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

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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 defining the highest VO_2 in children, this measure is often replaced by the peak VO_2 (VO_{2peak}), the highest VO_2 measured during CPET (7,19).

Questions can be raised about the validity of the VO_{2peak} 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 (HR_{peak}) in these studies were significantly lower compared with values observed in healthy children. Therefore, this lower VO_{2peak} might be due to a really lower VO_{2peak} or to an incapability of the patient to reach a true VO_{2peak}. Moreover, the VO_{2peak} 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 VO_{2peak} (6). The OUES describes the linear relation between the VO_2 and the common logarithm of the minute ventilation (Log V_E) 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 VO_{2peak} in populations unable to

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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 (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 μg salbutamol). Forced vital capacity (FVC) and 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 corrival, 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 $W \cdot min^{-1}$ 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 HR_{peak} >180 beats per minute or a respiratory exchange ratio (RER) at peak exercise (RER_{peak}) >1.0 (5).

Calculations

Peak exercise variables were taken as the average value during the last 30 s of CPET. Minute ventilation (VE), VO_2, carbon dioxide output (VCO_2), and the respiratory exchange ratio ($RER = VCO_2/VO_2$) 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 VO_{2peak} (VT%). Ventilatory efficiency (VE/VO_2-slope) and the ventilatory drive (VE/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: $VO_2 = a \cdot \text{Log}(VE) + b$, in which the constant 'a' represents the rate of increase in 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 (OUES/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 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 OUES/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_1 of 81.52 ± 15.57% of predicted and a RV/TLC ratio of 35.78 ± 10.15%, CF patients suffered from mild to moderate airflow obstruction.

\<<<<<<<<<<TABLE 1>>>>>>>>>>\

\<<<<<<<<<<TABLE 2>>>>>>>>>>\

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_{peak} (p = .037), and significantly lower values for WR_{peak}/kg (p < .001), VO_{2peak} (p = .020), VO_{2peak}/kg (p < .001), VO_{2peak}/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_{peak} and peak VE (VE_{peak}) 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_{2peak} in both groups.

\<<<<<<<<<<TABLE 3>>>>>>>>>>\

The mean values of the absolute OUES 100, OUES 75, and OUES 50 in the children with moderate CF were 2598.7 ± 642.9, 2487.1 ± 610.5, and 2220.1 ± 546.1 respectively (2703.9 ± 637.2; 2664.1 ± 695.1, and 2547.2 ± 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.

\<<<<<<<<<<FIGURE 1>>>>>>>>>>\

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

\<<<<<<<<<<TABLE 4>>>>>>>>>>\

A post hoc analysis was performed to elucidate the nonlinearity of the OUES/BSA in patients with CF. The VO_2, Log VE, VE, VE/VO_2-slope, VE/VCO_2-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_2 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_2/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_2-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>>>>>>>>>>\
\<<<<<<<<<<TABLE 5>>>>>>>>>>\

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 VO_{2peak}/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 VO_{2peak}/kg and the VT in these patients.

When the OUES is calculated, the V_E 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 VO_2 and VO_2/kg at this exercise intensity, resulting in a reduced efficiency of ventilation during submaximal exercise as specified by both the VE/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 VO_2 and VO_2/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/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 VO_2 kinetics in relation to their 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 VCO_2. Numerous studies found the 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 VO_2 together with the excessively increasing V_E will lower the OUES. Our current study results indicate that 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 VD/VT ratio (37). An increased VD/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 VD/VT ratio (13,36). In the current study, children with moderate CF had a stable, but significantly higher estimated VD/VT ratio throughout the last part of CPET.

Only the OUES 50/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 VO_{2peak} and an increased estimated VD/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 FEV_1. The CF patients in our current study had a mean percentage of predicted 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 VO_{2peak}, and an increased estimated VD/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.

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Figure Captions

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. * $p < .05$; †† $p < .01$; ††† $p < .001$.

Figure 2 — The components of the OUES, the Log VE (graph a) and the VO_2 (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_2 = oxygen uptake. * $p < .05$; ** $p < .01$.

Table 1 Subject characteristics; mean ± ***SD***, [range].

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

	Absolute values		Percentage of predicted values [a]	
FVC (L)	3.83 ± 0.83	[2.20–4.99]	97.3 ± 10.5	[59.9–107.4]
FEV_1 (L)	2.71 ± 0.65	[1.43–4.03]	81.5 ± 15.6	[45.7–106.5]
Tiffeneau index	0.72 ± 0.15	[0.53–1.12]	85.3 ± 17.7	[62.7–132.8]
RV (L)	1.91 ± 0.55	[1.06–3.40]	166.8 ± 45.8	[103.0–298.0]
TLC (L)	5.38 ± 0.91	[3.26–6.79]	106.0 ± 11.0	[85.0–126.0]
RV/TLC ratio (%)	35.78 ± 10.15	[21.59–65.38]	152.7 ± 42.3	[93.0–276.0]

Abbreviations: FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; RV = residual volume; TLC = total lung volume. [a] reference values from Zapletal et al. (42).

Table 3 Peak exercise variables and the VT; mean ± ***SD*** [range].

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

Abbreviations: HR_{peak} = peak heart rate; RER_{peak} = peak respiratory exchange ratio; VE_{peak} = peak minute ventilation; VO_{2peak} = peak oxygen uptake; VT = ventilatory threshold; VT%=ventilatory threshold expressed as a percentage of peak oxygen uptake; WR_{peak} = peak work rate. [a]: reference values from Ten Harkel et al. (35). * 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_{2peak}/kg ($mL \cdot min^{-1} \cdot kg^{-1}$)	.547**	.411	.707**	.466*	.781**	.536*
VO_{2peak}/kg (% of predicted)	.395	.385	.544*	.447*	.632**	.511*
VT ($mL \cdot min^{-1}$)	.552**	.350	.730**	.459*	.774**	.541**
VE/VCO_2-slope	-.100	-.416	-.148	-.430*	-.213	-.405
Estimated VD/VT ratio	.441*	.133	.427*	.263	.366	.239
FEV_1 (% of predicted) [a]	-	-.085	-	-.119	-	-.114
Tiffeneau index [a]	-	-.212	-	-.263	-	-.324
RV/TLC ratio [a]	-	-.059	-	-.107	-	-.215

Abbreviations: BSA = body surface area; FEV_1 = 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_{peak} = peak minute ventilation; VE/VCO_2-slope = ventilatory drive; VO_{2peak} = peak oxygen uptake; VT = ventilatory threshold. * $p<.05$; ** $p<.01$. [a]: variables not measured in the healthy participants.

Table 5 Exercise variables at the three different relative exercise intensities (% of total exercise duration); mean ± ***SD***

	50		75		100	
	Healthy	Cystic Fibrosis	Healthy	Cystic Fibrosis	Healthy	Cystic Fibrosis
VO_2/kg ($mL \cdot kg^{-1} \cdot min^{-1}$)	30.48 ± 5.97	24.54 ± 3.92***	40.63 ± 8.50	32.58 ± 5.72**	47.92 ± 7.91	39.16 ± 9.46**
VE/kg ($L \cdot kg^{-1} \cdot min^{-1}$)	0.73 ± 0.15	0.71 ± 0.13	1.14 ± 0.24	1.01 ± 0.18	1.66 ± 0.37	1.50 ± 0.37
Estimated VD/VT ratio (%)	15.98 ± 2.10	21.57 ± 3.96***	16.4 ± 1.8	22.1 ± 3.8***	16.8 ± 1.8	23.0 ± 4.0***
VE/VO_2-slope	21.89 ± 3.19	24.79 ± 5.43*	27.8 ± 5.3	29.4 ± 4.4	34.4 ± 5.1	36.1 ± 5.7
VE/VCO_2-slope	24.72 ± 2.91	26.02 ± 3.87	25.7 ± 3.0	26.5 ± 3.1	28.0 ± 3.1	29.2 ± 3.8#

Abbreviations: VD/VT ratio = physiological dead space ventilation; VE = minute ventilation; VE/VCO_2-slope = ventilatory drive; VE/VO_2-slope = ventilatory efficiency; VO_2 = oxygen uptake. [#] Mann-Whitney *U* test. * p<.05; ** p<.01; *** p<.001.