The Oxygen Uptake Efficiency Slope

WHAT DO WE KNOW?

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- **PURPOSE:** To summarize what is currently known about the oxygen uptake efficiency slope (OUES) as an objective and independent submaximal measure of cardiorespiratory fitness in health and disease.
- **METHODS:** A literature search was performed within the following electronic databases—PubMed, Cochrane Library, Embase, Web of Science, CINAHL, PsycINFO, Scopus, and MEDLINE—using the search terms "OUES," "oxygen uptake efficiency slope," and "ventilatory efficiency." The search identified 51 articles. Selection, evaluation, and data extraction were accomplished independently by 2 authors.
- **RESULTS:** Twenty-four studies satisfied all inclusion criteria: 17 cross-sectional studies and 7 intervention studies. The results indicated that the OUES is relatively independent of exercise intensity, correlates highly with other exercise parameters, appears to have discriminative value, and is sensitive to the effects of physical training in patients with cardiac disease. Oxygen uptake efficiency slope values are considerably influenced by anthropometric variables and show large interindividual variation.
- **CONCLUSION:** Oxygen uptake efficiency slope is an independent and reproducible measure of cardiorespiratory function that does not require maximal exercise. It greatly reduces test variability because of motivational and subjective factors and is reliable and easily determinable in all subjects. Although OUES appears not interchangeable with maximal parameters of cardiopulmonary function, it seems to be a useful submaximal alternative in subjects unable to perform maximal exercise.

KEY WORDS

exercise parameter

OUES

oxygen uptake efficiency slope

ventilatory efficiency

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Exercise testing is widely used in clinical practice to assess the response of both patients and healthy people to exercise. Maximal oxygen uptake ($\dot{V}O_{2max}$), the highest rate at which an individual can utilize oxygen during exercise, is widely recognized as the single best measure of aerobic fitness.[1] Theoretically, it is defined as the point at which oxygen uptake ($\dot{V}O_2$) reaches a plateau despite further increases in work rate; however, a true plateau is not always attained during standard incremental exercise testing.[2,3] Therefore, this objective measure is regularly replaced by the rate of oxygen uptake that occurs at peak exercise ($\dot{V}O_{2peak}$),[4-7] even though $\dot{V}O_{2peak}$ measurement is influenced by patient characteristics and motivation, the selected exercise protocol, and the experience of the tester to determine the peak during exercise.[4,8-10]

A number of indices that do not require maximal exercise have been introduced, including the oxygen uptake at the ventilatory anaerobic threshold (VAT), the slope of the regression line between minute ventilation ($\dot{V}_E$) and carbon dioxide production ($\dot{V}_{CO2}$) ($\dot{V}_E/\dot{V}_{CO2}$ slope), and the extrapolated maximal oxygen uptake (EMOC).[7,11-13] However, several limitations have been reported in the literature with regard to these measures.[7] Ventilatory anaerobic threshold, for example, is not identifiable in all subjects,[8,14] and controversy remains with regard to the reproducibility of this measurement, since seldom a distinct point of change in ventilation can be identified.[15-17] Moreover, VAT appears to be protocol dependent and its value is considerably influenced by the nutritional state of the subject (eg, carbohydrate loaded or depleted).[8,16] Although the prognostic value of the $\dot{V}_E/\dot{V}_{CO2}$ slope is robust in patients with heart failure (HF)[18] and it has the advantage of being derived from multiple data points throughout the exercise, the linearity of this slope appears to be lost beyond the so-called second anaerobic threshold, leading to dependency on exercise duration.[17,19] Furthermore, weak inverse correlations with $\dot{V}O_{2max}$ were reported for this slope.[15,20,21] Finally, extrapolating the "true" $\dot{V}O_{2max}$ by using a quadratic function (EMOC) appears to be intensity dependent and has not proved useful enough to be widely adopted.[13,21,22]

In an attempt to develop an objective and independent submaximal measure of cardiorespiratory reserve, Baba et al[21] introduced the oxygen uptake efficiency slope (OUES) in 1996. The OUES represents the rate of increase of $\dot{V}O_2$ in response to a given $\dot{V}_E$ during incremental exercise, indicating how effectively oxygen is extracted and taken into the body.[21] Physiologically, the OUES is based on the development of metabolic acidosis (which depends on the distribution of blood to the working skeletal muscles), muscle mass, oxygen extraction and utilization, and the physiologic pulmonary dead space,[21] which is affected by the perfusion in the lungs and their structural integrity. Cardiovascular, musculoskeletal, and respiratory functions are thus incorporated into a single index.[7]

Oxygen uptake efficiency slope is calculated from the linear relation of $\dot{V}O_2$ versus the logarithm of $\dot{V}_E$ during exercise; that is, $\dot{V}O_2 = \log_{10} \dot{V}_E + b$. The slope a in this formula represents the rate of increase in $\dot{V}O_2$ in response to $\dot{V}_E$ and is defined as the OUES, whereas b is the intercept.[21] The index can be graphically presented if $\dot{V}O_2$ is plotted on the y-axis and the logarithm of $\dot{V}_E$ is plotted on the x-axis. As such, OUES provides an estimation of the efficiency of ventilation with respect to $\dot{V}O_2$, with greater slopes indicating greater ventilatory efficiency. In fact, the OUES reflects the absolute rate of increase in $\dot{V}O_2$ per 10-fold increase in ventilation and thereby indicates how effectively oxygen is transferred by the lungs and used in the periphery. The logarithmic transformation of $\dot{V}_E$ is aimed at linearizing the otherwise curvilinear relation of $\dot{V}O_2$ versus $\dot{V}_E$, thus making the OUES theoretically independent of the patient-achieved effort level.

To our knowledge, the only known review article pertaining to the OUES was written by Baba.[23] The author concluded that OUES appears to provide an objective, effort-independent estimation of cardiorespiratory reserve, even in pediatric populations and adults with HF.[23] Since these first results were promising, OUES has been used and suggested in the literature.[7] Thorough understanding and examination of the OUES are required to assess its usefulness and justify its use in both clinical practice and scientific research. Therefore, the aim of this review is to summarize what is currently known about the OUES.

METHODOLOGY

A systematic literature search was conducted for eligible articles (published up to January 2009) within the following electronic databases: PubMed, Cochrane Library, Embase, Web of Science, CINAHL, PsycINFO, Scopus, and MEDLINE. Each database has its own indexing term, and thus search terms included were developed for each database. The primary search terms included "OUES," "oxygen uptake efficiency slope," and "ventilatory efficiency." Furthermore, reference tracking of all the identified articles was performed.

Inclusion Criteria

Articles were included if they fulfilled the following criteria: (1) the original study assessed OUES characteristics (eg, reliability, reproducibility, determinants, usefulness, interprotocol agreement, and clinical/prognostic/discriminative value), compared OUES values to other cardiorespiratory variables, or investigated the effects of a specific intervention on the OUES; (2) the study was published in a peer-reviewed journal up to January 2009; and (3) the full-text article was available in the English, German, French, or Dutch language.

Exclusion Criteria

Case studies, letters, theses, and meeting abstracts and all other studies that did not fulfill the inclusion criteria were excluded.

Validity Assessment

The systematic search strategy identified 51 potentially relevant references. Two independent researchers screened the search results for potentially eligible studies. When titles and abstracts suggested that a study was potentially eligible for inclusion, a full-text article of the study was obtained. Disagreements between the 2 authors regarding study eligibility were resolved by discussion until consensus was reached or, where necessary, a third independent researcher acted as adjudicator. Twenty-four articles matched all inclusion criteria. A flowchart of the selection procedure and reasons for the exclusion of articles are depicted in Figure 1.

RESULTS

Overall, a total of 24 articles (of which 17 cross-sectional studies and 7 intervention studies) were considered appropriate for this review. Among these studies, the OUES has been investigated in healthy adults (n = 7),[4,24-29] in adult patients with a chronic condition (n = 15),[4,8,14,18,21,22,28,30-36] and in children (n = 5).[19,21,37-39] The results of aforementioned studies are described below. The effects of specific interventions on the OUES are considered thereafter. All included studies are presented in Table 1.

OUES in Healthy Adults

The OUES has been studied in a total of 1187 healthy adults between 19 and 96 years of age. Health was defined as the absence of cardiac, respiratory, or other diseases, as confirmed by physical examination.[4,24-29] In addition, 4 studies performed electrocardiographic assessment[4,25,28,29] and 1 study also performed spirometric and echocardiographic assessment.[28] The participants in the study by Pogliaghi et al[27] underwent an exercise stress test to evaluate possible exclusion criteria and pathological response to exercise.

Correlations With Other Measures of Cardiorespiratory Function

Pichon et al[25] assessed correlations with $\dot{V}O_{2max}$ and showed significant correlations ($P < .001$) for both maximal ($r = 0.79$) and submaximal ($r = 0.77$ and $r = 0.65$ for OUES at 85% and 75% of the maximal aerobic running speed, respectively) OUES. Moreover, $\dot{V}O_{2max}$ predicted by OUES did not significantly differ from measured $\dot{V}O_{2max}$.[25] Correlations between OUES and $\dot{V}O_{2peak}$ were highly significant as well ($r = 0.72$-0.96 [0.83, 0.88, 0.91, 0.94, 0.96, 0.83, 0.89, 0.82, 0.89]; $P < .001$),[4,24-29] even if only the first half of exercise duration was used for OUES calculation ($r = 0.92$).[28] The relationship with the VAT appeared to be moderately high to strong ($r = 0.66$, $r = 0.76$, $r = 0.78$ for maximal OUES; $r = 0.59$, $r = 0.75$, $r = 0.80$, $r = 0.83$, $r = 0.70$ for submaximal OUES).[26,27,29]

Influence of Exercise Duration and Intensity

No significant differences were found between OUES at submaximal and maximal exercises.[4,27,29] One study[28] even demonstrated that OUES values calculated from the first half of exercise did not significantly differ from values calculated from the second half or the entire exercise test data. However, another study reported significantly higher values of OUES calculated from data up to 75% and 85% of maximal running speed than those obtained from the entire test data.[25] Since several authors discussed the issue of limited prospective utility of a time-based approach to the calculation of submaximal OUES values,[14,38] Pogliaghi et al[27] calculated the OUES from data obtained up to 60% and 80% of the heart rate reserve. No significant

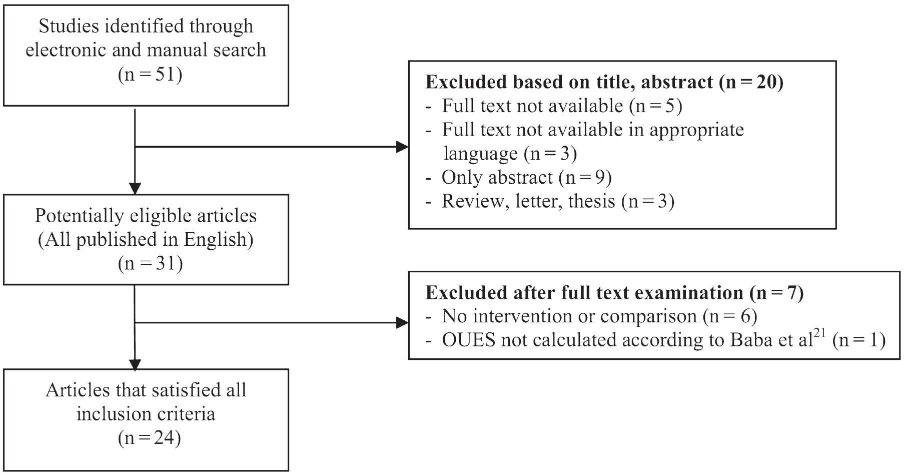

Figure 1. Flowchart of study selection and exclusion criteria. Abbreviation: OUES, oxygen uptake efficiency slope.

Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope

	First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
Adults						
Healthy	Baba, et al[24]	19 (11 M/8 F)	21 ± 1 Range: 19-40	Cycle ergometer exercise tests (maximal), 2 times within 7 d. Initial workload 0 W (2 min), increment 20 or 30 or 40 W/min. Intertest reproducibility with Bland-Altman COR.	OUES, VAT, $\dot{V}O_{2peak}$, HR_{max}	Correlations between OUES and $\dot{V}O_{2peak}$ ($r = 0.91$-.94). Excellent reproducibility of $\dot{V}O_{2peak}$ and OUES (COR 16% and 20%, respectively), VAT less reproducible (COR 31%).
	Pichon et al[25]	50 M	24 ± 9.9	Treadmill exercise tests (maximal), using a standardized protocol. Warm-up (5 min) between 7 and 10 km/h, increment 1 km/h/min. Bland-Altman for agreement.	OUES (at 75%, 85%, and 100% of MAS), VAT, $\dot{V}O_{2max}$, RER, HRmax, MAS	Correlations with $\dot{V}O_{2max}$: OUES-100 ($r = 0.79$), OUES-85 ($r = 0.77$), OUES-75 ($r = 0.65$), and VAT ($r = 0.71$). OUES at 75% and 85% of MAS significantly greater than OUES at 100%. $\dot{V}O_{2max}$ predicted by OUES not significantly different from measured $\dot{V}O_{2max}$. Limits of agreement (Bland-Altman) ±10.5 mL O_2/min/kg.
	Mourot et al[26]	15 F (8 E/7 C)	E: 21.8 ± 3.3 C: 21.7 ± 1.9	Cycle ergometer exercise tests (maximal), both before and after the intervention period. Initial workload 0 W (3 min), increment 30 W/3 min. Intertest reproducibility with Bland-Altman COR. Intervention: 6 wk, 3 times/wk intermittent SWEET (cycling).	OUES (at 75%, 90%, and 100% of ET), VAT, $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}O_{2peak}$, Vd/VAT, RER	Correlations with $\dot{V}O_{2peak}$: OUES at 75%, 90%, and 100% ($r = 0.65$, $r = 0.71$, $r = 0.72$) and VAT ($r = 0.83$). Correlations between OUES at 75%, 90%, and 100% and VAT ($r = 0.59$, $r = 0.69$, $r = 0.66$). Strong correlations between OUES at 75%, 90%, and 100% of ET ($r = 0.80$-0.95). No significant differences in OUES, $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}_E/\dot{V}O_2$, and Vd/VAT after training, despite increased $\dot{V}O_{2peak}$ and delayed VAT.
	Pogliaghi et al[27]	29 (18 M/11 F)	M: 68.6 ± 5.8 F: 67.1 ± 3.8 Age > 60	Cycle ergometry exercise tests (maximal). Initial workload 50 W (3 min), increment 10 W/min.	OUES (at 75%, 90%, and 100% of ET, and 60% and 80% of HRreserve), $\dot{V}O_{2peak}$	No significant differences between OUES at 75%, 90%, and 100% of ET or between OUES at 100% and HRreserve-based measures of OUES (OUES 80% HRreserve and OUES 60% HRreserve).
	Mollard et al[29]	24 M (10 T/14 UT)	T: 29 ± 5 UT: 27 ± 5	Cycle ergometer exercise tests (maximal). Initial workload 60 W (3 min), increment 30 W/2 min. Intervention: Each subject measured on 4 simulated altitudes (0, 1000, 2500, and 4500 m).	OUES (at 80% and 100% of ET), VAT, $\dot{V}O_{2peak}$	Correlations for OUES at 80% and 100% with $\dot{V}O_{2peak}$ ($r = 0.83$-0.89) and VAT ($r = 0.70$-0.83). OUES at 80% similar to OUES at 100% in all conditions. No reduction in OUES at 1000 m. OUES declined faster in T subjects than in UT subjects during exercise in hypoxia.

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Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope (*Continued*)

	First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
Patients	Baba et al[8]	50 with HF: NYHA I (12 M/7 F) NYHA II (14 M/6 F) NYHA III (4 M/7 F)	I: 61.1 ± 7.9 II: 65.9 ± 8.3 III: 67.7 ± 10.2	Treadmill exercise tests (maximal), using the symptom-limited original or modified Bruce protocol.	OUES (at 75%, 90%, and 100% of ET), VAT, $\dot{V}O_{2peak}$	Correlation between OUES and $\dot{V}O_{2peak}$ ($r = 0.78$). No significant differences and excellent agreement between OUES at 75%, 90%, and 100% (ICC = 0.99) Significant differences in OUES, $\dot{V}O_{2peak}$, and VAT between NYHA functional classes (I-III).
	Van Laethem et al[32]	80 with HF: 45 with and 35 without LVD	With LVD: 64 ± 6 Without LVD: 58 ± 10	Cycle ergometer exercise test (maximal), using a ramp protocol. Initial workload 20 W, increment 10 W/min.	OUES (at 50%, 75%, and 100% of ET), VAT, $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}O_{2peak}$	Correlations with $\dot{V}O_{2peak}$: VAT ($r = 0.81$), OUES/kg ($r = 0.78$), OUES ($r = 0.68$), and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.49$). Values obtained from data up to 50%, 75%, and 100% of ET did significantly differ for $\dot{V}O_{2peak}$ and $\dot{V}_E/\dot{V}CO_2$ slope, whereas OUES/kg remained stable. OUES at 75% differed <3.0% from OUES at 100%. OUES and other submaximal parameters significantly lower in patients with LVD.
	Davies et al[22]	243 with HF (212 M/31 F): NYHA I-IV	59 ± 12	Treadmill exercise tests (maximal), following a modification of the Bruce protocol	OUES (at 50% and 100% of ET), VAT, $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}_E/\dot{V}O_2$ slope, RER	Correlations for OUES with $\dot{V}O_{2peak}$ ($r = 0.81$), VAT (0.62), and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.62$). Values obtained from the first 50% of exercise and those obtained with full data differed 1% for OUES vs 25% for $\dot{V}O_{2peak}$. OUES values were significantly lower than predicted on the base of age, sex, and BSA. OUES values fell with worsening symptoms. In a multivariable prediction model, OUES was the only significant independent prognostic variable.
	Defoor et al[14]	590 with CAD (512 M/78 F)	55.1 ± 9.7	Cycle ergometer exercise tests (maximal), initial workload 20 W, increment 30 W/3 min. Intervention: 3-mo supervised exercise training program, mean frequency 2.21 ± 0.49 times/wk, mean intensity 80.9 ± 10.3% of HR_{peak}.	OUES (at RER = 1.0 and at 90% and 100% of ET), VAT, $\dot{V}_E/\dot{V}CO_2$ slope	Correlations with $\dot{V}O_{2peak}$: OUES at the various ETs ($r = 0.84$-0.89) and VATs ($r = 0.86$). No differences between OUES values at 90% and 100%, but significantly higher values at RER = 1.0. OUES, $\dot{V}O_{2peak}$, and VAT increased significantly after training, whereas the $\dot{V}_E/\dot{V}CO_2$ slope mildly decreased. Multiple regression analysis revealed training frequency as the strongest determinant for the change in OUES. Changes in $\dot{V}O_{2peak}$ correlated better with changes in OUES ($r = 0.61$) and VAT ($r = 0.55$) than with changes in $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.17$).

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Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope (*Continued*)

First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
Trenell et al[30]	10 with MM (3 M/7 F)	42 ± 14	Cycle ergometer exercise tests (submaximal: 80% HR_{max}), individually tailored work rates, increment every 2 min. Intervention: 3-mo aerobic exercise therapy (cycling), 3 times/wk.	OUES, HRR-$\dot{V}O_2$	Significant improvement in OUES, but no significant increase in HRR-$\dot{V}O_2$ after exercise therapy in patients with MM.
Van de Veire et al[31]	214 with CAD (182 M/32 F): NYHA I-III	67 ± 8	Cycle ergometer exercise tests (maximal).	OUES, $\dot{V}O_{2peak}$, $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}O_{2max}$, RER	Correlations with $\dot{V}O_{2peak}$: OUES/kg ($r = 0.79$) and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.29$). Significant differences between patients with intermediate $\dot{V}O_{2peak}$ values differing from each other in terms of indices of progressive LV remodeling, systolic dysfunction, and neurohormonal activation.
Van Laethem et al[40]	160 with CAD (132 M/28 F)	68 ± 5 Age > 60	Cycle ergometer exercise tests (maximal), using a ramp or gradual protocol. Initial workload 50 W, increment 25 W/min. Bland-Altman for agreement.	OUES, $\dot{V}O_{2peak}$, VAT, $\dot{V}_E/\dot{V}CO_2$ slope	Correlations with $\dot{V}O_{2peak}$: OUES ($r = 0.73$), OUES/kg ($r = 0.84$), VAT ($r = 0.85$), and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.44$). OUES/kg and VAT best submaximal predictors of $\dot{V}O_{2peak}$. Significant differences between measured $\dot{V}O_{2peak}$ and estimated $\dot{V}O_{2peak}$ predicted by OUES/kg in patients with severely decreased or preserved exercise capacity, but not in patients with intermediate exercise capacity. Significant differences between measured $\dot{V}O_{2peak}$ and estimated $\dot{V}O_{2peak}$ predicted by VAT within all subgroups.
Arena et al[18]	341 with HF (283 M/58 F)	56.3 ± 14.2	Treadmill exercise tests (maximal), following a ramping protocol.	OUES and $\dot{V}_E/\dot{V}CO_2$ slope (both at 50% and 100% of ET), $\dot{V}O_{2peak}$	Correlations for OUES (at 50% and 100%) with $\dot{V}O_{2peak}$ ($r = 0.65$, $r = 0.73$) and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.61$, $r = -0.65$). ROC curve analysis demonstrated statistically significant classification schemes for both $\dot{V}_E/\dot{V}CO_2$ slope and OUES calculations as well as $\dot{V}O_{2peak}$ (all areas under the ROC curve ≥0.74). Area under the ROC curve for the $\dot{V}_E/\dot{V}CO_2$ slope at 100% was significantly greater than for $\dot{V}O_{2peak}$ and OUES at 50% and 100%.

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Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope (*Continued*)

	First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
	Van Laethem et al[35]	35 with HF (26 M/9 F): NYHA II-III	54 ± 9	Cycle ergometer tests (maximal) at the start, the middle, and the end of the intervention, using a gradual protocol. Initial workload 25 W, increment 10 W/min. Intervention: 6-mo cardiac rehabilitation program, 2 times/wk.	OUES (at 90% and 100% of ET), $\dot{V}O_{2peak}$, VAT, $\dot{V}_E/\dot{V}CO_2$ slope, RER	Excellent correlation between OUES at 90% and 100% of ET ($r = 0.97$). OUES, $\dot{V}O_{2peak}$, VAT, and $\dot{V}_E/\dot{V}CO_2$ slope improved during the first part of the ET period; only VAT continued to improve in the second part. Improvement in OUES correlated significantly better with improvements in $\dot{V}O_{2peak}$ ($r = 0.64$-0.77) than in any other included exercise parameter.
	Van Laethem et al[34]	30 HTx patients	59.9 ± 9.1	Cycle ergometer exercise tests (maximal), using a stepwise incremental protocol. Initial workload 25 W, increment 10 or 25 W/min. Intervention: HTx.	OUES, $\dot{V}O_{2peak}$, VAT, $\dot{V}_E/\dot{V}CO_2$ slope, RER	Correlations for OUES/kg with $\dot{V}O_{2peak}$ ($r = 0.63$), VAT ($r = 0.92$), and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.49$) before HTx. Changes in OUES/kg after HTx significantly correlated with changes in $\dot{V}O_{2peak}$ and VAT (both $r = 0.63$), but not with changes in $\dot{V}_E/\dot{V}CO_2$ slope or marked improvements in central hemodynamics or resting lung function.
	Arena et al[33]	337 with HF (280 M/57 F) (normal weight, overweight, and obese)	56.5 ± 14.1	Treadmill exercise tests, using a conservative ramping protocol.	OUES, BMI	Significant correlation between OUES and BMI ($r = 0.32$). OUES differ significantly among all 3 BMI groups, with the most favorable value found in the obese subgroup. OUES prognostically significant in normal weight (optimal threshold: ≤/>1.2, hazard ratio: 3.7, 95% CI: 1.4-9.9, $P = .01$), overweight (optimal threshold: ≤/>1.5, hazard ratio: 3.9, 95% CI: 1.3-11.1, $P = .01$), and obese (optimal threshold: ≤/>1.7, hazard ratio: 4.1, 95% CI: 1.4-12.8, $P = .01$) subgroups.
	Gademan et al[36]	34 with HF E: 19 M/1 F C: 13 M/1 F NYHA II-III	E: 60 ± 9 C: 63 ± 10	Cycle ergometer exercise tests (maximal) at baseline and after 4 wk (C) or after the exercise training program (E). Initial workload 5 W, increment 5 W/30 s. Intervention: 30 sessions exercise training, 2-3 times/wk.	OUES (at 75%, 90%, and 100% of ET), $\dot{V}O_{2peak}$, $\dot{V}_E/\dot{V}CO_2$ slope	No significant differences between OUES at 75%, 90%, and 100% of ET. Experimental group showed a significant increase in $\dot{V}O_{2peak}$ (14%), OUES (19%), OUES/kg (17%), OUES 75 (21%), and OUES 90 (22%) and a decrease in $\dot{V}_E/\dot{V}CO_2$ slope (14%) after training. Control group showed slight improvements in OUES but significantly higher increases in the experimental group.
Healthy vs patients	Hollenberg et al[4]	1010 998 healthy (419 M/579 F) 12 M with HF	Median: 68 Range: 53-96	Treadmill exercise tests (maximal), following the Cornell modification of the Bruce protocol. 725 healthy subjects were tested again after 2 y.	OUES (at 75%, 90%, and 100% of ET), $\dot{V}O_{2peak}$, RER	OUES correlated with $\dot{V}O_{2peak}$ in both men ($r = 0.88$) and women ($r = 0.83$). OUES at 75% differed only 1.9% from OUES at 100%. On serial tests, OUES less variable than exercise duration or $\dot{V}O_{2peak}$. OUES declined linearly with age. Strong correlation with FEV_1 and smoking history. OUES values in patients with HF much lower than those of healthy elderly.

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Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope (*Continued*)

	First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
	Giardini et al[28]	88 35 healthy (18 M/17 F), 53 with heart disease: Fontan (10 M/13 F) M/S (18 M/12 F)	Healthy: 25 ± 9 Fontan: 20 ± 6 M/S: 27 ± 10	Cycle ergometer tests (maximal). Initial workload 10 W, increment 10 W/min.	OUES (from the first 50%, the last 50%, and 100% of the exercise data), $\dot{V}O_{2peak}$, $\dot{V}_E/\dot{V}CO_2$ slope	No significant differences between OUES, OUES 0-50, and OUES 50-100, and no differences between measured and predicted values of OUES in healthy subjects, patients with M/S and Fontan who were not cyanotic at rest. In patients with Fontan who were cyanotic at rest, OUES 0-50 differed significantly from OUES and OUES 50-100 and measured and predicted values of both OUES and OUES 50-100 differed significantly as well.
Children						
Healthy	Baba et al[37]	16 (10 M/6 F)	12.7 ± 2.8	Treadmill exercise tests (maximal), using both the Bruce protocol and the RIS protocol. Bland-Altman for agreement.	OUES, VAT, $\dot{V}O_{2max}$, RER	No between-protocol differences in mean values of OUES, VAT, and $\dot{V}O_{2max}$. Interprotocol variability lower for OUES (+17% to −18%) than for $\dot{V}O_{2max}$ (+24 to −20%) and VAT (+31% to −31%).
	Marinov et al[38]	60 (30 M/30 F) 30 normal weight, 30 obese	11 ± 1.1	Treadmill exercise tests (maximal), using a modification of the Balke protocol. Initial elevation 6%, increment 2%/min, constant velocity 5.4 km/h.	OUES (at VAT and 100%), $\dot{V}O_{2peak}$, RER	High correlations for OUES with $\dot{V}O_{2peak}$ ($r = 0.91$), oxygen pulse = $\dot{V}O_2$/HR ($r = 0.80$), and anthropometric variables (height, BSA, FFM, age, weight; $r = 0.78$-0.88). Strong correlation between OUES at VAT and at 100% ($r = 0.98$); difference only 1.1%. No significant differences between OUES in obese and OUES in nonobese children; slightly higher OUES in obese group.
	Drinkard et al[39]	150 (22 M/21 F normal weight, 42 M/65 F obese)	Normal weight: 14.8 ± 1.7 Obese: 14.4 ± 1.5	Cycle ergometer tests (maximal). Initial workload 0 W (4 min), increment 15 or 20 W/min. Bland-Altman for agreement.	OUES (at LI, 150% of LI, and 100% of ET), LI, $\dot{V}O_{2peak}$, RER	OUES significant predictors of $\dot{V}O_{2peak}$ for both groups at all exercise intensities, despite limits of agreement as high as 30% to 34%. Significant increase in OUES with increasing exercise intensity in both groups. When adjusted for lean body mass, $\dot{V}O_{2peak}$ and OUES at all exercise intensities lower in overweight subjects.
	Marinov et al[19]	114 (58 M/56 F)	Range: 7-18	Treadmill exercise tests (maximal), using a modification of the Balke protocol. Initial elevation 6%, increment 2%/min, constant velocity 5.4 km/h.	OUES (at VAT and 100%), $\dot{V}O_{2max}$, $\dot{V}O_{2peak}$, RER	Correlation between OUES and $\dot{V}O_{2peak}$ ($r = 0.92$). No significant difference between OUES at VAT and at 100%. Steady trend for $\dot{V}O_{2peak}$, V_E, and OUES to increase in the age span of 7 to 14 y. Rise more strongly correlated with height than with age. $\dot{V}O_{2peak}$ and OUES significantly higher in boys than in girls. Very high linear correlations between OUES and anthropometric variables (BSA, weight, FFM, height, age; $r = 0.76$-0.86).

(*continues*)

Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope (*Continued*)

	First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
Healthy vs patients	Baba et al[21]	144 (83 M/61 F) 36 healthy, 108 with heart disease	11.7 ± 4.4	Treadmill exercise tests (maximal), using the standardized Bruce protocol.	OUES (at 75%, 90%, 100%), VAT, $\dot{V}_E/\dot{V}CO_2$ slope, EMOC, $\dot{V}O_{2max}$	Correlation with $\dot{V}O_{2max}$ stronger for OUES (r = 0.94) than for other submaximal measures (VAT: r = 0.86, $\dot{V}_E/\dot{V}CO_2$ slope: r = 0.15, EMOC: r = 0.23). Deviation of the estimated $\dot{V}O_{2max}$ from the measured $\dot{V}O_{2max}$ smallest for the $\dot{V}O_{2max}$ predicted by OUES. No differences in OUES between 90% and 100% of exercise; at 75% of exercise slightly lower OUES.

Abbreviations: BMI, body mass index; BSA, body surface area; C, control group; CAD, coronary artery disease; COR, coefficient of repeatability; E, experimental group; EMOC, extrapolated maximal oxygen uptake; ET, exercise time; FEV_1, forced expired volume in 1 second; FFM, fat-free mass; HF, heart failure; HRreserve, heart rate reserve; HRR-$\dot{V}O_2$, heart rate restricted oxygen uptake; HTx, orthotropic heart transplantation; ICC, intraclass correlation coefficient; LI, lactate inflection point. LVD, left ventricular dysfunction; MAS, maximal aerobic speed; MM, mitochondrial myopathy; M/S, Mustard/Senning operation; NYHA, New York Heart Association; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio; RIS, rapidly increasing staged; ROC, receiver operating characteristic; SWEET, square-wave endurance exercise training; T, trained subjects; UT, untrained subjects; VAT, ventilatory threshold; $\dot{V}CO_2$, CO_2 elimination; Vd/VAT, dead space to tidal volume ratio; V_E, minute ventilation; $\dot{V}O_2$, oxygen uptake.

differences were found between these heart rate reserve–based OUES calculations and OUES obtained from the entire exercise test data. The study of Hollenberg and Tager[4] adopted another alternative by comparing the OUES in individuals who achieved different exercise intensities. The authors divided their subjects into 3 groups according to the peak respiratory exchange ratio (RER_{peak}) achieved. Results of this study indicated that OUES values were similar in subjects with an RER_{peak} of either 1.00 to 1.09 or ≥1.10, whereas significantly lower values were obtained in subjects with RER_{peak} <1.0. However, these subjects were older, had shorter exercise durations, and reached lower values of $\dot{V}O_{2peak}$ and FEV_1 (forced expired volume in 1 second) than those who reached RER_{peak} >1.0.

Reproducibility

Only 1 study assessed the reproducibility of the maximal OUES, $\dot{V}O_{2peak}$, and VAT.[24] Agreement between 2 exercise tests separated by a time interval of maximal 7 days was better for $\dot{V}O_{2peak}$ and OUES (coefficients of repeatability 16% and 20%, respectively) than for VAT (coefficient of repeatability 31%), indicating that VAT is less reproducible compared with OUES and $\dot{V}O_{2peak}$. It seems that $\dot{V}O_{2peak}$ was less reproducible in this study than is often reported in the literature (Coefficient of variation <10%).

Influence of sex and basic anthropometric variables

Oxygen uptake efficiency slope values appeared to be significantly higher in males than in females (2492 ± 471 vs 1741 ± 418, with $P < .05$),[27] and the results of a large cross-sectional study (n = 998) suggest that OUES declines linearly with age in healthy elderly.[4] This latter article examined which variables contributed significantly to the prediction of OUES. They introduced the following prediction equations—1 for men and 1 for women—on the basis of age and body surface area (BSA in m^2):

$$\text{Men: OUES} = 1320 - (26.7 \times \text{age}) + (1394 \times \text{BSA})$$
$$\text{Women: OUES} = 1175 - (15.8 \times \text{age}) + (841 \times \text{BSA})$$

OUES in Adults With Chronic Conditions

Oxygen uptake efficiency slope characteristics have been investigated in 2179 patients, aged between 16 and 89 years, with various conditions of the heart, including HF,[4,8,18,22,32-36] coronary artery disease (CAD)[14,31,40] and congenital heart disease.[28] One study included patients with mitochondrial myopathy,[30] in which OUES was used as an outcome measure to assess the effects of exercise therapy on exercise capacity.

Correlations with other measures of cardiorespiratory function

The study of Baba et al[24] provided moderately high to strong correlations (r = 0.78 for 18 subjects who reached maximal exercise intensity; r = 0.68 when all subjects were included) between maximal OUES and $\dot{V}O_{2max}$ in patients with HF. Correlations with $\dot{V}O_{2peak}$ values ranged from moderately high to strong (r = 0.68, r = 0.73, r = 0.81; $P < .001$) as well.[4,18,22,32] Similar correlation coefficients between OUES and $\dot{V}O_{2peak}$ were reported in patients with CAD (r = 0.73, r = 0.84, r = 0.89; $P < .001$).[14,40] Oxygen uptake efficiency slope standardized for body mass (OUES/kg) also correlated strongly with $\dot{V}O_{2peak}$ (r = 0.79, r = 0.84; $P < .001$) in these patients.[1,31,35] One of the intervention studies[14] demonstrated that training-induced changes in $\dot{V}O_{2peak}$ correlated better with changes in OUES (r = 0.61; $P < .001$) and VAT (r = 0.55; $P < .001$) than with changes in the $\dot{V}_E/\dot{V}CO_2$ slope (r = −.13 to −0.17; $P < .001$) in patients with CAD. Another exercise training study in patients with HF[34] showed that improvements in $\dot{V}O_{2peak}$ correlated significantly better ($P < .01$) with the training-induced changes in OUES (r = 0.64-0.77) than with those of any other included exercise parameter (VAT, $\dot{V}_E/\dot{V}CO_2$ slope, W_{peak}, RER_{peak}) ($r < 0.55$).

Influence of exercise duration/intensity

Various studies suggested that the OUES remains relatively stable over the entire exercise duration,[8,32,36] whereas others found that OUES at 50% and OUES up to RER = 1.0 differed significantly from OUES obtained from the full data.[14,22] In terms of percentages, these differences between submaximal and maximal values were very small for OUES (1%-2%),[4,22] whereas more profound differences were found for $\dot{V}O_{2peak}$ (25%).[22] In line with these findings, Van Laethem et al[32] showed that shortened exercise duration affected both $\dot{V}O_{2peak}$ and $\dot{V}_E/\dot{V}CO_2$ slope, whereas OUES remained stable.

Influence of sex and basic anthropometric variables

The only study primarily examining the influence of anthropometric variables[33] found that OUES differed significantly ($P < .05$) between 3 subgroups of patients with HF differing in body mass index (BMI): normal weight, overweight, and obese. Interestingly, the most favorable values were found in the obese subgroup.

Discriminative ability and prognostic value

Several studies examining exercise capacity in patients with HF[8,32] or CAD[31,40] reported significant differences in OUES values between New York Heart Association functional classes (I-III) or subgroups based on other variables, such as left ventricular dysfunction, neurohormonal activation, exercise capacity, and BMI. Two studies[4,22] demonstrated that OUES values in patients with HF were significantly lower than the values predicted by the prediction equations for healthy adults as introduced by Hollenberg and Tager.[4] Furthermore, Davies et al[22] identified OUES as the only significant independent prognostic variable in a multivariable prediction model and found that OUES values were lower with worsening symptoms.

OUES in Healthy Children

Five studies examined the OUES in 415 healthy children between 6 and 18 years of age. Physical examinations revealed that the children were in good health and took no medication that might affect exercise performance.[19,24,37-39] All subjects were moderately active, but not engaged in regular training activities. The overweight adolescents in the study by Drinkard et al[39] were in good general health but were required to have a BMI greater than 95th percentile for age, sex, and race and at least 1 obesity-related comorbid condition (primarily hyperinsulinemia and/or dyslipidemia). All subjects in this latter study underwent a 12-lead electrocardiogram to ensure the absence of cardiac diseases. One study[21] included children with heart disease as well, but in the results no distinction was made between healthy children and patients.

Correlations with other measures of cardiorespiratory function

Baba et al[21] found significantly stronger correlations with $\dot{V}O_{2max}$ for OUES (r = 0.94) than for other submaximal measures of cardiorespiratory function, including VAT (r = 0.86), $\dot{V}_E/\dot{V}CO_2$ slope (r = 0.15), and EMOC (r = 0.28). The deviation of the estimated $\dot{V}O_{2peak}$ from the measured $\dot{V}O_{2peak}$ appeared to be smallest for the estimated $\dot{V}O_{2max}$ predicted by OUES[21] and strong correlations were found with $\dot{V}O_{2peak}$ (r = 0.91 − 0.92) and oxygen pulse (r = 0.80).[19,38] The study of Drinkard et al[39] demonstrated a significant relationship between OUES and $\dot{V}O_{2peak}$ at several exercise intensities for both obese and nonobese adolescents. Bland-Altman plots comparing measured $\dot{V}O_{2peak}$ with estimated $\dot{V}O_{2peak}$ predicted from OUES, however, showed large limits of agreement (30%-34% of average $\dot{V}O_{2peak}$).[39]

Influence of exercise duration

Two studies[21,39] found that the submaximal OUES was slightly, however significantly, lower than the maximal OUES calculated from the entire exercise test data. Conversely, another study[38] found higher submaximal OUES values, whereas a fourth study[19] did not find any effects of exercise duration on the OUES.

Protocol dependency

The only study[37] examining protocol dependency of the maximal OUES did not find significant differences in OUES, VAT, or $\dot{V}O_{2max}$ values obtained with 2 different protocols for treadmill exercise testing. Interprotocol variability was found to be smallest for the OUES (limits of agreement −18% to 17%).

Influence of sex and basic anthropometric variables

In a cross-sectional study by Marinov et al,[19] a steady trend was observed for $\dot{V}O_{2peak}$, $\dot{V}_E$, and OUES to increase in the age span of 7 to 14 years. Both OUES and $\dot{V}O_{2peak}$ appeared to be significantly higher in boys than in girls.[19,38] Dividing these variables by lean body mass removed the sex differences almost completely; however, it did not remove the differences in the individual age and height groups. The increases in $\dot{V}O_{2peak}$ and OUES appeared to be more strongly correlated with height than with age.[19] Studies examining the relationship between OUES and anthropometric variables found that OUES was strongly correlated with BSA, height, weight, lean body mass, and age.[19,38] Absolute values of OUES at VAT and over the entire exercise testing data appeared to be significantly higher in severely overweight adolescents (mean BMI 40.0 ± 8.0 kg/m^2) compared with their nonoverweight peers.[38] These findings are in line with the results of Arena et al,[33] who also found the most favorable OUES values in the obese subgroup of adult patients with HF. Conversely, when expressed relative to lean body mass, exercise parameters were significantly lower in overweight than in nonoverweight adolescents.[19,38]

To assess which factors influence OUES in the pediatric population, Marinov and Kostianev[38] applied stepwise regression analysis and introduced the following equation to predict OUES from height (cm) and BSA (m^2) ($r^2 = 0.793$; standard error of estimate = 369; n = 60):

$$\text{OUES} = -3346.9 + 28.08 \times \text{height} + 794.2 \times \text{BSA}$$

More recently, Marinov et al[19] introduced another equation to predict OUES in healthy children, including BSA and gender as the main determinants ($R^2 = 0.765$; standard error of estimate = 316; n = 114):

$$\text{OUES} = -398 + 1958.1 \times \text{BSA} - 199.5 \times \text{gender}$$

OUES in Children with Chronic Conditions

Only 1 study[21] examined the OUES in 108 children with heart disease. However, in this study, no distinction was made between the healthy participants and those suffering from heart disease. The results of this study are discussed earlier.

Intervention Studies

Seven studies examined the effects of a particular intervention on the OUES; however, none applied a randomized controlled design. The interventions included exercise training,[14,26,30,34,36] orthotropic heart transplantation,[35] and hypoxia.[29]

Exercise training induced significant improvements in $\dot{V}O_{2peak}$, OUES, and VAT in a large number of patients with cardiac disease.[14,34,36] The study of Defoor et al[14] showed that the training-induced changes in $\dot{V}O_{2peak}$ correlated with changes in OUES ($r = 0.61$; $P < .001$) and in VAT ($r = 0.55$; $P < .001$). These relations remained significant after adjusting for age, gender, body height and weight, and training intensity and frequency ($r = 0.57$ and $r = 0.52$; $P < .001$, respectively). Stepwise multiple regression analysis revealed training frequency ($r = 0.249$; $P < .001$) as the strongest determinant for the change in OUES with physical training and that the change in VAT was the largest contributor to the change in OUES.[14]

Patients with mitochondrial myopathy also showed significantly higher OUES values following aerobic exercise therapy, whereas no significant increases were demonstrated in heart rate–restricted $\dot{V}O_2$.[30] One study,[27] however, did not find significant changes in the OUES and $\dot{V}_E/\dot{V}CO_2$ slope after intermittent endurance training in healthy young women, despite significant increases in $\dot{V}O_{2peak}$ and VAT.

The study of Van Laethem et al[35] investigated the OUES in patients before and after heart transplantation. Significant improvements ($P < .05$) in OUES were found during the first year after surgery, but similar to other exercise parameters, OUES remained considerably impaired when compared with age- and gender-normalized values. The changes in OUES after heart transplantation highly correlated with the changes in other exercise variables ($\dot{V}O_{2peak}$ and VAT), but not with marked improvements in central hemodynamics or resting lung function. The latter might suggest that the increase in OUES is elicited by beneficial alterations in the skeletal musculature after heart transplantation rather than by improvements in central hemodynamics or resting lung function.

In a study concerning the responsiveness of the OUES to hypoxia in healthy subjects with a broad range of cardiorespiratory fitness,[29] both maximal and submaximal OUES values were influenced by oxygen availability and utilization by active tissues. Mild hypoxia did not significantly alter OUES values, but more severe hypoxia at higher simulated altitudes caused significant reductions in OUES. An interesting finding was that the OUES declined faster in trained than in untrained subjects.

DISCUSSION

The results of this review indicate that OUES is an objective and reproducible measure with broad applicability. Oxygen uptake efficiency slope is relatively independent of exercise intensity/duration, correlates highly with other exercise parameters, appears to have discriminative value, and is sensitive to the effects of physical training in adult cardiac populations. However, OUES values are considerably influenced by anthropometric variables and show large interindividual variation.

Correlation Between OUES and Other Exercise Parameters

Strong correlations were found between OUES (submaximal and maximal) and $\dot{V}O_{2peak}$. Using correlation and regression analysis, several authors concluded that the assessment of OUES was accurate enough as a substitute of $\dot{V}O_{2max}$.[4,8,22,24,29,32,34,37] However, a strong statistical correlation between 2 parameters is not necessarily a proof for the interchangeability of these parameters.[40] Bland-Altman analysis assessing interindividual variability showed wide 95% confidence intervals.[25,39,40] These findings indicate that although OUES and $\dot{V}O_{2peak}$ are highly correlated, interindividual variation exists in OUES values, which might limit the clinical utility of this parameter. Since OUES was not able to reliably predict $\dot{V}O_{2max}$, it appears not interchangeable with this "golden standard."[25,39,40] Nonetheless, Pichon et al[25] compared the submaximal OUES with the VAT, which is widely used in clinical practice, and showed that the submaximal OUES provided a better approximation of measured $\dot{V}O_{2max}$ compared with the VAT. Various studies revealed that compared with other submaximal parameters, OUES is strongly correlated with the VAT[21,26,27,29] and with the submaximal $\dot{V}_E/\dot{V}CO_2$ slope.[18] However, relationship differences of OUES and VAT between studies are not fully understood and identified; different approaches for determining the VAT and even different exercise protocols (Table 1) might contribute to these differences in relationships.

Influence of Exercise Duration/Intensity on OUES

The logarithmic transformation of $\dot{V}_E$ is aimed at linearizing the otherwise curvilinear relation of $\dot{V}O_2$ versus $\dot{V}_E$, thus making the OUES theoretically independent of the patient-achieved maximal effort level. Many studies confirmed that submaximal and maximal OUES values were highly correlated.[8,26,34,38] The use of submaximal exercise data did not alter OUES values in most studies,[8,19,27-29,32,36] and in those where shortened exercise duration did affect the OUES,[4,14,21,22,25,38,39] only small differences were reported. However, controversy exists with regard to the submaximal OUES values. Some studies[14,25,38] found significantly higher submaximal OUES values as compared with maximal OUES values, whereas others did not find differences[8,19,27-29,32,36] or suggested a tendency toward lower submaximal values.[4,21,39] We could not identify explanatory factors for these inconsistent findings; however, it might be related to the underlying disease. The validity of the OUES might be different across patient groups.

Despite the fact that the submaximal OUES values are calculated in numerous studies, important characteristics (such as interprotocol agreement, reproducibility, discriminative ability, and prognostic value) are examined only for the maximal OUES in the majority of studies. Since the original purpose of the OUES was to provide a submaximal measure of cardiorespiratory function, which could be used as a substitute for $\dot{V}O_{2peak}$ in (clinical) populations unable to perform maximal exercise, it would be more appropriate to examine these characteristics for the submaximal OUES. Three studies[14,26,36] examined the responsiveness to exercise training for the submaximal OUES and 2 of these showed a significant increase in submaximal OUES values following exercise training in patients with HF[36] or CAD.[14] A study by Mollard et al[29] indicated that the submaximal OUES was sensitive to the effects of hypoxia during exercise. Only 1 study[18] assessed the prognostic value of the submaximal OUES and demonstrated that it, like the maximal OUES, was a significant predictor of mortality in patients with HF.

Sensitivity of OUES

Results of the intervention studies suggest that OUES is sensitive to change after exercise training in patients with CAD, HF, or mitochondrial myopathy and, thus, can be used to evaluate the progression of exercise capacity in the aforementioned populations following rehabilitation or training programs in these patient groups. Several authors have concluded that OUES is a more consistent parameter than $\dot{V}O_{2peak}$, since $\dot{V}O_{2peak}$ is effort, protocol, and observer dependent.[4,32,36] In populations with cardiac conditions, exercise capacity appears to be primarily restricted by underperfusion of both the lungs and the skeletal muscles. An increase in OUES suggests that a similar $\dot{V}O_2$ is achieved with lower ventilatory cost.[14,35,36] This might be due to direct training-induced improvements in pulmonary function (eg, increased alveolar capillary membrane perfusion and capillary blood flow) and/or muscular function (eg, increased capillary density, blood flow, and mitochondrial density) in these patient populations. In subjects without cardiopulmonary limitations, however, measures of ventilatory efficiency, and consequently OUES, might not be the most appropriate to assess the effects of training. This has been observed in the healthy young women who participated in the study of Mourot et al.[26]

It is striking that the responsiveness of OUES to exercise training or other interventions has never been investigated in pediatric populations and, moreover, that none of the intervention studies on OUES involved randomized controlled trials. Further, more research is required to determine whether an increase in OUES in patients is associated with an improved prognosis.

OUES in Patients

The study of Davies et al[22] was the first study that examined the prognostic value of the OUES in patients with HF. They found that its prognostic value was stronger compared to the best available existing measures of exercise physiology, including $\dot{V}O_{2peak}$, VAT, and $\dot{V}_E/\dot{V}CO_2$ slope. Other studies, similar to this finding, suggested strong discriminative value of the OUES in patients with HF or CAD.[4,8,31,32] Hence, OUES appears to be useful for the quantification of exercise performance in these patients.[40] In patients with CAD, OUES is significantly reduced.[14,32,34] Patients who have undergone percutaneous transluminal coronary angioplasty with or without prior myocardial infarction have significantly higher OUES values compared with patients after coronary artery bypass grafting.[14] This may be explained by a higher disease severity, preoperative and postoperative deconditioning, and the impact of chest surgery on lung perfusion and structural integrity in the latter group. Furthermore, OUES is impaired in CAD patients with arterial fibrillation as compared with those with normal sinus rhythm;[14] this is likely because of the impact of decreased oxygen delivery on the working muscles in patients with arterial fibrillation owing to lower stroke volume and CO response during exercise.[41] The study of Arena et al[18] showed that OUES was a significant predictor of mortality in patients with HF, though they also concluded that the $\dot{V}_E/\dot{V}CO_2$ slope maintained an optimal prognostic value. However, the $\dot{V}_E/\dot{V}CO_2$ slope was calculated from maximal exercise in their study. When only submaximal data were used for OUES determination, this superiority of the $\dot{V}_E/\dot{V}CO_2$ slope compared with the OUES was no longer significant. Although OUES appears to have good discriminative ability in these populations, further investigation is required for exploring the prognostic power of OUES in the risk stratification of patient with other (chronic) conditions. In addition, future studies should examine the relationship between OUES and other markers of physiologic function reflecting disease severity (eg, Doppler echo, cardiac magnetic resonance imaging, brain natriuretic peptide concentrations in blood, or pulmonary pressure).

Both the $\dot{V}_E/\dot{V}CO_2$ slope and OUES could potentially be used to identify a subgroup within CAD patients with intermediate $\dot{V}O_{2peak}$, who might have a worse outcome. Arena et al[18] reported that although OUES is a significant prognostic marker in patients with HF, the $\dot{V}_E/\dot{V}CO_2$ slope calculated with all exercise data remained prognostically superior. Davies et al[22] performed a similar analysis, though they concluded that OUES was the best predictor of mortality. In this latter study, patients were tested between 1992 and 1996, while only 2.6% of the participants of Arena et al[18] underwent testing before 1997. Given the changes in HF management since the 1990s, the findings of Arena et al[18] may be more reflective of present-day clinical practice.

OUES in Children

Mean submaximal OUES values in healthy children are significantly lower than those in healthy adult populations (1900-2200 vs 2910-4300, respectively).[19,24,25,28,29,38,39] An interesting finding is that the OUES increases linearly with age during childhood,[19] whereas it was found to decrease linearly with age in healthy elderly.[4] Correlation coefficients with other exercise parameters in children are similar to those found in healthy adults. However, caution is recommended when interpreting OUES as an exercise parameter in the development course of childhood, since OUES is considerably influenced by anthropometric variables.[19,38]

To our knowledge, only 1 study examined OUES in children with chronic conditions. Baba et al[21] included both healthy children and children with various conditions of the heart. However, the study population was very heterogeneous, and furthermore, no distinction was made between the patients and healthy children in their results. Thus, as far as we know, no studies are published that compare OUES values in children with various (chronic) diseases with those in healthy peers. As a consequence, it is currently not known whether the OUES is able to discriminate between healthy children and children with various (chronic) diseases or disabilities. Moreover, none of the included studies investigated the effects of pubertal stages on OUES, despite the fact that exercise capacity is known to be influenced by this developmental milestone. Future research should address this interesting issue.

OUES Versus VAT

Oxygen uptake efficiency slope determination involves calculating the slope of the relationship between $\dot{V}_E$ and $\dot{V}O_2$ rather than a single cross-sectional determination with substantial inter- and intraobserver variability during exercise, like the VAT. As a consequence, OUES is objectively identifiable in all subjects and seems to be sufficiently reproducible.[24] Moreover, the slope is derived from multiple data points throughout the exercise test and, therefore, provides more profound physiological information. Oxygen uptake efficiency slope includes both metabolic acidosis and physiologic pulmonary dead space and hence displays the status of both systemic and pulmonary perfusion, whereas VAT primarily represents the status of blood distribution to the working muscles rather than perfusion to the lungs.[21] Also, caution has to be taken when reporting about data measured at different anaerobic thresholds to avoid mixing up methods;[17] this is not applicable for OUES, because it concerns a single fixed and simple mathematical formula. Furthermore, VAT values can be considerably influenced by the nutritional state of the subject (eg, carbohydrate loaded or depleted). Baba et al[24] have stated that this is not the case for OUES values.

OUES Versus $\dot{V}_E/\dot{V}CO_2$ Slope

Both the OUES and $\dot{V}_E/\dot{V}CO_2$ slope reflect ventilatory efficiency and have the advantage of being derived from multiple data points throughout the exercise. Contrary to the $\dot{V}_E/\dot{V}CO_2$ slope, OUES appears to be relatively independent of patient-achieved effort level.

OUES differs in theory from the $\dot{V}_E/\dot{V}CO_2$ slope in that it considers changes in ventilation in terms of scale factor, that is, in multiples of the baseline value. Consequently, any abnormalities that increase ventilation by a constant proportion, both at rest and during exercise, will not directly influence OUES. Only abnormalities that increase ventilation during exercise by a greater proportion than at rest will cause a decline in OUES values. Oxygen uptake efficiency slope may therefore quantify the specific pattern of ventilatory response to exercise having automatically "controlled" for abnormalities present at rest.[22]

Correlation coefficients with traditional measures of cardiopulmonary function, including $\dot{V}O_{2max}$, $\dot{V}O_{2peak}$, and VAT, reported for OUES were much stronger than for the $\dot{V}_E/\dot{V}CO_2$ slope.[15,20,21] The latter, which is related to physiologic pulmonary dead space, is affected mainly by perfusion to the lungs. Oxygen uptake efficiency slope, affected both by metabolic acidosis and by physiologic pulmonary dead space, reflects the status of both systemic and pulmonary perfusion, which seems to account for the superiority of OUES concerning the correlation with traditional parameters.[42]

The prognostic value of both slopes in predicting morbidity and mortality is confirmed in patients with HF or CAD.[18,22,31] Defoor et al,[14] however, reported that the $\dot{V}_E/\dot{V}CO_2$ slope might be less suitable than OUES to evaluate the effects of physical training in CAD patients without an increased $\dot{V}_E/\dot{V}CO_2$ slope at baseline measurement. They found that changes in VAT contributed most to the changes in OUES than in the $\dot{V}_E/\dot{V}CO_2$ slope. In addition, Van Laethem et al[35] found that the training-induced changes in OUES correlated better with the changes in $\dot{V}O_{2peak}$ in patients with HF than the changes in the $\dot{V}_E/\dot{V}CO_2$ slope.

Several studies examined the relationship between underlying pathophysiology and an abnormally elevated $\dot{V}_E/\dot{V}CO_2$ slope in patients with HF. The mechanisms appear to be multifaceted with both central and peripheral contributions.[18] Such studies are lacking for OUES thus far. Additional research is required to examine the mechanism behind the abnormally low OUES observed in patients with HF.[18] Furthermore, future research should reveal which submaximal efficiency slope appears most useful in clinical practice with various patient populations.

Interpretation of OUES

During the analysis of the different studies it became clear that OUES was expressed in various entities, which can be confusing. In fact, OUES represents the slope of a regression line and forms the quotient of $\dot{V}O_2$ (mL/min) and log $\dot{V}_E$ (L/min). As a result, OUES formally has no entity.

Drinkard et al[39] attempted to predict $\dot{V}O_{2peak}$ from OUES values in a pediatric population and did not find significant differences between the actual $\dot{V}O_{2peak}$ and the $\dot{V}O_{2peak}$ predicted by the submaximal OUES. However, the authors identified a significant bias in overweight adolescents. This is in line with the results of Pichon et al,[25] who found that the $\dot{V}O_{2max}$ predicted by the OUES did not significantly differ from measured $\dot{V}O_{2max}$. Since OUES is not able to reliably predict $\dot{V}O_{2max}$, it appears not interchangeable with the "gold standard." However, we suppose that the OUES is not meant to predict maximal exercise parameters. The index itself provides an objective and independent measure of cardiorespiratory function, reflecting the efficiency of ventilation with regard to the oxygen uptake during exercise. The interpretation of its values is dependent on comparison with adequate reference values, comparisons between (groups of) subjects, or comparisons within subjects (eg, to detect individual changes in ventilatory efficiency over time or following a specific intervention).

Normalization of OUES

Since OUES is considerably influenced by anthropometric variables, it is recommended to normalize its values for body size, especially in children. Maximal indices such as $\dot{V}O_{2peak}$ are also known to be strongly influenced by changes in body size. Therefore, $\dot{V}O_{2peak}$ is often normalized by body weight;[43] however, the influence of body mass is not entirely compensated by this method.[44] The study of Marinov and Kostianev[38] showed that normalizing $\dot{V}O_{2peak}$ for BSA (depends on both weight and height) compensates for the differences between different weight groups. Since height, weight, lean body mass, and BSA are strongly correlated with OUES,[19] normalizing its values for one of these parameters seems appropriate, especially in pediatric populations. Previous studies have normalized OUES by body weight, lean body mass (a surrogate for muscle mass), or BSA. From a physiological perspective, we presume that BSA provides the best indication of total pulmonary volume, taking both height and weight into account. However, which adjustment is most useful in normalizing the OUES has to be further investigated.

Applications to Practice and Implications for Further Research

There is a need for adequate reference values for the OUES in (healthy) adults and children. Appropriate reference values should be generated with respect to age, gender, race, and other factors such as maturation and anthropometrics. To our knowledge, influences of puberty on the OUES have not been investigated. Since puberty causes significant changes in body composition, muscle strength, $\dot{V}_{Emax}$, ventilatory equivalent, and physical activity patterns,[45] it might also influence ventilatory efficiency (OUES). Future studies should address the aforementioned variables.

Also, it is currently unknown whether the submaximal OUES is able to differentiate between healthy children and children with a (chronic) disease. Previous findings suggest that OUES has discriminative value in adults;[4,8,22,31,32] however, further research is required to assess its discriminative ability in different pediatric populations.

Furthermore, the responsiveness of the OUES to exercise training has never been addressed in pediatric (patient) populations. Results from adult studies suggest that the OUES increases following physical training in both patients with CAD and those with HF. The training-induced changes in OUES parallel those in $\dot{V}O_{2peak}$ in cardiorespiratory-limited populations,[14,34] showing that OUES is sensitive to improvement in exercise tolerance. Therefore, OUES would seem to be clinically useful to monitor changes in exercise performance and effects of physical training in adults, particularly in those who can perform only submaximal exercise. Several authors have stated that the OUES is more robust than the $\dot{V}O_{2peak}$, since maximal workload assessed during a symptom-limited exercise test can be influenced by multiple factors.[4,32,36] However, none of these studies involved randomized controlled trials and the responsiveness of the OUES in pediatric populations remains the subject of further research.

It is currently unknown whether the type of ergometer affects OUES determination. The included studies used both a treadmill ergometer or a cycle ergometer for OUES determination and various exercise protocols. Since $\dot{V}O_{2peak}$ values are usually higher with a treadmill protocol[46] and since OUES is highly correlated with $\dot{V}O_{2peak}$, it is likely that the OUES could be influenced by the type of ergometer. The only study assessing interprotocol agreement showed excellent intraindividual agreement between OUES obtained with 2 different treadmill protocols, unlike VAT and $\dot{V}O_{2max}$.[37] However, no additional studies are yet published to confirm these findings. Whether values of OUES are ergometer and/or protocol dependent thus remains the subject of future research.

SUMMARY

OUES appears to be a reproducible measure of cardiorespiratory function that does not require maximal exercise. It greatly reduces test variability because of motivational and subjective factors and is reliable and easily determinable in all subjects when respiratory gas analysis systems with breath-by-breath or mixing chamber are used. Despite the strong correlations with $\dot{V}O_{2peak}$ and $\dot{V}O_{2max}$, OUES appears not interchangeable with these maximal exercise parameters. Nonetheless, OUES seems to be a promising alternative submaximal exercise parameter to assess cardiorespiratory function in subjects unable to perform maximal exercise, like children and patients with progressed disease states. However, appropriate reference values for both adult and pediatric populations are required.

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