Nagoya J. Med. Sci. **59.** 55 ~ 62, 1996

OXYGEN INTAKE EFFICIENCY SLOPE: A NEW INDEX OF CARDIORESPIRATORY FUNCTIONAL RESERVE DERIVED FROM THE RELATIONSHIP BETWEEN OXYGEN CONSUMPTION AND MINUTE VENTILATION DURING INCREMENTAL EXERCISE

REIZO BABA, MD*, MASAMI NAGASHIMA, MD*, MASAHIKO GOTO, MD*, YOSHIKO NAGANO, MD*, MITSUHIRO YOKOTA, MD, PhD, FACC†, NOBUO TAUCHI, MD‡, KENJI NISHIBATA, MD‡, Nagoya, Japan

**Department of Pediatrics and †Department of Clinical Laboratory Medicine, Nagoya University School of Medicine, Nagoya, Japan*
‡Department of Pediatric Cardiology, Ogaki Municipal Hospital, Gifu, Japan

ABSTRACT

We investigated the usefulness of the oxygen intake efficiency slope (OIES) as a submaximal measure of cardiorespiratory functional reserve. OIES was derived from the relationship between oxygen consumption ($\dot{V}O_2$; ml/min) and minute ventilation ($\dot{V}E$; l/min) during incremental exercise, which was determined by the following equation: $\dot{V}O_2 = a \log\dot{V}E + b$, where "a" represents OIES, which shows the effectiveness of ventilation. Maximal oxygen consumption ($\dot{V}O_2max$) is effort-dependent. There is no standard submaximal measurement of cardiorespiratory reserve that provides generally acceptable results. Exercise tests were performed by 17 normal volunteers on an ergometer using a symptom-limited Ramp protocol. Expired gas was continuously analyzed. OIES was calculated using the first 75%, 90% and 100% of exercise data. We also determined the following submaximal parameters: the ventilatory anaerobic threshold (VAT), the slope of the minute ventilation-carbon dioxide production relationship ($\dot{V}E$-$\dot{V}CO_2$ slope), and the extrapolated maximal oxygen consumption (EMOC). We analyzed the relationship between OIES, other submaximal parameters and $\dot{V}O_2max$, and examined the effects of submaximal exercise on OIES. The correlation coefficient of the logarithmic curve-fitting model was 0.991 ± 0.006. OIES and $\dot{V}O_2max$ were significantly correlated ($r = 0.966$, $p < 0.0001$). The correlation between OIES and $\dot{V}O_2max$ was stronger than the correlation between $\dot{V}O_2max$ and VAT, the $\dot{V}E$-$\dot{V}CO_2$ slope and EMOC. OIES values for 100% and 90% of exercise were identical; OIES for 75% of exercise was slightly lower (3%). Our results suggested that OIES may provide an objective, effort-independent estimation of cardiorespiratory functional reserve.

Key Words: Oxygen intake efficienty slope, Anaerobic threshold, Extrapolated maximal ocygen consumption, Exercise testing

INTRODUCTION

Maximal oxygen consumption ($\dot{V}O_2max$), defined as the point at which oxygen consumption ($\dot{V}O_2$) 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

Correspondence: Reizo Baba, MD., Department of Pediatrics, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan
TEL: 81-52-741-2111 FAX: 81-52-731-6137

may be influenced by the patient's motivation and by the observer.

Several submaximal indices, including the ventilatory anaerobic threshold (VAT), the slope of the minute ventilation ($\dot{V}E$)-carbon dioxide production ($\dot{V}CO_2$) relation ($\dot{V}E$-$\dot{V}CO_2$ slope), and the extrapolated maximal oxygen consumption (EMOC) have been used to evaluate cardiopulmonary functional reserve without requiring subjects to perform maximal exercise. VAT 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 that the ability to reproduce VAT results can be affected by the exercise protocol, the method of detection and the evaluator.[8–10] 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 $\dot{V}O_2$max,[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" $\dot{V}O_2$max using a quadratic function, but the validity of the parameter has yet to be confirmed by other investigators. Thus, the clinical usefulness of these submaximal parameters as substitutes for $\dot{V}O_2$max is limited.

In an attempt to develop an objective and independent measure of cardiorespiratory functional reserve, we have introduced 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 have defined as the "oxygen intake efficiency slope" or "OIES" may be a useful submaximal index of cardiorespiratory functional reserve.

In the present study, we describe the determination of OIES, analyze the relationship between OIES, other submaximal parameters and $\dot{V}O_2$max, and examine the effects of exercise intensity on OIES.

METHODS

Subjects

We recruited 17 Japanese subjects, 12 males and 5 females (mean age: 25 ± 13 years, range: 8–52 years) with a normal medical history and physical examination from the medical staff of our hospital and their children. The subjects (and their parents, if the subject was younger than 20 years of age) gave informed consent for participation in the study.

Exercise protocol

Exercise tests were performed in an upright position on an electromagnetically braked cycle ergometer (232C model 50, Combi Co., Ltd., Tokyo, Japan). After a 3-min rest on the ergometer, subjects began exercising with a 1-min warm-up at 30 watts, 60 rpm; the workload was increased in 1-watt steps every 5 seconds until the subjects could no longer move the pedals on the ergometer. An electrocardiogram and the heart rate were monitored throughout the test using the Stress Test System (ML-5000, Fukuda Denshi, Tokyo, Japan). Cuff blood pressure was also measured every minute with an automatic indirect manometer (STBP-680F, Collin Denshi, Nagoya, Japan).

Analysis of Expired Gas

$\dot{V}CO_2$ (ml/min, STPD), $\dot{V}O_2$ (ml/min, STPD), $\dot{V}E$ (l/min, BTPS), tidal volume, respiratory rate and the 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 was processed using a 5-breath moving average. The $\dot{V}O_2max$ was calculated by averaging values obtained during the final 30 seconds of exercise.

The anaerobic threshold was defined as the level of $\dot{V}O_2$ at which at least one of the following occurred:[15,16] (i) an increase in $\dot{V}E/\dot{V}O_2$ without a simultaneous increase in $\dot{V}E/\dot{V}CO_2$; (ii) an increase in end-tidal oxygen partial pressure without a simultaneous decrease in end-tidal carbon dioxide partial pressure and (iii) the disappearance of the linear relationship 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 a comparison between the slope of $\dot{V}E$ and $\dot{V}CO_2$ using linear regression analysis 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 relationship between $\dot{V}O_2$ and $\dot{V}E$ (Figure 1a):

$$\dot{V}O_2 = a \log\dot{V}E + b, \qquad \text{(Equation 1)}$$

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

$$d\dot{V}O_2 \,/\, d\dot{V}E = a\,(1 \,/\, \log e10) \,/\, \dot{V}E$$

where "a" is 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 $\log\dot{V}E$ (Figure 1b). With this equation, a steeper slope indicates an improved oxygen uptake during exercise. Therefore we defined the constant "a" as OIES. We hypothesize that OIES may be an index of cardiorespiratory reserve. Theoretically, measurement of this index would not reqire maximal effort by the patient, but inaccurate values may be obtained if only the data from the early phase of exercise is used. Thus, we also calculated the data using the values obtained from the first 90% and 75% of the exercise duration.

We analyzed the relationships between $\dot{V}O_2max$ and submaximal parameters of cardiorespiratory functional reserve. We also analyzed the deviation of the estimated $\dot{V}O_2max$ from the measured $\dot{V}O_2max$. The estimated $\dot{V}O_2max$ was determined using the regression equations between $\dot{V}O_2max$ and VAT, the $\dot{V}E$-$\dot{V}CO_2$ slope and OIES. For EMOC, EMOC values were

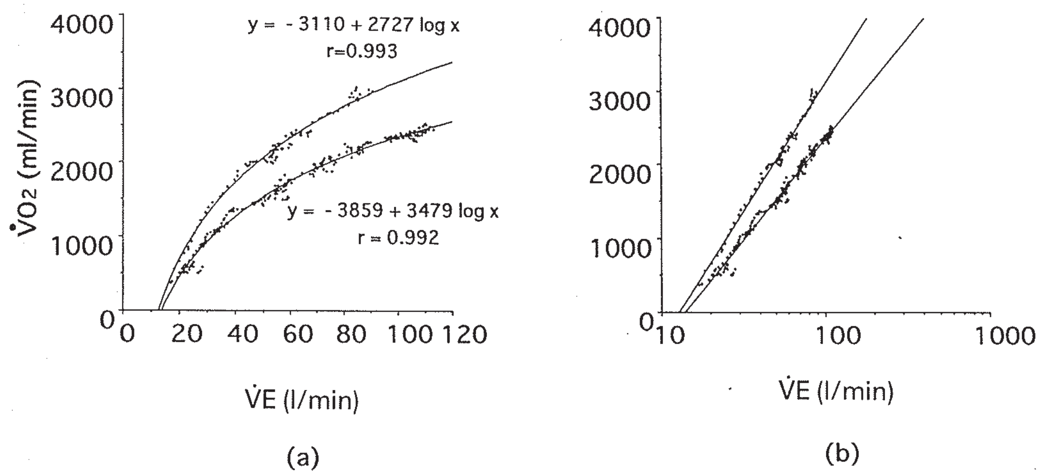

Fig 1: The relationship between $\dot{V}O_2$ and $\dot{V}E$ during incremental exercise in 2 representative subjects (a 13-year-old and a 29-year-old male). For each set of data, $\dot{V}O_2$ is expressed as the logarithmic function of $\dot{V}E$. The data are presented in 2 forms: (a) and (b) semilog plots of the x-axis.

defined as the estimated $\dot{V}O_2max$. Because $\dot{V}O_2max$, VAT, EMOC and OIES are considered to be a function of body weight, while the $\dot{V}E$-$\dot{V}CO_2$ slope is not, the relationships between $\dot{V}O_2max$ and these parameters were analyzed with and without standardizing the data by body weight.

Statistical analysis

Values are expressed as the mean ± SD. The relationships between $\dot{V}O_2max$ and submaximal parameters, and the correlations between OIES values determined at different exercise intensities were assessed by linear regression analysis. Differences in OIES at different levels of exercise intensity were assessed by analysis of variance (ANOVA). If a significant difference was detected by the F test, mean values were analyzed by Scheffe's F-test. Correlation coefficients were analyzed by ANOVA after application of Fischer's Z-transformation. A "p" value less than 0.05 was considered statistically significant.

RESULTS

Exercise was usually terminated at the onset of fatigue. VAT was determined in 16 (94%) of the 17 subjects. The mean expired gas analysis data was as follows: $\dot{V}O_2max$: 2342 ± 651 ml/min; VAT: 1328 ± 508 ml/min; $\dot{V}E$-$\dot{V}CO_2$ slope: 26.0 ± 3.7; EMOC: 3425 ± 1328 ml/min and OIES: 2691 ± 691.

$\dot{V}O_2$ and $\dot{V}E$ were significantly correlated at 100%, 90%, and 75% of exercise (Table 1), although the correlation coefficients decreased with a decrease in the percentage of exercise duration. OIES for 90% of exercise was identical to that for 100% of exercise (Table 1). A slightly, but significantly, lower OIES was obtained for the first 75% of exercise ($p < 0.05$) (Table 1). OIES determined from 100% exercise was significantly correlated with OIES values for 90% and 75% of exercise (Figure 2).

OIES and $\dot{V}O_2max$ were significantly correlated (Figure 3). $\dot{V}O_2max$ estimated from this relationship was 100 ± 7% (range: 84 to 112%) of the observed values, including a 101% value in one subject whose VAT was undetectable. $\dot{V}O_2max$ and OIES were also significantly correlated for 90% and 75% of exercise ($r = 0.965$ and 0.947, respectively). The correlation coefficients for the relationship between $\dot{V}O_2max$ and VAT, the $\dot{V}E$-$\dot{V}CO_2$ slope and EMOC were

Table 1. The effects of submaximal exercise data on OIES and on the correlation coefficient of the logarithmic curve fitting model between oxygen consumption and minute ventilation during incremental exercise.

r for 100% of exercise	r for 90% of exercise	r for 75% of exercise	OIES (90%) / OIES (100%)	OIES (75%) / OIES (100%)
0.991 ± 0.006	0.990±0.006	0.987 ± 0.007*	1.00 ± 0.03	0.97 ± 0.05†

*: significantly lower ($p < 0.05$) than the correlation coefficient for 100% of exercise; †: significantly lower ($p < 0.05$) than the OIES for 100% of exercise.

Abbreviations: OIES = oxygen intake efficiency slope; OIES (100%) = OIES derived from all exercise data; OIES (90%) = OIES derived from the first 90% of exercise data; OIES (75%) = OIES derived from the first 75% of exercise data; r = correlation coefficient of the logarithmic curve fitting model between oxygen consumption and minute ventilation during incremental exercise.

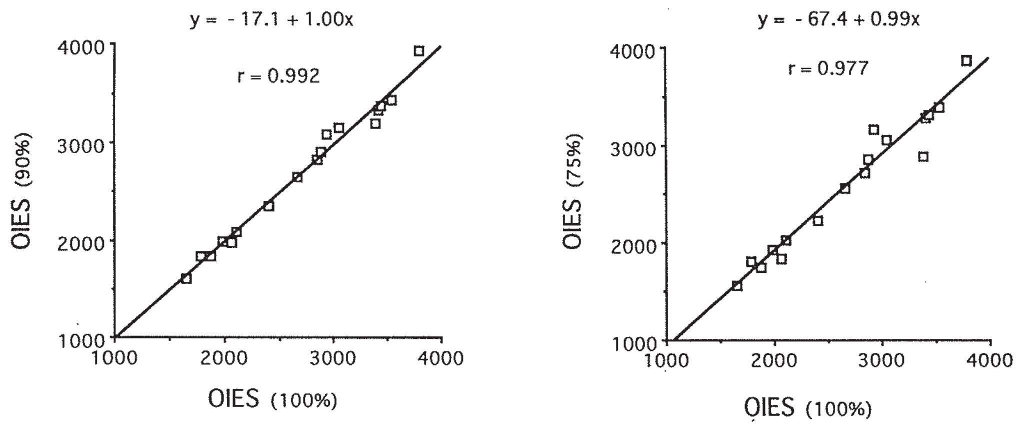

Fig 2: The effects of various levels of exercise intensity on OIES. OIES (100%), OIES (90%) and OIES (75%) are the values of OIES determined from the data of the entire exercise protocol, the first 90% of exercise and the first 75% of exercise, respectively.

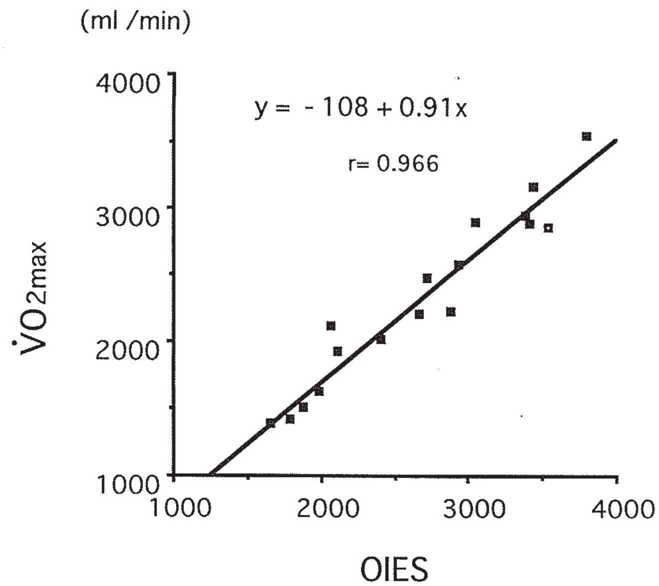

Fig 3: The relationship between $\dot{V}O_2$max and OIES.

lower than for the relationship between $\dot{V}O_2$max and OIES (Table 2). 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 OIES (Table 2).

Table 2. Correlation coefficients of the relationship between $\dot{V}O_2max$ and submaximal parameters of cardiorespiratory functional reserve and the estimated $\dot{V}O_2max$ derived from these parameters.

	Data not standardized by body weight		Data standardized by body weight	
Parameter	Correlation coefficient with $\dot{V}O_2max$	Estimated $\dot{V}O_2max$ / measured $\dot{V}O_2max$ (%)	Correlation coefficient with $\dot{V}O_2max$	Estimated $\dot{V}O_2max$ / measured $\dot{V}O_2max$ (%)
VAT	0.869 ($p < 0.01$)	102 ± 13	0.744 ($p < 0.01$)	102 ± 13
$\dot{V}E$-$\dot{V}CO_2$ slope			0.457	103 ± 19
ECOM	0.675 ($p < 0.01$)	146 ± 40	0.427	146 ± 40
OIES	0.966 ($p < 0.01$)	100 ± 7	0.925 ($p < 0.01$)	100 ± 7

Values were computed both with and without data standardised by body weight.
Estimates of $\dot{V}O_2max$ based on VAT, $\dot{V}E$-$\dot{V}CO_2$ slope and the OIES were calculated from the regression equations of the relationship between the $\dot{V}O_2max$ and these parameters. EMOC values were used as estimated $\dot{V}O_2max$ values.
Abbreviations: EMOC = extrapolated maximal oxygen consumption; OIES = oxygen intake efficiency slope; VAT = oxygen uptake at the ventilatory anaerobic threshold; $\dot{V}E$-$\dot{V}CO_2$ slope = the slope of the linear relation between minute ventilation and carbon dioxide production; $\dot{V}O_2max$ = oxygen uptake at maximal exercise.

DISCUSSION

$\dot{V}O_2max$ is an index of the integrated response of all the systems involved in exercise, and is considered to be 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 have suggested that "the plateau concept" has limited application during standard exercise testing.[2,3] Also, maximal exercise is not physiological and can be dangerous, as most patients do not regularly engage in strenuous exercise. Thus, $\dot{V}O_2max$ may not be the best clinical index of cardiorespiratory functional reserve.

A number of indices that do not require maximal exercise have been used as substitutes for $\dot{V}O_2max$. The ventilatory anaerobic threshold, which is widely used as a submaximal estimate of aerobic power, has been shown to be correlated with $\dot{V}O_2max$.[18] However, a major drawback of VAT is that it is not identifiable in all subjects, as was the case in one of our subjects. In addition, VAT is a subjective measurement and thus is subject to substantial inter- and intra-observer variability.[8,10] The $\dot{V}E$-$\dot{V}CO_2$ slope and EMOC have also been proposed as effort-independent parameters, but their clinical usefulness and their correlation with $\dot{V}O_2max$ have not been confirmed.

OIES, the slope of the regression curve expressing the relationship 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, OIES indicates the effectiveness of ventilation during exercise.

In the present study, OIES was significantly correlated with $\dot{V}O_2max$; the correlation coefficient for OIES was higher than the correlation coefficient for VAT, the $\dot{V}E$-$\dot{V}CO_2$ slope and EMOC. The correlation between $\dot{V}O_2max$ and OIES was not largely affected by whether the exercise test was maximal or submaximal.

The relationship between $\dot{V}O_2$ and $\dot{V}E$ has been used in the past to determine VAT. Orr et al. have proposed a three-segment linear regression model for estimation of VAT.[19] This model is based on the theory that the excessive carbon dioxide production induced by lactate buffering stimulates ventilation, and that therefore, excessive ventilation should be observed only after the onset of lactic acidosis. However, VAT is usually difficult to detect by this method because metabolic acidosis is not the only factor that controls exercise ventilation.[15] Myers et al. observed an elevated ventilatory equivalent for oxygen in patients with chronic congestive heart failure throughout the exercise protocol, suggesting that excessive ventilation in this population was not related to metabolic acidosis per se.[20] According to the logarithmic functional model used in the present study, a higher OIES indicated a more effective ventilatory response before and after the occurrence of VAT, suggesting that lactate buffering is not the only exercise factor that stimulates ventilation. A number of factors other than metabolic acidosis are thought to influence ventilation during incremental exercise, including the sensitivity of neural[21] and chemoreceptor-mediated[22,23] ventilatory control, the pulmonary capillary wedge pressure,[24] and the degree of the ventilation-perfusion mismatch.[25] The interaction among these factors appears to control exercise ventilation, resulting in a non-linear, logarithmic increase in $\dot{V}O_2$ in association with increases in $\dot{V}E$.

Although previous studies have shown that $\dot{V}O_2max$ is positively correlated with VAT,[18] and inversely correlated with the $\dot{V}E$-$\dot{V}CO_2$ slope,[11–13] these correlations were not strong in the present study, and estimates of $\dot{V}O_2max$ based on these parameters showed significant deviations from the measured $\dot{V}O_2max$. EMOC often exceeded $\dot{V}O_2max$ in the present study, which is inconsistent with the results of a previous study in which EMOC was similar to and significantly correlated with $\dot{V}O_2max$.[14] The weaker correlation between EMOC and $\dot{V}O_2max$ observed in the present study may have resulted from the use of a bicycle rather than a treadmill exercise test. Bicycle exercise is frequently associated with the limiting symptom of leg fatigue rather than with breathlessness, preventing subjects from achieving their true maximal exercise.[26] It is likely that the submaximal exercise due to the use of an ergometer did not result in an adequate hyperventilatory response and maintained a more linear relationship between $\dot{V}O_2$ against $\dot{V}CO_2$, resulting in an overestimation of extrapolated $\dot{V}O_2max$ values. If precise estimates of $\dot{V}O_2max$ by this method require maximal or near-maximal effort (which contradicts the findings of Buller et al.[14]), the clinical usefulness of EMOC may be limited.

Theoretically, OIES can be determined without the need for maximal effort on the part of subjects. In the present study, OIES values determined from the first 90% and 100% of the exercise data were identical; OIES determined from the first 75% of exercise was an average of 3.1% lower. These findings indicate that OIES is useful for estimating cardiorespiratory reserve from submaximal exercise.

In summary, our results suggest that OIES is significantly correlated with $\dot{V}O_2max$. OIES did not require the performance of maximal exercise, and thus was a completely objective measurement. Hence, OIES may be a clinically useful estimate of the cardiorespiratory functional reserve in individuals 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. OIES derived from this model offers a new, objective, effort-independent method for estimating cardiorespiratory functional reserve.

REFERENCES

1) Taylor, H.L., Buskirk, E. and Austin, H.: Maximal oxygen intake as an objective measurement of cardiorespiratory performance. *J. Appl. Physiol.*, 8, 73–80 (1955).
2) Myers, J., Walsh, D., Buchanan, N. and Froelicher, V.F.: Can maximal cardiopulmonary capacity be recognized by a plateau in oxygen uptake? *Chest*, 96, 1312–1316 (1989).
3) Rowland, T.W. and Cunningham, L.N.: Oxygen uptake plateau during maximal treadmill exercise in children. *Chest*, 101, 485–489 (1992).

4) Weber, K.L., Kinsewitz, G.T., Janicki, J.S. and Fishman, A.P.: Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation*, 65, 1213–1223 (1982).
5) Limpkin, D.P., Perrins, J. and Poole-Wilson, P.A.: Respiratory gas exchange in the assessment of patients with impaired ventricular function. *Br. Heart J.*, 54, 321–328 (1985).
6) Metra, M., Raddino, R., Cas, L.D. and Visioli, O.: Assessment of peak oxygen consumption, lactate and ventilatory thresholds and correlation with resting and exercise hemodynamic data in chronic congestive heart failure. *Am. J. Cardiol.*, 65, 1127–1133 (1990).
7) Sullivan, M.J. and Cobb, F.R.: The anaerobic threshold in chronic heart failure. Relation to blood lactate, ventilatory basis, reproducibility, and response to exercise training. *Circulation*, 81, 1147–1158 (1990).
8) Yeh, M.P., Gardner, R.M., Adams, T.D., Yanowitz, F.G. and Crapo, R.O.: "Anaerobic threshold": problems of determination and validation. *J. Appl. Physiol.*, 55, 1178–1186 (1983).
9) Gladden, L.B., Yates, J.W., Stremel, R.W. and Stamford, B.A.: Gas exchange and lactate anaerobic thresholds: inter- and intra-evaluator agreement. *J. Appl. Physiol.*, 58, 2082–2089 (1985).
10) Shimizu, M., Myers, J., and Buchanan, N.: The ventilatory threshold: method, protocol, and evaluator agreement. *Am. Heart J.*, 122, 509–516 (1991).
11) Metra, M., Cas, L.D., Panina, G. and Visioli, O.: Exercise hyperventilation, chronic congestive heart failure, and its relation to functional capacity and hemodynamics. *Am. J. Cardiol.*, 70, 622–628 (1992).
12) Buller, N.P. and Poole-Wilson, P.A.: Mechanism of the increased ventilatory response to exercise in patients with chronic heart disease. *Br. Heart J.*, 63, 281–283 (1990).
13) Clark, A.L., Swan, J.W., Laney, R., Connely, M., Sommerville, J. and Coats, A.J.S.: The role of right and left ventricular function in the ventilatory response to exercise in chronic heart failure. *Circulation*, 89, 2062–2069 (1994).
14) Buller, N.P. and Poole-Wilson, P.A.: Extrapolated maximal oxygen consumption: a new method for the objective analysis of respiratory gas exchange during exercise. *Br. Heart J.*, 59, 212–217 (1988).
15) Beaver, W.L., Wasserman, K. and Whipp, B.J.: A new method for detecting anaerobic threshold by gas exchange. *J. Appl. Physiol.*, 60, 2020–2027 (1986).
16) Wasserman, K., Hansen, J.E., Sue, D.Y., Whip, B.J. and Casaburi, R.: Principles of exercise testing and interpretation. 2nd ed. pp. 62–64 (1994), Lea and Febiger, Philadelphia.
17) Clark, A.L., Poole-Wilson, P.A. and Coats, A.J.: Effects of motivation of the patient on indices of exercise capacity in chronic heart failure. *Br. Heart J.*, 71, 162–165 (1994).
18) Itoh, H., Taniguchi, K., Koike, A. and Doi, M.: Evaluation of severity of heart failure using ventilatory gas analysis. *Circulation*, 81 (suppl), II31–37 (1990).
19) Orr, G.W., Green, H.J., Hughson, R.L. and Bennet, G.W.: A computer linear regression model to determine ventilatory anaerobic threshold. *J. Appl. Physiol.*, 52, 1349–1352 (1982).
20) Myers, J, Salleh, A, Buchanan, N, et al.: Ventilatory mechanisms of exercise intolerance in chronic heart failure. *Am. Heart J.*, 124, 710–719 (1992).
21) Mateika, J.H. and Duffin, J.: Coincidental changes in electromyographic activity and ventilation during two consecutive incremental exercise tests. *Eur. J. Appl. Physiol.*, 68, 54–61 (1994).
22) Casaburi, R., Whipp, B.J. and Wasserman, K.: Ventilatory and gas exchange dynamics in response to sinusoidal work. *J. Appl. Physiol.*, 42, 300–311 (1977).
23) Paterson, D.J.: Potassium and ventilation in exercise. *J. Appl. Physiol.*, 72, 811–820 (1992).
24) Franciosa, J.A., Leddy, C.L., Wilen, M. and Schwaltz, M.: Relation between hemodynamic and ventilatory responses in determining exercise capacity in severe congestive heart failure. *Am. J. Cardiol.*, 53, 127–134 (1984).
25) Wagner, P.D.: Ventilation-perfusion matching during exercise. *Chest*, 101 (suppl), S192–198 (1992).
26) Fletcher, G.F., Balady, G., Froelicher, V.F., Hartley, L.H., Haskell, W.L. and Pollock, M.L.: Exercise standards: a statement for healthcare professionals from the American Heart Association. *Circulation*, 91, 580–615 (1995).