

## Educational Review

## Cardiopulmonary Exercise Testing in Children and Adolescents

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Cardiopulmonary exercise testing (CPET) is a clinical testing that allows for the analysis of gas exchange during exercise. Maximal oxygen uptake ( $\dot{V}O_2\text{max}$ ), a comprehensive index of cardiac, respiratory, and skeletal muscular functions, is one of the 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 ( $\dot{V}E/\dot{V}CO_2$  slope) is often used as a prognostic marker of cardiac failure. The oxygen uptake efficiency slope (OUES) is a submaximal index of cardiorespiratory functional reserve, and correlates strongly with  $\dot{V}O_2\text{max}$ . This marker is utilized as a prognostic tool for various heart diseases including congenital heart defects.

**Keywords:** cardiopulmonary exercise testing, oxygen uptake efficiency slope, peak oxygen uptake, anaerobic threshold, exercise testing

## Introduction

In our everyday clinical practices of pediatric cardiology, various clinical tests at rest, (e.g., chest X-ray, electrocardiogram, echocardiography, blood gas analysis, serum biochemical tests), are essential and indispensable for their evaluation. These tests can only observe, in a sense, physiological functions of the patients in an extraordinarily sedentary and unloaded circumstance; not at all their status during daily activities such as playing, exercising, standing, or sleeping. Therefore, appropriate evaluations of their physiological and cardiopulmonary responses to various stresses are essential in our clinical practices.

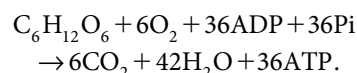
Cardiopulmonary exercise testing (CPET) is a test indispensable for the evaluation of functional reserve in subjects with cardiorespiratory diseases, predicting their prognosis, and effectiveness of treatment.<sup>1)</sup> Therefore, this review overviews the basics of measurements obtained from CPET sessions, that is, maximal oxygen uptake ( $\dot{V}O_2\text{max}$ ), anaerobic threshold (AT), the minute ventilation ( $\dot{V}E$ )-carbon dioxide output ( $\dot{V}CO_2$ ) regres-

sion slope ( $\dot{V}E/\dot{V}CO_2$  slope), and the oxygen uptake efficiency slope (OUES), mainly in pediatric population.

What Does the  $\dot{V}O_2\text{max}$  Mean?

The  $\dot{V}O_2\text{max}$  shows the “maximal power output” of an examinee, which is determined comprehensively by the reserve functions of the circulatory system, respiratory system, and the skeletal muscles.<sup>2)</sup> This is one of the important and accurate prognostic indices of patients with heart failure.

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,



ATP is called as “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 duration of time (usually per minute) is

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proportional to the amount of energy produced in the body during the period. In other words, this represents the work rate (power output) of the subject. Although we cannot directly measure the power produced by the body, we can do so indirectly by measuring the amount of oxygen taken into the body in a certain duration of time, that is, the oxygen uptake ( $\dot{V}O_2$ ). Therefore, measuring the maximal amount of oxygen an examinee can take into the body per a unit of time ( $\dot{V}O_{2\max}$ ) is nothing other than indicating the maximal energy output the person can produce.

With the Fick's law,  $VO_2$  is described as:

$$\dot{V}O_2 = C.O. \times (CaO_2 - C_V O_2) = C.O. \times (C_{PV} - C_{PA})$$

where C.O. is cardiac output, and  $CaO_2$ ,  $C_V O_2$ ,  $C_{PV}$  and  $C_{PA}$ , are oxygen contents in arterial, mixed venous, pulmonary venous, and pulmonary arterial blood, respectively. The C.O. indicates the function of the heart. The product  $CaO_2 - C_V O_2$  represents efficiency of oxygen utility by the skeletal muscles, and the  $C_{PV} - C_{PA}$  the function of oxygen intake by the lungs. Thus,  $\dot{V}O_{2\max}$  can be considered as an index of comprehensive reserves of cardiac, skeletal muscular, and respiratory functions. A normal value of  $\dot{V}O_{2\max}$  for a male subject who does not regularly exercise is about 30–40 mL/min/kg, and the value is slightly lower in a woman.

### Limitation of the $\dot{V}O_{2\max}$

The  $\dot{V}O_{2\max}$  is only a “conceptual gold standard”. Maximal exercise is often difficult and sometimes dangerous because it may lead to myocardial ischemia.<sup>3,4</sup> The physicians therefore have to compromise by using submaximal measurements. The most frequently used measurement in this respect is the peak  $\dot{V}O_2$ , the value at the end of incremental exercise testing. The following 3 indices do not need maximal exercise, either; namely, anaerobic threshold (AT), the slope of the minute ventilation ( $\dot{V}E$ )/ carbon dioxide production ( $\dot{V}CO_2$ ) regression, and the oxygen uptake efficiency slope (OUES).

### AT and Ventilatory Threshold

Since the 1920s, the phenomenon that serum lactate concentration rises during strenuous exercise has been known. Lactate is 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. They named the phenomenon as AT.<sup>5</sup> This hypothesis was so persuasive that many researchers and clinicians believed it. Then, researchers reported that the threshold can be determined non-invasively by analyzing expired gas during incremental exercise testing. This was named as 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 mitochondria of the skeletal muscle which leads to anaerobic energy production,<sup>6</sup> 2) lactate is produced from the skeletal muscles at any level of exercise intensity,<sup>7-9</sup> 3) the serum lactate levels are determined by the balance between its production and clearance,<sup>10,11</sup> and 4) accordingly, there is not any “threshold” of the serum lactate levels.<sup>12,13</sup> These studies have brought a tide of “abandon faith” for AT to most researchers today.

Although they 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, either. In fact, significant lactate accumulation in the blood does not occur under the exercise intensity below the AT levels. Cardiac ischemia hardly occurs below the AT levels; that is why exercise intensity at the AT level is often set for cardiac rehabilitation. Also, the AT is still widely utilized in the practices of athletic training, because appropriate training can suppress the blood level 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 after training at the relative exercise intensities of the 55–75% of  $\dot{V}O_{2\max}$ .<sup>14</sup>

Usually, AT (VT) can be determined by the CPET.<sup>15</sup> Most commonly, it is determined as the level of exercise intensity (or  $\dot{V}O_2$ ) at which the ventilatory equivalent of the oxygen ( $\dot{V}E/\dot{V}O_2$ ) begins to increase during incremental exercise.<sup>15</sup> Similarly, AT is the point at which the end-expiratory partial pressure of oxygen begins to increase,<sup>15</sup> or the first point of departure from linearity of  $\dot{V}CO_2$  plotted against  $\dot{V}O_2$ .<sup>16</sup>

### The $\dot{V}E/\dot{V}CO_2$ Regression Slope

The alveolar ventilation equation concisely addresses the relation among the minute alveolar ventilation ( $\dot{V}A$ ),

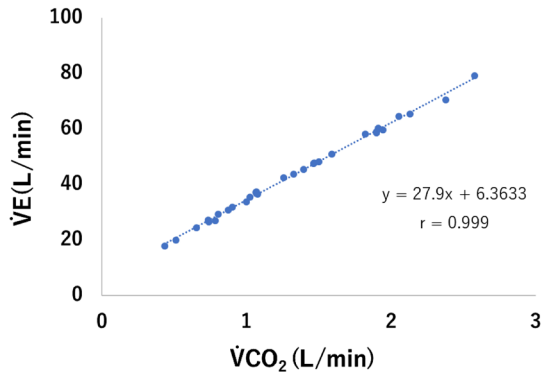


Fig. 1 Relationship between minute ventilation ( $\dot{V}E$ , the vertical axis) and carbon dioxide production ( $\dot{V}CO_2$ , the horizontal axis) during incremental exercise obtained from a 12-year-old girl

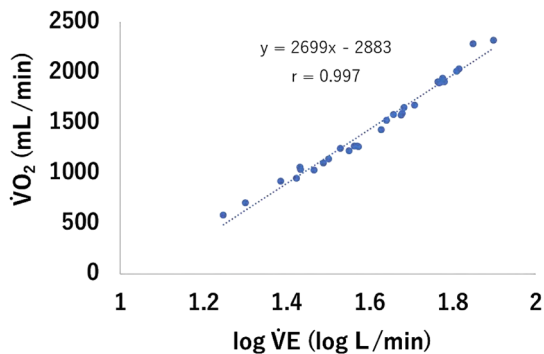


Fig. 2 Relationship between minute ventilation ( $\dot{V}E$ , the horizontal axis) and oxygen uptake ( $\dot{V}O_2$ , the vertical axis) during incremental exercise (the same examinee as in Fig. 1). The horizontal line is logarithmically plotted. The slope of the regression curve (2699 in this figure) is defined as the oxygen uptake efficiency slope (OUES)

$\dot{V}CO_2$ , and the arterial partial pressure of carbon dioxide ( $PaCO_2$ ), namely:

$$\dot{V}A = 863 \times \dot{V}CO_2 / PaCO_2$$

When we replace  $\dot{V}A$  with a more easily measurable parameter  $\dot{V}E$ , this equation can be rewritten as:

$$\dot{V}E = 863 \times \dot{V}CO_2 / (PaCO_2 \times (1 - Vd/Vt))$$

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

We can consider that  $\dot{V}E$  is expressed as a linear equation of  $\dot{V}CO_2$ , as  $PaCO_2$ ,  $Vd$  and  $Vt$  are relatively stable during exercise. In reality, the relation between  $\dot{V}E$

and  $\dot{V}CO_2$  during incremental exercise testing is linear from just before maximal exercise until the respiratory compensation point (Fig. 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  $\dot{V}E$  and  $\dot{V}CO_2$ . Therefore, the slope of the  $\dot{V}E/\dot{V}CO_2$  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.<sup>17-19)</sup>

### Oxygen Uptake Efficiency Slope

Fig. 2 shows the relation between  $\dot{V}O_2$  and  $\dot{V}E$  during incremental exercise. Note that the  $x$ -axis is logarithmically plotted. Therefore, their relation can be described as:

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

where  $a$  and  $b$  are constants.

The relation can be observed with high values of regression coefficients regardless of subjects or exercise protocol.<sup>20)</sup> When the equation above is differentiated by  $\dot{V}E$  on both sides:

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

This equation shows that the increment of  $\dot{V}O_2$  against  $\dot{V}E$  is determined by  $\dot{V}E$  and the constant 'a' ( $1/\ln 10 \approx 0.4343$ ). Therefore, the constant 'a' indicates the rate of the increase in  $\dot{V}O_2$  at a certain minute ventilation  $\dot{V}E$ . We have named the slope 'a' as the oxygen uptake efficiency slope (OUES).<sup>20)</sup> The OUES is a measure of the ability to increase  $\dot{V}O_2$  per 10-fold rise in minute ventilation. In other words, a steeper slope (or, a greater value of the 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 prominent features of the OUES is the fact that this index strongly correlates with  $\dot{V}O_{2max}$ .<sup>20-25)</sup> Another feature is that this can be accurately calculated without imposing maximal exercise on the examinee. The OUES is defined as the slope of the logarithmic relation between  $\dot{V}O_2$  and  $\dot{V}E$  during incremental exercise. This means that submaximal exercise data is theoretically sufficient for its calculation.<sup>20, 26)</sup> Also, the OUES can be used as prognostic indicators of patients with

heart failure.<sup>27-31)</sup>

The clinical application of the OUES in the pediatric population has also been reported. Bongers and coauthors have provided sex- and age-related normative values for OUES which facilitates the interpretation of the OUES in children.<sup>32)</sup> Hossri and coauthors also have published reference values of the OUES and concluded that the OUES is a marker when differentiating preserved functional capacity from abnormal one in children and adolescents even at the submaximal level of exercise, regardless of with and without congenital heart disease.<sup>33)</sup> 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 the OUES provide superior prognostic information to maximal exercise data for predicting cardiac morbidity in patients with the Fontan circulation.<sup>34)</sup> The association between the OUES and cardiac morbidity was independent of relevant baseline clinical information.<sup>34)</sup> Moreover, Tsai and coauthors showed, in 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  $\dot{V}O_2$ , are useful predictors of cardiac-related hospitalization.<sup>35)</sup>

### Conflicts of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### Editors' Comments

Editor A) This article describes a basic idea of cardiopulmonary exercise testing, focusing on four parameters. These were comprehensibly explained from a mathematical, a physiological, or a historical aspect. The Editorial members do hope that this educational article could contribute to enhancement of basic knowledge in this field.

Editor B) While exercise testing has been hardly applied for kids, its importance in the CHD clinic is expanding with the increasing number of grown-up CHD patients. This short review written by R. Baba introduced very basic concept of exercise testing, and examples of its application for CHD patients. Although the learners must refer to a decent textbook to acquaint themselves with the cardiopulmonary exercise testing, we hope this article can evoke intellectual curiosity of the readers' and may guide them where to start learning.