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Exercise

Oxygen Uptake Efficiency Slope: An Index of Exercise Performance and Cardiopulmonary Reserve Requiring Only Submaximal Exercise

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OBJECTIVES We sought to evaluate, in adults, the efficacy of the Oxygen Uptake Efficiency Slope (OUES), an index of cardiopulmonary functional reserve that can be based upon a submaximal exercise effort.

BACKGROUND Maximal oxygen uptake ($\dot{V}O_{2\ max}$), the most reliable measure of exercise capacity, is seldom attained in standard exercise testing. The OUES, which relates oxygen uptake to total ventilation during exercise, was proposed by Baba and coworkers (7) in a study of pediatric cardiac patients. They felt this submaximal index of cardiopulmonary reserve might be more practical than $\dot{V}O_{2\ max}$ and more appropriate than the commonly used peak oxygen consumption ($\dot{V}O_{2\ peak}$).

METHODS Treadmill exercise tests with simultaneous respiratory gas measurement were performed in 998 older subjects free of clinically recognized cardiovascular disease and 12 male patients with congestive heart failure. During incremental exercise, oxygen uptake was plotted against the logarithm of total ventilation, and the OUES was determined.

RESULTS The OUES, when calculated only from the first 75% of the exercise test, differed by 1.9% from the OUES calculated from 100% of exercise time in subjects with a peak respiratory exchange rate ≥1.10. On serial tests the OUES was less variable than exercise duration or $\dot{V}O_{2\ peak}$. It correlated strongly with $\dot{V}O_{2\ max}$, with forced expiratory volume in 1 s and negatively with a history of current smoking. The OUES declined linearly with age in both women and men. A small sample of patients with congestive heart failure had OUES values much lower than those of older subjects without cardiovascular disease.

CONCLUSIONS The OUES is an objective, reproducible measure of cardiopulmonary reserve that does not require a maximal exercise effort. It integrates cardiovascular, musculoskeletal and respiratory function into a single index that is largely influenced by pulmonary dead space ventilation and exercise-induced lactic acidosis. (J Am Coll Cardiol 2000;36:194–201) © 2000 by the American College of Cardiology

The ability to substitute a submaximal for a maximal exercise test to classify individuals by their exercise capacity and to estimate their cardiopulmonary reserve has long been a frequently sought goal. Although the measurement of maximal oxygen uptake ($\dot{V}O_{2\ max}$) is frequently used as the most reliable measure of overall exercise capacity, this value is seldom attained in standard exercise testing. It demands a maximal effort by the individual and also requires the oxygen uptake to plateau, despite continuing exercise and increasing workload. Thus, its usefulness is limited mainly to trained, normal subjects and is of little value when applied to the study of certain groups of individuals such as the elderly or those with various disease states. Consequently, this objective measurement is often replaced by the peak oxygen consumption ($\dot{V}O_{2\ peak}$), the rate of oxygen consumption that occurs at peak exercise. This substitution, however, is unsatisfactory because this measurement is strongly influenced by the patient's motivation and the tester's subjective choice of test end point. Because of these limitations, as well as the fact that exhaustive exercise tests do not mimic the daily life activities of patients or the elderly, investigators have attempted to derive a reproducible index of overall exercise performance that would be based solely on a submaximal exercise effort (1–3). One such commonly used measurement to assess and eliminate the influence of subjective motivation is the ventilatory threshold, a marker that identifies the onset of significant muscular anaerobic metabolism. However, despite its obvious value, the ventilatory threshold is difficult to obtain in many healthy subjects and in as many as up to 25% of patients with congestive heart failure (CHF) (4). Moreover, it is calculated by several different methods and is subject to considerable interobserver variability (5,6).

Baba and co-workers (7) have developed and reported an index, the Oxygen Uptake Efficiency Slope (OUES), which appears to provide an objective estimation of cardiopulmonary function even at submaximal exercise. In their study, the value of the OUES remained essentially unchanged regardless of whether all data points for the entire maximal

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Abbreviations and Acronyms

BSA	= body surface area
CHF	= congestive heart failure
ECG	= electrocardiogram
FEV_1	= forced expiratory volume in 1 s
OUES	= Oxygen Uptake Efficiency Slope
RER	= respiratory exchange ratio
$\dot{V}CO_2$	= carbon dioxide production
$\dot{V}E$	= minute ventilation
$\dot{V}O_2$	= oxygen consumption
$\dot{V}O_{2\,max}$	= maximal oxygen uptake
$\dot{V}O_{2\,peak}$	= peak oxygen consumption

test were used, or only those for the first 75% or 90% of the test. Although this index, derived from data from a submaximal test, looked promising, its generalizability was questionable because mainly young subjects were studied—108 with heart disease (mean age 11.7) and only 36 normal subjects (mean age 12.9 years). In this study we describe the characteristics of the OUES for a large, relatively healthy, free-living adult population over 55 years of age whose demographics and exercise performance previously have been reported (8) and contrast them with the OUES of a small group of male patients with CHF.

METHODS

Subjects. Nine hundred and ninety-eight subjects (579 women and 419 men) who were relatively healthy were tested between June 1993 and March 1995. They were free of known cardiac disease (myocardial infarction by history or by electrocardiogram [ECG], history of angina, coronary artery angioplasty or bypass grafting), cerebrovascular disease (history of stroke, transient ischemic attacks or carotid artery surgery) and musculoskeletal impairment (use of a cane or walker, lower extremity arthritis that significantly impaired walking) and were otherwise medically able to complete safely a full treadmill exercise test. The study was approved by the Committee on Human Research, University of California, San Francisco and the Committee for the Protection of Human Subjects, University of California, Berkeley. Written, informed consent was obtained from all subjects. Seven hundred and twenty-five of these subjects were tested again two years later. We analyzed the tests of 82 of these subjects who showed the greatest difference in exercise duration between both tests (5th percentile), as well as the tests of 52 persons who exercised to the same extent on both tests, in order to compare the degree of variation of the OUES with that of the exercise duration. Also, we randomly selected the treadmill exercise tests of a second group of 12 male patients with CHF (New York Heart Association class II–III) who had been tested recently as part of their clinical evaluation to measure their $\dot{V}O_{2\,peak}$. We computed the OUES for these patients and compared them with those of the healthy, older subjects. These subjects were selected for comparison before calculation of their OUES.

Treadmill exercise testing. The procedures followed before exercise testing were previously reported (8). Subjects were exercised on a computer-driven treadmill (CASE 15, Marquette Electronics, Inc.) using the Cornell modification of the Bruce treadmill exercise protocol (9). The 12-lead ECG was monitored continuously during exercise. Subjects were exercised to their self-determined maximal capacity or until the physician stopped the test because of symptoms, ECG changes or undue rise in blood pressure. Subjects were instructed that they could stop the test whenever they felt the need to do so.

Respiratory gas measurements. Continuous breath-to-breath respiratory gas measurements were obtained using a Medical Graphics Cardiopulmonary Exercise (CPX) system. Direct measurements of oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}E$), respiratory rate and several derived variables such as the respiratory exchange ratio (RER, i.e., $\dot{V}O_2/\dot{V}CO_2$), oxygen pulse ($\dot{V}O_2$/HR) and the ventilatory equivalents for oxygen ($\dot{V}E/\dot{V}O_2$) and carbon dioxide ($\dot{V}E/\dot{V}CO_2$) were obtained. The flow meters and gas analyzers were calibrated daily for accuracy and linearity with a syringe of known volume and with precisely analyzed gas mixtures. Additionally, the gas analyzers were checked by autocalibration before each test. Output from the gas analyses were sampled at 15 s intervals and stored for use in the calculation of the OUES. Maximum expiratory maneuvers also were performed, which included a flow volume loop for measurement of forced expiratory volume in 1 s (FEV_1).

Measures of cardiopulmonary fitness. The $\dot{V}O_{2\,peak}$ and the duration of exercise were used as major measures to evaluate physical fitness and to compare with the OUES. The OUES reflects the relationship between oxygen uptake ($\dot{V}O_2$ in ml/min) and total ventilation ($\dot{V}E$ in L/min) and is best described by a single exponential function in almost all subjects. This index was determined by the method of Baba and coworkers (7) who used the following equation:

$$\dot{V}O_2 = a \log_{10}\dot{V}E + b$$

When $\dot{V}O_2$ in ml/min is plotted on the *y* axis and $\dot{V}E$ in L/min is plotted on the semilog transformed *x* axis, the slope of this linear relationship, "a", represents the OUES. An example of this relationship before and after logarithmic transformation is shown in Figure 1. Whereas $\dot{V}E$ is usually represented on the *y* axis and $\dot{V}O_2$ on the *x* axis, we chose to reverse this convention so that a steeper slope would represent a more efficient oxygen uptake. Thus, for any given amount of ventilation, the steeper the slope, the greater the oxygen uptake, and, conversely, the more shallow the slope, the greater the amount of ventilation required for any given oxygen uptake (since many disease states are associated with hyperventilation). In order to evaluate its usefulness as a cardiopulmonary index derived from a submaximal exercise test, the OUES was also calculated

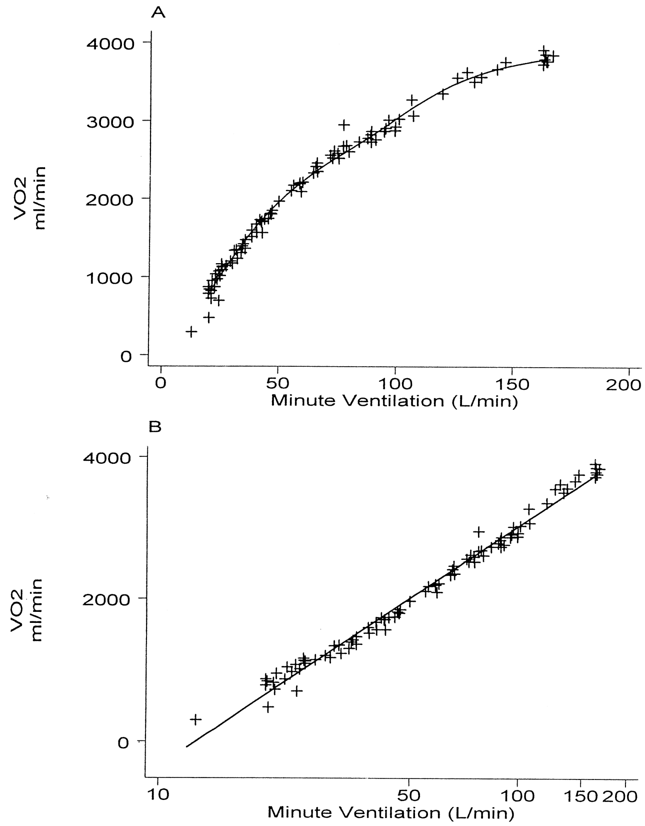

Figure 1. The relationship between oxygen uptake and total ventilation during incremental exercise in a healthy 60-year-old man. Linear **(top)** and semilog (*x*-axis) plots of the data **(bottom)** are presented.

from data taken from the first 75%, 90% and 100% of the exercise duration in the subset of 429 subjects (206 women, 223 men) with an RER ≥1.10, who were considered to have achieved a maximal effort. Additionally, the OUES of these subjects were used to correlate with their $\dot{V}O_{2\ max}$.

Lean body mass (bioelectric impedance) measurements. Before the onset of exercise, with the subject in the supine position, whole body resistance and reactance were obtained for the determination of bioelectric impedance (Body Composition Analyzer Model B1A-101; RJL Systems, Clinton Twp, Michigan) as previously described (8). Lean body mass was estimated with "Weight Manager Version 2.0" software (RJL Systems). Thus, the estimation of lean body mass used a proprietary algorithm that may have been based only in part on a sample of elderly patients and might not reflect accurately our own population. However, we are using it as an adjustment procedure—to remove the contribution of body fat—rather than to report actual distributions of lean body mass. Thus, measurements of $\dot{V}O_2$/kg body weight that were provided by the CPX system as well as fitted OUES were subsequently corrected for estimated lean body mass.

Statistics. All categorical variables were compared with the Pearson chi-square or the Cochran Mantel Haenzel test (PROC FREQ of SAS [Cary, North Carolina]). Groups of continuous variables were compared with parametric or nonparametric tests (PROC GLM and PROC NPAR1WAY of SAS). Tests for normality were carried out with the "Sktest" of STATA (College Station, Texas). Ordinary least squares and weighted least squares regression analyses were carried out with the "Regress" procedure of STATA. For calculation of OUES, individual-level regressions of $\dot{V}O_2$ versus ventilation were based on data after the first 2 min of exercise. Examination of individual plots of $\dot{V}O_2$ versus the semilogarithmic transform of ventilation indicated that a linear fit was acceptable after 2 min for virtually all subjects. Thus, a regression slope for each subject was calculated from data beginning at 2 min of exercise, and the OUES slopes were used for analysis. The inverse of the variance of the slope estimates for each individual was used as the weight in regression analyses to account for the differences in the numbers of time points available for each subject. The fit of all regressions was evaluated with analyses of the distribution of residuals and with leverage and influence plots when appropriate.

Table 1. Characteristics of Study Population

	Women (n = 579)	Men (n = 419)
General		
Age*	67 (53–89)	68 (54–96)
Body Surface Area (M^2)*	1.73 (1.32–2.28)	1.99 (1.61–2.60)
Smoking (% never/% current)	51.1/7.9	35.1/6.0
No underlying health condition (%)†	75.7	81.1
Diabetes mellitus (%)‡	2.1	5.3
Intermittent claudication (%)	7.4	5.8
Current asthma, chronic bronchitis, emphysema (%)	5.9	4.3
Cancer (except nonmelanoma skin) (%)	13.5	11.7
Cardiac medications (%)§	7.8	6.8
Treadmill Exercise Test¶		
Peak $\dot{V}O_2$ (ml/min kg^{-1})	21.2 ± 4.6	26.5 ± 6.1
Peak $\dot{V}E$ (L/min)	47.0 ± 12.2	75.8 ± 21.6
Peak heart rate (beats/min)	148 ± 19	149 ± 19
RER at peak exercise	1.07 ± 0.10	1.10 ± 0.09
Exercise duration (min)	10.6 ± 3.9	13.2 ± 4.6
OUES ([ml/min O_2])/[L/min VE])	1599 ± 322	2334 ± 511

*median (range); †self-report of no asthma, chronic bronchitis/emphysema, cancer, liver or kidney disease, diabetes mellitus, vascular disease, Parkinson's Disease; ‡all medical conditions are self-reported; §digoxin, beta-adrenergic receptor blockers, calcium channel blockers; ¶mean ± SD.

RESULTS

The clinical characteristics of the subjects and their performance characteristics on treadmill exercise testing are shown in Table 1. More detailed data on the physical performance characteristics of this group have been reported previously (8).

Four hundred and twenty-nine subjects (206 women, 223 men) reached a peak RER ≥1.10 and were considered to have performed maximal exercise. In these subjects, the OUES derived from data taken from the first 75% or 90%

Table 2. Comparison of OUES at 100%, 90% and 75% of Exercise Duration

	OUES*	Mean Difference† vs. 100% (95% CI)	% Mean Difference vs. 100% (95% CI)
At 75% exercise	1,959 ± 532	−38 ± 6.7 (−51, −25)	−1.9% (−2.6%, −1.3%)
At 90% exercise	1,996 ± 555	1 ± 3.2 (−6, 7)	0.03% (−0.3%, 0.3%)
At 100% exercise	1,997 ± 563		

*Mean ± SD (men and women grouped together); †mean ± SE.
CI = confidence interval; OUES = Oxygen Uptake Efficiency Slope.

of exercise did not differ meaningfully from the OUES derived from data for the entire exercise test (Table 2). The OUES correlated highly with $\dot{V}O_{2\,peak}$ (and probably $\dot{V}O_{2\,max}$ in this group) (r = 0.83 for women, 0.88 for men).

The OUES declines linearly with age in both women and men (Fig. 2) and is best fit by a simple linear model in which OUES = age + body surface area (BSA). Thus:

$$\text{for women, OUES} = 1{,}175 - (15.8\cdot\text{age}) + (841\cdot\text{BSA})$$

$$\text{for men, OUES} = 1{,}320 - (26.7\cdot\text{age}) + (1{,}394\cdot\text{BSA})$$

There was a significant difference between men and women in the intercept and in the age and BSA coefficients (evaluated in a joint regression model with [age·gender] and [gender·BSA] interaction terms). The OUES was divided by percent lean body mass to account for gender-specific differences in oxygen consumption that are related to differences in muscle mass. The lean body mass-adjusted OUES was regressed on BSA (Fig. 3) and on age for males and females. The BSA coefficients between sexes were no longer significant, but men still had a steeper decline with age (data not shown).

The OUES correlated not only with $\dot{V}O_{2\,max}$, as noted above, but also correlated significantly with FEV_1 and smoking history. The age-adjusted correlations with FEV_1 were 0.17 ($p < 0.005$) and 0.22 ($p < 0.000$) for women and men, respectively. When cigarette smoking was added to the above regression models, male current and ex-smokers had significantly lower OUES than nonsmoking men, with the reduction being about four-fold greater in current smokers than in ex-smokers (Table 3). In women, smokers had borderline lower OUES than nonsmokers and ex-smokers. When FEV_1 was added to these regression models, FEV_1 was significantly related to OUES in both sexes. Moreover, by adding FEV_1 to the model, the effect of current smoking on OUES in women was reduced by 33%. The effect of smoking on OUES in men was not altered meaningfully by addition of FEV_1 to the model.

To compare the OUES and other exercise variables in individuals who achieved different exercise intensities, we divided the subjects into three groups according to the peak RER achieved (Table 4): Group 1 = RER < 1.00, Group 2 = RER 1.00 to 1.09, Group 3 = RER ≥ 1.10. The

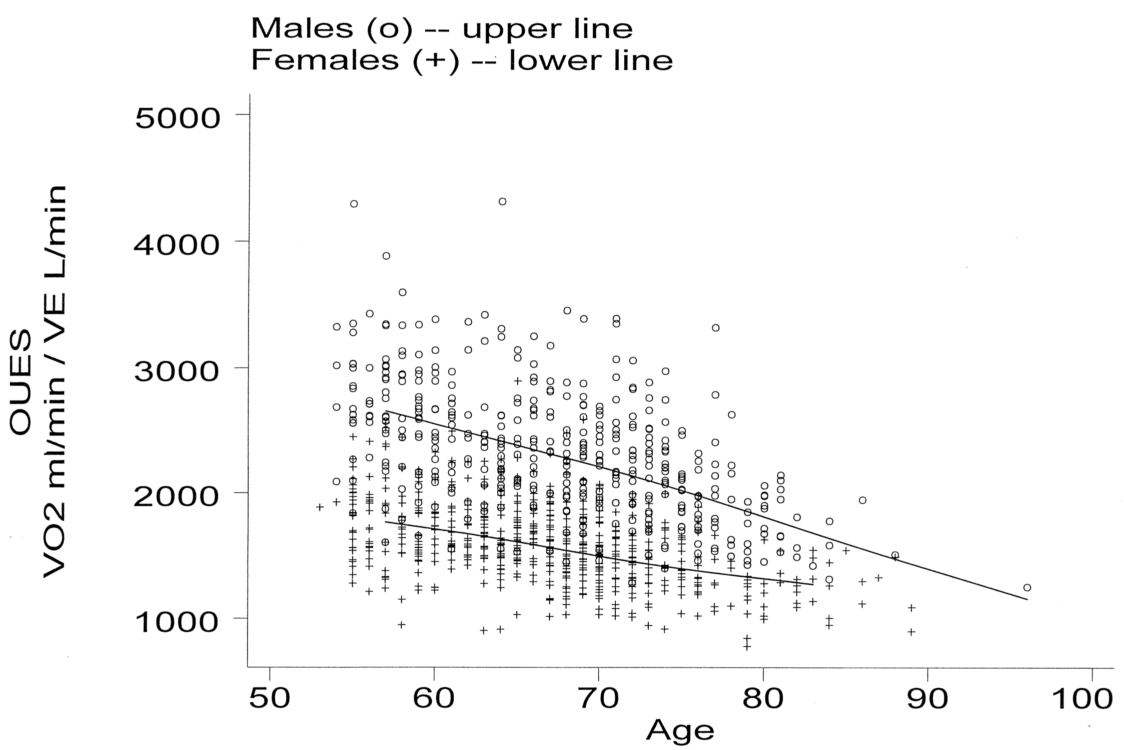

Figure 2. Effect of age on Oxygen Uptake Efficiency Slope (OUES) in men **(top line)** and women **(bottom line).**

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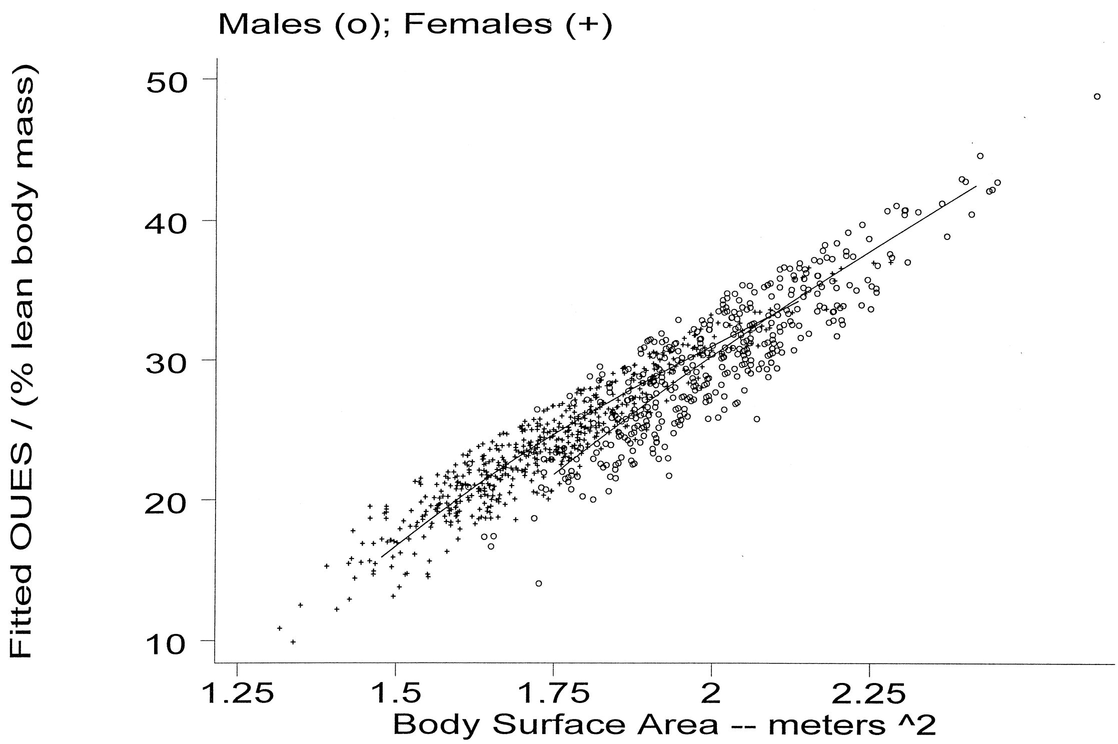

Figure 3. Effect of body surface area on Oxygen Uptake Efficiency Slope (OUES) adjusted for percentage of lean body mass.

OUES was similar for same gender subjects with a peak RER of either 1.00 to 1.09 or RER $\geq$1.10 (groups 2 and 3). Group 1 subjects, whose RER was <1.00, had a significantly smaller OUES than did the two other groups ($p <$ 0.01 for women, <0.005 for men). However, these group 1 subjects were older, had shorter exercise times and lower peak oxygen uptakes, had lower FEV_1 and had a greater frequency of current smokers. All such differences in physiological attributes would contribute to the lower OUES that was found in this group of subjects. Thus, the OUES probably accurately reflects the cardiopulmonary reserve even in these subjects who failed to achieve an RER >1.00.

To estimate the level of variability to be expected from repeated determinations of OUES in an individual, we compared the values derived from two exercise tests done by subjects who completed round 1 and round 2 separated by two years. The OUES for the 728 subjects who completed both tests showed no significant differences for the group. However, from the testing sessions, it was apparent that motivational factors were operative and that many of the subjects did not exert themselves to the same extent on the second exercise test compared with the first. To determine what effect extreme differences in exercise duration exerted on the OUES, we analyzed individuals whose exercise duration differed most markedly between the two tests, subjects whose differences represent the largest 5% of the difference distributions: group I (round 1 > round 2), group II (round 1 < round 2) and a third group who exercised to the same degree on both tests, group III (round 1 = round 2) (Table 5). In group I, women exercised 48% less and men 31% less during round 2 than round 1; however, their OUES was only 7% and 11% lower, respectively. In group II, women exercised 80% longer and men 52% longer on the second test; however, their OUES differed by only 1.5% and 8%, respectively. The similarity of the OUES despite the large differences in exercise duration between rounds 1 and 2 suggests that very little change in cardiopulmonary reserve had occurred between the two tests and that the differences in exercise duration were due largely to motivational factors. In group III, the OUES of 37 women and 15 men, whose

Table 3. Regression Equations to Predict OUES

Prediction Model	Women	Men
Age, BSA	OUES = 1,175 − (15.8·age) + (841·BSA)	OUES = 1,320 − (26.7·age) + (1,394·BSA)
Age, BSA, Smoking status	OUES = 1,215 − (16.0·age) + (829·BSA) −67 (for current smoker) −7 (for ex-smoker)	OUES = 1,510 − (27.9·age) + (1,367·BSA) −282 (for current smoker) −70 (for ex-smoker)
Age, BSA, Smoking status, FEV_1	OUES = 944 − (13.3·age) + (767·BSA) + (93·FEV_1) −45 (for current smoker) −9 (for ex-smoker)	OUES = 1,376 − (26.0·age) + (1,278·BSA) + (61·FEV_1) −251 (for current smoker) −76 (for ex-smoker)

BSA = body surface area in M^2; FEV_1 = forced expiratory volume in 1 s in L.

Table 4. Characteristics of Subjects Grouped by Peak Exercise RER

	Women (n = 579)			Men (n = 419)		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
	RER < 1.00	RER 1.00–1.09	RER ≥ 1.10	RER < 1.00	RER 1.00–1.09	RER ≥ 1.10
n	119	254	206	38	158	223
OUES	1,512 ± 308*	1,615 ± 333	1,608 ± 313	2,087 ± 482†	2,361 ± 521	2,356 ± 500
Exercise duration	8.0 ± 2.9	10.9 ± 3.6	11.7 ± 4.0	8.8 ± 3.5	12.9 ± 4.4	14.2 ± 4.4
Peak $\dot{V}O_2$/kg	18.2 ± 3.4	21.8 ± 4.6	22.1 ± 4.3	20.4 ± 4.8	25.4 ± 5.5	28.3 ± 5.9
Max FEV_1	1.92 ± 0.48	2.20 ± 0.48	2.34 ± 0.43	2.52 ± 0.71	2.93 ± 0.69	3.20 ± 0.70
% current smokers	9	11	4	13	5	5
Age	69.3 ± 6.9	66.7 ± 7.4	65.0 ± 6.7	71.6 ± 7.3	68.7 ± 8.0	66.0 ± 7.2

FEV_1 = forced expiratory volume in 1 s; OUES = Oxygen Uptake Efficiency Slope; RER = respiratory exchange ratio; $\dot{V}O_2$ = oxygen consumption.
*$p < 0.01$ group 1 vs. group 2, 3; †$p < 0.005$ group 1 vs. group 2, 3.

exercise duration was exactly the same on the two tests, differed by less than 1.5% (by 1.3% and −1.4%, respectively). Thus, use of the OUES greatly reduces test variability due to motivational and subjective factors—factors that can strongly influence test results when exercise duration or $\dot{V}O_{2\,peak}$ are used as test end points.

Because patients with CHF are well known to have an increased ventilation for a given oxygen uptake, we sought to describe the characteristics of the OUES in such patients. In a small pilot study, we calculated the OUES for a small group of 12 men with CHF. Their OUES as well as their $\dot{V}O_{2\,peak}$ were markedly depressed when compared with those of our healthy subjects. Most of their values fell well below the 95% prediction limits for our population-based elderly subjects (Fig. 4).

DISCUSSION

The OUES, originally described by Baba and co-workers (7) in a group of pediatric patients, is an index that

Table 5. Comparison of Treadmill Exercise Tests Two Years Apart (Round 1 vs. Round 2)

Group I (Round 1 > 2) (Greatest Difference—5%)	Women (n = 21)		Men (n = 18)	
	Exercise (min)	OUES	Exercise (min)	OUES
Round 1	12.5 ± 3.3	1,707 ± 361	15.1 ± 4.6	2,597 ± 474
Round 2	6.6 ± 2.3	1,585 ± 287	10.4 ± 4.8	2,300 ± 434
Difference	−5.9 ± 1.4	−122 ± 246	−4.7 ± 0.8	−297 ± 297
(95% CI)	(−6.5, −5.4)	(−214, −29)	(−5.0, −4.4)	(−415, −179)
% Difference	**−48%**	**−7%**	**−31%**	**−11.4%**
(95% CI)	(−52%, −43%)	(−12.5%, −1.7%)	(−33%, −29%)	(−16%, −6.9%)

Group II (Round 1 < 2) (Greatest Difference—5%)	Women (n = 23)		Men (n = 20)	
	Exercise (min)	OUES	Exercise (min)	OUES
Round 1	7.6 ± 3.2	1,617 ± 221	10.5 ± 3.3	2,306 ± 356
Round 2	13.8 ± 3.1	1,640 ± 231	15.9 ± 3.3	2,495 ± 374
Difference	6.1 ± 1.8	23 ± 197	5.4 ± 1.4	−189 ± 244
(95% CI)	(5.5, 6.8)	(−47, 94)	(4.9, 6.0)	(95, 283)
% Difference	**+80%**	**+1.5%**	**+52%**	**+8.2%**
(95% CI)	(72%, 88%)	(−2.9%, 5.8%)	(47%, 57%)	(4.1%, 12.3%)

Group III (Round 1 = 2)	Women (n = 37)		Men (n = 15)	
	Exercise (min)	OUES	Exercise (min)	OUES
Round 1	10.5 ± 4.3	1,581 ± 282	12.75 ± 4.81	2,380 ± 756
Round 2	10.5 ± 4.3	1,602 ± 321	12.75 ± 4.81	2,347 ± 711
Difference	0.0	−21 ± 179	0.0	−33 ± 231
(95% CI)	N/A	(−39, 80)	N/A	(−160, 94)
% Difference	N/A	**+1.3%**	N/A	**−1.4%**
(95% CI)		(−2.4%, 5.1%)		(−6.7%, 4%)

Means ± SD.
CI = confidence interval; OUES = Oxygen Uptake Efficiency Slope.

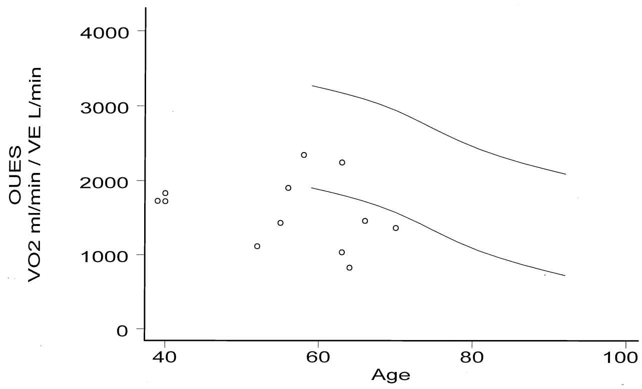

Figure 4. Relationship of Oxygen Uptake Efficiency Slope to age in 12 men with congestive heart failure. **Solid lines** represent the 95% prediction intervals for 419 normal elderly men without cardiovascular disease.

integrates the functional capacities of several organ systems, primarily cardiovascular, pulmonary and skeletal muscle, during exercise. It reflects the relationship between oxygen uptake and total ventilation during incremental exercise and is best described by a single exponential function, the exponent of which is termed "the OUES." The transformed logarithmic regression is linear in almost all subjects, and, therefore, the OUES (unlike $\dot{V}O_{2\,max}$) does not require a maximal exercise effort for its valid estimation. The OUES differed by less than 2% when it was calculated from data collected during the first 75% of the exercise test (less than 0.5% when the first 90% was used) compared with the OUES derived from data from the entire (100%) exercise duration. The OUES correlated strongly with $\dot{V}O_{2\,max}$ in the subset of patients who exerted maximally (RER $\geq$ 1.10) and who probably did achieve a true $\dot{V}O_{2\,max}$. Moreover, the OUES was similar for subjects who achieved a peak RER of 1.00 to 1.09 to the OUES of those who reached an RER $\geq$1.10. Most of the differences in OUES between subjects who achieved a peak RER below versus above 1.00 could be explained by underlying host differences (Table 4) rather than by limitations of the OUES estimations. Therefore, it appears likely that the OUES will have broad applicability not only for a general population but also for patients with various disease states. It can provide an objective index of cardiopulmonary function—one that is practical and more easily attained than $\dot{V}O_{2\,max}$—and one that is less influenced by subjective, motivational factors than the $\dot{V}O_{2\,peak}$. Moreover, the OUES appears to be quite reproducible. In subjects who exercised to a similar extent in tests conducted two years apart, the OUES varied by less than 1.5%. Even in the 5th percentile of individual subjects whose exercise duration varied most widely between tests conducted two years apart, the difference in the OUES was much smaller than the differences in exercise duration and is more likely to reflect true changes in cardiopulmonary reserve than do the changes in exercise duration.

Factors that influence the OUES. Major factors that influence the OUES and the ventilatory response to exercise and that can be predicted from the modified alveolar gas equation (10) are: 1) CO_2 production (derived from muscle aerobic metabolism as well as from the pH buffering function of bicarbonate), 2) arterial pCO_2 (CO_2 setpoint), and 3) physiologic pulmonary dead space ventilation. Thus, a large OUES and steep slope depend on a substantial mass of working muscle, a vigorous and unimpaired flow of blood to these muscles, efficient extraction and utilization of oxygen by these muscles and the delayed appearance of lactic acidosis. Deconditioned subjects or patients with certain diseases, such as CHF, who develop lactic acidosis earlier during exercise will be expected to have a diminished OUES. Additionally, physiologic dead space ventilation, which depends on the structural integrity of the lungs and the adequacy of pulmonary perfusion, will importantly influence the ventilatory response to exercise and, therefore, the OUES.

This study was not designed to assess the relative contributions of each of the above physiological factors to the composite OUES. However, we did establish the important influence on the OUES of age, BSA (to normalize total pulmonary volume) and lean body mass (a surrogate for muscle mass). In this relatively healthy population, OUES declined linearly with age in both women and men, although the rate of decline in men was greater than that in women. The extent to which these gender differences are due to differences in such variables as physical activity, medical conditions and medication effects is the subject of ongoing investigation in this population. In addition, correction of OUES for lean body mass removed most of the gender difference due to BSA (Fig. 3) but did not alter gender differences that were related to age (data not shown). The extent to which this gender-specific age difference is due to a true gender-effect or to limitations in our estimates of lean body mass (see Methods section) is not clear.

Decline in OUES with age and disease. The decline in the OUES associated with age reflects changes that are occurring in multiple organ systems including the heart, lungs, blood vessels and skeletal muscles and possibly the nervous system. To an even greater degree, the OUES also reflects changes that occur with disease that go beyond the changes seen in our older subjects. Thus, patients with decreased FEV_1, as well as current smokers, had significantly reduced OUES, probably mainly due to increased dead space ventilation. Also, the few patients with CHF whose tests we analyzed exhibited OUES values far below the lower limits of an even older, normal population even when such values were not adjusted for age. Once again, the earlier onset of lactic acidosis during exercise, as well as the excessive hyperventilation observed in such patients (1,11–13), probably account for the severely reduced OUES found in these patients. Thus, in a small sample of patients with CHF, the OUES shows promise in differentiating CHF patients from normal subjects. However, a larger, more comprehensive study is needed to establish this relationship more firmly. Because the OUES incorporates, in a single index, cardiovascular factors that determine oxygen uptake as well as pulmonary factors that influence the ventilatory response to exercise, the OUES promises to be a sensitive and important new clinical and research tool.

Conclusions. This study confirms and extends to adults the findings of Baba and co-workers (7), who established the OUES as a new index of cardiopulmonary reserve in children. Unlike $\dot{V}O_{2\,max}$, the OUES does not require a maximal effort and is reliable when derived from submaximal exercise. As such, it is a more objective and less variable measure of integrated cardiopulmonary functional status than either the widely used $\dot{V}O_{2\,peak}$ or exercise duration and is less influenced by subjective and motivational factors. Not only does it reflect the level of cardiovascular and musculoskeletal function but it also incorporates, into a single index, respiratory function as well. In the relatively healthy elderly population that we studied, the OUES declined with age. The OUES was able to detect impairment in subjects with a low FEV_1 and in subjects who were current smokers (compared with non- or ex-smokers) independent of FEV_1. Moreover, it clearly differentiated a small sample of male patients with CHF from older, but relatively healthy, individuals.

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REFERENCES

1. Weber KL, Kinsewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation 1982;65:1213–23.
2. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020–7.
3. Buller MP, Poole-Wilson PA. Extrapolated maximal oxygen consumption: a new method for the objective analysis of respiratory gas exchange during exercise. Br Heart J 1988;59:212–7.
4. Cohen-Solal A, Benessiano J, Himbert D, et al. Ventilatory threshold during exercise in patients with mild to moderate chronic heart failure: determination, relation with lactate threshold and reproducibility. Int J Cardiol 1991;30:321–7.
5. Yeh MP, Gardner RM, Adams TD, et al. "Anaerobic threshold": problems of determination and validation. J Appl Physiol 1983;55:1178–86.
6. Gladden LB, Yates JW, Stremel RW, Stamford BA. Gas exchange and lactate anaerobic thresholds: inter- and intraevaluator agreement. J Appl Physiol 1985;58:2082–9.
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;28:1567–72.
8. Hollenberg M, Ngo LH, Turner D, Tager IB. Treadmill exercise testing in an epidemiologic study of elderly subjects. J Gerontol: Biol Sci 1998;53A:259–67.
9. Okin PM, Ameisen O, Kligfield P. A modified treadmill exercise protocol for computer-assisted analysis of the ST segment/heart rate slope: methods and reproducibility. J Electrocardiol 1986;19:311–8.
10. Wasserman K, Hansen JE, Sue DY, et al. Principles of Exercise Testing. 2nd ed. Philadelphia: Lea & Febiger, 1994.
11. Koike A, Hiroe M, Taniguchi K, Marumo F. Respiratory control during exercise in patients with cardiovascular disease. Am Rev Resp Dis 1993;147:425–9.
12. Sullivan MJ, Higginbotham MB, Cobb FR. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. Circulation 1988;77:552–9.
13. Wasserman K, Zhang YY, Gitt A, et al. Lung function and exercise gas exchange in chronic heart failure. Circulation 1997;96:2221–7.