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ORIGINAL ARTICLE

Exercise testing in patients with cystic fibrosis—importance of ventilatory parameters

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Abstract

Background Ventilatory parameters obtained during exercise predict survival in several chronic diseases; however, long-term changes in exercise ventilatory parameters in patients with cystic fibrosis (CF) have yet to be examined and potential differences between sexes in CF are unknown.

Purpose We sought to examine the change in exercise ventilatory parameters over time in patients with CF and determine if the change is different between sexes.

Methods Exercise capacity (VO_2 peak) and exercise ventilatory parameters (V_E/VO_2 peak, V_E/VCO_2 peak, and V_E/VCO_2 slope) were determined from a maximal cardio-pulmonary test on a cycle ergometer on two visits separated by 39 ± 16 months in 20 patients with CF (10 female, 10 male).

Results No differences between sexes were observed at visit 1 (all $p > 0.05$). Overall, exercise ventilatory parameters significantly ($p < 0.05$) deteriorated between visits, with no change ($p > 0.05$) in VO_2 peak. Moreover, compared to males, female patients exhibited greater deteriorations in V_E/VO_2 peak ($p = 0.001$), V_E/VCO_2 peak ($p = 0.002$), and V_E/VCO_2 slope ($p = 0.016$) between visits.

Conclusions These data in patients with CF indicate that exercise ventilatory parameters decline over time despite no change in VO_2 peak, and female patients exhibit a more rapid deterioration compared to males.

Keywords Exercise capacity · Pulmonary function · Ventilatory efficiency

Abbreviations

BMI	Body mass index
CF	Cystic fibrosis
CPET	Cardio-pulmonary exercise test
DXA	Dual-energy X-ray absorptiometry
$FeCO_2$	Fraction of expired CO_2
FEV_1	Forced expiratory volume in 1 s
FFM	Fat-free mass
FVC	Forced vital capacity
MVV	Maximum voluntary ventilation
$PaCO_2$	Partial pressure of arterial CO_2
RR	Respiratory rate
VCO_2	Volume of carbon dioxide output
V_D/V_T	Dead space-to-tidal volume ratio
V_E	Minute ventilation
VO_2	Volume of oxygen consumption
V_T	Tidal volume
VT	Ventilatory threshold

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Introduction

A hallmark characteristic of cystic fibrosis (CF) is exercise intolerance, exhibited by a reduction in exercise capacity (VO_2 peak) (Lands et al. 1992; Troosters et al. 2009) that predicts mortality, independent of lung function (Nixon et al. 1992; Pianosi et al. 2005). Several factors contribute

to exercise intolerance in CF including skeletal muscle dysfunction, dysfunctional oxygen uptake kinetics, and abnormal pulmonary mechanics (Fielding et al. 2015; Gruet et al. 2017; Troosters et al. 2009; McKone et al. 2005). However, while the accelerated long-term decline in lung function and exercise capacity in patients with CF has been well-documented (Corey et al. 1976; Penketh et al. 1987; Cantin 1995; Pianosi et al. 2005), long-term changes in ventilatory responses to exercise in CF remain unclear.

The slope of minute ventilation to ventilatory CO_2 output during exercise (V_E/VCO_2) has important prognostic value in patients with heart failure and pulmonary hypertension, even outperforming VO_2 peak as a predictor of survival (Kleber et al. 2000; MacGowan and Murali 2000; Schwaiblmair et al. 2012). The high prognostic value of the V_E/VCO_2 slope in other clinical populations may be partly explained by the fact that it is effort-independent, and thus less susceptible to false interpretation due to early test termination either by the patient or investigator. Indeed, achieving maximal effort during a cardio-pulmonary exercise test (CPET) is dependent on a range of factors including the testing protocol used, intrinsic motivation of the participant, and the participant's perceived exertion (Takken et al. 2017). Routine exercise testing in CF is now recommended (Hebestreit et al. 2015); therefore, monitoring changes in exercise ventilatory parameters may provide enhanced prognostic value in CF compared to traditional exercise outcomes such as VO_2 peak.

A substantial body of evidence demonstrates higher mortality in female patients with CF compared to their male counterparts (Dodge et al. 2007; MacKenzie et al. 2014; Rosenfeld et al. 1997); a phenomenon which is not explained by factors including nutritional status, pulmonary function, or airway microbiology (FitzSimmons 1993). Across varying levels of disease severity [classified by forced expiratory volume in 1 s (FEV_1)], lower absolute peak workload and relative VO_2 peak have been observed in female patients with CF compared to males (Orenstein and Nixon 1991). In healthy children, sex has been implicated as a potential modifier of exercise ventilatory dynamics. Smaller females exhibit a higher V_E for a given VO_2 compared to larger females, while no such trend exists in males (Godfrey et al. 1971). In CF, longitudinal data in young adults suggest a similar degree of change between sexes in lung function, exercise capacity, and V_E peak (Moorcroft et al. 1997). While several indices of ventilatory efficiency during exercise have been shown to be similar between sexes at a single time point (Orenstein and Nixon 1991), it is unknown how sex influences long-term changes in exercise ventilatory parameters, particularly as disease severity worsens. Therefore, the purpose of this study was to examine longitudinal changes in exercise ventilatory parameters in patients with CF and compare the magnitude of change between sexes.

Methods

Participants

Data from 20 patients with CF (10 males, 10 females) age 8–42 years old were available for this retrospective analysis. Participants were excluded if they (1) had a $FEV_1 < 50\%$ of predicted, (2) had a resting oxygen saturation (SpO_2) < 85%, (3) self-reported to be a smoker, (4) were diagnosed with pulmonary hypertension, (5) were diagnosed with sleep apnea or sleep disorders, (6) had a clinical diagnosis of cardiovascular disease, hypertension, or CF-related diabetes, or (7) were prescribed any vaso-active medications (i.e., nitrates, beta blockers, ACE inhibitors, etc.).

All data were routinely collected in the Laboratory of Integrative Vascular and Exercise Physiology at the Georgia Prevention Institute from patients who were participating in various ongoing research studies. Non-interventional patient data (i.e., observational data collection only) on two separate visits [visit 1 (baseline) and visit 2], were required for the present analysis. Patients were only tested if they had been clinically stable (no exacerbations, need for antibiotic treatment, or major change in medical status) for at least 2 weeks prior to testing. In addition, data were included from patients who were taking standard CF therapy [i.e., bronchodilators, daily multivitamin supplements (e.g., AquADEK), and pancreatic enzyme supplements]. Data from patients who were on CFTR modulators (e.g., lumacaftor, ivacaftor); however, were not included in the analysis. Data were collected over a 6 year period between December 2010 and November 2016. All protocols were approved by the Institutional Review Board at Augusta University and all methods were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed assent/consent was obtained by all participants and parents of minors prior to participation.

Participant characteristics and pulmonary function testing

Participant testing included assessments of height, weight, and calculated BMI. Body composition (fat percent and fat-free mass [FFM]) was determined using dual-energy X-ray absorptiometry (DXA; QDR-4500W, Hologic, Waltham, MA). Routine spirometric function testing was performed according to the American Thoracic Society standards (American Thoracic Society 1995). Percent predicted data were determined using the current reference standards available at the time of testing [National

Health and Nutrition Examination Survey (NHANES) III (Hankinson et al. 1999) or the 2012 European Respiratory Society Task Force guidelines (Quanjer et al. 2012)].

Cardio-pulmonary exercise test (CPET)

At each visit, a CPET was performed on a cycle ergometer using the Godfrey protocol to determine exercise capacity as previously described by our group (Tucker et al. 2017). Briefly, expired gases were analyzed in a mixing chamber by a TruOne® 2400 metabolic cart (ParvoMedics, Sandy, UT) and analyzed as 30 s averages to obtain VO_2 peak and peak minute ventilation (V_E peak). Ventilatory threshold (VT) was determined using the v-slope method (Beaver et al. 1986) for calculation of percent VO_2 peak at VT. Additional ventilatory parameters including the ratio of V_E to both VO_2 and carbon dioxide output (VCO_2) at peak exercise (V_E/VO_2 peak and V_E/VCO_2 peak, respectively), end-tidal CO_2 ($P_{ET}CO_2$), and the V_E/VCO_2 slope, were determined according to previously published methodology (Schwaiblmair et al. 2012; Fielding et al. 2015). Maximum voluntary ventilation (MVV) was calculated as 27.7(FEV_1) + 8.8(predicted FEV_1) for patients aged ≤ 18 years (Stein et al. 2003) or $FEV_1 \times 40$ for patients aged > 18 years (Wasserman et al. 2005) and expressed relative to peak V_E (V_E/MVV). Respiratory rate (RR), tidal volume (V_T, corrected for dead space of the breathing apparatus), and fractional expired CO_2 ($FeCO_2$) were determined from the metabolic cart at rest and during exercise.

Statistical analyses

All analyses were performed using SPSS version 24 (IBM Corporation, Somers, NY). Descriptive statistics were generated and range as well as normality checks performed. Two-way repeated measures ANOVA (sex by time) were used to determine group differences in the change over time for all outcomes. Preliminary analyses revealed non-significant associations between the time between visits 1 and 2 and the primary outcome variables (changes in lung function, VO_2 peak, and the V_E/VCO_2 slope). Therefore, time between visits was not included as a covariate in the regression model. The Greenhouse–Geisser correction was applied when the assumption of sphericity was violated. Effect sizes [partial eta squared (η_P^2)] are reported for the interaction terms of the ANOVA, where values of 0.01, 0.06, and 0.14 correspond to small, medium, and large effects, respectively (Cohen 1988). Pearson correlations were used to examine associations between baseline disease severity (FEV_1, % predicted) and changes in exercise ventilatory parameters. Comparisons of baseline (visit 1) participant characteristics were performed using independent group *t* tests. DXA scans were unable to be completed on two female patients, therefore values of FFM, body fat %, and VO_2 relative to FFM are presented with an $n = 8$ in this group. An alpha < 0.05 was considered statistically significant for all analyses. Data are presented as mean ± standard deviation (SD) unless stated otherwise.

Results

Participant characteristics

The majority (15/20) of patients were homozygous for the ΔF508 CFTR mutation (seven males, eight females), two were ΔF508/G551D (one male, one female), two were ΔF508/621 + 1G->T (one male, one female), and one male was homozygous for (TG)11-5T. Participant characteristics are presented in Table 1. At visit 1, severity of lung disease was normal in 12 patients (seven males, five females), mild in six patients (two males, four females), and moderate in two patients (one male, one female). At visit 2, disease severity was normal in seven patients (five males, two females), mild in seven patients (two males, five females), and moderate in six patients (three male, three female). There were no differences in age ($p = 0.217$), BMI ($p = 0.228$), FEV_1 ($p = 0.215$), or FEV_1/FVC ($p = 0.733$) between males and females. At visit 1, height ($p = 0.004$), weight ($p = 0.013$), FFM ($p < 0.001$), and FVC ($p = 0.001$) were all higher in males vs. females, whereas % body fat was lower in males ($p < 0.001$). Overall, the average collection time between visits was 39 ± 16 (range 7–71) months. Importantly, the average time between visits was similar ($p = 0.222$) between males and females [35 ± 20 (range 7–71) vs. 43 ± 10 (range 26–54) months, respectively].

Age, height, weight, BMI, and % body fat all increased between visits, independent of sex (all $p < 0.05$). Overall, FEV_1 (% predicted) decreased over time ($F_{(1,18)} = 22.1$, $p < 0.001$); however, FFM ($F_{(1,18)} = 39.7$, $p = 0.496$), FVC ($F_{(1,18)} = 39.7$, $p = 0.357$), and FVC/FEV_1 ($F_{(1,18)} = 39.7$, $p = 0.548$) did not change. No differences between sexes were observed for changes in any other variable (all $p > 0.05$).

Ventilatory parameters during exercise and exercise capacity

At visit 1, V_E/VO_2 peak (33.4 ± 6.9 vs. 36.1 ± 8.1, $p = 0.432$), V_E/VCO_2 peak (30.5 ± 3.9 vs. 30.4 ± 3.7, $p = 0.954$), and the V_E/VCO_2 slope (28.5 ± 3.8 vs. 27.8 ± 3.5, $p = 0.705$) were not different between females and males, respectively. Overall, V_E/VO_2 peak (Δ10.0 ± 8.1, $F_{(1,18)} = 54.6$, $p < 0.001$), V_E/VCO_2 peak (Δ4.9 ± 4.4, $F_{(1,18)} = 39.7$, $p < 0.001$), and the V_E/VCO_2 slope (Δ4.2 ± 3.6, $F_{(1,18)} = 36.8$, $p < 0.001$) all significantly increased over time. Females, however, exhibited a significantly greater change in V_E/VO_2 peak ($F_{(1,18)} = 16.4$,

Table 1 Participant demographics and parameters of exercise capacity collected from the CPET at visits 1 and 2

Variable	Visit 1		Visit 2		Change	
	Males	Females	Males	Females	Males	Females
Demographics						
Age (years)	20.4 ± 11.4	15.1 ± 6.9	23.2 ± 10.9†	18.7 ± 6.0†	2.8 ± 1.6	3.6 ± 1.3
Height (cm)	169 ± 17	148 ± 11*	171 ± 14†	156 ± 5†	2 ± 4	9 ± 9
Weight (kg)	60.6 ± 16.2	42.6 ± 12.8*	67.3 ± 15.3†	49.3 ± 8.9†	6.7 ± 5.0	6.8 ± 8.8
BMI (kg/m^2)	20.8 ± 3.0	19.1 ± 3.1	22.7 ± 2.9†	19.6 ± 3.9†	1.9 ± 1.5	0.5 ± 2.6
Fat-free mass (kg)[a]	48.5 ± 12.5	30.4 ± 5.9*	48.7 ± 11.7	31.5 ± 2.9	0.2 ± 3.2	1.1 ± 4.6
Body fat (%)[a]	14.5 ± 3.0	27.0 ± 7.2*	22.3 ± 5.8†	33.3 ± 4.7†	7.8 ± 4.8	6.3 ± 4.7
FVC (L)	4.69 ± 1.47	2.74 ± 0.58*	4.60 ± 1.62	3.01 ± 0.52	− 0.10 ± 0.47	0.27 ± 0.35
FEV_1 (% predicted)	96.1 ± 20.8	85.4 ± 16.1	85.6 ± 24.3†	77.6 ± 13.5†	− 10.5 ± 9.1	− 7.8 ± 8.3
FEV_1/FVC	0.78 ± 0.10	0.77 ± 0.06	0.76 ± 0.1	0.77 ± 0.05	− 0.02 ± 0.07	0.01 ± 0.04
Exercise parameters						
VO_2 peak (L/min)	2.08 ± 0.72	1.20 ± 0.21*	2.15 ± 0.64	1.34 ± 0.18	0.07 ± 0.38	0.14 ± 0.16
VO_2 peak (ml/min/kg)	34.1 ± 6.2	29.4 ± 6.0	32.3 ± 5.8	27.5 ± 4.0	− 1.9 ± 5.6	− 1.9 ± 3.8
VO_2 peak (ml/min/kgFFM)[a]	42.4 ± 7.2	41.4 ± 6.0	44.6 ± 8.0	43.1 ± 4.4	2.2 ± 9.2	1.8 ± 4.3
VO_2 peak (% predicted)	79.6 ± 14.1	67.6 ± 7.2*	79.9 ± 15.9	74.3 ± 8.3	0.3 ± 11.4	6.7 ± 7.8
VO_2 peak at VT (%)	55.4 ± 9.2	56.5 ± 5.6	53.7 ± 13.7	61.2 ± 6.2	− 1.7 ± 12.0	4.7 ± 9.5
V_E (L/min)	74.2 ± 30.1	41.3 ± 13.7*	83.6 ± 18.4†	64.9 ± 10.0†	9.4 ± 27.6	23.6 ± 9.9
V_E/MVV (%)	63.7 ± 23.1	59.9 ± 17.2	80.5 ± 28.6†	88.9 ± 22.2†	16.8 ± 29.8	29.0 ± 12.6
V_E/VCO_2 slope at VT	21.1 ± 4.6	21.7 ± 2.0	21.0 ± 3.1	23.0 ± 2.9	0.0 ± 5.2	1.3 ± 2.9
Workload at VT (W)	83 ± 38	41 ± 14*	80 ± 30	57 ± 16	− 6 ± 19	13 ± 20
Peak work (W)	157 ± 48	95 ± 27*	169 ± 39†	117 ± 19†	12 ± 21	22 ± 17
Peak work (W/kg)	2.6 ± 0.3	2.4 ± 0.6	2.5 ± 0.3	2.4 ± 0.3	0.0 ± 0.4	0.0 ± 0.6
Max heart rate (bpm)	165 ± 23	168 ± 14	169 ± 17	172 ± 13	4 ± 20	5 ± 20

Values are mean ± SD

BMI body mass index, *FEV_1* forced expiratory volume in 1 s, *FFM* fat-free mass, *FVC* forced vital capacity, *MVV* maximum voluntary ventilation, *V_T* ventilatory threshold, *V_E* peak ventilation

*Significant difference versus males at visit 1 ($p < 0.05$)

†Significant change from visit 1, independent of sex ($p < 0.05$)

[a]$n = 8$ in females

$p = 0.001$, $\eta_P^2 = 0.48$), V_E/VCO_2 peak ($F_{(1,18)} = 12.8$, $p = 0.002$, $\eta_P^2 = 0.42$), and the V_E/VCO_2 slope ($F_{(1,18)} = 7.0$, $p = 0.016$, $\eta_P^2 = 0.28$) compared to males (Fig. 1). In contrast, absolute VO_2 peak ($F_{(1,18)} = 2.4$, $p = 0.138$), VO_2 peak relative to body mass ($F_{(1,18)} = 3.0$, $p = 0.100$) and FFM ($F_{(1,16)} = 1.3$, $p = 0.276$) did not change over time, nor were there any differences in the magnitude of change between sexes ($p = 0.614$, 0.996, and 0.903, respectively). At visit 1, no differences in RR were present between males and females at rest (21 ± 4 bpm vs. 20 ± 6 bpm, $p = 0.585$), during VT (23 ± 8 bpm vs. 24 ± 6 bpm, $p = 0.728$), or at peak exercise (38 ± 10 bpm vs. 40 ± 8 bpm, $p = 0.612$). However, RR increased significantly between visits in females relative to males at rest (Δ6 ± 4 bpm vs. − 2 ± 5 bpm, $F_{(1,18)} = 13.9$, $p = 0.002$, $\eta_P^2 = 0.44$) and during VT (Δ3 ± 5 bpm vs. − 3 ± 5 bpm, $F_{(1,18)} = 7.2$, $p = 0.015$, $\eta_P^2 = 0.29$), but not at peak exercise (Δ8 ± 7 bpm vs. 5 ± 13 bpm, $F_{(1,18)} = 0.5$, $p = 0.494$, $\eta_P^2 = 0.03$).

As illustrated in Fig. 2, while $FeCO_2$ at peak exercise was similar between groups at visit 1 ($p = 0.725$), there was a significantly greater reduction ($F_{(1,18)} = 6.4$, $p = 0.021$, $\eta_P^2 = 0.26$) between visits in female patients, although $FeCO_2$ was not significantly different ($p = 0.073$) between groups at visit 2 (Fig. 2a). Similarly, there were no differences in peak $P_{ET}CO_2$ between groups at visit 1 ($p = 0.715$), however, females exhibited a significantly greater decline ($F_{(1,18)} = 12.9$, $p = 0.002$, $\eta_P^2 = 0.42$) and lower peak $P_{ET}CO_2$ at visit 2 ($p = 0.017$; Fig. 2b).

Independent of sex, V_E peak ($F_{(1,18)} = 12.7$, $p = 0.002$), V_E/MVV ($F_{(1,18)} = 20.0$, $p < 0.001$), and absolute peak workload ($F_{(1,18)} = 15.6$, $p = 0.001$) significantly increased over time (Table 1). There were no significant changes over time in % predicted VO_2 peak ($F_{(1,18)} = 2.6$, $p = 0.126$), VO_2 peak at VT ($F_{(1,18)} = 0.4$, $p = 0.542$), workload at VT ($F_{(1,17)} = 0.7$, $p = 0.409$), V_E/VCO_2 slope at VT ($F_{(1,18)} = 0.4$, $p = 0.512$), relative peak workload

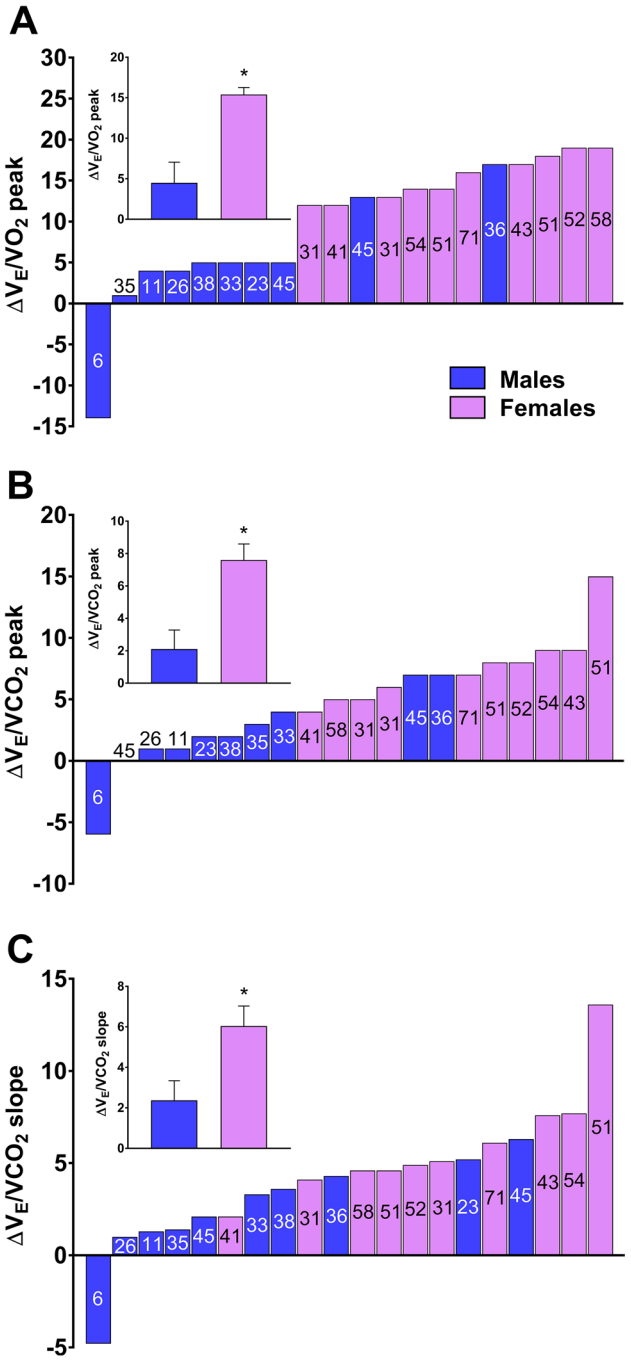

Fig. 1 Individual and mean (inset) changes in the ratio of minute ventilation (V_E) to oxygen uptake (VO_2) at peak exercise (**a**), V_E to carbon dioxide output (VCO_2) at peak exercise (**b**), and the V_E to VCO_2 slope (**c**) in male and female patients between visits 1 and 2. The time between visits (months) is presented with each column for each patient. Asterisk significantly greater in females vs. males ($p \leq 0.016$)

($F_{(1,18)} = 0.0$, $p = 0.964$), or max heart rate during exercise ($F_{(1,18)} = 0.9$, $p = 0.364$). In addition, the magnitude of change for these variables was not different between sexes (all $p > 0.05$).

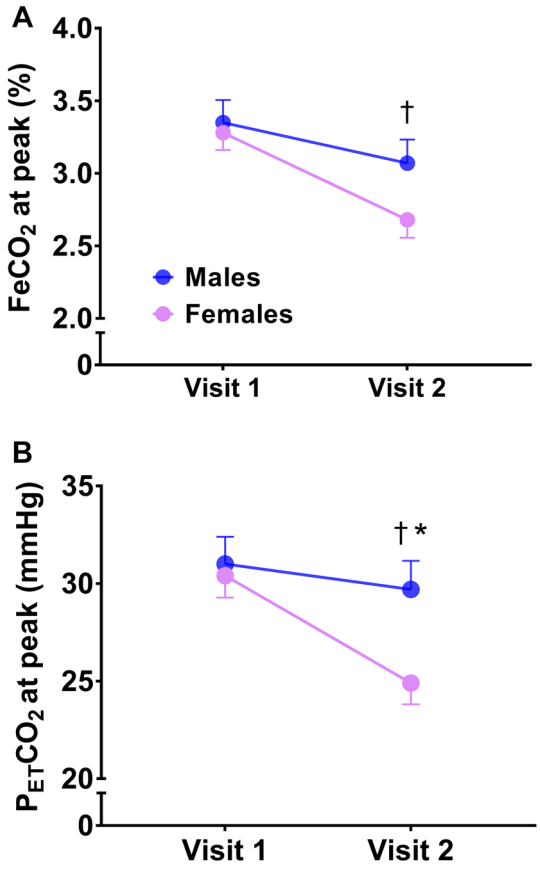

Fig. 2 Group changes between visits in $FeCO_2$ at peak exercise (**a**) and $P_{ET}CO_2$ at peak exercise (**b**). Dagger significant group by time interaction; asterisk significant difference between groups at visit 2 ($p = 0.017$)

Relationships between disease severity and $FeCO_2$ and changes in ventilatory parameters during exercise

As illustrated in Fig. 3, in the overall sample (males and females combined), there were significant associations between baseline disease severity (FEV_1, % predicted) and changes in exercise ventilatory parameters. Specifically, baseline FEV_1 was negatively associated with changes in V_E/VCO_2 peak ($r = -0.545$, $p = 0.013$; Fig. 3a) and the V_E/VCO_2 slope ($r = -0.469$, $p = 0.037$; Fig. 3b) but not V_E/VO_2 peak ($r = -0.404$, $p = 0.077$; Fig. 3c). Changes in FEV_1 were not significantly associated with concomitant changes in exercise ventilatory parameters (all $p > 0.05$). Significant negative associations were also present between changes in $FeCO_2$ at peak (%) and changes in V_E/VO_2 peak ($r = -0.842$, $p < 0.001$; Fig. 3d), V_E/VCO_2 peak ($r = -0.772$, $p < 0.001$; Fig. 3e) and the V_E/VCO_2 slope ($r = -0.742$, $p < 0.001$; Fig. 3f).

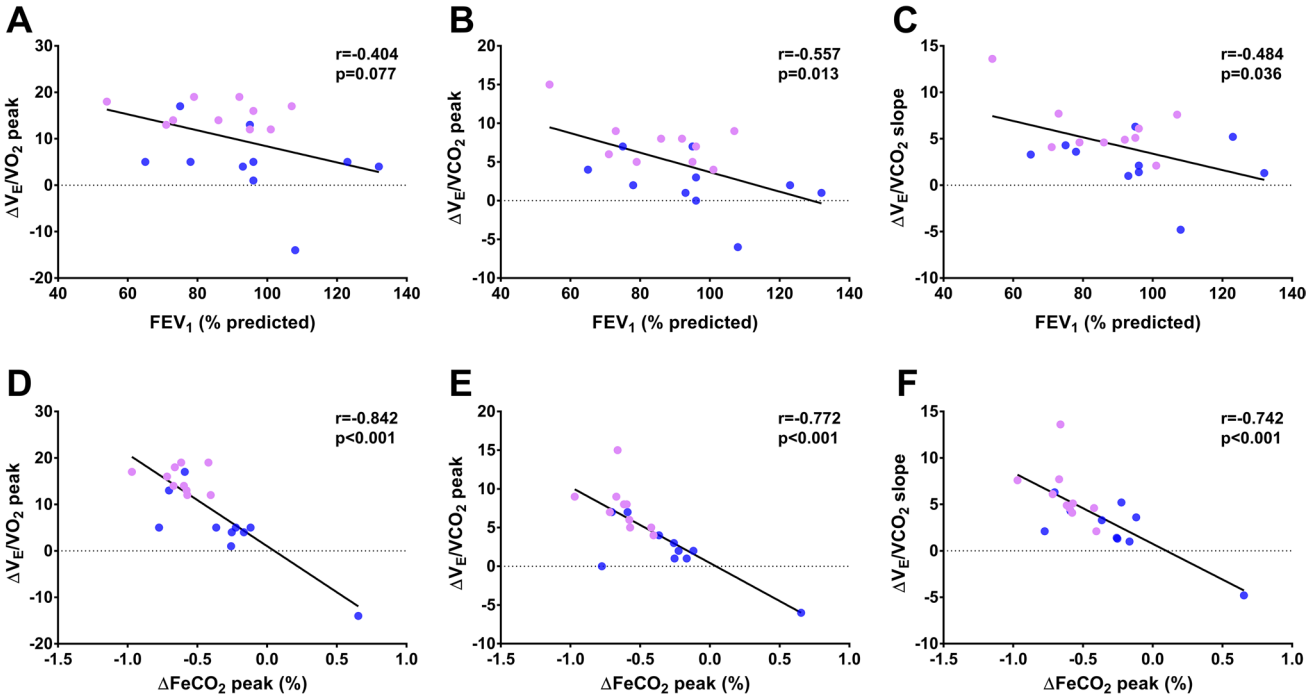

Fig. 3 Associations between baseline FEV_1 (% predicted) and changes in exercise ventilatory parameters (**a**–**c**) and between changes in $FeCO_2$ at peak and exercise ventilatory parameters (**d**–**f**). Lilac and blue dots indicate female and male patients, respectively

Discussion

Exercise capacity (VO_2 peak) predicts survival in patients with CF. Exercise ventilatory parameters provide prognostic utility in other diseases (Guazzi et al. 2003; MacGowan and Murali 2000; Schwaiblmair et al. 2012) and data from the present study indicate that patients with CF exhibit a deterioration in exercise ventilatory parameters over a period of ~3 years, despite non-significant changes in VO_2 peak. In addition, female patients exhibited a more pronounced deterioration in exercise ventilatory parameters compared to males.

The ventilatory response during exercise evaluates ventilatory efficiency and can be influenced by factors such as CO_2 production and the ventilatory dead space-to-tidal volume (V_D/V_T) ratio (Guazzi et al. 2003). In the present study, there was an overall worsening in exercise ventilatory parameters over time, with no significant change in VO_2 peak. The second novel finding is that female patients exhibited a significantly greater deterioration in exercise ventilatory parameters compared to males (Fig. 1), despite similar rates of decline in lung function and VO_2 peak. Importantly, the average time between visits was not significantly different between males and females ($p = 0.222$). Moreover, even when controlling for this factor by including it as a covariate in the regression model, the significant sex by time interaction remained for changes in exercise ventilatory parameters, suggesting that the time between visits did not significantly influence our findings. This sex disparity may be explained, in part, by the observed reduction in CO_2 production and/or reduced chemosensitivity to arterial PCO_2 ($PaCO_2$) during exercise in females relative to males. In the present study, RR increased between visits in females compared to males at rest (Δ6 bpm vs. − 2 bpm) and during VT (Δ3 bpm vs. − 3 bpm), and females exhibited a significantly lower $FeCO_2$ at rest (2.23% vs. 2.75%) and tendency for lower $FeCO_2$ at peak exercise (2.67% vs. 3.07%, $p = 0.073$) compared to males at visit 2 (Fig. 2a). Previous work in children and young adults with CF suggests that as disease severity worsens (demonstrated via declining FEV_1) there is an increase in the respiratory muscle load that is predominated by decreased lung compliance (Hart et al. 2002). As a compensatory mechanism, respiratory rate increases to maintain ventilation but is unable to efficiently clear CO_2. While not significantly different at either visit 1 or visit 2, FEV_1 (% predicted) was lower in female patients by ~9–10 percentage points. This raises the possibility that disease severity progressed to a point in female patients between visits where lung compliance was compromised enough to impair ventilatory mechanics during exercise, possibly due to changes in airway obstruction and/or mucus plugging. Indeed, increased airflow accompanying the increased RR in females may have also contributed to greater airway dead space (Thin et al. 2004). Unfortunately, using end-tidal PCO_2 to estimate $PaCO_2$ is unreliable in pulmonary diseases such as CF (Pianosi and Hochman 1996) and therefore,

V_D/V_T could not be accurately assessed non-invasively in the present investigation. Future studies examining longitudinal changes in lung compliance/resistance and airway dead space in combination with exercise ventilatory parameters are warranted to further our understanding of sex-mediated changes in exercise ventilatory efficiency in CF.

Previous work suggests that long-term maintenance of exercise capacity in CF may be attributed to a number of factors including improved nutritional status (Moorcroft et al. 1997), typically evidenced via weight gain. Indeed, both groups exhibited significant increases in body mass and BMI over time; however, the change was not different between sexes. Exercise capacity was maintained between visits, yet a steep decline in exercise ventilatory parameters was observed. Accordingly, the decline in ventilatory efficiency during exercise may precede reductions in exercise capacity, suggesting that ventilatory dynamics during exercise may be a more sensitive prognostic indicator of changes in exercise tolerance in CF compared to VO_2 peak. In addition, while the longitudinal changes in lung function and exercise capacity in the present study are consistent with a previous report (Moorcroft et al. 1997), the observed sex disparity in exercise ventilation changes is unique to this investigation and may provide further insight into the increased mortality rate that is observed in female patients with CF compared to males (Dodge et al. 2007; MacKenzie et al. 2014).

Longitudinal data from Pianosi et al. indicate that disease severity (FEV_1, % predicted) contributes to the rate of decline in exercise capacity (Pianosi et al. 2005). Indeed, findings from the present study follow a similar trend to this previous observation as baseline FEV_1 was significantly associated with changes in exercise ventilatory parameters (Fig. 3). Accordingly, the present data suggest that a greater rate of decline in exercise ventilatory parameters occurs in patients with greater disease severity, suggesting a role of disease severity as a contributing factor towards the deterioration in ventilatory efficiency during exercise. However, changes in FEV_1 over time were not significantly associated with concomitant changes in exercise ventilatory parameters.

Experimental considerations

Physical activity level has been shown to independently predict exercise capacity in patients with CF (Hebestreit et al. 2006). Given the importance of maintaining VO_2 peak in this population (Nixon et al. 1992; Pianosi et al. 2005), regular physical activity is recommended for patients with CF (Philpott et al. 2010). In the present study, concomitant changes in exercise training status and/or habitual physical activity levels were not monitored over the observation period. Thus, it is unclear how potential changes in these variables may have contributed to the observed changes in exercise ventilatory parameters. Moreover, habitual physical activity patterns can be different between sexes in CF, particularly during childhood, as boys tend to be more physically active than girls (Schneiderman-Walker et al. 2005). Future studies should seek to examine longitudinal changes in exercise ventilatory parameters in patients with CF while simultaneously controlling for the added influence of changes in physical activity and/or exercise training status.

Independent of sex, age has been shown to be a major determinant of exercise ventilatory control. Not only do healthy children demonstrate greater CO_2 chemosensitivity during exercise compared to adults (Gratas-Delamarche et al. 1993), an age-related decline in ventilatory responses to exercise has also been reported in patients with CF throughout childhood (Pianosi and Wolstein 1996). In the present study, while the difference in age between males and females was not statistically significant at visit 1 (20 years vs. 15 years, $p = 0.217$), it could be reasoned that the accelerated decline in ventilatory efficiency in females may have been due to differences in physical maturation compared to their male counterparts. However, there was no association between age at visit 1 and changes in V_E/VCO_2 slope ($r = 0.031$, $p = 0.897$) suggesting that group differences in maturation was likely not a significant contributing factor.

Conclusions

In summary, data from this study in patients with CF suggest that (1) the worsening in exercise ventilatory parameters may precede the decline in VO_2 peak, and (2) females exhibit a greater deterioration in exercise ventilatory parameters over time compared to males, despite similar changes in VO_2 peak and lung function. Given the disproportionate mortality risk between sexes in CF, these data support further investigation into the potential prognostic value of exercise ventilatory parameters in patients with CF. Future studies using a larger cohort, coupled with multiple experimental visits and a longer observation are warranted to further our understanding of the interrelationships between sex, disease severity, and long-term changes in exercise ventilatory parameters in patients with CF.

Author contributions MAT and RAH conceived the study; MAT, NS, PRM, JL, RHC, CF, and KTM recruited patients and collected data; MAT and RAH analyzed and interpreted data and drafted the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Compliance with ethical standards

Conflict of interest None to declare.

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