

REVIEW ARTICLE | PHYSICAL ACTIVITY AND EXERCISE SERIES

# Physiological Principles of Exercise

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## Introduction

Understanding the principles of exercise physiology is essential for clinicians. Cardiorespiratory fitness (CRF), one of the key outcomes of an exercise test,<sup>1-3</sup> is an indicator of future cardiac, metabolic, and other health events. In 2016, the American Heart Association recommended that CRF be added as a vital sign, given its importance in predicting cardiovascular disease and all-cause mortality.<sup>4</sup> Knowledge of a patient's CRF also informs the implementation of lifestyle-based strategies to reduce cardiovascular risk and can empower patients to effect behavioral changes. Yet CRF remains undervalued and underutilized in cardiovascular disease prevention and management.

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### MEASURING ACTIVITY LEVEL AND CARDIORESPIRATORY FITNESS

Performing physical work results in a pronounced increase in oxygen (O<sub>2</sub>) utilization by the working tissues, predominantly in skeletal muscle. Oxygen uptake ( $\dot{V}O_2$ ) represents the rate at which an individual uses oxygen to generate adenosine triphosphate (ATP), the primary energy currency of cells. Thus,  $\dot{V}O_2$  reflects the integrated function of the cardiovascular, pulmonary, musculoskeletal, and autonomic nervous systems.<sup>5,6</sup> The main pathways for ATP generation are oxidative phosphorylation, which relies on O<sub>2</sub> delivery from the cardiorespiratory system and for concurrent carbon dioxide (CO<sub>2</sub>) removal, and O<sub>2</sub>-independent substrate-level phosphorylation (often referred to as “anaerobic metabolism”) (Fig. 1). Exercise intensity dictates the metabolic demand and, therefore, the relative contributions of these pathways. The integration of these systems is described by the Fick equation:

Oxygen uptake = Cardiac output × arteriovenous oxygen difference (a-vO<sub>2</sub> difference)

$$\dot{V}O_2 = Q_c \times (C_aO_2 - C_vO_2)$$

To measure  $\dot{V}O_2$  the volume and concentration of O<sub>2</sub> and CO<sub>2</sub> in inspired and expired gas are directly measured during incremental exercise. Maximal oxygen uptake ( $\dot{V}O_{2\text{ max}}$ ) is the gold standard measure to quantify CRF.<sup>5,6</sup>  $\dot{V}O_{2\text{ max}}$  varies across the population and changes over the course of a person's lifetime based on age, sex, body composition, health status, and training. To allow for comparison between individuals,  $\dot{V}O_{2\text{ max}}$  is often normalized to body mass. In the absence of exercise training,  $\dot{V}O_{2\text{ max}}$  declines by approximately 1% (0.4 to 0.5 ml/kg/minute) per year. However, maintenance of physical activity along with ideal

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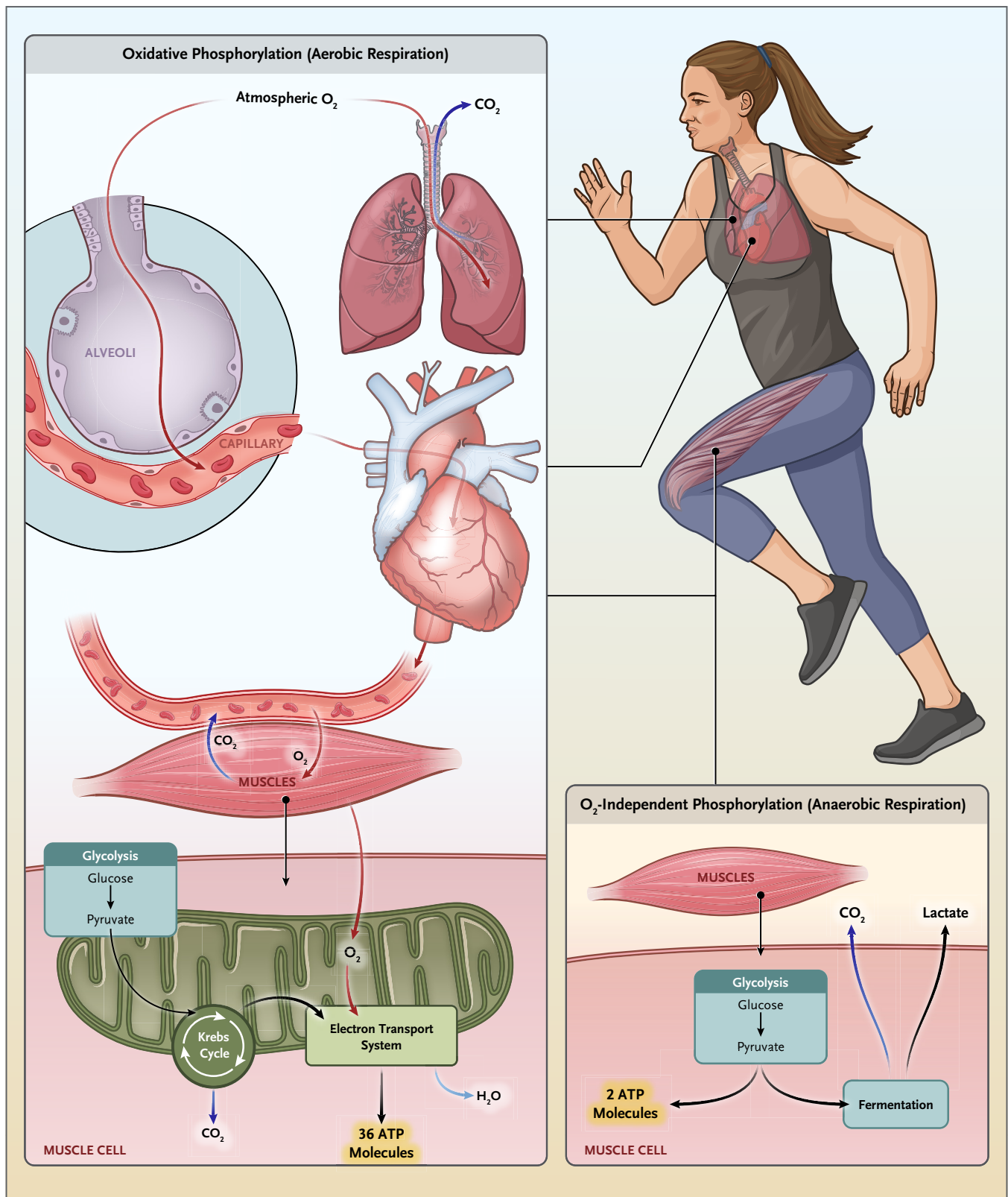


Figure 1. Aerobic and Anaerobic Respiration During Physical Activity.

ATP denotes adenosine triphosphate;  $CO_2$ , carbon dioxide;  $H_2O$ , water; and  $O_2$ , oxygen.

body weight with aging can attenuate this decline. Some studies suggest an accelerated decline in  $\dot{V}O_2$  max after 40 to 50 years of age, particularly after 70 years of age.<sup>2,7,8</sup> The relationship between  $\dot{V}O_2$  and workload is linear until maximal effort.  $\dot{V}O_2$  max is commonly used as an outcome measure in exercise physiology research, clinical exercise testing, and sports performance analysis to assess cardiorespiratory function, quantify energy expenditure, and prescribe exercise intensity for training and rehabilitation purposes.

To categorize a patient's CRF, the measured  $\dot{V}O_2$  max can be compared with a predicted value. Multiple equations exist to estimate  $\dot{V}O_2$  max based on the workload achieved during submaximal exercise (e.g., speed, grade, and duration on a treadmill or watts on a cycle ergometer) when a direct measurement of  $\dot{V}O_2$  is not available. However, these estimations are only a guide and can be heavily influenced by technique (e.g., holding on to the side rails of the treadmill). In the absence of  $\dot{V}O_2$  max data, indirect measures of CRF may be used. Metabolic equivalents (METs) are a convenient, standardized way to describe the intensity of physical activities relative to rest. In healthy male individuals, one MET is estimated to be equivalent to a  $\dot{V}O_2$  of 3.5 ml/kg/minute and represents resting in the seated position. This conversion is commonly used in healthy men and women despite limited validation in diverse cohorts. Competitive endurance athletes are able to achieve more than 20 METs of activity. During treadmill exercise, METs can only be reliably estimated if the patient is not using any upper-body supports. The *Adult Compendium of Physical Activities* was developed to standardize the measurement and classification of energy expenditure during a wide variety of activities for use in research and clinical practice when physical activity levels are self-reported.<sup>9</sup> This resource gives an estimate of the  $\dot{V}O_2$  requirement of a wide variety of occupational, recreational, physical conditioning, and self-care activities ([Box 1](#)).

In most individuals at sea level,  $\dot{V}O_2$  max is limited by maximal cardiac output (i.e., oxygen delivery). Importantly,  $\dot{V}O_2$  correlates linearly with cardiac output ( $Q_c$ ) during exercise.<sup>10</sup> In healthy adults during physical activity, 5 to 6 liters per minute of  $Q_c$  are required for every 1 liter of oxygen uptake.<sup>9</sup> The term  $\dot{V}O_2$  peak is often used instead of  $\dot{V}O_2$  max, particularly if repeat testing is not completed to verify that the individual is reaching their maximal limit, or the patient has noncardiac symptoms that limit their performance in advance of reaching their true maximum.

### Box 1: Activity Levels and Their Metabolic Equivalent Values

Light activity	2.0–2.9 metabolic equivalents (METs)	Slow walking, light housework, arts and crafts
Moderate activity	3.0–5.9 METs	Walking (3.0 miles per hour [mph]), sweeping floors, slow ballroom dancing
Vigorous activity	≥6.0 METs	Walking (4.0 mph), jogging (5–7 mph), shoveling, swimming

### SUBSTRATE UTILIZATION

At rest, the body uses carbohydrates and fats to generate ATP (36 ATPs per molecule of glucose) through aerobic metabolism. The resting respiratory quotient is the ratio of  $CO_2$  produced to  $O_2$  consumed at rest and varies based on diet: carbohydrates=1.0, fats=0.71, and mixed=0.85. The respiratory exchange ratio, akin to the respiratory quotient during rest, reflects the balance of energy sources used for ATP production as the body relies on additional nonoxidative pathways to increase the work rate once aerobic metabolism is maximized.

At lower intensities of exercise, the predominant fuel source is fat. As exercise intensity and power output increase, fatty acid oxidation decreases and carbohydrate utilization increases, eventually exceeding fatty acid oxidation.<sup>11</sup> The shift in predominant fuel source is due in part to increases in sympathetic nervous system activity, contraction-induced muscle glycogenolysis, and changes in muscle fiber recruitment patterns.<sup>12–14</sup> This “crossover” from predominantly fatty acid oxidation to carbohydrate utilization represents the complex interplay between the nervous system, musculoskeletal system, and metabolism required to meet the energy requirements of sustained exercise.<sup>11</sup>

### CARDIOVASCULAR FUNCTION IN EXERCISE

The heart, the main pump of the cardiovascular system, must effectively deliver oxygen-saturated hemoglobin to metabolically active tissues and receive desaturated blood loaded with  $CO_2$  for transport to and elimination by the lungs.  $Q_c$  is the volume of blood pumped by the heart to the body's tissues each minute and is the product of heart rate (HR) and stroke volume (SV). At the onset of exercise,  $Q_c$  increases through changes in HR as mediated by the

autonomic nervous system and an increase in SV. The initial rise in HR is facilitated primarily through vagal withdrawal and governed by central command. As exercise intensity approaches the maximal steady state, sympathetic stimulation further contributes to increases in HR. Trained individuals have both higher vagal tone at rest and a lower intrinsic HR and, therefore, have a lower HR at rest and with submaximal exercise. In contrast, maximum HR is not affected by training and may actually be lower in trained individuals. Medications, such as atrioventricular nodal blockers, can attenuate the HR response to exercise. As maximal exercise capacity is approached, the rate of HR increase slows. The inflection point at which the linear relationship between work rate and HR becomes curvilinear is known as the Conconi HR.<sup>15</sup> In healthy untrained individuals, it often occurs as 50 to 70% of  $\dot{V}O_2$  max. While maximal HR can be estimated by a variety of equations, given the high variability among individuals, it is never to be used as an end point for a maximal exercise test.<sup>16</sup>

SV (calculated as EDV–ESV, or  $Q_c$ /HR) depends on the volume of blood in the ventricle at the end of diastole (end-diastolic volume, EDV, or preload), which is determined by the residual volume at the end of systole (end-systolic volume, ESV) and venous return. With exercise, muscular contractions around the veins in the extremities pump blood back to the heart and increase venous return (also known as “muscle pump”). Venous return is also increased during inspiration due to negative intrathoracic pressure (also known as “ventilatory pump”). This rise in venous return increases preload and, therefore, the left ventricular volume, which further increases SV through the Frank-Starling mechanism. Increased inotropy also increases SV and is influenced by myocardial fiber stretch, vagal withdrawal, sympathetic activation, and circulating catecholamines.<sup>17</sup> Thus, SV is influenced by preload, afterload, and contractility. In healthy individuals, SV can increase by 100% or more with exercise. As HR does not increase with exercise training, the primary cardiac adaptation for increasing  $Q_c$  in response to exercise training is through the augmentation of SV through physiologic eccentric myocardial hypertrophy (i.e., increase in wall thickness proportional to increase in radius), referred to as exercise-induced cardiac remodeling. Maximal exercise  $Q_c$  can increase by at least fivefold above resting values with training, and by even higher magnitudes in elite athletes.<sup>18</sup>

Inotropy is the ability of the cardiac myocyte to generate force and velocity in response to electrical stimulation. At a cellular level, the contraction of cardiac myocytes is primarily driven by the release of calcium ions from intracellular

stores in response to depolarization of the cell membrane. This influx of calcium triggers a series of molecular events that ultimately lead to the shortening of the contractile proteins actin and myosin within the myocyte, resulting in cell contraction and systole. By this mechanism, SV is increased through reductions in ESV. Calcium reuptake by the cytosol and sarcoplasmic reticulum restores calcium gradients during diastole and requires large amounts of ATP. Large increases in venous return during exercise are a more efficient means for increasing SV through the Frank-Starling mechanism, as described above. In trained endurance athletes, this increase in preload passively fills the ventricle in early diastole and stretches the cardiac myofilaments. The stretch of cardiac myofilaments enhances calcium sensitivity, allowing for more effective and efficient force generation.

With each systolic contraction, the heart must generate sufficient pressure to overcome the wall tension resulting from the pressure and radius of the ventricle (as demonstrated by the Law of Laplace). Afterload is the total myocardial wall stress generated during systolic ejection and is determined chiefly by left ventricular cavity size, wall thickness, and left ventricular systolic pressure. During dynamic exercise, arterial systolic blood pressure increases largely due to increased  $Q_c$  as well as reflexive increases in sympathetic vasoconstriction in nonexercising vascular beds. Additionally, increased venous return increases the EDV and ventricular radius, further increasing wall stress. Collectively, these exercise-induced responses lead to an increase in afterload. At rest, skeletal muscles receive approximately 15 to 20% of the total blood flow, which can increase to 80 to 85% during exercise.<sup>19</sup> The vasoconstrictor response is attenuated in working skeletal muscle due to locally released vasoactive signals, a process termed functional sympatholysis, resulting in a significant reduction in systemic vascular resistance. The interaction between sympathetic outflow and sympatholysis redistributes blood from less active tissue to meet the metabolic demands of working skeletal muscle.

Myocardial oxygen uptake ( $\dot{M}VO_2$ ) is the internal work that the heart must perform to meet its own  $O_2$  requirements, and is directly tied to HR, contractility, preload, and afterload.  $\dot{M}VO_2$  increases with exercise due to increased HR, afterload, inotropy, and preload. The myocardium meets its increased  $O_2$  demand through increases in blood flow through the coronary arteries that is achieved primarily through local vasodilation of the arterioles and enhanced flow-mediated dilation of the large epicardial arteries. Coronary flow reserve is the maximal augmentation of



blood flow through the coronary arteries above the resting volume. During exercise, if the coronary flow reserve is inadequate, a patient will experience myocardial ischemia.

## PULMONARY FUNCTION DURING EXERCISE

Enabling gas exchange between the atmosphere and the circulatory system, the lungs are the primary interface with the environment. Diffusion of  $O_2$  and  $CO_2$  occurs across the alveolar–capillary membrane driven by gradients in partial pressure (alveolar–capillary gradient) and is perfusion limited in healthy adults; that is, the rate of gas uptake is limited by capillary blood flow and not by diffusion across the alveolar–capillary membrane. Minute ventilation ( $V_E$ ) is the amount of gas that enters the lungs per minute and is calculated as the product of  $V_T$  and respiratory rate.

At the onset of exercise,  $V_E$  increases in response to increased  $O_2$  uptake and  $CO_2$  production.<sup>20</sup> This response is largely accomplished through increases in  $V_T$ . Exercise is also associated with a reduction in dead space, areas of the lung that are ventilated but not perfused. The reduction in dead space is accomplished through increased ventilation, as well as recruitment of alveolar capillaries in the setting of increased  $Q_c$ , and results in improved ventilation–perfusion matching. Once  $V_T$  doubles, the respiratory rate becomes dominant in augmenting  $V_E$ . Further increases in  $V_T$  would require more effort (and more blood flow) to ventilate distended or less compliant regions of the lungs and are therefore not favored physiologically. If exercise persists beyond the maximal point of aerobic metabolism, ventilation increases out of proportion to  $O_2$  uptake to compensate for the development of metabolic acidosis and maintain an appropriate blood pH.

Ventilatory changes with exercise are regulated by a combination of central command (motor and premotor regions of the brain relating to volitional/motor control), muscle afferent feedback, and metabolic inputs.<sup>21</sup> As exercise intensity approaches an individual's maximum steady-state, ventilation and  $CO_2$  production ( $\dot{V}CO_2$ ) exceed the increase in  $O_2$  utilization ( $\dot{V}O_2$ ) and  $CO_2$  clearance increases to compensate for progressive metabolic acidosis (i.e., exercise-induced changes in blood pH). This point, termed the ventilatory threshold, is the work rate that an individual can sustain for a prolonged period. It is one of the markers defining the maximal steady state of exercise.

In healthy individuals, ventilation is rarely the limiting factor in peak/maximal exercise. Therefore, the assessment of pulmonary function requires a more nuanced analysis of exercise data. One strategy to fully understand pulmonary limitations

is the  $V_E/\dot{V}CO_2$  nadir. This is considered the most reproducible indicator of ventilatory efficiency across age, sex, and exercise modality.<sup>22</sup> The  $V_E/\dot{V}CO_2$  nadir occurs just prior to the development of respiratory compensation (the onset of increased ventilation in response to evolving acidosis) and, in healthy individuals, corresponds to the  $V_E/\dot{V}CO_2$  at the ventilatory threshold. Evaluation of ventilatory efficiency is most useful at levels below the ventilatory threshold to limit the influence of other pulmonary limitations to exercise performance, such as mechanical limitations to inspiratory capacity, excess work of breathing and diaphragmatic fatigue, and/or the rapid transit of blood through the alveolar capillaries limiting diffusion time with high  $Q_c$  even in the absence of hypoxia. The slope of the  $V_E/\dot{V}CO_2$  relationship (i.e., ventilatory efficiency) has clinical implications. A slope of less than 30 is considered normal in healthy individuals, not accounting for the effects of age and sex. In patients with heart failure with reduced ejection fraction, a  $V_E/\dot{V}CO_2$  slope equal to or greater than 34 is associated with an increased risk for mortality and hospitalization.<sup>23</sup>

Patients have a ventilatory limitation to exercise when  $V_E$  approaches maximal ventilatory capacity. This is estimated by real-time comparison of an exercise tidal flow–volume loop within a maximal flow–volume loop. The overlay of these tidal flow–volume loops allows for the visualization of the available ventilatory capacity and the reserve for increasing tidal volume ( $V_T$ , within forced vital capacity) and/or respiratory rate (flow reserve).<sup>24</sup> However, this technique, often termed “breathing reserve,” is limited as it requires the calculation of a theoretical maximal flow–volume loop. Ventilatory demand rises in response to increasing exercise intensity.  $V_T$  expansion is achieved through both a decrease in end-expiratory lung volume (EELV) and an increase in end-inspiratory lung volume (EILV). In healthy individuals during heavy exercise, EILV approaches total lung capacity (TLC; up to 80 to 85%). As tidal expiratory flow approaches its maximum, EELV may increase, resulting in dynamic lung hyperinflation (defined as an increase in EELV from rest to peak exercise of more than 0.15 l).<sup>25</sup> When this occurs, EILV gets closer to TLC as  $V_T$  increases. Breathing near TLC is a major contributor to increased work of breathing and exertional dyspnea.<sup>26</sup> While this phenomenon can occur in healthy individuals during heavy exercise, it is a more common compensatory mechanism in respiratory diseases such as chronic obstructive pulmonary disease. Dynamic lung hyperinflation and high EELV/EILV can also occur with normal aging and in patients with obesity. If it is not possible to measure operational lung volumes (i.e., EILV and EELV), one can estimate

ventilatory reserve by the relationship between maximal exercise ventilation ( $\dot{V}_{E\max}$ ) and maximal voluntary ventilation (MVV) defined as:

$$\text{Ventilatory reserve} = 1 - ([\text{MVV} - \dot{V}_{E\max}]/\text{MVV}) \times 100$$

MVV can be measured directly with a 12- to 15-second maneuver or estimated from spirometry as the forced expiratory volume in 1 second ( $\text{FEV}_1$ )  $\times$  40.

## LACTATE AND VENTILATORY THRESHOLDS

Often occurring in tandem with the ventilatory threshold, the lactate threshold describes the exercise intensity at which the concentration of lactate in the blood rises faster than it can be cleared. A common misconception is that this rise in the levels of lactate is the cause of muscle soreness and fatigue and suggests poor perfusion. Instead, lactate serves as a link between glycolysis (anaerobic metabolism) and mitochondrial respiration (aerobic metabolism) through the lactate shuttle and is utilized as a preferred fuel in working skeletal and cardiac muscle.<sup>11,27</sup> At high intensities of exercise, increases in blood lactate concentration represent a crossover to predominantly carbohydrate utilization for fuel to support ongoing muscle activity.

As  $\text{O}_2$  demand increases with progressive exercise intensity, glycolysis supplements aerobic metabolism before the maximum rate of energy production through oxidative phosphorylation is exceeded. The increased utilization of glycolysis results in the production of lactic acid, which is buffered by sodium bicarbonate ( $\uparrow\text{Lactic acid} + \text{NaHCO}_3 \leftrightarrow \text{Na-lactate} + \uparrow\text{CO}_2 + \text{H}_2\text{O} + 2\text{ATP}$ ).  $\text{CO}_2$  production rises relative to  $\text{O}_2$  utilization due to lactic acid buffering, leading to increased stress on the respiratory system.

The point during exercise at which the increase in  $\dot{V}_E$  and  $\text{CO}_2$  production ( $\dot{V}\text{CO}_2$ ) exceeds the increase in  $\text{O}_2$  utilization ( $\dot{V}\text{O}_2$ ) and  $\text{CO}_2$  clearance is termed the ventilatory threshold.<sup>28</sup> In untrained, healthy individuals, the ventilatory threshold occurs at 50 to 60% of  $\dot{V}\text{O}_{2\max}$ .<sup>29-31</sup> The ventilatory threshold can be measured in multiple ways. One technique is the V-slope method, which involves plotting the relationship between  $\dot{V}_E$  and  $\dot{V}\text{O}_2$  during incremental exercise testing. The point at which there is a nonlinear increase in the  $\dot{V}_E/\dot{V}\text{O}_2$  ratio represents the ventilatory threshold. Multiple alternative assessments can be utilized to identify the ventilatory threshold, including the ventilatory equivalent method (the intensity of exercise at which the ventilatory equivalent of  $\text{O}_2$  [ $\dot{V}_E/\dot{V}\text{O}_2$ ] rises without a commensurate rise in the ventilatory equivalent of  $\text{CO}_2$  [ $\dot{V}_E/\dot{V}\text{CO}_2$ ]), the excess  $\text{CO}_2$  method (the intensity of exercise that results in an increase from steady state to an

excess of  $\text{CO}_2$  production), and changes in end-tidal partial pressures of  $\text{O}_2$  and  $\text{CO}_2$ . The V-slope method is often the preferred method as it is reliable and repeatable.

## PERIPHERAL OXYGEN EXTRACTION

The peripheral component that determines  $\dot{V}\text{O}_2$  is the arteriovenous oxygen difference (a- $\text{vO}_2$  difference), which is the amount of oxygen extracted and utilized by tissues to sustain a given level of activity. The a- $\text{vO}_2$  difference is determined by a combination of factors, including the redistribution of blood flow to exercising muscles (from cutaneous, renal, and splanchnic circulation), capillary density, the number and size of the mitochondria in the muscle cells, and the  $\text{O}_2$  and  $\text{CO}_2$  gradients. In healthy individuals, active tissues can extract more oxygen per milliliter of blood flow as demand increases.

## Conclusion

A normal exercise response is the integration of the cardiac, pulmonary, hematologic, musculoskeletal, and neurologic systems. Understanding the body's integrated response to exercise enables us to improve health and human performance with respect to both prevention and disease management. These basic principles of exercise physiology inform the interpretation of cardiopulmonary exercise tests and underly patients' functional capacity. The interpretation and utility of cardiopulmonary exercise testing will be covered in a future article in this series.

## Disclosures

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