Feasibility and inter-reporter variability of submaximal outcomes derived from cardiopulmonary exercise testing in people with advanced cystic fibrosis lung disease

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Shareable abstract (@ERSpublications)
Meaningful submaximal CPET data can be obtained in most people with advanced CF lung disease whilst experienced CPET operators demonstrate close agreement in their delineation and reporting of submaximal CPET measures in this population https://bit.ly/429zs68

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Abstract

Background Cardiopulmonary exercise testing (CPET) provides prognostic information in people with advanced cystic fibrosis lung disease (pwACFLD). This project aimed to ascertain feasibility and inter-reporter variability in the identification of submaximal CPET outcomes for pwACFLD as potential predictors of prognosis where no peak exercise data are available.

Methods We utilised data from an international retrospective multicentre study involving pwACFLD, for whom raw CPET data were available. Two experienced operators independently reviewed and analysed CPET tests with a focus on three pre-defined measures: oxygen uptake (V'_{O_2}) at the anaerobic threshold (AT), the breathing reserve index at the AT (BRIAT), and the slope of the minute ventilation to carbon dioxide production ratio (V'_E/V'_{CO_2}-slope). We calculated intra-class correlation coefficients (ICCs) with their 95% confidence intervals (CI), and limits of agreement using the Bland–Altman method.

Results The original cohort included 174 pwACFLD. Among those, raw CPET data were available for 101 individuals, of which 89 tests were of sufficient technical quality for submaximal analysis. In 72 out of 89 technically acceptable tests (81%), the AT could be confidently identified by both operators. Furthermore, ICCs indicated good-to-excellent inter-reporter agreement for V'_{O_2} at the AT (ICC 0.79, 95% CI 0.62–0.88), the V'_E/V'_{CO_2}-slope (0.95, 95% CI 0.93–0.97) and BRIAT (0.76, 95% CI 0.63–0.85).

Conclusions Submaximal CPET data can be reliably obtained in most pwACFLD by trained CPET operators. Future studies may ascertain the prognostic value of submaximal CPET outcomes in pwACFLD.

Introduction

Cardiopulmonary exercise testing (CPET) is considered the gold standard measure of aerobic fitness in people with cystic fibrosis (CF) [1]. The "prognostic value of CPET in CF study group" have previously shown the prognostic importance of maximal cardiopulmonary exercise testing for people with CF (pwCF) [2], and further demonstrated that CPET outcomes provide prognostic information in pwCF and advanced (forced expiratory volume in 1 s (FEV_1) ⩽40%) CF lung disease [3].

Whilst acquisition of maximal exercise data is desirable, performing CPET may be challenging for people with advanced CF lung disease (pwACFLD) due to marked reductions in exercise performance and/or concerns about patient safety on maximal testing. Submaximal, relatively effort-independent tests to obtain

information on performance up to and beyond the first ventilatory threshold (VT1, herein referred to as anaerobic threshold (AT)) may be both clinically and prognostically useful for pwACFLD. Submaximal measures provide information on breathing reserve, and the level of fitness and physical conditioning that underpins the timing of onset of non-oxidative energy generation and blood lactate accumulation. Understanding the timing of onset of the AT can aid the devising of training programmes for people with CF [4, 5].

Submaximal exercise testing measurements include oxygen uptake (V'_{O_2}) at the AT, minute ventilation (V'_E) at the AT, breathing reserve index at the AT (BRIAT) and the minute ventilation to carbon dioxide production (V'_E/V'_{CO_2})-slope. BRIAT is reported to be a predictor of mortality in those with advanced CF lung disease [6], whilst exploratory data in a small paediatric study also demonstrated that BRIAT may be of prognostic usefulness for children with CF [7]. The nadir and slope of the V'_E/V'_{CO_2} ratio are also postulated to be highly important in determining ventilatory insufficiency in those with CF lung disease [8] and have been shown to be of predictive value [2].

The aim of this analysis was to: 1) ascertain the feasibility of obtaining submaximal CPET data in pwACFLD; and 2) determine inter-reporter variability in the delineation of the submaximal measurements listed above in pwACFLD.

Materials and methods

Study subjects and study design

We retrospectively collected "real-world" health-related data pertaining to lung health and other aspects of CF care (including data from CPET) from pwACFLD aged ⩾10 years and with FEV_1 ⩽40% predicted, who had performed a CPET on a cycle ergometer with 1-min step or ramp protocols between 1 January 2008 and 31 December 2017 and for whom follow-up information on death or lung transplantation was available for the 2 years (730 days) after CPET was performed [3]. Studies were deemed to be acceptable maximal tests if European Respiratory Society Task Force criteria [9] were met. For each individual, only one test was included for analysis. If multiple tests were available within the period of interest, we requested data from the most recent valid test. All tests were performed without oxygen supplementation. The methods of data collection are more fully described in an earlier publication reporting on this study cohort [3]. In addition to CPET data, contributors also provided information on CFTR genetics, lung function, CF comorbidities and relevant microbiology for each included subject.

To ascertain the feasibility and inter-reporter variability in the delineation of submaximal measurements in pwACFLD, CPET raw data (where available) were reviewed and analysed by two experienced CPET operators (P. Jamieson and P. Burns). Both "CPET reporters" (clinical respiratory physiologists each with >15 years' CPET experience) were blinded to the clinical characteristics of patients being reported other than those that were necessary to analyse CPET data. An assessment of study quality was undertaken independently, by each of the reporters, who were blinded to each other's quality assessment and patient outcome. Dual analyses of CPET data only took place in those studies where there was agreement on technical acceptability. Various maximal and submaximal exercise testing measures were extracted for data analysis including peak work rate (W_{peak}), peak V'_{O_2} ($V'_{O_{2peak}}$), V'_{O_2} at the AT, V'_E at the AT, BRIAT and V'_E/V'_{CO_2}-slope (analysed from the start of incremental cycling up to respiratory compensation point (RCP)).

Whilst numerous measures can be extracted from CPET, our analyses were limited to those shown to yield prognostic value in cardiopulmonary diseases including heart failure [10–12] and CF [6, 7], and those that are useful for stratifying surgical risk [13], or aiding the development of individualised training programmes [14] including in CF [4].

Data handling and ethical approval

All data including CPET raw data files were collected with REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee, USA) [15]. Database entries were monitored to minimise errors. Ethical approval was obtained from contributors' respective research ethics committees, if required. These approvals are all detailed in the online supplement of an earlier publication for this study cohort [3]. The manuscript was prepared following STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) reporting guidelines [16].

Analysis of CPET data

Raw CPET data were obtained from multiple sites and, as such, were stored in a variety of standards, from breath-by-breath, to various time-averaged formats such as 10-s, 30-s and 1-min intervals.

CPET raw data were downloaded from the REDCap site, and were anonymised and subsequently transferred to the two CPET reporters (P. Jamieson and P. Burns) for analysis within a customised CPET analysis tool in Microsoft Excel. This tool allowed the data to be presented in the standard Wasserman 9-panel configuration [17, 18], alongside additional graphic representation; enabling independent review of data, as well as standardised analysis and interpretation across heterogeneous datasets.

Tests were assessed for duration, frequency of gas exchange measurements/averaging settings and data quality. Tests were then deemed to be either suitable or unsuitable for further analysis, *e.g.* physiologically implausible data were removed. Identification of the AT was attempted by the V-slope method with verification by visual assessment of ventilatory equivalent and end-tidal gas measures [19]. Those tests where AT could be reliably identified by both CPET reporters were further analysed to acquire further measurements including V'_E at AT, BRIAT and V'_E/V'_{CO_2}-slope.

Statistical analysis

Data are reported as mean±SD or n (%). Data from spirometry using Global Lung Initiative reference values [20] and CPET [21, 22] were converted to per cent predicted values and z-scores. Mean bias and limits of agreement (95% confidence intervals) were ascertained using Bland–Altman analyses [23]. Intra-class correlation coefficients (ICCs) using a two-way mixed effects model were calculated for inter-reporter agreement. ICC values were interpreted in accordance with published classification of reliability guidelines [24]: <0.50, poor; 0.50–0.75, moderate; >0.75–0.90, good; and >0.90, excellent.

As there are no data available on submaximal CPET outcomes in pwACFLD, no assumptions were made and no *a priori* sample size calculation was performed. We did not imput missing values. We undertook

TABLE 1 Demographics for the analysis population with CPET raw data (submaximal analysis cohort) and the entire study cohort

Variables	Submaximal analysis cohort	Entire study population
Subjects, n	89	174
Age years	31.2±9.0	30.0±9.2
Sex, female	36 (40.5)	72 (41.4)
Height m	1.7±0.1	1.7±0.1
Weight kg	58.4±12.3	57.5±13.6
BMI kg·m^{-2}	20.4±3.0	20.3±3.4
Lung function		
FEV_1 % predicted	32.7±5.0	30.9±5.8
FEV_1 z-score	−5.2±0.4	−5.4±0.4
FEV_1 L	1.2±0.3	1.1±0.3
FVC % predicted	57.3±12.4	52.3±13.1
FVC z-score	−3.6±1.1	−4.1±1.2
FVC L	2.6±0.8	2.3±0.8
CFTR genotype		
Both alleles from classes I–III	79 (88.8)	150 (86.2)
At least one class IV–V allele	8 (9.0)	18 (10.3)
At least one allele unknown/not available	2 (2.2)	6 (3.5)
CFTR modulator therapy		
At the time of CPET	19 (21.3)	24 (13.8)
CF-related pathogens[#]		
Pseudomonas aeruginosa	61 (68.5)	130 (74.7)
Burkholderia cepacia complex	10 (11.2)	13 (7.5)
Nontuberculosis mycobacteria	3 (3.4)	8 (4.6)
Comorbidities		
Pancreatic insufficiency	75 (84.3)	146 (83.9)
CF-related diabetes	40 (44.9)	81 (46.5)
Cardiac disease	2 (2.2)	4 (2.3)

Data are presented as mean±SD or n (%) of the study sample, unless indicated otherwise. CPET: cardiopulmonary exercise testing; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; CFTR: cystic fibrosis transmembrane conductance regulator; CF: cystic fibrosis. [#]: presence of infection(s) in the last 12 months prior to cardiopulmonary exercise testing.

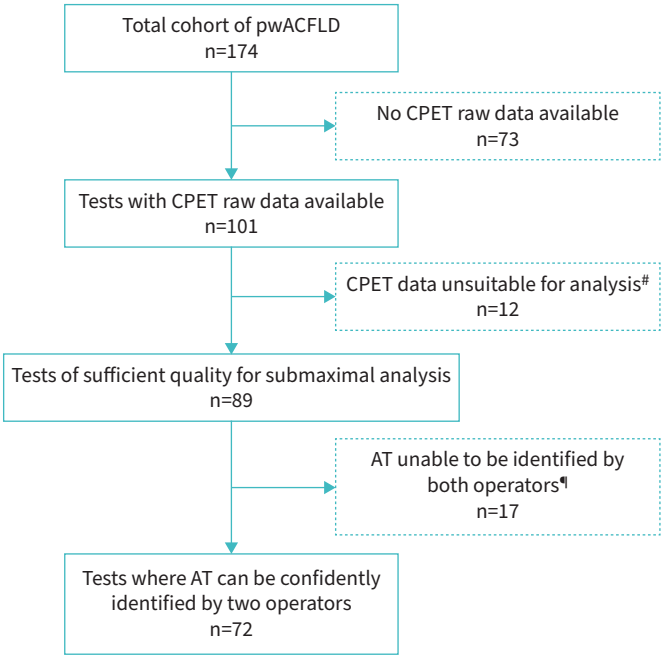

FIGURE 1 Flow diagram delineating the suitability of cardiopulmonary exercise testing (CPET) tests in people with advanced cystic fibrosis lung disease (pwACFLD) for submaximal analysis. #: reasons for CPET data being unsuitable for analysis include the following reasons: constant work rate rather than incremental test, no V'_{CO_2} measurement, heart rate (HR) dropout, breath-by-breath data not physiologically plausible, HR falling through the test, HR above 200 beats·min^{-1} and constant, insufficient resolution on the V'_{O_2} and V'_{CO_2} data plots, nonlinear work rate protocol. ¶: reason for not being able to reliably identify anaerobic threshold (AT) included the following: starting respiratory exchange ratio >1.00, V'_E/V'_{O_2} not rising as expected, and studies with insufficient or uninterpretable data where it was impossible to confidently identify AT. V'_{O_2}: oxygen uptake; V'_{CO_2}: carbon dioxide production; V'_E/V'_{CO_2}: minute ventilation to carbon dioxide production ratio.

secondary analyses utilising an existing dataset [3], and all statistical analyses were undertaken using R, Version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 174 pwACFLD, CPET raw data were available for 101; with 89 tests deemed to be of sufficient technical quality for analysis (see table 1 for patient characteristics). These 89 subjects ranged in age from 11.8 to 53 years. In 72 out of 89 (81%), AT could be reliably identified by both CPET reporters (figure 1). Outcome measures achieved at peak exercise are displayed in table 2.

ICCs indicate good-to-excellent agreement between reporters for V'_{O_2} at the AT, V'_E/V'_{CO_2}-slope and BRIAT (table 3). Bland–Altman plots showing limits of agreement for the three outcomes of interest are displayed in figure 2.

Discussion

This is the first international multicentre study evaluating the feasibility of obtaining submaximal CPET data in pwACFLD, as well as the inter-reporter variability of interpreting these submaximal outcomes in pwACFLD. First, we found that the identification of the AT is possible in most pwACFLD. Secondly, we found good-to-excellent inter-reporter concordance for interpreting these key submaximal outcomes, with acceptable limits of agreement; especially for the V'_E/V'_{CO_2}-slope, despite these being measures reliant on reporter selection.

Studies evaluating the ability to identify and report submaximal data in exercise-limited subjects are not unique to CF. In cohorts where preoperative CPET has been utilised to stratify surgical risk, there are several examples assessing inter-reporter concordance in identifying submaximal CPET outcomes [25–27]. Franssen and colleagues [27] studied the identification of V'_{O_2} at the AT by 26 CPET operators. Their study utilised data from 12 subjects undertaking CPET prior to major (hepatopancreatobiliary) abdominal

TABLE 2 Cardiopulmonary exercise testing outcomes at peak exercise for the submaximal analysis cohort and the entire study population

Variables	Submaximal analysis cohort	Entire study population
Subjects, n	89	174
Duration of exercise s	424±125	373±149
$V'_{O_{2peak}}$ L·min^{-1}	1.3±0.4	1.2±0.5
$V'_{O_{2peak}}$ mL·min^{-1}·kg^{-1}	22.4±6.9	21.5±7.1
$V'_{O_{2peak}}$ % predicted	47±12	46±14
W_{peak} W	102.2±36.9	93.4±38.9
W_{peak} W·kg^{-1}	1.7±0.6	1.6±0.6
W_{peak} % predicted	56±16	52±18
HR_{peak} beats·min^{-1}	152±20	149±19
HR_{peak} % predicted	84±10	83±10
RER_{peak}	1.1±0.1	1.1±0.1
$V'_{E_{peak}}$ L·min^{-1}	45.7±14.5	45.7±14.8
$f_{R_{peak}}$ breaths·min^{-1}	41.1±9.5	41.2±9.6
$V_{T_{peak}}$ L	1.5±0.6	1.2±0.5
$V'_{E_{peak}}/MVV_{pred}$ %	93.0±21.7	94.9±22.5
$S_{pO_{2peak}}$, %$^{\#}$	90.9±4.6	89.9±6.0

Data are presented as mean±SD or n (%), unless indicated otherwise. $V'_{O_{2peak}}$: peak oxygen uptake; W_{peak}: peak work rate; HR_{peak}: peak heart rate; RER_{peak}; respiratory exchange ratio at peak exercise; $V'_{E_{peak}}$; peak minute ventilation; $f_{R_{peak}}$: breathing frequency at peak exercise; $V_{T_{peak}}$: tidal volume at peak exercise; MVV: maximum voluntary ventilation (calculated as forced expiratory volume in 1 s×40); $S_{pO_{2peak}}$: oxygen saturation at peak exercise by pulse oximetry. $^{\#}$: data were available for 141 out of 174 people with advanced cystic fibrosis lung disease (pwACFLD) in the entire study population and 69 out of 89 pwACFLD in the submaximal analysis cohort.

surgery, and reported an ICC of 0.76 (0.57–0.93) which is comparable to the ICC (0.79) reported in our study [27]. A larger study of preoperative CPET tests by ABBOTT and colleagues [26] analysed interobserver variability across 28 different CPET operators with close agreement for identification of V'_{O_2} at the AT with an ICC (95% CI) of 0.83 (0.75–0.90). These data also demonstrate a similar ICC to that reported in our study, though with narrower confidence intervals representing the larger (2125 CPET tests) sample size [26].

It also needs to be highlighted that despite ICC values indicating good-to-excellent reporter concordance, there are outliers where poor agreement was reached. This perhaps reflects the subjectivity that is associated with identifying the AT and analysing submaximal data in general, but more specifically that this can be more difficult in subjects with ventilatory limitation. The lack of concordance is most marked in those subjects who had the greatest degrees of ventilatory limitation, in whom the application of standard criteria for assessment of AT may not hold so well.

There is likely to be disagreement in identification of the AT between using the V-slope method and ventilatory equivalents as ventilatory equivalents will fall throughout the test in a subject with severe ventilatory limitation; whereas these methods have greater agreement with one another for the identification of the AT in subjects with lesser degrees of ventilatory limitation.

TABLE 3 Limits of agreement and intra-class correlation coefficients of inter-reporter measurement for submaximal cardiopulmonary exercise testing measures in people with advanced cystic fibrosis lung disease

Variable	Operator 1	Operator 2	Mean bias (95% CI)	Cases outside LOA	ICC (95% CI)
V'_{O_2} at AT mL·min^{-1}	918±283	838±262	−80 (−119 to −42)	4	0.79 (0.62 to 0.88)
V'_E/V'_{CO_2}-slope	27.1±6.6	27.1±6.2	−0.001 (−0.41 to 0.41)	8	0.95 (0.93 to 0.97)
BRIAT	0.58±0.15	0.55±0.14	−0.03 (−0.054 to −0.009)	7	0.76 (0.63 to 0.85)

Data are mean±SD or mean bias (95% CI) or lower and upper limits of agreement (95% CI). LOA: limits of agreement; ICC: intraclass correlation coefficient; V'_{O_2}: oxygen uptake; AT: anaerobic threshold; V'_E/V'_{CO_2}-slope: slope of the minute ventilation to carbon dioxide production ratio; BRIAT: breathing reserve at the anaerobic threshold.

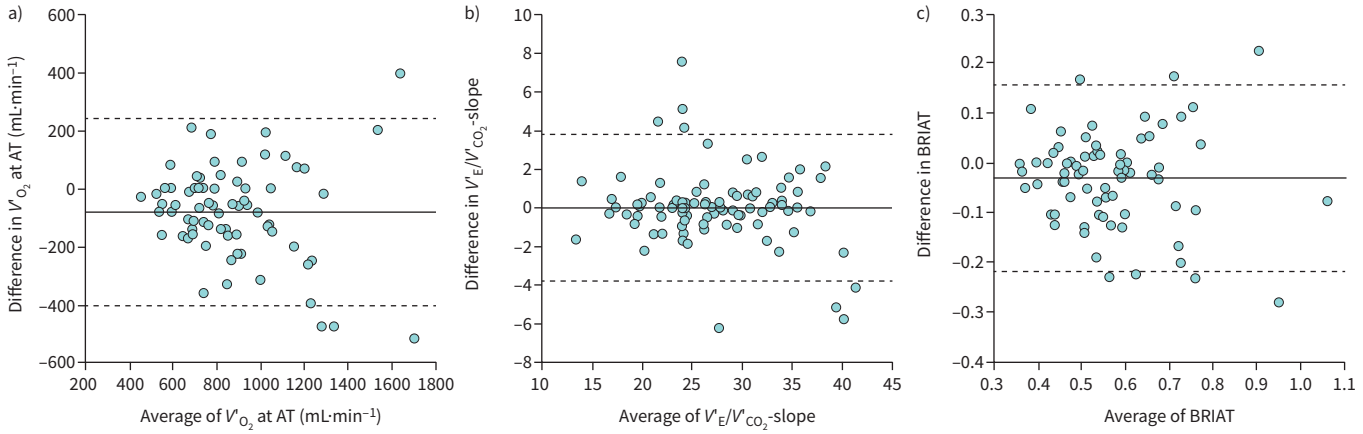

FIGURE 2 Bland–Altman plots demonstrating mean bias and limits of agreement for plotting of a) V'_{O_2} at AT, b) V'_E/V'_{CO_2}-slope and c) BRIAT in people with advanced cystic fibrosis lung disease. The solid line in each panel depicts the mean bias, and the dotted lines depict the upper and lower limits of agreement (*i.e.*, mean bias±1.96 standard deviations). V'_{O_2} at AT: oxygen uptake at the anaerobic threshold; V'_E/V'_{CO_2}-slope: slope of the minute ventilation to carbon dioxide production ratio; BRIAT: breathing reserve index at the anaerobic threshold.

Study strengths and limitations

The main strength of the study is the heterogeneous dataset sourced from various CF centres in Australia, Europe and North America, which likely enhances its applicability to a broader population of individuals with ACFLD, and a wider range of test sites. However, due to the retrospective nature of the study, which considered CPET tests conducted between 2008 and 2017, raw CPET data were available for only about 50% of the original study cohort [3]. Nonetheless, the sub-population of pwACFLD for which raw CPET data analysis was possible was comparable to the entire study cohort with respect to lung disease severity, CF-related comorbidities and CPET outcomes. Additionally, the study timeframe predates the widespread availability of highly effective CFTR modulator therapy; we believe that whilst this means there may now be fewer pwACFLD, it does not detract from the study findings with regards to identifying and reporting submaximal CPET outcomes for those that pwCF continue to have advanced lung disease. The heterogeneity of CPET data with respect to averaging times and workload protocols may also limit the generalisability of study findings, but serve to illustrate the difficulties that may be faced when studies in the "real-world" are undertaken, especially when the design is a retrospective one. Finally, CPET test data for this study were analysed and reported by two highly experienced CPET operators; the success rate of determining the AT may be lower for less experienced operators. Although overall ICCs were good, one needs to be aware of the potential for discrepancy in the identification of submaximal measures, especially in those with severe ventilatory limitation.

Future research

Our study has demonstrated CPET is possible in pwACFLD, with good-to-excellent inter-reporter reliability for submaximal outcomes. Novel prognostic tools are needed to aid the prediction of mortality in algorithms for lung transplant listing [28], with the consideration of the prognostic value of CPET outcomes (including submaximal measures) being recommended as a priority for prospective research studies [28, 29], most recently in pwACFLD [28, 30]. Carefully designed studies to use a variety of CPET outcomes including submaximal data may allow a greater understanding of risk stratification for pwACFLD, as well as offering the ability to measure interventions such as pulmonary rehabilitation or exercise training programmes in this important subgroup of people with CF.

Conclusion

In conclusion, our data demonstrate that meaningful submaximal CPET data can be obtained in most pwACFLD, whilst experienced CPET operators demonstrate close agreement in their delineation and reporting of submaximal CPET measures in this population.

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