REPRODUCIBILITY OF MAXIMAL CARDIOPULMONARY EXERCISE TESTING FOR YOUNG CYSTIC FIBROSIS PATIENTS

Running head: Reproducibility of CPET for young CF patients

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2. Williams, C. A., **Saynor, Z. L.,** Barker, A. R. & Oades, P. J. The reliability of maximal cardiopulmonary exercise testing for young cystic fibrosis patients. *J Cyst Fibros*, 2012;11(Suppl 1):S35.

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ABSTRACT

Background: The reproducibility of cardiopulmonary exercise testing (CPET) has not been established in young cystic fibrosis (CF) patients using a valid protocol.

Methods: Thirteen 7-18 year olds completed three CPETs, separated by 48 h and 4-6 weeks. CPET involved a ramp-incremental cycling test with supramaximal verification.

Results: Maximal oxygen uptake was repeatedly determined with no learning effect and typical errors expressed as a coefficient of variation ($TE_{CV\%}$) of 9.3% (48 h) and 13.3% (4-6 weeks). The reproducibility of additional parameters of aerobic function [gas exchange threshold ($TE_{CV\%}$: 11.2%, 16.8%); $\dot{V}O_2$ mean response time ($TE_{CV\%}$: 37.8%, 89.4%); $\dot{V}O_2$ gain ($TE_{CV\%}$: 17.4%, 24.5%)] and clinical utility [e.g. $SpO_{2\%}$ ($TE_{CV\%}$: 2.2%, 3.1%); ventilatory drive ($\dot{V}_E/\dot{V}CO_2$-slope) ($TE_{CV\%}$: 7.8%, 17.7%)] was also established over the short- and medium-term, respectively.

Conclusion: These results establish limits of variability to determine meaningful changes over the short- and medium-term for CPET outcomes in young CF patients.

Keywords: Cystic fibrosis; exercise testing; maximal oxygen uptake; cardiorespiratory fitness; reproducibility.

INTRODUCTION

A cardiopulmonary exercise test (CPET) is considered the 'gold-standard' method for evaluating aerobic fitness [maximal oxygen uptake ($\dot{V}O_{2max}$)] in patients with mild-to-moderate cystic fibrosis (CF). The European CF Society (ECFS) Exercise Working Group recently promoted CPET as *the* exercise testing method of choice for this patient group. Moreover, the ECFS Clinical Trials Network Standardisation Committee has called for assessment of the validity, reproducibility and feasibility of outcome measures utilised in CF and advocated research into the most appropriate exercise test for paediatric patients[1].

Recently, our research group presented a combined incremental and supramaximal (S_{max}) verification CPET protocol, which is superior at determining valid $\dot{V}O_{2max}$ in young CF patients compared to a ramp only protocol[2]. $\dot{V}O_{2max}$ is currently the principle outcome from a CPET, as it has been shown to be an independent predictor of CF patient mortality[3]. However, a more comprehensive evaluation of patients' cardiorespiratory fitness may be gained from CPET, through the quantification of submaximal parameters of aerobic (lactate threshold (LT), the kinetics of $\dot{V}O_2$ and work efficiency) and ventilatory ($\dot{V}_E/\dot{V}CO_2$-slope and oxygen uptake efficiency slope (OUES)[4]) function. Submaximal outcomes may be especially useful in the clinical environment, as patients may not be able or willing to provide a maximal effort.

Unfortunately, insufficient data exists regarding the reproducibility of CPET in CF patients and that which does exist has utilised testing protocols which cannot verify a 'true' maximal effort[e.g.5,6]. Moreover, the only paediatric study to address this issue[5] did not measure $\dot{V}O_{2max}$. Quantifying reproducibility enables researchers and clinicians to understand the variation associated with outcome measures[7] and to determine meaningful changes[8]. Consequently, inferences regarding therapeutic interventions or disease-related changes in CPET derived parameters cannot currently be discerned with certainty in these patients.

Therefore, this study sought to establish the short- (48 h) and medium-term (4-6 weeks) reproducibility of maximal and submaximal indicators of cardiorespiratory fitness using our recently validated CPET protocol.

MATERIAL and METHODS

Study population. Thirteen young patients (Table 1) with mild-to-moderate CF were recruited from outpatient CF clinics at the Royal Devon and Exeter NHS Foundation Trust Hospital (RD&E). Inclusion criteria comprised a CF diagnosis based on clinical features, sweat chloride > 60 mmol·L^{-1} / 100 mg and genotyping. Stable lung function within 10% of best in the preceding 6 months and no increase in symptoms or weight loss 2 weeks prior to testing was obligatory. Unstable non-pulmonary comorbidities or acute infections warranted exclusion. Disease severity was graded using the Schwachman score[9] and routine clinical measurements obtained as part of patients' annual review by their multidisciplinary CF clinical care team (Table 1). Ethics approval was granted by the South West NHS Research Ethics Committee and written informed consent and assent obtained from parents/guardians and patients, respectively. Patients arrived at the laboratory in a rested state, at least 2 h post-prandial and having refrained from caffeine for > 2 h. All patients were instructed to continue maintenance medications as usual throughout the duration of their study involvement.

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, at each visit. Skin folds were measured to the nearest 1 mm on the right-hand side of the body at the biceps brachii, tricep, subscapula and suprailiac regions (Harpenden; British Indicators, Burgess Hill, UK). Forced vital capacity (FVC) and forced expiratory volume in 1-s (FEV_1) were also assessed at each

visit to the laboratory, using flow-volume loop spirometry (MicroMedical MicroLoop 3535, Numed, Sheffield, UK). The best of three consistent exhalations (< 5% variability) was recorded, in accordance with the British Thoracic Society (1994) guidelines. All lung function measurements were expressed as a percentage predicted normal, using appropriate reference data[10].

Exercise testing protocol. Following familiarisation, exercise was performed on a cycle ergometer [Lode Excalibur or Lode Corival, Groningen, The Netherlands]. The experimental protocol was identical to our previous study[2], using combined exhaustive ramp-incremental and S_{max} verification tests. Following 3-min warm-up (20 W), patients completed an incremental ramp cycling test, whereby resistance increased at a predetermined rate (10-25 $W \cdot min^{-1}$). Ramp rate was dependent on patients' age, height and fitness level, to elicit ~8-12 minute test durations. Patients maintained ~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 (20 W cycling) and 10-min passive seated recovery followed. S_{max} verification of $\dot{V}O_{2max}$ was then performed, whereby 3-min warm-up (20 W) preceded a 'step' transition to a constant work rate equivalent to 110% peak power output. This work rate was maintained until voluntary exhaustion. Five minutes active recovery (20 W cycling) completed the CPET.

Following test one (T_1), all procedures were repeated 48 h (short-term; T_2) and 4-6 weeks (medium-term; T_3) later, at a similar time of day. Medium-term clinical stability was monitored T_1-T_3, with disease considered unstable if a pulmonary exacerbation developed, a change in pulmonary medications was required, chest signs on physical examination altered, or a ≥10% decline in pulmonary function was recorded.

Experimental measures. *Gas analysis.* Prior to each test, the metabolic cart (Metalyzer 3B Cortex, Biophysik, Leipzig, Germany) was calibrated using gases of known concentration, and the turbine volume transducer using a 3 L calibration syringe (Hans Rudolph, Kansas City, MO). Breath-by-breath pulmonary gas exchange and ventilation were measured and averaged to 15-s time bins. The highest 15-s stationary average $\dot{V}O_2$ from the ramp and S_{max} protocols[2] represented $\dot{V}O_{2max}$.

Submaximal gas exchange parameters. The LT was non-invasively identified using the gas exchange threshold (GET)[11] and confirmed through visual inspection of the ventilatory equivalents for $\dot{V}O_2$ and $\dot{V}CO_2$[12]. The $\dot{V}O_2$ mean response time (MRT) was determined using the time from the onset of the ramp test to the intersection point between the baseline $\dot{V}O_2$ and a backwards extrapolation of the slope of $\dot{V}O_2$ as a function of time. The $\dot{V}O_2$ 'gain' ($\Delta\dot{V}O_2/\Delta$ WR) was determined by regression of the 'linear' portion of the $\dot{V}O_2$ response against power output. The OUES for the entire exercise duration ($OUES_{100}$) and up to the GET ($OUES_{GET}$) were derived from the slope of the linear function between $\dot{V}O_2$ ($mL \cdot min^{-1}$) and log $\dot{V}_E$ ($L \cdot min^{-1}$)[4]. The $\dot{V}_E/\dot{V}CO_2$–slope (ventilatory drive) was calculated using linear regression during the entire CPET[13].

Additional measures: Heart rate (HR) was determined every 5-s (PhysioFlow, PF-05, Manatec Biomedical, Paris, France), with the highest 15-s value taken as peak HR (HR_{peak}). Fingertip arterial O_2 saturation ($SpO_{2\%}$) was measured on a beat-by-beat basis via pulse oximetry (NONIN, Avant 4000, NONIN Medical Inc., USA). Subjective ratings of perceived exertion (RPE) and dyspnoea (RPD) were recorded 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[2].

Analysis. Data are expressed as means and standard deviations unless otherwise stated. Reproducibility was assessed using a downloadable spreadsheet[14]. Following initial analyses to ensure distribution normality and heteroscedasticity, paired samples *t*-tests examined differences between tests with significance set at $p < 0.05$. Change in the mean, intraclass correlation coefficients (ICCs), absolute typical error (TE) and TE expressed as a percentage of the coefficient of variation ($TE_{CV\%}$), were calculated (with 90% confidence limits) for short- (T_1-T_2) and medium-term (T_1-T_3) pairwise comparisons.

RESULTS

One patient was lost to follow-up at T_3, due to reasons unrelated to the study. Table 1 summarises patients' (n=13) baseline physical characteristics. Clinical stability was defined by symptoms, changes in patients' treatment, spirometric variables and body mass over the course of the study (T_1-T_3). All patients remained clinically stable and with no change in symptoms, treatment, body mass [50.89 (17.26) vs. 50.98 (17.17) kg; p = 0.63], BMI [21.23 (7.79) vs. 21.18 (7.61) kg·m^2; p = 0.97] or lung function [FVC: 3.12 (1.08) vs. 3.03 (1.04) L; p = 0.10; FEV_1: 2.53 (0.88) vs. 2.48 (0.87) L; p = 0.10]. Stability predated T_1 (i.e. recruitment) and was maintained beyond T_3.

Maximal and submaximal physiological responses from the CPET are presented in Table 2. Short- (T_1-T_2) and medium-term (T_1-T_3) reproducibility data from CPET derived measures are presented in Tables 3 and 4 respectively. The reproducibility for $\dot{V}O_{2max}$ is presented in Figure 1. The GET and $OUES_{GET}$ were identifiable in all patients at T_1 and 12 (92%) patients at T_2 and T_3. MRT was detected in 11 (85%) patients from T_1-T_3.

When compared with this combined approach (ramp and S_{max}), $\dot{V}O_{2max}$ obtained using the traditional ramp only method was significantly lower at both T_2 [1.76 (0.56) vs. 1.63

(0.52) L·min^{-1}; p = 0.01] and T_3 [1.69 (0.55) vs. 1.62 (0.54) L·min^{-1}; p = 0.07], with a trend towards significance at T_1 [1.77 (0.57 vs. 1.68 (0.56) L·min^{-1}; p = 0.07], as has been previously demonstrated[2]. Moreover, $\dot{V}O_{2max}$ using the combined approach was also associated with smaller error over both the short- [TE: 0.15 (0.12-0.23) vs. 0.23 (0.17-0.38) L·min^{-1}; $TE_{CV\%}$: 9.3 (6.9-14.3) vs. 13.5 (9.5-23.3) %] and medium-term [TE: 0.16 (0.12-0.25) vs. 0.19 (0.14-0.32) L·min^{-1}; $TE_{CV\%}$: 13.3 (9.9-20.9) vs. 15.5 (10.9-26.9) %] when compared with a ramp test in isolation.

DISCUSSION

The principle finding of this study was that CPET was reproducible when determining $\dot{V}O_{2max}$ [short-term (T_1-T_2) ICC: 0.94; medium-term (T_1-T_3) ICC: 0.93], with no significant learning effect and short- and medium-term TEs of 150 mL (Δ9%) and 160 mL (Δ13.3%). Of the additional maximal parameters, HR (3.2%, 7.8%), SaO_2% (2.2%, 3.1%) and RPE (7.8%, 7.6%) appear to hold acceptable short- and medium-term reproducibility, respectively. Submaximal measures were identifiable in most cases, with the $\dot{V}_E/\dot{V}CO_2$-slope (7.8%), $\dot{V}_E/\dot{V}CO_2$ at the GET (8.8%), $\dot{V}_E/\dot{V}O_2$ at the GET (10.2%), the GET (11.2%) and $OUES_{100}$ (12.0%) demonstrating promising reproducibility over 48 h. However, an increased $TE_{cv\%}$ was observed for submaximal parameters at 4-6 weeks, with three ($\dot{V}O_2$ gain, $OUES_{GET}$, $\dot{V}O_2$ MRT) TEs increasing above 20% (24.5%, 45.4%, 89.0%, respectively). Excluding the latter two variables ($OUES_{GET}$ and $\dot{V}O_2$ MRT), good short- and medium-term agreement was observed for all measures, highlighting the potential for CPET outcomes to be used to monitor disease progression and/or the effect of therapeutic interventions.

Our data contribute significantly to the literature because the reproducibility of $\dot{V}O_{2max}$ has not been established in CF using a valid protocol. Reproducibility over time is crucial when evaluating the efficacy of treatments (e.g. antimicrobials, mucolytics and gene mutation

targeted therapies) which may accrue over weeks or months, as well as monitoring exercise training interventions (4-6 weeks). To our knowledge, only one study has examined the reproducibility of S_{max} verified (treadmill) $\dot{V}O_{2peak}$ in a paediatric clinical population[15], reporting an 8.2% (100 mL) variation in young spina bifida patients over a 2 week period. Using a solitary traditional ramp test, variations of 6.9%[6] and 8.5%[16] have been reported over 4 weeks in CF adults for $\dot{V}O_{2peak}$. The reproducibility estimate for $\dot{V}O_{2max}$ in the present study is therefore similar (9.3% and 13.3%) to these earlier studies[6,16] and confirms CPET as a reproducible assessment tool. Whilst the compromised validity of performing traditional ramp tests, such as the popular Gofrey protocol, in isolation has previously been demonstrated[2] and substantiated herein, the present study in paediatric CF patients also highlights a larger within-subject variation in $\dot{V}O_{2max}$ over both the short- (13.5 vs. 9.3 %) and medium-term (15.5 vs. 13.3 %) when compared with the combined ramp and S_{max} approach. Only one study[5] has previously investigated CPET reproducibility in CF children, but is limited due to methodological concerns. Firstly, only three outcome measures (peak power output, $SaO_{2\%}$ and HR) were obtained, offering limited interpretation of aerobic fitness. Moreover, an intermittent sprint cycle test preceded the ramp test, which likely caused fatigue and may explain, in part, their low ramp test duration (~4 min).

Outcome measures which can assess patients' ability to perform at intensities similar to activities of daily living are also important. Submaximal measures hold specific value when maximal exercise performance is limited by ventilatory capacity and/or effort[2,4]. Furthermore, the GET can improve independent of $\dot{V}O_{2max}$[e.g.12,17] and facilitates the identification of individualised exercise intensities within specific intensity domains (i.e. at a %GET or %Δ) for young CF patients[e.g.18]. The present study employed a cluster of measures and two independent observers to identify the GET in 12 of 13 (92%) patients for all tests, with TE of 11.2% (or 110 mL) and 16.8% (or 140 mL) over the short- and medium-

term, respectively. Using similar methodology, our laboratory has previously reported a similar GET detection rate (100%) in healthy children, with a reproducibility estimate of ~8%[19]. The present findings challenge previous reports suggesting difficulties in non-invasively detecting the GET and ventilatory threshold in patients with chronic respiratory disease and airflow limitation[e.g.20], likely due to the mild disease severity and subsequently normal ventilatory drive of our patients. The $\dot{V}O_2$ gain was associated with reasonable TE of 17.4% and 24.5% over the short- and medium-term, respectively. The $\dot{V}O_2$ MRT was associated with considerably greater short- (37.8%) and medium-term (89.4%) variation. These submaximal measures, especially the MRT, may therefore be less useful than the GET.

Ventilatory efficiency is best described by relating $\dot{V}O_2$ and $\dot{V}CO_2$ dynamics to $\dot{V}_E$[21]. The $\dot{V}_E$-$\dot{V}O_2$ relationship is optimally described through the OUES[21], which is theoretically resistant to early test termination and intra- and inter-observed variability[22]. In the current study, $OUES_{100}$ was detectable in all tests and the $OUES_{GET}$ detectable in all patients at T_1 and 92% at T_2 and T_3. Short- and medium-term TEs of 12.0% and 15.3% were associated with the $OUES_{100}$, compared with 8.3% documented in adult CF patients over a 4 week period[16]. Similar variations of 7.8% and 17.7% were documented for the $\dot{V}_E/\dot{V}CO_2$-slope in the present study. As the $OUES_{GET}$ was associated with increased short- (17.9%) and medium-term (45.4%) error and lower detection rate compared to the $OUES_{100}$, the $OUES_{100}$ appears a more robust outcome measure.

The present study provides the reproducibility for maximal and submaximal parameters over the short- and medium-term. Our data denote that $\dot{V}O_{2max}$ changes exceeding 9% (150 mL) and 13% (160 mL) may indicate a change attributable to therapeutic intervention or disease progression over the short- and medium-term, respectively. The TE

must, however, be considered relative to an established smallest worthwhile change (SWC), to estimate how many participants are needed to observe a 'meaningful' effect[7,8,24].

Using Hopkins' formula[7] for the estimation of sample size [$n=8(CV^2/d^2)$], *CV* and *d* can be substituted for TE and SWC, respectively. While the present study has documented the *CV*, the value of *d* is uncertain for CPET outcomes in CF. Cox and Elkins[23] recently raised concerns regarding how 'clinically worthwhile' exercise training interventions are for patients with CF, given that the SWC for outcome measures had yet to be established. However, the mean annual rate of $\dot{V}O_{2max}$ decline could, for example, be used to determine the SWC in $\dot{V}O_{2max}$, since it reportedly predicts CF patient survival[29]. Using Pianosi and colleagues'[29] annual $\dot{V}O_{2max}$ decline and the fitness of our similarly aged patients, a ~6% increase in $\dot{V}O_{2max}$ relative to baseline fitness would be required to prevent a meaningful drop in prognostic stratification. Using 6% as the SWC and a 13.3% TE, 5 patients would be required to detect a change in $\dot{V}O_{2max}$ from a 4-6 week intervention that would be considered meaningful and clinically worthwhile.

Determining the extent to which changes in outcome measurements relate to a given reference measure is essential to the clinical utility of CPET. Responsiveness to intervention has been conceptually described as a signal-to-noise ratio[7,8,24], whereby the TE represents the 'noise' and any intervention-induced effect, the 'signal'. Data concerning $\dot{V}O_{2max}$ responsiveness within CF are sparse[26]. Of the available evidence, studies have reported training-related improvements in $\dot{V}O_{2max}$ ranging from ~10-20%[e.g.26,27,28]. Using our established long-term TE, the aerobic training improvement could be considered meaningful with a signal-to-noise ratio of ~1.5:1.0 for a ~20% improvement, but questionable, with a signal to noise ratio of ~0.8:1.0 for a 10% improvement. Unfortunately, the signal-to-noise ratio for most parameters is unknown. If future intervention studies provided more comprehensive CPET data, this would permit more informed data interpretation, as

researchers could select measurements with higher signal-to-noise ratios, whilst also considering their sensitivity.

Standardising CPET procedures will enable a larger empirical database of CF patients to accumulate and, longitudinally, enhance our understanding of the link between physiological dysfunction during exercise and patients' prognostic stratification. Whilst $\dot{V}O_{2peak}$ possesses recognised prognostic value[3], the $\dot{V}_E/\dot{V}CO_2$-slope and OUES have demonstrated superior prognostic information in other clinical populations[e.g.21,30] and warrant investigation in CF, particularly given that although patients remained clinically stable throughout the present study, increased medium-term noise was associated with submaximal parameters. This may indicate value in detecting subtle clinical changes, which current clinical assessments cannot. CPET to assess therapeutic interventions also requires investigation.

In conclusion, $\dot{V}O_{2max}$ was reproducible over 48-h (Δ150 mL; Δ9.3%) and 4-6 wks (Δ160 mL; Δ13.3%). Supplementary maximal and submaximal parameters should be incorporated to comprehensively assess aerobic function. The present study provides a reproducible CPET protocol for young patients with mild-to-moderate CF and will inform sample size and power calculations when planning interventional studies that use cardiorespiratory fitness as an endpoint.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

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All authors read and approved the manuscript. CAW, ZLS and ARB conceived and designed the study; ZLS and PJO coordinated testing, whilst ZS completed the data collection; ZLS

and ARB analysed the data; CAW, ZS, ARB and PJO partook in data interpretation; ZLS wrote the manuscript and CAW, ARB and PO revised the manuscript; CAW acts as guarantor. This study was supported by a small grant from the RD&E. Gratitude is expressed to the NIHR Exeter Clinical Research Facility, Owen Tomlinson, David Childs and the RD&E CF team for their support throughout. Finally, we would like to thank the patients who kindly volunteered their time to be involved.

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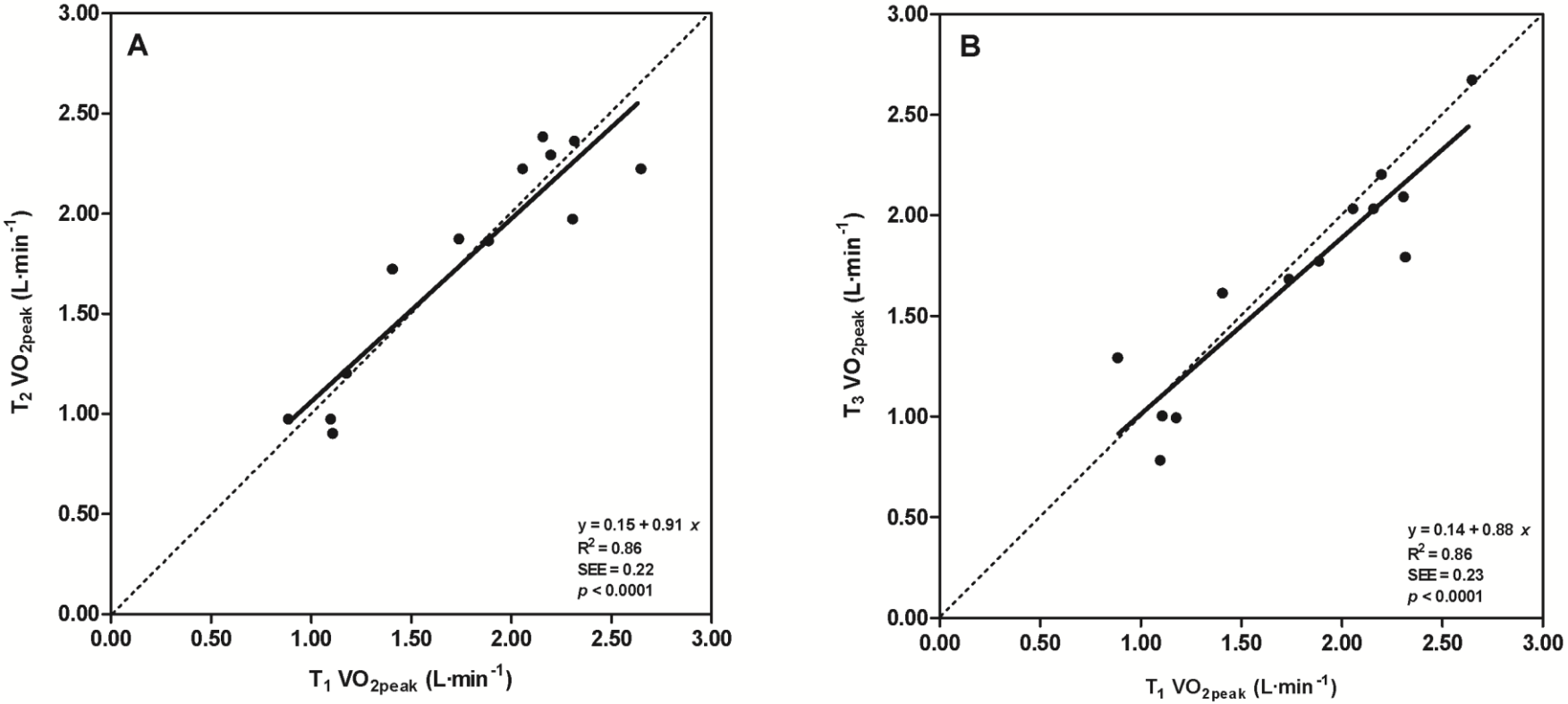
FIGURE LEGENDS

Figure 1. Line of identity plot for $\dot{V}O_{2max}$ over both the short- [48 h (1a)] and medium-term [4-6 weeks (1b)].

Figure 1.


A
B
3.00
2.50
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T2 VO2peak (L·min-1)
T1 VO2peak (L·min-1)
T3 VO2peak (L·min-1)
y = 0.15 + 0.91 x
R2 = 0.86
SEE = 0.22
p < 0.0001
y = 0.14 + 0.88 x
R2 = 0.86
SEE = 0.23
p < 0.0001

TABLES

Table 1. Patients' baseline anthropometric and pulmonary function data upon initiation into the study (*n* = 13; 4 females).

Variable	Value (mean ± SD)	Range
Age (years)	12.81 ± 3.26	7.57-18.44
Stature (m)	1.53 ± 0.16	1.23-1.74
Body mass (kg)	50.89 ± 17.26	24.35-83.50
BMI ($kg \cdot m^2$)	21.18 ± 3.86	14.19-28.24
SSkF (mm)	43 ± 13	24-67
Gender	m = 9, f = 4	-
CFTR genotype:	-	-
Homozygote ΔF508	9	-
ΔF508/P67L	1	-
ΔF508/ 621+IG ➔T	1	-
ΔF508/ 2184delA	1	-
ΔF508/ G55ID	1	-
Chronic P. Aeruginosa infection [a]	"chronic," *n* = 2; "intermittent," *n* = 4	"free," *n* = 5 "never," *n* = 2
Shwachman score	82 ± 6	67-91
Northern score [b]	4 ± 1	2-6
FVC [% predicted (L)]	103.5 ± 15.0 (3.3 ± 1.2)	79.0-127.0 (1.6-5.1)
FEV_1 [% predicted (L)]	91.7 ± 17.8 (2.7 ± 1.0)	65.0-120.0 (1.4-4.1)

Values are means ± SD, with the range also displayed where suitable, unless otherwise stated.
BMI, body mass index; SSkF, sum of skinfolds; 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; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; [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 2. Patients' physiological responses to CPET during the three visits.

Variable	*n*	Test 1	Test 2	Test 3
Maximal exercise parameters	-	-	-	-
$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	13	1.77 (0.57)	1.76 (0.56)	1.68 (0.55)
HR_{peak} ($b \cdot min^{-1}$)	11	190 (12)	186 (14)	186 (19)
SpO_2 (%)	13	95 (3)	96 (1)	96 (3)
RPE	13	9 (2)	9 (2)	9 (1)
RPD	13	7 (3)	6 (3)	8 (3)
Ramp peak power output (W)	13	157 (55)	148 (62)	145 (65)
Submaximal parameters	-	-	-	-
GET ($L \cdot min^{-1}$)	12	1.00 (0.22)	0.93 (0.21)	1.05 (0.29)
MRT (s)	11	42 (15)	65 (17)	54 (26)
$\dot{V}O_2$ gain ($mL \cdot min^{-1} \cdot W^{-1}$)	12	8.01 (1.36)	8.11 (1.22)	7.73 (2.64)
$OUES_{100}$ ($mL \cdot min^{-1} \cdot logL^{-1}$)	12	803 (227)	789 (181)	799 (218)
$OUES_{GET}$ ($mL \cdot min^{-1} \cdot logL^{-1}$)	12	797 (223)	730 (188)	756 (389)
$\dot{V}_E/\dot{V}CO_2$-slope	12	34.13 (4.51)	33.26 (3.25)	32.14 (5.39)
$\dot{V}_E/\dot{V}O_2$ at the GET	12	28.57 (5.45)	28.63 (3.84)	28.09 (4.58)
$\dot{V}_E/\dot{V}CO_2$ at the GET	12	28.07 (3.96)	29.15 (5.43)	27.95 (5.51)

Values are means ± SD, with the range also displayed unless otherwise stated.

$\dot{V}O_{2max}$, maximal oxygen uptake; HR_{peak}, peak heart rate; SpO_2%, end-exercise arterial oxygen saturation; RPE, end-exercise rating of perceived exertion; RPD, end-exercise rating of perceived dyspnoea; ramp; incremental ramp test; GET, non-invasive estimate of the lactate threshold which was verified by the ventilatory threshold; MRT, mean response time; $\dot{V}O_2$ gain, oxygen cost of exercise; $OUES_{100}$, oxygen uptake efficiency slope for the entire duration of the ramp test; $OUES_{GET}$, OUES to the GET; $\dot{V}_E/\dot{V}CO_2$-slope, ventilatory drive; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for oxygen uptake; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide.

Table 3. Short-term (48 h) test-retest reproducibility (T_1-T_2) of CPET derived measures.

Variable	*N*	Change in the mean	*p*-value	TE (90% CL)	$TE_{CV\%}$ (90% CL)	ICC	*p*-value
Lung function	-	-	-	-	-	-	-
FVC (L)	13	0.01	0.79	0.08 (0.05-0.11)	3.1 (2.3-4.7)	1.00	<0.01
FEV_1 (L)	13	-0.02	0.48	0.07 (0.06-0.11)	2.7 (2.0-4.1)	0.99	<0.01
Maximal exercise parameters	-	-	-	-	-	-	-
$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	13	-0.01	0.91	0.15 (0.12-0.23)	9.3 (6.9-14.3)	0.94	<0.01
HR_{peak} ($b \cdot min^{-1}$)	11	-4	0.14	6 (4-9)	3.2 (2.3-5.1)	0.83	<0.01
SpO_2 (%)	13	1	0.42	2 (2-3)	2.2 (1.7-3.4)	0.03	0.91
RPE	13	0.1	0.72	0.5 (0.4-0.8)	7.8 (5.8-12.0)	0.91	<0.01
RPD	13	-1.3	0.09	1.7 (1.3-2.6)	63.7 (45.1-111.0)	0.60	0.05
Ramp peak power output (W)	13	-9	0.11	14 (11.21)	21.6 (16.0-34.6)	0.95	<0.01
Submaximal parameters	-	-	-	-	-	-	-
GET ($L \cdot min^{-1}$)	12	-0.06	0.17	0.11 (0.08-0.16)	11.2 (8.2-17.8)	0.80	<0.01
MRT (s)	11	25	<0.01	13 (10-21)	49.1 (34.4-89.0)	0.65	0.05
$\dot{V}O_2$ gain ($mL \cdot min^{-1} \cdot W^{-1}$)	12	0.10	0.84	1.18 (0.84-2.01)	17.4 (12.0-31.2)	0.18	0.62
$OUES_{100}$ ($mL \cdot min^{-1} \cdot logL^{-1}$)	12	-14.12	0.74	100.85 (75.41-156.39)	12.0 (8.9-19.2)	0.79	<0.01
$OUES_{GET}$ ($mL \cdot min^{-1} \cdot logL^{-1}$)	12	-67.20	0.23	127.89 (95.63-198.31)	17.9 (13.1-39.1)	0.66	0.03
$\dot{V}_E/\dot{V}CO_2$-slope	12	-0.88	0.42	2.54 (1.90-3.94)	7.8 (5.8-12.3)	0.63	0.03
$\dot{V}_E/\dot{V}O_2$ at the GET	12	0.06	0.96	3.19 (2.38-4.94)	10.2 (7.5-16.2)	0.59	0.05
$\dot{V}_E/\dot{V}CO_2$ at the GET	12	1.09	0.32	2.57 (1.92-3.99)	8.8 (6.5-14.0)	0.75	0.01

Values are reported as means (95% confidence limits). TE, typical error; $TE_{CV\%}$, TE expressed as a percentage of the coefficient of variation; ICC, intra-class correlation coefficient. See table 2 for list of abbreviations for exercise outcomes.

Table 4. Medium-term (4-6 weeks) test-retest reproducibility from baseline (T_1-T_3) of CPET derived measures.

Variable	*N*	Change in the mean	*p*-value	TE (90% CL)	$TE_{CV\%}$ (90% CL)	ICC	*p*-value
Lung function	-	-	-	-	-	-	-
FVC (L)	13	-0.08	0.09	0.11 (0.08-0.16)	3.4 (2.6-5.2)	0.99	<0.01
FEV_1 (L)	13	-0.07	0.07	0.08 (0.06-0.12)	3.4 (2.5-5.1)	0.99	<0.01
Maximal exercise parameters	-	-	-	-	-	-	-
$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	13	-0.09	0.21	0.16 (0.12-0.25)	13.3 (9.9-20.9)	0.93	<0.01
HR_{peak} ($b \cdot min^{-1}$)	11	-5	0.49	14 (10-22)	7.8 (5.7-12.7)	0.30	0.38
SaO_2 (%)	13	1	0.60	3 (2-5)	3.1 (2.2-5.2)	-0.28	0.40
RPE	13	0.3	0.22	0.6 (0.5-0.9)	7.6 (5.7-11.8)	0.85	<0.01
RPD	13	0.3	0.68	1.9 (1.4-2.8)	38.5 (27.9-63.8)	0.47	0.13
Ramp peak power output (W)	13	-12	0.05	14 (11-22)	19.8 (14.7-31.6)	0.95	<0.01
Submaximal parameters	-	-	-	-	-	-	-
GET ($L \cdot min^{-1}$)	12	0.05	0.40	0.14 (0.11-0.22)	16.8 (12.3-27.2)	0.74	0.01
MRT (s)	11	16	0.12	22 (16-34)	89.0 (60.1-175.8)	0.25	0.48
$\dot{V}O_2$ gain ($mL \cdot min^{-1} \cdot W^{-1}$)	12	-0.28	0.72	1.85 (1.31-3.15)	24.5 (16.8-45.0)	0.24	0.40
$OUES_{100}$ ($mL \cdot min^{-1} \cdot logL^{-1}$)	12	-4.29	0.92	107.28 (80.21-166.35)	15.3 (11.3-24.7)	0.80	<0.01
$OUES_{GET}$ ($mL \cdot min^{-1} \cdot logL^{-1}$)	12	-40.69	0.61	188.78 (141.15-292.73)	45.4 (32.3-78.6)	0.69	0.01
$\dot{V}_E/\dot{V}CO_2$-slope	12	-2.00	0.32	4.66 (3.49-7.23)	17.7 (12.9-28.7)	0.13	0.71
$\dot{V}_E/\dot{V}O_2$ at the GET	12	-0.47	0.72	3.13 (2.34-4.86)	10.1 (7.4-16.0)	0.66	0.03
$\dot{V}_E/\dot{V}CO_2$ at the GET	12	-0.12	0.90	2.38 (1.78-3.69)	9.4 (6.9-14.9)	0.79	<0.01

Values are reported as means (95% confidence limits). TE, typical error; $TE_{CV\%}$, TE expressed as a percentage of the coefficient of variation; ICC, intra-class correlation coefficient. See table 2 for list of abbreviations for exercise outcomes.