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Exercise Physiology and Cardiopulmonary Exercise Testing

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ABSTRACT

Aerobic, or endurance, exercise is an energy requiring process supported primarily by energy from oxidative ATP synthesis. The consumption of oxygen and production of carbon dioxide in muscle cells are dynamically linked to oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) at the lung by integrated functions of cardiovascular, pulmonary, hematologic, and neurohumoral systems. Maximum oxygen uptake ($\dot{V}O_{2max}$) is the standard expression of aerobic capacity, and a predictor of outcomes in diverse populations. While commonly limited in young fit individuals by the capacity to deliver oxygen to exercising muscle, it may become limited by impairment within any of the multiple systems supporting cellular or atmospheric gas exchange. In the range of available power outputs, endurance exercise can be partitioned into different intensity domains representing distinct metabolic profiles and tolerances for sustained activity. Estimates of both $\dot{V}O_{2max}$ and the lactate threshold, which marks the upper limit of moderate intensity exercise, can be determined from measures of gas exchange from respired breath during whole body exercise. Cardiopulmonary exercise testing (CPET) includes measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ along with heart rate and other variables reflecting cardiac and pulmonary responses to exercise. Clinical CPET is conducted for persons with known medical conditions to quantify impairment, contribute to prognostic assessments, and help discriminate among proximal causes of symptoms or limitations for an individual. CPET is also conducted in persons without known disease as part of the diagnostic evaluation of unexplained symptoms. Although CPET quantifies a limited sample of the complex functions and interactions underlying exercise performance, both its specific and global findings are uniquely valuable. Some specific findings can aid in individualized diagnosis and treatment decisions. At the same time, CPET provides a holistic summary of an individual's exercise function, including effects not only of the primary diagnosis, but also of secondary and coexisting conditions.

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40 **KEYWORDS**

41 Oxygen uptake; Exercise intensity; CPET; Respiration; Power-duration relationship.

EXERCISE PHYSIOLOGY OVERVIEW

Introduction

The ability to sustain physical activities, including those for daily living, recreation, occupation or structured exercise depends on the capacity for oxygen transport and utilization. Endurance (or aerobic) exercise, such as walking or running, involves repeated muscle contraction that depends on oxidative energy provision in which oxygen is consumed and carbon dioxide produced. Multiple organ systems link oxidative metabolism in involved tissues, predominantly exercising muscle (internal respiration), to gas exchange with the atmosphere at the lung (external respiration). Other chapters in this publication detail the physiology of many processes fundamental to exercise, including tissue metabolism and gas exchange, gas transport in the circulation, the mechanics of breathing, control of ventilation, and pulmonary gas exchange. This chapter will touch briefly on muscle bioenergetics and the cardiovascular and pulmonary responses to exercise that support gas exchange. The range of endurance exercise is described in terms of discrete domains of intensity, characterized with respect to oxygen uptake, blood lactate and sustainability. With this as background, the measurements for characterizing exercise function that are typically available from a cardiopulmonary exercise test (CPET) will be reviewed along with examples of their applications in clinical practice.

Skeletal Muscle Bioenergetics and Oxidative Metabolism

Skeletal muscle contraction, along with other cellular processes, is powered by energy from adenosine triphosphate (ATP). ATP in skeletal muscle is maintained at low concentration (~8.2mM), and ATP demand can increase >100-fold from the resting level (~1 mM/min) at the onset of muscle contractions.[1] As such, muscle ATP could be depleted within seconds of exercise onset, if not for a parallel increase in ATP supply. Metabolic pathways for ATP synthesis are activated quickly, and in proportion to the metabolic demand of the exercise task. These pathways include substrate level phosphorylation in the

myocyte cytoplasm i.e., breakdown of phosphocreatine and glycolysis/glycogenolysis that forms lactate, and oxidative phosphorylation in muscle mitochondria. These pathways are common to all muscle cells, although differing fiber types within and between active muscles vary in their metabolic profiles, some being oxidative in nature (slow, type I) and others glycolytic (fast, type IIx). Intermediate fibers (fast, type IIa) share features of fast contractile properties, but can be highly oxidative in their metabolism. Muscle also contains hybrid fibers that express more than one myosin heavy chain. Skeletal muscle thus presents a continuum of pure and hybrid fiber types that bridge the range of metabolic demand.[2]

Exercise intensities that can be well-sustained are characterized by the recruitment of motor-units that have a high expression of oxidative metabolism. As exercise intensity and energy demand increase, more glycolytic and less fatigue resistant fibers are activated. Despite this, even at the highest levels of endurance exercise, the vast majority of ATP supply is still derived from oxidative phosphorylation, which depends on transport of oxygen from the mouth to muscle mitochondria where oxygen consumption occurs. Exercise can therefore be quantified by the corresponding rate of pulmonary oxygen uptake ($\dot{V}O_2$), and the capacity for exercise (or *aerobic capacity*) by the maximum rate of oxygen uptake ($\dot{V}O_{2max}$).

Substrate provision for exercise is predominately carbohydrates and fatty acids, with protein having little role except under conditions of starvation. The maximum rate of ATP supply from glycolysis/glycogenolysis (~1.1 mM ATP/s) is approximately twice that of carbohydrate oxidation (0.6 mM ATP/s), which is in turn approximately twice that of fatty acid oxidation (0.3 mM ATP/s).[1] During the first minutes of exercise, bioenergetics initially relies on substrate level phosphorylation (phosphocreatine breakdown and glycolysis/glycogenolysis), during which time carbohydrate oxidation is rapidly being activated and rises to meet the energy demands of the task. With sustained moderate intensity exercise there is progressive shift over time towards a higher proportion of fatty acid substrate. However, maximal rates of energy provision from fatty acid oxidation are limited, and therefore fatty

acid oxidation contributions to ATP supply are at their greatest during sustained moderate exercise intensities. Reliance on carbohydrate oxidation and substrate level phosphorylation increases as exercise intensity increases above moderate.

Maximum Oxygen Uptake ($\dot{V}O_{2max}$)

Among healthy persons, $\dot{V}O_{2max}$ has a wide range, varying by age, sex, muscle strength, and genomics, and is modifiable by exercise training. Average values can range from around 40 ml/min/kg in sedentary young adults to less than 20 ml/min/kg in older persons, and may be 60-80 ml/min/kg in conditioned endurance athletes. The normal limitation to $\dot{V}O_{2max}$ in trained young men is generally considered to lie in oxygen delivery processes, as aerobic capacity can be modified acutely by changes in arterial oxygen concentration.[3,4] This implies a metabolic reserve in skeletal muscle at maximal exercise in trained individuals. In very physically fit individuals, however, cardiovascular capacity for oxygen delivery may be sufficiently well-developed that constraints on pulmonary ventilation and gas exchange become evident, especially in endurance trained women.[5] For older, or more sedentary individuals, peripheral limitations in muscle mass and/or metabolic capacity for oxidative energy supply may dictate aerobic capacity.[3,6] Determinants of aerobic capacity may thus vary across the spectrum of apparently healthy individuals, and of course pathologic dysfunction of any component can impose limitation constraining $\dot{V}O_{2max}$.[e.g.,7-9]

Lactate Threshold

It has long been recognized that metabolic acidosis associated with lactate accumulation develops with strenuous exercise,[10] typically evident around 50% of $\dot{V}O_{2max}$.[11] The degree of lactate elevation portends intolerance for sustained activity.[12] The profile of arterial blood lactate concentration as a function of $\dot{V}O_2$ is therefore of great interest in characterizing cardiorespiratory fitness or severity of chronic disease (**Figure 1**)[12] and has been described and quantified in a number of ways.[13] It is most commonly

characterized as a threshold phenomenon during a progressive exercise test (where power output, and therefore metabolic demand, increases linearly with time), and defined by a *lactate threshold* (LT). The well-recognized relationship between ischemia and metabolic acidosis (Pasteur effect), along with observations that experimentally induced changes in oxygen delivery can acutely shift the $\dot{V}O_2$–lactate relationship,[14-19] was originally interpreted to mean the LT identified a state above which oxygen delivery failed to fully meet the oxidative metabolic requirements of exercise. In the 1960's Wasserman and McIlroy thus proposed estimating LT based on pulmonary gas exchange (see below), as a means of identifying cardiovascular impairment, and termed this the *anaerobic threshold* (AT).[20] Studies using labeled tracers to track the dynamics of lactate metabolism[21] have since demonstrated that lactate is produced in muscle throughout the entire range of exercise, participates in numerous metabolic pathways, and is a preferred substrate for energy production in many tissues.[22] Rather than marking the onset of lactate *production*, therefore, the LT reflects the metabolic rate at which lactate accumulation in the arterial blood outstrips its clearance. The estimated LT derived from gas exchange measurements has since been given a number of names including the *gas exchange threshold (GET)*, *lactic acidosis threshold (LAT)* and *ventilatory threshold (VT)*, although the AT remains in common use.[22]

Cardiovascular Responses to Exercise

The circulatory system is a central component of the exercise response. Cardiac output and exercising muscle blood flow increase in close proportion with metabolic rate with a ratio of between 5 and 6 L/min increase in blood flow for each liter increase in $\dot{V}O_2$ (**Figure 2A,B,D**), mediated by increases in both cardiac stroke volume and heart rate (**Figure 2E,F**).[23-25] Stroke volume increases by ~50% between rest and moderate intensity during upright exercise; there is little additional increase in stroke volume at higher intensities, and potentially a decline at very high heart rates (**Figure 2F**).[26,27] Heart rate increases progressively across the range of achievable exercise, with the peak value determined predominantly by age, independent of sex or level of conditioning.[28] In normal healthy individuals, heart rate and cardiac

output approach or reach individual maximal values (± 20 bpm) during a progressive exercise test. Endurance-trained individuals have higher than average stroke volume at rest and during exercise, due to a combination of greater ventricular filling (end-diastolic volume) and faster diastolic filling time, increased left ventricular ejection time and contractility, decreased afterload and/or greater blood volume. These adapatations are associated with lower resting heart rate and a shallower slope of relationship between heart rate and $\dot{V}O_2$, allowing these individuals to reach a greater $\dot{V}O_2$peak at peak heart rate during a progressive exercise test.[27]

The great majority of the increase of cardiac output during exercise is directed to the exercising muscle (**Figure 2D**), with concomitant reduction in flow to renal and splanchnic vascular beds.[26] The increase and redistribution of cardiac output in response to exercise result from a complex set of neural reflexes including both feedforward and feedback mechanisms. The feedforward component is termed central command,[29,30] referring to parallel afferent output from the central nervous system to both motor and cardiovascular structures. The effects include an abrupt increase in heart rate due to reduction of resting parasympathetic outflow to the heart, along with an increase in sympathetic outflow stimulating cardiac contractility, resulting in a near-instantaneous augmentation of heart rate, stroke volume and cardiac output at exercise onset. Essential to the cardiac output response is an increase in venous return to support preload.[31] This is mediated in part by the skeletal muscle pump, which trans-locates blood from dependent capacitance beds towards central venous vessels.[31,32] In health, thoracic pressure changes associated with ventilation also contribute to maintaining left ventricular preload.[33] Autonomic mediated increases in venous tone of splanchnic and peripheral veins may also contribute to redistribution of blood flow, though the role of these mechanisms is debated.[34,35]

Simultaneously, afferent signals traveling in type III and IV fibers provide feedback from mechanoreceptors and metaboreceptors in skeletal muscle to activate the exercise pressor reflex.[36] The pressor reflex constitutes a diffuse increase in sympathetic outflow, to increase vascular resistance and

decrease blood flow to regions with low metabolic needs. This is critical to maintenance of systemic blood pressure, which would otherwise drop precipitously, compromising perfusion of both active muscle and vital organs. Titration of systemic blood pressure during exercise is under the feedback control of the baroreflex, which operates at a higher pressure set point during exercise than rest,[37] such that mean arterial pressure rises.

The overall effect of these control mechanisms is that blood flow to the brain is preserved during exercise, and blood flow to active skeletal muscle and cardiac muscle is increased. Skin perfusion is also increased for heat dissipation, depending on exercise duration and environmental conditions. Blood flow to respiratory muscles increases in line with their oxygen consumption requirements, as ventilatory work increases.

A balance of central and peripheral mechanisms ultimately determines blood flow to the exercising muscle (**Figure 2D**). Local products of metabolism and/or responses triggered by metabo- or mechano-sensing result in local vasodilation.[26,38] Titration of muscle blood flow to its metabolic needs reflects a balance of local vasodilating processes and persistent sympathetic tone, the result of which are reflected in systemic oxygen extraction (arterio-venous O_2 concentration difference, $C(a\text{-}v)O_2$; **Figure 2C**). The locomotor muscles are the major contributor to increased oxygen extraction during exercise, and muscle venous PO_2 declines steeply with increasing work rate to a relatively stable nadir (~15-20 mmHg). The nadir venous PO_2 differs little whether exercise is above or below LT, but muscle venous oxy-hemoglobin saturation and oxygen content are lower at higher work rates, due to a shift in oxyhemoglobin dissociation curve as a result of increases in venous H^+ and CO_2 (the Bohr shift).[39] As a result, $C(a\text{-}v)O_2$ across exercising muscle (or the systemic circulation) increases progressively as $\dot{V}O_2$ rises (**Figure 2C**), even as average muscle capillary PO_2 remains relatively stable. The latter, together with longitudinal capillary recruitment to increase red blood cell apposition to muscle capillary endothelium, facilitates capillary to myocyte O_2 diffusion as work rate increases.[40] Approaching peak exercise, vascular

resistance towards the respiratory muscles may decline more than towards the exercising limbs, thereby diverting an increasingly-greater fraction of the cardiac output away from the exercising limbs, potentially limiting muscle oxygen consumption.[41]

Ventilation and Pulmonary Mechanics

Similar to the cardiovascular responses, minute ventilation ($\dot{V}_E$) increases immediately at the onset of exercise. The increase in $\dot{V}_E$ at moderate intensity exercise is predominately through increased tidal volume and, at higher intensities, by progressive increase in breathing frequency (f). This pattern helps to ameliorate increases in the work of breathing by expanding tidal volume (V_T) over the most linear range of respiratory system compliance, constraining further increase where tissue compliance falls steeply. Breathing mechanics are generally viewed as not limiting to exercise in healthy non-athletes, as there is an apparent 'breathing reserve' at peak exercise i.e., maximum voluntary ventilation (MVV) considerably exceeds $\dot{V}_E$ at peak exercise (**Figure 3A**). Similarly, V_T as a fraction of inspiratory capacity (IC) does not typically exceed ~70%, so there is also an inspiratory reserve volume, and flow rates of spontaneous breaths remain below maximal forced flows (**Figure 3A**). This pulmonary reserve contrasts with cardiovascular responses, where a reserve in heart rate and cardiac output is typically are absent in a progressive exercise test. Exceptions to the above pattern occur in endurance-trained individuals, and particularly trained females, whose capacity for oxygen delivery and utilization have increased to the point at which mechanical ventilatory reserves can be reduced or exhausted.[5] In these, the demand for high flow rates to service the ventilatory demand may cause dynamic hyperinflation–an increase in end-expiratory lung volume–as flow rates at low lung volumes become limiting (**Figure 3B,C**).[42]

Control of $\dot{V}_E$ during exercise includes both feedforward and feedback neural processes. Central command is credited with an immediate increase in $\dot{V}_E$. Group III/IV metabo- and mechano-receptors in peripheral muscle,[43,44] and stretch-receptors in the venous vasculature and cardiac muscle,[45] contribute

afferent feedback input that may influence exercise ventilation, although considerable redundancy exists and the precise mechanism awaits discovery.[43] Titration of $\dot{V}_E$ after the initial hyperpnea is attributed to chemical responsiveness, evidenced by stability of arterial PCO_2 (P_aCO_2), which is maintained very close to resting values during exercise below LT. The mechanisms preserving P_aCO_2 in such a narrow range in the face of dynamic changes in $\dot{V}CO_2$ remain incompletely understood. For exercise above LT, there is an additional increment in $\dot{V}_E$, which compensates for the metabolic acidosis by reducing P_aCO_2, partially mitigating the increase in arterial H^+.

Pulmonary Gas Exchange

Pulmonary gas exchange is discussed in detail elsewhere this series. In healthy individuals, alveolar ventilation ($\dot{V}_A$) increases considerably more than pulmonary perfusion ($\dot{Q}$) during exercise. Also, the relative dispersion of $\dot{Q}$ increases in heavy exercise in trained individuals, but to a lesser degree than for $\dot{V}_A$,[44] meaning that $\dot{V}_A/\dot{Q}$ mismatch increases in exercise, likely contributing to gas exchange inefficiency. Hyperventilation and $\dot{V}_A/\dot{Q}$ mismatch contribute to widening of the alveolar-arterial PO_2 difference ($P(A\text{-}a)O_2$) from ~5 mmHg at rest to ~25 mmHg in heavy intensity exercise in trained individuals. In some athletes, high intensity exercise leads to exercise induced arterial hypoxemia, attributed to a combination of a relative hypoventilation (due to respiratory mechanical contratints in those with high ventilatory demand), diffusion limitation, $\dot{V}_A/\dot{Q}$ mismatch and intrapulmonary shunting, although the contribution of each is still debated.[46-49] The increase in body temperature and metabolic acidosis above LT shift the oxyhemoglobin dissociation curve rightward, which also reduces S_aO_2 relative to P_aO_2. These effects are exacerbated by exercise training and may be marked in highly conditioned athletes.[50]

Despite the greater overall increase in $\dot{V}_A$ relative to that of $\dot{Q}$, the increased challenges to gas exchange efficiency during moderate and high-intensity exercise, and the increased CO_2 concentration of the pulmonary perfusate, the ratio of $\dot{V}_E$ relative to $\dot{V}CO_2$ decreases with exercise. $\dot{V}_E/\dot{V}CO_2$ is reduced from

values of around 40 at rest to 20-30 during moderate intensity exercise, implying more efficient elimination of CO_2 per unit increase in $\dot{V}_E$. For exercise above LT, $\dot{V}_E/VCO_2$ values rise above their nadir values due to increased $\dot{V}_E$ that compenses for the metabolic acidosis. Standard expressions of gas exchange efficiency can be calculated during exercise using arterial blood gas measures and corresponding gas exchange data. For O_2 exchange, this is the $P(A\text{-}a)O_2$ for which the P_AO_2 is calculated from the alveolar gas equation:

$$PAO_2 = FiO_2 *(P_B\text{-}47) – PaCO_2/R$$

Where P_B is barometric pressure and R is the simultanously measured ratio of $\dot{V}CO_2/\dot{V}O_2$. As noted previously, in healthy individuals $P(A\text{-}a)O_2$ increases progressively during exercise.

For CO_2 exchange, efficiency is calculated as the physiologic dead space volume to tidal volume ratio (V_D/V_T), using the Enghoff modification of the Bohr equation, which reflects the degree of difference in the partial pressures of CO_2 in exhaled breath compared to arterial blood:

$$V_D/V_T = [P_aCO_2 – (\dot{V}CO_2/\dot{V}_E)] / PaCO_2$$

Where $\dot{V}CO_2/\dot{V}_E$ is used to quantify mixed expired PCO_2 (P_ECO_2).

Using this approach, the calculated V_D/V_T reflects not only the truly un-perfused portion of each breath (dead space), but also the effect on CO_2 elimination of areas that are underperfused relative to ventilation (e.g., high $\dot{V}_A/Q$ regions).[51] In healthy individuals V_D/V_T decreases progressively over the course of graded exercise.[52] The decrease in V_D/V_T is attributable in considerable part to the greater increase in V_T relative to the much smaller increase in anatomic dead space. While it would seem likely that recruitment of the pulmonary capillary circulation due to increased perfusion would also tend to reduce high $\dot{V}_A/Q$ regions during exercise, analyses of $\dot{V}_A/Q$ distribution using the multiple inert gas

elimination technique have not demonstrated a reduction in $\dot{V}_A/Q$ mismatch from rest to moderate exercise in healthy people.[53]**xercise Intensity**

How long an exercise task can be maintained at a given power output i.e., endurance or exercise tolerance, is clearly of importance with respect to sustaining personal, occupational or athletic activities. While endurance athletic performance may be broadly correlated with $\dot{V}O_{2max}$, stratifying work rates into discrete domains of exercise intensity, defined by metabolic factors influencing exercise tolerance for the individual, affords more precise prediction of exercise tolerance. Key features of this are illustrated in **Figure 4** which shows changes in $\dot{V}O_2$, tolerable duration and lactate concentration over time for 4 endurance work rates in healthy individual.[54] These responses illustrate 3 discrete intensity domains; moderate, heavy and very heavy (the latter has also been termed severe). It must be acknowledged that there are a number of models proposed to classify exercise intensity, and both the models and the distinctions derived from them have limitations.

Moderate Intensity Exercise

Moderate intensity exercise encompasses work rates below LT and is characterized by a $\dot{V}O_2$ response that increases from baseline to reach a new steady state (**Figure 4A**). This occurs within 2 to 3 minutes in healthy individuals. The increment in steady state $\dot{V}O_2$ relative to work rate has a consistent relationship of 9-11 ml/min/watt. This relationship varies little between individuals by age, state of training, or even in chronic disease conditions, and reflects the intrinsic bioenergetics of skeletal muscle aerobic metabolism when carbohydrate is the primary substrate. In the moderate intensity domain, there may be a transient rise in lactate concentration in the earliest minutes of exercise, but this intensity is characterized by the ability to stabilize lactate concentration at or below the resting value (**Figure 4C**). Moderate intensity exercise can therefore be sustained for hours, and its energy demands met by

wholly aerobic ATP supply. Endurance time for moderate intensity exercise might well be dictated by factors external to the exercise itself.

It is perhaps worth noting that an intensity domain below moderate likely exists (light intensity exercise), and would describe a range of power outputs that could be sustained functionally indefinitely, i.e. measured in units of months. The $\dot{V}O_2$ and blood lactate characteristics in this domain would be essentially the same as moderate intensity exercise, but the maximum metabolic rate for light intensity would be much lower. It has been suggested, based on running data from the transcontinental Race Across the USA (RAUSA), that light intensity exercise may be limited by the rate at which the alimentary system can provide nutrition to sustain exercise of this type; elite athletes being limited in this domain to metabolic rates of ~10 mL/min/kg.[55]

Heavy Intensity Exercise

Exercise in the heavy intensity domain (work rates above LT but below critical power (CP; see below)) is characterized by an elevated but stable lactate concentration (typically ~2-4mM) and a $\dot{V}O_2$ response that may take up to 20 minutes after exercise onset to reach dynamic equilibrium (**Figure 4A,C**).[55] Exercise in the heavy intensity domain has reduced efficiency, demonstrated by the attainment of a $\dot{V}O_2$ that is 0.5 ml/min/watt greater than the expected value of 9-11 ml/min/watt i.e. an ~5% reduction in work efficiency. This additional $\dot{V}O_2$ is termed the $\dot{V}O_2$ "slow component" and is thought to relate to the effects of muscle fatigue on increasing the ATP demand to maintain mechanical output.[56-58] Exercise in this domain is terminated without reaching $\dot{V}O_{2max}$. Most exercise tasks in the heavy domain would be sustainable for ~1 hour, and potentially more, depending on factors such as muscle glycogen storage, body temperature or hydration status, or other environmental conditions.[59]

Very Heavy Intensity Exercise

Work rates above CP are termed very heavy (or severe). The upper work rate limit of this domain varies depending on the model used, but in any case, these work rates are characterized by the attainment of $\dot{V}O_{2max}$ at the tolerable limit. In the very heavy intensity domain both $\dot{V}O_2$ and lactate concentration increase throughout exercise (**Figure 4A,C**).[60,61] Here, the $\dot{V}O_2$ slow component can cause $\dot{V}O_2$ increments to reach values of ~14 ml/min/watt, equivalent to a ~40% loss of work efficiency.[60] Exercise in the very heavy intensity domain illustrates the classical definition of $\dot{V}O_{2max}$,[62] because no matter the work rate used in this domain, $\dot{V}O_2$ reaches the same value at the tolerable limit. Exercise in this domain is typically limited to less than ~30 minutes and is highly dependent on motivation.

Power-Duration Relationship and Exercise Tolerance

The inverse relationship between work rate and tolerable duration in the very heavy intensity domain is termed the power-duration relationship and is hyperbolic in nature (**Figure 4B**). Extrapolation of this power-duration relationship identifies an asymptote, which is termed *critical power* (CP). CP demarks a metabolic rate above which a dynamic equilibrium in $\dot{V}O_2$, lactate concentration and muscle metabolism can no longer be achieved, and is therefore the upper boundary of heavy intensity exercise.[63-65] CP is typically about half way between work rates at LT and $\dot{V}O_{2max}$, but can vary widely (~30-80%) by age or state of training.[11]

Summary of Exercise Intensity

The concept of distinct intensity domains (**Figure 4**) provides a framework for considering the capacity for various activities ranging from those that can be performed for hours at a time with minimal metabolic perturbation, to those having energy requirements above $\dot{V}O_{2\ max}$, but which can nevertheless be performed for a finite duration. Intensity domains may be demarked by LT, CP and $\dot{V}O_{2max}$, which are each modifiable (both in absolute terms and in their relative proportions) by exercise training or chronic disease. LT and $\dot{V}O_{2max}$ can be assessed by gas exchange using incremental exercise tests, as discussed in

the next section. CP demarcates heavy from very heavy intensities, and is relevant to exercise prescription and for optimizing athletic performance, but is more challenging to identify. .

CARDIOPULMONARY EXERCISE TESTING (CPET)

Introduction to CPET

Cardiopulmonary exercise testing (CPET) incorporates measurement of ventilation and pulmonary gas exchange along with electrocardiogram (ECG) and blood pressure, during a standardized exercise stress. Here we describe elements of routine clinical CPET, commonly measured variables and their relevance to some common conditions, and applications of CPET in medical practice.

Protocols and procedures

Most CPET utilizes graded (incremental), symptom-limited protocols, in which work rate is increased progressively over a single uninterrupted test to maximum tolerated level. Extensive experience has resulted in established practice standards[66-70] and a defined safety profile[71-73] for this kind of exercise stress.

Treadmill or cycle ergometer are most commonly used for CPET in clinical practice; both engage a large, although not identical, mass of skeletal muscle. Most individuals reach a higher $\dot{V}O_2$ on treadmill testing,[74,75] so this is arguably preferred for eliciting truly maximal responses. Also, patients with hypoxemic lung disease typically have more marked arterial oxygen desaturation on treadmill testing compared with cycle,[76,77] and patients dependent on rate-adaptive pacemakers may have a greater pacemaker response on treadmill. On the other hand, because the body weight is supported during cycling, it may be preferable for individuals with severe impairment, or with gait or balance difficulties. There is less body movement during cycling, which minimizes motion artifact in ECG or other signals,

and the ergonomics of cycling are less variable than of walking in the face of changing work rate, so cycle exercise allows more precise quantification of external work rate.[78] In some circumstances, such as evaluation of competitive athletes or individuals in highly physical occupations, it may be desirable to customize exercise formats or ergometers to mimic the sport or occupation.

There are many eponymous graded exercise testing protocols in clinical use. While all may serve to elicit maximal responses, they may be less suited for discrimination of submaximal variables e.g., LT. These are best identified from tests with gradual and linear transition of work rates through intensity domains. Recommended protocols for CPET thus begin, after a baseline of rest, with a nominal (moderate intensity) work rate, continued for several minutes for establishment of a steady state, followed by increases in work rate in frequent equal increments or as a continuous "ramp" function.[79,80] Conventional wisdom is that peak performance is optimized when the graded portion of a CPET is 8-12 minutes in duration,[80] but longer or shorter tests should have similar peak results in most cases.

The work profile represented by graded tests is designed to span the aerobic range in a short period of time, and not intended to mimic spontaneous daily activities. Responses to laboratory tests may thus not extrapolate directly to other modes of exercise. Routine CPET also does not measure all potential aspects of exercise pathophysiology. These limitations notwithstanding, graded, symptom-limited CPET protocols provide a meaningful profile of exercise function in a defined set of variables, and can be readily repeated for serial assessments. Other protocols, utilizing constant work rates, may be used e.g., to mimic recreational or occupational conditions, for bronchoprovocation, or address other specific questions. Constant work rate exercise protocols for determination of endurance time are especially useful for serial testing in studies of clinical interventions.[11] This is due to the shape of the power-duration curve (**Figure 4B**), for which small increments in peak or threshold values translate into substantial increases in endurance time over the asymptotic range of the relationship.[81,82]

Measurements

Primary physical measurements in CPET are: respiratory flow rates, gas tensions in respired breath, and time. From these are calculated $\dot{V}_E$, V_T, f, $\dot{V}O_2$, $\dot{V}CO_2$ and end-tidal partial pressures of O_2 ($P_{ET}O_2$) and CO_2 ($P_{ET}CO_2$). Additional variables are derived from these including slopes, quotients, or differences of the values. Typically, additional instrumentation is used to measure: heart rate (HR) and ECG; pulse oximetry (SpO_2); blood pressure (BP); and work rate (WR), which can be measured when using a cycle ergometer, or estimated when using a treadmill. Widely available commercial instruments calculate $\dot{V}_E$ and gas exchange, most commonly on a breath-by-breath basis,[83] and include software that automates calibration, calculations, data storage and reporting. This makes CPET readily adaptable to clinical settings, but also distances the user from the measurement processes, so attention to quality control and data validation remain essential to ensure accuracy.[83-85]

CPET Variables

Variables typically reported from non-invasive CPET are grouped here under broad headings of those most related to: (1) Oxygen delivery and utilization i.e., cardiovascular and metabolic; (2) Mechanics of breathing; and (3) Efficiency of pulmonary gas exchange.[78] These processes are highly interdependent and interactive, so such grouping should be taken as a practical approach to organizing data rather than an implication that the underlying processes can be viewed in isolation.

Oxygen Delivery and Utilization (Figures 5 and 6):

- **Peak oxygen uptake ($\dot{V}O_{2peak}$)**. As identified earlier, $\dot{V}O_{2max}$ is a task specific value which, in health, is primarily a reflection of the cardiovascular capacity for oxygen delivery, but may be limited by constraint or disease in other organ systems. The classical definition of $\dot{V}O_{2max}$ is rarely met during CPET, so the highest $\dot{V}O_2$ value, averaged over the last 20-30 seconds of the test, is termed the $\dot{V}O_{2peak}$ (**Figure 5A**). Adding a brief 'confirmation' bout of high work rate exercise at

the end of the graded test has been proposed to determine if the definition of $\dot{V}O_{2\,max}$ is satisfied,[86-88] but this is not widely utilized.

- **Oxygen uptake to work rate slope ($\Delta\dot{V}O_2/\Delta WR$)**. For a linear increase work rate (WR) over time (after a short lag related to $\dot{V}O_2$ kinetics), there is progressive increase of $\dot{V}O_2$ which has a slope similar to the 9-11 ml/min/watt established from moderate intensity steady state exercise measures. This slope is typically near-linear over the duration of a graded test, as shown in **Figure 5A**. The apparent absence of the $\dot{V}O_2$ "slow component" in the upper range is attributable to the slow $\dot{V}O_2$ kinetics being obscured by the relatively rapid progression in work rate .[89,90] Consistent with this, upward or downward deviation of the slope above LT is apparent with particularly slow or rapid work rate incrementation, respectively.[91]

  Abnormally low $\Delta\dot{V}O_2/\Delta WR$ slopes are sometimes evident in disorders of oxygen delivery, e.g., metabolic myopathy[92] or oxygen delivery e.g., cardiovascular disease,[92] and downward deflection of an initially normal slope may mark the onset of exercise-induced myocardial ischemia.[93] These low slopes do not indicate higher metabolic efficiency, but rather failure to keep pace with rising oxygen requirements in the non-steady state conditions of the test.[94] This is mirrored in the recovery phase as a slow progression of $\dot{V}O_2$ to re-attain its baseline rate.[92]

  Ergonomic factors can also alter the $\Delta\dot{V}O_2/\Delta WR$ slope, particularly during treadmill exercise as gait changes following adjustments in grade or speed can change economy of movement. Also, use of handrails to support the body weight can markedly reduce the actual work being performed. For these and other reasons, $\Delta\dot{V}O_2/\Delta WR$ slope is usually only interpreted for cycle tests.

- **Peak heart rate (HR)**. HR is usually identified from the RR interval of the ECG signal, calculated over several cardiac cycles, and peak HR averaged over the same interval as other peak values

(**Figure 5B**). Peak HR is age-dependent, but with a SD of ~10 beats/min in healthy unmedicated individuals, it has a wide normal range.

- **Oxygen pulse ($\dot{V}O_2$/HR or O_2 pulse)**. The Oxygen pulse[95] (**Figure 5B**) has units of ml of O_2 per heart beat. This variable is derived from expressing $\dot{V}O_2$ in terms of the Fick relationship, with each side of the equation divided by HR. This identifies that O_2 pulse, which is easily determined from non-invasive measures, is numerically equal to the product of cardiac SV and O_2 extraction, important functions that are less readily measured:

$$\dot{V}O_2 = Q \times C(a\text{-}v)O_2 \qquad \text{(Fick Relationship)}$$

$$\dot{V}O_2/HR = SV \times C(a\text{-}v)O_2 \quad (O_2 \text{ pulse})$$

Peak O_2 pulse is increased in the setting of isolated chronotropic impairment, reflecting the associated augmentation of SV. Low values conversely might reflect reduced SV, however, constraint of $C(a\text{-}v)O_2$ due to anemia, hypoxemia or impaired peripheral oxygen diffusion or utilization might also be responsible. A plateau of O_2 pulse at a low value, despite increasing work rate, suggests a low maximal SV and/or $C(a\text{-}v)O_2$, or reciprocal changes in the two factors.

- **Chronotropic index ($\Delta HR/\Delta\dot{V}O_2$)**. Heart rate is normally a linear function of $\dot{V}O_2$ (**Figure 6A**).[96] In endurance trained individuals the relationship is shifted downward due to greater resting and exercising SV. Shallow slopes can result from impaired chronotropy, and a steep or steepening slope can result from cardiovascular or muscle impairments.

- **The gas exchange threshold (GET).** Non-invasive estimation of LT is made using combined gas exchange and ventilatory criteria.[97] The primary relationship to identify GET is the plot of $\dot{V}CO_2$ relative to $\dot{V}O_2$ (termed the "V-slope"), which inflects upward to exceed a baseline slope of ~1.0 **(Figure 6A)** (not to be confused with a respiratory exchange ratio value of 1.0; **Figure 6B**). The

acceleration of $\dot{V}CO_2$ relative to $\dot{V}O_2$ reflects the output of additional CO_2 from bicarbonate buffering of the metabolic acidosis, which augments the rate of CO_2 from oxidative metabolism.[11,92,97] Hyperventilation of any cause would also be associated with an inflection in the $\dot{V}CO_2$-$\dot{V}O_2$ relationship, and so is usually excluded by review of other variables. Specifically, in the absence of spurious hyperventilation, an inflection of $\dot{V}_E/\dot{V}O_2$ (also termed ventilatory equivalent for O_2) and $P_{ET}O_2$ precede changes in $\dot{V}_E/\dot{V}CO_2$ (ventilatory equivalent for CO_2) and $P_{ET}CO_2$, reflecting an immediate response of $\dot{V}_E$ to the excess CO_2 and delayed response to metabolic acidosis (see also **Figure 10A,C**).[92]

- **Respiratory exchange ratio (RER; $\dot{V}CO_2/\dot{V}O_2$)**. Under steady state conditions of rest or moderate exercise RER may range from 0.71 to 1.0 and is linearly proportional to the mix of substrate being oxidized by the whole body (fatty acids = 0.71; carbohydrates = 1.0). However, under non-steady state conditions – where a graded CPET is entirely non-steady state – RER is also a function of differing kinetics of $\dot{V}O_2$ and $\dot{V}CO_2$, the progressive rise in the proportion of gas exchange arising from exercising muscle, and, in the range above LT, the additional CO_2 evolved from acid buffering and hyperventilation. These two latter responses cause RER to increase progressively from LT to peak exercise such that an end exercise value above ~1.1 is expected (**Figure 6B**). The exact value of RER attained on a maximal test is variable, however, as it is affected by the test protocol..[e.g.,86] So while end exercise RER is often used in the assessment of test adequacy, no single cut off RER value identifies whether a test is maximal. In the immediate post exercise period, there is nomally a further steep increase in RER, due to the more rapid kinetics of $\dot{V}O_2$ relative to $\dot{V}CO_2$ as they recover towards their resting baselines. Transient episodes of hyper- or hypo-ventilation can distort the normal pattern of RER during a CPET, as $\dot{V}CO_2$ is affected by these to a much greater extent than $\dot{V}O_2$.

Breathing Mechanics (Figures 7, 8 and 9)

- **Peak ventilation ($\dot{V}_E$) and breathing reserve (BR)**. BR refers to the absolute or percent difference of peak $\dot{V}_E$ (**Figure 7**) and the capacity for pulmonary ventilation, with the latter conventionally taken as the maximum voluntary ventilation (MVV) (**Figure 7**). A BR of less than 15% of MVV has been proposed as indicating ventilatory limitation,[70] resulting either from low breathing capacity and/or from high $\dot{V}_E$ demand. Because the MVV maneuver is not always performed, or not performed optimally, estimates of MVV from FEV_1 multiplied by a factor of 35 - 40 are often used to estimate MVV. As the MVV is itself a rough estimate of breathing capacity, and peak $\dot{V}_E$ may be affected by test protocol, the BR is not a particularly precise measure.

- **Tidal volume (V_T) and breathing frequency (f).** Initial increases in $\dot{V}_E$ are primarily by increase in V_T up to a V_T approaching ~70% of IC, after which V_T remains relatively stable and breathing frequency rises (**Figure 7**; see also **Figure 9**). Individuals' breathing patterns vary related to respiratory system compliance and other factors.[98] However, some notable patterns diverging from normal may be identified. An oscillatory breathing pattern is seen in some individuals with severe heart failure.[98] Oscillatory breathing is characterized by cyclic variations in $\dot{V}_E$, primarily due to V_T, but also affecting other variables, with a period of 50-100 seconds, and is recognized as an indicator of poor prognosis in heart failure. Other patterns observed in individuals with unexplained dyspnea and termed "dysfunctional breathing", include highly irregular variation in tidal volumes or overt hyperventilation.[99,100] Another distinct cause of exertional dyspnea, exercise-inducedlaryngeal obstruction, is characterized by more subtle changes in inspiratory time and flow rates that may not overtly alter the V_T and f pattern.[101]

- **Expiratory flow limitation (EFL)**. Mechanical constraints on breathing, in both health and disease, are most likely to occur during expiration.[102] EFL is often quantified as the percentage (%EFL) of exhaled tidal volume corresponding to maximal flow rates, based on analysis of flow volume loops (**Figure 8A**).[102] For this, spontaneous breaths are positioned within maximal loops[42] anchored on the volume axis by serial measures of inspiratory capacity (IC) (**Figure 8B**). To avoid errors related to exertional changes in airway tone, the maximal loop should ideally be measured immediately post exercise, and to avoid artifacts from thoracic gas and airway compression, should be constructed from a series of submaximal efforts.[103] Other approaches to detecting flow limitation include application of negative pressure at the mouth during exhalation[104] or geometric analysis of the spontaneous tidal expiratory flow volume relationships.[105] Identification of EFL is of significance as the factor leading to changes in operational lung volumes and dynamic hyperinflation described below.
- **Operational lung volumes.** Increases in V_T during exercise are predominantly a result of increase in end inspiratory lung volume (EILV) (**Figure 8B**), usually with additional decrease in end expiratory volume (EELV) due to active exhalation (also see **Figure 3A**). Changes in IC measured during CPET are used to infer reciprocal changes in EELV, assuming, of course, that the IC maneuvers are consistently maximal, and not compromised by respiratory muscle fatigue or inspiratory airflow obstruction. These measures are of particular relevance to obstructive lung disease,[106] as a decrease in IC implies increased EELV, termed "dynamic hyperinflation" (DH) resulting from EFL and incomplete exhalation. With DH, V_T cycles over higher absolute lung volumes, which may include the flat portion of the respiratory compliance curve, and causes intrinsic positive end expiratory pressure, which increase work of breathing. These changes are associated with dramatic increase in dyspnea, occurring when inspiratory reserve volume (IRV) decreases below a critical value.[107] Importantly, DH can occur across a broad spectrum of COPD

severity (**Figure 9**), making this a particularly valuable assessment when symptoms seem disproportionate to resting lung function impairment.

Pulmonary Gas Exchange Efficiency (Figure 10)

- **Oxygen saturation by pulse oximetry (SpO_2)**. Adequacy of oxygenation can be assessed non-invasively by pulse oximetry estimates of SaO_2 (**Figure 10C**). Oximetry is most useful for tracking changes in hypoxemic patients during exercise. Because a number of factors affect the accuracy of exercise pulse oximetry,[108,109] unexpected low values may require verification.

- **Ventilatory efficiency ($\dot{V}_E/\dot{V}CO_2$ nadir and $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ slope)**. The relationship of $\dot{V}_E$ to $\dot{V}CO_2$ has emerged as an important CPET outcome, reflecting disease severity, gas exchange inefficiency, and prognosis in both pulmonary[110] and cardiovascular[111] diseases. It is characterized either as the absolute ratio $\dot{V}_E/\dot{V}CO_2$ at its nadir shortly after GET (**Figure 10A**), or the slope of $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ (**Figure 10B**). The slope is most appropriately measured over the linear portion of the relationship, prior to development of respiratory compensation for metabolic acidosis (as indicated in **Figure 10B**). The $\dot{V}_E/\dot{V}CO_2$ relationship can be seen as determined by the set point for P_aCO_2 and the effective V_D/V_T:

$$\dot{V}_E/\dot{V}CO_2 = 863/P_aCO_2 * (1-V_D/V_T)$$

Elevation of $\dot{V}_E/\dot{V}CO_2$ thus occurs in diverse conditions associated with alterations in pulmonary $\dot{V}_A/\dot{Q}$, ventilatory drive, and/or acid base balance.

Considerable attention has been given to $\dot{V}_E/\dot{V}CO_2$ in heart failure, and relating it to elevated V_D/V_T.[112] Elevated $\dot{V}_E/\dot{V}CO_2$ also, although not always,[113] results from some degree of hypocapnia, reflecting heightened ventilatory drive. The increased ventilatory drive has been

linked to heightened stimulus from peripheral mechano- or ergo-receptors[114] and/or chemoreceptors in the carotid bodies.[115] The basis for the increased physiologic V_D/V_T in heart failure has eluded simple explanation. Reduced tidal volume may be a factor and was identified as the major determinant of elevated V_D/V_T in one analysis.[116] In a review of the physiology of respiratory dead space, Robertson reminds us[51] that well-established models of pulmonary gas exchange[117] predict that any increased $\dot{V}_A/Q$ inhomogeneity (even in the absence of true dead space) will lead to an increase in calculated V_D/V_T, and that this effect will be amplified as the overall $\dot{V}_A/Q$ ratio rises. Although overall $\dot{V}_A/Q$ rises during exercise even in healthy individuals, in heart failure, augmented ventilatory drive, low resting cardiac output, and constraint of the exercise cardiac output response together can result in an exceptionally high overall $\dot{V}_A/Q$. Several factors therefore, including augmented ventilatory stimulation, impaired cardiac output, and constrained breathing mechanics, appear to contribute to high $\dot{V}_E/\dot{V}CO_2$ in heart failure.

- **End tidal gas tensions**. End tidal gas tensions are easily measured but challenging to interpret. End tidal PCO_2 ($P_{ET}CO_2$) at rest is normally 1-3 mmHg less than P_aCO_2. With exercise $P_{ET}CO_2$ initially increases to values exceeding arterial. However, at the onset of respiratory compensation for a metabolic acidosis, $P_{ET}CO_2$ begins to decrease (**Figure 10C**). Thus, $P_{ET}CO_2$ cannot be equated to $PaCO_2$; a resting $P_{ET}CO_2$ above the normal P_aCO_2 range strongly implies hypercapnia, but low values, whether at rest or exercise, can result from either low P_aCO_2 or elevated V_D/V_T.

Low $P_{ET}CO_2$ is one of multiple CPET findings with negative prognostic implication in cardiovascular conditions such as heart failure and pulmonary arterial hypertension. Comparison of $P_{ET}CO_2$ with P_ECO_2, may help distinguish among potential underlying causes. Although P_ECO_2 is always lower than $P_{ET}CO_2$ due to the diluting effect of physiologic dead space, both are reduced relative to normal when V_D/V_T is elevated. When elevated V_D/V_T is due to

uneven ventilation (i.e., obstructive airways disease) as opposed to altered perfusion (e.g., heart failure or pulmonary vascular disease), the difference between P_ECO_2 and $P_{ET}CO_2$ is particularly marked. This is postulated to result from the fact that $P_{ET}CO_2$ in airways disease reflects exhalate from those lung regions with the longest ventilatory time constants, which tend also to have low $\dot{V}_A/\dot{Q}$.[118]

End tidal PO_2 ($P_{ET}O_2$) at rest is also close to arterial P_aO_2. $P_{ET}O_2$ begins to rise before $P_{ET}CO_2$ starts to decline during incremental exercise due to ventilatory changes associated with the GET, so along with $\dot{V}_E/\dot{V}O_2$, the $P_{ET}O_2$ is used in identification of GET.[97]

A distinct pattern of end tidal gas tensions occurs during CPET when there is exercise-induced right to left shunt, evident in some congenital cardiac lesions[119] or pulmonary hypertension with coincident patent foramen ovale.[120] The onset of shunting results in acute augmentation of $\dot{V}_E$, preventing the hypercapnia that would otherwise result from the acute increase in venous admixture. This is marked by a decrease in $P_{ET}CO_2$ and reciprocal increase in $P_{ET}O_2$, which is distinquished from pure hyperventilation by stability of $PaCO_2$.[119]

- **Alveolar arterial PO_2 difference ($P(A\text{-}a)O_2$) and Deadspace fraction of the tidal volume (V_D/V_T).** As shown earlier, these expressions of gas exchange efficiency are calculated from measures of arterial blood gases and gas exchange. Substituting $P_{ET}CO_2$ or a derivative thereof for P_aCO_2 in the V_D/V_T calculation systematically overestimates the value when normal, and underestimates it when elevated.[121] Transcutaneous PCO_2 ($P_{tc}CO_2$) devices measure arterialized capillary PCO_2, which is a closer estimate of stable P_aCO_2, although, because of the long response time of the electrode, do not accurately track acute changes in P_aCO_2,[122,123] limiting its use over portions of a CPET, especially into recovery.

Additional Measurements

- **Symptoms.** The symptom(s) leading to termination of exercise during CPET, and how they correspond to symptoms in daily activities, are important to ascertain. Standard rating scales of symptoms, such as the Borg rating of perceived exertion or modified scales for intensity of dyspnea or leg fatigue are readily administered during exercise and have high degrees of within subject repeatability.[124] In obstructive lung disease, a marked increase in dyspnea is likely when mechanical limits of breathing are approached, such as a V_T/IC ~70-80% and $\dot{V}_E$/MVV exceeding ~80%, (**Figure 10**).[125] Other exertional symptoms such as chest pain or lightheadedness are of importance in both diagnostic and safety considerations.

- **ECG**. Serial or continuous recording of ECG is used to identify cardiac rhythm and repolarization patterns as well as to calculate heart rate.

- **Blood pressure**. Systolic and mean arterial pressures, typically measured by auscultation, rise with exercise. Diastolic pressure typically decreases during treadmill exercise and rises during cycle tests.

Interpretation of CPET measures includes their comparison with appropriately selected reference values, of which there are many.[126] Differences among reference values can reflect differences in study cohorts with respect to demographics, levels of fitness, genetic profile, testing procedures, environmental (e.g., altitude) and other factors. There is also overlap in ranges of many variables in health and disease, which complicates strict demarcation of normal from abnormal ranges. For patients with known disease, comparisons may be more meaningfully made with data from relevant clinical cohorts for whom significance of particular variable values are known.

Applications of CPET

In clinical practice CPET is used to measure integrated exercise function of individuals with known conditions, to aid in prognostic assessment, and to identify reasons for a particular

individual'ssymptoms or limitations. CPET additionally has a role in diagnostic evaluation of symptomatic individuals in the absence of known or attributable disease.

Functional Assessment

$\dot{V}O_{2peak}$ quantifies cardiorespiratory fitness in healthy persons, and impairment in chronic disease. The latter is not necessarily predictable from static tests of organ function, which are largely insensitive to secondary systemic effects of disease, and to the confounding effects of additional co–morbid conditions. Integrated functional assessment may be relevant to establishment of disability,[127] or for exercise training or rehabilitation prescription, among other uses. Objective measures of functional capacity is particularly valuable in complex or heterogenous conditions. Congenital heart diseases, for example, are a diverse set of life-long conditions with wide ranges of exercise capacity even within anatomic diagnoses.[128] Clinical guidelines for the care of adults with congenital heart diseases[129] recommend objective exercise testing for baseline and serial assessment of function for many of these due to the limitations of assessment by history and anatomy alone.[128]

Prognosis

Many clinical applications of CPET are based on the prognostic significance of exercise function, which can be demonstrated in virtually any clinical population.[130-135] A well described example of this is chronic heart failure. Based on the recognized relationship between $\dot{V}O_{2peak}$ and prognosis, Mancini et al.[136] reported using $\dot{V}O_{2peak}$ to prioritize heart transplantation, deferring transplant for candidates whose $\dot{V}O_{2peak}$ was above 14 ml/min/kg, due to its predicting low risk of near-term mortality. These and scores of subsequent observations not only confirm the prognostic relevance of $\dot{V}O_{2peak}$ in heart failure, but also support the feasibility of maximal exercise testing of individuals with chronic disease and demonstrate that CPET results have sufficient physiologic meaning to be valuable in clinical decision making. Other variables derived from CPET, including $\dot{V}_E/\dot{V}CO_2$, $P_{ET}CO_2$ and oscillatory breathing patterns, also have

615 prognostic significance in heart failure and are recommended components of a multi-variable approach
616 to risk stratification.[130,137-140] The absolute risk predicted by given values of these variables has changed
617 with evolution of heart failure therapy, but they have remained relevant to the evaluation of patients
618 with advanced disease.[141]

619 Another prognostic use of CPET is risk stratification for anticipated stresses, including high-risk elective
620 surgery. While self-reported exercise capacity is a standard component of surgical risk assessment,[142]
621 there is interest in using objective measures of function when circumstances permit.[143] Much of the data
622 in this area identifies GET as the primary predictive variable, with values of 9-11 ml/min/kg
623 distinguishing between higher and lower risk of complications following major abdominal
624 procedures.[144,145] In addition to informing risk-benefit discussions, this has potential to aid in resource
625 management by identifying patients with a relatively favorable risk profile.[146]

626 Lung resection surgery presents a unique challenge in preoperative assessment, as it includes both
627 procedural risk and the permanent loss of pulmonary function. Risk stratification algorithms include
628 assessment of $\dot{V}O_{2peak}$ for selected individuals with anatomically resectable lung cancers.[147,148] Increased
629 risk of perioperative complications are associated with preoperative $\dot{V}O_{2peak}$ less than 15 ml/min/kg, and
630 concerns for unacceptable mortality with values below 10 ml/min/kg.[149] These criteria may be less
631 predictive of complications with minimally invasive surgical approaches.[150]

632 Additional conditions for which use of CPET is reported in risk stratification include hypertrophic
633 cardiomyopathy,[151] pulmonary arterial hypertension[152] and individuals with structural heart disease
634 considering sports participation[129] or pregnancy.[129,153,154]

635 ***Phenotyping***

636 Many chronic diseases are systemic in nature and the cause of associated impairment may be
637 heterogeneous and multifactorial. In heart failure, factors contributing to exercise limitation may

include defects in chronotropy, SV, vascular endothelial function, pressor response or skeletal muscle function; the relative importance of these varying among individuals even within clinical phenotypes based on ejection fraction.[144,155] Similarly, in COPD, individuals' limitations may differ with respect to the role of breathing mechanics[156,157] cardiovascular responses[158,159] or skeletal muscle function.[160,161] CPET can contribute to distinguishing critical factors of limitation which is central to the goal of individualizing therapy. Aspects of breathing mechanics are particularly amenable to non-invasive assessments, whereas defining hemodynamic and peripheral features and deciphering complex cardiopulmonary interactions[162] can require more specialized measures.[7]

CPET for Diagnostic Assessment

In clinical practice, CPET is often performed in individuals without known disease as part of the diagnostic evaluation of exertional dyspnea or other symptoms.[163] The distribution of conditions ultimately found to be responsible for dyspnea varies considerably.[164-169] and the diagnostic yield of CPET is thus likely to vary by clinical setting. Consensus among experienced users is that information gained from CPET is most helpful when part of a comprehensive assessment including history, risk factors and other clinical information.[70,170,171]

Performance of CPET for diagnostic purposes sometimes leads to a specific diagnosis e.g., when the presenting symptoms are reproduced during testing and accompanied by a distinct finding such as stridor indicative of upper airway dysfunction. Of the myriad processes that can cause exertional dyspnea, however, few have completely unique findings on CPET, and the range of factors that can constrain exercise or precipitate symptoms can easily exceed simple algorithmic approaches to identifying them. More commonly, therefore, the goal of diagnostic CPET is to broadly distinguish among abnormalities such as outlined in the categories identified above.[170] Evidence for impairment in one or more of these areas can serve to narrow an otherwise extensive differential diagnosis and so aid

661 in targeting additional specific diagnostics. Normal results can be useful as well, although do not
662 necessarily exclude pathology, as normal ranges for some variables are wide, such that decrements from
663 a previously trained state may occur without falling outside normal ranges. There are also aspects of the
664 exercise response that are not measured in routine testing.

665 Diagnostic potential of CPET can be expanded by additional measurements based on pre-test likelihood
666 of diagnoses, for example, direct laryngoscopy for suspected upper airway dysfunction,[172] or
667 echocardiography for structural or hypertensive heart disease.[173,174]

668 The addition of peripheral arterial and central venous catheterization to basic CPET procedures has been
669 termed invasive CPET (iCPET)[175] and allows quantifying central vascular pressures, cardiac output and
670 $C(a\text{-}v)O_2$ during exercise. This extends diagnostic capability to a number of hemodynamically defined
671 conditions,[176] including exercise induced pulmonary arterial hypertension, or pulmonary venous
672 hypertension due to left ventricular dysfunction. Other findings, while non-specific, can significantly
673 narrow diagnostic possibilities. For example, the finding of an excessively high slope of cardiac output
674 relative to $\dot{V}O_2$ implies either failure of autonomic regulation of distribution of cardiac output[177] or
675 impaired utilization of oxygen due to metabolic myopathy.[178]

676 **Conclusion**

677 Performance of exercise entails the interactive function of multiple organ systems. Exercise testing is
678 unique among clinical tools in that it reflects the aggregate effects of impairment in those individual
679 systems' functions, along with effects of compensatory responses and/or secondary or co-existing
680 conditions, on overall aerobic capacity. Measures of $\dot{V}O_2$ peak and GET identify the ranges of attainable
681 and sustainable exercise work rates for an individual, which can be considered in the context of those
682 for healthy or clinical reference populations. While non-specific, these are both functionally meaningful
683 and also may have powerful predictive value of use in clinical decision making. Additional measurements

684 from CPET characterize more specific aspects of cardiopulmonary exercise responses, which may offer
685 insight into the basis of an individual's symptoms or limitations.

686

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690

691 **CONFLICT OF INTEREST**

692 Harry Rossiter reports consulting fees from Omniox Inc., contributor royalties from *Wasserman and*
693 *Whipp's Exercise Testing and Interpretation* textbook, and is involved in contracted clinical research with
694 Boehringer Ingelheim, GlaxoSmithKline, Novartis, AstraZeneca, Astellas, United Therapeutics, Genentech
695 and Regeneron. He is a visiting Professor at the University of Leeds, UK.

696 Kathy Sietsema reports royalties from *Wasserman and Whipp's Exercise Testing and Interpretation*
697 textbook.

FIGURE LEGENDS

Figure 1. Change in arterial lactate concentration (LAC) as a function of oxygen uptake ($\dot{V}O_2$) during incremental cycle ergometry. Data are for healthy sedentary (filled circles) and active (open triangles) individuals and patients with cardiovascular disease (open circles). Resting lactate concentration is similar across groups. The $\dot{V}O_2$ at which lactate concentration increases is reduced in patients and increased in active individuals, compared with sedentary. mEq/L, milliequivalents per liter. Reproduced with permission from Wasserman.[12]

Figure 2. Changes in cardiovascular variables during incremental cycle ergometry in endurance trained young men (n=8). $\dot{V}O_2$ increases essentially linearly relative to power output **(A)**. The increase in cardiac output **(B)** is also linear through most of exercise, but plateaued in these subjects at ~80% peak power, corresponding to a decline in stroke volume **(F)**, and is compensated by an increase in systemic O_2 extraction ($C(a\text{-}v)O_2$) **(C)** and heart rate **(E)**. Essentially all the increase in cardiac output from rest to peak exercise is directed towards the legs during this cycling exercise **(D)**. Modified with permission from Mortensen et al.[25]

Figure 3. Pulmonary flow volume loops in health. **A)** Flow-volume response to exercise in the average fit healthy young adult during incremental exercise plotted within the maximal flow volume loop. In this population, end-expiratory lung volume (EELV) progressively decreases with exercise, and expiratory flow limitation is only present near EELV over a small portion of the tidal volume (V_T). Considerable room exists to increase ventilation even at peak exercise. Similar responses are also shown for the fit aged adult **(B)** and the young endurance athlete **(C)**. The older adult **(B)** represents a group of individuals with a mild decline in lung function but maintenance of a high ventilatory demand. Flow limitation occurs at low work rates and $\dot{V}_E$ demand (40 L/min) and end-inspiratory lung volume at peak exercise reaches a higher percent of total lung capacity. This group has significant ventilatory constraint at peak

721 exercise. The fit young athlete **(C)** represents a group of individuals with normal lung function but
722 excessive ventilatory demands. EELV initially decreases during exercise like the average fit adult, but
723 increases as significant expiratory flow limitation occurs. By peak exercise in the majority of these
724 subjects, significant ventilatory constraint is observed similar to the aged, fit adult. Reproduced with
725 permission from Johnson et al.[42]

726 **Figure 4. Exercise intensity domains and the power-duration relationship.** Schematic of characteristics
727 of three different exercise intensity domains: moderate (<LT), heavy (>LT but <CP) and very heavy (>CP).
728 In panels A and C physiologic responses are shown for one moderate, one heavy and two very heavy
729 intensity exercise bouts. Panel B shows the endurance time for the two very heavy intensity work rates
730 connected by the individual power-duration relationship. **A)** $\dot{V}O_2$ for heavy or very heavy exercise is
731 higher than would be predicted (dotted lines) from steady-state increments in the moderate range,
732 increasing to reach $\dot{V}O_{2max}$ in very intensity exercise. **B)** Endurance time is a hyperbolic function of work
733 rate, with an asymptote at critical power (CP). **C)** Stable lactate concentration is reached for moderate
734 and heavy intensity, but not in very heavy intensity exercise. LT, Lactate threshold. CP, Critical power.
735 Reproduced with permission from Rossiter.[54]

736 **Figure 5**. **$\dot{V}O_2$, $\dot{V}CO_2$, work rate (WR) and heart rate (HR) during incremental cycle exercise.** Data are
737 from a cycle ergometer CPET performed by a healthy 48-year-old woman. The protocol was three
738 minutes of rest, three minutes of pedaling without resistance followed by incremental increase in WR at
739 a rate of 15 watts/min, and two minutes of active recovery without resistance; protocol phases are
740 demarcated by vertical dotted lines. **A)** $\dot{V}O_2$ (closed circle), $\dot{V}CO_2$ (open triangle) and work rate (solid
741 line) plotted as a function of time in minutes. The diagonal dashed blue line parallels the $\dot{V}O_2$ data
742 beginning shortly after onset of incremental work and has a slope of ~10 ml/min/watt (i.e., parallel with

743 work rate when scaled appropriately). **B)** HR (closed circle) and $\dot{V}O_2$/HR (open circle) plotted as a
744 function of time in minutes.

745 **Figure 6. Oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and heart rate (HR) relationships for the**
746 **same CPET described in Figure 5**. . **A)** HR (solid circle) increases linearly relative to $\dot{V}O_2$. The horizontal
747 and vertical dashed lines indicate the predicted peak HR and $\dot{V}O_2$, respectively for this individual. $\dot{V}CO_2$
748 (open circle) a function of $\dot{V}O_2$ ("V-slope"). Diagonal solid line references a slope of 1.0 for this
749 relationship, and the blue arrow identifies the inflection point to a steeper slope, typical of the gas
750 exchange threshold (GET). **B)** Respiratory exchange ratio (RER) calculated as $\dot{V}CO_2/\dot{V}O_2$, plotted as a
751 function of time. RER increases towards 1.0 during moderate exercise and more steeply above GET.
752 Arrow indicates RER at time corresponding to GET identified from V-slope, at which RER typically is still
753 below a value of 1.0.

754 **Figure 7**. **Ventilation and Breathing pattern from the same CPET described in Figure 5**. **A)** Ventilation
755 ($\dot{V}_E$) as a function of time in minutes (solid circle). Also plotted are systolic blood pressure (SBP, red
756 circles) and diastolic blood pressure (DBP, green circles). **B)** Tidal volume (V_T) as a function of $\dot{V}_E$ (solid
757 circles) and periodic measurement of inspiratory capacity (IC) (yellow symbols). Horizontal dashed lines
758 indicate resting measures of vital capacity [VC (PFT)] and inspiratory capacity [IC (PFT)]. Vertical solid line
759 indicates maximal voluntary ventilation (MVV). The horizontal blue arrow indicates the breathing
760 reserve defined by the difference between peak $\dot{V}E$ and MVV, and vertical blue arrow the inspiratory
761 reserve volume, defined by the difference between V_T and IC.

762 **Figure 8. Operational lung volumes during exercise. A)** Resting and peak exercise spontaneous flow
763 volume loops within maximal flow volume loop (dark line) of an individual with chronic obstructive
764 pulmonary disease. **B)** Tidal volumes relative to total lung volume during graded exercise. DH, dynamic
765 hyperinflation. EELV, end expiratory lung volume. EILV, end inspiratory lung volume. EFL, expiratory flow

limitation. ERV, expiratory reserve volume. IC, inspiratory capacity. IRV, inspiratory reserve volume. MFVL, maximal flow volume loop. TLC, total lung capacity. V_{FL}, volume of flow limitation. V_T, tidal volume. WR, work rate. W, watts. Reproduced with permission from O'Donnell et al.[157]

Figure 9. **Relationships of ventilation, operational lung volumes and dyspnea during exercise across a spectrum of chronic obstructive lung disease (COPD) severity**. Group mean values for quartiles of patients stratified by forced expiratory volume in 1 second (FEV_1) during constant work rate cycle exercise at 75% of incremental peak work rate. Values shown at matched time points in exercise, and at individual V_T inflection points (defined by plateau of V_T as $\dot{V}_E$ continues to rise), and at peak exercise. **A**) V_T/IC related to $\dot{V}_E$: All patients increase V_T up to a limit of V_T/IC ≈ 70-80%, regardless of severity of lung dysfunction, but the rate of rise is faster, and the threshold reached sooner, for progressively worse lung function. **B**) Dyspnea related to V_T/IC: Dyspnea increases markedly around a threshold of V_T/IC ≈ 70-80% regardless of severity of lung dysfunction. **C)** Dyspnea related to $\dot{V}_E$: Dyspnea increases more quickly, and severe dyspnea is reached at lower levels of $\dot{V}_E$, with progressive severity of lung dysfunction. **D)** Same relationship as in C, but with $\dot{V}_E$ expressed as %peak: Dyspnea rises equally for all severities of lung dysfunction. Reproduced with permission from O'Donnell et al.[125]

Figure 10. Variables related to gas exchange efficiency for the same CPET described in Figure 5. **A)** Ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$; solid triangle) and for O_2 ($\dot{V}_E/\dot{V}O_2$; open circle). Blue arrow indicates typical finding of GET reflected in upward inflection of $\dot{V}_E/\dot{V}O_2$, without coincident increase in $\dot{V}_E/\dot{V}CO_2$. **B)** $\dot{V}_E$ as a function of $\dot{V}CO_2$. The dashed blue line is the $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ slope fit to the linear range of data, prior to respiratory compensation for metabolic acidosis. **C)** Values of end tidal PCO_2 ($P_{ET}CO_2$; solid red circle), end tidal PO_2 ($P_{ET}O_2$; solid blue circle), transcutaneous PCO_2 ($TcPCO_2$; green circle), and pulse oximeter estimate of arterial oxygen saturation (SpO_2; purple triangle). Blue arrow indicates tyupical finding of GET reflected in upward inflection of $P_{ET}O_2$ without coincident decrease in $P_{ET}CO_2$.

789 $TcPCO_2$ and SpO_2 signals are both subject to instrument delay times so changes in values lag other

790 variables and time axis.

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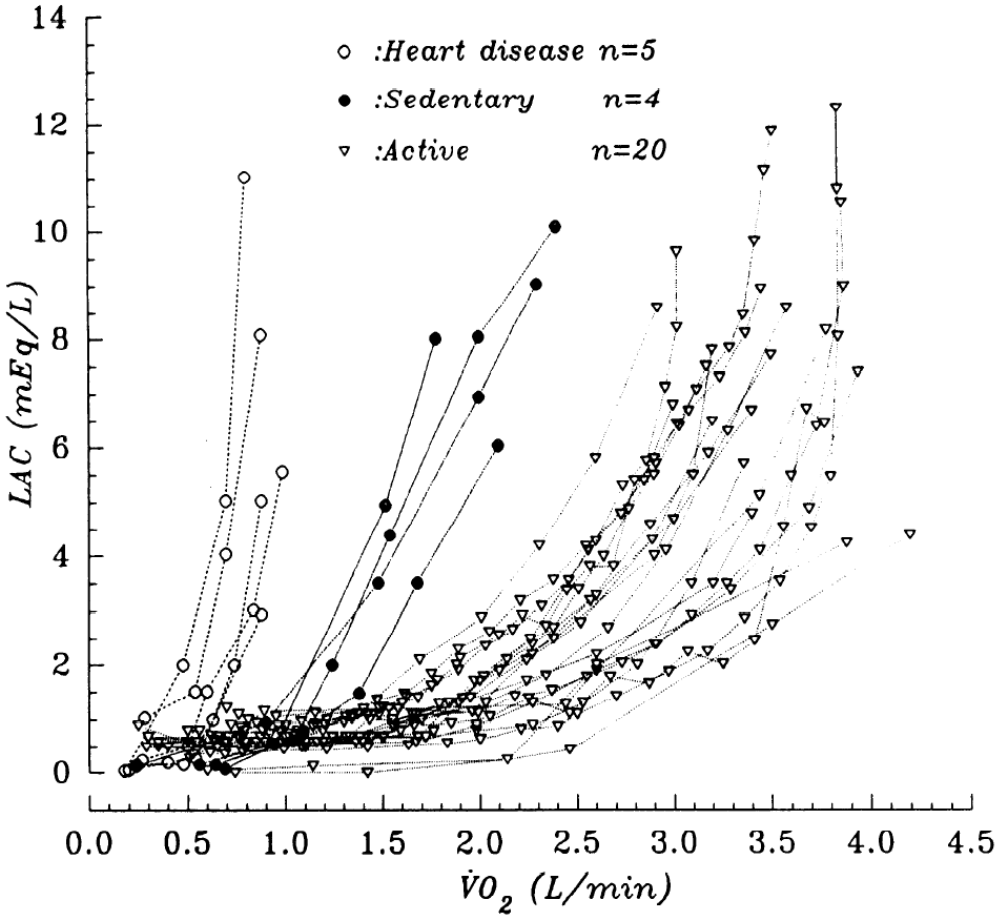
:Heart disease n=5
:Sedentary n=4
:Active n=20
LAC (mEq/L)
$\dot{V}O_2$ (L/min)
0
2
4
6
8
10
12
14
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5

Figure 1

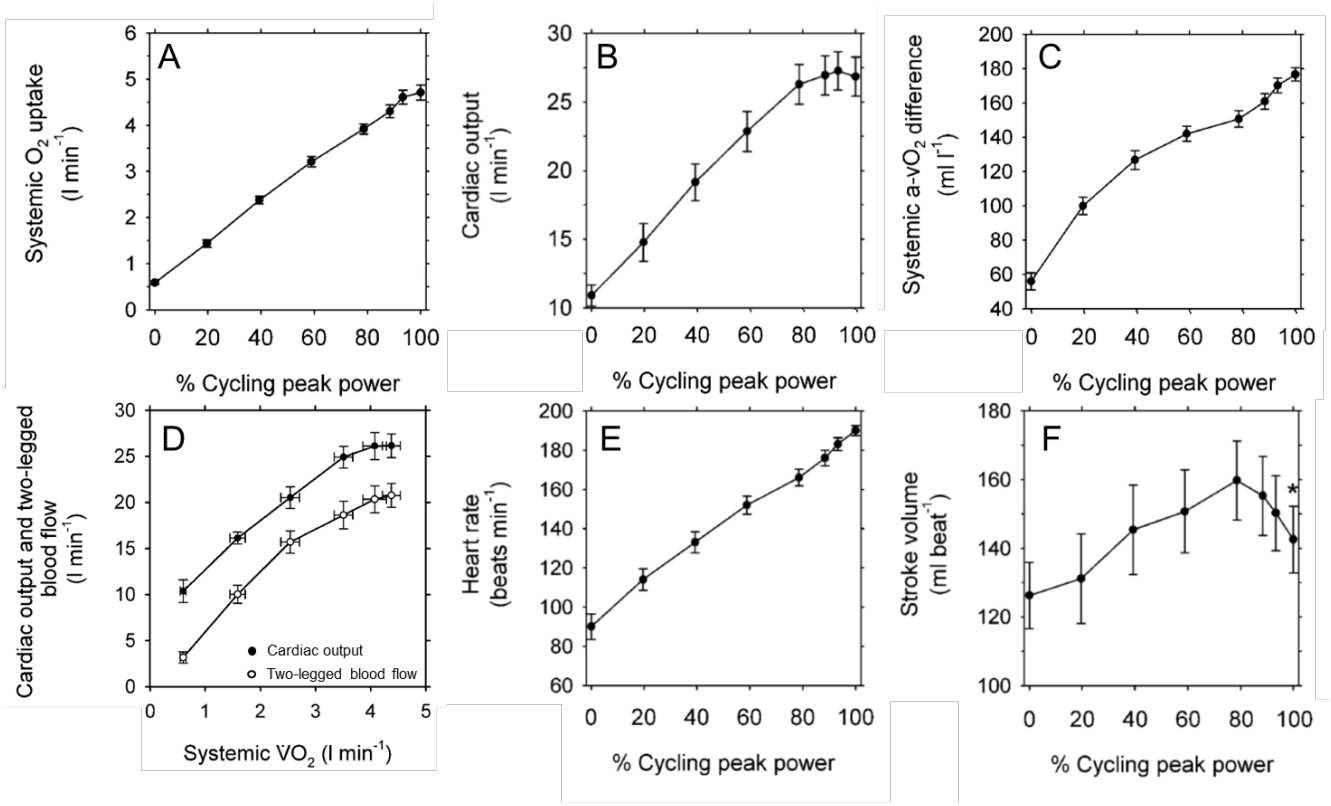
A
Systemic O_2 uptake (l min^{-1})
% Cycling peak power
B
Cardiac output (l min^{-1})
% Cycling peak power
C
Systemic a-vO_2 difference (ml l^{-1})
% Cycling peak power
D
Cardiac output and two-legged blood flow (l min^{-1})
Cardiac output
Two-legged blood flow
Systemic $\dot{V}O_2$ (l min^{-1})
E
Heart rate (beats min^{-1})
% Cycling peak power
F
Stroke volume (ml beat^{-1})
*
% Cycling peak power

Figure 2

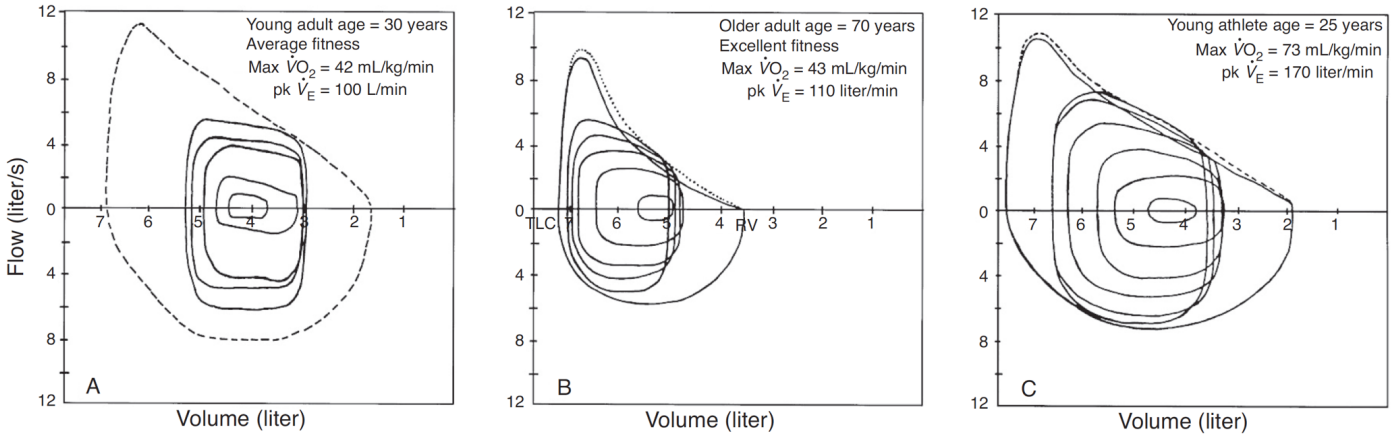
Young adult age = 30 years
Average fitness
Max $\dot{V}O_2$ = 42 mL/kg/min
pk $\dot{V}_E$ = 100 L/min
Flow (liter/s)
Volume (liter)
A
Older adult age = 70 years
Excellent fitness
Max $\dot{V}O_2$ = 43 mL/kg/min
pk $\dot{V}_E$ = 110 liter/min
TLC
RV
Volume (liter)
B
Young athlete age = 25 years
Max $\dot{V}O_2$ = 73 mL/kg/min
pk $\dot{V}_E$ = 170 liter/min
Volume (liter)
C

Figure 3

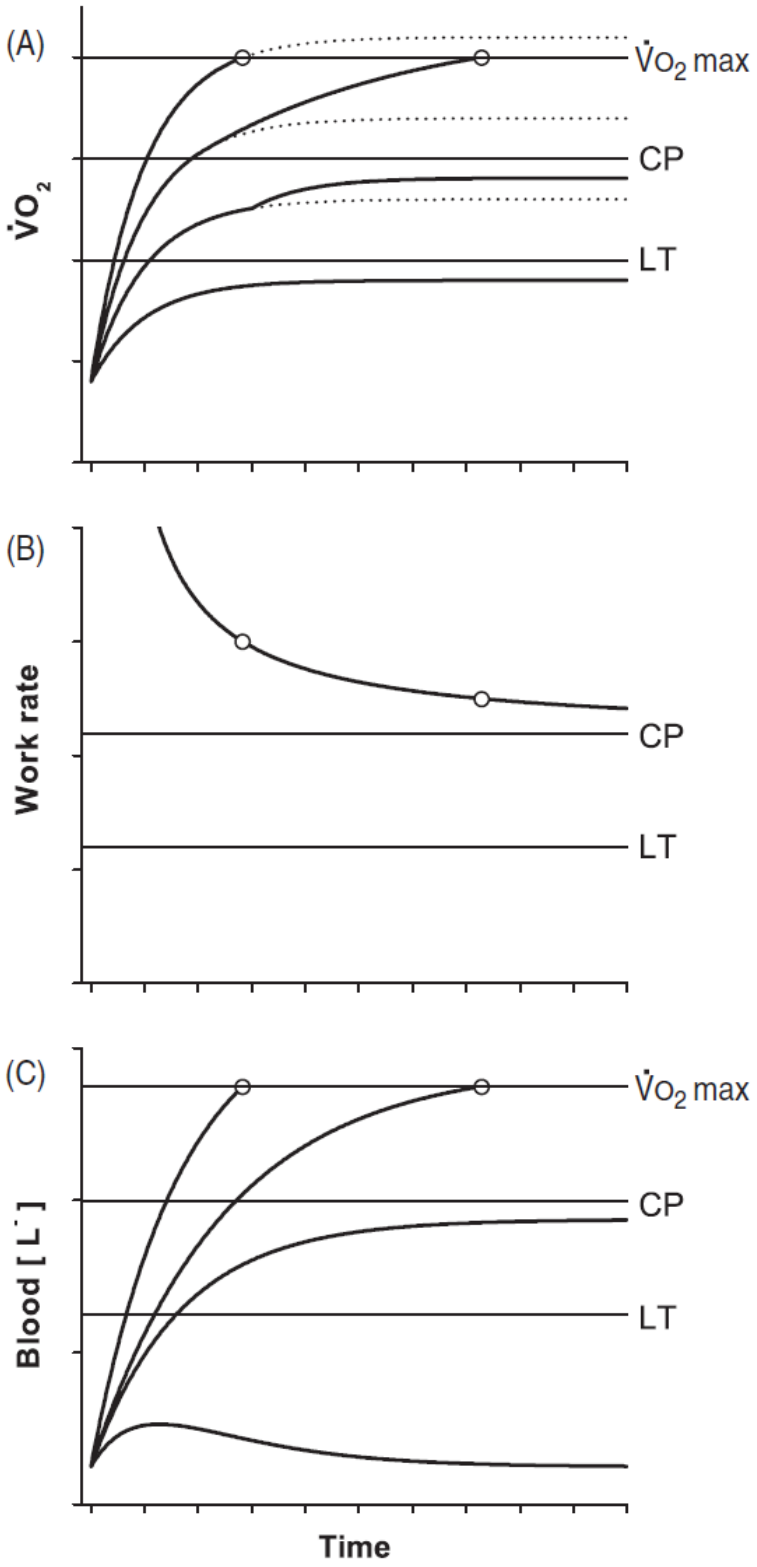
(A)
$\dot{V}O_2$
$\dot{V}O_2$ max
CP
LT
(B)
Work rate
CP
LT
(C)
Blood [L˙]
$\dot{V}O_2$ max
CP
LT
Time

Figure 4

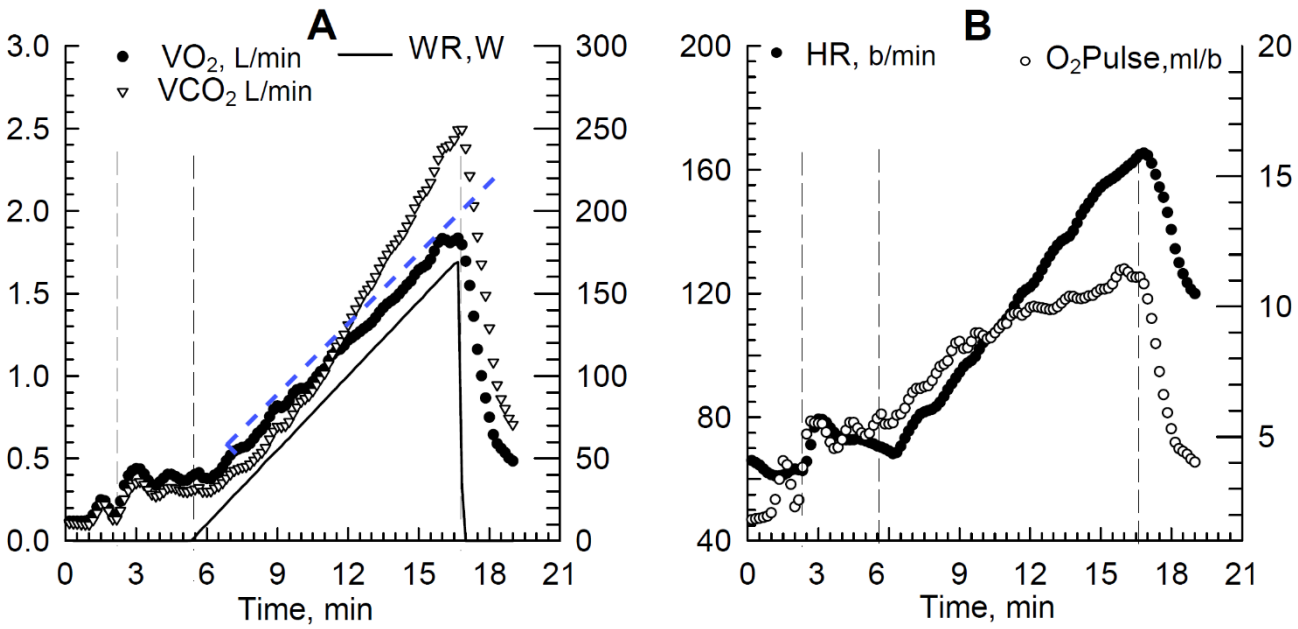
A
VO2, L/min
VCO2 L/min
WR,W
3.0
2.5
2.0
1.5
1.0
0.5
0.0
300
250
200
150
100
50
0
0 3 6 9 12 15 18 21
Time, min
B
HR, b/min
O2Pulse,ml/b
200
160
120
80
40
20
15
10
5
0 3 6 9 12 15 18 21
Time, min

FIGURE 5

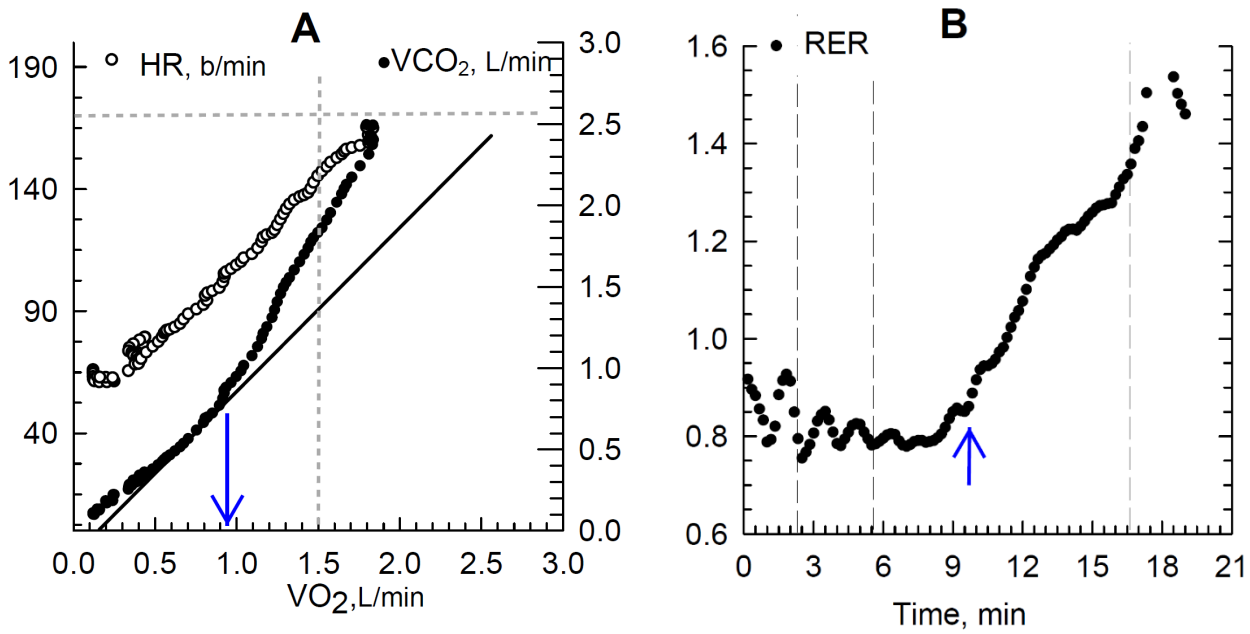

Figure 6

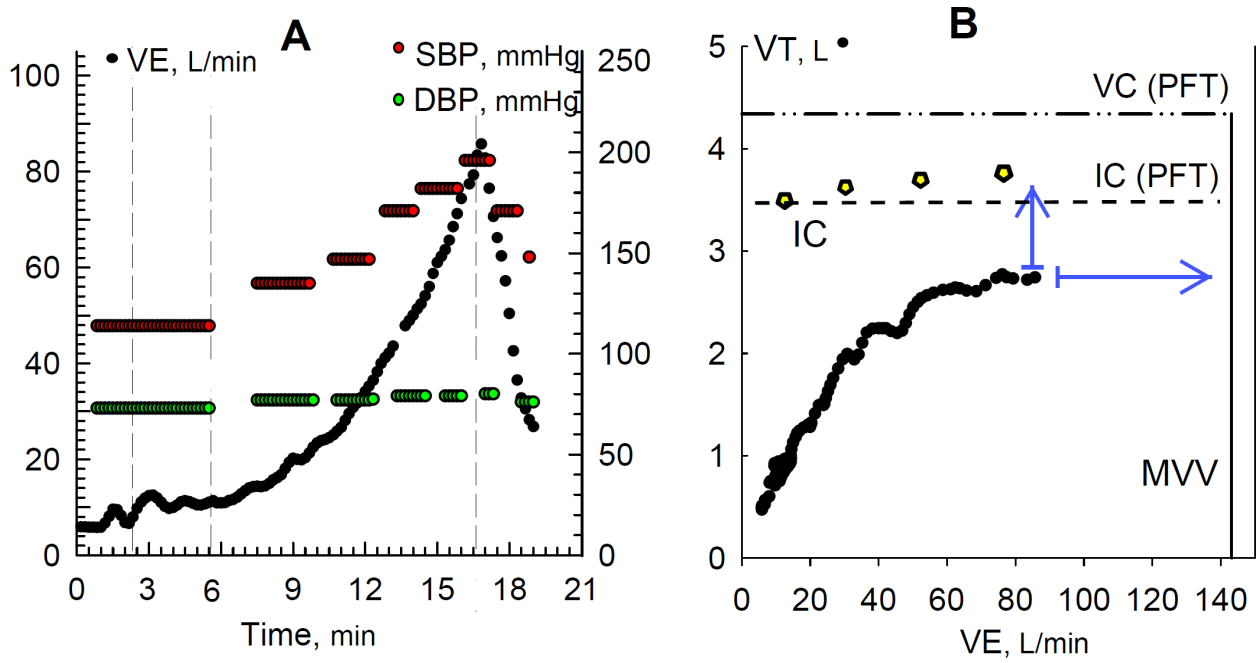

Figure 7

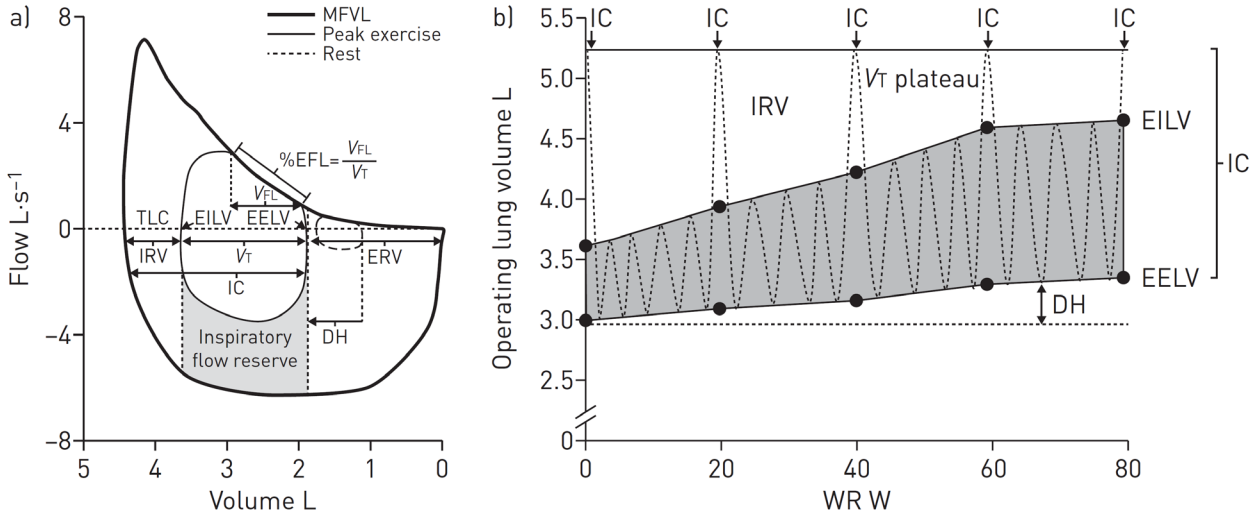
a)
MFVL
Peak exercise
Rest
%EFL=$\frac{V_{FL}}{V_T}$
V_{FL}
TLC
EILV
EELV
IRV
V_T
IC
ERV
Inspiratory flow reserve
DH
Flow L·s^{-1}
Volume L
b)
IC
V_T plateau
IRV
EILV
EELV
IC
DH
Operating lung volume L
WR W

Figure 8

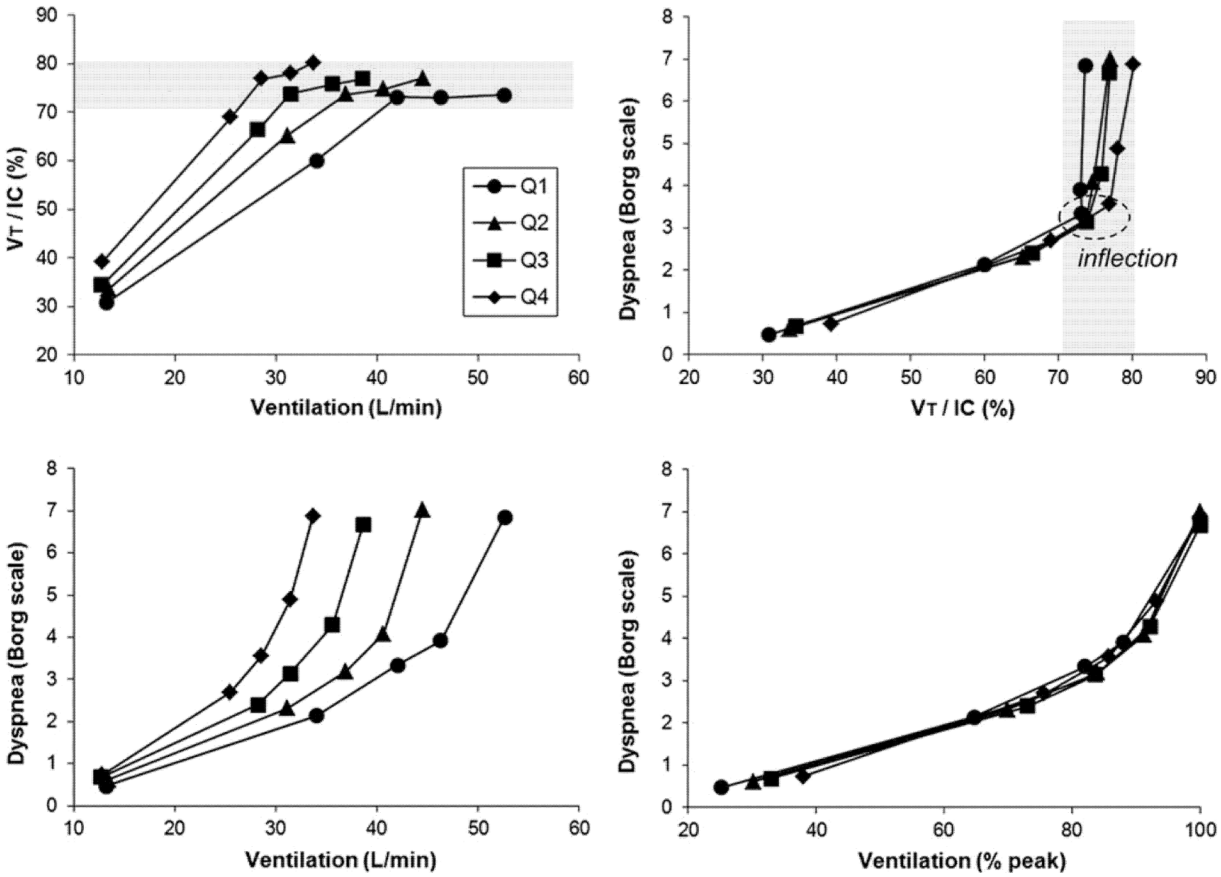
VT / IC (%)
Ventilation (L/min)
Q1
Q2
Q3
Q4
Dyspnea (Borg scale)
VT / IC (%)
inflection
Dyspnea (Borg scale)
Ventilation (L/min)
Dyspnea (Borg scale)
Ventilation (% peak)

Figure 9

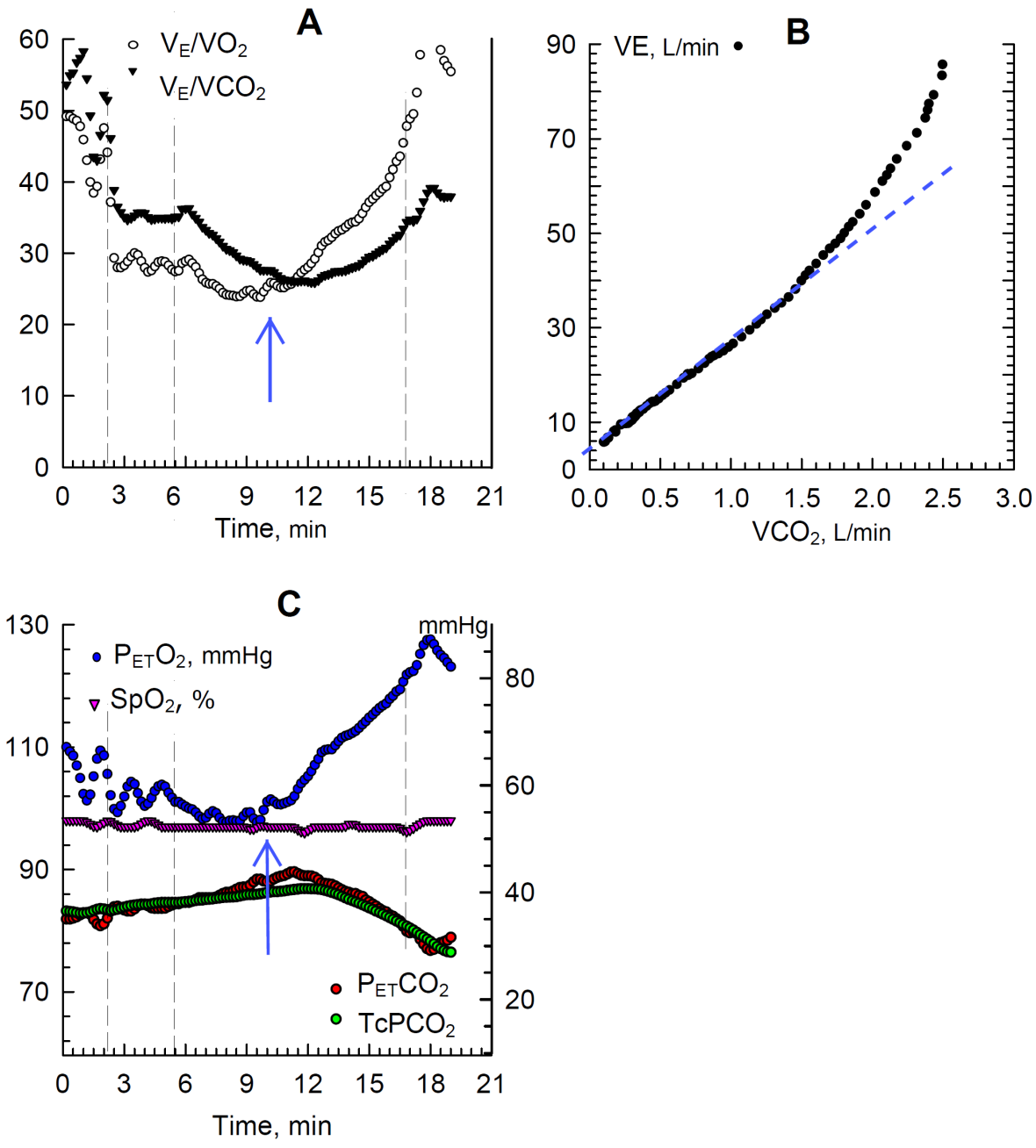
A
V_E/VO_2
V_E/VCO_2
Time, min
B
VE, L/min
VCO_2, L/min
C
mmHg
$P_{ET}O_2$, mmHg
SpO_2, %
$P_{ET}CO_2$
$TcPCO_2$
Time, min

Figure 10