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REVIEW ARTICLE

Importance of Physical Activity and $\dot{V}O_2\text{max}$: Five Major Determinants of $\dot{V}O_2\text{max}$

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ABSTRACT

Cardiorespiratory fitness (CRF) is defined as the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity and is usually expressed as maximal oxygen uptake ($\dot{V}O_2\text{max}$) during maximal exercise testing. There are five major determinants of $\dot{V}O_2\text{max}$: functions of the heart, lung, kidney, muscle, and blood (hemoglobin). Cardiac output, pulmonary diffusion capacity, oxygen-carrying capacity, renal function, and other peripheral limitations like muscle diffusion capacity, mitochondrial enzymes, and capillary density are all examples of $\dot{V}O_2\text{max}$ determinants. $\dot{V}O_2\text{max}$, measured by cardiopulmonary exercise testing, provides what is probably the most sensitive assessment of the effect of new therapy on the function of any diseased organ system whose major function is to couple pulmonary gas exchange to cellular respiration. For example, it is important to determine whether new medical, surgical, and rehabilitative procedures can effectively intervene to improve the gas transport capability of a diseased organ system.

<Key-words>

physical activity, physical inactivity, $\dot{V}O_2\text{max}$, rehabilitation

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I. Physical inactivity (PI)

Physical inactivity (PI), which is associated with increased morbidity, loss of health-related quality of life, and substantial healthcare expenditure, is estimated to be the fourth leading cause of death worldwide (Medibank Private, 2007; Martin, Beelerb, Szucs et al., 2001; Katzmarzyk, Janssen, 2004; Chenoweth, Leutzinger, 2008; Zelle, Klaassen, Van, et al., 2017). It is an established risk factor for the development of common noncommunicable diseases (NCD) (World Health Organization, 2010), with approximately 6–10% of all deaths from NCD attributable to PI (Kohl, Craig, Lambert, et al., 2012). Approximately one-third of the global population does not engage in the minimum weekly amount of physical activity (PA) recommended by the WHO, which is 150 min of moderate-intensity aerobic PA throughout the week, at least 75 min of vigorous-intensity aerobic PA throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity (Zelle, Klaassen, Van et al., 2017; World Health Organization, 2010; Kohl, Craig, Lambert et al., 2012).

The association between PI and poor outcomes is also established for patients with cardiac disease, pulmonary disease, and chronic kidney disease (Cacciatore, Amarelli, Ferrara et al., 2018; Waschki, Kirsten, Holz et al., 2011; Beddhu, Baird, Zitterkoph et al., 2009). Patients with cardiac disease, pulmonary disease, or renal disease typically engage in a lower level of PA than does the general population, which can induce a catabolic state including reduced neuromuscular functioning, reduced exercise tolerance, and reduced cardiorespiratory fitness (CRF).

II. Cardiorespiratory fitness (CRF) and $\dot{V}O_2\text{max}$

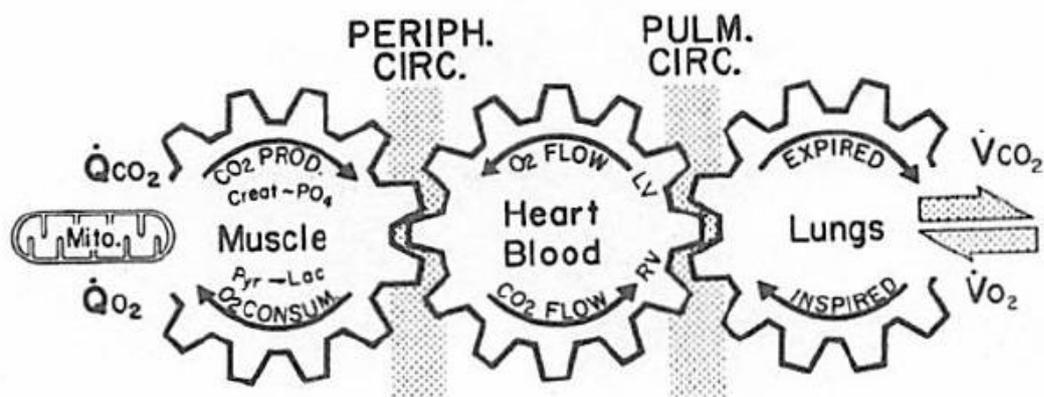
CRF is an important consideration, in addition to PA, as it is a strong predictor of mortality (Sieverdes, Sui, Lee et al., 2010; Blair, Kohl, Paffenbarger et al., 1989); low CRF presents a particularly high risk of death compared to other common risk factors, such as diabetes, high cholesterol, or hypertension (Blair, Sallis, Hutber et al., 2012). CRF is defined as the ability of the circulatory and respiratory systems to supply oxygen during sustained PA and is usually expressed as maximal oxygen uptake ($\dot{V}O_2\text{max}$) during maximal exercise testing (Caspersen, Powell, Christenson et al., 1985). In 2016, the American Heart Association published a scientific statement (Ross, Blair, Arena et al., 2016) recommending that CRF, quantifiable as $\dot{V}O_2\text{max}$, be regularly assessed and utilized as a clinical vital sign. This statement was based on the mounting evidence that lower CRF levels are associated with high risk of cardiovascular disease, all-cause mortality, and mortality rates stemming from various types of cancers.

$\dot{V}O_2\text{max}$ is expressed either as an absolute rate in, for example, liters of oxygen per minute (L/min) or as a relative rate in, for example, milliliters of oxygen per kilogram of

body mass per minute (e.g., mL/ (kg · min)). The latter expression is often used to compare the performance of endurance athletes and patients.

III. Major determinants for $\dot{V}O_2\text{max}$

Wasserman showed gas transport mechanisms for coupling cellular (internal) to pulmonary (external) respiration (Figure 1) (Wasserman, 1999).



(Wasserman, 1999)

<Figure 1> Gas transport mechanisms for coupling cellular to pulmonary respiration

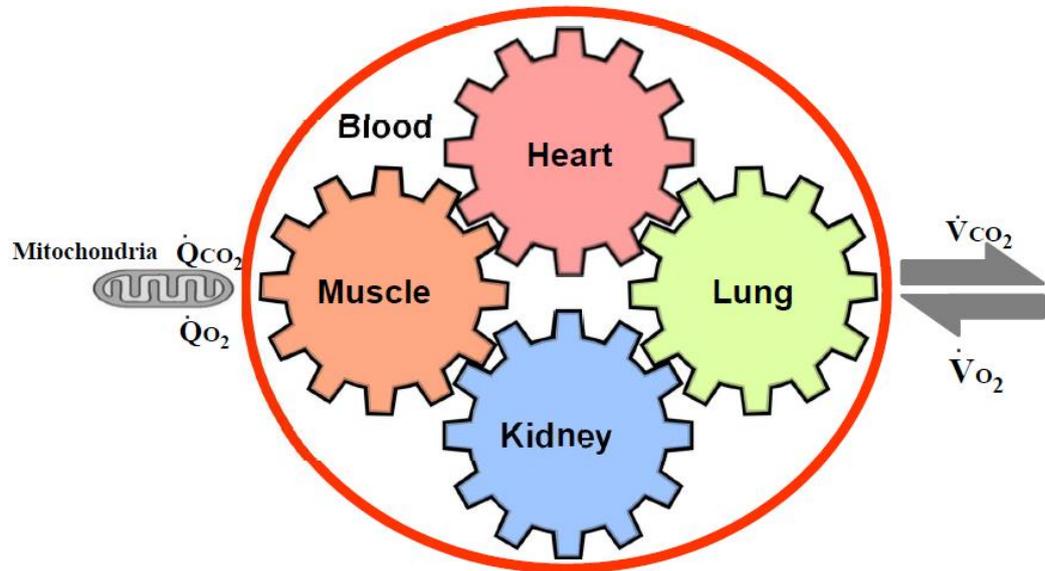
$\dot{Q}CO_2$; minute newly produced CO_2 , $\dot{Q}O_2$; minute O_2 utilization

$\dot{V}CO_2$; minute CO_2 output, $\dot{V}O_2$; minute O_2 taken up from the alveoli.

The gears represent the functional interdependence of the physiological components of the system. The large increase in O_2 utilization by the muscles ($\dot{Q}O_2$) is achieved by the increased extraction of O_2 from the blood perfusing the muscles, the dilatation of selected peripheral vascular beds, an increase in cardiac output (stroke volume and heart rate), an increase in pulmonary blood flow by recruitment and vasodilatation of pulmonary blood vessels, and finally, an increase in ventilation. O_2 is taken up ($\dot{V}O_2$) from the alveoli in proportion to the pulmonary blood flow and degree of O_2 desaturation of hemoglobin in the pulmonary capillary blood.

Recent findings suggest that metabolic acidosis in chronic kidney disease (CKD) patients promotes muscle protein wasting and protein-energy wasting (PEW) by increasing protein degradation (Caso & Garlick, 2005) and reducing protein synthesis (Bailey, Wang & England, 1996). As a result, muscle mass maintenance is impaired in CKD patients with altered protein turnover rates (Mitch, 1997). Adding to sarcopenia, metabolic acidosis, protein-energy wasting, angiotensin II, and myostatin overexpression in uremia contribute to muscle wasting etiology in CKD (Fahal, 2014). Moreover, the drug erythropoietin (EPO) can boost $\dot{V}O_2\text{max}$ significantly in both humans and other mammals (Kolb, 2010). Therefore, Kohzuki suggested that there are five major

determinants for $\dot{V}O_2\text{max}$: functions of the heart, lung, kidney, muscle, and blood (Figure 2) (Kohzuki, 2018).



(Kohzuki, 2018)

<Figure 2> Gas transport mechanisms for coupling cellular to pulmonary respiration: five major determinants for $\dot{V}O_2\text{max}$

$\dot{Q}CO_2$; minute newly produced CO_2 , $\dot{Q}O_2$; minute O_2 utilization

$\dot{V}CO_2$; minute CO_2 output, $\dot{V}O_2$; minute O_2 taken up from the alveoli.

Cardiac output, pulmonary diffusion capacity, oxygen-carrying capacity, renal function, and other peripheral limitations like muscle diffusion capacity, mitochondrial enzymes, and capillary density are all examples of $\dot{V}O_2\text{max}$ determinants.

IV. Factors limiting exercise

Symptoms that stop people from performing exercise are fatigue, dyspnea, angina, or claudication (Wasserman, 1999).

The exact mechanisms of fatigue remain a topic of debate. Because lactic acidosis accompanies an increased rate of anaerobic ATP production, it is tempting to attribute fatigue to the intracellular consequences of exercise lactic acidosis. Low cellular pH, increased inorganic phosphate, impaired calcium release from the sarcoplasmic reticulum, and decreased ATP levels have also been proposed as mediators of fatigue (Wasserman, 1999).

Dyspnea is a common abnormal consequence of exercise. It occurs in patients with relatively ineffective ventilation, such as in patients with a high fraction of the breath which is physiological dead space (low gas exchange efficiency), and in those with hypoxemia, metabolic acidosis, or impaired ventilatory mechanics. Sedentary subjects usually experience fatigue rather than dyspnea as their limiting symptom during exercise involving large muscle groups. Because of the reduction in maximal ventilatory capacity with aging, elderly people may experience exertional dyspnea at maximum exercise rather than fatigue (Wasserman, 1999).

Pain in the chest or other related areas is the most common symptom of patients with coronary artery disease. This reflects an inadequate O₂ supply to the myocardium relative to the myocardial O₂ demand. Reducing the O₂ demand by decreasing myocardial work or increasing myocardial O₂ supply can eliminate angina. Reducing O₂ demand, however, may necessitate a reduced maximal work capacity. That is, the patient may be forced to trade a less active lifestyle for anginal relief (Wasserman, 1999).

Claudication occurs because of an O₂ supply/demand imbalance in the muscles of the exercising extremity. Because walking at a normal pace requires approximately 20-fold increase in O₂ utilization by the muscles of locomotion, the ability to increase blood flow to the lower extremities is critically important to be able to walk without pain. If atherosclerotic changes in the conducting vessels to the lower extremity limit the increase in leg blood flow, an O₂ supply/demand imbalance will result (Wasserman, 1999).

V. Exercise testing

As super-aged society has come, the number of persons with multimorbidity and multiple disabilities (MMD) (Kohzuki, 2014) and their needs of rehabilitation have increased rapidly more than expected (Kohzuki, 2014). Exercise testing offers the investigator the unique opportunity to study simultaneously the cellular, cardiovascular, and ventilatory systems' responses under conditions of precisely controlled metabolic stress. Exercise testing with appropriate gas exchange measurements can also serve to grade the adequacy of cardiorespiratory function. For example, exercise testing might not only distinguish between lung and cardiovascular disease, but also it may be used to distinguish one cardiovascular disease from another as the cause of exercise limitation. For instance, coronary artery disease, chronic heart failure, and peripheral vascular disease may be distinguished by the pattern of abnormal gas exchange response to exercise (Wasserman, 1997).

VI. Conclusions

There are five major determinants for $\dot{V}O_2\text{max}$, such as functions of the heart, lung, kidney, muscle, and blood (hemoglobin). Cardiac output, pulmonary diffusion capacity, oxygen-carrying capacity, renal function, and other peripheral limitations like muscle diffusion capacity, mitochondrial enzymes, and capillary density are all examples of $\dot{V}O_2\text{max}$ determinants. $\dot{V}O_2\text{max}$, measured by cardiopulmonary exercise testing, provides what is probably the most sensitive assessment of the effect of new therapy on the function of any diseased organ system whose major function is to couple pulmonary gas exchange to cellular respiration. For example, it is important to determine whether new medical, surgical, and rehabilitative procedures can effectively intervene to improve the gas transport capability of a diseased organ system.

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CONTENTS

ORIGINAL ARTICLES

Using Videos to Analyze the Effectiveness of START Education for Japanese Nursing Students

Kazuyuki AKINAGA et al., 1

Effects of the OSCE to Motivate Students to Learn Before Clinical Practice

Yuko FUJIO et al., 13

The Current Status and Its Implications of Public-Private Partnerships for Official Development Assistance in Korea: Focusing on Disability-Inclusive Development Cooperation

Juhee HWANG et al., 25

Effects of a Structured 8-week Nordic Walking Exercise Program on Physical Fitness in the Japanese Elderly

Kimiko YAMAMOTO et al., 38

Study of "Individuality" on Nursing Care Job

Kimiko YAMAMOTO et al., 52

SHORT PAPERS

A Comparison of the Factor Structure of the Self-Harm Antipathy Scale and related Demographic Characteristics between Korea and Japan

Yoshimi AOKI et al., 66

Issues of Specific Educational Curriculum Development for Resource Rooms and Special Needs Classes in Japanese High Schools

Mitsuyo SHIMOJO et al., 76

REVIEW ARTICLES

Importance of Physical Activity and $\dot{V}O_{2max}$: Five Major Determinants of $\dot{V}O_{2max}$

Masahiro KOHZUKI et al., 85

Importance of Physical Exercise in Oldest-old Adults: A Literature Review Study

Chaeyoon CHO et al., 93
