Curr Treat Options Cardio Med (2021) 23: 49
DOI 10.1007/s11936-021-00928-z

Sports Cardiology (M Wasfy, Section Editor)

Cardiopulmonary Exercise Testing in Athletes: Expect the Unexpected

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Published online: 12 May 2021

This article is part of the Topical Collection on *Sports Cardiology*

Keywords Cardiopulmonary exercise testing · Athlete · Exercise testing · V̇O2

Abstract

Purpose of review Cardiopulmonary exercise testing (CPET) is a tool designed to assess the integrated function of the cardiac, pulmonary, vascular, and musculoskeletal systems to produce an exercise effort. CPET may be performed for performance purposes as part of optimizing a training program or for clinical purposes in athletes with established cardiovascular disease or in those with symptoms suggestive of cardiopulmonary pathology. Most normative values used for CPET parameters have been derived in the general population, in whom there will be expected differences in exercise physiology as compared to a trained athlete. In this review, our goal is to examine current available data on expected findings on CPET in athletes, highlight how these differ from the general population-derived normative values, and identify areas in need of further research to optimize the application of CPET in athletes.

Recent findings Athletes demonstrate differences in exercise hemodynamic and gas exchange profiles as compared to non-athletes including higher cardiac output, faster heart rate recovery, higher peak $\dot{V}O_2$, higher prevalence of exercise-induced arterial hypoxemia, and lower breathing reserve.

Summary CPET is an important tool to optimize performance and assess for underlying pathology in an athletic population. The impact of routine, vigorous physical activity on exercise physiology should be integrated into determination of what constitutes a normal CPET result in an athletic individual.

Introduction

Cardiopulmonary exercise testing (CPET) is a unique tool that couples gas exchange measurement, including the uptake of oxygen ($\dot{V}O_2$) and exhaled carbon dioxide ($\dot{V}CO_2$), with traditional exercise testing parameters such as the electrocardiogram (ECG), blood pressure (BP), and peripheral oxygen saturation (SpO_2). The addition of gas exchange allows for CPET to assess the integrated function of the cardiac, pulmonary, vascular, and musculoskeletal systems to produce an exercise effort. CPET is used in non-clinical settings in athletes for the purpose of assessing fitness and optimizing training programs. In clinical practice, CPET is more broadly utilized in the assessment of dyspnea of unknown etiology, evaluation of exercise intolerance, prognosis and risk stratification in the setting of established pathology, and the assessment of response to therapeutic interventions [1]. As CPET is applied in athletes, particularly in these clinical contexts, it is important to note that the prescribed normal ranges of gas exchange parameters have been derived in the general population, in whom exercise physiology stands to differ from that of a highly trained athlete. We will review prior work that has described CPET findings in athletic populations and identify gaps in our knowledge as to what constitutes a "normal athlete CPET" with the goal of optimizing the clinical application of CPET in the care of athletic patients.

Normal exercise physiology

During normal exercise, the primary purpose of the cardiovascular system is to provide oxygenated blood to the skeletal muscles to support the metabolic demands of local mitochondria. To meet these demands, the cardiac output (CO) increases to maintain adequate blood flow to the metabolically active tissues. Initial increases in CO are largely due to an increased stroke volume (SV) from increased venous return secondary to skeletal muscle contraction and blood redistribution from the splanchnic system. With continual exercise, heart rate (HR) will also increase, which further contributes to CO ($CO = SV \times HR$). The extraction of oxygen at the tissue level is largely dependent on the oxygen content (CaO_2) of the blood [CaO_2 (ml/dL) = hemoglobin (Hgb) × 1.36 × arterial O_2 saturation (SaO_2) + 0.0031 × partial pressure of O_2 (PaO_2)] and the oxidative potential and peripheral extraction by local mitochondria. Therefore, to be able to support metabolically active tissues, the heart needs to appropriately augment CO, the lungs need to adequately oxygenate blood and remove carbon dioxide, and the mitochondria of muscular tissue need to use oxygen for the creation of energy. This coordinated function of the cardiovascular, pulmonary, vascular, and musculoskeletal systems is ultimately reflected by the oxygen uptake and consumption of peripheral tissues ($\dot{V}O_2$). Historically, the concept of $\dot{V}O_2$ (oxygen uptake from the environment into tissues) was first presented by Hill et al. in the 1920s [2] and subsequently has become a vital metric in the evaluation of exercise performance as well as diagnosis and prognosis of cardiovascular pathology.

As limits in oxidative metabolism are reached during ongoing graded exercise efforts or during intense "burst" activity, the body utilizes other methods of metabolism, including glycolysis, to augment the energy produced by ongoing oxidative or "aerobic" metabolism. With increasing glycolytic metabolism, the blood lactate level will rise at a progressively steeper rate. The increase in lactic acid leads to increased bicarbonate levels to buffer the acidic hydrogen ions

from lactate dissociation. This will lead to an increased $\dot{V}CO_2$ relative to $\dot{V}O_2$ as the body increases ventilation to compensate for the increased bicarbonate. Accordingly, the ventilatory anaerobic threshold (VAT) in CPET may be defined as the point at which the slope of $\dot{V}CO_2$ plotted relative to $\dot{V}O_2$ inflects to become steeper or through other complementary methods using gas exchange [3].

For athletes, sport type plays a large role in determining the mix of aerobic/oxidative versus anaerobic/glycolytic metabolism utilized to generate the required energy for skeletal muscle contraction during exercise. For example, athletes in high dynamic sporting disciplines (e.g., distance running, cross-country skiing) will perform much of their recovery training at intensities that will not outstrip the capacity of aerobic/oxidative pathways, with interspersed workouts targeting their VAT or higher intensities. Conversely, athletes practicing in sports that are primarily static (e.g., weight lifting) spend proportionally more of their time in "burst" activities that depend on anaerobic/glycolytic or other metabolic pathways and less in low to moderate efforts utilizing primarily aerobic/oxidative metabolism [4]. The mix of training will impact what training-related adaptations should be expected on CPET. In Table 1, we outline how the exercise physiology of trained athletes, primarily those that practice sports with a moderate to high dynamic component, does and does not differ from that of the general population, highlighting aspects that stand to impact findings on CPET.

CPET protocols

The primary goal of most CPETs is to have a participant exercise at an increasing workload until the point of clinical exhaustion, exertional symptoms, or a clinical contraindication to continued exercise. The most common exercise equipment utilized in clinical practice for a CPET is a treadmill or upright cycle ergometer, with the choice determined by the type of individual being tested (e.g., non-athlete versus athlete, sport type, orthopedic issues) and goals of testing (e.g., accurate serial blood pressure monitoring is more easily accomplished on cycle ergometer).

Table 1. Physiologic parameters and their response to exercise in untrained individuals versus athletes

CPET parameter	Untrained individual	Athlete
Heart rate	↑	↑
Stroke volume	↑	↑↑
Cardiac output	↑	↑↑
Blood pressure	↑	↑/↑↑
SpO_2	↔/↓	↔/↓/↓↓
$\dot{V}O_2$	↑	↑↑
O_2 pulse	↑	↑↑
Breathing reserve	↓	↓/↓↓

Graded exercise protocols

In a graded exercise test, a participant usually performs a warm-up with a low level of work and then is subsequently exposed to an increasing workload throughout the test. Graded tests are the most commonly employed for exercise tests that utilize gas exchange measurement. For tests performed on the treadmill, the increased workload is performed by varying the speed, elevation, or both. For cycle ergometer tests, the patient is instructed by the exercise physiologist to keep a constant cadence on the bicycle, while the resistance is increased throughout the test. The two main forms of graded exercise testing are ramp and incremental protocols.

In a continuous ramp protocol, the workload is slowly increased continuously and linearly throughout the exercise test. The steepness of the ramp protocol (e.g., 10 W/min vs. 30 W/min on the cycle ergometer) is tailored to a patient's exercise tolerance, with a goal test duration of between 8 and 12 min given that shorter tests may not allow for optimal interpretation of gas exchange parameters and longer tests may be ended because of orthopedic factors (leg fatigue) rather than cardiopulmonary symptoms [5]. The main benefit of continuous ramp protocols is the absence of any abrupt increases in work, which creates a more linear and interpretable response in gas exchange parameters [6].

Incremental "step" protocols consecutively increase the workload by a set quantity at given time intervals throughout a test, which leads to a step-wise increase in work-load. For exercise treadmill testing, the most common incremental protocol used in the general population is the Bruce protocol [7]. The standard Bruce treadmill protocol starts at 1.7 mph at a 10-degree incline, and then every 3 min, the incline is increased by 2 degrees, and the speed is increased by 1 mph, which results in relatively large and unequal increases in METs with each stage. Because of the large increase in METs per stage, test termination may occur before a true maximal effort [6]. Gas exchange plots may also be difficult to interpret with abrupt changes in exercise intensity. Other incremental protocols have been created to provide smoother transitions between stages with either fixed speeds [8, 9] or minimal changes in grade with increasing speeds throughout testing [10].

For endurance athletes with a high baseline aerobic/oxidative capacity, ramp-based protocols require a much higher rate of increase in work rate to achieve target test time. This can be accomplished by either a more aggressive watt ramp on the cycle ergometer or a higher baseline speed or more aggressive incline increment on the treadmill. Specific incremental "step" treadmill protocols have been modified to account for the increased aerobic capacity of athletes [11]. Clinical laboratories caring for athletes may use established protocols or may establish their own in conjunction with their exercise physiologists and based on the available equipment and the type of athletes evaluated in their practice. Examples of a continuous ramp and incremental "step" protocol in an athlete and non-athlete are presented in Fig. 1.

Non-graded and customized exercise protocols

For many competitive athletes, graded exercise testing does not recreate the activity that they experience during real-life practice and competition. This can be problematic for athletes with exertional symptoms because a graded

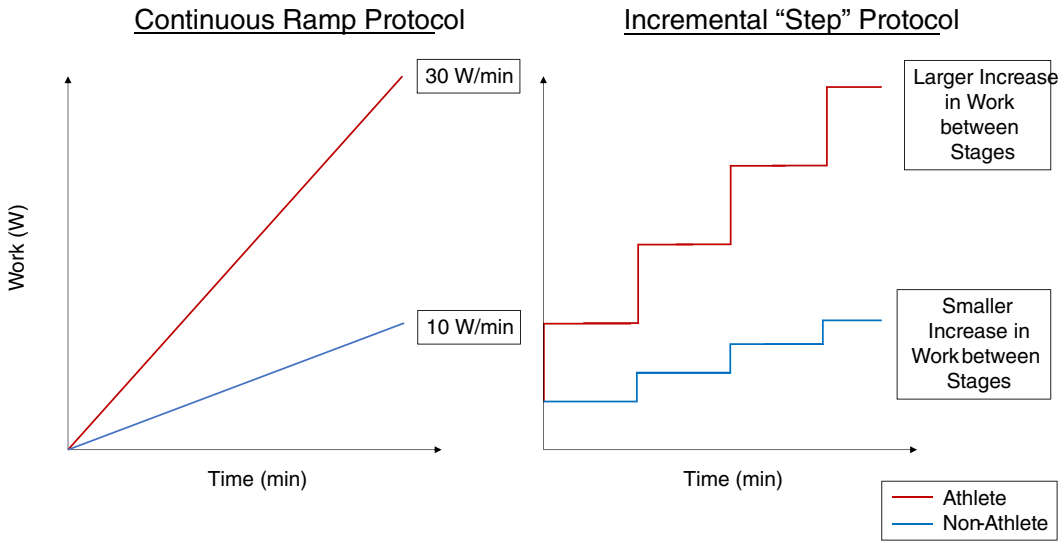

Fig. 1. Examples of cardiopulmonary exercise testing protocols in athletes vs. untrained individuals. The panels exclude a "warm-up" period.

protocol may not successfully reproduce an athlete's symptoms. In these instances, consideration should be given to adding further exercise provocation to the testing session that is customized to maximize yield. We previously examined the addition of non-graded customized exercise provocation (e.g., sprints, steady-state exercise, race simulation, boxing, burpees, wall sits, plyometrics) following an initial unrevealing graded, maximal effort CPET test in symptomatic patients presenting for CPET. The additional non-graded testing reproduced symptoms in 39% and led to a clinically actionable diagnosis in 21% [12]. Typically, these non-graded protocols do not include gas exchange measurement and instead focus on output from other testing components (e.g., ECG, SpO_2, BP, achieved work).

CPET parameters in athletes

Reference ranges for CPET parameters

Numerous prior publications have presented reference ranges and predictive equations for CPET parameters [13, 14•], of which the most commonly used predictive equations for peak $\dot{V}O_2$ were derived from small cohorts of individuals in the general population [15, 16]. These reference standards are used to predict if a patient falls into a normal range based on their baseline demographics (e.g., age, sex, body size). While these reference ranges are very helpful in defining normal vs. abnormal physiologic responses to exercise in populations that match those in which they were derived, they are less useful in athletic patients. For example, a symptomatic athlete may present with a supra-normal peak $\dot{V}O_2$ on CPET despite significant cardiac pathology due to training-related adaptations in all the other systems required to produce an exercise effort. In this instance, the supra-normal peak $\dot{V}O_2$ provides false reassurance. Conversely, as detailed below, training-related adaptations may paradoxically cause other CPET parameters (e.g., SpO_2, breathing reserve) to fall into an abnormal

range that in the general population may be suggestive of pathology but in the athlete is entirely physiologic. To overcome these limitations of standard normal ranges for CPET, others have published their athlete-specific CPET findings, though the small size and athlete composition of these studies has limited their uptake for utilization in clinical practice in the care of athletes [17–19]. A comparison of guideline recommendations for normative values for selected CPET parameters is presented in Table 2.

Heart rate response and recovery

The HR response in athletes who undergo exercise testing is similar to the general population in that HR linearly increases with exercise as the body's mechanism to increase CO to support metabolically active tissues. The most commonly used age-predicted HR functions are [220-age] [21], [210-(age × 0.65)] [22], and [208-(age × 0.7)] [23]. While these equations were created in the general population, they are often applied to athletes and have had variable predictive ability depending on the athlete cohort tested [24–26]. In athletes with supra-normal peak $\dot{V}O_2$, the HR/work relationship will be shifted, such that the same incremental change in work will result in a smaller change in HR in an athlete as compared to untrained individual. This reflects a superior SV

Table 2. Comparison of guideline-derived normative values for selected CPET parameters

CPET parameter*	2003 ATS/ACCP guidelines [1]	2012 EACPR/AHA guidelines [20]
Maximum heart rate	>90% age-predicted HR_{max}	≥85% age-predicted HR_{max} HR increase 10 bpm per every 3.5 ml/kg/min of $\dot{V}O_2$
Heart rate recovery	N/A	>12 bpm recovery after 1 min recovery or cool down period
Blood pressure	Absolute BP <220/90 mmHg	SBP increase 10 mmHg per every 3.5 ml/kg/min of $\dot{V}O_2$ Absolute SBP 210 mmHg males, 190 mmHg in females DBP stable or fall
SpO2	N/A	SpO2 ≥ 95% (rest and exercise) SpO2 should not decrease by >5%
$\dot{V}O_{2max}$	> 84% predicted	Percent predicted values should be ≥100%
O_2 pulse	> 80% predicted	Continual linear rise throughout exercise with possible plateau approaching maximal exertion
Breathing reserve	≥ 15%	> 20%
$\dot{V}E/\dot{V}CO_2$ slope	<34 slope at VAT	<30 slope throughout exercise

Definition of abbreviations: *BP* blood pressure, *BPM* beats per minute, *SBP* systolic blood pressure, *CPET* cardiopulmonary exercise testing, HR_{max} maximum heart rate, *MVV* maximal voluntary ventilation, *SpO2* oxygen saturation, *VAT* ventilatory anaerobic threshold, $\dot{V}O_{2max}$ maximum $\dot{V}O_2$

*Maximum heart rate prediction: multiple equations are recommended in the 2003 ATS/ACCP guidelines including [210-(age × 0.65)] and [202–0.72(age)]. The 2012 EACPR/AHA guidelines do not provide a predictive equation

$\dot{V}O_{2max}$: prediction equations presented in the 2003 ATS/ACCP guidelines are from Jones [15] and Wasserman [16]. Predictive equations from 2012 EACPR/AHA guidelines are from Wasserman [16]

Breathing reserve: the 2003 ATS/ACCP guidelines present normal ($\dot{V}E$/MVV ×100) <85% (MVV = directly measured of FEV1×35–40), and the 2012 EACPR/AHA guidelines presented normal $\dot{V}E$/MVV ≤0.80 (MVV = FEV1 ×40). Both of these normal values were converted to breathing reserve using the equation (1- $\dot{V}E$/MVV) ×100

$\dot{V}E/\dot{V}CO_2$ slope: the 2012 EACPR/AHA guidelines also remark that a slight increase in advanced age possible

response and other training-induced adaptations including improvement in exercise economy [27].

Heart rate recovery (HRR) after exercise has a complex physiology involving changes within the sinus node, sympathetic nervous system, parasympathetic nervous system, and central mechanisms regulating autonomic balance [28]. In normal subjects, there is a rapid decline in heart rate in the first 30 s after exercise, followed by a continual downtrend [29]. An abnormal HRR has been defined in guidelines [20, 30] as a decrease in HR <12 beats per minute after 1 min of stopping exercise. This cut-point has been shown to have prognostic significance in the general population [31]. Prior studies have consistently shown that trained subjects have a faster HRR that untrained subjects [29, 32–35]. HRR has also been shown to be responsive to detraining, with slower HRR documented within 4 weeks after the athlete stops training [36, 37]. Therefore, as HRR is tightly linked with training status in athletes and is easily measurable, it has been proposed as a tool for monitoring training response and exercise prescription [38, 39].

Blood pressure response

The normal BP response during CPET includes a rise in systolic blood pressure (SBP) with increasing work rates and stable or a slight decrease in diastolic blood pressure (DBP). If there is an inadequate rise in SBP during exercise (< 20–30 mmHg), this may indicate underlying pathology (e.g., aortic outflow obstruction, severe left ventricular (LV) dysfunction, myocardial ischemia, or medication effect) [5]. An exaggerated BP response to exercise is also clinically important as multiple studies have demonstrated that excessive rise, particularly of the DBP, predicts incident hypertension (HTN) and cardiovascular events [40, 41]. While the American and European hypertension guidelines do not define an upper limit of normal for peak exercise BP [42, 43], others have suggested a SBP of 210 mmHg in men and 190 mmHg in women [44]. Current American Heart Association (AHA) guidelines for exercise testing provide a relative indication for terminating exercise testing if SBP is >250 mmHg or DBP >115 mmHg [45].

In athletes, the absolute and relative increase in CO with exercise testing may be several-fold higher than in untrained individuals. SBP will obligately rise with CO even with a normal peripheral vascular response. Due to the high CO achieved by athletes, the upper limit of normal for peak exercise SBP that is clinically important in athletes may differ [46, 47]. Importantly, a recent study showed that athletes exceeding SBP of 220 mmHg in males and 200 mmHg in females had a 3.6 fold higher risk of incident HTN over 6.5 years of follow-up, suggesting exercise BP has similar prognostic value as in the general population [48•]. While defining the range of exercise SBP response relative to CO rise in healthy athletes may help refine the normal peak exercise SBP range, for now this remains the same as that used in the general population. Failure of the DBP to fall or an increase in DBP remains an important marker of abnormal peripheral vascular response to exercise in athletes.

Oxygen saturation

Exercise-induced arterial hypoxemia (EIAH) in healthy individuals during exercise testing is a commonly described phenomenon [49–52]. The mechanism

of EIAH is thought to be a complex combination of relative hypoventilation and altered pulmonary gas exchange (mostly due to diffusion limitation and ventilation/perfusion ($\dot{V}/Q$) mismatch). Specific suggested mechanisms of EIAH include extravascular lung water accumulation, increased blood viscosity, cytokine release, and pulmonary capillary stress failure [49, 50, 52–54]. There have also been multiple prior suggested definitions for EIAH including a reduction in the partial pressure of O_2 (PaO_2) with a range of 5–10 mmHg, $SpO_2 < 90$–95%, and/or decrease in SpO_2 by 4% from baseline values [49, 52]. Ranges are provided given there have been many different definitions reported. Dempsey et al. recommended the following classification system for EIAH: mild EIAH (SpO_2 of 93–94.9%), moderate EIAH, (SpO_2 of 88–92.9%), and severe EIAH ($SpO_2 < 88\%$) [49].

EIAH has been shown to affect male and female athletes of all ages in numerous different endurance sports [52]. A recent study performed in 124 young, highly trained male distance runners (age 19–39) reported a prevalence of EIAH between 70 and 84% depending on the definitions utilized ($SpO_2 \leq 93\%$ or $SpO_2 \leq 91\%$, respectively) [55]. Studies in young and masters athletes have also shown that EIAH can occur as early as 40% of $\dot{V}O_{2max}$ during exercise testing [56, 57]. The most susceptible groups for EIAH are thought to be older individuals and female athletes [52]. The prevalence of EIAH in healthy athletes in the above studies suggests that this finding can be expected to be present on a sizable proportion of CPETs. In this context, it should be integrated with other parameters (symptoms, spirometry, other gas exchange parameters) in assessing whether it is clinically important. The overall impact of EIAH on exercise performance remains unclear.

Maximal VO2

The $\dot{V}O_{2max}$ represents the maximal uptake of oxygen from the environment transported to the mitochondria to perform physical work [58]. In exercising humans, the primary limiting factor for $\dot{V}O_{2max}$ has classically been thought to be the ability of the cardiorespiratory system to deliver oxygen to tissues and not skeletal muscle O_2 extraction [59]. $\dot{V}O_{2max}$ is calculated from graded exercise testing as the highest value obtained during the test averaged over at least 30 s of symptom-limited exercise [1]. Absolute $\dot{V}O_{2max}$ is measured in L/min or ml/min. Since $\dot{V}O_{2max}$ is directly related to body size, as larger individuals have a higher muscle mass, measurements of $\dot{V}O_{2max}$ are also adjusted for body size and reported in ml/kg/min. Significant contributors to individual variation in $\dot{V}O_{2max}$ include body size, age, sex, genetic factors, red blood cell volume, and exercise training [59]. Prior studies have suggested that $\dot{V}O_{2max}$ decreases by 3–6% every 10 years starting from age 20–30 and > 20% every 10 years from age 70 and beyond [60]. Exercise training is thought to increase an individual's $\dot{V}O_{2max}$ mainly through expansion of red blood cell volume and an increase in SV, which both will lead to increase oxygen delivery to metabolically active tissues [61].

Due to these training-related adaptations, athletes from dynamic sporting disciplines presenting for clinical CPET will on average demonstrate $\dot{V}O_{2max}$ values in excess of that which are predicted by the commonly used predictive equations [15, 16]. There have been two prior meta-analyses in male [19] and female [17] athletes that have provided equations for $\dot{V}O_{2max}$ in an athletic

cohort. Other small studies have also attempted to establish $\dot{V}O_{2max}$ equations in specific populations of athletes [62]. None of these have been included in guidelines [1] or widely applied in clinical practice. Malek et al. performed a cross-validation study of commonly utilized $\dot{V}O_{2max}$ equations, including those of Jones and Wasserman [15, 16], in 142 aerobically trained males and females performing a CPET on a cycle ergometer [18]. Malek et al. found none of the equations that based $\dot{V}O_{2max}$ prediction off of typical demographic parameters were accurate in trained individuals. The only equations with acceptable predictive ability included maximal work obtained from the performed exercise test itself as a predictor of $\dot{V}O_{2max}$, which is of limited utility in clinical practice as changes in $\dot{V}O_{2max}$ due to important cardiopulmonary disease will also result in changes in peak work [63]. Until better predictive equations for application to clinical CPET in athletes are available, exercise labs may attempt to define ranges of expected $\dot{V}O_{2max}$ based on the athletic populations that they commonly encounter. "Normal" $\dot{V}O_{2max}$ by current predictive equations in athletes should be interpreted in context of the clinical presentation, type of sport, type of training, and other testing.

Arterial oxygen pulse

The arterial O_2 pulse is a measurement of the peripheral oxygen extracted per heartbeat during exercise (O_2 pulse= $\dot{V}O_2$/HR) and, as reflected by the Fick equation ($\dot{V}O_2$ = HR × SV × arteriovenous oxygen difference), represents the product of SV and O_2 extraction. Since O_2 extraction rises linearly and predictably across the spectrum of exercise capacity [64], the shape of the O_2 pulse curve may be utilized to gain insight into the change in SV during a graded exercise test [65–67]. In theory, the development of exercise-induced myocardial ischemia may lead to LV dysfunction, subsequent loss of SV augmentation, and therefore a plateau or fall in O_2 pulse augmentation during exercise. Similarly, valvular heart disease may impose limits to forward SV that change dynamically during exercise. Guidelines have therefore suggested O_2 pulse evaluation may be useful in the evaluation of obstructive coronary artery disease (CAD) [5, 20], given the inherent limitations of electrocardiogram (ECG)-only exercise testing. However, clinical application of O_2 pulse assessment is limited by lack of consensus regarding normal SV response to exercise [68] as well as debate as to whether the O_2 pulse is a reliable reflection of SV [69].

Multiple prior studies in general population cohorts have investigated whether a plateau in the O_2 pulse curve during exercise improves the diagnostic capability of CPET for obstructive CAD with conflicting results [70–78]. Previous studies in asymptomatic athletes have shown that ECG-only stress tests have poor diagnostic performance for myocardial ischemia [79–82], so the addition of the O_2 pulse as derived from CPET has been postulated as a method to improve diagnostic performance. However, no substantial evidence exists supporting the diagnostic performance of the O_2 pulse for obstructive CAD in an athletic cohort. Given the fact that athletes are more likely to have a physiologic plateau in $\dot{V}O_{2max}$ [83] and may exhibit different temporal changes in SV throughout exercise as compared to untrained individuals [68, 84], it is difficult to know if applying results derived in the general population is appropriate. This remains an important area of future investigation.

Breathing reserve

Breathing reserve is defined as one minus the ratio between maximal ventilation ($\dot{V}E$) during exercise and estimated maximum voluntary ventilation (MVV) derived from resting spirometry performed before CPET (1- [peak $\dot{V}E$/MVV]). The estimated MVV can be calculated directly from a 12- or 15-s maneuver of deep and rapid breathing or by equation methods [forced expiratory volume in 1 s (FEV1) × 40]. In normal individuals, lung capacity is not the limiting factor in exercise, and as such a normal breathing reserve is considered greater than ≥0.20 at peak exercise [5, 20], meaning this percentage of estimated total lung capacity remains untapped. This metric is important for identifying pulmonary mechanical limits to exercise, such as those that might be presenting in the setting of obstructive or restrictive lung disease.

While the cardiovascular, hematologic, and muscular systems undergo physiologic adaptations to high-level exercise, traditionally the pulmonary mechanical system has not been thought to have the ability to significantly adapt to exercise [85]. A few small studies have shown that respiratory muscle training can lead to improved respiratory muscle endurance in athletes [86]. One study also found swimmers to have larger static lung volumes and increased pulmonary diffusion capacity when compared to athletic controls [87], although it is unclear how these potential changes relate to exercise performance. Interestingly, healthy athletes frequently have a calculated BR of 0% at peak exercise indicating all available lung mechanical capacity has been utilized. In the setting of normal resting spirometry and supranormal $\dot{V}O_2$, this is thought to reflect a secondary pulmonary mechanical limitation conferred by the highly trained cardiovascular system, which is typically the sole limiting factor in untrained healthy individuals. It is not clear why certain healthy, fit athletes reach a pulmonary mechanical limit and others do not. It is also unknown whether equations that estimate MVV apply equally well in athletes and non-athletes. Overall, the implications of pulmonary mechanical limitation and the impact on performance in athletes are an area in need of future research [85, 88–91].

Ventilatory efficiency

Ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$) is derived from the ratio of pulmonary ventilation ($\dot{V}E$) and production of carbon dioxide ($\dot{V}CO_2$) and is thought to reflect right ventricular-pulmonary vascular (RV-PV) function during exercise [92]. Ventilation is tightly associated with pCO_2 during exercise because $\dot{V}E$ is driven by the amount of carbon dioxide present. The $\dot{V}E/\dot{V}CO_2$ slope (from initiation to peak exercise) is widely used in heart failure (HF) patients where it has been shown to have prognostic implications [93–95]. A $\dot{V}E/\dot{V}CO_2$ slope (from initiation to peak exercise) cutoff of >34–36 has been shown to accurately identify high-risk patients with heart failure with reduced ejection fraction (HFrEF) and is the most predictive measure of poor outcomes for HFrEF patients undergoing CPET [96, 97]. Importantly, in many individuals, the $\dot{V}E/\dot{V}CO_2$ slope may be non-linear, with steepening of the slope after achievement of the VAT [98]. Accordingly, a recent study assessed the predictive ability of $\dot{V}E/\dot{V}CO_2$ slope at different time points throughout exercise (pre-VAT, post-VAT, nadir) in a cohort of patients with preserved LV systolic function referred for exercise testing, and $\dot{V}E/\dot{V}CO_{2\ nadir}$ was found to be better predictive of adverse

hemodynamics during exercise and poor outcomes than $\dot{V}E/\dot{V}CO_2$ measured throughout exercise [99].

Studies in athletes have identified that $\dot{V}E/\dot{V}CO_2$ does not seem to be associated with $\dot{V}O2_{max}$ [100], and $\dot{V}E/\dot{V}CO_2$ slopes do not seem to significantly vary based on athletic performance, training status, or ergometer type [101–103]. Available athlete data suggest that despite many training-related adaptations to the RV and vascular system, ventilatory efficiency may be fixed [101]. Interestingly, in clinical practice, it is not unusual to observe $\dot{V}E/\dot{V}CO_2$ values, particularly when measured throughout the exercise effort, that fall above the normal thresholds (>30) in healthy athletes (i.e., suggestive of impaired ventilatory efficiency), typically driven by a high end-exercise slope. The mechanisms behind this finding and why it develops in some athletes versus others are unknown. Physiologically, two possible explanations include adaptive end-exercise-induced hyperventilation and an upper limitation to alveolar CO_2 delivery. Future work should target identifying mechanisms of end-exercise elevation in $\dot{V}E/\dot{V}CO_2$ as well as defining what portion of the $\dot{V}E/\dot{V}CO_2$ slope best identifies latent pathology in athletic patients.

Conclusion

CPET provides a window into the unique exercise physiology of an athlete. This physiology is important to understand both in the management of athletes presenting for clinical care and because it provides mechanistic insight into how exercise training can be applied in all populations. Future research in CPET is needed to better define normal ranges of CPET parameters that reflect athletes' physiology and more optimally identify important cardiopulmonary diagnoses.

Compliance with Ethical Standards

Conflict of Interest
Bradley J. Petek, Sarah K. Gustus, and Meagan M. Wasfy declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance

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