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Maximal Aerobic Capacity and the Oxygen Uptake Efficiency Slope as Predictors of Large Artery Stiffness in Apparently Healthy Subjects

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Abstract

PURPOSE—Large artery stiffness is now recognized as an important marker of cardiovascular health. The purpose of the present investigation was to assess the relationship between large artery stiffness and the oxygen uptake efficiency slope (OUES) and to determine if the OUES is a viable surrogate for maximal oxygen uptake (VO_{2max}) in a multivariate regression analysis developed to estimate large artery stiffness.

METHODS—Two hundred seventy-five apparently healthy subjects (149 males; age=48.1±15.8 yrs/126 females; age=47.0±15.3 yrs) participated in this study. Subjects underwent maximal cardiopulmonary exercise testing to determine VO_{2max} and the OUES. The OUES was calculated using 50% and 100% of the exercise data. Measurement of aortic wave velocity (AWV in meters/second) was obtained via magnetic resonance imaging.

RESULTS—Pearson product moment correlation analysis revealed VO_{2max} ($r = -0.49, P < .001$), the OUES calculation using 50% of exercise data ($r = -0.25, P < .001$) and the OUES calculation using 100% of the exercise data ($r = -0.34, P < .001$) were all significantly related to AWV. However, only VO_{2max} was retained in a linear regression (also including age and resting systolic blood pressure) used to predict AWV.

DISCUSSION—Previous research has demonstrated a relationship between VO_{2max} and AWV, which was also found in the present study. While the OUES was significantly correlated with AWV, it does not appear to be an adequate replacement for VO_{2max} when attempting to gauge large artery compliance.

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CONDENSED ABSTRACT The relationship between large artery stiffness to maximal oxygen uptake (VO_{2max}) and oxygen uptake efficiency slope (OUES) were assessed. Although both were significantly correlated with large artery stiffness, the relationship with VO_{2max} was superior. OUES does not appear to be an adequate replacement for VO_{2max} when attempting to gauge arterial compliance.

Keywords

arterial stiffness; cardiopulmonary exercise test; ventilatory efficiency; risk assessment

Initial evidence indicates large artery stiffness may be an important marker of cardiovascular health. Several investigations have shown subjects with increased arterial stiffness are at a higher risk for adverse events.¹⁻⁶ Moreover, several easily obtained variables have demonstrated a significant relationship with arterial stiffness, allowing for its prediction by regression analysis.⁷⁻¹⁰ Of these variables, age, resting systolic blood pressure (SBP), and maximal aerobic capacity ($\text{VO}_{2\text{max}}$) appear to be some of the more relevant predictors of arterial stiffness. While the measurement of age and SBP are simple and straightforward, several measurements may be used to express aerobic fitness. Although $\text{VO}_{2\text{max}}$ is the most widely accepted marker of aerobic fitness¹¹, other measures obtained from exercise testing have recently been proposed as potential surrogates for this long established gold standard. The oxygen uptake efficiency slope (OUES) is 1 such measure that has recently gained considerable attention.¹² The OUES, derived from the linear relationship between oxygen uptake (y-axis) and the logarithmic transformation of minute ventilation (x-axis), has been postulated to reflect the integrated function and health of the pulmonary, cardiovascular and skeletal muscle systems during aerobic exercise. Previous studies have demonstrated the OUES 1) to be strongly correlated with $\text{VO}_{2\text{max}}$ ^{13,14}; 2) to reflect varying degrees of cardiovascular health/disease severity¹⁵; and 3) to possess prognostic value¹⁶. The OUES is purported to be independent of subject effort and can be obtained during submaximal exercise, both of which are potential advantages over $\text{VO}_{2\text{max}}$. The fact that the OUES can be obtained submaximally may prove to be advantageous from a staffing, and therefore economical standpoint, given direct supervision is less of a necessity, even in populations at higher risk for or diagnosed with cardiovascular disease. Moreover, a submaximal test is more comfortable for the patient and removes requirements to put forth a maximal effort in order to obtain a valid measure of aerobic capacity.

In the present practice of cardiopulmonary exercise testing, $\text{VO}_{2\text{max}}$ continues to be the most frequently assessed variable in the assessment of individual overall cardiovascular health and risk for future adverse events. Given the strong correlation between $\text{VO}_{2\text{max}}$ and the OUES, this latter variable may also prove to be clinically relevant. This may be particularly advantageous given the OUES can be derived from submaximal testing, creating a more favorable staffing and budgetary scenario for cardiopulmonary exercise laboratories. To our knowledge, there is an overall lack of research examining the ability of OUES to reflect varying degrees of cardiovascular health. More specific to the present study, unlike $\text{VO}_{2\text{max}}$, we are unaware of any previous investigation that has examined the relationship between OUES and arterial stiffness, the latter potentially being an important marker of cardiovascular health with prognostic implications. The purpose of the present investigation is to therefore assess this relationship and determine if the OUES is a viable surrogate for $\text{VO}_{2\text{max}}$ in a multivariate regression analysis developed to estimate large artery stiffness.

METHODS

Apparently healthy subjects (N=275, 149 male/126 female) were recruited for this study from the general public in and surrounding Richmond, VA. A flyer describing the study was a primary recruitment tool for this study. Inclusion criteria consisted of the ability to successfully put forth a near-maximal to maximal effort during the exercise test without an abnormal hemodynamic/electrocardiogram (ECG) response during testing. Exclusion criteria included history of myocardial infarction, angina or stroke; evidence of coronary heart disease, peripheral arterial disease, or diabetes; pregnancy, age <21 yrs; and magnetic resonance

imaging contraindications (eg ferromagnetic implants, claustrophobia). Subjects who reported tobacco use (8%) was asked to refrain from using such products on the day(s) study measurements were performed. Subjects were also asked to not consume alcohol on the day(s) of data collection. One and 4 subjects were taking a beta-blocker and calcium channel blocker, respectively. These subjects were maintained on their prescribed medication regimen during the study. Written informed consent was obtained from all subjects prior to testing. Approval from the institutional review board at Virginia Commonwealth University was obtained before study initiation.

Data Collection

Height, weight, resting heart rate (HR) and resting blood pressure (BP) were measured for all participants. Resting BP values represent the average of 5 separate recordings for each subject on 2 separate occasions that were 12-24 hours apart. Blood samples via venipuncture were obtained after overnight fasting. Body mass index (BMI) in kilograms per meters squared (kg/m^2) and Framingham 10-year risk for developing cardiovascular disease¹⁷ were determined for each subject.

Cardiopulmonary Exercise Testing—Physician-supervised maximal exercise tests were conducted using a modified Balke treadmill exercise protocol. Ventilatory expired gas analysis was performed using a metabolic cart, which was calibrated prior to each test in standard fashion (Vmax Spectra29, SensorMedics, Inc., Yorba Linda, CA). Monitoring consisted of continuous 12-lead ECG and BP measurements at regular intervals during the exercise test. Blood pressure measurements were obtained using an automated device (Tango, Suntech Medical, Morrisville, NC) and were confirmed by the cardiologist supervising the test via headphone. Subjects were encouraged to exercise to muscular fatigue. Test termination criteria followed American Heart Association/American College of Cardiology guidelines.^{18,19}

Maximal oxygen uptake ($\text{VO}_{2\text{max}}$ in $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was defined as the final 20-second averaged value during the last stage of the exercise test. Peak respiratory exchange ratio (RER) was also recorded as the final 20-second averaged value during the last stage of the exercise test. The OUES ($\text{VO}_2 = a \log_{10} \text{VE} + b$)¹² was calculated by spreadsheet software (Microsoft Excel, Seattle, Washington) using 50% (OUES₅₀), calculated from the first half of the set of 20-second averaged data points, and 100% (OUES₁₀₀) of the exercise data. Specifically, VO_2 and VE data used to calculate the OUES were expressed in liters/minute. Minute ventilation was logarithmically transformed and the slope between VO_2 (y-axis) and VE (x-axis) was determined. The difference between OUES₁₀₀ and OUES₅₀ was also determined. While no previous investigations have specifically examined the reliability of the OUES, other CPX variables have demonstrated excellent reproducibility.²⁰ Maximal heart rate was defined as the highest value obtained during the final stage of the exercise test. Percent of age-predicted maximal heart achieved during maximal exercise was determined $[(\text{maximal heart rate}/220 - \text{age}) \times 100]$. Percent-predicted $\text{VO}_{2\text{max}}$ and the OUES were also derived from the equations proposed by Wasserman et al²¹ and Hollenberg and Tager¹⁴, respectively.

Assessment of Arterial Stiffness—Aortic wave velocity (AWV in m/sec) in the descending thoracic aorta was measured using rapid acquisition magnetic resonance (MR) techniques that have been previously described.²² Briefly, all MR examinations were performed on a 1.5T whole-body MR unit (Vision, Siemens Medical Solutions, Erlangen, Germany). Subjects were positioned supine on a standard spine array receiver coil, and centered in the magnet using the xiphisternum as an anatomical landmark. Electrocardiogram gating was used to synchronize MR acquisitions to the early systolic portion of the cardiac cycle. After acquiring transaxial and sagittal scout images of the thoracic aorta, cardiac-triggered AWV measurements were performed as described previously.²³ The strategy of the

measurement is to simultaneously record the initial systolic flow velocity waveforms at 2 sites within the descending thoracic aorta, separated by a known distance (84 mm). Since the flow propagation rate is finite, a distinct delay can be discerned between the 2 velocity waveforms. The separation distance divided by this observed delay time yields the AWV. Five individual wave velocity measurements were acquired, analyzed, and then averaged to determine an overall AWV for each subject.

Blood Analysis—Blood lipids were quantitated utilizing a Roche automated clinical chemistry analyzer (Laval, Quebec). Specific methodologies for determinants in human serum and plasma are as follows 1) total cholesterol (TC) - an enzymatic based in vitro test for direct quantitative cholesterol determination; 2) triglycerides (TG) - quantitative determination of triglycerides with glycerol blanking; 3) high density lipoprotein (HDL) - an enzymatic in vitro assay for direct quantitative HDL-cholesterol determination; 4) low density lipoprotein (LDL) - a homogeneous enzymatic in vitro assay for direct quantitative LDL-cholesterol determination.

Statistical Analysis

All continuous variables are reported as means $\pm$ standard deviation. Paired *t*-testing compared differences between the OUES₅₀ and OUES₁₀₀ calculations. The difference in AWV and VO_{2max} between subjects whose OUES decreased to those who demonstrated no change or an increase from the submaximal (OUES₅₀) to maximal (OUES₁₀₀) calculations was assessed by unpaired *t*-testing. Pearson product moment correlation was used to assess the relationship between AWV and key resting and cardiopulmonary exercise test variables as well as the relationship between VO_{2max} and the OUES. Three multivariate regression analyses to predict AWV (Stepwise method; entry and removal values 0.10 and 0.05, respectively) were then performed using VO_{2max}, OUES₁₀₀ and OUES₅₀. The same resting variables were used in each multivariate regression. All statistical tests with a *P*-value < .05 were considered statistically significant.

RESULTS

Key resting and exercise measurements are presented in Table 1. The overall group appeared to be in very good health and at low-risk for cardiovascular disease as indicated by mean resting HR, resting BP, 10-year Framingham risk score, lipids, VO_{2max}, and OUES. Mean values for both percent of age-predicted maximal heart rate achieved ($\sim 100\%$) and peak RER (> 1.0) indicate an overall excellent subject effort during exercise testing. Paired *t*-test results indicate OUES₅₀ and OUES₁₀₀ calculations were not significantly different (*P* = .49).

Correlation results between AWV and other variables of interest are listed in Table 2. Age, resting SBP, and VO_{2max} demonstrated the strongest correlations with AWV. Resting DBP, total cholesterol, HDL, triglycerides, OUES₅₀, and OUES₁₀₀ also demonstrated significant relationships with AWV, although the strength of these relationships was weaker. Scatter plots illustrating the relationship between AWV and VO_{2max}, OUES₅₀, and OUES₁₀₀ are provided in Figure 1. The relationship between VO_{2max} and both OUES₁₀₀ ($r = .76$, $P < .001$) and OUES₅₀ ($r = .62$, $P < .001$) was significant. Moreover, the correlation between OUES₁₀₀ and OUES₅₀ was very robust ($r = .90$, $P < .001$). Interestingly, a significant negative correlation was found between a lower OUES change from the 50% to 100% calculations and AWV ($r = -.22$, $P < .001$). The 129 subjects who demonstrated a negative OUES change had a significantly higher AWV compared to the 146 who demonstrated no change or an increase (6.6 ± 1.9 vs. 6.0 ± 1.8 , $P = .004$). The correlation between VO_{2max} and the OUES change from the 50% to 100% calculations was also significant ($r = .33$, $P < .001$) as was the difference in maximal aerobic capacity between subjects who demonstrated a negative OUES change compared to

those who demonstrated no change or an increase (35.4 ± 10.8 vs. 41.5 ± 12.3 $\text{mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P < .001$).

Linear regression analysis results are listed in Table 3. Age, SBP, resting HR, total cholesterol and triglycerides were included in all 3 regression analyses, while $\text{VO}_{2\text{max}}$, OUES₁₀₀ and OUES₅₀ were each used 1 time. Both DBP and LDL were excluded from linear regression due to their significant correlations with SBP ($r = 0.71$, $P < .001$) and total cholesterol ($r = 0.89$, $P < .001$), respectively. Maximal aerobic capacity (model 1) was retained in the linear regression while both expressions of the OUES were removed. Resting HR was removed from the regression analysis including $\text{VO}_{2\text{max}}$ but was retained in both models including OUES calculations. Total cholesterol and triglycerides were not retained in any of the regression analyses. Furthermore, the regression equation including $\text{VO}_{2\text{max}}$ produced the highest and lowest R^2 and standard error of estimate values, respectively.

DISCUSSION

The results of the present study indicate both $\text{VO}_{2\text{max}}$ and submaximal/maximal OUES calculations are significantly correlated with AWW in apparently healthy individuals. However, while the OUES has been proposed as a surrogate for $\text{VO}_{2\text{max}}$ in previous studies, and demonstrated a strong correlation in this study, the relationship between large artery stiffness and the classic measure of aerobic capacity ($\text{VO}_{2\text{max}}$) was more robust. Moreover, only $\text{VO}_{2\text{max}}$ was retained in a multivariate linear regression analysis developed to predict AWW. Several previous investigations have shown the OUES to have potential value in reflecting cardiopulmonary health and predicting adverse events.^{15,16} The fact that the OUES is generally linear, allowing for a meaningful calculation from a submaximal exercise test, and is independent of subject effort are 2 key advantages this new CPX variable potentially holds over $\text{VO}_{2\text{max}}$. Our results, however, indicate the OUES cannot replace $\text{VO}_{2\text{max}}$ in the estimation of aortic stiffness.

While there was no difference in OUES₅₀ and OUES₁₀₀ by paired *t*-test, subjects with a subtle decline in this CPX variable from submaximal to maximal exercise did demonstrate a significantly higher AWW and lower $\text{VO}_{2\text{max}}$ compared to subjects demonstrating no change or an increase. The correlation between OUES₁₀₀ and both AWW and $\text{VO}_{2\text{max}}$ was also higher compared to OUES₅₀. It has previously been suggested that the OUES, calculated from submaximal and maximal exercise data are interchangeable.²⁴ The results of the present study indicate that determination of the OUES using all of the exercise data during a symptom-limited test provides better resolution with respect to variation in large artery stiffness and aerobic capacity, supporting the continued use of maximal assessments. A similar trend has been found for the minute ventilation/carbon dioxide production slope in patients with heart failure.²⁵ In this investigation, the minute ventilation/carbon dioxide production slope using all exercise data was prognostically superior to submaximal calculations. Future investigations should determine if this trend is consistent for other markers of cardiovascular function.

Modification of the Fick equation ($\text{VO}_{2\text{max}} = Q_{\text{max}} * a\text{-vO}_2 \text{ diff}_{\text{max}}$; where Q_{max} =cardiac output at maximal exercise and $a\text{-vO}_2 \text{ diff}_{\text{max}}$ = the difference in oxygen concentration between arterial and venous blood at maximal exercise) illustrates the factors influencing aerobic capacity.¹¹ Of the central (cardiac output) and peripheral (oxygen extraction in skeletal muscle) component of this equation, it is the former that is the primary determinant of $\text{VO}_{2\text{max}}$. The assessment of $\text{VO}_{2\text{max}}$ therefore provides a good reflection of cardiac function, assuming the subject has put forth a maximal effort. The OUES purportedly reflects the integrated function of the pulmonary, cardiac and skeletal muscle systems. To our knowledge, no investigation has assessed how the health of each of these physiologic systems independently contributes to variation in the OUES. Previous research has found subjects with mitochondrial myopathy

present with an abnormally elevated relationship between minute ventilation and VO_2 .²⁶ It therefore appears that the ability of skeletal muscle to produce aerobic energy during exercise significantly impacts the relationship between ventilation and oxygen uptake during exercise, which is reflected by the OUES. Perhaps our finding of a stronger relationship between aortic stiffness and $\text{VO}_{2\text{max}}$ is a function of this CPX variable ability to better reflect central function as compared to the OUES. Along this hypothesis, measures assessing peripheral physiologic function, such as flow mediated dilation and mitochondrial capacity, may demonstrate a better correlation with the OUES compared to $\text{VO}_{2\text{max}}$. We recognize the proposed hypothesis is speculative at this point, based on an understanding of a link between the CPX response and physiologic function. Future research should therefore be directed toward determining the relationship between a host of physiologic measures, reflecting both central and peripheral function, and variables obtained from CPX.

The subjects included in the present study were all deemed apparently healthy and, on average, presented with a high aerobic capacity as indicated by percent-predicted $\text{VO}_{2\text{max}}$ and OUES values both exceeding 100%. The ability to extrapolate these findings to other populations with lower fitness levels and/or a diagnosis of cardiac/pulmonary disease is therefore limited. This is an inherent limitation of this study, which should be addressed by future research. Moreover, subject effort, as mentioned previously, is of paramount importance to accurately determining aerobic capacity. A mean peak RER exceeding 1.10 in the present investigation indicates the group as a whole put forth an excellent effort during exercise.²⁷ The relationship between aortic stiffness and $\text{VO}_{2\text{max}}$ may not be as robust in exercise tests terminated prior to maximal exertion. Caution should therefore also be taken in extrapolating these findings to any subject or group where submaximal effort during exercise is suspected.

In conclusion, CPX continues to be a valuable tool in assessing cardiovascular, pulmonary and skeletal muscle health. Measurement of maximal aerobic capacity remains a primary focal point in CPX. Other measures, such as the OUES, have been proposed as surrogates for $\text{VO}_{2\text{max}}$ that equally represent physiologic health during a submaximal exercise test. Large artery stiffness has gained recognition as an important marker of cardiovascular health with prognostic implications. Previous investigations have demonstrated $\text{VO}_{2\text{max}}$ is significantly associated with larger artery stiffness, a finding confirmed in the present investigation. While maximal and submaximal expressions of the OUES were likewise significantly correlated with large artery stiffness, the strength of these relationships did not approach that found with $\text{VO}_{2\text{max}}$. Moreover, calculation of the OUES with all exercise data during a maximal exercise test may be preferable to submaximal expressions, although $\text{VO}_{2\text{max}}$ still appears to be the variable of choice in this instance. Therefore, with respect to estimating aortic stiffness in the apparently healthy population, the assessment of maximal aerobic capacity continues to play a valuable role.

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Figure 1. Scatter plots of relationship between aortic wave velocity and exercise variables

1a: Maximal oxygen uptake ($\text{VO}_{2\text{max}}$), $r = -.49$, $P < .001$

1b: Oxygen uptake efficiency slope using all exercise data (OUES_{100}), $r = -.34$, $P < .001$

1c: Oxygen uptake efficiency slope using first half of exercise data (OUES_{50}), $r = -.25$, $P < .001$

Abbreviations, AWV, aortic wave velocity

TABLE 1
KEY RESTING AND EXERCISE MEASUREMENTS

Variable	Mean	Standard Deviation
Baseline Data		
Age (yrs)	47.6	±15.6
BMI (kg/m ²)	25.0	±4.5
Resting heart rate (bpm)	65.2	±11.6
Resting systolic pressure (mmHg)	123.6	±14.9
Resting diastolic pressure (mmHg)	73.5	±8.4
10-year Framingham Risk (%)	5.6	±6.8
Lipid Analysis		
Total cholesterol (mg/dL)	190.7	±34.5
LDL (mg/dL)	113.9	±29.6
HDL (mg/dL)	59.9	±17.2
Triglycerides (mg/dL)	110.7	±81.5
Cardiopulmonary Exercise Test		
VO ₂ max (ml•kg ⁻¹ •min ⁻¹)	38.7	±12.0
%-Predicted VO ₂ max	127.0	±27.4
Maximal heart rate (bpm)	173.3	±18.0
Age-predicted maximal heart rate (%)	100.7	±.08
OUES ₅₀	3.05	±.95
%-Predicted OUES ₅₀	128.7	±31.7
OUES ₁₀₀	3.06	±.97
%-Predicted OUES ₁₀₀ (%)	128.7	±29.4
Difference between OUES ₅₀ and OUES ₁₀₀	.02	±.43
Peak respiratory exchange ratio	1.16	±.07
Arterial Stiffness		
Aortic wave velocity (meters/second)	6.3	±1.9

Abbreviations: BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; VO₂max, maximal aerobic capacity; OUES, oxygen uptake efficiency slope

TABLE 2
PEARSON PRODUCT MOMENT CORRELATION RESULTS FOR AORTIC
WAVE VELOCITY

Variable	R-value	P-value
Baseline Data		
Age (yrs)	.58	<.001*
BMI (kg/m ²)	.06	.32
Resting heart rate (bpm)	.13	.03*
Resting systolic pressure (mmHg)	.46	<.001*
Resting diastolic pressure (mmHg)	.32	<.001*
Lipid Analysis		
Total cholesterol (mg/dL)	.22	<.001*
LDL (mg/dL)	.15	.01*
HDL (mg/dL)	.10	.10
Triglycerides (mg/dL)	.14	.03*
Cardiopulmonary Exercise Test		
VO _{2max} (ml•kg ⁻¹ •min ⁻¹)	-.49	<.001
OUES ₅₀	-.25	<.001
OUES ₁₀₀	-.34	<.001
Difference between OUES ₅₀ and OUES ₁₀₀	-.22	<.001

Abbreviations: BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; VO_{2max}, maximal aerobic capacity; OUES, oxygen uptake efficiency slope

TABLE 3
LINEAR REGRESSION ANALYSIS RESULTS FOR THE DETERMINATION
OF AWV*

Variable Entered	R-value	R ²	Standard Error of the Estimate
Linear Regression A (VO_{2max})			
Age	.58	.34	1.53
VO _{2max}	.64	.42	1.44
SBP	.67	.45	1.40
Equation: AWV (m/sec) = 2.55 + 0.44(Age) - 0.43(VO _{2max} in ml•kg ⁻¹ •min ⁻¹) + 0.27(SBP in mmHg)			
Linear Regression B (OUES₁₀₀)			
Age	.58	.34	1.53
SBP	.62	.39	1.48
Resting HR	.65	.42	1.44
Equation: AWV (m/sec) = -2.23 + 0.06(Age) + 0.03(SBP in mmHg) + 0.03(Resting HR in beats per min) Note: OUES ₁₀₀ removed from regression (p=0.06)			
Linear Regression C (OUES₅₀)			
Age	.58	.34	1.53
SBP	.62	.39	1.48
Resting HR	.65	.42	1.44
Equation: AWV (m/sec) = -2.23 + .06(Age) + .03(SBP in mmHg) + .03(Resting HR in beats per min) Note: OUES ₅₀ removed from regression (P=.55)			

* The cardiopulmonary exercise testing variable used in regressions A, B and C were VO_{2max}, OUES₁₀₀ and OUES₅₀, respectively. Abbreviations: AWV, aortic wave velocity; VO_{2max}, maximal aerobic capacity; SBP, systolic blood pressure; HR, heart rate; OUES, oxygen uptake efficiency slope