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The oxygen uptake efficiency slope in children with congenital heart disease: construct and group validity

BC Bongers[1], HJ Hulzebos[1], AC Blank[2], M van Brussel[1] and T Takken[1]

Abstract

Objective: The oxygen uptake efficiency slope (OUES) has been proposed as an independent and objective alternative to the peak oxygen uptake (VO_{2peak}), which does not require maximal exercise. The aim of this study was to investigate the construct and group validity of the OUES in children with congenital heart disease (CHD).

Methods: Thirty-one patients with CHD, of which 16 patients (mean age ± SD 11.2 ± 2.7 years) with a Fontan repair and 15 patients (mean age ± SD 13.2 ± 3.6 years) with surgical repair of tetralogy of Fallot (ToF) completed a symptom-limited cardiopulmonary exercise test. The OUES was calculated and normalized for body surface area at three different exercise intensities: (1) using 100% of the exercise data; (2) using the first 75% of the exercise data; and (3) using exercise data up to the ventilatory threshold (VT). Furthermore, peak oxygen uptake (VO_{2peak}), VT, ventilatory efficiency (V_E/VO_2-slope), and ventilatory drive (V_E/VCO_2-slope) were calculated and compared with values of 46 healthy children (mean age ± SD 12.2 ± 2.4 years).

Results: In all three groups, the OUES values determined at the three different exercise intensities were not significantly different from each other. Moreover, the OUES was significantly reduced in the children with CHD, with significantly lower values in the Fontan patients compared to ToF. Strong correlations were found between the OUES and both the VO_{2peak} and VT in Fontan and ToF patients.

Discussion: The OUES provides a valid measure of cardiopulmonary fitness in children with CHD, which is independent of exercise intensity and strongly correlated with VO_{2peak} and VT (construct validity). Furthermore, the OUES is capable of differentiating between healthy children and children with CHD and between Fontan and ToF patients (group validity). Therefore, the OUES may be a valid, effort-independent parameter of cardiopulmonary fitness in children with CHD.

Keywords

Oxygen uptake efficiency slope, congenital heart disease, exercise testing, children

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Introduction

The importance of cardiopulmonary exercise testing (CPET) is becoming more accepted in clinical practice. The results of CPET can be used at all stages of clinical assessment (e.g. diagnosis and characterization of disease severity, progression, prognosis, and response to treatment).[1,2] In children with congenital heart disease (CHD), the main indication for CPET is the evaluation of aerobic capacity.[3] Since cardiopulmonary function testing at rest cannot predict an individual's aerobic capacity reliably,[4] the measurement of the maximal oxygen uptake (VO_{2max}) during CPET is currently the only modality that provides an accurate and objective indication of (maximal) aerobic capacity.

Classically, the VO_{2max} describes a point at which there is no further increase in oxygen uptake (VO_2), despite further increases in exercise intensity.[5] Unfortunately, the VO_{2max} cannot be measured directly in individuals who are unable or unwilling to perform

[1]Child Development and Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands. [2]Department of Pediatric Cardiology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands.

Corresponding author:
Tim Takken, Child Development and Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, KB.02.056.0, P.O. Box 85090, 3508 AB Utrecht, The Netherlands
Email: t.takken@umcutrecht.nl

at maximal effort. Moreover, a true plateau in VO_2 is seldom attained during CPET.[6–10] In practice however, the VO_{2max} is interchangeable with the VO_2 measured at peak exercise (VO_{2peak}).[11–13] Still, measuring the VO_{2peak} is influenced by the patients' motivation, the exercise protocol, and the skills and experience of the tester.[13–18]

To avoid latter influence, Baba et al.[19] introduced the oxygen uptake efficiency slope (OUES) for children with CHD, which includes a sub-maximal parameter that might act as an alternative for the VO_{2peak}. The OUES describes the relation between the VO_2 and the common logarithm of the minute ventilation (V_E) throughout CPET, representing how efficiently oxygen is extracted by the lungs and used in the periphery. Similar to the relationship between the minute ventilation (V_E) and the clearance of carbon dioxide (CO_2) produced by metabolically active tissues (ventilatory drive, V_E/VCO_2-slope), its linearity during the last part of CPET implies that the use of sub-maximal exercise data on or after the ventilatory threshold (VT) does not significantly alter the OUES results.[12,13,20–22]

The OUES has been extensively investigated in healthy adults and in adult patients within a wide range of heart conditions, including heart failure,[13,15,20,23–31] coronary artery disease,[32–35] and CHD.[36] However, only one study[19] addressed the OUES in children with various cardiac conditions. In this latter study, no distinction was made between healthy children and children with CHD. Thus, at presents, the applicability of the OUES in pediatric patients with CHD is unknown.[37] Therefore, the current study aims to investigate the construct validity and group validity of the OUES in children with CHD in order to assess its usefulness in these patients. Construct validity will be studied using OUES values determined at different exercise intensities and using the associations between the OUES and other indices for cardiopulmonary fitness (e.g. the VO_{2peak}, VT, and V_E/VCO_2-slope). Group validity will be determined comparing the OUES data between children with CHD and healthy controls.

Materials and methods

Participants

The study population consisted of 31 children with CHD (mean age ± SD 12.1 ± 3.2; range 8.0–18.8 years) from the Wilhelmina Children's Hospital, University Medical Center Utrecht, who underwent CPET as part of their regular check-up. Within the CHD population of this study, 16 patients (mean age ± SD 11.2 ± 2.7); range 8.2–16.5 years) had a total cavopulmonary connection (Fontan circulation). Mean age ± SD at first surgery in these patients was 2.7 ± 6.5 months. After the Fontan procedure, 12 patients (75%) had a morphologically left systemic ventricle and four patients (25%) had a morphologically right systemic ventricle. The remaining 15 patients with CHD (mean age ± SD 13.0 ± 3.5; range 8.0–18.8 years) had undergone surgical repair of tetralogy of Fallot (ToF) at a mean age ± SD of 19.6 ± 29.6 months. Characteristics of the ToF patients are shown in Table 1.

In addition, we used the exercise data retrieved from 46 healthy children (mean age ± SD 12.2 ± 2.4; range 7.9–16.8 years) who underwent CPET in our laboratory. The healthy participants included family members of our hospital staff and children living in the neighborhood of the hospital. No healthy control had cardiac, vascular, pulmonary, or musculoskeletal disease. Informed consent was obtained from the parents and, if older than 12 years of age, from the children as well. The research protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands.

Anthropometry

Prior to CPET, anthropometric measurements were completed in all participants, including body mass (BM) (kg) and body height (m) using an electronic

Table 1. Characteristics obtained from echocardiography after corrective surgery in tetralogy of Fallot patients ($n = 15$)

Variable	ToF patients *n* (%)
Initial corrective surgery:	
VSD patch	15 (100)
Infundibulectomy	15 (100)
Commissurotomy	4 (27)
TAP	10 (67)
No outflow tract patch	1 (7)
Pulmonary regurgitation:	
Slight	2 (13)
Mild	1 (7)
Moderate	3 (20)
Severe	9 (60)
RV size:	
Normal	4 (27)
Slightly enlarged	4 (27)
Moderately enlarged	6 (40)
Severely enlarged	1 (7)
RV function:	
Normal/enhanced	14 (93)
Slightly reduced	1 (7)

RV: right ventricle, TAP: transannular patch, VSD: ventricular septal defect.

scale (Seca, Hamburg, Germany) and a stadiometer (Ulmer Stadiometer, Ulm, Germany) respectively. Body mass index (BMI) (kg/m^2) was calculated as the BM in kilograms divided by the square of the body height in meters. Standard deviation (SD) scores ware calculated for BMI for age using Dutch growth charts.[38] For the estimation of the body surface area (BSA) (m^2), the equation of Haycock et al.[39] was used, which is validated in infants, children, and adults.

Cardiopulmonary exercise test

All patients underwent CPET using an electronically braked cycle ergometer (Lode Corival, Groningen, The Netherlands). After assessment of baseline cardiopulmonary values, the work rate was increased by a constant increment of 10, 15, or 20 W/min, depending on the estimated fitness level to bring the patient to his or her limit between 8 and 12 minutes of exercise. During the CPET, patients had to maintain a pedaling rate between 60 and 80 rotations per minute (rpm). This protocol continued until the patient stopped because of volitional exhaustion, despite strong verbal encouragement of the investigators. Heart rate (HR) was monitored using a 12-lead electrocardiogram (Hewlett-Packard, Amstelveen, The Netherlands) and the peripheral measured oxygen saturation (SpO_2%) at the index finger by pulse oximetry (Nellcor 200 E, Nellcor, Breda, The Netherlands).

During CPET, participants breathed through a facemask (Hans Rudolph, Kansas City, MO) connected to a calibrated respiratory gas analysis system (Jaeger Oxycon Pro, Care Fusion, Houten, The Netherlands). Expired gas was passed through a flowmeter (Triple V volume transducer), an oxygen (O_2) analyzer, and a carbon dioxide (CO_2) analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath V_E, VO_2, CO_2 production (VCO_2), and the respiratory exchange ratio ($RER = VCO_2/VO_2$) averaged at 10-second intervals. Maximal effort was reached when participants showed clinical signs of intense effort, were unable to maintain the required pedaling speed, and when at least one of the following criteria was met: HR at peak exercise (HR_{peak}) >180 beats per minute or RER at peak exercise (RER_{peak}) >1.0. Absolute peak values were calculated as the average value over the last 30 seconds during the maximal CPET. The point at which a change in the linear slope of the relationship between the VCO_2 and VO_2 was detected, was defined as the VT, according to the V-slope method.[40] The V_E/VO_2-slope and V_E/VCO_2-slope were calculated by linear least squares regression of the relation between the V_E and the VO_2 and VCO_2 respectively during the entire CPET. The OUES was calculated by a linear least squares regression of the VO_2 on the common logarithm of the V_E, by using the following equation[19]: $VO_2 = a \log(V_E) + b$. In this equation, the constant 'a' stands for the regression coefficient (called the OUES) and 'b' represents the intercept. A steeper slope, reflected by a higher OUES, represents a more efficient VO_2: a smaller ventilation quantity is required for a certain VO_2 (Figure 1). For the determination of the OUES 100, all data gained during the CPET were included, whereas for the determination of the OUES 75, data up to 75% of the exercise duration were included in the analyses. The OUES VT was calculated by means of the collected exercise data up to the VT. Absolute exercise

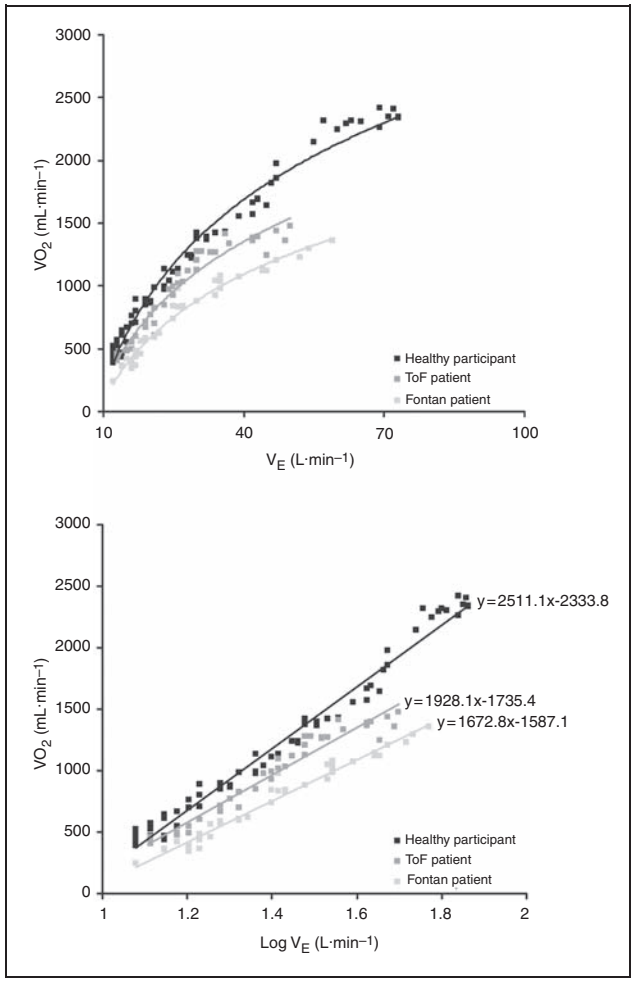

Figure 1. Relation between the oxygen uptake and the minute ventilation during a cardiopulmonary exercise test in a healthy 13-year-old boy, in a sex- and age-matched patient with tetralogy of Fallot, and in a sex- and age-matched Fontan patient. The values of the oxygen uptake efficiency slope are 2511.1, 1928.1, and 1672.8 respectively, and the data are presented as linear (top graph) and semilog plots of the x-axis (bottom graph).
ToF: tetralogy of Fallot, V_E: minute ventilation, VO_2: oxygen uptake.

variables were expressed as relative values as well, by dividing the absolute values by BM or BSA. Due to the variable anthropometric changes in children as a result of their growth, development, and maturation, our research group recently recommended normalizing OUES values relative to BSA or fat free mass in children, since this reduced the variability between participants to the greatest extent.[41]

Statistical analysis

The Statistical Package for the Social Sciences (SPSS, version 15.0; SPSS Inc., Chicago, USA) was used for the data analysis. Shapiro-Wilk tests for normality were used to evaluate the distribution of the data. One-way analysis of variance (ANOVA) was performed on the anthropometric data to test for significant differences between the three groups. Kruskal-Wallis ANOVA was applied on the exercise data to test for significant differences between groups (group validity). Within-group differences between the OUES values determined at different exercise intensities were evaluated with a Friedman test (construct validity). Additional post-hoc comparisons were performed on the one-way ANOVA outcomes to identify the exact significant differences by using Fisher's least significant difference (LSD) tests. Mann-Whitney U tests with Holm's sequential Bonferroni adjustment were performed on the Kruswal-Wallis ANOVA outcomes to locate the exact significant differences between the groups. Receiver-operator characteristic (ROC) curves analysis was used to identify the cut-off value of percentage of predicted OUES 75/BSA values between children with CHD and healthy controls. OUES 75/BSA values were predicted using the following formula OUES $75/BSA = 998.833 + (46.362 \times \text{age})$, which was established in our sample of healthy children. Spearman correlation coefficients were calculated to examine associations between exercise variables and the OUES (construct validity). Data are presented as mean values (SD). A p-value <0.05 was considered statistically significant.

Results

Anthropometric characteristics of the healthy children, ToF patients, and Fontan patients are shown in Table 2. Body height, BM, and BSA, were significantly lower in Fontan patients compared with their healthy peers. Moreover, Fontan patients were younger, underwent their first surgical procedure at a younger age, and had significantly lower values for body height, BM, and BSA compared with ToF patients. No significant anthropometric differences between ToF patients and healthy children were found. A normal BMI for age was found in all three groups.

All participants exercised to exhaustion without any adverse events. They all performed a sufficient level of effort indicated by a $RER_{peak} > 1.0$ in all participants. The results of the CPETs are shown in Table 3. HR_{peak} was significantly lower in the children with CHD compared with their healthy counterparts; however, it was not significantly different between Fontan and ToF patients. The $SpO_2\%$ at rest and at peak exercise ($SpO_2\%_{peak}$) were significantly lower in Fontan patients compared with ToF patients and the healthy participants, whereas only $SpO_2\%_{peak}$ was significantly lower in ToF compared with the healthy children. Work rate at peak exercise (W_{peak}) normalized for BM appeared to be significantly higher in the healthy group, and additionally, a significant difference has been found within CHD, as expected, with significantly lower values in Fontan patients compared with the ToF patients.

Significantly lower values for VO_{2peak} normalized for BM were attained within the CHD groups. Within CHD, Fontan patients accomplished significantly lower

Table 2. Characteristics of the participants in the study

	Healthy participants $n=46$	ToF patients $n=15$	p^a	Fontan patients $n=16$	p^b	p^c
Sex (male/female)	27/19	9/6		10/6		
Age at first surgery (months)	–	12.4 (7.8)	–	2.7 (6.5)	–	<.001[d]
Age at CPET (years)	12.2 (2.4)	13.2 (3.5)	NS	11.2 (2.7)	NS	.049
Body height (m)	1.6 (0.1)	1.6 (0.2)	NS	1.4 (0.1)	.003	.030
BM (kg)	44.7 (13.4)	44.2 (14.5)	NS	34.9 (6.4)	.009	.042
BMI (kg/m^2)	17.9 (2.6)	17.8 (3.0)	NS	16.6 (2.1)	NS	NS
BMI (SD)	−0.1 (0.9)	−0.5 (1.2)	NS	−0.5 (1.2)	NS	NS
BSA (m^2)	1.4 (0.3)	1.4 (0.3)	NS	1.2 (0.1)	.013	.036

BM: body mass, BMI: body mass index, BSA: body surface area, CPET: cardiopulmonary exercise testing, ToF: tetralogy of Fallot.
[a]Healthy versus ToF. [b]Healthy versus Fontan, [c]ToF versus Fontan, [d]Mann-Whitney U test. All values are presented as means (SD).

Table 3. Cardiopulmonary exercise test results of the participants

	Healthy participants	ToF patients	p^a	Fontan patients	p^b	p^c
HR_{peak} (beats/min)	193.0 (7.4)	175.3 (20.9)	<.001	166.3 (19.4)	<.001	NS
RER_{peak} (VCO_2/VO_2)	1.15 (0.07)	1.24 (0.11)	.008	1.15 (0.13)	NS	.009
SpO_2 at rest (%)	98.3 (1.7)	98.3 (2.5)	NS	94.1 (4.8)	<.001	.001
SpO_{2peak} (%)	97.1 (2.4)	94.6 (4.2)	.029	87.1 (8.2)	<.001	.007
W_{peak}/BM (W/kg)	4.0 (0.6)	3.5 (0.6)	.029	2.7 (0.7)	<.001	.002
VO_{2peak}/BM (ml/kg/min)	49.1 (7.7)	40.9 (6.1)	<.001	32.8 (9.1)	<.001	.002
V_{Epeak}/BM (l/kg/min)	1.7 (0.3)	1.5 (0.3)	.024	1.4 (0.5)	<.002	NS
VT (ml/min)	1488 (479)	1257 (393)	NS	797 (168)	<.001	.001
V_E/VCO_2-slope	29.8 (3.6)	28.4 (5.2)	NS	36.0 (5.7)	<.001	.001
V_E/VO_2-slope	37.3 (6.1)	34.7 (8.1)	NS	42.0 (8.2)	NS	.013
OUES 100/BSA	1576 (286)	1374 (262)	.024	1108 (234)	<.001	.008
OUES 75/BSA	1569 (301)	1381 (287)	.038	1110 (213)	<.001	.013
OUES VT/BSA	1570 (307)	1357 (260)	.006	1084 (236)	<.001	.010

BM: body mass, BSA: body surface area, HR_{peak}: peak heart rate, OUES: oxygen uptake efficiency slope, RER_{peak}: peak respiratory exchange ratio (VCO_2/VO_2), $SpO_{2(peak)}$: peripheral measured oxygen saturation (at peak exercise), ToF: tetralogy of Fallot, V_{Epeak}: peak minute ventilation, V_E/VCO_2-slope/V_E/VO_2-slope: ventilatory equivalents for carbon dioxide and oxygen respectively, VO_{2peak}: peak oxygen uptake, VT: ventilatory threshold, W_{peak}: peak work load.

[a]Healthy versus ToF, [b]Healthy versus Fontan, [c]ToF versus Fontan. All values are presented as means (SD).

VO_{2peak}/BM values compared with ToF patients. The VT was found to be significantly reduced in Fontan patients compared with both ToF patients and healthy participants, whereas no significant difference was found between ToF patients and healthy children. The V_E/VCO_2-slope was significantly increased in Fontan patients compared with both ToF patients and the healthy controls.

Within all three groups, the OUES 100, OUES 75, OUES VT were not significantly different between each other (Figure 2 and Table 3). However, the absolute OUES values showed a large variation within each group, which was reduced using normalization for BSA. The OUES/BSA was significantly lower in the children with CHD compared with the healthy children, and within CHD, significantly lower values were observed in the Fontan patients compared with ToF patients. ROC analysis showed that the OUES 75/BSA had a sensitivity of 64% and specificity of 87% to differentiate between patients with CHD and healthy children using a OUES cut-off value of 83% of predicted (area under the curve: 0.816, $p < 0.001$).

As can be appreciated from Table 4, the OUES 100/BSA and OUES 75/BSA correlated significantly with the VO_{2peak}/BM (r ranging from 0.571 to 0.611), VT (r ranging from 0.624 to 0.775), and V_E/VCO_2-slope (r ranging from −0.574 to −0.750) in CHD. However, the VO_{2peak}/BM correlated not significantly ($r = 0.435$, with $p > 0.05$) with the OUES 75/BSA in Fontan patients. In addition, only the VT correlated significantly with the OUES VT/BSA ($r = 0.536$) in Fontan patients, whereas both the VT ($r = 0.557$) and the VO_{2peak}/BM ($r = 0.750$) were significantly correlated with the OUES VT/BSA in ToF patients. No significant association was observed between the OUES and the drop in SpO_2% during the CPET. Overall, associations weakened when a smaller amount of data points were used for the calculation of the OUES, with the OUES VT having the lowest correlation coefficients with other exercise parameters.

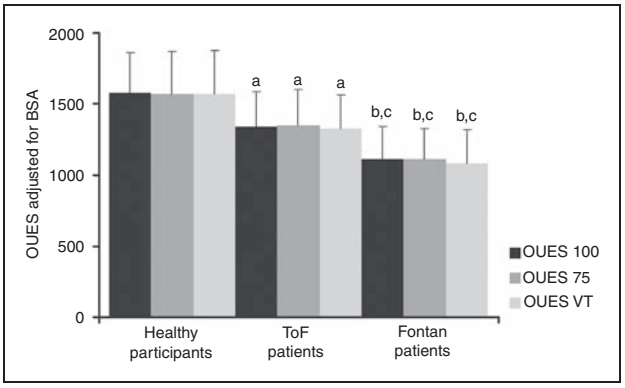

Figure 2. Oxygen uptake efficiency slope values normalized for body surface area at different exercise intensities in the healthy children, tetralogy of Fallot patients, and Fontan patients; data are expressed as mean ± SD. BSA: body surface area, OUES: oxygen uptake efficiency slope, ToF: tetralogy of Fallot. [a]significant difference between healthy and ToF, [b]significant difference between healthy and Fontan, [c]significant difference between ToF and Fontan.

Table 4. Spearman correlation coefficients between the oxygen uptake efficiency slope and other exercise parameters

	ToF patients		
	OUES 100/BSA	OUES 75/BSA	OUES VT/BSA
VO_{2peak}/BM (ml/kg/min)	.611 (p = .016)	.571 (p = .026)	.750 (p = .001)
VT (ml/min)	.775 (p = .001)	.704 (p = .003)	.557 (p = .031)
V_E/VCO_2-slope	−.639 (p = .010)	−.668 (p = .007)	−.400 (NS)
SpO_2 drop (%)	.027 (NS)	.236 (NS)	.396 (NS)
	Fontan patients		
	OUES 100/BSA	OUES 75/BSA	OUES VT/BSA
VO_{2peak}/BM (ml/kg/min)	.606 (p = .013)	.435 (NS)	.324 (NS)
VT (ml/min)	.652 (p = .006)	.624 (p = .010)	.536 (p = .032)
V_E/VCO_2-slope	−.750 (p = .001)	−.574 (p = .020)	−.456 (NS)
SpO_2 drop (%)	−.150 (NS)	−.211 (NS)	−.374 (NS)

BM: body mass, BSA: body surface area, OUES: oxygen uptake efficiency slope, SpO_2: peripheral measured oxygen saturation, ToF: tetralogy of Fallot, V_E/VCO_2-slope: ventilatory equivalent for carbon dioxide, VO_{2peak}: peak oxygen uptake, VT: ventilatory threshold.

Discussion

The aim of the present study was to investigate the construct and group validity of the OUES in children with CHD. Assessing its construct validity, we found that the OUES values, calculated at three different exercise intensities, did not differ from each other. This demonstrates the linear relation between the logarithm of the V_E and the VO_2 through progressive exercise in both healthy children and children with CHD. It is in line with other studies in various patient groups claiming that the OUES theoretically includes an effort-independent measure of cardiopulmonary fitness.[13,15,19,22–24,42–45] This is an essential characteristic when a patient is either unwilling or unable to deliver a maximal effort during CPET.

The only study[19] that investigated the OUES characteristics in children with CHD previously reported a slightly, but significantly, lower OUES 75 compared with the OUES 100, which seems to be inconsistent with the findings in our current study. However, the authors made no distinction between healthy children and children with heart disease. The only study[36] that examined the OUES characteristics in adult patients with CHD reported, in agreement with our study, significantly lower VO_{2peak} and OUES values, and significantly higher V_E/VCO_2-slope values in Fontan patients compared with both healthy controls and patients who underwent a Mustard or Senning repair for transposition of the great arteries (TGA). Contrary to our results, they found a nonlinear relationship between the logarithm of the V_E and the VO_2 throughout the CPET within Fontan patients. However, subgroup analysis revealed that this nonlinearity of the OUES was only present in cyanotic Fontan patients (SpO_2 at rest <95%). A secondary subgroup analysis in our study showed that the OUES maintains its linearity throughout the CPET in Fontan patients who have a SpO_2 at rest <95% ($n = 8$). Other studies investigating the linearity of the OUES in adult patients with heart disease confirm our results by concluding that the OUES remains relatively stable over the entire exercise duration (in heart failure[13,15,20,24,26,28] and coronary artery disease[35]), while others found that the OUES using the first 50% of the exercise data (heart failure[23]) and the OUES using data up to RER = 1.0 (coronary artery disease[32]) differed significantly from the OUES 100.

Furthermore, the OUES, was significantly related to other indices of cardiopulmonary fitness (VO_{2peak}, VT, V_E/VCO_2 slope), showing its construct validity as well. However, associations weakened when a smaller amount of data points were used for the calculation of the OUES, with the OUES VT having the lowest correlation coefficients with other exercise parameters. These correlations are slightly lower compared with those reported by Baba et al.[19] between both the OUES 100 and OUES 75 with the VO_{2peak} ($r = 0.941$ and $r = 0.946$ respectively) in children with heart disease. The associations found by Giardini et al.[36] between the OUES calculated at different exercise intensities and the VO_{2peak} in adult patients with CHD were slightly higher as well ($r = 0.812$–0.922 within Mustard and Senning patients and $r = 0.719$–0.891 within Fontan patients). Confirming our current results, the correlations in the latter study appeared to

be weaker using only the first 50% of the exercise data ($r = 0.719$).

The current study also showed that children with CHD attained significantly lower OUES values, with significantly lower OUES values for Fontan patients compared with ToF patients. Thus, the OUES possessed sufficient discriminative power to distinguish between patients with CHD and their healthy counterparts (group validity). The lower OUES values can be explained by the significantly increased V_E/VCO_2-slope in Fontan patients, which indicates a significant ventilation-perfusion mismatch,[46] resulting in an increased physiological dead space to tidal volume ratio (V_D/V_T).[47] Patients with ToF might also have a persistent ventilation-perfusion mismatch and/or the inability to increase pulmonary blood flow appropriately with exercise.[48] Moreover, just as in Fontan patients, the velocity of the increase of VO_2 at the onset of exercise is slowed,[49] increasing the dependency on anaerobic energy sources. Together with the impaired skeletal muscle metabolism in chronic heart failure,[50] this causes a higher contribution from anaerobic energy sources (metabolic acidosis) at lower workloads, which is reflected by the reduced VT within Fontan patients in this study. Indeed, these above mentioned factors might explain the reduced OUES values in CHD, since the OUES is physiologically based on the V_D/V_T and the point where lactic acid begins to accumulate.[19–21,26]

Limitations to this study

The patients with CHD who were referred for CPET had undergone completion of Fontan circulation or repair for ToF from a single tertiary center. This could have led to a biased sample. In addition, there was a large, unavoidable, heterogeneity in the physiology of the studied patients. Although this heterogeneity makes exact comparison difficult, our included patients are representative for a tertiary children's hospital, which strengthens the generalization of the current findings. Furthermore, the sample of CHD patients included only Fontan and ToF patients. Whether the OUES is a valid indicator of cardiopulmonary fitness in other pediatric CHD patient groups (e.g. TGA, cardiac shunts, pulmonary hypertension) needs additional research.

Recommendations

The OUES appears to be a useful parameter of cardiopulmonary fitness in children with CHD. However, in our opinion the OUES has not been introduced in order to predict VO_{2peak} or to act as a substitute for VO_{2peak} measurements. Therefore, interpretation of OUES values should be based on adequate reference values, comparison between (groups of) subjects, or comparisons within subjects (e.g. in order to evaluate the cardiopulmonary response to a specific training regime). Additionally, maximal exercise testing yields specific information regarding adaptations of the cardiopulmonary system during progressive exercise (e.g. development of exercise-induced arrhythmias, development of exercise-induced ischemia, assessment of anti-arrhythmic drug efficacy), which does not always occur during sub-maximal exercise testing. Thus, although the OUES is an effort-independent measure of cardiopulmonary fitness, which adds useful information about the cardiopulmonary response during progressive exercise, it remains unknown whether the OUES provides information above that of the more established measures such as VO_{2peak} and the VT.

As recommended previously,[40] we advise normalization of the OUES for BSA since this reduces the variability in OUES values to the greatest extent and compensates for the development in anthropometry in children due to growth and maturation. Furthermore, associations with other exercise variables weakened when a smaller amount of data points were used for its determination. Therefore, it seems to be important that the child continues exercising as long as possible towards his peak level in order to gain as many data points for the calculation of the OUES.

Conclusion

In summary, the current study provides evidence that the OUES has a good construct and group validity in children with CHD. It proved to be independent of exercise intensity and strongly correlated with VO_{2peak} and VT (construct validity) as well as being capable of differentiating between healthy children and children with CHD, and, within CHD, between Fontan and ToF patients (group validity). Therefore, the OUES could be used as a valid, objective, and effort-independent measure of cardiopulmonary fitness in children with CHD.

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Conflict of interest

The authors have no conflicts of interest.

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