A protocol to determine valid $\dot{V}O_{2max}$ in young cystic fibrosis patients

Abstract

Objectives: Measuring aerobic fitness ($\dot{V}O_{2max}$) via a maximal cardiopulmonary exercise test (CPET) is an important clinical tool in cystic fibrosis (CF). This study sought to establish: (1) the validity of traditional criteria to verify maximal efforts during a ramp CPET; and (2) whether $\dot{V}O_2$ measured during an exhaustive CPET represents a valid $\dot{V}O_{2max}$ in paediatric patients, using a subsequent exhaustive supramaximal (S_{max}) exercise test. **Design.** Cross-sectional. **Method:** Fourteen patients (7-18 y; 10 male) completed an exhaustive ramp test to determine $\dot{V}O_{2max}$. Following 15-min recovery, S_{max} (110% ramp peak power output) was performed. **Results:** Ramp test $\dot{V}O_{2peak}$ was significantly higher than $\dot{V}O_2$ documented at traditional endpoint criteria, including a RER of 1.00 (0.99 ± 0.47 vs. 1.83 ± 0.78 L·min^{-1}, $p < 0.001$) and 1.10 (1.36 ± 0.59 vs. 1.83 ± 0.78 L·min^{-1}, $p < 0.001$), despite 100% of patients satisfying these two criteria. Only 23% and 75% of patients satisfied the 95% age-predicted heart rate (HR) maximum and 180 beats·min^{-1} criteria. Whilst mean ramp and S_{max} $\dot{V}O_{2peak}$ were not significantly different (1.83 ± 0.78 vs. 1.82 ± 0.67 L·min^{-1}; $p = 0.88$), at the individual level S_{max} elicited a 'meaningful' (> 9%) increase in $\dot{V}O_{2peak}$ (range 9.9 – 38.3%) compared with $\dot{V}O_{2peak}$ from the ramp test in 3 of 14 cases (21.4%). **Conclusions:** Traditional criteria significantly underestimate $\dot{V}O_{2max}$ in young CF patients. Conversely, S_{max} can confirm when 'true' $\dot{V}O_{2max}$ is achieved. The use of S_{max} following CPET represents an appropriate method to measure $\dot{V}O_{2max}$ in young CF patients.

Key words: Exercise test; cystic fibrosis; supramaximal verification; physical fitness; paediatric physician; lungs.

Introduction

Exercise testing is a valuable investigative tool in young people with chronic diseases, such as cystic fibrosis (CF). Although lung function traditionally measures disease severity, it cannot accurately predict exercise capacity[17,24]. Current standards for CF management therefore recommend at least annual exercise testing[10], however current provision is unsatisfactory[4,24]. Cardiopulmonary exercise testing (CPET), incorporating measurement of pulmonary gas exchange, provides the most precise measure of exercise capacity [maximal oxygen uptake ($\dot{V}O_{2max}$)] in mild-to-moderate CF. Furthermore, $\dot{V}O_{2max}$ holds suggested value in prognostic stratification of patients[17].

$\dot{V}O_{2max}$ represents the integrated capacity of the pulmonary, cardiovascular and muscular systems to uptake and utilise O_2 during intense exercise and is traditionally identified by a $\dot{V}O_2$ plateau upon exhaustion despite an increasing work rate[20]. Since only a minority of young people display this response[20,4,2], the term $\dot{V}O_{2peak}$ is commonly used, defined as the highest $\dot{V}O_2$ attained during an exhaustive test[4]. To verify a 'maximal effort', reliance therefore falls upon secondary criteria, encompassing subjective indicators of effort (sweating, facial flushing, hyperpnoea) and objective secondary criteria (heart rate (HR), respiratory exchange ratio (RER) and/or blood lactate concentration ($La_{[B]}$)). Unfortunately, most previous studies in CF have not specified their verification criteria. In those which have, there is some disparity, with objective criteria including RER >1.00[13,15] and >1.10[17] and HRs of 180 beats per minute[13,15] and 95% of age-predicted maximum[25,26]. Such criteria are dependent on arbitrary values which often underestimate 'true' $\dot{V}O_{2max}$ and have thus been deemed invalid for healthy children[4] and young spina bifida patients[11]. It is conceivable that secondary criteria are equally unsuitable for young CF patients. Documenting a valid $\dot{V}O_{2max}$ is crucial to the clinical utility of CPET within CF. Accepting submaximal values could distort clinical interpretation and underestimate patients' prognosis, influencing decisions regarding clinical intervention and/or exercise prescription.

It is important that new conceptual advances within exercise physiology continue to be incorporated within clinical practice. A procedure termed the 'verification phase', where CPET is followed by an individualised supramaximal 'step' test to exhaustion (S_{max}), can ensure the valid determination of $\dot{V}O_{2max}$ in healthy children[4], sedentary adults[3], active middle-aged and older adults[19,9] and adolescent spina bifida patients[10]. Supramaximal exercise denotes exercise above the highest peak power achieved during a preceding exhaustive CPET. While S_{max} has been safely implemented in paediatric spina bifida patients[11] and patients with chronic heart failure[8], the utility, safety and feasibility for young CF patients is unknown. The study aimed to establish the validity of CPET derived $\dot{V}O_{2max}$ and the utility of S_{max} to provide a robust measure of $\dot{V}O_{2max}$ in young CF patients. We hypothesised that: 1) traditional verification criteria would significantly underestimate 'true' $\dot{V}O_{2max}$; and 2) the $\dot{V}O_{2max}$ obtained during a traditional incremental ramp test would not significantly differ to that from a subsequent S_{max} verification test, thus providing a valid measure of $\dot{V}O_{2max}$.

Methods

Fourteen young patients (Table 1) with mild-to-moderate CF, regularly partaking in physical activity as is suggested by clinical disease management guidelines, participated in this study. Inclusion criteria comprised a diagnosis of CF based on clinical features, an abnormal sweat test (sweat chloride > 60 $mmol \cdot L^{-1}$ / 100 mg sweat) and genotyping. Stable lung function within 10% of best in the preceding 6 months and no symptomatic increase or weight loss within 2 weeks was mandatory. Unstable non-pulmonary comorbidities and/or acute infection warranted excluded. Disease severity was graded using the Schwachman score (SS) as part of patients' annual clinical review (Table 1). Ethical approval was granted by the South West NHS Research Ethics Committee and informed written consent and assent obtained from parents/guardians and patients, respectively. Body mass was measured to the nearest 0.01 kg and stature to the nearest 0.01 m. Pulmonary function, assessed via spirometry (MicroMedical MicroLoop 3535), determined forced vital capacity (FVC) and forced expiratory volume in 1-s (FEV_1) (Table 1). Pubertal staging was self-assessed (boys ≥10 and girls ≥8 y) according to pubic hair classification[28] (Table 1) following testing.

Exercise was performed on cycle ergometers [Lode Excalibur, Groningen, The Netherlands; Lode (paediatric)]. Following 3-min warm-up (20 W), patients completed an incremental ramp test, whereby resistance increased at a predetermined rate (10-25 $W \cdot min^{-1}$), ensuring ~8-12 min 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. Peak power output was recorded upon exhaustion. Five minutes warm-down (20 W) and 10-min seated recovery followed. S_{max} was subsequently undertaken, whereby 3-min cycling (20 W) preceded a 'step' transition to a constant work rate equivalent to 110% of peak power output. This work rate was maintained until exhaustion, followed by 5-min recovery (20 W).

Gas analysers were 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 (Metalyzer 3B Cortex, Biophysik, Leipzig, Germany; Metasoft v.3.9.7) were measured using a face mask and, following 1-s interpolation, averaged to 15-s time bins which was subsequently used for all parameters. When appropriately calibrated the accuracy of measuring volume and gas fractions are 2% and 0.1%, respectively. The highest 15-s stationary average represented $\dot{V}O_{2peak}$. HR was determined at 5-s intervals (PhysioFlow, PF-05, Manatec Biomedical, Paris, France) and peak HR (HR_{peak}) taken as the highest 15-s mean value. Transcutaneous O_2 saturation (SpO_2%) was determined on a beat-by-beat basis via pulse oximetry (Avant 4000, NONIN Medical Inc., USA). A fingertip capillary blood sample (~5 µL) was taken within 30-s of exhaustion following the ramp and analysed for $La_{[B]}$ (Lactate Pro, Arkray, Japan). Subjective ratings of perceived exertion (RPE) and dyspnoea (RPD) were recorded upon exhaustion using the pictorial children's effort rating table (P-CERT)[12] and the 0-10 category-ratio (CR-10) scale[7], respectively.

The presence of a $\dot{V}O_2$ plateau was determined using methodology more comprehensively described elsewhere[10,19]. Briefly, analysis requires a linear regression over the 'linear' portion of the VO_2

response. The $\dot{V}O_2$ profile at exhaustion was subsequently characterised by extrapolating this linear regression function to exhaustion and isolating the final 60-s of data to examine the residuals against the extrapolated line. A negative residual indicated a deceleration in $\dot{V}O_2$ against power output and was considered a 'plateau' when the magnitude of the residuals was ≥ 5% of the projected $\dot{V}O_2$ (i.e. $\dot{V}O_2$ was ≤ 95% of the projected $\dot{V}O_2$). A positive residual ≥ 5% of the projected $\dot{V}O_2$ represented acceleration and positive or negative residuals <5% of the peak power output projected $\dot{V}O_2$ were categorised as a linear responses[21]. Secondary verification criteria ($\dot{V}O_2$ at an RER of 1.00[13,15] and 1.10[16], a HR of 180 b·min^{-1} [13,15] and 95% age-predicted HR_{max} [25,26] were selected within the current study based on their use within CF patients, whilst $La_{[B]}$ ≥ 6 mmol·L^{-1} is often utilised in paediatric studies.

Data are expressed as means and standard deviations unless otherwise stated and significance set at $p < 0.05$. Paired samples *t*-tests determined mean differences between ramp and S_{max} $\dot{V}O_{2peak}$. Linear regression and Bland and Altman limits of agreement analysis[6] (mean bias and 95% confidence limits [95% CL]) examined the agreement between ramp and S_{max} $\dot{V}O_{2peak}$. A greater than 9% increase was considered a 'meaningful' change between ramp and S_{max} derived $\dot{V}O_{2peak}$. This value is considered the typical within-subject short-term variation of $\dot{V}O_{2max}$ in paediatric CF patients, established using unpublished data from within our laboratory. Analyses were performed using SPSS v.18.0 (Chicago, Illinois, USA) and GraphPad Prism (GraphPad Software Inc., San Diego, California, USA).

Results

Mean ramp test duration was 9 min 27 s ± 3 min 16 s, resulting in a peak power output of 174 ± 84 W. Mean $\dot{V}O_{2peak}$ was 1.83 ± 0.78 L·min^{-1} (34.23 ± 6.57 mL·kg^{-1}·min^{-1}). Ramp $\dot{V}O_{2peak}$ was not significantly different to the $\dot{V}O_{2peak}$ predicted by the linear extrapolation of the $\dot{V}O_2$-power output relationship (1.83 ± 0.84 L·min^{-1}; $p = 0.99$). Mean goodness of fit (R^2) for the linear function was 0.84 ± 0.19. Analysis of patients' $\dot{V}O_2$-power output profiles revealed a single plateau upon exhaustion,

with 13 patients characterised by a linear $\dot{V}O_2$ response (Table 2). The mean 'gain' ($\Delta\dot{V}O_2/\Delta WR$) of patients' $\dot{V}O_2$ response to the ramp was 7.81 ± 1.57 $mL \cdot min^{-1} \cdot W^{-1}$.

All patients satisfied the RER > 1.00 and >1.10 criteria (Table 2). However, the $\dot{V}O_2$ at a RER of 1.00 (0.99 ± 0.47 $L \cdot min^{-1}$) was lower than that recorded at exhaustion (1.83 ± 0.78 $L \cdot min^{-1}$; $p < 0.001$), representing only 54% of $\dot{V}O_{2peak}$. Similarly, the $\dot{V}O_2$ at RER of 1.10 (1.36 ± 0.59 $L \cdot min^{-1}$; $p < 0.001$) were lower than $\dot{V}O_2$ upon exhaustion, representing only 74% of $\dot{V}O_{2peak}$. Bland and Altman analysis demonstrated the RER of 1.00 and 1.10 criteria to underestimate $\dot{V}O_{2max}$ by a mean bias of –1.10 $L \cdot min^{-1}$ (95% CL: -1.68 to -0.01 $L \cdot min^{-1}$, Figure 1a) and -0.47 $L \cdot min^{-1}$ (95% CL: -1.02 to 0.08 $L \cdot min^{-1}$, Figure 1b), respectively. Mean $La_{[B]}$ following the ramp was 9.5 ± 13.1 $mmol \cdot L^{-1}$ (n = 13). Ten patients satisfied the ≥ 6 $mmol \cdot L^{-1}$ criteria (Table 2).

Due to data loss, HR is presented for 12 patients with a HR_{peak} of 188 ± 12 $b \cdot min^{-1}$. Nine patients satisfied achieved 180 $b \cdot min^{-1}$ (Table 2), whilst 3 attained 95% age-predicted maximum (equating to 196 ± 2 $beats \cdot min^{-1}$; Table 2). In those patients satisfying the HR criteria, $\dot{V}O_2$ at 180 $beats \cdot min^{-1}$ (1.75 ± 0.60 $L \cdot min^{-1}$) and 95% of their age-predicted maximum (1.72 ± 0.50 $L \cdot min^{-1}$) was lower than that recorded upon exhaustion (1.98 ± 0.84 and 2.04 ± 0.53 $L \cdot min^{-1}$, respectively), representing 88% and 84% of $\dot{V}O_{2peak}$, respectively. Bland and Altman analysis revealed 180 $beats \cdot min^{-1}$ and 95% age-predicted maximum criteria to underestimate $\dot{V}O_{2max}$ by a mean bias of -0.23 $L \cdot min^{-1}$ (95% CL: -0.85 to 0.39 $L \cdot min^{-1}$; Figure 1c) and -0.32 $L \cdot min^{-1}$ (95% CL: -0.46 to -0.18 $L \cdot min^{-1}$), respectively.

Mean S_{max} duration was 1 min 23 s ± 0 min 20 s and elicited a similar $\dot{V}O_{2peak}$ to the ramp, despite exercising at a higher power output (191 ± 93 W, Table 3). Bland Altman analysis for ramp and S_{max} $\dot{V}O_{2peak}$ revealed a mean bias of -0.00 $L \cdot min^{-1}$ (95% CL: -0.46 to 0.46 $L \cdot min^{-1}$) or 1.0% (95% CL: -22.5% to 24.5%). No significant differences were observed for HR_{peak}, end-exercise SaO_2%, RPE or RPD during ramp and S_{max} testing (Table S1).

S_{max} increased $\dot{V}O_{2peak}$ above ramp $\dot{V}O_{2peak}$ in 7 patients (50%) (Table 4; Figure 2), 3 (21%) of which were deemed clinically important rises (i.e. >9 % change). Based on this criterion, S_{max} confirmed a valid $\dot{V}O_{2max}$ in 11/14 (79%) patients and identified 3 (21%) cases where a 'true' $\dot{V}O_{2max}$ was not obtained, with an average $\dot{V}O_2$ increase of 20.3 ± 15.7% or 0.33 ± 0.21 $L \cdot min^{-1}$. No significant relationship existed between S_{max} duration and the difference between the ramp and S_{max} $\dot{V}O_{2peak}$ (r=0.29; p=0.32).

Discussion

This study sought to establish the validity of traditional $\dot{V}O_{2max}$ verification criteria and establish the utility of S_{max} in young CF patients. Results revealed four principle findings: 1) a $\dot{V}O_2$ plateau is rarely observed upon exhaustion; 2) adherence to secondary traditional criteria underestimates $\dot{V}O_{2max}$; 3) in most cases (78.6%), S_{max} did not increase $\dot{V}O_{2peak}$ thus confirming a valid $\dot{V}O_{2max}$; and 4) S_{max} identified those whose initial CPET $\dot{V}O_{2peak}$ was not a 'true' maximum. These findings have significant implications for the assessment and interpretation of CPET in young CF patients in a clinical and research setting.

In this study only one $\dot{V}O_2$ plateau was documented upon exhaustion during CPET. While this is the first study to document the $\dot{V}O_2$ profile of young CF patients during ramp exercise, Werkman *et al.*[30] recorded a plateau in 5 of 16 adolescents with CF during step exercise to exhaustion. However, the latter study employed a fixed $\dot{V}O_2$ plateau criterion (< 2.1 $mL \cdot kg^{-1} \cdot min^{-1}$), which was originally developed on adults during a discontinuous running protocol consisting of steady-state stages[29] and is unlikely to account for the altered O_2 cost of exercise reported in young CF patients[16]. This was accounted for in our study, using an extrapolated linear function from each participant's $\dot{V}O_2$-power output profile prior to exhaustion. Our findings indicate that young CF patients rarely satisfy the conventional criteria of a $\dot{V}O_2$ plateau during CPET.

Secondary criteria have therefore been adopted to verify $\dot{V}O_{2max}$ in young people, however they often underestimate $\dot{V}O_{2max}$ or reject a 'true' measure within healthy children[20,4]. Such criteria may be equally unsuitable for clinical paediatric populations. The present investigation confirms this notion. Achieving an RER > 1.00 was the least robust criterion, underestimating on average by 46% (Figure 1a). Achieving a RER > 1.10, 180 beats·min^{-1} (Figure 1c) and 95% of age-predicted HR_{max} underestimated $\dot{V}O_{2max}$ by an average of 26%, 12% and 16%, respectively. Although HR criteria appear more robust, their use is limited as five patients (36%) failed to achieve a HR of 180 beats·min^{-1}, and eleven (79%) failed to achieve 95% of their age-predicted HR_{max}, one of whom exhibited a $\dot{V}O_2$ plateau. Given the emerging evidence base to reject secondary criteria in healthy children[4,20] and adults[18] and now young CF patients, their use as a verification tool is limited and should be discontinued.

S_{max} verification ensures that if the $\dot{V}O_{2peak}$ obtained during a CPET is 'truly' maximal, then performing exercise above peak power output from a preceding ramp test should not elicit a further increase in $\dot{V}O_2$, thus satisfying the primary plateau criterion. Limited application of S_{max} in clinical populations is plausible, as poor exercise tolerance and slow $\dot{V}O_2$ kinetics[14] may preclude the attainment of $\dot{V}O_{2max}$. The present study has demonstrated, however, that S_{max} can verify $\dot{V}O_{2max}$ in CF. Additionally, mean S_{max} duration was 85 ± 26 s, which is comparable with healthy children (91 ± 26 s) exercising at 105% peak power[4]. No adverse incidents were encountered, substantiating previous reports that exercise testing is safe in mild-to-moderate CF[21].

Although mean S_{max} $\dot{V}O_{2peak}$ was comparable with traditional ramp testing, S_{max} elicited meaningful rises in 3 of 14 (21%) cases (range 9.9-38.3%; Figure 2), findings comparable to young spina bifida[11] [5 of 20 (33%)] and adult chronic heart failure (21%)[8] patients. In healthy children, S_{max} increased $\dot{V}O_{2peak}$ (potentially negligible) in only 1 of 13 cases (8%)[4]. These findings support S_{max} as a safe and powerful tool in CF patients to validate $\dot{V}O_{2max}$ measurement.

Werkman *et al.*[30] recently examined the feasibility of a steep ramp test (SRT) to verify $\dot{V}O_{2max}$ in adolescent CF patients. The authors concluded that $\dot{V}O_{2peak}$ from traditional CPET reflected 'true' $\dot{V}O_{2max}$. Although, not discussed by these authors, it is clear that 4 of their 13 patients experienced a potentially meaningful rise in $\dot{V}O_2$ during the SRT (see figure 2, page 19), which is comparable to the S_{max} increase in $\dot{V}O_{2peak}$ herein. This supports the present findings that S_{max} confirmation is an essential addition to traditional CPET to confirm a 'true' $\dot{V}O_{2max}$ in young patients with cystic fibrosis.

Individual patient data is of interest to the clinician, in that those with the greatest increase in $\dot{V}O_{2max}$ resulting from S_{max} were patients about whom there were treatment adherence concerns (e.g. patients 3 and 14). Conversely, those with lower S_{max} $\dot{V}O_{2peak}$ versus the ramp were typically physically active and more accomplished in sporting activities (e.g. patients 1 and 6). Although patients 3 and 14 possessed slightly lower $\dot{V}O_{2peak}$ scores when expressed relative to body mass, their lower fitness are unlikely solely attributable to more severe disease, since superior fitness was recorded for a number of patients with lower scores on all aspects of the disease profile (Table 1). Their scores likely represent poor motivation during CPET which may be indicative of motivation in other aspects of their disease management.

Combining a traditional ramp CPET with a S_{max} test permits the identification of a valid $\dot{V}O_{2max}$. This protocol can be safely and effectively undertaken within a single laboratory visit and offers clear guidelines and a superior validation of $\dot{V}O_{2max}$ than current methods. To utilise $\dot{V}O_{2max}$ in prognostic stratification[17], it is essential that 'true' measurements are obtained. Accepting submaximal or rejecting 'true' values could distort clinical application and interpretation. Since healthy adults do not always plateau, S_{max} may be useful for adult CF patients. However, as more severe disease is associated with aging in CF, the safety and tolerance of S_{max} in older patients warrants investigation. Whether a further S_{max} test, at a higher percentage of peak power output, could verify $\dot{V}O_{2max}$ in the cases where $\dot{V}O_{2peak}$ increased significantly is also unknown, although utility of a subsequent, more intense verification test to verify $\dot{V}O_{2max}$ has been demonstrated in healthy adults[22]. From a practical

viewpoint, S_{max} verification is straightforward to implement as the imposed power output is calculated from ramp test peak power output on an individual basis and, clinically, may minimise the costs associated with re-tests when the validity of test results is questionable.

Conclusion

In conclusion, S_{max} verification is a safe and well-tolerated tool to determine valid $\dot{V}O_{2max}$ in young CF patients. Although the present uptake of CPET is poor within the clinical management of young people with mild-to-moderate CF[24,5], the European CF Society (ECFS) Exercise Working Group have recently recognised such testing as *the* method of choice when assessing aerobic fitness in this patient population. Consequently, it is recommended that S_{max} verification replace traditional criteria for confirming a 'true' $\dot{V}O_{2max}$ measurement in young CF patients with mild-to-moderate disease.

Practical implications:

- Aerobic fitness ($\dot{V}O_{2max}$) measurement can help predict survival in cystic fibrosis.
- Criteria commonly used to confirm $\dot{V}O_{2max}$ tend to underestimate 'true' fitness. Conversely, a 'supramaximal' exercise test can confirm 'true' measurements.
- Underestimating $\dot{V}O_{2max}$ could result in incorrect interpretation of patients' fitness, prognosis and/or the influence of a therapeutic intervention.
- It is recommended that S_{max} be adopted when performing CPET on young CF patients in the clinical or research environments.

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Tables

Table 1. Patients' baseline anthropometric and clinical data.

Patient (Gender)	Pubertal maturity	Age (years)	Stature (m)	Body mass (kg)	BMI ($kg \cdot m^2$)	CFTR genotype	*C. PSA*[a]	SS	Northern score[b]	FVC [% predicted (L)]		FEV_1 [% predicted (L)]	
1 (M)	3	13.4	164.9	62.1	23.1	Δ F508 /ΔF508	I	85	4	127	(4.58)	120	(4.07)
2 (M)	4	16.7	177.0	85.0	29.4	Δ F508 /ΔF508	F	87	4	112	(4.95)	87	(3.60)
3 (M)	4	13.4	167.9	69.7	24.1	Δ F508/P67L	F	80	3	101	(3.57)	112	(3.04)
4 (F)	1	7.6	123.6	24.0	16.1	Δ F508 /621+IG ⩾T	F	89	3	112	(1.62)	108	(1.43)
5 (M)	4	9.9	141.2	41.8	21.1	Δ F508 /ΔF508	C	85	4	106	(2.47)	93	(2.04)
6 (M)	2	11.2	141.9	44.8	22.8	Δ F508 /ΔF508	F	79	5	96	(2.23)	65	(1.39)
7 (M)	3	13.9	174.6	89.8	28.1	Δ F508 /ΔF508	I	82	4	123	(5.11)	97	(3.84)
8 (F)	1	12.2	135.0	32.5	18.1	Δ F508 / 2184delA	N	81	3	125	(2.19)	101	(1.95)
9 (M)	1	11.1	149.5	32.1	14.4	Δ F508 /ΔF508	I	67	6	79	(2.19)	67	(1.71)
10 (M)	2	16.1	151.6	44.1	19.3	Δ F508 /ΔF508	F	75	3	93	(2.69)	69	(1.83)
11 (M)	2	14.9	170.3	56.7	19.5	Δ F508 / G55ID	C	82	6	115	(4.55)	110	(4.06)
12 (M)	1	7.8	135.1	43.6	25.0	Δ F508 /ΔF508	N	91	2	112	(2.40)	108	(1.92)
13 (F)	2	16.6	166.0	65.0	25.0	Δ F508 /ΔF508	F	88	3	99	(3.46)	85	(2.95)
14 (F)	4	18.4	172.0	58.0	20.2	Δ F508 /ΔF508	I	81	3	85	(3.53)	82	(2.98)
Mean	**2**	**13.1**	**1.5**	**55.5**	**21.9**	**-**	**-**	**82**	**4**	**104; 3.30**		**92; 2.66**	
(SD)	**(1)**	**(3.32)**	**(0.17)**	**(19.3)**	**(4.31)**	**-**	**-**	**(6)**	**(1)**	**(15; 1.2)**		**(18; 1.0)**	
[range]	**[1-4]**	**[7.57-18.4]**	**[1.23-1.74]**	**[24.4-87.9]**	**[14.4-29.4]**	**-**	**-**	**[67-91]**	**[2-6]**	**[79-127; 1.62-5.11]**		**[65-120; 1.39-4.07]**	

Values are means ± SD, with the range also displayed where suitable, unless otherwise stated. BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; C. *PSA*, chronic *Pseudomonas aeruginosa* infection; I, intermittent; F, free; C, chronic; N, never; SS, 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. Ramp test responses in relation to traditional verification criteria.

Patient	Gender	Age (y)	Ramp VO_{2peak} ($L \cdot min^{-1}$)	VO_2 plateau	VO_2 at RER >1.00 ($L \cdot min^{-1}$)	VO_2 at RER >1.10 ($L \cdot min^{-1}$)	VO_2 at 180 $b \cdot min^{-1}$ ($L \cdot min^{-1}$)	VO_2 at 95% age-predicted HR ($L \cdot min^{-1}$)	$La_{[B]} \geq 6$ $mmol \cdot L^{-1}$
1	M	13.4	2.32	No	0.96	1.58	-	-	Yes
2	M	16.7	3.78	Yes	2.30	3.09	2.76	N/A	Yes
3	M	13.4	2.05	No	0.79	1.23	1.94	N/A	Yes
4	F	7.6	0.84	No	0.47	0.73	N/A	N/A	DNC
5	M	9.9	1.39	No	0.73	1.08	1.39	N/A	No
6	M	11.2	1.74	No	1.12	1.42	1.50	1.50	Yes
7	M	13.9	2.16	No	1.25	1.53	-	-	Yes
8	F	12.2	1.18	No	0.83	1.06	1.11	N/A	Yes
9	M	11.1	1.03	No	0.71	0.94	N/A	N/A	No
10	M	16.1	1.72	No	0.96	1.45	1.45	1.37	Yes
11	M	14.9	2.65	No	1.50	1.89	2.40	2.28	Yes
12	M	7.8	1.11	No	0.83	0.79	1.02	N/A	No
13	F	16.6	2.16	No	0.75	1.32	2.16	N/A	Yes
14	F	18.4	1.49	No	0.71	0.96	N/A	N/A	Yes

DNC, did not consent to blood sampling for assessment of end-exercise blood lactate concentration ($La_{[B]}$); N/A, not achieved; - , Loss of PhysioFlow data. VO_{2peak}, peak oxygen uptake; RER, respiratory exchange ratio; HR, heart rate (n=12); $La_{[B]}$, blood lactate concentration; ramp; incremental ramp test.

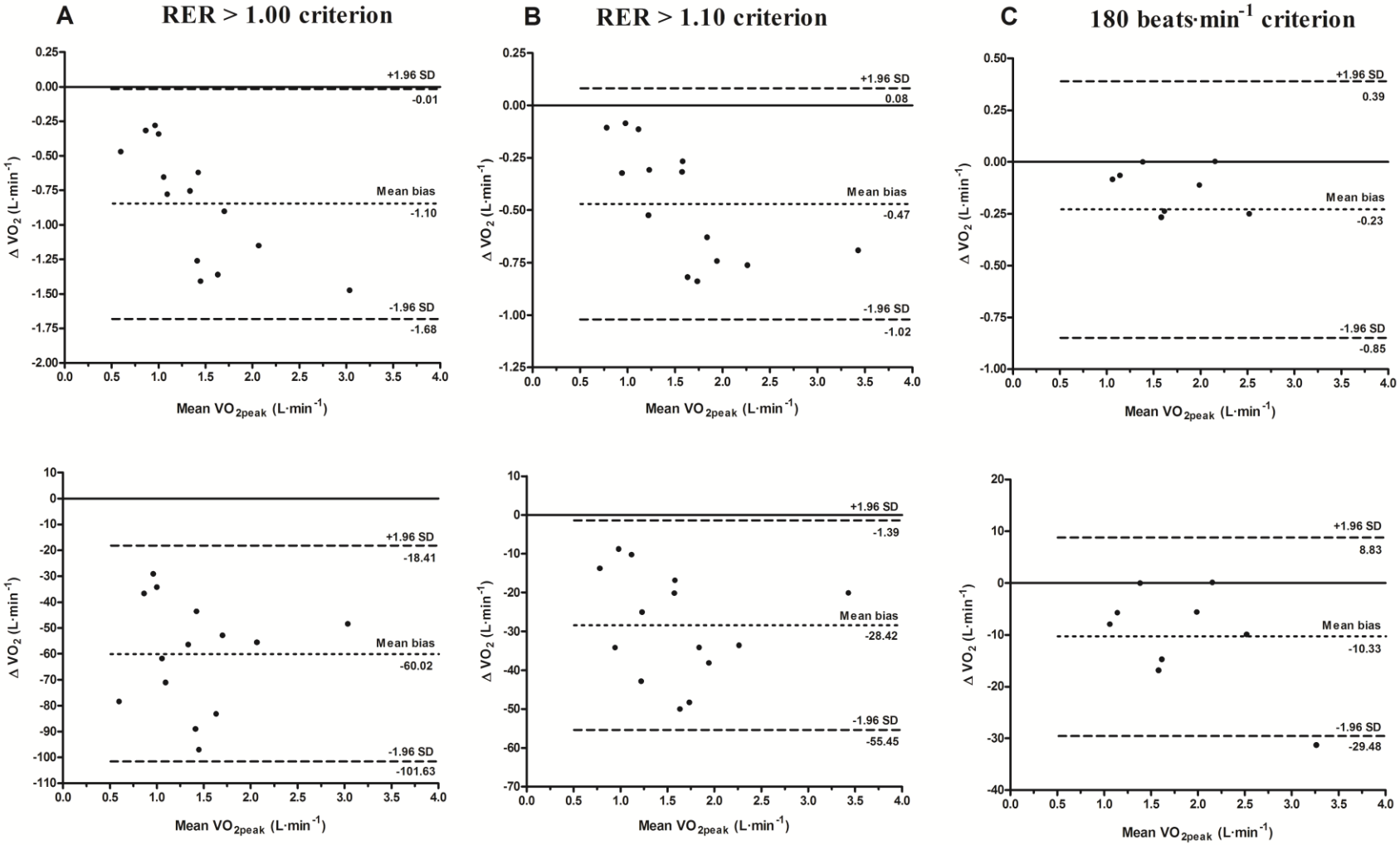
Table 3. Decision to accept $\dot{V}O_{2peak}$ using a combined ramp and S_{max} exercise test

Patient (Gender)	Age (years)	Ramp VO_{2peak} ($L \cdot min^{-1}$)	S_{max} VO_{2peak} ($L \cdot min^{-1}$)	ΔChange ($L \cdot min^{-1}$)	% Change	True VO_{2max} obtained?
1 (M)	13.4	2.32	2.01	-0.31	-13.4	Yes (ramp)
2 (M)	16.7	3.78	3.35	-0.43	-8.5	Yes (ramp)
3 (M)	13.4	2.05	2.31	+0.26	+12.7	No
4 (F)	7.6	0.84	0.89	+0.05	+6.0	Yes (S_{max})
5 (M)	9.9	1.39	1.41	+0.02	+1.4	Yes (S_{max})
6 (M)	11.2	1.74	1.57	-0.17	-9.8	Yes (ramp)
7 (M)	13.9	2.16	1.99	-0.17	-7.9	Yes (ramp)
8 (F)	12.2	1.18	1.11	-0.07	-5.9	Yes (ramp)
9 (M)	11.1	1.03	1.10	+0.07	+6.8	Yes (S_{max})
10 (M)	16.1	1.72	1.89	+0.17	+9.9	No
11 (M)	14.9	2.65	2.47	-0.18	-6.8	Yes (ramp)
12 (M)	7.8	1.11	1.11	0	0	Yes (either)
13 (F)	16.6	2.16	2.20	+0.04	+1.9	Yes (S_{max})
14 (F)	18.4	1.49	2.06	+0.57	+38.3	No

$\dot{V}O_{2max}$, maximal oxygen uptake; ramp; incremental ramp test; S_{max}, supramaximal exercise test.

Supplementary Material

Figure S1. Bland and Altman plots for the secondary criteria typically used during CPET of young CF patients. Plots show the mean bias (floating dotted line) and 95% confidence limits (floating dashed lines) for the oxygen uptake ($\dot{V}O_2$) recorded at an RER of ≥ 1.00 (A), an RER of ≥ 1.10 and (B) a heart rate of 180 beats·min^{-1} (C) compared with the actual $\dot{V}O_2$ recorded at exhaustion from the traditional ramp test in absolute terms (top row) and as a percentage of the difference (bottom row).


A
RER > 1.00 criterion
B
RER > 1.10 criterion
C
180 beats·min-1 criterion
+1.96 SD
-0.01
Mean bias
-1.10
-1.96 SD
-1.68
+1.96 SD
0.08
Mean bias
-0.47
-1.96 SD
-1.02
+1.96 SD
0.39
Mean bias
-0.23
-1.96 SD
-0.85
+1.96 SD
-18.41
Mean bias
-60.02
-1.96 SD
-101.63
+1.96 SD
-1.39
Mean bias
-28.42
-1.96 SD
-55.45
+1.96 SD
8.83
Mean bias
-10.33
-1.96 SD
-29.48
Δ VO2 (L·min-1)
Mean VO2peak (L·min-1)

S2. The agreement between the peak oxygen uptake ($\dot{V}O_{2peak}$) recorded at exhaustion during ramp and S_{max} testing. Plots show the mean bias (floating dotted line) and 95% confidence limits (floating dashed lines) for the $\dot{V}O_2$ recorded at exhaustion during ramp and S_{max} exercise in absolute terms (A) and as a percentage of the difference (B), according to Bland and Altman (1986).

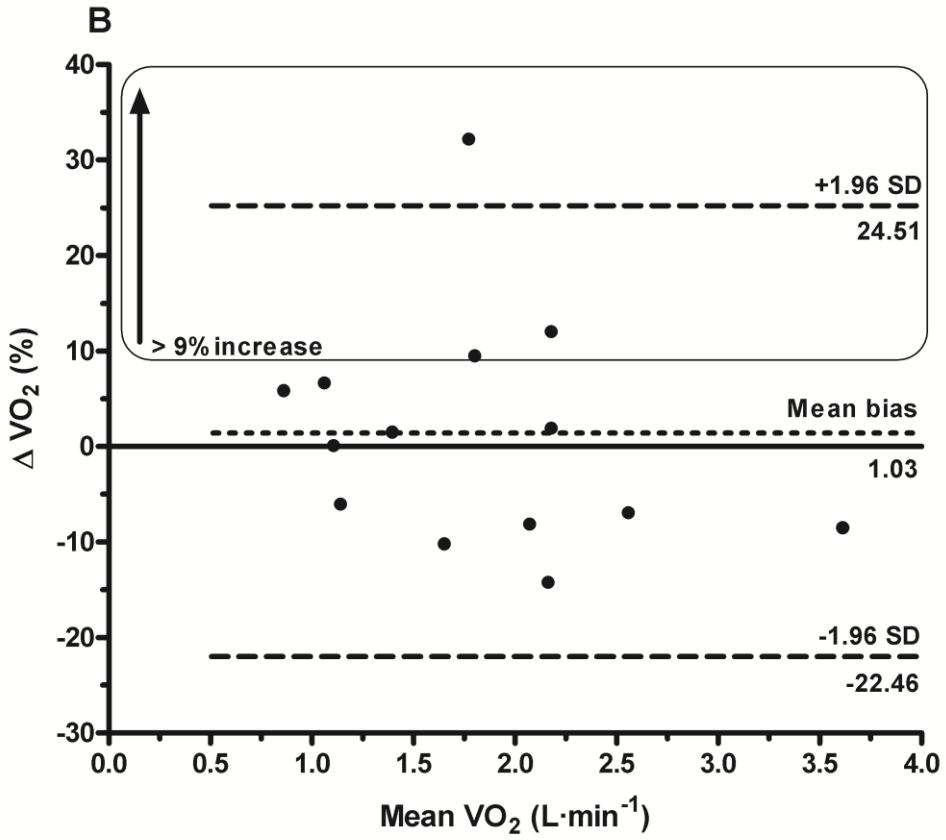


Table S1. Peak physiological responses during the ramp and S_{max} tests

Variable	Ramp		S_{max}		*p*-value
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	1.83 ± 0.78	[0.84-3.77]	1.83 ± 0.69	[0.89-3.46]	0.98
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	34.23 ± 6.57	[25.23-47.54]	34.46 ± 5.65	[23.32-44.42]	0.83
RER_{peak}	1.29 ± 0.10	[1.15-1.49]	1.23 ± 0.12	[0.99-1.34]	0.07
HR_{peak} ($b \cdot min^{-1}$, n=12)	188 ± 12	[170-208]	183 ± 13	[158-201]	0.08
SpO_2%	96 ± 2	[90-99]	95 ± 3	[90-98]	0.19
RPE	8 ± 2	[5-10]	8 ± 3	[4-10]	0.37
RPD	6 ± 2	[2-10]	7 ± 3	[4-10]	0.26

Values are means ± SD, with the range also displayed in parenthesis unless otherwise stated.
$\dot{V}O_{2peak}$, peak oxygen uptake; RER_{peak}, peak respiratory exchange ratio; 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; S_{max}, supramaximal exercise test.