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Review Article

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Cardiopulmonary Exercise Testing in Children and Adolescents: Focusing on the Oxygen Uptake Efficiency Slope

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Abstract

Cardiopulmonary Exercise Testing (CPET) is a clinical testing that allows for the analysis of gas exchange during exercise. Maximal oxygen uptake (VO_2max), comprehensive index of cardiac, respiratory, and skeletal muscle functions, is one of the most important measurements obtained in CPET. Anaerobic threshold, the exercise intensity at which lactate starts to accumulate in the blood, is widely used, as it represents an exercise level that is not too strenuous, but not too mild. The Minute Ventilation/Carbon Dioxide Output relationship (VE/VCO_2 slope) is often used as a prognostic marker of cardiac failure. The Oxygen Uptake Efficiency Slope (OUES), a submaximal index of cardiorespiratory functional reserve, correlates strongly with VO2max and is utilized as a prognostic tool for various heart diseases including congenital heart defects.

Keywords

Cardiopulmonary exercise testing; Oxygen uptake; Oxygen uptake efficiency slope

Introduction

In our everyday clinical practices of pediatric cardiology, various clinical tests at rest, e.g., chest x-ray, electrocardiogram, echocardiogram, blood gas analysis, serum biochemical tests, etc. are essential and indispensable for their evaluation. However, these clinical tests at rest can only observe, in a sense, extraordinary sedentary unloaded physiological functions of the patients, not at all their status during everyday activities like playing, exercising, standing, or sleeping. Therefore, appropriate evaluations of their physiological and cardiopulmonary responses to various stresses are essential in our clinical practices.

CPET is a test indispensable for the evaluation of functional reserve in subjects with cardiorespiratory diseases, predicting their prognosis, and effectiveness of treatment [1]. Therefore, this review overviews the basics of various measurements obtained from CPET sessions, e.g., VO_2max, Anaerobic Threshold (AT), the VE, VCO_2 regression slope (VE/VCO_2 slope), and the OUES, in mainly pediatric population.

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What does the VO2max mean?

The VO_2max, one of the most important and accurate prognostic indices of patients with heart failure, shows the "maximal power output" of a subject, which is determined comprehensively by the reserve functions of the circulatory, respiratory, and the skeletal muscles [2].

When one mole of glucose is aerobically metabolized, a total of 6 moles of oxygen is used and 36 moles of Adenosine Triphosphate (ATP) is produced, namely:

$$C_6H_{12}O_6+6O_2+36ADP+36Pi \rightarrow 6CO_2+42H_2O+36ATP$$

ATP is called "currency of energy" which produces certain amount of energy (30.5 kJ/mol) when it is hydrolyzed to ADP. The proportional relationship addressed in this chemical formula tells us that measuring the amount of oxygen utilized in (or taken into) the body in a certain period (usually in a minute) is proportional to the amount of energy produced in the body during the period, i.e., measuring the work rate (power output) of the subject. Although we cannot measure the power produced by the body directly, we can measure it indirectly by measuring the amount of oxygen taken into the body in a certain period, i.e., the oxygen uptake (VO_2). Therefore, measuring the maximal amount of oxygen one can take into the body in a certain period is nothing other than measuring the maximal energy output a person can produce.

With the Fick's LAW, VO2 is described as:

$$VO_2 = C.O.\times(CaO2\text{-}CVO2) = C.O.\times(C_{PV}\text{-}C_{PA}),$$

where C.O. is minute cardiac output, CaO_2, C_VO_2, C_{PV} and C_{PA}, are oxygen content of the arterial, mixed venous, pulmonary venous, and pulmonary arterial blood. As C.O., CaO_2 - C_VO_2, and CaO_2 - C_VO_2 indicate the functions of the heart, efficiency of skeletal muscular oxygen utility, and oxygen intake function of the lungs, respectively, VO_2max can be considered as an index of comprehensive reserves of cardiac, skeletal muscular, and respiratory functions. A normal value of VO_2max for a normal, non-regularly exercising man is about 30-40ml/min/kg, with slightly lower value in a woman.

Limitation of the VO_2max

The VO_2max is, however, only a "conceptual gold standard". Maximal exercise is often difficult and sometimes dangerous because it may lead to myocardial ischemia [3,4]. We therefore have to compromise by using submaximal measurements. The most frequently used measurement is the peak VO_2, the value at the end of incremental exercise testing. Other indices that do not need maximal exercise are anaerobic threshold (AT), the slope of the Minute Ventilation (VE)/ Carbon Dioxide Production (VCO_2) regression, and the OUES.

AT and ventilatory threshold

Since the 1920s, the phenomenon of the rise in serum lactate concentration during strenuous exercise has been known, which is

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produced in the working skeletal muscles. In the 1960s, Wasserman and coworkers hypothesized that the production of lactate was associated with the ischemia of the muscles above a certain level of exercise intensity, and named the phenomenon as AT [5]. This hypothesis was persuasive and many a researchers and clinicians believed it. Then, researchers reported that the use of expired gas analysis during incremental exercise testing can detect the threshold non-invasively, and named it Ventilatory Threshold (VT). These studies have made the AT the mainstream of the exercise physiology and exercise cardiology during the 1980s and 1990s. However, studies afterwards have proved that

1) Any level of exercise intensity cannot cause ischemia of the skeletal muscle mitochondria which leads to anaerobic energy production [6],

2) Lactate is produced from the skeletal muscles at any level of exercise intensity [7-9],

3) The serum lactate levels are determined by the balance between its production and clearance [10,11], and

4) Therefore, there is not any "threshold" of the serum lactate levels [12,13]. These studies have led most researchers today to "abandon faith" for AT.

Although most researchers today believe that the AT theory that Wasserman advocated has been disproven, the AT is still widely used in our clinical practices. It is because AT represents the exercise intensity that is not too strenuous but not too mild. In fact, significant lactate accumulation in the blood does not occur under the exercise intensity below the AT levels. Also, cardiac ischemia hardly occurs below the AT levels, which often makes the AT level exercise intensity for cardiac rehabilitation. Also, the AT is still widely used in the practices of athletic training, as appropriate training can suppress the blood levels of lactate under the same exercise intensity. For example, Hurley and coauthors have shown that a 12-week exercise program elicited significantly lower lactate concentrations at the same relative exercise intensities of the 55–75% of VO_2max after training [14].

Usually, AT (VT) can be determined by the CPET [15]. Most commonly, it is determined as the level of exercise intensity (or VO_2) at which the Ventilatory Equivalent of the oxygen (VE/VO_2) begins to increase during incremental exercise [15]. Also, the point at which the end-expiratory partial pressure of oxygen begins to increase [15], or the first point of departure from linearity of VCO_2 plotted against VO_2 [16].

The VE/VCO2 regression slope

The alveolar ventilation equation concisely addresses the relation among the minute Alveolar Ventilation (VA), VCO_2, and the arterial partial Pressure of Carbon Dioxide ($PaCO_2$), namely:

$$VA = 863 \times VCO_2/PaCO_2.$$

When we replace VA with a more easily measured parameter VE, this equation can be rewritten as:

$$VE = 863 \times VCO_2/(PaCO_2 \times (1-Vd/Vt)),$$

where, Vd and Vt represent dead space ventilation and tidal volume, respectively.

We can consider that VE is expressed as a linear equation of VCO_2, as $PaCO_2$, Vd and Vt are relatively stable during exercise. Actually, the relation between VE and VCO_2 during incremental exercise testing shows linear just before maximal exercise until the respiratory compensation point (Figure 1). The slope of the regression equation shows the efficiency of ventilation during exercise. In patients with heart failure, pulmonary blood flow cannot distribute evenly to their alveoli, causing greater values of Vd, which leads to steeper linear relation between VE and VCO_2. Therefore, the slope of the VE/VCO_2 regression shows the ventilatory response to exercise. Also, there have been many studies that show the relation of the regression slope and the prognosis of patients with heart failure [17-19].

Oxygen uptake efficiency slope

As shown in Figure 2 the relation between VO_2 and VE during incremental exercise. Note that the x-axis is logarithmically plotted. Therefore, their relation can be described as:

$$VO_2 = a \log VE + b$$

where a and b are constants.

The relation can be observed with high values of regression coefficients regardless of subjects and exercise protocol [20]. Differentiation of the both sides of the equation above by VE gives:

$$d\,VO_2/dVE = a \ln 10/VE.$$

This equation shows that the increment of VO_2 against VE is determined by VE and the constant a. Therefore, the constant a

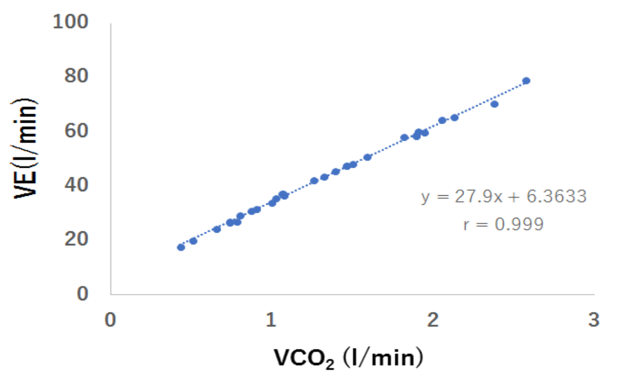

Figure 1: Relationship between minute ventilation (VE, the vertical axis) and carbon dioxide production (VCO2, the horizontal axis) during incremental exercise obtained from a 12-year old girl.

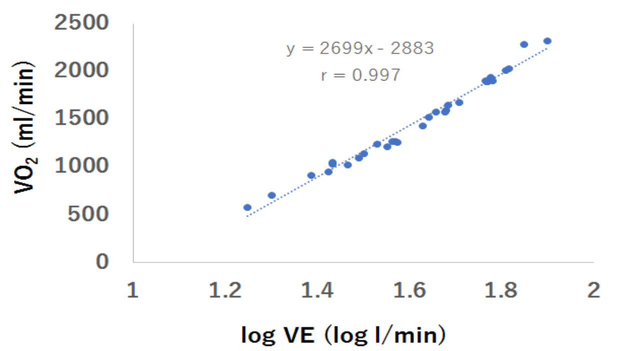

Figure 2: Relationship between minute ventilation (VE, the horizontal axis) and oxygen uptake (VO2, the vertical axis) during incremental exercise. The subject is the same as in Fig. 1. The horizontal line is logarithmically plotted. The slope of the regression curve (2699 in this figure) is defined as the Oxygen Uptake Efficiency Slope (OUES).

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indicates the rate of the increase in VO_2 at a certain minute ventilation VE. We have named the slope a the OUES [20]. The OUES is a measure of the ability to increase VO2 per 10-fold rise in minute ventilation. In other words, a steeper slope (or, a greater value of OUES) shows that the subject can take oxygen into the body without excessively increasing ventilation, i.e., without causing shortness of breath.

One of the most prominent features of OUES is that this index is strongly correlated with VO2max [20]. Baba et al. [20] have reported in 1996, using patients with a variety of pediatric cardiac diseases, that the regression coefficient was 0.941. The close correlation is also shown in various populations, e.g., healthy adults (r=0.966) [21], healthy children (r=0.920) [22], obese and non-obese children (r=0.91) [23,24], and adult patients with heart failure (r=0.78) [25].

Another feature of OUES is that this can be accurately calculated without imposing maximal exercise on subjects. As the OUES is defined as the slope of the logarithmic relation between VO2 and VE during incremental exercise, submaximal exercise data is theoretically sufficient for its calculation. In fact, Baba and coauthors have shown that calculation of the OUES with the first 90% and 75% of incremental exercise data are almost identical to measurements obtained from maximal data using populations of children [20], adults with heart failure [24], and healthy adults [21]. Also, Akkerman et al. [26] have shown, with a population of 46 children that the OUES values are consistent between those calculated with maximal and submaximal exercise data up to the AT. This strong point is clinically important in children who often cannot understand why they must perform "maximal" exercise testing, or in patients with cardiac diseases on whom imposing maximal exercise is dangerous.

OUES is now often used as prognostic indicators of cardiac patients. One of the most important studies would be one that Davies et al. [27] have published in the European Heart Journal in 2006. This study has analyzed the prognosis of 243 patients with heart failure using the measurements of OUES, peak VO_2, VT, and the VE/VCO_2 regression slope, and has shown that only OUES is the independent risk factor of death when multivariable model was used, with the cut-off value of 1.47 ml/min/log (l/min) [27]. Then, Arena et al. [28] have analyzed the prognosis of adult patients with heart failure, with the end-points of death, cardiac transplantation, or implantation of Ventricular Assist Device (VAD), and have shown that both the VE/VCO2 regression slope and the OUES are independent risk factors, with the area under the curves (AUCs) of 0.73 and 0.74, respectively. Further, Myers et al. [29] using a large cohort of 2625 patients with heart failure, have shown that a scoring system with a combination of the OUES, the VE/VCO_2 regression slope, the heart rate reserve, end-expiratory partial pressure of carbon dioxide (PetCO2), and peak VO_2 is a strong prognostic marker of the patients. Recently, Coeckelberghs et al. [30] have shown that the OUES is an independent predictor for all-cause and cardiovascular mortality in patients with coronary artery disease, irrespective of a truly maximal effort during CPET. Also, Tang et al. [31] have shown that the OUES provides prognostic information for predicting clinical worsening and mortality in patients with idiopathic pulmonary hypertension.

The clinical applications of the OUES in pediatric populations have also been reported. Bongers et al. [32] have provided sex and age-related normative values for OUES which facilitates the interpretation of OUES in children. Hossri et al. [33] also have published reference values of OUES and concluded that OUES is a marker tool in the differentiation between preserved or abnormal functional capacity in children and adolescents with and without congenital heart disease, even at the submaximal level of exercise. Recently, several studies have shown the prognostic values of the OUES in patients with congenital heart diseases. Chen and coauthors have reported that submaximal exercise parameters including OUES provide superior prognostic information to maximal exercise data for predicting cardiac morbidity in Fontan patients [34]. Moreover, the association between the OUES and cardiac morbidity is independent of relevant baseline clinical information [34]. Also, Tsai et al. [35] have shown, using forty post-surgical patients with tetralogy of Fallot younger than 12 years old, that the OUES normalized by body surface area, as well as peak VO_2, are useful predictors of cardiac-related hospitalization.

Conclusion

As the OUES is now considered as an excellent and useful parameter of exercise tolerance and gas exchange efficiency, many a guidelines and textbooks today describe it as an independent item. We expect future development and clinical applications of this parameter.

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