

# Validity of the Oxygen Uptake Efficiency Slope in Children With Cystic Fibrosis and Mild-to-Moderate Airflow Obstruction

**Bart C. Bongers, Erik H.J. Hulzebos,  
Bert G.M. Arets, and Tim Takken**

Wilhelmina Children's Hospital, University Medical Center Utrecht

**Purpose:** The oxygen uptake efficiency slope (OUES) has been proposed as an 'effort-independent' measure of cardiopulmonary exercise capacity, which could be used as an alternative measurement for peak oxygen uptake ( $VO_{2peak}$ ) in populations unable or unwilling to perform maximal exercise. The aim of the current study was to investigate the validity of the OUES in children with cystic fibrosis (CF). **Methods:** Exercise data of 22 children with CF and mild to moderate airflow obstruction were analyzed and compared with exercise data of 22 healthy children. The OUES was calculated using data up to three different relative exercise intensities, namely 50%, 75%, and 100% of the total exercise duration, and normalized for body surface area (BSA). **Results:** Only the OUES/BSA using the first 50% of the total exercise duration was significantly different between the groups. OUES/BSA values determined at different exercise intensities differed significantly within patients with CF and correlated only moderately with  $VO_{2peak}$  and the ventilatory threshold. **Conclusion:** The OUES is not a valid submaximal measure of cardiopulmonary exercise capacity in children with mild to moderate CF, due to its limited distinguishing properties, its nonlinearity throughout progressive exercise, and its moderate correlation with  $VO_{2peak}$  and the ventilatory threshold.

Maximal cardiopulmonary exercise capacity, as measured during incremental cardiopulmonary exercise testing (CPET), is a good prognostic factor for survival in patients with cystic fibrosis (CF; 28). The maximal oxygen uptake ( $VO_{2max}$ ) is generally considered the most reliable single measure of an individual's maximal cardiopulmonary exercise capacity, reflecting the highest rate at which someone can consume oxygen during exercise with large muscle groups (34). Classically,  $VO_{2max}$  requires a maximal effort with the leveling-off of oxygen uptake ( $VO_2$ ) despite continuing exercise and increasing work rate (WR; 19). Many healthy children as well as patients do not show such a plateau in  $VO_2$  during exercise. However, since a number of authors (4,30) showed that this leveling-off of  $VO_2$  is not essential for

---

Bongers, Hulzebos, and Takken are with the Child Development and Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands. Arets is with the Dept. of Pediatric Respiratory Medicine, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands.

defining the highest  $\text{VO}_2$  in children, this measure is often replaced by the peak  $\text{VO}_2$  ( $\text{VO}_{2\text{peak}}$ ), the highest  $\text{VO}_2$  measured during CPET (7,19).

Questions can be raised about the validity of the  $\text{VO}_{2\text{peak}}$  in children with CF during maximal exercise (40). Some authors have reported a reduced exercise capacity during CPET in children with CF compared with healthy peers (18,20,33,41), however, the observed peak heart rates ( $\text{HR}_{\text{peak}}$ ) in these studies were significantly lower compared with values observed in healthy children. Therefore, this lower  $\text{VO}_{2\text{peak}}$  might be due to a really lower  $\text{VO}_{2\text{peak}}$  or to an incapability of the patient to reach a true  $\text{VO}_{2\text{peak}}$ . Moreover, the  $\text{VO}_{2\text{peak}}$  can be strongly influenced by the patients' motivation, the selected exercise protocol, and the experience of the tester (3,8,19). Because of these limitations and the difficulty in performing a maximal effort during CPET, there has been a search for alternative indices that could be obtained without performing a maximal effort.

The oxygen uptake efficiency slope (OUES) might act as an alternative for the  $\text{VO}_{2\text{peak}}$  (6). The OUES describes the linear relation between the  $\text{VO}_2$  and the common logarithm of the minute ventilation (Log VE) throughout CPET. Theoretically, due to the linearity of the OUES throughout CPET, this measurement should be resistant to disruption by early termination during CPET (2,19). Since the original rationale of the OUES was to provide a submaximal measure of cardiopulmonary exercise capacity, which could be used as a possible alternative for the  $\text{VO}_{2\text{peak}}$  in populations unable to perform maximal exercise, the aim of the current study was to investigate whether the OUES could be used as a valid, submaximal measure of cardiopulmonary exercise capacity in children with CF.

## Methods

### Subjects

Children with CF were measured for anthropometry, lung function, and cardiopulmonary exercise capacity as part of regular evaluation measures during the annual medical check-up in the CF Center of the Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands. Data from children with a stable clinical condition, no active musculoskeletal disorders, and a forced expiratory volume in one second ( $\text{FEV}_1$ )  $>30\%$  predicted were analyzed.

In addition, for each patient with CF we examined exercise data from a healthy subject. All healthy children were by definition free from chronic diseases, and were not on medications that might affect their exercise capacity. Written informed consent was obtained from the parents and from the children. The medical ethics committee of our institution approved the study protocol.

### Lung Function Tests

In the children with CF, spirometry and body plethysmography were performed using a pneumotach system and a volume-constant plethysmograph (Master Laboratory system, Jaeger, Wuerzburg, Germany) after bronchodilator inhalation (800 mg salbutamol). Forced vital capacity (FVC) and  $\text{FEV}_1$  were obtained from maximal flow volume curves, after which the Tiffeneau index was calculated. The highest value for residual volume (RV) and the lowest value for total lung volume (TLC) were used to calculate the RV/TLC ratio.

## Cardiopulmonary Exercise Testing

CPET was performed using an electronically braked cycle ergometer (Lode corral, Lode, Groningen, the Netherlands). After assessment of baseline cardiopulmonary values during a three minute rest period, the test started with one minute of unloaded cycling. Thereafter, the workload was increased by a constant increment of 15 or 20  $\text{W}\cdot\text{min}^{-1}$  intervals according to the Godfrey protocol (14). Subjects were instructed to maintain a pedaling speed between 60 and 80 rpm. Strong verbal encouragement was given until the patient stopped because of voluntary exhaustion. Heart rate (HR) was monitored by three-lead ECG (Hewlett-Packard, Amstelveen, the Netherlands) and oxygen saturation at the index finger by pulse oximetry (Nellcor 200 E, Nellcor, Breda, the Netherlands). During the exercise tests, subjects breathed continuously through a facemask (Hans Rudolph Inc, Kansas city, MO) and breath-by-breath respiratory gas analysis and volume measurements were performed with gas analyzers for oxygen and carbon dioxide (Jaeger Oxycon Pro, Care Fusion, Houten, the Netherlands) and a flowmeter (Triple V volume transducer). Output from the gas analyzers and flowmeter were averaged at 10-s intervals and stored for further use. Effort was considered to be at a maximal level when the subject showed clinical signs of intense effort and was unable to maintain the required pedaling speed and when at least one of the following criteria was met: a  $\text{HR}_{\text{peak}} > 180$  beats per minute or a respiratory exchange ratio (RER) at peak exercise ( $\text{RER}_{\text{peak}} > 1.0$ ) (5).

## Calculations

Peak exercise variables were taken as the average value during the last 30 s of CPET. Minute ventilation (VE),  $\text{VO}_2$ , carbon dioxide output ( $\text{VCO}_2$ ), and the respiratory exchange ratio ( $\text{RER} = \text{VCO}_2/\text{VO}_2$ ) were calculated from conventional equations. The estimated ventilatory dead space ventilation (VD/VT ratio) was calculated by using the end-tidal partial pressure of carbon dioxide. The ventilatory threshold (VT) was determined according to the V-slope method and also expressed as a percentage of  $\text{VO}_{2\text{peak}}$  (VT%). Ventilatory efficiency ( $\text{VE}/\text{VO}_2$ -slope) and the ventilatory drive ( $\text{VE}/\text{VCO}_2$ -slope) were calculated using all exercise data. The OUES was evaluated at three different exercise intensities by making use of the following equation:  $\text{VO}_2 = a \cdot \text{Log}(\text{VE}) + b$ , in which the constant 'a' represents the rate of increase in  $\text{VO}_2$  in response to an increase in VE, called the OUES (regression coefficient) and 'b' corresponds to the intercept (6). For the determination of the OUES 100, all data gained during CPET were used, whereas for the determination of the OUES 75 and the OUES 50, only data up to 75% and 50% of the total exercise duration were used respectively. To reduce the variability between subjects due to growth and maturation, calculated OUES values were normalized for BSA ( $\text{OUES}/\text{BSA}$ ; 1).

## Statistical Analyses

All data were analyzed using the Statistical Package for the Social Sciences version 15.0; SPSS Inc., Chicago, IL). Tests for normality were performed on the data with the Shapiro-Wilk test. As appropriate, independent samples T-tests or Mann-Whitney U tests were performed on the anthropometric and the exercise variables to test for significant differences between the two groups. Repeated measures analysis of variance (ANOVA) was used to evaluate the differences in  $\text{OUES}/\text{BSA}$

values calculated at the three different exercise intensities within the two groups. Additional post hoc analyses with Bonferroni adjustment for multiple testing were performed on the outcomes of the repeated-measures ANOVA tests to locate the exact significant differences. Pearson correlation coefficients were calculated to examine the relationship between exercise and lung function variables and the OUES/BSA. Significance was a priori set at the .05 level.

## Results

Twenty-two children with CF and 22 healthy children, 11–18 years of age, 13 boys and 9 girls in each group, were included in this study. Subject characteristics are shown in Table 1. Anthropometric data for the two groups differed not significantly. Children with CF were significantly older than the healthy controls ( $p = .002$ ) and they had significantly lower height for age and weight for age  $SD$ -scores ( $p = .006$  and  $.002$  respectively). Lung function characteristics of the children with CF are shown in Table 2. With a FEV<sub>1</sub> of  $81.52 \pm 15.57\%$  of predicted and a RV/TLC ratio of  $35.78 \pm 10.15\%$ , CF patients suffered from mild to moderate airflow obstruction.

All subjects terminated CPET due to voluntary exhaustion, without adverse effects. The results of CPET are presented in Table 3. In the patients with moderate CF we found significantly higher values for RER<sub>peak</sub> ( $p = .037$ ), and significantly lower values for WR<sub>peak</sub>/kg ( $p < .001$ ), VO<sub>2peak</sub> ( $p = .020$ ), VO<sub>2peak</sub>/kg ( $p < .001$ ), VO<sub>2peak</sub>/kg expressed as a percentage of predicted ( $p = .001$ ), and the VT ( $p = .031$ ). Patients with moderate CF also had a significantly higher estimated VD/VT ratio at peak exercise ( $p < .001$ ). HR<sub>peak</sub> and peak VE (VE<sub>peak</sub>) values were not significantly different between children with moderate CF and their healthy peers and the VT occurred at an average of ~67% of VO<sub>2peak</sub> in both groups.

**Table 1 Subject Characteristics; Mean  $\pm$  SD, [Range]**

	Healthy children $n = 22$		Children with cystic fibrosis $n = 22$	
Gender (male/female)	13/9		13/9	
Age (years)	14.2 $\pm$ 1.5	[11.9–16.8]	15.7 $\pm$ 1.5	[11.8–18.7]**
Height (m)	1.67 $\pm$ 0.10	[1.45–1.91]	1.68 $\pm$ 0.09	[1.52–1.80]
Height for age $SD$ -scores	0.15 $\pm$ 0.88	[-1.33–2.15]	-0.69 $\pm$ 1.04	[-2.37–1.71]**
Weight (kg)	53.9 $\pm$ 12.1	[33.0–81.7]	53.9 $\pm$ 6.8	[35.0–63.0]
Weight for age $SD$ -scores	0.05 $\pm$ 0.86	[-1.48–2.05]	-0.69 $\pm$ 0.64	[-2.12–0.56]**
Weight for height $SD$ -scores	-0.04 $\pm$ 0.78	[-1.27–1.35]	-0.36 $\pm$ 0.92	[-1.89–1.31]
BMI (kg·m <sup>-2</sup> )	19.2 $\pm$ 2.6	[15.7–25.5]	19.3 $\pm$ 1.9	[15.2–23.4]
BMI for age $SD$ -scores	-0.02 $\pm$ 0.79	[-1.34–1.50]	-0.33 $\pm$ 0.74	[-1.56–1.06]
BSA (m <sup>2</sup> )	1.57 $\pm$ 0.22	[1.14–2.02]	1.60 $\pm$ 0.14	[1.25–1.81]

Abbreviations: BMI = body mass index; BSA = body surface area (calculated applying the equation of Haycock et al. (16));  $SD$ -scores = standard deviation scores (calculated using Dutch normative values (12)). \*\*  $p < .01$ .

**Table 2 Lung Function Characteristics of the Children With Moderate Cystic Fibrosis; Mean  $\pm$  SD, [Range]**

	Absolute values		Percentage of predicted values <sup>a</sup>	
	Mean $\pm$ SD	[Range]	Mean $\pm$ SD	[Range]
FVC (L)	3.83 $\pm$ 0.83	[2.20–4.99]	97.3 $\pm$ 10.5	[59.9–107.4]
FEV <sub>1</sub> (L)	2.71 $\pm$ 0.65	[1.43–4.03]	81.5 $\pm$ 15.6	[45.7–106.5]
Tiffeneau index	0.72 $\pm$ 0.15	[0.53–1.12]	85.3 $\pm$ 17.7	[62.7–132.8]
RV (L)	1.91 $\pm$ 0.55	[1.06–3.40]	166.8 $\pm$ 45.8	[103.0–298.0]
TLC (L)	5.38 $\pm$ 0.91	[3.26–6.79]	106.0 $\pm$ 11.0	[85.0–126.0]
RV/TLC ratio (%)	35.78 $\pm$ 10.15	[21.59–65.38]	152.7 $\pm$ 42.3	[93.0–276.0]

Abbreviations: FEV<sub>1</sub> = forced expiratory volume in one second; FVC = forced vital capacity; RV = residual volume; TLC = total lung volume. <sup>a</sup> reference values from Zapletal et al. (42).

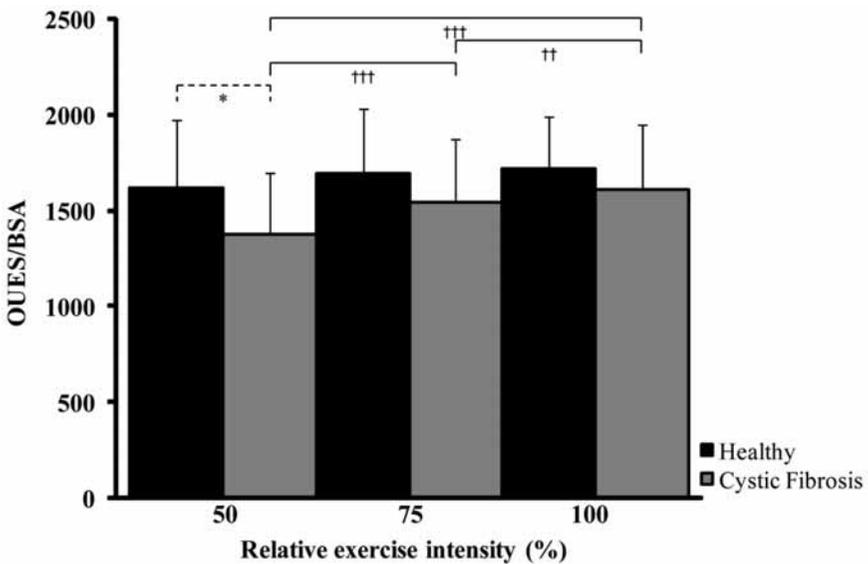
**Table 3 Peak Exercise Variables and the VT; Mean  $\pm$  SD [Range]**

	Healthy children		Children with cystic fibrosis	
	Mean $\pm$ SD	[Range]	Mean $\pm$ SD	[Range]
HR <sub>peak</sub> (beats·min <sup>-1</sup> )	191.9 $\pm$ 7.2	[180–204]	188.1 $\pm$ 9.1	[166–206]
RER <sub>peak</sub>	1.15 $\pm$ 0.06	[1.01–1.28]	1.20 $\pm$ 0.10	[0.96–1.37]*
WR <sub>peak</sub> /kg (Watt·kg <sup>-1</sup> )	4.07 $\pm$ 0.61	[2.57–5.00]	3.41 $\pm$ 0.54	[2.61–4.71]***
VO <sub>2peak</sub> (mL·min <sup>-1</sup> )	2677.4 $\pm$ 698.6	[1725.0–4140.0]	2222.1 $\pm$ 547.4	[1368.0–3304.0]*
VO <sub>2peak</sub> /kg (mL·min <sup>-1</sup> ·kg <sup>-1</sup> )	49.9 $\pm$ 7.9	[33.6–62.9]	40.9 $\pm$ 7.8	[29.2–61.8]***
VO <sub>2peak</sub> /kg (% of predicted)	111.9 $\pm$ 18.9	[71.6–144.4]	91.7 $\pm$ 18.1	[66.0–131.6]** <sup>a</sup>
VE <sub>peak</sub> (L·min <sup>-1</sup> )	91.9 $\pm$ 28.1	[44.6–149.5]	87.5 $\pm$ 22.0	[47.0–139.0]
VE <sub>peak</sub> /kg (L·min <sup>-1</sup> ·kg <sup>-1</sup> )	1.7 $\pm$ 0.4	[0.8–2.4]	1.6 $\pm$ 0.3	[0.9–2.3]
Estimated peak VD/VT ratio (%)	16.8 $\pm$ 1.8	[11.7–19.3]	23.0 $\pm$ 4.0	[15.7–30.3]***
VT (mL·min <sup>-1</sup> )	1794.0 $\pm$ 487.5	[1166.0–2767.0]	1492.3 $\pm$ 408.2	[781.0–2465.0]*
VT% (of VO <sub>2peak</sub> )	67.2 $\pm$ 7.7	[57.8–86.7]	67.3 $\pm$ 8.8	[50.2–78.3]

Abbreviations: HR<sub>peak</sub> = peak heart rate; RER<sub>peak</sub> = peak respiratory exchange ratio; VE<sub>peak</sub> = peak minute ventilation; VO<sub>2peak</sub> = peak oxygen uptake; VT = ventilatory threshold; VT%=ventilatory threshold expressed as a percentage of peak oxygen uptake; WR<sub>peak</sub> = peak work rate. <sup>a</sup>: reference values from Ten Harkel et al. (35). \* p<.05; \*\* p<.01; \*\*\* p<.001.

The mean values of the absolute OUES 100, OUES 75, and OUES 50 in the children with moderate CF were  $2598.7 \pm 642.9$ ,  $2487.1 \pm 610.5$ , and  $2220.1 \pm 546.1$  respectively ( $2703.9 \pm 637.2$ ;  $2664.1 \pm 695.1$ , and  $2547.2 \pm 685.6$  for the healthy controls respectively; no significant between group differences). Concerning the capability of the OUES to distinguish between healthy children and children with moderate CF, only the OUES 50/BSA appeared to be significantly different between the two groups (see Figure 1), with lower values achieved in the children with moderate CF ( $p = .016$ ). Figure 1 also shows the effect of exercise duration on the OUES/BSA, thereby showing its linearity characteristics within the two groups. The OUES 50/BSA in children with moderate CF appeared to be significantly lower than both the OUES 75/BSA (8.86%) and the OUES 100/BSA (12.69%). In addition, the OUES 75/BSA was significantly lower than the OUES 100/BSA (4.20%). In contrast, no significant within group differences were found between the OUES 100/BSA, OUES 75/BSA, and OUES 50/BSA in the healthy children.

Correlations between the OUES/BSA determined at different relative exercise intensities and exercise and lung function variables are summarized in Table 4. In children with moderate CF, the OUES/BSA correlated moderately with the  $VO_{2peak}/kg$  ( $r$  ranging from .411 to .536),  $VO_{2peak}/kg$  expressed as a percentage of predicted ( $r$  ranging from .385 to .511), and the VT ( $r$  ranging from .350 to .541), whereas moderate to strong correlations were found between the OUES/BSA and the  $VO_{2peak}/kg$  ( $r$  ranging from .547 to .781),  $VO_{2peak}/kg$  expressed as a percentage of predicted ( $r$  ranging from .395 to .632), and VT ( $r$  ranging from .552 to .774) in the healthy children. Overall, associations weakened when a smaller amount of



**Figure 1** — The OUES values normalized for BSA at the three different relative exercise intensities (% of total exercise duration); mean + *SD*. Abbreviations: BSA = body surface area; OUES = oxygen uptake efficiency slope. \*: between group difference; †: differences within the group with cystic fibrosis patients. \*  $p < .05$ ; ††  $p < .01$ ; †††  $p < .001$ .

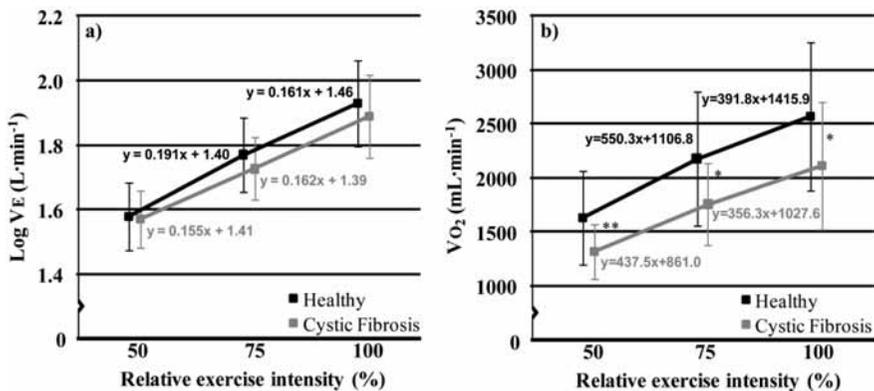
**Table 4 Pearson Correlations Between the OUES Normalized for BSA at the Three Different Relative Exercise Intensities and Exercise and Lung Function Variables**

	OUES 50/BSA		OUES 75/BSA		OUES 100/BSA	
	Healthy	Cystic fibrosis	Healthy	Cystic fibrosis	Healthy	Cystic fibrosis
VO <sub>2peak</sub> /kg (mL·min <sup>-1</sup> ·kg <sup>-1</sup> )	.547**	.411	.707**	.466*	.781**	.536*
VO <sub>2peak</sub> /kg (% of predicted)	.395	.385	.544*	.447*	.632**	.511*
VT (mL·min <sup>-1</sup> )	.552**	.350	.730**	.459*	.774**	.541**
VE/VCO <sub>2</sub> -slope	-.100	-.416	-.148	-.430*	-.213	-.405
Estimated VD/VT ratio	.441*	.133	.427*	.263	.366	.239
FEV <sub>1</sub> (% of predicted) <sup>a</sup>	-	-.085	-	-.119	-	-.114
Tiffeneau index <sup>a</sup>	-	-.212	-	-.263	-	-.324
RV/TLC ratio <sup>a</sup>	-	-.059	-	-.107	-	-.215

Abbreviations: BSA = body surface area; FEV<sub>1</sub> = forced expiratory volume in one second; OUES = oxygen uptake efficiency slope; RV = residual volume; TLC = total lung volume VD/VT ratio = physiological dead space ventilation; VE<sub>peak</sub> = peak minute ventilation; VE/VCO<sub>2</sub>-slope = ventilatory drive; VO<sub>2peak</sub> = peak oxygen uptake; VT = ventilatory threshold. \*  $p < .05$ ; \*\*  $p < .01$ . <sup>a</sup>: variables not measured in the healthy participants.

data points were used for the calculation of the OUES, with OUES 50/BSA having the lowest correlation coefficients with the VO<sub>2peak</sub>/kg and the VT. No significant associations were observed between the OUES/BSA and lung function parameters.

A post hoc analysis was performed to elucidate the nonlinearity of the OUES/BSA in patients with CF. The VO<sub>2</sub>, Log VE, VE, VE/VO<sub>2</sub>-slope, VE/VCO<sub>2</sub>-slope, and the estimated VD/VT ratio were obtained at 50%, 75%, and 100% of the total exercise duration as the average value of 30 s (see Figure 2 and Table 5). Figure 2 illustrates that the Log VE (graph a) appears to be similar in both groups at 50% of the total exercise duration, whereas patients with CF achieve lower, but not significantly, Log VE values at 75% and 100% of the total exercise duration ( $p = .191$  and  $.291$  respectively). In contrast, Figure 2 demonstrates significantly lower VO<sub>2</sub> values (graph b) attained by the children with CF at all three different relative exercise intensities ( $p = .007$ ,  $.011$ , and  $.022$  at 50%, 75%, and 100% of the total exercise duration respectively), remaining relatively constant. Table 5 confirms these findings with the VE/kg and the VO<sub>2</sub>/kg and also shows that corresponding to the observation of a significantly lower OUES 50/BSA (see Figure 1,  $p = .016$ ), these findings lead to a significantly higher VE/VO<sub>2</sub>-slope at 50% of the exercise duration in children with CF ( $p = .036$ ). Accompanying analysis revealed that during the entire range of CPET, children with CF have significantly higher RER values (data not shown). More specifically, the greatest differences were found at rest and throughout low exercise intensities.



**Figure 2** — The components of the OUES, the Log VE (graph a) and the VO<sub>2</sub> (graph b), determined at the three different relative exercise intensities (% of total exercise duration). For both groups regression lines with their coefficients are presented between the mean values at 50% of the exercise duration and the mean values at 75% of the exercise duration as well as between the mean values at 75% of the exercise duration and the mean values at 100% of the exercise duration. Abbreviations: Log VE = common logarithm of the minute ventilation; VO<sub>2</sub> = oxygen uptake. \*  $p < .05$ ; \*\*  $p < .01$ .

**Table 5 Exercise Variables at the Three Different Relative Exercise Intensities (% of Total Exercise Duration); Mean  $\pm$  SD**

	50		75		100	
	Healthy	Cystic fibrosis	Healthy	Cystic fibrosis	Healthy	Cystic fibrosis
VO <sub>2</sub> /kg (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	30.48 $\pm$ 5.97	24.54 $\pm$ 3.92***	40.63 $\pm$ 8.50	32.58 $\pm$ 5.72**	47.92 $\pm$ 7.91	39.16 $\pm$ 9.46**
VE/kg (L·kg <sup>-1</sup> ·min <sup>-1</sup> )	0.73 $\pm$ 0.15	0.71 $\pm$ 0.13	1.14 $\pm$ 0.24	1.01 $\pm$ 0.18	1.66 $\pm$ 0.37	1.50 $\pm$ 0.37
Estimated VD/VT ratio (%)	15.98 $\pm$ 2.10	21.57 $\pm$ 3.96***	16.4 $\pm$ 1.8	22.1 $\pm$ 3.8***	16.8 $\pm$ 1.8	23.0 $\pm$ 4.0***
VE/VO <sub>2</sub> -slope	21.89 $\pm$ 3.19	24.79 $\pm$ 5.43*	27.8 $\pm$ 5.3	29.4 $\pm$ 4.4	34.4 $\pm$ 5.1	36.1 $\pm$ 5.7
VE/VCO <sub>2</sub> -slope	24.72 $\pm$ 2.91	26.02 $\pm$ 3.87	25.7 $\pm$ 3.0	26.5 $\pm$ 3.1	28.0 $\pm$ 3.1	29.2 $\pm$ 3.8#

Abbreviations: VD/VT ratio = physiological dead space ventilation; VE = minute ventilation; VE/VCO<sub>2</sub>-slope = ventilatory drive; VE/VO<sub>2</sub>-slope = ventilatory efficiency; VO<sub>2</sub> = oxygen uptake. # Mann-Whitney U test. \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$ .

## Discussion

To our knowledge, this is the first study that investigated the characteristics of the OUES/BSA in children with CF and mild to moderate airflow obstruction and compared these values with healthy children. The main findings implicate that even though children with moderate CF had a significantly reduced  $\text{VO}_{2\text{peak}}/\text{kg}$ , only the OUES 50/BSA was significantly lower in patients with moderate CF. Moreover, the OUES depends on exercise intensity in the children with moderate CF due to its nonlinearity during the last part of CPET. Further, the OUES correlated only moderately with the  $\text{VO}_{2\text{peak}}/\text{kg}$  and the VT in these patients.

When the OUES is calculated, the VE is logarithmically transformed to produce a linear slope, which makes it an exercise intensity independent measure which is resistant to disruption by early termination during CPET (2,3,19). However, in contrast to the construct of the OUES and our healthy children, the OUES appeared to be nonlinear in our patients with moderate CF. A post hoc analysis (see Figure 2 and Table 5) showed that both groups achieved similar VE values at 50% of the total exercise duration (Log VE and VE/kg). However, children with moderate CF achieve a significantly lower  $\text{VO}_2$  and  $\text{VO}_2/\text{kg}$  at this exercise intensity, resulting in a reduced efficiency of ventilation during submaximal exercise as specified by both the VE/ $\text{VO}_2$ -slope (see Table 5) and the OUES/BSA using exercise data up to 50% of the total exercise duration (see Figure 1). When exercise progresses to 75% and 100% of the total exercise duration, children with moderate CF maintain a significantly reduced  $\text{VO}_2$  and  $\text{VO}_2/\text{kg}$  (see Figure 2 and Table 5), however, children with moderate CF also ventilate less compared with their healthy peers at 75% and 100% of the total exercise duration (not statistically significant). As a consequence, the efficiency of ventilation in children with moderate CF approaches values attained by their healthy peers, as indicated by the VE/ $\text{VO}_2$ -slope using 75% and 100% of the total exercise duration (see Table 5) and the OUES 75/BSA and OUES 100/BSA (see Figure 1).

Slowed  $\text{VO}_2$  kinetics in relation to their  $\text{VCO}_2$  kinetics during submaximal exercise in patients with moderate CF might be a possible explanation for the efficiency of ventilation moving toward values achieved by healthy children. This implies a greater dependency on anaerobic glycolysis at lower exercise intensities which stimulates the VE due to an increased  $\text{VCO}_2$ . Numerous studies found the  $\text{VO}_2$  kinetics to be slowed in CF and also reported significantly elevated RER values during exercise (17,22,25). An elevated RER suggests a greater contribution of carbohydrate metabolism. Altered substrate utilization in CF (10,27,31), might explain the increased RER at rest and for the lower exercise intensities.

Regardless a clear rationale for its nonlinearity, the OUES seems to be an exercise intensity dependent measure in children with moderate CF. Hence, the OUES seems to be invalid as an effort-independent measure of cardiopulmonary exercise capacity in children with mild to moderate CF. Gruet et al. (15) investigated the linearity characteristics of the OUES in adult patients with moderate CF and reported a limited dependency on exercise duration. They determined the OUES using the first 50%, 60%, 70%, 80%, and 100% of the exercise duration. They found the OUES values determined at 50% and 60% to be significantly lower compared with the OUES values determined at higher exercise intensities. Previous studies conducted in other pediatric populations, including a study in healthy and obese

children (1,11,23) and a study in healthy children and children with heart disease (6) confirm our current findings concerning the nonlinearity of the OUES during the last part of CPET. In contrast, other studies found no difference between the OUES values at different exercise intensities in healthy children (1,24) and children with congenital heart disease (9).

Regarding the distinguishing properties of the OUES, we expected the OUES to be significantly decreased in children with moderate CF compared with their healthy peers. The OUES physiologically depends on the point where lactic acid begins to accumulate (37). Patients with moderate CF are likely to have a reduced aerobic capacity (33,27,26) leading to an earlier accumulation of lactic acid, which in theory affects the OUES negatively. A study of Klijn et al. (21) suggested a shift toward a lower contribution of aerobic energy production, and hence, a greater dependency on anaerobic energy production during exercise in children with moderate CF. This will induce a reflex hyperventilation (38). The lack of a concomitant increase in  $\text{VO}_2$  together with the excessively increasing  $\text{VE}$  will lower the OUES. Our current study results indicate that  $\text{VT}\%$  was not significantly different between the patients with moderate CF (67.3%) and their healthy peers (67.2%). This might be due to the fact that our center is strongly stimulating physical activity in patients with CF. It has been documented that children with CF with higher physical activity levels have a lower disease severity and a significantly better aerobic capacity, anaerobic capacity, nutritional status and a higher health-related quality of life (32). Moreover, a higher aerobic capacity has been associated with a significantly lower mortality in CF (28). In addition, the OUES physiologically depends on the  $\text{VD}/\text{VT}$  ratio (37). An increased  $\text{VD}/\text{VT}$  ratio will importantly influence the ventilatory response to exercise (19) leading to a reduced OUES. It is reported that patients with mild or moderate CF are wasting ventilation during exercise because of a higher  $\text{VD}/\text{VT}$  ratio (13,36). In the current study, children with moderate CF had a stable, but significantly higher estimated  $\text{VD}/\text{VT}$  ratio throughout the last part of CPET.

Only the OUES  $50/\text{BSA}$  was significantly lower in patients with moderate CF, despite the above stated hypothesis concerning a reduced OUES in CF and the current study outcomes of both a reduced  $\text{VO}_{2\text{peak}}$  and an increased estimated  $\text{VD}/\text{VT}$  ratio. In contrast with our current study, the recent study conducted in adult patients with CF (15) reported significantly lower OUES values in adult patients with moderate CF. Hollenberg et al. (19) also found significantly reduced OUES values in subjects with a decreased  $\text{FEV}_1$ . The CF patients in our current study had a mean percentage of predicted  $\text{FEV}_1$  of 81.5%, which is considered to be mild (29). A possible explanation for our current results is that although the included patients with moderate CF had a significantly reduced  $\text{VO}_{2\text{peak}}$ , and an increased estimated  $\text{VD}/\text{VT}$  ratio, they were not enough ventilatory limited during CPET to cause a significantly reduced OUES. Whether the OUES is a valid indicator of cardiopulmonary exercise capacity in a sample of (older) patients with more severe CF needs additional research.

## Study Limitations

A limitation of the study was the relatively small sample size including 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 population CF patients in a tertiary CF center. Furthermore, the estimated VD/VT ratio cannot be accurately predicted from the end-tidal partial pressure of carbon dioxide in patients with an increased VD/VT ratio due to lung disease (39), so caution must be taken with the interpretation of these results.

## Conclusion

As a measure of cardiopulmonary exercise capacity derived from submaximal exercise data, the OUES seems to be of limited value in children with CF and mild to moderate airflow obstruction. This is attributable to its limited ability to distinguish between children with moderate CF and healthy peers together with its nonlinearity during the last part of CPET and its moderate correlations with  $VO_{2peak}$  and the VT.

## Acknowledgments

This study was presented as an abstract at the annual North American Cystic Fibrosis conference (NACFC) 2010 in Baltimore and at the XXVIIIth Pediatric Work Physiology (PWP) conference 2011 in Mawgan Porth, Cornwall. Drs. Bart C. Bongers was supported by an unconditional grant from Stichting BIO Kinderrevalidatie, Arnhem, the Netherlands. There are no conflicts of interest.

## References

1. Akkerman, M., M. van Brussel, B.C. Bongers, E.H. Hulzebos, and T. Takken. Oxygen uptake efficiency slope in healthy children. *Pediatr. Exerc. Sci.* 22:431–441, 2010.
2. Akkerman, M., M. van Brussel, H.J. Hulzebos, L. Vanhees, P.J.M. Helders, and T. Takken. The oxygen uptake efficiency slope: WHAT DO WE KNOW? *J. Cardiopulm. Rehabil. Prev.* 30:357–373, 2010.
3. Andreacci, J.L., L.M. LeMura, S.L. Cohen, E.A. Urbansky, S.A. Chelland, and S.P. Von Duvillard. The effects of frequency of encouragement on performance during maximal exercise testing. *J Sports Sci.* 20:345–352, 2002.
4. Armstrong, N., J.R. Welsman, and R.J. Winsley. Is peak VO<sub>2</sub> a maximal index of children's aerobic fitness? *Int. J. Sports Med.* 17:356–359, 1996.
5. Armstrong, N., and J.R. Welsman. Aerobic fitness. In: *Paediatric Exercise Science and Medicine*, 2nd ed., N. Armstrong and W. van Mechelen (Eds.). Oxford: Oxford University Press, 2008, pp. 101.
6. Baba, R., M. Nagashima, M. Goto, et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J. Am. Coll. Cardiol.* 28:1567–1572, 1996.
7. Baba, R., M. Nagashima, Y. Nagano, M. Ikoma, and K. Nishibata. Role of the oxygen uptake efficiency slope in evaluating exercise tolerance. *Arch. Dis. Child.* 81:73–75, 1999.
8. Baba, R., K. Tsuyuki, Y. Kimura, et al. Oxygen uptake efficiency slope as a useful measure of cardiorespiratory functional reserve in adult cardiac patients. *Eur. J. Appl. Physiol.* 80:397–401, 1999.
9. Bongers, B.C., H.J. Hulzebos, A.C. Blank, M. van Brussel, and T. Takken. The oxygen uptake efficiency slope in children with congenital heart disease: construct and group validity. *Eur. J. Cardiovasc. Prev. Rehabil.* 18:384–392, 2011.

10. De Meer, K., J.A.L. Jeneson, V.A.M. Gulmans, J. van der Laag, and R. Berger. Efficiency of oxidative work performance of skeletal-muscle in patients with cystic-fibrosis. *Thorax*. 50:980–983, 1995.
11. Drinkard, B., M.D. Roberts, L.M. Ranzenhofer, et al. Oxygen-uptake efficiency slope as a determinant of fitness in overweight adolescents. *Med. Sci. Sports Exerc.* 39:1811–1816, 2007.
12. Fredriks, A.M., S. van Buuren, J.M. Wit, and S.P. Verloove-Vanhorick. Body index measurements in 1996–7 compared with 1980. *Arch. Dis. Child.* 82:107–112, 2000.
13. Godfrey, S., and M. Mearns. Pulmonary function and response to exercise in cystic fibrosis. *Arch. Dis. Child.* 46:144–151, 1971.
14. Godfrey, S. *Exercise testing in children: applications in health and disease*. London: W.B. Saunders Company Ltd., 1974, pp. 1–168.
15. Gruet, M., J. Brisswalter, L. Mely, and J.M. Vallier. Clinical utility of the oxygen uptake efficiency slope in cystic fibrosis patients. *J. Cyst. Fibros.* 9:307–313, 2010.
16. Haycock, G.B., G.J. Schwartz, and D.H. Wisotsky. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J. Pediatr.* 93:62–66, 1978.
17. Hebestreit, H., A. Hebestreit, A. Trusen, and R.L. Hughson. Oxygen uptake kinetics are slowed in cystic fibrosis. *Med. Sci. Sports Exerc.* 37:10–17, 2005.
18. Hjeltne, N., J.K. Stanghelle, and D. Skyberg. Pulmonary function and oxygen uptake during exercise in 16 year old boys with cystic fibrosis. *Acta Paediatr. Scand.* 73:548–553, 1984.
19. Hollenberg, M., and I.B. Tager. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J. Am. Coll. Cardiol.* 36:194–201, 2000.
20. Keochkerian, D., M. Chlif, S. Delanaud, R. Gauthier, Y. Maingourd, and S. Ahmaidi. Breathing pattern adopted by children with cystic fibrosis with mild to moderate pulmonary impairment during exercise. *Respiration.* 75:170–177, 2008.
21. Klijn, P.H., S.W. Terheggen-Lagro, C.K. van der Ent, J. van der Net, J.L. Kimpen, and P.J.M. Helders. Anaerobic exercise in pediatric cystic fibrosis. *Pediatr. Pulmonol.* 36:223–229, 2003.
22. Kusenbach, G., R. Wieching, M. Barker, U. Hoffmann, and D. Essfeld. Effects of hyperoxia on oxygen uptake kinetics in cystic fibrosis patients as determined by pseudo-random binary sequence exercise. *Eur. J. Appl. Physiol.* 79:192–196, 1999.
23. Marinov, B., and S. Kostianev. Exercise performance and oxygen uptake efficiency slope in obese children performing standardized exercise. *Acta Physiol. Pharmacol. Bulg.* 27:59–64, 2003.
24. Marinov, B., S. Mandadzhieva, and S. Kostianev. Oxygen-uptake efficiency slope in healthy 7- to 18-year-old children. *Pediatr. Exerc. Sci.* 19:159–170, 2007.
25. Massin, M.M., J. Leclercq-Foucart, and J-P. Sacre. Gas exchange and heart rate kinetics during binary sequence exercise in cystic fibrosis. *Med. Sci. Monit.* 6:55–62, 2000.
26. Moorcroft, A.J., M.E. Dodd, and A.K. Webb. Exercise testing and prognosis in adult cystic fibrosis. *Thorax*. 52:291–293, 1997.
27. Moser, C., P. Tirakitsoontorn, E. Nussbaum, R. Newcomb, and D.M. Cooper. Muscle size and cardiorespiratory response to exercise in cystic fibrosis. *Am. J. Respir. Crit. Care Med.* 162:1823–1827, 2000.
28. Nixon, P.A., D.M. Orenstein, S.F. Kelsey, and C.F. Doershuk. The prognostic value of exercise testing in patients with cystic fibrosis. *N. Engl. J. Med.* 327:1785–1788, 1992.
29. Pauwels, R.A., A.S. Buist, P.M. Calverley, C.R. Jenkins, and S.S. Hurd, GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am. J. Respir. Crit. Care Med.* 163:1256–1276, 2001.

30. Rowland, T.W. Does peak VO<sub>2</sub> reflect VO<sub>2</sub>max in children?: evidence from supra-maximal testing. *Med. Sci. Sports Exerc.* 25:689–693, 1993.
31. Selvadurai, H.C., J. Allen, T. Sachinwalla, J. Macauley, C.J. Blimkie, and P.P. van Asperen. Muscle function and resting energy expenditure in female athletes with cystic fibrosis. *Am. J. Respir. Crit. Care Med.* 168:1476–1480, 2003.
32. Selvadurai, H.C., C.J. Blimkie, P.J. Cooper, C.M. Mellis, and P.P. van Asperen. Gender differences in habitual activity in children with cystic fibrosis. *Arch. Dis. Child.* 89:928–933, 2004.
33. Shah, A.R., D. Gozal, and T.G. Keens. Determinants of aerobic and anaerobic exercise performance in cystic fibrosis. *Am. J. Respir. Crit. Care Med.* 157:1145–1150, 1998.
34. Shephard, R.J., C. Allen, A.J. Benade, et al. The maximum oxygen intake. An international reference standard of cardiorespiratory fitness. *Bull. World Health Organ.* 38:757–764, 1968.
35. Ten Harkel, A.D.J., T. Takken, M. Van Osch-Gevers, and W.A. Helbing. Normal values for cardiopulmonary exercise testing in children. *Eur. J. Cardiovasc. Prev. Rehabil.* 18:48–54, 2011.
36. Thin, A.G., J.D. Dodd, C.G. Gallagher, M.X. Fitzgerald, and P. McLoughlin. Effect of respiratory rate on airway deadspace ventilation during exercise in cystic fibrosis. *Respir. Med.* 98:1063–1070, 2004.
37. Van Laethem, C., J. Bartunek, M. Goethals, P. Nellens, E. Andries, and M. Vanderheyden. Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. *Am. Heart J.* 149:175–180, 2005.
38. Wasserman, K. Anaerobic threshold and cardiovascular function. *Monaldi Arch. Chest Dis.* 58:1–5, 2002.
39. Wasserman, K., J.E. Hansen, D.Y. Sue, W.W. Stringer, and B.J. Whipp. *Principles of exercise testing and interpretation: including pathophysiology and clinical applications*, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2005, pp. 559.
40. Werkman, M.S., H.J. Hulzebos, P.B. van de Weert-van Leeuwen, H.G.M. Arets, P.J.M. Helder, and T. Takken. Supramaximal verification of peak oxygen uptake in adolescents with cystic fibrosis. *Pediatr. Phys. Ther.* 23:15–21, 2011.
41. Wideman, L., C.F. Baker, P.K. Brown, L.A. Consitt, W.T. Ambrosius, and M.S. Schechter. Substrate utilization during and after exercise in mild cystic fibrosis. *Med. Sci. Sports Exerc.* 41:270–278, 2009.
42. Zapletal, A., M. Samenek, and T. Paul. Lung function in children and adolescents: methods, reference values. In: *Progress in respiration research*, H. Herzog (Ed.). Basel: Karger, 1987, pp. 114–218.