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Oxygen Uptake Efficiency Slope: A New Index of Cardiorespiratory Functional Reserve Derived From the Relation Between Oxygen Uptake and Minute Ventilation During Incremental Exercise

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Objectives. **We investigated the usefulness of a new variable, oxygen uptake efficiency slope (OUES), as a submaximal measure of cardiorespiratory functional reserve. The OUES is derived from the relation between oxygen uptake ($\dot{V}O_2$ [ml/min]) and minute ventilation ($\dot{V}E$ [liters/min]) during incremental exercise and is determined by $\dot{V}O_2 = a \log \dot{V}E + b$, where a = OUES, which shows the effectiveness of $\dot{V}O_2$.**

Background. **Maximal oxygen uptake ($\dot{V}O_2max$) is effort dependent. There is no standard submaximal measurement of cardiorespiratory reserve that provides generally acceptable results.**

Methods. **Exercise tests, following a standard Bruce protocol, were performed on a treadmill by 108 patients with heart disease and 36 normal volunteers. Expired gas was continuously analyzed. The OUES was calculated from data of the first 75%, 90% and 100% of exercise duration. We also determined the following submaximal variables: the ventilatory anaerobic threshold (VAT), the slope of the regression line of the minute ventilation–carbon dioxide production relation ($\dot{V}E$-$\dot{V}CO_2$ slope) and the extrapolated maximal oxygen consumption (EMOC). We analyzed the relation of OUES and other submaximal variables against $\dot{V}O_2max$ and examined the effects of submaximal exercise on OUES.**

Results. **The correlation coefficient of the logarithmic curve-fitting model was 0.978 ± 0.016 (mean ± SD). The OUES and $\dot{V}O_2max$ had a significant correlation (r = 0.941, p < 0.0001). The correlation between $\dot{V}O_2max$ and OUES was stronger than that between $\dot{V}O_2max$ and VAT, the $\dot{V}E$-$\dot{V}CO_2$ slope or EMOC. The OUES values for 100% and 90% of exercise were not different from each other (at an alpha value of 0.05 and treatment effect of 170 the power of the test [1 − beta] was 0.90); OUES for 75% of exercise was slightly lower (3.5%).**

Conclusions. **Our results suggest that OUES may provide an objective, effort-independent estimation of cardiorespiratory functional reserve that is related both to pulmonary dead space and to metabolic acidosis.**

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Maximal oxygen uptake ($\dot{V}O_2max$), defined as the point at which oxygen uptake ($\dot{V}O_2$) reaches a plateau despite further increases in work rate, has been proposed as an objective measure of cardiorespiratory function (1). However, a true plateau in $\dot{V}O_2$ during incremental exercise is rare (2,3). Therefore, $\dot{V}O_2max$ is effort dependent, and its measurement may be influenced by the patient's motivation and by the observer.

Several submaximal indexes, including ventilatory anaerobic threshold (VAT), the slope of the regression line showing the relationship between minute ventilation ($\dot{V}E$) and carbon dioxide production ($\dot{V}CO_2$) ($\dot{V}E$–$\dot{V}CO_2$ slope), and extrapolated maximal oxygen consumption (EMOC), have been used to evaluate cardiopulmonary functional reserve without requiring subjects to perform maximal exercise. Ventilatory anaerobic threshold has been found to be useful for assessing the degree of dysfunction in patients with heart disease (4–7) and for evaluating the effects of training (7). However, studies have suggested (8–10) that the ability to reproduce VAT results can be affected by the exercise protocol, the method of detection, and the evaluator. The $\dot{V}E$–$\dot{V}CO_2$ slope has been used to evaluate the ventilatory response of patients with cardiac disease. Although the $\dot{V}E$–$\dot{V}CO_2$ slope has been found to be inversely correlated with $\dot{V}O_2max$ (11–13), the correlation is weak (11,13). Buller et al. (14) have advocated EMOC as a simple and objective method to extrapolate the "true" $\dot{V}O_2max$ using a quadratic function, but the validity of EMOC has yet to be confirmed by other investigators. Thus, the clinical usefulness of these submaximal variables as a substitute for $\dot{V}O_2max$ is limited.

In an attempt to develop an objective and independent measure of cardiorespiratory functional reserve, we introduce a single-segment logarithmic curve-fitting model to describe the ventilatory response to exercise. We hypothesize that one of the constants of the equation, which we define as the "oxygen uptake efficiency slope" (OUES), may be a useful submaximal index of cardiorespiratory functional reserve.

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Abbreviations and Acronyms

EMOC = extrapolated maximal oxygen consumption
OUES = oxygen uptake efficiency slope
VAT = ventilatory anaerobic threshold
$\dot{V}CO_2$ = carbon dioxide production
$\dot{V}E$ = minute ventilation
$\dot{V}O_2$ = oxygen uptake
$\dot{V}O_2$max = maximal oxygen uptake

In the present study, we describe the determination of OUES, analyze the relation of OUES and other submaximal variables versus $\dot{V}O_2$max and examine the effects of exercise intensity on OUES.

Methods

Subjects. A total of 144 Japanese subjects (83 male, 61 female; mean [±SD] age 11.7 ± 4.4 years, range 5.8 to 29.0; 108 with heart disease, 36 normal subjects) were included in the study. The spectrum of heart disease is shown in Table 1. Five postoperative patients with congenital heart disease had a pacemaker implanted, and five had replacement of an atrioventricular valve. The normal subjects (20 male, 16 female), determined by medical history and a physical examination, were significantly older than the patients (12.9 ± 5.2 vs. 11.2 ± 4.0 years, $p < 0.05$) and had a higher body weight (42.2 ± 15.5 vs. 35.0 ± 14.0 kg, $p < 0.05$). They were recruited from the medical staff of our hospital and their children. The subjects (or their parents, if the subject was <20 years old) gave informed consent for participation in the study.

Table 1. Diagnosis of Study Subjects

Diagnosis	No. of Subjects (male/female)
CHD (post-ICR)	
TOF	21 (15/6)
VSD	19 (10/9)
d-TGA	11 (7/4)
ASD	8 (6/2)
CAVC	4 (1/3)
PA-VSD	4 (1/3)
PAVC	3 (3/0)
Others	15 (6/9)
Total	84 (48/36)
CHD (without ICR)	5 (4/1)
Acquired heart disease	6 (5/1)
Arrhythmias	
CAVB	4 (1/3)
SSS	4 (2/2)
Advanced AVB	2 (0/2)
Other arrhythmias	3 (3/0)
Total	13 (6/7)
Normal	36 (20/16)
Total	144 (83/61)

ASD = atrial septal defect; AVB = atrioventricular block; CAVB = complete atrioventricular block; CAVC = complete atrioventricular canal defect; CHD = congenital heart disease; d-TGA = complete transposition of the great arteries; ICR = intracardiac repair; PAVC = partial atrioventricular canal defect; PA-VSD = pulmonary atresia with ventricular septal defect; SSS = sick sinus syndrome; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

Exercise protocol. Exercise tests were performed on a treadmill (MAT-2500, Fukuda Denshi Co. Ltd., Tokyo, Japan) after a symptom-limited standard Bruce protocol. The electrocardiogram and heart rate were monitored throughout the test with the Stress Test System (ML-5000, Fukuda Denshi). Cuff blood pressure was also measured every minute with an automatic indirect manometer (STBP-680F, Collin Denshi, Nagoya, Japan).

Analysis of expired gas. The $\dot{V}CO_2$ (ml/min [standard temperature and pressure, dry]), $\dot{V}O_2$ (ml/min [standard temperature and pressure, dry]), $\dot{V}E$ (liters/min [body temperature, pressure and saturation]), tidal volume, respiratory rate and mixed expiratory carbon dioxide concentration were continuously measured on a breath by breath basis with a Minato AE-280 Metabolic Measurement Cart (Minato Medical Science, Osaka, Japan) equipped with an oxygen and carbon dioxide analyzer. Respiratory flow was measured by the thermal dissipation technique. To reduce breath by breath "noise," data were processed with a five-breath moving average. The $\dot{V}O_2$max was calculated by averaging values obtained during the final 30 s of exercise.

Anaerobic threshold was defined as the level of $\dot{V}O_2$ at which at least one of the following occurred (15,16): 1) an increase in $\dot{V}E/\dot{V}O_2$ without a simultaneous increase in $\dot{V}E/\dot{V}CO_2$; 2) an increase in end-tidal oxygen partial pressure without a simultaneous decrease in end-tidal carbon dioxide partial pressure; and 3) the disappearance of the linear relation between $\dot{V}CO_2$ and $\dot{V}O_2$ (the V slope method).

The $\dot{V}E$–$\dot{V}CO_2$ slope was determined by linear regression analysis of the relation between $\dot{V}E$ and $\dot{V}CO_2$ during exercise, with data obtained before the occurrence of respiratory compensation (11,12). The EMOC was derived from the maximal value obtained from a fitting curve that plotted $\dot{V}O_2$ as a quadratic function of $\dot{V}CO_2$ (17).

The following equation was used to determine the relation between $\dot{V}O_2$ and $\dot{V}E$ (Fig. 1, top):

$$\dot{V}O_2 = a \log \dot{V}E + b;$$

the differential of this equation by $\dot{V}E$ yields

$$d\dot{V}O_2/d\dot{V}E = a(1/\log_e 10)/\dot{V}E,$$

where a = the constant that represents the rate of increase in $\dot{V}O_2$ in response to $\dot{V}E$. Semilog transformation of the x-axis showed a linear relation between $\dot{V}O_2$ and log $\dot{V}E$ (Fig. 1, bottom). With this equation, a steeper slope indicates improved oxygen uptake during exercise. Therefore, we define the constant "a" as the OUES. We hypothesize that OUES may be an index of cardiorespiratory reserve. Theoretically, measurement of this index would not require maximal effort by the patient, but to ensure accurate values we calculated the

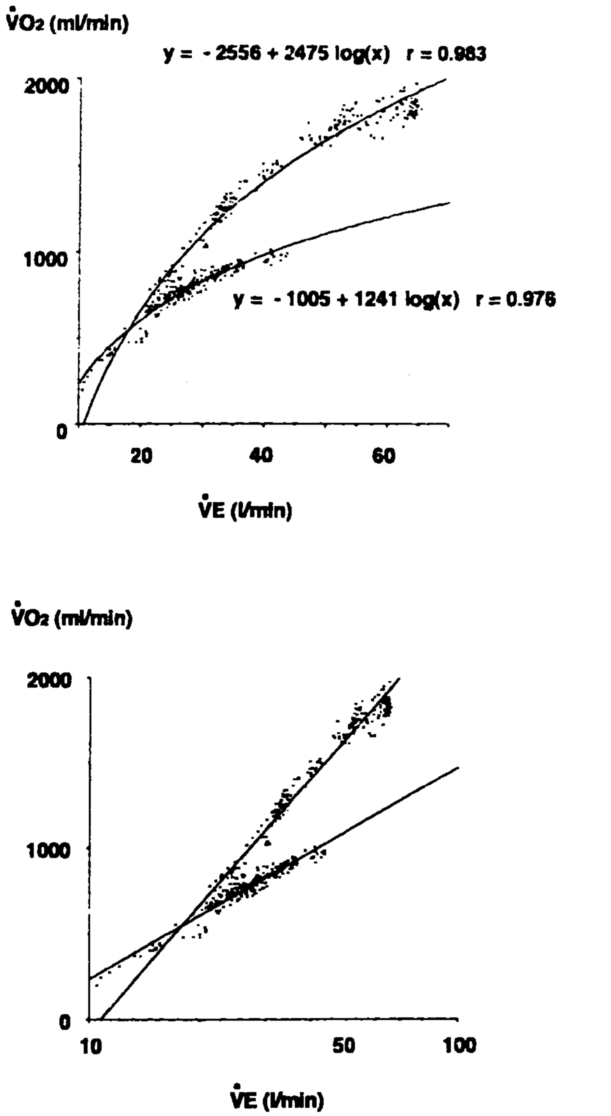

Figure 1. Relation between oxygen uptake ($\dot{V}O_2$) and minute ventilation ($\dot{V}E$) during incremental exercise in two representative subjects (**top**, 13-year old girl with sick sinus syndrome; **bottom**, 15-year old girl with truncus arteriosus who underwent Rastelli operation). For each set of data, $\dot{V}o_2$ is expressed as the logarithmic function of $\dot{V}$E. The data are presented as linear (**top**) and semilog plots of the x-axis (**bottom**).

data using the values obtained from the first 75% and 90%, as well as 100%, of the exercise duration.

We analyzed the relation between $\dot{V}o_2$max and submaximal variables of cardiorespiratory functional reserve. We also analyzed the deviation of the estimated $\dot{V}o_2$max from the measured $\dot{V}o_2$max. The estimated $\dot{V}o_2$max was determined with regression equations between $\dot{V}o_2$max and VAT, between $\dot{V}o_2$max and the $\dot{V}$E–$\dot{V}co_2$ slope and between $\dot{V}o_2$max and OUES. The EMOC values were defined as the estimated $\dot{V}o_2$max. The relation between $\dot{V}o_2$max and these variables were analyzed with and without standardizing the data by body weight because $\dot{V}o_2$max, VAT, EMOC and OUES are considered to be functions of body weight, whereas the $\dot{V}$E–$\dot{V}co_2$ slope is not.

Statistical analysis. Results are expressed as mean value ± SD. Differences in mean values between patients and normal subjects were tested by unpaired *t* test. The relation between $\dot{V}o_2$max and submaximal variables, and the correlations between OUES values determined at different exercise intensities were assessed by linear regression analysis. Differences in OUES at different levels of exercise intensity were assessed by analysis of variance. If a significant difference was detected by the F test, mean values were analyzed by the Scheffés F test. Differences in EMOC at different levels of exercise intensity were tested by the Friedman test because the distribution of EMOC values were nonnormal. Differences in the mean values of correlation coefficients at different levels of exercise intensity were analyzed by analysis of variance after application of the Fisher Z transformation. Comparisons of correlation coefficients between $\dot{V}o_2$max and submaximal variables were tested using the table of the normal distribution after application of the Z transformation. Coincidence of regression slopes and regression intercepts were tested using the table of t distribution. A p value <0.05 was considered statistically significant.

Results

Exercise was usually terminated at the development of fatigue. Ventilatory anaerobic threshold was not determined in 11 (8%) of 144 subjects; EMOC was not determined in 17 patients (12%) because of the positive values of the constant for the χ^2 term of the regression equation; and the $\dot{V}$E–$\dot{V}co_2$ slope and OUES were determined in all patients. The mean expired gas analysis data were 1,630 ± 680 ml/min for $\dot{V}o_2$max; 910 ± 340 ml/min for VAT; 31.1 ± 5.4 for $\dot{V}$E–$\dot{V}co_2$ slope; 4,100 ± 800 ml/min for EMOC; and 1730 ± 620 for OUES.

The exercise intensities at 90% and 75% of exercise duration corresponded to 88.6 ± 7.2% and 79.1 ± 7.9% of $\dot{V}o_2$max, respectively. The results of the Friedman test indicated that the values of EMOC were significantly reduced as exercise intensity decreased ($p < 0.001$). Values for $\dot{V}o_2$ and log $\dot{V}$E had a significant correlation at 100%, 90% and 75% of exercise time (Table 2), although the correlation coefficients decreased with percent of exercise duration; OUES for 90% of exercise time was not different from OUES for 100% of exercise time (Table 2). At an alpha value of 0.05 and treatment effect of 170 (~10% of the mean values), the power of the test (1 − beta) was 0.90. A slightly, but significantly, lower OUES was obtained for the first 75% of exercise ($p < 0.01$) (Table 2). Values for OUES determined from 100% exercise duration were significantly correlated with those for 90% and 75% of exercise (Fig. 2).

Values for $\dot{V}o_2$max and OUES were significantly correlated, and the regression lines between $\dot{V}o_2$max and OUES obtained from the data for the different exercise levels were almost identical ($p > 0.05$) (Fig. 3). The $\dot{V}o_2$max estimated from the relation between $\dot{V}o_2$max and OUES (100% of exercise duration) was 101.5 ± 13.8% (range 71.6 to 146.8%) of the observed values, including a 113.4 ± 14.3% value for the 11 subjects whose VAT was undetectable. Correlation coefficients for the relation between $\dot{V}o_2$max and VAT, $\dot{V}$E–$\dot{V}co_2$ slope and EMOC were significantly lower than those for the

Table 2. Effects of Submaximal Exercise Data on Oxygen Uptake Efficiency Slope and on Correlation Coefficient of Logarithmic Curve-Fitting Model Between Oxygen Uptake and Minute Ventilation During Incremental Exercise

Correlation Coefficient (mean ± SD)			OUES (90%)/OUES (100%) (mean ± SD)	OUES (75%)/OUES (100%) (mean ± SD)
For 100% of Exercise	For 90% of Exercise	For 75% of Exercise		
0.978 ± 0.016	0.975 ± 0.017*	0.967 ± 0.023*	0.988 ± 0.039	0.965 ± 0.078†

*Significantly lower ($p < 0.01$) than correlation coefficient for 100% of exercise. †Significantly lower ($p < 0.01$) than oxygen uptake efficiency slope (OUES) for 100% of exercise. OUES (100%), OUES (90%) and OUES (75%) = OUES derived from all exercise data, from first 90% of exercise and from first 75% of exercise, respectively.

relation between $\dot{V}o_2$max and OUES (Table 3). The deviation of the estimated $\dot{V}o_2$max from the measured $\dot{V}o_2$max was smallest for the estimated $\dot{V}o_2$max predicted by OUES (Table 3).

Discussion

Drawbacks of existing variables and superiority of OUES. An index of the integrated response of all the systems involved in exercise, $\dot{V}o_2$max is considered the most important measurement obtained from an exercise test. A test is considered maximal when there is no further increase in oxygen uptake despite further increases in the work load. However, recent studies (2,3) have suggested that "the plateau concept" has limited application during standard exercise testing. Also, maximal exercise can be dangerous because most patients do not regularly engage in strenuous exercise. Thus, $\dot{V}o_2$max may not be the most practical clinical index of cardiorespiratory functional reserve.

A number of indexes that do not require maximal exercise have been used as a substitute for $\dot{V}o_2$max. Widely used as a submaximal estimate of aerobic power, ventilatory anaerobic threshold has been shown to be correlated with $\dot{V}o_2$max (18). However, a major drawback of VAT is that it is not identifiable in all subjects, as was the case with 11 of our subjects. In addition, VAT is a subjective measurement and is thus subject to substantial interobserver and intraobserver variability (8,10). Although previous studies have shown (11–13) that the $\dot{V}$E–$\dot{V}co_2$ slope is inversely correlated with $\dot{V}o_2$max, the correlation was not strong in the present study, and estimates of $\dot{V}o_2$max based on $\dot{V}$E–$\dot{V}co_2$ showed a significant deviation from the measured $\dot{V}o_2$max. The EMOC often largely exceeded $\dot{V}o_2$max in the present study, which is inconsistent with the results of a previous study (14) in which EMOC was similar to and significantly correlated with $\dot{V}o_2$max. Moreover, our results showed that a weaker exercise intensity tends to result in a reduced EMOC value. These findings indicate that EMOC

Figure 2. Effects of various levels of exercise intensity OUES: OUES (100%), OUES (90%) and OUES (75%) are the values of OUES determined from the data of the entire exercise protocol and the first 90% and 75% of exercise, respectively. **Solid lines** = regression lines; **dashed lines** = lines of identity.

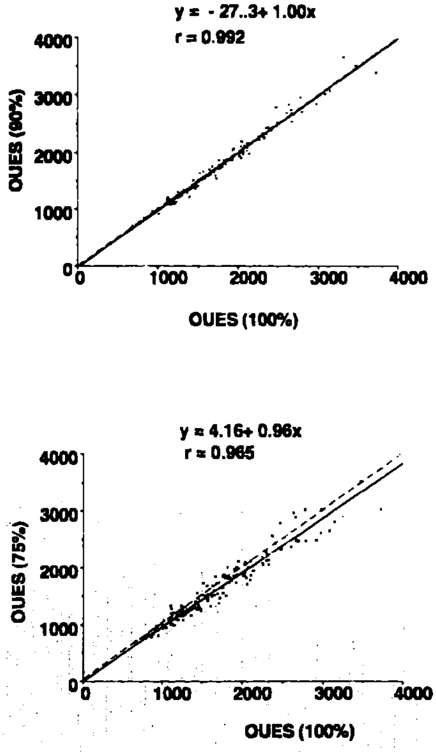

Figure 3. Relation between $\dot{V}o_2$max and OUES obtained from the data of the three different levels of exercise intensity. These regression lines were not statistically different from one another ($p > 0.05$). OUES 100%, 90% and 75% as in Figure 2.

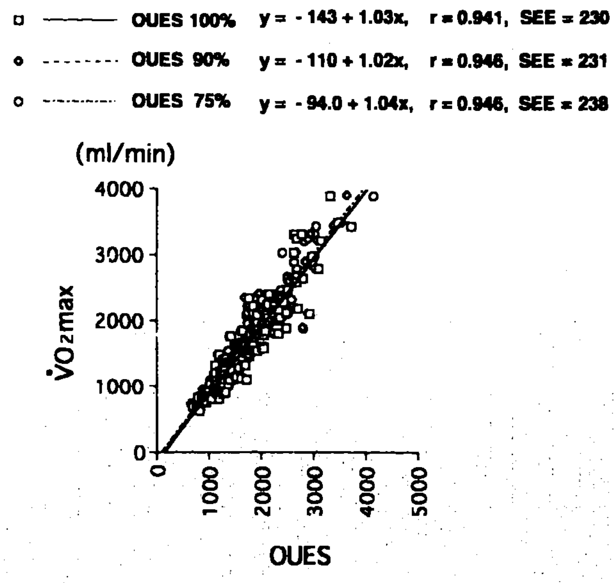

Table 3. Correlation Coefficients of Relation Between Oxygen Uptake at Maximal Exercise and Submaximal Variables of Cardiorespiratory Functional Reserve and Estimated Oxygen Uptake at Maximal Exercise Derived From These Variables*

	Data Not Standardized by Body Weight			Data Standardized by Body Weight		
Variable	Correlation Coeff With $\dot{V}O_2$max	p Value	Est $\dot{V}O_2$max/Meas $\dot{V}O_2$max (% [mean ± SD])	Correlation Coeff With $\dot{V}O_2$max	p Value	Est $\dot{V}O_2$max/Meas $\dot{V}O_2$max (% [mean ± SD])
VAT	0.861†	< 0.01	104 ± 19	0.639†	< 0.01	107 ± 15
$\dot{V}E$–$\dot{V}CO_2$ slope				0.152†		104 ± 20
EMOC	0.227†	< 0.01	231 ± 396	0.321†	< 0.01	231 ± 396
OUES	0.941	< 0.01	101 ± 14	0.817	< 0.01	101 ± 11

*Estimates of oxygen uptake at maximal exercise ($\dot{V}O_2$max) based on oxygen uptake at ventilatory anaerobic threshold (VAT), slope of linear relation between minute ventilation and carbon dioxide production ($\dot{V}E$–$\dot{V}CO_2$ slope) and oxygen uptake efficiency slope (OUES) were calculated from the regression equations of the relation between $\dot{V}O_2$max and these variables; extrapolated maximal oxygen uptake (EMOC) values were used as estimated (Est) $\dot{V}O_2$max values. †Significantly smaller ($p < 0.01$) than correlation coefficient (Coeff) for $\dot{V}O_2$max and OUES. Meas = measured.

is not a reliable submaximal variable of cardiorespiratory functional reserve.

Physiologic basis of OUES. In the present study, OUES was significantly correlated with $\dot{V}O_2$max; the correlation coefficient for OUES was higher than that for VAT, $\dot{V}E$–$\dot{V}CO_2$ slope and EMOC. The correlation between $\dot{V}O_2$max and OUES was not greatly affected by whether the exercise test was maximal or submaximal.

Oxygen uptake efficiency slope, the slope of the logarithmic regression curve expressing the relation between $\dot{V}O_2$ and $\dot{V}E$ represents the rate of increase in $\dot{V}O_2$ in response to a given $\dot{V}E$. Thus, OUES is a variable that indicates how effectively oxygen is extracted and taken into the body.

At present, three factors are known to affect the $\dot{V}E$–$\dot{V}O_2$ relation according to the modified alveolar gas equation: 1) the arterial carbon dioxide set point ($PaCO_2$); 2) metabolic carbon dioxide production ($\dot{V}CO_2$); and 3) the ratio of pulmonary dead space to tidal volume (Vd/Vt). Sullivan et al. (7) reported that patients with chronic heart failure and normal subjects did not differ in arterial carbon dioxide set point during exercise. In contrast, a number of investigators (5,19) have demonstrated that patients with chronic heart failure show earlier metabolic acidosis and thus have higher mixed venous lactate levels for the same absolute amount of work, which induces excessive carbon dioxide production. The excessive carbon dioxide production stimulates ventilation and leads to lower values of OUES as well as earlier VAT and respiratory compensation in patients with chronic heart failure. Hence, it is obvious that this "VAT concept" plays an important role in determining the OUES value. However, physiologic pulmonary dead space, as the alveolar gas equation indicates, is another major factor that affects the $\dot{V}E$–$\dot{V}O_2$ relation. Previous studies (7,20) have indicated that exercise hyperpnea in the presence of chronic heart failure is attributed to increased physiologic dead space, most likely due to attenuated pulmonary perfusion and partly to abnormal breathing pattern.

In patients with chronic heart failure, perfusion to both the working muscles and the lungs is reduced. Ventilatory anaerobic threshold, the point at which lactic acidosis begins, primarily represents the status of blood distribution to the working muscles rather than perfusion to the lungs. The $\dot{V}E$–$\dot{V}CO_2$ slope, which is related to physiologic pulmonary dead space, is affected mainly by perfusion to the lungs. The OUES, affected both by metabolic acidosis and by physiologic pulmonary dead space, is a variable that indicates the status of both systemic and pulmonary perfusion, which seems to account for the superiority of OUES concerning correlation coefficients of $\dot{V}O_2$max. Therefore, OUES is physiologically based on 1) the development of metabolic acidosis, which is controlled by the distribution of blood to the skeletal muscles; and 2) the physiologic dead space, which is affected by the perfusion to the lungs.

Summary. The OUES can be determined without requiring maximal effort on the part of subjects. In the present study, OUES values determined from the first 90% and from 100% of the exercise data were identical; OUES determined from the first 75% of exercise was an average of 3.5% lower. These findings indicate that OUES is useful for estimating cardiorespiratory reserve from submaximal exercise.

Our results suggest that OUES is significantly correlated with $\dot{V}O_2$max; OUES did not require the performance of maximal exercise, and thus was a completely objective measurement. Another advantage of OUES is that it can be determined in all patients. Thus, OUES may be a clinically useful estimate of cardiorespiratory functional reserve in patients with heart failure in whom maximal effort exercise may be harmful.

The logarithmic equation $y = a \log x + b$ provided an accurate mathematical model for analysis of respiratory gas exchange during incremental exercise. The OUES derived from this model offers a new, objective, effort-independent method for estimating cardiorespiratory functional reserve.

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