Journal of Exercise Science & Fitness

Maximal Oxygen Consumption and Oxygen Uptake Efficiency in Adolescent Males

--Manuscript Draft--

Manuscript Number:	JESF-D-20-00075R2
Article Type:	Full Length Article
Keywords:	Exercise testing; oxygen uptake efficiency slope; oxygen uptake efficiency plateau; maximal oxygen consumption; adolescents; Fitness
Corresponding Author:	Sinead Sheridan CUHK HONG KONG
First Author:	Sinead Sheridan, PhD
Order of Authors:	Sinead Sheridan, PhD
	Andrew McCarren, PhD
	Gray Cleona, PhD
	Ronan P. Murphy, PhD
	Michael Harrison, PhD
	Stephen H.S Wong, PhD
	Moyna M. Niall, PhD
Abstract:	Background/Objective Measures of oxygen uptake efficiency (OUE) have been used to evaluate cardiorespiratory fitness (CRF) in adolescents unable to perform maximal exercise. The oxygen uptake efficiency slope (OUES) and oxygen uptake efficiency plateau (OUEP) have been proposed as surrogates for maximal oxygen consumption ($\dot{V}O_{2max}$). We assessed the validity of the OUES and OUEP as predictors of $\dot{V}O_{2max}$ in healthy male adolescents. Methods Sixty-three healthy male adolescents aged 15.40 ± 0.34 years underwent an incremental treadmill test to determine $\dot{V}O_{2max}$, OUES and OUEP. OUE throughout the test was assessed by dividing each $\dot{V}O_2$ value by the corresponding minute ventilation ($\dot{V}_E$) value. OUEP was determined as the 90 sec average highest consecutive values for OUE. OUES was determined using data up to the ventilatory threshold (VT) by calculating the slope of the linear relation between $\dot{V}O_2$ and the logarithm of $\dot{V}_E$. Results Limits of agreement for $\dot{V}O_{2max}$ predicted by OUES (± 13.3 mL.kg^{-1}.min^{-1}) and OUEP (± 16.7 mL.kg^{-1}.min^{-1}) relative to $\dot{V}O_{2max}$ were wide and a magnitude bias was found for OUES and OUEP as predictors of $\dot{V}O_{2max}$ (p<0.001). Conclusion The OUES and OUEP do not accurately predict $\dot{V}O_{2max}$ in male adolescents and should not replace $\dot{V}O_{2max}$ when assessing CRF in this population.
Suggested Reviewers:	
Opposed Reviewers:	
Response to Reviewers:	

THE CHINESE UNIVERSITY OF HONG KONG 香港中文大學

SHATIN · NT · HONG KONG · 香港 新界 沙田 · TEL : (852) 3943 6096 電話 : (852) 3943 6096 FAX : (852) 2603 5781 圖文傳真 : (852) 2603 5781 EMAIL : sports@cuhk.edu.hk 電子郵箱 : sports@cuhk.edu.hk

Sports Science & Physical Education Department 體育運動科學系

11th October 2020

Dear Editor-in-Chief

We wish to submit the original research article entitled "Maximal Oxygen Consumption and Oxygen Uptake Efficiency in Adolescent Males" for consideration by the Journal of Exercise Science and Fitness. We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

Measures of oxygen uptake efficiency (OUE) including the oxygen uptake efficiency slope (OUES) and oxygen uptake efficiency plateau (OUEP) have been proposed as surrogates for $\dot{V}O_{2max}$. This has been based on their strong correlations with $\dot{V}O_{2peak/max.}$ However, a strong correlation between these measures of OUE and $\dot{V}O_{2peak/max}$ does not take into account their interchangeability. In this paper, we showed, using Bland Altman analysis, that both the OUES and OUEP do not reliably predict $\dot{V}O_{2max}$ in apparently healthy adolescents with a wide range of fitness and should not be used as a replacement for $\dot{V}O_{2max}$, particularly in clinical practice, to assess CRF in adolescents.

We believe that this manuscript is appropriate for publication by the Journal of Exercise Science and Fitness as it is the first study to assess the concurrent validity of the OUES and the OUEP as predictors of $\dot{V}O_2$max in an adolescent population.

We have no conflicts of interest to disclose.

Thank you for your consideration of this manuscript.

Yours sincerely

Sinead Sheridan

Sinead Sheridan Ph.D
Department of Sports Science and Physical Education
The Chinese University of Hong Kong
Shatin, Hong Kong SAR

We would like to express our greatest appreciation to the editor and reviewers for their valuable comments. The manuscript has been thoroughly revised based on the comments and point-to-point responses have now been provided with this resubmission. All the further minor revisions are highlighted in green in the revised manuscript.

Reviewer #1:

Reviewer #1: The authors have addressed all my concerns, and the quality of manuscript has improved.

Thank you.

Reviewer #2.

1. In the abstract, the authors haven't defined VE as "minute ventilation" yet. Please double check.

Response Thank you for your comment. This has been revised accordingly.

2. For introduction, the first and second paragraphs are repeated. (It seems that the second paragraph is from the old version). Please revise.

Response: Thank you for your comment. The second paragraph has been deleted.

3. For figure 1a and 1b, the authors revised the "x-axis" as "measured VO2max" based on a previous comment. However, it is noted that the figure caption is still written as ".....plotted against their mean".

Response: Thank you for your comment. The caption for the figures has now been changed accordingly.

Also in the "Statistical Analysis", it is highlighted that "the differences between measured $\dot{V}$ O2max and estimated $\dot{V}$ O2max measured from OUES and OUEP were regressed against the means of the measured and estimated $\dot{V}$ O2max from OUES and OUEP". The authors should thus clarify the correct x-variable and cite relevant literature/ studies that use the same regression equation before.

The X-axis is usually the average of 2 measures in a Bland Atlman plot, (Altman & Bland, 1983). However, we have changed the x-axis in the previous revision to accommodate the reviewers request. We can revert to the original if necessary depending on the reviewers request.

Altman, D.G. and Bland, J.M., 1983. Measurement in medicine: the analysis of method comparison studies. *Journal of the Royal Statistical Society: Series D (The Statistician)*, *32*(3), pp.307-317.

A similar analysis has previously been conducted by Pichon et al (2002). Reference has been provided below.

Pichon A, Jonville S, Denjean A. Evaluation of the interchangeability of VO2MAX and oxygen uptake efficiency slope. *Can J Appl Physiol.* 2002;27:589-601.

Title Page

Category of paper: Full Length Article

Article Title: Maximal Oxygen Consumption and Oxygen Uptake Efficiency in Adolescent Males

Running head: Validity of OUES and OUEP in Adolescents

Sinead Sheridan[1, 2] (sineadsheridan@cuhk.edu.hk); + 00852-3943-6085

Andrew McCarren[3] (amcarrent@dcu.ie); +00353-1700-8456

Cleona Gray[4] (cgray@mater.ie);

Ronan P. Murphy[2] (ronan.murphy@dcu.ie); +00353-1700-8824

Michael Harrison[5] (MHARRISON@wit.ie); +00353- 5130- 2161

Stephen H.S Wong[1] (hsswing@cuhk.edu.hk); +00852-3943- 6095

Niall M. Moyna[2] (niallmoyna@dcu.ie); +00353-1700-8802

[1] Department of Sports Science and Physical Education, The Chinese University of Hong Kong, Hong Kong

[2] School of Health and Human Performance, Dublin City University, Dublin, Ireland

[3] Insight, Dublin City University, Ireland,

[4] Mater Misericordiae University Hospital, Dublin, Ireland

[5] Department of Sport and Exercise Science, Waterford Institute of Technology, Waterford, Ireland

Correspondence: Sinead Sheridan, Department of Sports Science and Physical Education, The Chinese University of Hong Kong, Shatin, NT, Hong Kong Email: sineadsheridan@cuhk.edu.hk

Tel: + 00852-3943-6085

Word Count: 3879

Keywords: Exercise testing, oxygen uptake efficiency slope, oxygen uptake efficiency plateau, maximal oxygen consumption, adolescents, fitness

Title Page

Category of paper: Full Length Article

Article Title: Maximal Oxygen Consumption and Oxygen Uptake Efficiency in Adolescent Males

Running head: Validity of OUES and OUEP in Adolescents

Abstract

Background/Objective

Measures of oxygen uptake efficiency (OUE) have been used to evaluate cardiorespiratory fitness (CRF) in adolescents unable to perform maximal exercise. The oxygen uptake efficiency slope (OUES) and oxygen uptake efficiency plateau (OUEP) have been proposed as surrogates for maximal oxygen consumption ($\dot{V}O_{2max}$). We assessed the validity of the OUES and OUEP as predictors of $\dot{V}O_{2max}$ in healthy male adolescents.

Methods

Sixty-three healthy male adolescents aged 15.40 ± 0.34 years underwent an incremental treadmill test to determine $\dot{V}O_{2max}$, OUES and OUEP. OUE throughout the test was assessed by dividing each $\dot{V}O_2$ value by the corresponding minute ventilation ($\dot{V}_E$) value. OUEP was determined as the 90 sec average highest consecutive values for OUE. OUES was determined using data up to the ventilatory threshold (VT) by calculating the slope of the linear relation between $\dot{V}O_2$ and the logarithm of $\dot{V}_E$.

Results

Limits of agreement for $\dot{V}O_{2max}$ predicted by OUES (± 13.3 $mL \cdot kg^{-1} \cdot min^{-1}$) and OUEP (± 16.7 $mL \cdot kg^{-1} \cdot min^{-1}$) relative to $\dot{V}O_{2max}$ were wide and a magnitude bias was found for OUES and OUEP as predictors of $\dot{V}O_{2max}$ ($p<0.001$).

Conclusion

The OUES and OUEP do not accurately predict $\dot{V}O_{2max}$ in male adolescents and should not replace $\dot{V}O_{2max}$ when assessing CRF in this population.

Introduction

Cardiorespiratory fitness (CRF) is a powerful indicator of cardiovascular health in children and adolescents.[1] High CRF during childhood and adolescence is associated with a healthier cardiovascular profile during these years[1] and also later in adulthood.[2] Maximal oxygen consumption ($\dot{V}O_{2max}$), measured during a standardized cardiopulmonary exercise test (CPET), is considered the gold standard measure of CRF and is defined as the highest rate of oxygen uptake and utilization by the body during intense, maximal exercise that no further increases in work rate result in additional rises in $\dot{V}O_2$. [3] The conventional criterion for the attainment of $\dot{V}O_{2max}$ during a CPET is a levelling-off or plateau in $\dot{V}O_2$, and relies entirely on data from the last segment of a CPET. In such cases where the criteria for $\dot{V}O_{2max}$ attainment is not met , $\dot{V}O_{2peak}$ is recorded, which is the highest $\dot{V}O_2$ value attained during an incremental or other high intensity exercise test, designed to bring the subject to the limit of tolerance.[4] The ability to attain $\dot{V}O_{2max}$ during a CPET is strongly effort-dependent and sensitive to many factors including participant motivation.[5]

Oxygen uptake efficiency (OUE) measurement, which is the reciprocal of the ventilatory equivalent for oxygen ($\dot{V}O_2/\dot{V}_E$), provides an estimation of the efficiency of minute ventilation ($\dot{V}_E$) with respect to oxygen uptake ($\dot{V}O_2$).[6] As the OUE is not linear during the entire exercise period, the oxygen uptake efficiency slope (OUES), mathematically derived from the linear relation between $\dot{V}O_2$ and the logarithmic transformation of $\dot{V}_E$ during incremental exercise ($\dot{V}O_2 = a \log10 VE + b$, where a is the OUES and b is the intercept) has been proposed as an objective and effort-independent submaximal measure of exercise capacity[7] and a potential surrogate for $\dot{V}O_{2max}$.[8, 9] The logarithmic transformation of $\dot{V}_E$ reduces the curvature expected with increases in exercise intensity making the OUES resistant to disruption by the early termination of exercise.

Studies have shown that the OUES, calculated using only submaximal exercise data, is identical to the OUES calculated over the entire duration of a CPET.[10, 11] Furthermore, both maximal OUES and submaximal OUES are significantly related to $\dot{V}O_{2peak}$ in both normal weight and obese children and adolescents.[10, 12-14] There is evidence however, that OUES at submaximal and maximal exercise intensities exhibits a significant magnitude bias when used to predict $\dot{V}O_{2peak}$ in healthy adults[15] and adolescents[12] with varying levels of CRF, in that it over predicts $\dot{V}O_{2peak}$ at low levels of CRF and under predicts $\dot{V}O_{2peak}$ at high levels of CRF.

More recently, Sun et al., (2012) noted that the OUE when plotted against time, reaches its highest and briefly stable values/plateau (OUEP) at a moderate exercise intensity near the ventilator threshold (VT) before declining due to hyperventilation stimulated by the onset of metabolic acidosis.[16] A cross-sectional study involving 214 boys and girls aged between 8 - 19 years found that the OUEP was weak-to-moderately correlated with $\dot{V}O_{2peak}$ and the OUES was strongly correlated with $VO_{2peak.}$[6] Similar findings have been observed in healthy adults.[16] The validity of submaximal measures of CRF including the OUES and OUEP to accurately predict $\dot{V}O_{2max}$ in adolescents is of particular importance for disease risk identification and classification, given that $\dot{V}O_{2max}$ is not often attained in this cohort. While the validity of the majority of submaximal measures of CRF including OUES and OUEP have been based on their correlations with $\dot{V}O_{2peak/max}$, a strong correlation between OUES/OUEP and $\dot{V}O_{2peak/max,}$ does not take into account their interchangeability.[15] To date, only one previous study has assessed the interchangeability of OUES with measured $\dot{V}O_{peak}$ and found that the wide interindividual variation in OUES precluded its use in clinical practice as a predictor of $\dot{V}O_{2peak}$.[12] Furthermore, no previous studies have examined the interchangeability of the OUEP with $\dot{V}O_{2max}$.

The purpose of this study was to therefore assess the concurrent validity of the OUES and the OUEP as predictors of $\dot{V}O_{2max}$ in apparently healthy male adolescents by using Bland and Altman method [17], to compare the $\dot{V}O_{2max}$ value predicted from OUES and OUEP to the $\dot{V}O_{2max}$ measured during maximal exercise testing.

Methods

Participants and procedures

Sixty-three apparently healthy male adolescents (mean ± SD; age 15.40 ± 0.34 years) participated in the study. Initially, it was planned that females would participate in the study. However, during the recruitment phase of the study, many females were unwilling to participate and some females reported having an irregular menstrual cycle. Given that we wanted to control for the menstrual cycle in this study and that irregularity in the menstrual cycle would make this difficult, females were not included in the study. Exclusion criteria for male adolescents included current smokers, currently taking vasoactive medications, uncontrolled hypertension (SBP >180 mmHg, diastolic BP >100 mmHg) or any condition that precluded participants from engaging in moderate to vigorous exercise. Informed parental consent and child assent were obtained prior to participation. The study was approved by Research Ethics Committee at Dublin City University. Participants made a single visit to the research laboratory during which body composition, pubertal status and CRF were assessed. Participants refrained from physical activity for 24 h prior to the visit.

Anthropometry and Pubertal Assessment

A stadiometer and electronic scale (Seca 797, USA) were used to measure height (cm) and body mass (kg), respectively. Body mass index (BMI) was calculated as body mass in kilograms divided by height in metres-squared ($kg \cdot m^{-2}$). Age- and gender-specific BMI percentiles were calculated and Centers for Disease Control and Prevention (CDC) standards were used to classify participants as normal weight (BMI < 85th percentile), overweight (BMI ≥ 85th and < 95th percentile) and obese (BMI ≥ 95th percentile).[18] Participants self-reported their genital and pubic hair development using standardized Tanner drawings representing different stages of sexual maturity.[19] Participants were classified as pre-pubertal (Tanner 1), pubertal (Tanner II-IV) and post-pubertal (Tanner V) as previously described.[20]

Cardiopulmonary Exercise Testing

CPET was performed on a treadmill (Woodway ELG 55, Waukesha, WI) in a temperature-controlled laboratory environment (temperature 21.1°C, ambient humidity 60%, atmospheric pressure 750 mm Hg). The test consisted of a continuous incremental protocol designed to ensure that participants reached volitional exhaustion between 8 - 12 min. One month prior to the CPET, participants undertook a school-based 20 meter shuttle run test to estimate their level of CRF. Based on the number of shuttle runs completed, participants were classified as low CRF (LCRF) (0-40th percentile), moderate CRF (MCRF) (40-70th percentile), and high CRF (HCRF) (70th-100th percentile), in accordance with European age and gender specific percentiles for aerobic fitness.[21] Three separate protocols were then specifically developed to accommodate LCRF, MCRF and HCRF. Briefly, participants undertook a 2 min warm up on a 0% grade, which consisted of 2 min at 6.0 for $km.hr^{-1}$ for those with LCRF, 7.0 $km.hr^{-1}$ for those with MCRF and 9.0 $km.hr^{-1}$ for those HCRF After the warm-up, the treadmill velocity was increased to 7.0 for LCRF, 8.0 for MCRF and 11.0 $km.hr^{-1}$ for HCRF for 1 min and was then increased to 8.0, 10.0 and 12.0 or 13 $km.hr^{-1}$ in those with LCRF, MCRF and HCRF respectively, after which the speed remained constant and the grade was increased by 0.5% every 30 sec until volitional exhaustion. Respiratory metabolic responses were determined using standard open-circuit spirometry techniques (Sensormedics Vmax 229, SensorMedics Corp., CA). Prior to testing, the gas analyzers were calibrated with standard gases of known concentration. A mass flow sensor was used to collect breath-by-breath measurements of ventilation. A 3.0 L volume syringe was used to calibrate the mass flow sensor prior to each test. Heart rate was continuously recorded throughout the test using telemetry (Polar team 2 Pro, Polar Electro Inc., NY, USA) and rating of perceived exertion (RPE) was recorded during the last 15 sec of each min using the Borg 16 point category rating scale. Participants were verbally encouraged to give their maximal effort.

Criteria for Maximal Oxygen Consumption

Maximal oxygen consumption ($\dot{V}O_{2max}$) was determined using the highest consecutive 20 sec value. The test was deemed maximal if at least two of the following four criteria were satisfied: (i) a plateau in oxygen consumption (defined as a $\leq$2.0 $ml\cdot kg^{-1}\cdot min^{-1}$ change in $\dot{V}O_2$ during the last min of exercise) (ii) heart rate >200 bpm, (iii) RER >1.0 or (iv) volitional fatigue.[14]

Oxygen Uptake Efficiency

Oxygen uptake efficiency (OUE) throughout the CPET was assessed by dividing each $\dot{V}O_2$ value (ml/min) by the corresponding $\dot{V}_E$ value (L/min). The OUEP was then determined as the 90 sec average highest consecutive values for OUE [16]. OUES was determined on the respiratory data up to the VT by calculating the slope of the linear relation between $\dot{V}O_2$ (y-axis) and the logarithm of $\dot{V}_E$ (x-axis) through single regression analysis.[7] The VO_2 at the VT ($\dot{V}O_2VT$) was defined as the level of $\dot{V}O_2$ at which the linear relation between $\dot{V}CO_2$ and $\dot{V}O_2$ disappeared [22] and/or at which an increase in ventilatory equivalent for oxygen occurred ($\dot{V}_E\dot{V}O_2$) without a simultaneous increase in ventilatory equivalent for carbon dioxide ($\dot{V}_E\dot{V}CO_2$). The first minute of exercise was excluded because of the often irregular breathing pattern that is common at the onset of exercise. Relative values for $\dot{V}O_{2max}$, $\dot{V}O_2VT$, OUES and OUEP were calculated by dividing the absolute values by body mass.

Statistical Analysis

Statistical analyses was performed using SPSS for Windows statistical software (V22.0, SPSS Inc, IL). Continuous variables are expressed as mean ± SD. Estimates of $\dot{V}O_{2max}$ were calculated from the regression equation of the relation between $\dot{V}O_{2max}$ and OUES and $\dot{V}O_{2max}$ and OUEP. Bland and Altman[17] analyses was then used to examine the level of agreement between measured and estimated $\dot{V}O_{2max}$. Specifically, 2-tailed paired t-tests were conducted at $\alpha=0.05$, between the measured and estimated $\dot{V}O_2$max. To determine if there was measurement bias between objectively measured $\dot{V}O_{2max}$ and $\dot{V}O_{2max}$ predicted using OUES and OUEP, the differences between measured $\dot{V}O_{2max}$ and estimated $\dot{V}O_{2max}$ measured from OUES and OUEP were regressed against the means of the measured and estimated $\dot{V}O_{2max}$ from OUES and OUEP. Significance tests on the regression slope were applied to determine if there was measurement bias over the range of $\dot{V}O_{2max}$ values for OUES and OUEP. Univariate correlation analysis was conducted between $\dot{V}O_{2max}$, OUES and OUEP. The significance level was set at $\alpha = 0.05$ using a Bonferroni correction factor of 0.00625 (0.05/8).

RESULTS

Participant characteristics and CPET results

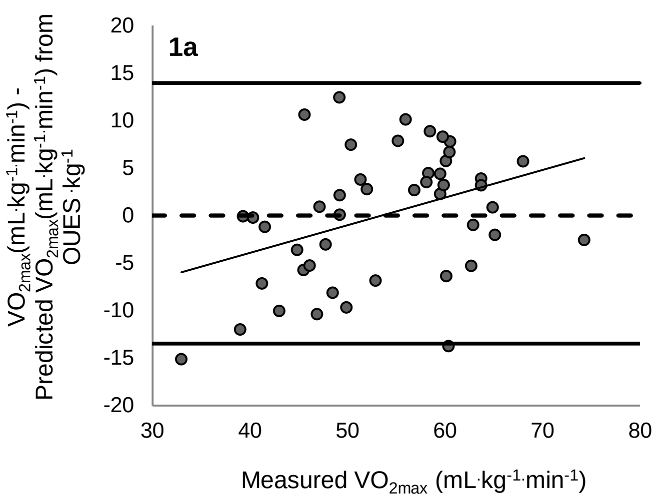
Participant characteristics and CPET results are presented in Table 1. 42 participants (63%) were classified as normal weight, 4 participants were overweight (16%) and 17 participants were obese. 55 participants self-reported that they were in the pubertal stage and 8 participants self-reported that they were in the post-pubertal stage All exercise tests were completed without any contraindications. At least two of the four predetermined criteria used to verify attainment of $\dot{V}O_{2max}$ were achieved by 94% of the participants. Almost all of the study participants (97%) achieved an RER value >1.0, 65% had a plateau in oxygen uptake and 41% achieved a HR > 200 bpm. OUEP was obtained in all participants. OUES was obtained in 46 participants as the VT could not be determined in 17 participants. Absolute and relative values for $\dot{V}O_{2max,}$ OUES and OUEP are summarized in Table 1.

Validity of OUES and OUEP as predictors of $\dot{V}O_{2max}$

Measured $\dot{V}O_{2max}$ ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) was significantly correlated with OUES ($r=0.77$, $p<0.001$) and OUEP ($r=0.53$, $p<0.001$). There was no significant difference between measured

$\dot{V}O_{2max}$ and $\dot{V}O_{2max}$ predicted by OUES (53. 5 ± 10.8 vs. 53.5 ± 8.3 mL·kg^{-1}·min^{-1}) and OUEP (52.8 ± 10.4 vs. 52.8 ± 5.9 mL·kg^{-1}·min^{-1}). The limits of agreement for $\dot{V}O_{2max}$ predicted by OUES, and OUEP relative to measured $\dot{V}O_{2max}$ were ±13.3 and ±16.7 mL·kg^{-1}·min^{-1}, respectively.

The regression model slopes of the difference between measured $\dot{V}O_{2max}$ and $\dot{V}O_{2max}$ predicted by OUES (b=0.291, t=2.735, p<0.001) and OUEP (b=0.684, t= 5.631, p<0.001) were significant, indicating a significant magnitude bias when using OUES and OUEP to predict $\dot{V}O_{2max}$ (Fig. 1). The cutoff points were 53.5ml kg^{-1}.min^{-1} and 52.7ml kg^{-1}.min^{-1} for under and over estimation for OUES and OUEP respectively. OUES overestimated $\dot{V}O_{2max}$ at a $\dot{V}O_2$ <53.5·mL·kg^{-1}·min^{-1} and underestimated $\dot{V}O_{2max}$ at a $\dot{V}O_2$ > 53.5 mL·kg^{-1}·min^{-1} and OUEP· overestimated $\dot{V}O_{2max}$ at a $\dot{V}O_2$ <52.7·mL·kg^{-1}·min^{-1} and underestimated $\dot{V}O_{2max}$ at a $\dot{V}O_2$ > 52.7 mL·kg^{-1}·min^{-1}.



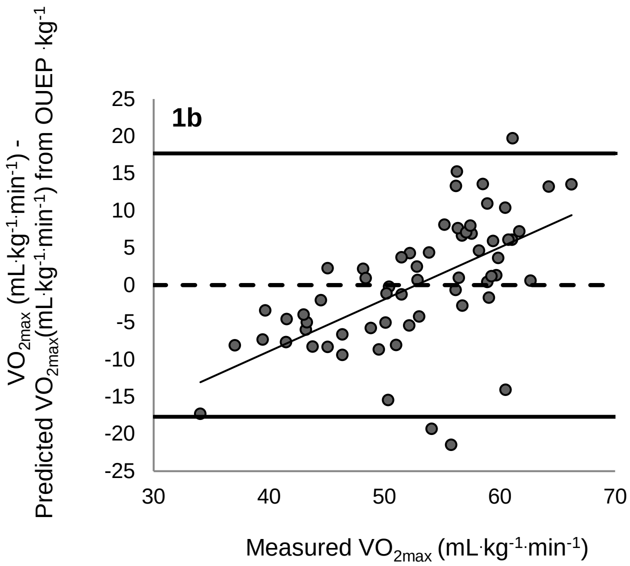


Figure 1. Difference between measured $\dot{V}O_{2max}$. (mL·kg^{-1}·min^{-1}) and (a) predicted $\dot{V}O_{2max}$ using OUES.kg^{-1} and (b) predicted $\dot{V}O_{2max}$ using OUEP.kg^{-1}

Discussion

The present study assessed the concurrent validity of the OUES and the OUEP as predictors of $\dot{V}O_{2max}$ in an adolescent population. The findings indicate that the large inter-individual variation and significant magnitude bias in both OUES and OUEP may impede their use as a predictor of $\dot{V}O_{2max}$ in healthy normal weight and overweight adolescents with varying levels of CRF.

$\dot{V}O_{2max}$ is considered to be the gold standard measurement for assessing cardiorespiratory fitness. The determination of $\dot{V}O_{2max}$ is based on the attainment of predetermined criteria which children and individuals with poor motivation and chronic disease are often unable to meet due to its effort dependency.[23] Similar to $\dot{V}O_{2max}$, both the OUES and OUEP provide an objective measure of cardiorespiratory function, reflecting the efficiency of ventilation with regard to oxygen uptake during exercise, but do not require maximal effort.[16, 24] Higher OUES and OUEP values indicate a more efficient VO_2 while lower values represent a lower VO_2 for any given $\dot{V}_E$. The OUEP represents the maximal and most efficient OUE which occurs at submaximal exercise intensities around the VT.[16] The OUES describes the slope of the linear relation between $\dot{V}O_2$ and the log transformation of $\dot{V}_E$. Theoretically, OUES should be robust to the early termination of exercise allowing it to be used as an objective, effort independent measure of cardiorespiratory fitness.[7, 25]

Studies in adults have found the OUES to be a reliable index of cardiorespiratory functional reserve.[5,19] Using correlation analysis, OUES was found to be an accurate replacement for $\dot{V}O_{2max}$ in healthy individuals and heart disease patients.[4,18] OUES and OUEP were both significantly correlated with $\dot{V}O_{2max}$ in the present study. The present findings are similar to previous studies involving healthy children and adolescents that reported a significant relation between both OUES and OUEP and $\dot{V}O_{2max}$ or $\dot{V}O_{2peak}$.[7, 10, 11, 13, 14] However, a strong correlation between OUES and OUEP with $\dot{V}O_{2max}$ or $\dot{V}O_{2peak}$ does not take into account their interchangeability.[15] The current study is the first study to assess the interchangeability of both the OUES and OUEP with measured $\dot{V}O_{2max}$ in an adolescent population. Although there were no significant differences between measured $\dot{V}O_{2max}$ and predicted $\dot{V}O_{2max}$ using OUES and OUEP, the limits of agreement varied greatly, indicating a significant magnitude bias. OUES and OUEP over predicted $\dot{V}O_{2max}$ at lower levels of CRF and under predicted $\dot{V}O_{2max}$ at higher levels of CRF. The heterogeneity in fitness levels in our study population, may have contributed to the variability in $\dot{V}O_{2max}$ values predicted from OUES and OUEP. Drinkard et al., (2007) also found a significant magnitude bias when OUES at the lactate inflection point, OUES at 150% of lactate infection and OUES at $\dot{V}O_{2peak}$ was used to predict $\dot{V}O_{2max}$ in both normal weight and overweight adolescents varying in levels of CRF.[12] The fact that both the OUES and OUEP over predicted $\dot{V}O_{2max}$ at lower levels of $\dot{V}O_2$ in the present study, suggests that they should not be used as a replacements for $\dot{V}O_{2max}$ to assess CRF in clinical practice, particularly in adolescents with low CRF who are a target for primary prevention of CVD.

The $\dot{V}O_2$ or workrate corresponding to the nonlinear increase in $\dot{V}_E$ during exercise demarcates the ventilatory anaerobic threshold (VT). Like OUES and OUEP, the $\dot{V}O_2$VT does not require a physiologically maximal exercise effort, and is considered to be more consistent with an individual's ability perform activities of daily living.[26] A major shortcoming of the VT measurement, is the fact that often it is not identifiable, and its measurement is subject to substantial intra-and inter- observer variability.[27, 28] Measurement of OUEP is an appealing alternative to $\dot{V}O_2$VT as it does not rely on VT determination. Furthermore, while data up to the

VT was used to calculate OUES in the present study, OUES does not necessarily need to rely on VT determination and can be calculated using a certain percentage of the max/peak exercise data i.e., 50%. A recent study calculated OUES using data up to 3, 4, 5 and 6 min of the exercise test and found that OUES determined from 5 min of exercise data was strongly related to $\dot{V}O_{2max}$ in obese children and adolescents.[29] However , while the OUES and OUEP are both objective and effort-independent submaximal measures of exercise capacity and are related to $\dot{V}O_{2max}$, their potential application for assessing CRF in a group or population setting for surveillance purposes is limited as they rely on the administration of a CPET in a laboratory setting which is expensive and not very feasible.

Key strengths of the present study is that it is the first study to concurrently assess the interchangeability of both the OUEP and OUES in an adolescent population. Our findings revealed that the OUEP and the OUES do not accurately predict $\dot{V}O_{2max}$ in a normal and overweight adolescents varying in CRF and should not be used as a replacement for $\dot{V}O_{2max}$ when assessing adolescents CRF. Accurate and routine monitoring of CRF in adolescents is of paramount importance given that it has been recently shown that low CRF in adolescence is independently associated with risk of heart failure in adulthood.[30] The present study included both normal weight and overweight obese adolescents. Body mass has been shown to influence OUES, with a larger body mass resulting in increased absolute OUES values.[13] To account for the influence of body mass, $\dot{V}O_{2max}$, OUES and OUEP values were normalized relative to body mass. Moreover, our findings are similar to that of a previous study that found a significant bias in OUES expressed relative to lean body mass when used predict $\dot{V}O_{2max}$ in normal and overweight adolescents with varying levels of CRF. [12]

A limitation of this study is use of the VT to calculate the OUES as 17 participants could not be included in the analysis. Future studies should employ a certain percentage of exercise data or duration of the exercise test to calculate OUES rather than relying on VT determination and should assess the validity of these measures of OUE as predictors of $\dot{V}O_{2max}$ Secondly, another limitation of the present study is that participants self-reported their pubertal status. The OUES has been shown to be influenced by maturation with an inverse relation observed between OUES and puberty stage.[31] While the majority of participants (87%) in the preset study self-reported that they were in the pubertal stage, 8% reported that they were post-pubertal. The disadvantage of using self-reported measures to assess pubertal status in adolescents is that there may be bias.

While we adjusted for body mass in the current study, a previous study showed that adjusting for body mass did not eliminate differences across maturational groups suggesting that qualitative factors such as oxidative metabolism may be responsible for the inverse relation observed between pubertal stage and the OUES. Thirdly, while we expressed $\dot{V}O_{2max}$, OUES and OUEP values relative to body mass, expressing these values relative to lean body mass would have allowed for better control of the influence of adiposity. Finally, this study was conducted in male adolescents only and therefore the findings cannot be generalized and extrapolated to female adolescents.

Conclusion

The OUES and OUEP do not reliably predict $\dot{V}O_{2max}$ and therefore should not be used in as a replacement for $\dot{V}O_{2max}$ to assess CRF in male adolescents.

Conflicts of Interest Statement: The authors have no conflicts of interest relevant to this article.

Funding/Support Statement: This work was supported by The Insight Centre for Data Analytics, Science Foundation Ireland (SFI 12/RC/2289) who assisted in analysis and interpretation of the study data.

References

1. Ortega F, Ruiz J, Castillo M, Sjöström M. Physical fitness in childhood and adolescence: a powerful marker of health. *Int J Obes (Lond).* 2008;32:1.

2. Kvaavik E, Klepp K-I, Tell GS, Meyer HE, Batty GD. Physical fitness and physical activity at age 13 years as predictors of cardiovascular disease risk factors at ages 15, 25, 33, and 40 years: extended follow-up of the Oslo Youth Study. *Pediatrics.* 2009;123:e80-e86.

3. Bassett DR, Jr., Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc.* 2000;32:70-84.

4. Whipp BJ, Ward SA. Physiological determinants of pulmonary gas exchange kinetics during exercise. *Med Sci Sports Exerc.* 1990;22:62-71.

5. Davies LC, Wensel R, Georgiadou P, et al. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur. Heart J.* 2006;27:684-690.

6. Bongers BC, Hulzebos EH, Helbing WA, Ten Harkel AD, Van Brussel M, Takken T. Response profiles of oxygen uptake efficiency during exercise in healthy children. *Eur. J. Prev. Cardiol.* 2016;23:865-873.

7. Baba R, Nagashima M, Goto M, 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.* 1996;28:1567-1572.

8. Baba R, Nagashima M, Nagano Y, Ikoma M, Nishibata K. Role of the oxygen uptake efficiency slope in evaluating exercise tolerance. *Arch Dis Child.* 1999;81:73-75.

9. Baba R, Tsuyuki K, Kimura Y, et al. Oxygen uptake efficiency slope as a useful measure of cardiorespiratory functional reserve in adult cardiac patients. *Eur J Appl Physiol Occup Physiol.* 1999;80:397-401.

10. Akkerman M, Brussel Mv, Bongers BC, Hulzebos EHJ, Helders PJM, Takken T. Oxygen Uptake Efficiency Slope in Healthy Children. *Pediatr. Exerc. Sci.*2010;22:431-441.

11. Marinov B, Mandadzhieva S, Kostianev S. Oxygen-uptake efficiency slope in healthy 7- to 18-year-old children. *Pediatr Exerc Sci.* 2007;19:159-170.

12. Drinkard B, Roberts MD, Ranzenhofer LM, et al. Oxygen-Uptake Efficiency Slope as a Determinant of Fitness in Overweight Adolescents. *Med Sci Sports Exerc.* 2007;39:1811-1816.

13. Marinov B, Kostianev S. Exercise performance and oxygen uptake efficiency slope in obese children performing standardized exercise. *Acta Physiol Pharmacol Bulg.* 2003;27:59-64.

14. Breithaupt PG, Colley RC, Adamo KB. Using the Oxygen Uptake Efficiency Slope as an Indicator of Cardiorespiratory Fitness in the Obese Pediatric Population. *Med Sci Sports Exerc.* 2012;24:357-368.

15. Pichon A, Jonville S, Denjean A. Evaluation of the interchangeability of VO2MAX and oxygen uptake efficiency slope. *Can J Appl Physiol.* 2002;27:589-601.

16. Sun X-G, Hansen JE, Stringer WW. Oxygen uptake efficiency plateau: physiology and reference values. *Eur. J. Appl. Physiol.* 2012;112:919-928.

17. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Int. J. Nurs.* 2010;47:931-936.

18. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11.* 2002:1-190.
19. Tanner J. *Growth at adolescence; with a general consideration for the effects of hereditary and environmental factors upon growth adn maturation from birth to maturity* 2nd ed. Oxford: Blackwell Scientific Publications; 1962.
20. Marlatt KL, Steinberger J, Dengel DR, et al. Impact of Pubertal Development on Endothelial Function and Arterial Elasticity. *J Pediatr-Us.* 2013;163:1432-1436.
21. Ortega FB, Artero EG, Ruiz JR, et al. Physical fitness levels among European adolescents: the HELENA study. *Brit J Sport Med.* 2011;45:20-29.
22. Beaver WL, Wasserman K, Whipp BJ. A New Method for Detecting Anaerobic Threshold by Gas-Exchange. *J Appl Physiol.* 1986;60:2020-2027.
23. Norman AC, Drinkard B, McDuffie JR, Ghorbani S, Yanoff LB, Yanovski JA. Influence of excess adiposity on exercise fitness and performance in overweight children and adolescents. *Pediatrics.* 2005;115:E690-E696.
24. Bongers BC, Hulzebos EH, Helbing WA, Harkel ADt, Brussel Mv, Takken T. Response profiles of oxygen uptake efficiency during exercise in healthy children. *Eur. J. Prev. Cardiol.* 2016;23:865-873.
25. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol.* 2000;36:194-201.
26. Albouaini K, Egred M, Alahmar A. Cardiopulmonary exercise testing and its application. *Heart.* 2007;93:1285-1292.
27. Gladden LB, Yates JW, Stremel RW, Stamford BA. Gas exchange and lactate anaerobic thresholds: inter- and intraevaluator agreement. *J. Appl. Physiol.* 1985;58:2082-2089.
28. Shimizu M, Myers J, Buchanan N, et al. The ventilatory threshold: method, protocol, and evaluator agreement. *Am. Heart J.* 1991;122:509-516.
29. Dias KA, Masterson CE, Wallen MP, et al. Assessment of the 5-minute oxygen uptake efficiency slope in children with obesity. *Pediatr. Exerc. Sci.* 2017;29:350-360.
30. Lindgren M, Åberg M, Schaufelberger M, et al. Cardiorespiratory fitness and muscle strength in late adolescence and long-term risk of early heart failure in Swedish men. *Eur. J. Prev. Cardiol.* 2017;24:876-884.
31. Rogowski MP, Guilkey JP, Stephens BR, Cole AS, Mahon AD. The influence of maturation on the oxygen uptake efficiency slope. *Pediatr. Exerc. Sci.* 2012;24:347-356.

Table 1 Participants characteristics and CPET results

	Mean (SD)	(Min – Max)
Age (yr.)	15.40 ± 0.34	14.00 – 16.00
Height (cm)	175.06 ± 6.44	154.40 - 187.00
Body mass (kg)	70.49 ± 14.88	47.45 - 116.20
BMI (kg·m^2)	23.01 ± 4.81	16.33 - 38.07
$\dot{V}O_{2max}$ (L·min^{-1})	3.66 ± 0.61	2.40 – 4.93
$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})	52.73 ± 10.34	25.40 – 73.00
$\dot{V}O_2$VT (mL·kg^{-1}·min^{-1})	45.40 ± 10.37	20.90 – 63.60
$\dot{V}O_2$VT (%)	84.50 ± 5.80	70.3 – 95.80
$\dot{V}_E$ (L·min^{-1})	94.60 ± 17.28	54.80- 139.03
OUES	4094.85 ± 937.82	1932.50 – 6104.00
OUES·kg^{-1}	60.04 ± 15.86	33.06 – 102.01
OUEP	47.96 ± 4.85	35.42 – 61.52
OUEP·kg^{-1}	0.70 ± 0.14	0.43 – 1.04
RER	1.11 ± 0.54	0.99- 1.29
RPE	18.89 ± 1.43	14.00- 20.00

BMI: Body mass index; $\dot{V}O_{2max}$: Maximal oxygen consumption; $\dot{V}O_2$VT: Oxygen uptake at the ventilatory threshold; $\dot{V}_E$: Minute ventilation; OUES: Oxygen Uptake Efficiency Slope; OUEP: Oxygen Uptake Efficiency Plateau; RER: Respiratory Exchange Ratio; RPE: Rating of Perceived Exertion.

Values are mean ±SD

Conflicts of Interest Statement: The authors have no conflicts of interest relevant to this article.

Sheridan Sinead: Conceptualization, Methodology, Investigation, Writing - Original draft preparation. **McCarren Andrew**: Formal analysis, Writing – Review & Editing. ***Gray Cleona****:* Writing – Review & Editing. **Murphy Ronan.P.:** Writing – Review & Editing. **Harrison Michael:** Writing – Review & Editing. **Moyna Niall.M.:** Conceptualization, Supervision, Writing – Review & Editing.