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Ventilatory response to exercise in adolescents with cystic fibrosis and mild-to-moderate airway obstruction

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Abstract

Data regarding the ventilatory response to exercise in adolescents with mild-to-moderate cystic fibrosis (CF) are equivocal. This study aimed to describe the ventilatory response during a progressive cardiopulmonary exercise test (CPET) up to maximal exertion, as well as to assess the adequacy of the ventilatory response for carbon dioxide (CO₂) exhalation. Twenty-two adolescents with CF (12 boys and 10 girls; mean ± SD age: 14.3 ± 1.3 years; FEV₁: 78.6 ± 17.3% of predicted) performed a maximal CPET. For each patient, data of a sex- and age matched healthy control was included (12 boys and 10 girls; mean ± SD age: 14.3 ± 1.4 years). At different relative exercise intensities of 25%, 50%, 75%, and 100% of peak oxygen uptake (VO_{2peak}), breathing pattern, estimated ventilatory dead space ventilation (VD/VT ratio), minute ventilation (VE) to CO₂ production relationship (VE/VCO₂-slope), partial end-tidal CO₂ tension (P_{ET}-CO₂), and the VE to the work rate (VE/WR) ratio were examined. VO_{2peak} was significantly reduced in CF patients (P = 0.01). We found no differences in breathing pattern between both groups, except for a significantly higher VE at rest and a trend towards a lower VE at peak exercise in patients with CF. Significantly higher values were found for the estimated VD/VT ratio throughout the CPET in CF patients (P < 0.01). VE/VCO₂-slope and P_{ET}-CO₂ values differed not between the two groups throughout the CPET. VE/WR ratio values were significantly higher in CF during the entire range of the CPET (P < 0.01). This study found an exaggerated ventilatory response (high VE/WR ratio values), which was adequate for CO₂ exhalation (normal VE/VCO₂-slope and P_{ET}-CO₂ values) during progressive exercise up to maximal exhaustion in CF patients with mild-to-moderate airway obstruction.

Keywords: Pulmonary physiology; Ventilation; Breathing pattern; Children

Background

Peak oxygen uptake (VO_{2peak}) is reported to be limited in patients with cystic fibrosis (CF) (Bongers et al. 2012; Hjeltnes et al. 1984; Keochkerian et al. 2008; Shah et al. 1998; Wideman et al. 2009). This reduction seems to have a multifactorial cause (Selvadurai et al. 2002). Respiratory, cardiovascular, as well as peripheral muscle function are reported as potential exercise limiting mechanisms (Almajed and Lands 2012). In patients with mild to moderate pulmonary disease, non-pulmonary factors, such as low muscle mass, impaired skeletal muscle function and centrally mediated oxygen delivery, seem to predominate

in limiting exercise capacity (Regnis et al. 1996; Moorcroft et al. 2005; Saynor et al. 2014). In more severe patients with CF (forced expiratory volume in one second (FEV₁) <60% of predicted), ventilatory constraints and impaired gas exchange become more important determinants.

Due to continuous airflow obstruction, as reflected by a decreased FEV₁ and dynamic hyperinflation, adolescents with CF have been described to develop a rapid shallow breathing pattern at rest (Hart et al. 2002) and during exercise (Keochkerian et al. 2005). This can be accompanied with a decreased ventilatory capacity and concomitant reduced VO_{2peak} (Keochkerian et al. 2008). Children and adolescents with CF with static hyperinflation at rest (residual volume to total lung capacity ratio (RV/TLC) >30%) seem to be more prone to a ventilatory limitation during exercise, which appears to be associated with decreased

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exercise performance (Sovtic et al. 2013; Werkman et al. 2010).

A recent study found that exercise limitation in adult patients with CF is multifactorial and that it was dominantly correlated with FEV₁ and nutritional and inflammatory status, but also with the magnitude of the overall ventilatory response during exercise (Pastré et al. 2014). In patients with severe airway obstruction (FEV₁ < 50% of predicted), multivariate analysis revealed the FEV₁ to be a significant independent predictor of exercise capacity, whereas the ratio between minute ventilation and carbon dioxide exhalation (VE/VCO₂ ratio) at peak exercise was the major determinant of exercise limitation in patients with mild-to-moderate disease (FEV₁ > 50% of predicted) (Pastré et al. 2014). However, knowledge about the ventilatory response to exercise in adolescent patients with mild to moderate CF is ambiguous and inconclusive. Several studies in mild-to-moderate adolescents with CF describe an exaggerated ventilatory response with a rapid shallow breathing pattern at rest (Hart et al. 2002) and during exercise (Keochkerian et al. 2008). On the contrary, a recent study in adolescents with mild CF did not find any evidence for a different ventilatory response and/or rapid shallow breathing pattern during exercise (Borel et al. 2014). As the two studies demonstrating exaggerated ventilatory responses were performed in adolescents with CF with lower FEV₁ values, this suggests that the ventilatory response to exercise is at least partially affected by the degree of airway obstruction.

Moreover, questions can be raised whether the adopted rapid shallow breathing pattern is beneficial as higher breathing frequencies seem to increase ventilatory dead space ventilation (VD/VT ratio), as has been reported in patients with CF waiting for lung transplantation (Thin et al. 2004). However, adding additional dead space volume during exercise in patients with mild CF lung disease had no influence on VO_{2peak} and the duration of the exercise test, and it even increased ventilation which was attributed to an increased tidal volume with no change in respiratory rate (Dodd et al. 2006). The increased dead space volume was accompanied by higher VE/VCO₂ ratios during exercise (Dodd et al. 2006). This finding in patients with mild CF suggests that the ventilatory response during exercise in adolescents with CF might differ with healthy controls and that this might alter during the course of the disease. Unfortunately the recent study of Borel et al. (2014), which focussed on ventilation during the entire range of exercise, only mentioned mechanical constraints influencing ventilation and did not discuss metabolic issues related to ventilation. Moreover, they included small and unequal groups of only prepubertal children.

As lung function decreases over time in most patients with CF, exercise capacity eventually becomes limited by

the lungs reaching their mechanical limits to expand (approximately at FEV₁ values ≤60%pred) (Almajed and Lands 2012). Insight in the breathing pattern during progressive exercise in adolescents with CF in a broad spectrum of lung function deterioration, as well as the adequacy of this ventilatory response for carbon dioxide (CO₂) exhalation, is clinically relevant for future therapeutic interventions. Therefore, the aim of the current study was 1) to describe the ventilatory response during a progressive cardiopulmonary exercise test (CPET) up to maximal exertion in adolescents with mild-to-moderate CF and 2) to assess the adequacy of the ventilatory response for CO₂ exhalation (determined from partial end-tidal carbon dioxide tension (P_{ET}CO₂)) throughout the CPET in mild-to-moderate patients with CF. Our hypothesis is that adolescents with CF develop an obstructive breathing pattern, combined with a relatively large VD/VT ratio, which limit CO₂ wash out.

Methods

Participants

Exercise data of twenty-two adolescents (12 boys and 10 girls from 12 to 17 years of age, mean ± SD age: 14.3 ± 1.3 years) with mild-to-moderate CF were randomly selected from the exercise database from the CF Center at the University Medical Center Utrecht. The database contained anonymous patient data of anthropometry, lung function and exercise capacity which was measured as part of usual care at the routine annual check-up. Therefore, all patients were free from acute pulmonary or gastrointestinal exacerbation at the time of testing. Testing procedures used in this study met the assumptions for standard of practice for the routine care of patients with CF. For each patient with CF, an age, sex and anthropometrically matched healthy control who performed a maximal CPET in our hospital retrospectively was selected (untrained and normal physical activity level). All participants and their guardians provided approval for inclusion of the data in research studies. After evaluation, the medical ethical committee of the University Medical Center Utrecht determined that inclusion of the data conformed to the regulations of the Dutch CF Registration and that inclusion of the data in this study met the ethical policies of the University Medical Center Utrecht, as well as the regulations of the Dutch government.

Anthropometric measures

Body mass and body height were determined using an electronic scale (Seca, Hamburg, Germany) and a stadiometer (Ulmer Stadiometer, Ulm, Germany) respectively. Body mass index (BMI) was calculated as the body mass in kilograms divided by the square of the body height in meters. Standard deviation (SD) scores were calculated

for body height for age, body mass for age, and BMI for age using Dutch normative values (Fredriks et al. 2000). The equation of Haycock et al. (1978), validated in infants, children, and adults, was used to obtain the participants' body surface area (BSA).

Spirometry and plethysmography

In the patients with CF, spirometry and plethysmography were performed by qualified lung function analysts of the CF Center at the University Medical Center Utrecht. Since the healthy controls were not known with any disease, spirometry and plethysmography was not performed in this group. In order to prevent the potential influence of bronchial reactivity during exercise, spirometry and plethysmography were performed after bronchodilation with salbutamol (800 µg). FEV₁ was obtained from flow volume curves (Masterscreen, Jaeger, Würzburg, Germany). Residual volume (RV) and total lung volume (TLC) were determined in a body plethysmograph (Master Lab system, Jaeger, Würzburg, Germany). The RV was expressed as a percentage of TLC (RV/TLC ratio) as well. In order to improve comparative possibilities with the reports of other studies in CF, we used the commonly used reference values of Zapletal et al. (1987) to express lung function values as percentage of predicted values.

Cardiopulmonary exercise test

All participants completed a maximal CPET using an electronically braked cycle ergometer (Jaeger Physis, Carefusion, Houten, The Netherlands) after bronchodilation with salbutamol. After three minutes of rest measurements, cycling started at a workload of 0 W. Then, the work rate (WR) was linearly incremented with a 15 W·min⁻¹ ramp protocol (Godfrey 1974) until the patient stopped due to volitional exhaustion, despite strong verbal encouragement. The test effort was considered maximal when the participant showed objective (heart rate (HR) at peak exercise (HR_{peak}) >180 beats·min⁻¹ and/or a respiratory exchange ratio (RER) at peak exercise (RER_{peak}) >1.0) (Armstrong and Welsman 2008) and subjective (unsteady biking, sweating, facial flushing, and clear unwillingness to continue despite encouragement) signs of maximal effort.

Throughout the CPET, participants breathed through a facemask (dead space volume 63 or 72 mL, dependent on size) (Hans Rudolph Inc, Kansas City, MO) that was connected to a calibrated metabolic cart (Oxycon Pro, Carefusion, Houten, the Netherlands). Gas analyzers were calibrated using gases of known concentration, whereas the flow meter was calibrated using a three-liter syringe (Hans Rudolph Inc, Kansas City, MO). Expired gas passed through a flow meter and a gas analyzer connected to a computer, which calculated breath-by-breath minute

ventilation (VE), oxygen uptake (VO₂), VCO₂ and RER from conventional equations. Output from the flow meter and gas analyzers were averaged over ten-second intervals and stored for further use. Relative VO_{2peak} (VO_{2peak}/kg) was calculated by dividing VO_{2peak} by body mass. HR was monitored continuously by a three-lead electrocardiogram (Hewlett-Packard, Amstelveen, Netherlands) and transcutaneous O₂ saturation at the index finger was measured by pulse oximetry (Nellcor 200 E, Nellcor, Breda, the Netherlands). Peak exercise parameters were defined as the highest values achieved within the last 30 seconds prior to exhaustion.

Data analysis

The ventilatory threshold was defined as the point at which the ventilatory equivalent for oxygen and the partial end-tidal oxygen tension reached a minimum and thereafter began to rise in a consistent manner, coinciding with an unchanged ventilatory equivalent for carbon dioxide and a peak in the P_{ET}CO₂ course (American Thoracic Society, American College of Chest Physicians 2003; Ohuchi et al. 1996). When this ventilatory equivalents

Table 1 Participant characteristics

	Healthy (n = 22)	CF (n = 22)	P-value
Sex (boy/girl)	12/10	12/10	NA
Age (years)	14.3 ± 1.4	14.3 ± 1.3	0.99
CF mutation class (I/II/IV/unknown) ^a	NA	9/27/1/6	NA
PA colonization (never/free of infection/intermittent/chronic) ^b	NA	6/1/6/9	NA
Body height (m)	1.67 ± 0.10	1.65 ± 0.09	0.61
Body height for age SDS ^c	0.17 ± 0.86	-0.18 ± 0.99	0.24
Body mass (kg)	53.9 ± 12.2	50.2 ± 7.2	0.31
Body mass for age SDS ^c	0.02 ± 0.83	-0.37 ± 0.64	0.13
BMI (kg · m ⁻²)	19.1 ± 2.6	18.5 ± 2.0	0.51
BMI for age SDS ^c	-0.09 ± 0.80	-0.34 ± 0.85	0.37
BSA (m ²)	1.57 ± 0.22	1.54 ± 0.14	0.72
FEV ₁ (L)	NA	2.52 ± 0.67	NA
FEV ₁ (%pred) ^d	NA	78.6 ± 17.3	NA
RV/TLC (%)	NA	33.5 ± 9.3	NA
VO _{2peak} /kg (mL · kg ⁻¹ · min ⁻¹)	49.1 ± 7.2	42.4 ± 8.7	<0.01**

Values are presented as mean ± SD.

Abbreviations: BMI body mass index, BSA body surface area, CF cystic fibrosis, CFTR cystic fibrosis transmembrane conductance regulator, FEV₁ forced expiratory volume in one second, NA not applicable, NS not statistically significant, RV/TLC residual volume to total lung capacity ratio, SDS standard deviation score.

**P < 0.01.

^aBased on the classification of CFTR alleles used by Green et al. (2010).

^bBased on the criteria of Lee et al. (2003).

^cReference values of Fredriks et al. (2000).

^dReference values of Zapletal et al. (1987).

method appeared to provide uncertain results for a participant's ventilatory threshold ($n = 4$, 18% in the CF patients, $n = 0$ in the healthy controls), the point at which the linear slope of the relation between the VCO_2 and VO_2 changed was taken as the ventilatory threshold, according to the V-slope method (Beaver et al. 1986). The ventilatory threshold (VO_2) was expressed as an absolute value, relative value (VO_2 normalized for body mass) and as a percentage of the attained VO_{2peak} . The estimated VD/VT ratio was calculated by using the $P_{ET}CO_2$. The graphical presentation of VE as a function of VCO_2 during the progressive CPET was used to determine the point at which VE increased out of proportion to VCO_2 , the respiratory compensation point.

Next to resting values, tidal volume, breathing frequency, VE , VD/VT ratio, and $P_{ET}CO_2$ were determined as an average of 30 seconds at different exercise intensities of 25%, 50%, 75% and 100% of VO_{2peak} . Both VE and tidal volume were adjusted for body mass as well. To allow for fair comparison, resting VO_2 was subtracted from VO_{2peak} . Subsequently, 25%, 50%, 75% and 100% of this delta VO_2 was calculated and summed with the resting VO_2 for each participant (CF patients and healthy controls). Furthermore, we calculated the VE to VO_2 relationship (VE/VO_2 -slope) and the VE to VCO_2 relationship (VE/VCO_2 -slope) at the same different exercise intensities by linear regression of the exercise data up to 25%, 50%, 75%, and 100% of VO_{2peak} using the least squares

Table 2 Exercise performance in the healthy adolescents and adolescents with CF

	Healthy (n = 22)	CF (n = 22)	P-value
Maximal values			
HR_{peak} (beats \cdot min $^{-1}$)	192 \pm 7	186 \pm 8	0.02*
RER_{peak}	1.15 \pm 0.08	1.19 \pm 0.09	0.16
WR_{peak} (W)	222 \pm 62	164 \pm 32	<0.01**
WR_{peak}/kg (W \cdot kg $^{-1}$)	4.2 \pm 0.6	3.3 \pm 0.5	<0.001***
VO_{2peak} (mL \cdot min $^{-1}$)	2638 \pm 685	2126 \pm 516	0.01*
VO_{2peak}/kg (mL \cdot kg $^{-1}$ \cdot min $^{-1}$)	49.1 \pm 7.2	42.4 \pm 8.7	<0.01**
VO_{2peak}/BSA (mL \cdot m 2 \cdot min $^{-1}$)	1667 \pm 259	1378 \pm 274	<0.01**
VCO_{2peak} (mL \cdot min $^{-1}$)	2963 \pm 871	2409 \pm 540	0.03*
VCO_{2peak}/kg (mL \cdot kg $^{-1}$ \cdot min $^{-1}$)	54.9 \pm 8.9	48.1 \pm 9.7	0.02*
$VE @ VO_{2peak}$ (L \cdot min $^{-1}$)	89.5 \pm 27.2	75.8 \pm 18.8	0.08
$VE/kg @ VO_{2peak}$ (L \cdot kg $^{-1}$ \cdot min $^{-1}$)	1.7 \pm 0.3	1.5 \pm 0.3	0.04*
Absolute tidal volume @ VO_{2peak} (mL)	1736 \pm 339	1616 \pm 373	0.32
Relative tidal volume @ VO_{2peak} (mL \cdot kg $^{-1}$)	32.7 \pm 4.8	32.2 \pm 6.4	0.98
Breathing frequency @ VO_{2peak} (breaths \cdot min $^{-1}$)	51 \pm 9	48 \pm 9	0.25
Estimated VD/VT ratio @ VO_{2peak} (%)	17 \pm 2	21 \pm 4	<0.001***
$P_{ET}CO_2 @ VO_{2peak}$ (mmHg)	36.3 \pm 3.2	38.2 \pm 3.7	0.10
VE/WR ratio @ VO_{2peak} (mL \cdot min $^{-1}$ \cdot W $^{-1}$)	399 \pm 57	476 \pm 71	<0.001***
Submaximal values			
Absolute ventilatory threshold (mL \cdot min $^{-1}$)	1439 \pm 381	1216 \pm 253	0.07
Relative ventilatory threshold (mL \cdot kg $^{-1}$ \cdot min $^{-1}$)	27.1 \pm 6.1	24.4 \pm 5.1	0.13
Ventilatory threshold (% VO_{2peak})	55 \pm 9	58 \pm 9	0.32
$P_{ET}CO_2 @ rest$ (mmHg)	31.8 \pm 2.4	33.5 \pm 3.2	0.03*
$P_{ET}CO_2 @ the ventilatory threshold$ (mmHg)	39.3 \pm 3.6	40.0 \pm 2.6	0.50
VE/VO_2 -slope up to the ventilatory threshold	20.5 \pm 3.2	23.7 \pm 5.1	0.02*
VE/VCO_2 -slope up to the respiratory compensation point	26.6 \pm 2.8	27.1 \pm 2.9	0.60

Values are presented as mean \pm SD.

Abbreviations: BSA body surface area, CF cystic fibrosis, HR_{peak} peak heart rate, NS not statistically significant, $P_{ET}CO_2$ partial end-tidal carbon dioxide tension, RER_{peak} peak respiratory exchange ratio, VCO_{2peak} peak carbon dioxide output, VCO_{2peak}/kg peak carbon dioxide output normalized for body mass, VD/VT ratio physiological dead space ventilation, VE minute ventilation, VE/kg minute ventilation normalized for body mass, VE/VCO_2 -slope slope of the relationship between minute ventilation and carbon dioxide output, VE/VO_2 -slope slope of the relationship between minute ventilation and oxygen uptake, VE/WR minute ventilation to work rate ratio, VO_{2peak} peak oxygen uptake, VO_{2peak}/kg peak oxygen uptake normalized for body mass, WR_{peak} peak work rate, WR_{peak}/kg peak work rate normalized for body mass.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

approach. We examined the participants' response of the VE to the WR (VE/WR ratio) at similar intensities. Data from the first minute of exercise were excluded since the breathing pattern during the first minute of exercise frequently appears to be unstable.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS, version 15.0; SPSS Inc., Chicago, IL) was used for the data-analysis. Shapiro-Wilk tests for normality were performed in order to evaluate the data distribution of each variable. Differences between adolescents with CF and their healthy counterparts in anthropometry and in exercise data at different exercise intensities were examined with Mann-Whitney U tests. Data are presented as mean values \pm SD. A P-value <0.05 was considered as statistically significant.

Results

Anthropometric data for the patients with CF and the healthy controls are presented in Table 1, with no significant anthropometric between-group differences. Lung function characteristics of the adolescents with CF are also shown in Table 1. Patients had mild-to-moderate airway obstruction (mean FEV₁ expressed as a percentage of predicted of $79 \pm 17\%$) and a mild-to-moderate degree of static hyperinflation (mean RV/TLC ratio of $34 \pm 9\%$). More specifically, 14 patients (5 boys and 9 girls) had an absolute RV/TLC ratio greater than 30%, which suggests static hyperinflation (Eid et al. 2000).

All participants performed a maximal effort during the CPET (mean test duration of 623 ± 139 and $659 \pm$

194 seconds for the CF patients and healthy controls respectively), and the results are presented in Table 2. Compared with the healthy controls, adolescents with CF attained significantly lower values for HR_{peak}, peak WR (WR_{peak}), WR_{peak}/kg, VO_{2peak}, VO_{2peak}/kg, VO_{2peak}/m² (normalized for BSA), peak VCO₂ (VCO_{2peak}), VCO_{2peak}/kg, and peak VE (VE_{peak}) normalized for body mass (VE_{peak}/kg), whereas they attained significantly higher values for the estimated VD/VT ratio at peak exercise, the VE/VO₂-slope up to the ventilatory threshold, P_{ETCO₂} at rest, and the VE/WR ratio at peak exercise.

Breathing pattern components, tidal volume and breathing frequency, adopted during exercise did not differ significantly between patients with CF and healthy adolescents, except for a significantly higher breathing frequency at rest (19 ± 3 versus 22 ± 5 breaths \cdot min⁻¹; $P = 0.02$) and a trend for lower absolute tidal volume values at or near maximal exercise in patients with CF (1.74 ± 0.34 versus 1.62 ± 0.37 L; $P = 0.32$). Consequently, VE at rest was significantly higher (11.5 ± 2.1 versus 13.8 ± 3.4 L \cdot min⁻¹; $P = 0.02$), whereas VE_{peak} (75.8 ± 18.8 versus 89.5 ± 27.2 L \cdot min⁻¹; $P = 0.08$) tended to be lower in patients with CF. VE normalized for body mass (VE/kg) was significantly higher at rest (0.2 ± 0.05 versus 0.3 ± 0.06 L \cdot kg⁻¹ \cdot min⁻¹; $P < 0.01$) and at 25% of VO_{2peak} (0.4 ± 0.07 versus 0.5 ± 0.08 L \cdot kg⁻¹ \cdot min⁻¹; $P = 0.03$) in the patients with CF. Values for breathing frequency divided by the tidal volume (rapid shallow breathing index) tended to be higher in patients with CF at rest (32 ± 13 versus 38 ± 13 ; $P = 0.14$) and at 25% of VO_{2peak} (27 ± 10 versus 32 ± 15 ; $P = 0.31$). Furthermore, estimated VD/VT ratio values were significantly higher during all

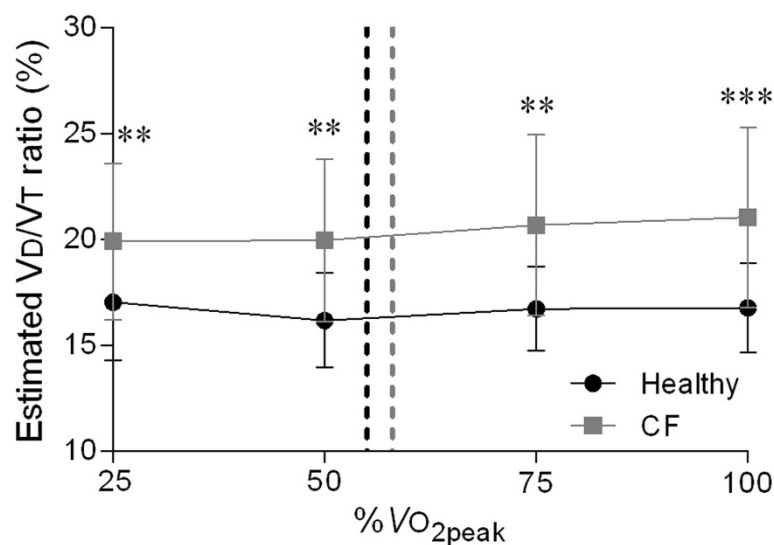


Figure 1 Changes in the estimated VD/VT ratio during exercise at similar percentages of VO_{2peak} in the healthy adolescents and the adolescents with CF. Dashed lines correspond to the ventilatory threshold in both groups. Abbreviations: CF = cystic fibrosis; VD/VT ratio = physiological dead space ventilation; VO_{2peak} = peak oxygen uptake. ** $P < 0.01$; *** $P < 0.001$.

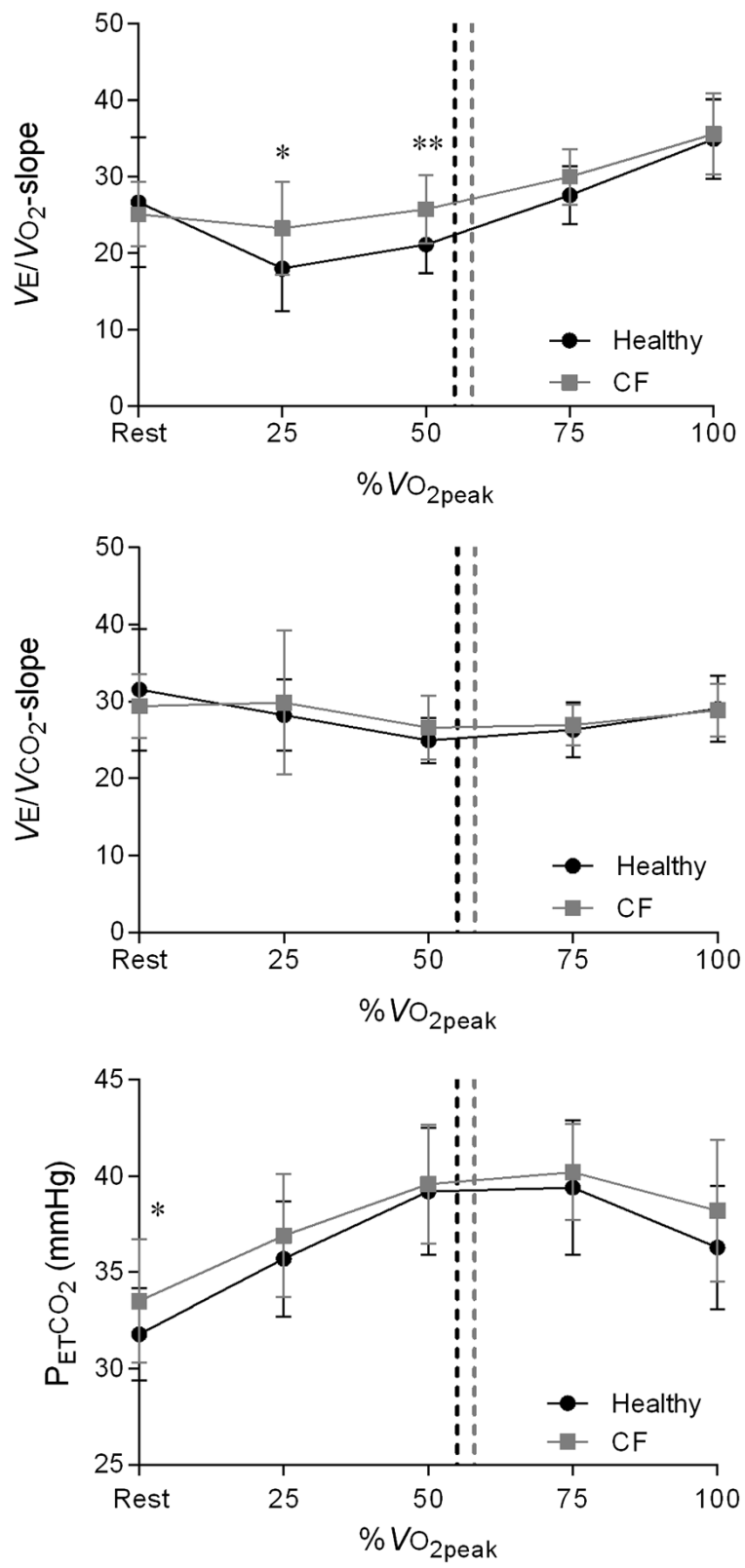


Figure 2 (See legend on next page.)

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Figure 2 Changes in VE/VO₂-slope, VE/VCO₂-slope, and P_{ET}CO₂ during exercise at similar percentages of VO_{2peak} in the healthy adolescents and the adolescents with CF. Dashed lines represent the ventilatory threshold in both groups. Abbreviations: CF = cystic fibrosis; P_{ET}CO₂ = partial end-tidal carbon dioxide tension; VE/VCO₂-slope = slope of the relationship between minute ventilation and carbon dioxide output; VE/VO₂-slope = slope of the relationship between minute ventilation and oxygen uptake; VO_{2peak} = peak oxygen uptake. *P < 0.05; **P < 0.01.

exercise intensities in patients with CF (see Figure 1, P < 0.01, P < 0.01, P < 0.01, and P < 0.001 at 25%, 50%, 75%, and 100% of VO_{2peak} respectively).

Figure 2 shows significantly higher VE/VO₂-slope values at 25% (P = 0.01) and 50% (P < 0.01) of VO_{2peak} in patients with CF, whereas VE/VCO₂-slope values differed not significantly between the two groups throughout the entire range of the CPET. Furthermore, Figure 2 demonstrates that, except for resting values (P = 0.03), P_{ET}CO₂ values differed not significantly between the two groups during the CPET.

Figure 3 represents the RER at rest and throughout progressive exercise in order to elucidate the higher VE/VO₂ ratios during sub-maximal exercise. At rest and during sub-maximal exercise, patients with CF attained significantly higher RER values (P < 0.001, P < 0.001, P < 0.001, P < 0.01, and P = 0.26 at rest, 25%, 50%, 75%, and 100% of VO_{2peak} respectively). The VE/WR ratio depicted in Figure 4 was significantly higher in CF during the entire range of the CPET (P < 0.01, P < 0.001, P < 0.001, and P < 0.001 at 25%, 50%, 75%, and 100% of VO_{2peak} respectively).

Discussion

The present study aimed to 1) describe the ventilatory response during a progressive CPET and 2) assess the

adequacy of the ventilatory response for CO₂ exhalation during exercise in mild-moderate adolescents with CF. First, we found an exaggerated ventilatory response during exercise. Second, this ventilatory response to exercise seems to be adequate for CO₂ exhalation in patients with mild-to-moderate CF. The latter is illustrated by a similar course of the VE/VCO₂-slope throughout exercise, higher RER values during sub-maximal exercise, and the ability to maintain P_{ET}CO₂ values within normal limits throughout the entire range of the CPET.

The basic physiological factors that determine and modify the ventilatory response to exercise are: 1) CO₂ output of the exercising muscles, 2) the arterial CO₂ set-point, 3) the VD/VT ratio, and 4) the change in the arterial pressure of CO₂ (PaCO₂) during exercise (Wasserman et al. 1996). Several of these concepts are addressed to in this study. First, muscular CO₂ output during (sub-)maximal exercise seems to be increased in patients with CF (Bongers et al. 2012; Hebestreit et al. 2005; Nguyen et al. 2014), which is illustrated in the current study by a higher RER. The higher RER in patients with CF is suggested to reflect a higher reliance on glucose oxidation to meet energy demands during exercise (Hebestreit et al. 2005; Nguyen et al. 2014). Altered substrate utilization in CF (de Meer et al. 1995; Moser et al. 2000; Selvadurai et al. 2003) might explain the increased RER at rest and for

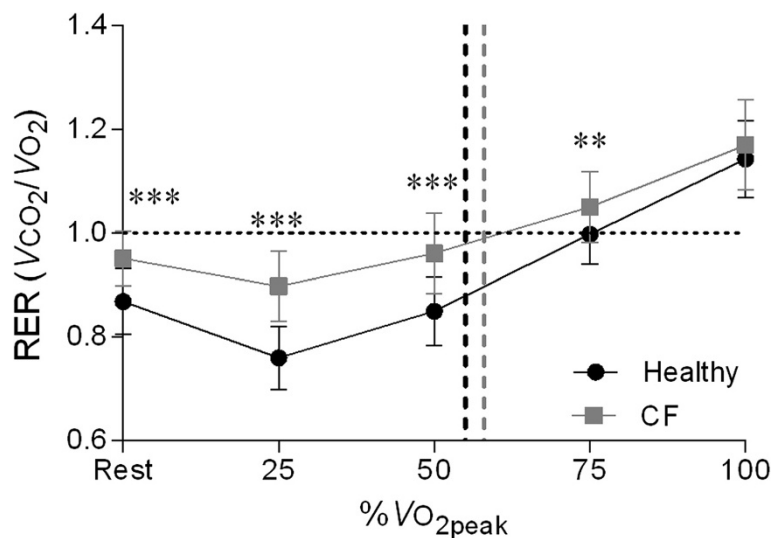


Figure 3 RER during exercise at similar percentages of VO_{2peak} in healthy adolescents and patients with CF. Vertical dashed lines correspond to the ventilatory threshold in both groups. Abbreviations: CF = cystic fibrosis; RER = respiratory exchange ratio; VO_{2peak} = peak oxygen uptake. **P < 0.01, ***P < 0.001.

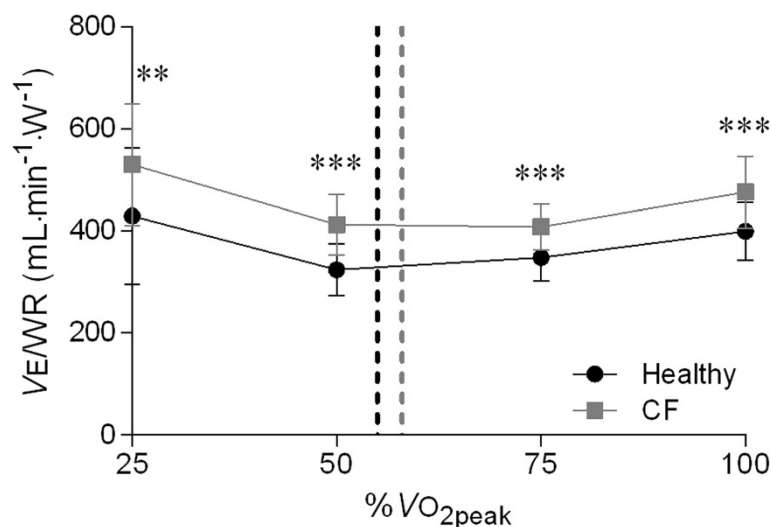


Figure 4 Changes in the VE/WR ratio during exercise at similar percentages of VO_{2peak} in healthy adolescents and patients with CF. Dashed lines correspond to the ventilatory threshold in both groups. Abbreviations: CF = cystic fibrosis; VE/WR = minute ventilation to work rate ratio; VO_{2peak} = peak oxygen uptake. ***P* < 0.01; ****P* < 0.001.

the lower exercise intensities. In addition, slowed VO₂ kinetics during exercise and recovery in patients with CF might also be a possible explanation for an increased RER during sub-maximal exercise (Kusenbach et al. 1999; Massin et al. 2000; Pouliou et al. 2001; Hebestreit et al. 2005; Stevens et al. 2009; Saynor et al. 2014). This results in a greater dependency on glycolytic energy systems at lower exercise intensities resulting in an increased VCO₂. Higher aerobic or anaerobic glycolytic energy expenditure during exercise increases ventilation as supported by a study in patients with familial mitochondrial myopathy (Heinicke et al. 2011). The current study showed an exaggerated VE relative to metabolic rate, indicated by high VE/VO₂-slope values and VE/WR ratios, as well as an elevated RER, with no apparent signs of pulmonary insufficiency.

Second, the VD/VT was significantly higher at all exercise intensities in patients with CF, which seems to be exaggerated with disease progression (post-hoc analysis, data not shown). High VD/VT values during exercise have previously been reported in patients with CF (Cerny et al. 1982; Coates et al. 1988; Thin et al. 2004; Wilkens et al. 2010). This, in combination with the trend of higher P_{ET}CO₂ in patients with CF, indicates an abnormal alveolar dead space ventilation (Wilkens et al. 2010), which might explain the relatively high VE values at rest and during sub-maximal exercise in patients with CF. Unfortunately, the exaggerated ventilatory response we found and the shift from oxidative to glycolytic energy metabolism, as shown by the attenuation of the RER slope at exercise intensities above 50% of VO_{2peak} when compared to healthy controls, seems not to be able to totally compensate the limited exercise capacity in

patients with CF (significantly reduced VO_{2peak}/kg and WR_{peak}/kg). Our results are in agreement with the study of Borel et al. (2014) who found no effect of mild CF on breathing pattern and breathing strategy during an incremental CPET. Although breathing pattern and breathing strategy of adolescents with CF were comparable with healthy controls, most studies still report a reduced exercise capacity in adolescents with CF (Almajed and Lands 2012; Rand and Prasad 2012; Saynor et al. 2014). Saynor et al. (2014) recently suggested that centrally mediated oxygen delivery might be the principally limiting the aerobic function of pediatric CF patients with mild-to-moderate airway obstruction during ramp incremental cycling exercise. However, based on the results of the study of Keochkerian et al. (2008) on the ventilatory response in children with CF, one would still expect that CF could alter the ventilatory response during a progressive CPET. The current study demonstrated no significant effect of CF on the ventilatory response for CO₂ exhalation (VE/VCO₂-slope and P_{ET}CO₂) to exercise in patients with CF with mild-to-moderate airway obstruction.

As described above, we found higher values for RER, VE/WR, and VE/VO₂-slope values during sub-maximal exercise. These results suggest a higher ventilatory demand rather than a higher ventilatory response during sub-maximal exercise in patients with mild CF. An explanation for the absence of an impact of CF on the ventilatory response to exercise is the mild-to-moderate severity of the lung disease in our population. Keochkerian et al. (2008) reported that the more severe the airway obstruction, the more rapid and shallow the breathing pattern.

The current study has some limitations. Firstly, by categorizing exercise intensity by %VO_{2peak}, there is no

standardization of exercise intensity relative to the ventilatory response for each participant. However, standardizing for exercise intensity relative to VO_2 ($\%\text{VO}_{2\text{peak}}$) was also done by other studies (Borel et al. 2014; Keochkerian et al. 2008). Since the ventilatory threshold occurred at a similar percentage of $\text{VO}_{2\text{peak}}$ in the pediatric CF patients and the healthy controls ($58 \pm 9\%$ versus $55 \pm 9\%$; $P = 0.32$), we believe that we did compare groups within the same physiological exercise intensity domain. Secondly, the sample size was relatively small and included mainly patients with CF with mild to moderate airflow obstruction. For this reason, these findings cannot be generalized to patients with severe airflow obstruction. Nevertheless, the current study sample is representative for the CF population in a tertiary CF Center. Thirdly, the estimated VD/VT ratio cannot be accurately predicted from the P_{ETCO_2} in patients with an increased VD/VT ratio due to lung disease (Wasserman et al. 2005), so caution must be taken with the interpretation of these results. Fourth, unfortunately we were not able to correct $\text{VO}_{2\text{peak}}$ for fat free mass as this variable was not routinely measured in patients with CF in the CF Center at the University Medical Center Utrecht. Finally, the used criteria for a maximal effort are subject to debate, especially in patients with CF. It has previously been demonstrated that traditional testing protocols and verification criteria significantly underestimate $\text{VO}_{2\text{peak}}$ in both healthy (Barker et al. 2011) and children with CF (Saynor et al. 2013). We did not verify the attainment of a true $\text{VO}_{2\text{peak}}$ with a supramaximal exercise testing procedure.

Implications and future research

As a higher ventilatory demand seems to be present during submaximal exercise in mild-moderate patients with CF, a small decline in ventilatory capacity might hamper the precarious balance between ventilation and homeostasis with further disease progression in patients with CF. The main findings presented in this study highlight the importance for the clinician to aim for attenuation of lung function decline even in patients with CF with a relatively preserved lung function ("normal" FEV_1). For future research it would be interesting to evaluate the latter hypothesis in patients with CF with more severe airway obstruction. Moreover, the differences we found during the course of sub-maximal exercise highlight the importance to evaluate the submaximal exercise response as well when interpreting a CPET, and not just focus on peak exercise parameters.

Conclusions

The current study found an exaggerated, but adequate ventilatory response to exercise for CO_2 exhalation in patients with CF with mild-to-moderate airway obstruction. The higher RER, VE/WR ratios, and VE/ VO_2 -slope values

during sub-maximal exercise point towards a higher ventilatory demand during sub-maximal exercise in patients with CF and mild-to-moderate lung disease.

Abbreviations

BMI: Body mass index; BSA: Body surface area; CF: Cystic fibrosis; CO_2 : Carbon dioxide; CPET: Cardiopulmonary exercise test; FEV₁: Forced expiratory volume in one second; HR: Heart rate; HR_{peak} : peak heart rate; P_{ETCO_2} : Partial end-tidal carbon dioxide tension; RER: Respiratory exchange ratio; RER_{peak} : Respiratory exchange ratio at peak exercise; RV: Residual volume; RV/TLC ratio: Residual volume to total lung capacity ratio; SD: Standard deviation; TLC: Total lung capacity; VCO_2 : Carbon dioxide production; $\text{VCO}_{2\text{peak}}$: Peak carbon dioxide production; VD/VT ratio: Ventilatory dead space ventilation ratio; VE: minute ventilation; VE_{peak} : peak minute ventilation; VE/ VO_2 -slope: minute ventilation to oxygen uptake slope; VE/ VCO_2 ratio: minute ventilation to carbon dioxide production ratio; VE/ VCO_2 -slope: minute ventilation to carbon dioxide production slope; VE/WR: minute ventilation to work rate ratio; VO_2 : Oxygen uptake; $\text{VO}_{2\text{peak}}$: peak oxygen uptake; WR: Work rate; WR_{peak} : peak work rate.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

BB participated in the design of the study, carried out data analysis and drafted the manuscript. MW carried out data analysis and drafted the manuscript. TT and EH participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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