \), respectively). Very large relationships were also evident between the GET and end-exercise \( \text{SpO}_2\% \) (\( r = -0.88, \pm 0.16 \)) and \( \text{O}_2 \) pulse (\( r = 0.98, \pm 0.03 \)) in CF. The relationship between the GET and \( \text{O}_2 \) pulse was very large in CON (\( r = 0.92, \pm 0.12 \)), however that with \( \text{SpO}_2\% \) was small (\( r = 0.10, \pm 0.55 \)). A moderate relationship (\( r = 0.39, \pm 0.49 \)) was also evident between the \( \dot{VO}_2 \) gain and MRT in CF, however this was small in CON (\( r = 0.01, \pm 0.55 \)).

**DISCUSSION**

This is the first study to examine the influence of mild-to-moderate CF on aerobic function and the dynamic adjustments in localised muscle (\textit{vastus lateralis}) fractional oxygen extraction (\( \Delta[\text{HHb}] \)) in paediatric patients during ramp incremental cycling exercise. As expected, CF
patients were characterised by impaired aerobic function, as displayed by a very likely reduced body mass or FFM normalised $\dot{V}O_{2\text{max}}$, a very likely lower $\dot{V}O_2$ gain and likely slower $\dot{V}O_2$ MRT. Contrary to the experimental hypothesis, however, this reduced aerobic fitness status did not have a clear effect upon the dynamics of the $\Delta[\text{HHb}]$ during ramp incremental exercise. Specifically, no clear shift in $c/d$ of the [HHb] response was evident when expressed relative to percentage PPO or $\dot{V}O_{2\text{max}}$ and relationships with the key parameters of aerobic fitness were small. Indicators of central $O_2$ delivery were, however, altered by CF. Specifically, end-exercise $\text{SpO}_2\%$ was most likely lower and correlated with $\dot{V}O_{2\text{max}}$ in the CF group only. Thus, these data show that the observed changes in the aerobic function of paediatric CF patients during incremental ramp cycling are likely related to alterations in muscle $O_2$ delivery, with no compensatory adjustment to the dynamics of muscle $O_2$ extraction within the microcirculation.

This study is unique for a number of reasons. It is the first to use a validated protocol (31) to document ‘true’ $\dot{V}O_{2\text{max}}$ in young CF patients. Consistent with earlier reports (18), $\dot{V}O_{2\text{max}}$ in CF patients was very likely lower than CON in this study, when normalised for both body mass and FFM. But importantly, the present results are robust since this study is the first to include a supramaximal $\dot{V}O_{2\text{max}}$ verification phase (31) within the CPET protocol, thereby removing the issue of previous studies, where aerobic fitness status may have been under represented due to invalid verification criteria (31).

Secondly, this study presents, for the first time, the four key parameters of aerobic function (38), allowing a comprehensive assessment of aerobic fitness in this patient group. Of the additional key parameters, CF patients presented with a very likely reduced $\dot{V}O_2$ gain and a likely slowed $\dot{V}O_2$ MRT, with no clear effect on the GET. Whilst slower pulmonary $\dot{V}O_2$ kinetics have been documented in CF patients during constant-load, moderate intensity cycling (14), the
present study extends these findings to the \( \dot{V}O_2 \) response at the onset of ramp incremental cycling. Although no clear influence upon the GET was evident, the functional gain during the moderate-intensity region of ramp exercise was very likely lower in CF, reflecting either an apparently greater skeletal muscle efficiency or impaired muscle O\(_2\) consumption. Shallower \( \Delta \dot{V}O_2/\Delta WR \) slopes during exercise have previously been reported in patients with CF (23), congenital heart disease (12) and juvenile dermatomyositis (12). However, steeper \( \Delta \dot{V}O_2/\Delta WR \) responses have also been observed in young CF patients (12). It would be misleading to interpret the reduced \( \Delta \dot{V}O_2/\Delta WR \) in the present findings as enhanced aerobic efficiency, particularly given the impairment in other parameters of aerobic function (i.e., \( \dot{V}O_{2\text{max}} \) and MRT). Given the moderate relationship between the \( \dot{V}O_2 \) gain and MRT in CF, the lower \( \Delta \dot{V}O_2/\Delta WR \) slope may be related to the slower pulmonary \( \dot{V}O_2 \) kinetics, such that the rise in \( \dot{V}O_2 \) was not sufficiently rapid to respond to the work rate increments during the CPET.

To our knowledge, this study is the first to report the \( \Delta [HHb] \) dynamics during ramp exercise in paediatric CF patients. Whilst pulmonary \( \dot{V}O_2 \) increased linearly with increasing work rate following an initial time lag, muscle \( \Delta [HHb] \) [reflecting the ratio of muscle O\(_2\) delivery to muscle O\(_2\) utilisation (Table 4; Figure 1)] increased in a nonlinear manner. This response was well characterised using a sigmoid function relative to WR and \( \dot{V}O_2 \) in both groups in the current study, which is consistent with previous reports in children and young and old adults during ramp cycling exercise (4,11,22).

Contrary to the study hypothesis, the \( \Delta [HHb] \) dynamics during ramp exercise were similar between CF and CON in the present study. That is, no clear effect of CF upon either the absolute and relative WR and \( \dot{V}O_2 \) corresponding to 50\% \( \Delta [HHb] \) amplitude was observed. This is despite previous reports that aerobic fitness has an effect upon the dynamic balance between
O₂ supply and demand and, consequently, the sigmoidal pattern of [HHb] during ramp incremental cycling exercise (4,22). Boone et al. (4) previously demonstrated that a higher aerobic fitness is associated with a rightward shift of the HHb response (relative to %PPO) in healthy adults and that the response correlated with parameters of aerobic fitness (i.e., VO₂max and the GET). The purported mechanism for this rightward shift in the HHb response was attributed to a higher oxidative capacity and/or altered muscle fibre distribution. The rate of fractional oxygen extraction has also been shown to be influenced by training status and enhanced O₂ delivery in trained versus untrained healthy girls (22). Since VO₂max was meaningfully reduced in CF patients in the present study, a more rapid increase in Δ[HHb] during ramp exercise would be expected. However, a previous study (11) comparing older (~ 70 years) and younger (~ 25 years) healthy adults, which observed alterations when expressed relative to absolute power output, did not observe any age-related differences in Δ[HHb] response dynamics when expressed as a function of %PPO, despite a reduced VO₂max in the older participants (30 vs. 49 mL·kg⁻¹·min⁻¹).

Some caution may, however, be applied when considering the present findings to suggest that there are no differences between the Δ[HHb] response of healthy and CF children and adolescents. Inter-patient differences (Figure 1) in the Δ[HHb] response suggest that the interpretation that the rate of muscle O₂ extraction is unaltered by CF may be too simplistic. When the distribution of the 90% CI for the effect of CF on the ΔHHb c/d was expressed relative to percentage VO₂max, the majority of the 90% CL distribution favoured a reduced rate of extraction (leftward shift: 9%; trivial: 22%; rightward shift: 69%). The unclear statistical outcome is, therefore, likely to reflect the large inter-patient variability present for this outcome. Indeed, inter-patient differences are not improbable given the complex nature and varied clinical
presentation of CF disease, meaning further comment on the responses shown in Figure 1 may be of clinical interest. Patient A, who has a left shift on the $\Delta$[HHb] response, is a physically mature boy with few complications and excellent lung function. In contrast, patient B (also male), whose $\Delta$[HHb] response is shifted to the right has poorer lung function, a worse chest x-ray score, nutritional concerns, and complications including CF related liver disease and impaired glucose tolerance. This is reflected in patient B having received 28 days of intravenous antibiotics, which signifies treatment intensification, within the preceding year. However, despite patient B’s poorer clinical profile, his $\dot{V}O_{2\text{max}}$ is markedly higher than patient A (49.4 vs. 32.6 mL·kg$^{-1}$·min$^{-1}$), which may have played a role in causing the rightward shift in the $\Delta$[HHb] response dynamics. However, it should be noted that we only found a small relationship between $\dot{V}O_{2\text{max}}$ and [HHb] $c/d$ in the present study.

Interestingly, the present findings of unaltered HHb response dynamics for the group are in line with a previous report by Rosenthal and colleagues (30), who observed similar O$_2$ extraction dynamics during exercise in young CF and their healthy counterparts, despite CF patients presenting with impaired aerobic function. When considered in reference to the Fick equation, these data may therefore suggest the impaired aerobic function is caused by a reduction in O$_2$ delivery. Altered cardiac function (17,28,3) and an inability to augment SV during exercise (30), which are likely to reduce central O$_2$ delivery, have previously been documented in CF and the most likely lower SpO$_2\%$ in the present study provides further support. Although it has been propositioned that CF patients can achieve apparently ‘normal’ cardiac output in the presence of reduced SV during exercise, through elevated HR (17,21), this compensation only appears viable at submaximal exercise intensities, as both CF and CON had similar heart rates at maximal exercise in this study. In accordance with our findings, a reduced (~ 24%) estimated SV (using
respiratory mass spectroscopy) at maximal exercise in young CF patients coupled with a similar HR response to healthy controls has previously been documented (30).

Although it has been hypothesised that patients limited by O\textsubscript{2} delivery during exercise would present with a compensatory increase in O\textsubscript{2} extraction at the local level (9), both this study and the previous study by Rosenthal et al. (30), using respiratory mass spectroscopy, observed no augmentation of O\textsubscript{2} extraction in the face of inadequate O\textsubscript{2} delivery during exercise (30). Whilst the previous authors could not determine the cause of this since no direct peripheral measurements were made, it was suggested that muscle metabolic issues resulting from chronic bronchial sepsis may contribute. Importantly, the present study utilising NIRS corroborates the observations of Rosenthal and colleagues (30) using a more direct measurement technique.

The relationships between parameters of aerobic function and mechanistic parameters indicative of O\textsubscript{2} delivery and extraction further emphasise the importance of O\textsubscript{2} delivery in explaining the impaired aerobic function in young CF patients. Although the relationships between key parameters of aerobic function and the rate of peripheral fractional O\textsubscript{2} extraction were small, stronger relationships with parameters of O\textsubscript{2} delivery were evident. Furthermore, whilst SpO\textsubscript{2\%} did not correlate with FFM normalised \( \dot{V}\text{O}_{2\text{max}} \) in healthy controls, a moderate correlation with end-exercise SpO\textsubscript{2\%} was observed in CF patients along with a large relationship between \( \dot{V}\text{O}_{2\text{max}} \) and the O\textsubscript{2} pulse. The relationships between \( \dot{V}\text{O}_{2} \) gain and end-exercise SpO\textsubscript{2\%} and O\textsubscript{2} pulse were also moderate and large, respectively. Similarly, very large relationships were evident between the GET and end-exercise SpO\textsubscript{2\%} and O\textsubscript{2} pulse.

There are a number of limitations of NIRS which must be acknowledged. Firstly, measurements are restricted to a specific area of interrogation over a, in this case, single heterogenous and superficial muscle, which may not represent whole body skeletal muscle blood
flow responses. However, the muscle deoxygenation response measured in the superficial and deeper muscle fibres using NIRS has been shown to reflect muscle oxygenation as measured using phosphorous quenching derived microvascular O$_2$ partial pressure within the same region of muscle (19). Whilst inter-site variation in the HHb response cannot be directly rectified, the device was secured to the same anatomical region for all participants to eradicate inter-individual regional differences within the m. vastus lateralis. Although the influence of adipose tissue at the area of interrogation was not directly determined, in line with recommendations, responses were standardised to the total [HHb] amplitude to provide a physiologic normalisation (4). Finally, the generalisability of these findings should be viewed in light of the small sample of Northern European CF patients recruited for this study.

To conclude, this was the first study to examine the influence of mild-to-moderate CF upon key parameters of aerobic function in paediatric patients. As expected, paediatric patients presented with impaired aerobic fitness compared with their healthy counterparts. Specifically, $\dot{V}O_{2\text{max}}$ and $\dot{V}O_2$ gain were very likely reduced and the MRT likely slowed. However, in contrast to the study hypothesis, NIRS derived [HHb] dynamics during ramp cycling exercise were similar between CF and CON. These findings support the notion of centrally mediated oxygen delivery principally limiting the aerobic function of young CF patients during ramp incremental cycling exercise.
ACKNOWLEDGMENTS / CONFLICTS OF INTEREST

The authors would like to thank the participants who volunteered to be involved and are grateful for the on-going support from the CF team at the Royal Devon & Exeter NHS Foundation Trust Hospital. This study was funded by a grant from the Royal Devon & Exeter NHS Foundation Trust. Results of the present study do not constitute endorsement of the American College of Sports Medicine and there are no conflicts of interest.
REFERENCES


FIGURES

**Figure 1.** Sigmoid models of normalised muscle deoxygenation ($\% \Delta [\text{HHb}]$) during ramp incremental exercise as a function of percentage peak oxygen uptake for 2 representative young cystic fibrosis patients (● black circles) of the leftward and rightward response patterns and their healthy age- and gender-matched control participants (dashed line; ○ white circles).

**Figure 2.** The relationship between maximal oxygen uptake ($\bar{V}O_{2\text{max}}$) and end-exercise arterial oxygen saturation ($SpO_{2\text{e}}$) and the maximal oxygen pulse in young cystic fibrosis patients.
Figure 1

A

CF patient: 13.9 y male
Weight: 85.5 kg
Height: 1.73 m
BMI: 28.6 kg/m²
FEV₁: 97% predicted
Normal glycaemic control
No CFRLD
Northern score: 4
Intermittent Pseudomonas Aeruginosa
IVAB days in last year: 0

B

CF patient: 16.1 y male
Weight: 44.0 kg
Height: 1.51 m
BMI: 19.3 kg/m²
FEV₁: 69% predicted
Impaired glucose tolerance
CFRLD
Northern score: 6
Free from Pseudomonas Aeruginosa
IVAB days in last year: 28

N.B. [HHb], concentration of deoxyhaemoglobin (and myoglobin); CFRD, CF-related diabetes; CFRLD, CF-related liver disease; IVAB, intravenous antibiotics.
Figure 2

A

SpO₂ (%) vs. VO₂max (mL·kg⁻¹·min⁻¹)

B

O₂ pulse (mL·beat⁻¹) vs. VO₂max (mL·kg⁻¹·min⁻¹)

r = 0.33, ±0.51

r = 0.58, ±0.41
TABLES

**Table 1.** Baseline anthropometric and pulmonary function data for young CF patients \((n = 10, 1\text{ female})\) and healthy age- and gender-matched controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CF (Mean ± SD)</th>
<th>CON (Mean ± SD)</th>
<th>Change, 90% CL</th>
<th>Inference (in CF)</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>12.7 ± 2.8</td>
<td>12.5 ± 2.8</td>
<td>0.2, ±2.2</td>
<td>Unclear</td>
<td>0.07</td>
</tr>
<tr>
<td>Stature (m)</td>
<td>1.53 ± 0.15</td>
<td>1.58 ± 0.19</td>
<td>-0.05, ±0.14</td>
<td>Unclear</td>
<td>-0.25</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>53.2 ± 20.0</td>
<td>50.5 ± 17.4</td>
<td>2.7, ±14.6</td>
<td>Unclear</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI (kg·m(^2))</td>
<td>22.0 ± 4.6</td>
<td>19.5 ± 2.7</td>
<td>2.4, ±3.0</td>
<td>Likely higher</td>
<td>0.60</td>
</tr>
<tr>
<td>BSA (m(^2))</td>
<td>1.51 ± 0.35</td>
<td>1.48 ± 0.35</td>
<td>0.03, ±0.27</td>
<td>Unclear</td>
<td>0.08</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>42.0 ± 14.6</td>
<td>41.3 ± 14.0</td>
<td>0.6, ±11.1</td>
<td>Unclear</td>
<td>0.04</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.36 ± 1.30</td>
<td>3.69 ± 1.33</td>
<td>-0.33, ±1.03</td>
<td>Unclear</td>
<td>-0.24</td>
</tr>
<tr>
<td>FVC [% predicted] (range)</td>
<td>102 ± 14</td>
<td>106 ± 10</td>
<td>-4, ±10</td>
<td>Unclear</td>
<td>-0.28</td>
</tr>
<tr>
<td>FEV(_1) (L)</td>
<td>2.69 ± 1.12</td>
<td>3.18 ± 1.18</td>
<td>-0.49, ±0.89</td>
<td>Unclear</td>
<td>-0.41</td>
</tr>
<tr>
<td>FEV(_1) [% predicted] (range)</td>
<td>97 ± 22</td>
<td>107 ± 10</td>
<td>-10, ±14</td>
<td>Likely lower</td>
<td>-0.55</td>
</tr>
</tbody>
</table>

Values are means ± SD. ES; Effect size; CI, confidence intervals; BMI, body mass index; FFM, fat-free mass (calculated using the equation of Slaughter et al. (33); FVC, forced vital capacity; FEV\(_1\), forced expiratory volume in 1 second. N.B. Parameters of pulmonary function are expressed as a percentage predicted normal using appropriate reference data (34).
Table 2. Baseline clinical characteristics for the young CF patients (n = 10, 1 female).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (mean ± SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFTR genotype:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygote ΔF508 (Class II mutation)</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>ΔF508/ 2184delA (Class II mutations)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>ΔF508/ G55ID (Class II/III mutations)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Chronic P. Aeruginosa infection (^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;chronic,&quot; n = 2;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;intermittent,&quot; n = 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;never,&quot; n = 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shwachman score</td>
<td>81 ± 7</td>
<td>67-91</td>
</tr>
<tr>
<td>Northern score (^b)</td>
<td>4 ± 1</td>
<td>2-6</td>
</tr>
<tr>
<td>Pancreatic insufficient</td>
<td>n = 10</td>
<td></td>
</tr>
<tr>
<td>CF-related diabetes</td>
<td>n = 3</td>
<td>-</td>
</tr>
<tr>
<td>CF-related liver disease</td>
<td>n = 3</td>
<td>-</td>
</tr>
<tr>
<td>IVABs (days in last year)</td>
<td>10 ± 15</td>
<td>0-42</td>
</tr>
</tbody>
</table>

Values are means ± SD, unless otherwise stated.

CFTR, cystic fibrosis transmembrane conductance regulator; P. Aeruginosa; Pseudomonas Aeruginosa; Shwachman score - scoring 4 separate aspects of the disease profile; general activity; physical examination; nutritional status; and chest radiographic findings, using the most recent clinical review information. A total of 100 points represents a perfect score of health; IVABs, intravenous antibiotics; \(^a\)According to Leeds Criteria, “chronic”, >50% of the preceding 12 months were P. aeruginosa culture positive; “intermittent”, ≤50% of the preceding 12 months were P. aeruginosa culture positive; “never”, no growth of P. aeruginosa for the previous 12 months, having previously been P. aeruginosa culture positive; “free”, P. aeruginosa has never been cultured.

\(^b\) Provides evidence of radiographic chest findings. Maximum score is 20, with 20 being the most severe.
Table 3. Maximal and submaximal physiologic responses of young CF patients and healthy age- and gender-matched controls to ramp incremental cycle exercise.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CF (Mean ± SD)</th>
<th>CON (Mean ± SD)</th>
<th>Change, 90% CI</th>
<th>Inference (in CF)</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximal exercise parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute $\dot{V}O_{2\text{max}}$ (L·min$^{-1}$)</td>
<td>1.93 ± 0.84</td>
<td>2.21 ± 0.79</td>
<td>-0.29, ±0.63</td>
<td>Unclear</td>
<td>-0.34</td>
</tr>
<tr>
<td>Relative $\dot{V}O_{2\text{max}}$ (mL·kg$^{-1}$·min$^{-1}$)</td>
<td>36.3 ± 7.6</td>
<td>43.9 ± 5.2</td>
<td>-7.6, ±5.1</td>
<td>Very likely lower</td>
<td>-1.11</td>
</tr>
<tr>
<td>$\dot{V}O_{2\text{max}}$/FFM (mL·kg$^{-1}$·min$^{-1}$)</td>
<td>45.5 ± 9.1</td>
<td>53.5 ± 6.4</td>
<td>-7.9, ± 6.1</td>
<td>Very likely lower</td>
<td>-0.96</td>
</tr>
<tr>
<td>$\dot{V}E_{\text{max}}$ (L·min$^{-1}$)</td>
<td>84.27 ± 33.07</td>
<td>99.31 ± 39.95</td>
<td>-15.04, ±28.53</td>
<td>Unclear</td>
<td>-0.39</td>
</tr>
<tr>
<td>HR$_{\text{max}}$ (beats·min$^{-1}$)</td>
<td>192 ± 11</td>
<td>190 ± 13</td>
<td>2, ±10</td>
<td>Unclear</td>
<td>0.18</td>
</tr>
<tr>
<td>$\dot{V}O_{2}$/HR$_{\text{max}}$ (mL·beat$^{-1}$)</td>
<td>9.78 ± 4.71</td>
<td>11.01 ± 3.39</td>
<td>-1.23, ±3.41</td>
<td>Unclear</td>
<td>-0.28</td>
</tr>
<tr>
<td>SpO$_2$ (%)</td>
<td>95 ± 2</td>
<td>97 ± 1</td>
<td>-3, ±1</td>
<td>Most likely lower</td>
<td>-1.63</td>
</tr>
<tr>
<td>Ramp PPO (W)</td>
<td>176 ± 94</td>
<td>205 ± 82</td>
<td>-30, ±69</td>
<td>Possibly lower</td>
<td>-0.32</td>
</tr>
<tr>
<td>Relative ramp PPO (W·kg$^{-1}$)</td>
<td>3 ± 1</td>
<td>4 ± 1</td>
<td>-0.7, ±0.5</td>
<td>Likely lower</td>
<td>-0.84</td>
</tr>
<tr>
<td>RPE</td>
<td>9 ± 2</td>
<td>6 ± 2</td>
<td>3, ±2</td>
<td>Most likely higher</td>
<td>1.46</td>
</tr>
<tr>
<td>RPD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Submaximal exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\dot{V}O_2$ at the GET (L·min$^{-1}$)</td>
<td>1.13 ± 0.41</td>
<td>1.20 ± 0.30</td>
<td>-0.07, ±0.28</td>
<td>Unclear</td>
<td>-0.20</td>
</tr>
<tr>
<td>GET$<em>{%}$ (% of $\dot{V}O</em>{2\text{max}}$)</td>
<td>61.3 ± 10.2</td>
<td>56.7 ± 8.4</td>
<td>4.6, ±7.3</td>
<td>Unclear</td>
<td>0.47</td>
</tr>
<tr>
<td>MRT (s)</td>
<td>49 ± 21</td>
<td>38 ± 11</td>
<td>11, ±13</td>
<td>Likely slower</td>
<td>0.63</td>
</tr>
<tr>
<td>$\Delta \dot{V}O_2/\Delta W$ (mL·min$^{-1}$·W$^{-1}$)</td>
<td>7.62 ± 1.67</td>
<td>9.05 ± 1.17</td>
<td>-1.44, ±1.12</td>
<td>Very likely lower</td>
<td>-0.95</td>
</tr>
</tbody>
</table>

Values are means ± SD.

$\dot{V}O_{2\text{max}}$, maximal oxygen uptake; $\dot{V}E_{\text{max}}$, maximal minute ventilation; MVV, maximal voluntary ventilation; HR$_{\text{max}}$, maximal heart rate; $\dot{V}O_2$/HR$_{\text{max}}$, maximal oxygen pulse; SpO$_2\%$, end-exercise arterial oxygen saturation measured at the fingertip; PPO, peak power output; RPE, end-exercise rating of perceived exertion; RPD, end-exercise rating of perceived dyspnoea; GET, non-invasive estimate of the lactate threshold which was verified by the ventilatory threshold; GET$_{\%}$, GET expressed as a percentage of $\dot{V}O_{2\text{max}}$; MRT, mean response time; $\Delta \dot{V}O_2/\Delta W$, oxygen cost of exercise (efficiency); $\dot{V}E/\dot{V}CO_2$-slope, ventilatory drive.
Table 4. Parameter estimates for normalised muscle deoxygenation (Δ[HHb]) as a function of absolute and percentage peak power output during ramp incremental cycling and the absolute and normalised ratio of HHb-to-pulmonary oxygen uptake above and below the GET and at exhaustion.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter expressed function of</th>
<th>CF (n = 9) (Mean ± SD)</th>
<th>CON (n = 9) (Mean ± SD)</th>
<th>Change, 90% CI</th>
<th>Inference (in CF)</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (%)</td>
<td>PPO</td>
<td>100.1 ± 18.0</td>
<td>96.1 ± 8.1</td>
<td>4.0, ±11.8</td>
<td>Unclear</td>
<td>0.27</td>
</tr>
<tr>
<td>d (%·W⁻¹)</td>
<td>PPO</td>
<td>0.1 ± 0.1</td>
<td>0.1 ± 0.0</td>
<td>0.0, ±0.1</td>
<td>Unclear</td>
<td>0.40</td>
</tr>
<tr>
<td>c/d (W)</td>
<td>PPO</td>
<td>98 ± 52</td>
<td>112 ± 54</td>
<td>-14, ±44</td>
<td>Unclear</td>
<td>-0.25</td>
</tr>
<tr>
<td>A (%)</td>
<td>%PPO</td>
<td>100.0 ± 17.8</td>
<td>96.1 ± 8.1</td>
<td>3.9, ±11.7</td>
<td>Unclear</td>
<td>0.26</td>
</tr>
<tr>
<td>d (%·%peak⁻¹)</td>
<td>%PPO</td>
<td>0.1 ± 0.1</td>
<td>0.1 ± 0.0</td>
<td>0.0, ±0.0</td>
<td>Unclear</td>
<td>0.16</td>
</tr>
<tr>
<td>c/d (%peak)</td>
<td>%PPO</td>
<td>47.1 ± 17.8</td>
<td>47.7 ± 9.1</td>
<td>-0.7, ±12.0</td>
<td>Unclear</td>
<td>-0.04</td>
</tr>
<tr>
<td>A (%)</td>
<td>ÛO₂max</td>
<td>88.2 ± 10.2</td>
<td>93.6 ± 6.8</td>
<td>-5.4, ±7.2</td>
<td>Likely lower</td>
<td>-0.59</td>
</tr>
<tr>
<td>d (%·L⁻¹)</td>
<td>ÛO₂max</td>
<td>13.3 ± 16.4</td>
<td>6.9 ± 4.3</td>
<td>6.3, ±10.4</td>
<td>Unclear</td>
<td>0.48</td>
</tr>
<tr>
<td>c/d (L)</td>
<td>ÛO₂max</td>
<td>1.27 ± 0.51</td>
<td>1.36 ± 0.52</td>
<td>-0.10, ±0.43</td>
<td>Unclear</td>
<td>-0.18</td>
</tr>
<tr>
<td>A (%)</td>
<td>%ÛO₂max</td>
<td>91.6 ± 9.0</td>
<td>93.5 ± 6.8</td>
<td>-1.9, ±6.6</td>
<td>Unclear</td>
<td>-0.23</td>
</tr>
<tr>
<td>d (%·%max⁻¹)</td>
<td>%ÛO₂max</td>
<td>0.2 ± 0.1</td>
<td>0.1 ± 0.0</td>
<td>0.0, ±0.1</td>
<td>Unclear</td>
<td>0.38</td>
</tr>
<tr>
<td>c/d (%max)</td>
<td>%ÛO₂max</td>
<td>66.9 ± 8.5</td>
<td>63.6 ± 5.7</td>
<td>3.3, ±6.0</td>
<td>Unclear</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Values are means ± SD unless otherwise stated. CF, cystic fibrosis; CON, healthy age- and gender-matched controls; A, amplitude of the change in the deoxygenated haemoglobin (Δ[HHb]) response; d, slope of sigmoid; c, constant that is dependent upon d and where c/d x-value corresponding to 50% A, respectively; sub-GET, mean for exercise performed below the gas exchange threshold (GET); supra-GET, mean for exercise performed above the GET; end-ex., final 60 s of the exhaustive ramp test; PPO, peak power output; ÛO₂max, maximal oxygen uptake. N.B. Due to technical issues [HHb] data is presented for 9 matched pairs.