



## Mini Review

# Physiological Principles of Cardiopulmonary Exercise Testing

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### Abstract

Of all currently available exercise tests, cardiopulmonary exercise testing (CPET) represents the gold standard that provides the most accurate and objective measure of cardiorespiratory fitness. This is achieved through a comprehensive evaluation of the pulmonary, cardiovascular, hematopoietic, neuropsychological, skeletal muscular and cellular oxidative systems involved in the (patho)physiological response to exercise. Therefore, CPET is ideally suited to quantify exercise tolerance and evaluate the underlying mechanism(s) of exertional dyspnea and exercise limitation in many clinical conditions. CPET can be seen as a complex test that requires specific knowledge of exercise physiology and gas exchange. The physiological principles required for understanding CPET are typically complex to teach, and comprehensive presentations may be initially considered too impractical. In this mini review we briefly describe the basics of exercise physiology and the key parameters that are vital for the understanding and interpretation of CPET.

**Keywords:** Physiology; Dyspnea; Gas Exchange; Exercise test; Cardiovascular; Respiratory.

### Introduction

Cardiorespiratory fitness has been shown to be an independent predictor of morbidity and mortality and can be considered a vital sign [1]. Physical exercise requires the interaction of cellular, cardiovascular and ventilatory systems to support gas exchange between the exercising muscular cells (internal respiration) and the pulmonary environment (external respiration). Defects in the coupling of external to internal respiration result in the gas exchange abnormalities characteristic of the limiting organ systems that are amplified by exercise stress. Cardiopulmonary exercise testing (CPET) is a maximal progressive exercise test that combines gas exchange measurement with traditional exercise testing parameters (electrocardiogram [ECG], blood pressure, and blood gas analysis).

It provides comprehensive and reproducible data on the interaction between ventilation, gas exchange, and cardiovascular

and musculoskeletal function, enables determination of deviations from normal and usually identifies which of multiple pathophysiological conditions (cardiocirculatory, pulmonary vascular or respiratory alone or in combination) is the leading cause of exercise intolerance.

Initially used in sports and exercise science to determine aerobic and anaerobic fitness thresholds in athletes, CPET is now being used in many clinical indications. The most common of these include [1-10]:

- determining the cause(s) and severity of exertional dyspnea, fatigue, exercise intolerance, reduced exercise performance or exercise-induced hypoxaemia;
- assessing peak exercise capacity and cardiorespiratory fitness; estimating prognosis in various disease states;
- assessing perisurgical and postsurgical complication risks;
- early detection and risk stratification of cardiovascular, pulmonary vascular and lung diseases, and musculoskeletal disorders;

- measuring the response to pharmacological and nonpharmacological treatment;
- designing personalised exercise training and cardiopulmonary rehabilitation programmes.

Current evidence suggests that CPET should be used more frequently in clinical practice, especially because the additional time required compared with less meaningful exercise tests is low in routine use [2-6]. A basic knowledge of exercise physiology and gas exchange is essential to analyse and interpret CPET findings. However, the physiological concepts required to understand CPET are typically complex to teach.

The objective of this mini review is to briefly describe the underlying principles of exercise physiology, including all the key parameters, that are relevant for the evaluation of CPET. For further information the reader is referred to the literature [2-8, 10-13].

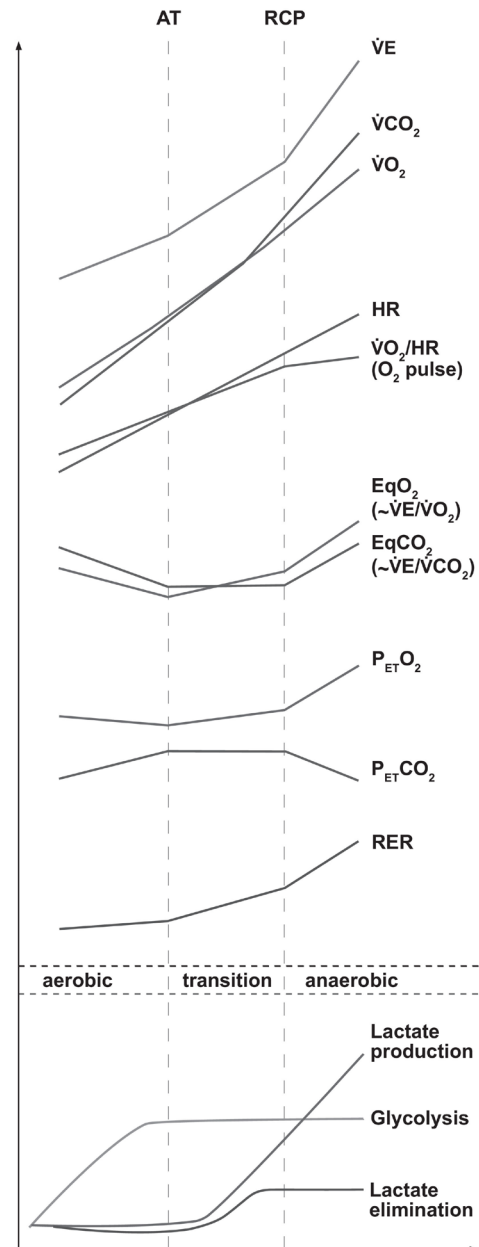
### Exercise physiology

CPET aims at maximally stressing the oxygen transport and utilizations systems. The transport of oxygen to metabolically active body tissues depends largely on cardiac output, haemoglobin (Hb) concentration, Hb oxygen saturation, arterial vascular tone and the density of the capillary network. Figure 1 shows characteristic alterations in key physiological parameters that occur as the exercise work rate is increased.

### Aerobic metabolism

The increasing energy requirements during exercise are mainly covered by aerobic glycolysis and lipolysis until the anaerobic threshold (AT) is reached.

As the work rate increases, oxygen uptake ( $\dot{V}O_2$ ) and carbon dioxide production ( $\dot{V}CO_2$ ) increase. The  $\dot{V}O_2$  uptake usually exceeds the  $\dot{V}CO_2$  increase during early exercise due to transient carbon dioxide ( $CO_2$ ) uptake into body stores. As a result, the respiratory exchange rate (RER: ratio of  $\dot{V}CO_2$  divided by  $\dot{V}O_2$ ) declines during the first minutes of moderate exercise (before AT). RER increases further because the respiratory quotient (RQ) of the muscle substrate glycogen is higher than at rest. It should be noted that RER (calculated by comparing exhaled gases to room air) estimates RQ (calculated at cellular level) only during rest and light to moderate aerobic exercise that does not result in lactate accumulation (before AT). With increasing work rate, a linear rise in heart rate (HR), oxygen pulse ( $\dot{V}O_2/HR$ ) and ventilation ( $\dot{V}E$  = minute ventilation) can be observed. Physiologically,  $\dot{V}E$  increases until tidal volume ( $V_T$ ) is fully utilised ( $\approx 60\%$  of vital capacity [VC]), thereafter  $\dot{V}E$  increases with a rise in breathing frequency (BF).



**Figure 1:** Principles of exercise physiology (modified from [11]); The characteristic changes in key variables of ventilation, cardiocirculation, pulmonary gas exchange and metabolism during progressive exercise work are shown; Anaerobic threshold (AT) documents the transition to mixed aerobic-anaerobic metabolism, respiratory compensation point (RCP) documents the transition to predominant anaerobic metabolism. Definition of abbreviations:  $EqCO_2$ , ventilatory equivalent of carbon dioxide;  $EqO_2$ , ventilatory equivalent of oxygen; HR: heart rate;  $O_2$ : oxygen;  $P_{ET}CO_2$ : end-tidal pressure of carbon dioxide;  $P_{ET}O_2$ : end-tidal pressure of oxygen;  $\dot{V}E$ : minute ventilation;  $\dot{V}CO_2$ : carbon dioxide output;  $\dot{V}O_2$ : oxygen uptake.

Exercise significantly improves ventilation/perfusion distribution (through increased pulmonary blood flow and deep breathing (increased  $V_T$ ) resulting in an enlarged gas exchange area. This improved efficiency is reflected by a decrease in the ventilatory equivalents  $EqO_2$  ( $\approx \dot{V}E/\dot{V}O_2$ ) and  $EqCO_2$  ( $\approx \dot{V}E/\dot{V}CO_2$ ) because more oxygen ( $O_2$ ;  $\dot{V}O_2 \uparrow$ ) is taken in and more carbon dioxide ( $CO_2$ ;  $\dot{V}CO_2 \uparrow$ ) is eliminated relative to ventilation. The lowest point (nadir) of the ventilatory equivalents is where the lungs are working most effectively (e.g, only a small volume must be ventilated to breath in one litre of  $O_2$  or breath out one litre of  $CO_2$ ).

The partial pressures of  $O_2$  ( $P_{ET}O_2$ ) and  $CO_2$  ( $P_{ET}CO_2$ ) measured at the end of exhalation (end-tidal [ET]) correspond to the alveolar pressures,  $PAO_2$  and  $PACO_2$ , in a healthy individual.  $P_{ET}CO_2$  increases slightly and peaks during early exercise, reflecting the elevated  $CO_2$  production in exercising muscles, while increased peripheral  $O_2$  extraction ( $\dot{V}O_2 \uparrow$ ) means that less  $O_2$  is exhaled ( $P_{ET}O_2 \downarrow$ ).

#### Aerobic-anaerobic transition zone

As the exercise work rate continues to increase, ventilation increases ( $PAO_2 \uparrow$  and  $PACO_2 \downarrow$ ) without any more oxygen being taken up by the blood (no further increase in  $PaO_2$  or arterial  $O_2$  content) because haemoglobin is already fully saturated with oxygen. As a result of the maximally utilised aerobic metabolism, additional adenosine triphosphate (ATP) is generated via anaerobic glycolysis (advantage: rapid oxygen-independent energy supply; disadvantage: low energy yield: [2 mol of ATP for each 1 mol

of glucose]). The acidic end product of anaerobic glycolysis is lactate. The resulting hydrogen ions ( $H^+$ ) are buffered by sodium bicarbonate ( $HCO_3^-$ ) to maintain a neutral pH:  $H^+ + HCO_3^- \rightarrow H_2O$  and  $CO_2$ . The resulting excess  $CO_2$  production stimulates a very strong ventilatory drive.

Due to this  $CO_2$ -induced increase in ventilation, significantly more  $CO_2$  is exhaled ( $\dot{V}CO_2 \uparrow$ ), while the increase in oxygen uptake ( $\dot{V}O_2 \uparrow$ ) continues to rise only in parallel with the work rate. Accordingly, the increase in  $\dot{V}CO_2$  is now significantly steeper than  $\dot{V}O_2$  (AT) which is associated with a rise in RER. Since  $\dot{V}E$  and  $\dot{V}CO_2$  increase almost proportionally, the ratio  $\dot{V}E/\dot{V}CO_2 \approx EqCO_2$  remains relatively constant. Consequently,  $P_{ET}CO_2$  ( $\approx PACO_2$ ) also transitions into a plateau (or drops off slightly). In contrast, the ratio of  $\dot{V}E/\dot{V}O_2 \approx EqO_2$  increases due to the relatively higher increase in  $\dot{V}E$  versus  $\dot{V}O_2$ . The end-expiratory or alveolar  $O_2$  ( $P_{ET}O_2$  [ $\approx PAO_2$ ]) also increases as a result of  $CO_2$ -mediated hyperventilation. The elevated  $O_2$  pulse tends to tail off during later exercise when the stroke volume cannot be further enhanced but the HR continues to rise linearly with increasing work.

**Note:** any pathophysiology that increases respiratory drive (e.g, dysfunctional breathing,  $PaCO_2 \uparrow$ ,  $pH \downarrow$ ) can cause or exacerbate dyspnea. In hyperventilation,  $CO_2$  elimination exceeds  $CO_2$  production (washout of body  $CO_2$  stores), with the opposite occurring in hypoventilation. The determination of both gas exchange thresholds (AT and respiratory compensation point [RCP]) - is summarized in Table 1.

**Table 1:** Threshold criteria for aerobic threshold and respiratory compensation point [2, 9, 14].

AT	RCP
<ul style="list-style-type: none"> <li>V-slope method*: first disproportional increase in <math>\dot{V}CO_2</math> vs <math>\dot{V}O_2</math></li> <li>Lowest point of <math>\dot{V}E/\dot{V}O_2</math> directly before <math>\dot{V}E/\dot{V}O_2</math> continuously increases (without a simultaneous increase in <math>\dot{V}E/\dot{V}CO_2</math>)</li> <li>Lowest point of <math>P_{ET}O_2</math> directly before <math>P_{ET}O_2</math> continuously increases (provided <math>P_{ET}CO_2</math> remains constant).</li> </ul>	<ul style="list-style-type: none"> <li>Disproportionate increase in <math>\dot{V}E</math> vs <math>\dot{V}CO_2</math></li> <li>Lowest point of <math>\dot{V}E/\dot{V}CO_2</math> directly before <math>\dot{V}E/\dot{V}CO_2</math> continuously increases</li> <li>Point of <math>P_{ET}CO_2</math> directly before <math>P_{ET}CO_2</math> continuously decreases</li> </ul>

Definition of abbreviations: AT, anaerobic threshold;  $CO_2$ , carbon dioxide; ET, end-tidal; HR, heart rate;  $O_2$ , oxygen; P, pressure; RCP, respiratory compensation point; VE, minute ventilation;  $\dot{V}E/\dot{V}CO_2$ , ventilatory equivalent for carbon dioxide;  $\dot{V}E/\dot{V}O_2$ , ventilatory equivalent for oxygen;  $\dot{V}CO_2$ , carbon dioxide output;  $\dot{V}O_2$ , oxygen uptake. \*Full details of the V-slope method can be found elsewhere [2, 9, 13, 14]. By combining several methods (3 - panel view) AT and RCP can be determined in most cases.

**Anaerobic metabolism**

As exercise intensity continues to increase, more and more lactate accumulates in the muscles because the buffer base capacity for lactate-associated H<sup>+</sup> is exhausted. The resulting metabolic lactic acidosis (pH↓) stimulates an additional strong central ventilatory drive (partial respiratory compensation of metabolic acidosis) beyond CO<sub>2</sub>-induced hyperventilation. As a result of the excessively increased ventilation, even more CO<sub>2</sub> is exhaled ( $\dot{V}CO_2\uparrow$ ), while  $\dot{V}O_2$  continues to increase only in parallel with the increasing work rate. Beyond the RCP,  $\dot{V}E$  increases at a greater rate than  $\dot{V}CO_2$  ( $\dot{V}E/\dot{V}CO_2\uparrow$ ), causing P<sub>ET</sub>CO<sub>2</sub> to decrease (increased ventilatory elimination of CO<sub>2</sub>). In addition, there is a disproportional increase in RER ( $\dot{V}CO_2/\dot{V}O_2$ ). The excessive increase in ventilation is associated with elevations of P<sub>ET</sub>O<sub>2</sub> and of the two ventilatory equivalents EqO<sub>2</sub> and EqCO<sub>2</sub>. In the anaerobic range,  $\dot{V}O_2$  continues to tail off relative to HR, resulting in a flattened O<sub>2</sub> pulse. Reaching the anaerobic range signals the impending termination of exercise.

**Note:** even though there is no standard for defining a maximal effort, maximal performance can be defined by the  $\dot{V}O_2$  reached at maximal effort (pending attainment of a respiratory exchange ratio; e.g., RER ≥ 1.15, lactate > 8 mmol/L) beyond which no further increases in  $\dot{V}O_2$  occur (plateau concept). Measuring peak  $\dot{V}O_2$  is the gold clinical standard to objectively determine exercise capacity in individuals who cannot attain a maximal response. Of course, normal values of key CPET parameters vary because there will be expected differences in exercise physiology between trained athletes and the general population (Table 2) [2, 8, 15, 16, 17].

**Recovery period (without figure)**

$\dot{V}E$  remains elevated for a short time (usually 2–3 min, but this depends on exercise intensity) due to respiratory compensation of lactic acidosis with increased ventilatory elimination of CO<sub>2</sub> (P<sub>ET</sub>CO<sub>2</sub> ↓). At the same time, the ventilatory equivalents for O<sub>2</sub> and CO<sub>2</sub>, RER (faster recovery of  $\dot{V}O_2$  [↓] vs.  $\dot{V}CO_2$  to baseline) and P<sub>ET</sub>O<sub>2</sub> also increase before they rapidly return to normal.

**Table 2:** Key physiological parameters and their response to exercise [2, 15, 16].

CPET variable	Measure	Elite athletes <sup>1</sup>	Normal/untrained
$\dot{V}O_2$	Exercise capacity	↑↑	↑
AT <sup>2</sup>	Proportion of aerobic metabolism at submaximal exercise levels	↑↑	↔/↓
O <sub>2</sub> pulse <sup>3</sup>	O <sub>2</sub> extraction by body tissue from the O <sub>2</sub> carried in each stroke volume	↑↑	↑
HR <sup>4</sup>	Normally limits exercise	↑	↑
$\dot{V}E$ <sup>5</sup>	Minute ventilation	↑↑	↑
V <sub>T</sub>	Tidal volume	↑↑	↑
BF	Breathing frequency	↑-↑↑	↑
BR <sup>6</sup>	Potential for further increasing ventilatory capacity	↓↓	↓
$\dot{V}E/\dot{V}CO_2$ <sup>7</sup>	Gas exchange efficiency and V/Q mismatch at submaximal exercise	↓	↔
P <sub>ET</sub> CO <sub>2</sub> <sup>7</sup>	Indirect measure of pulmonary gas exchange and V/Q mismatch	↑	↔

Definition of abbreviations: AT, anaerobic threshold; BR, breathing reserve; CO<sub>2</sub>, carbon dioxide; ET, end-tidal; HR, heart rate; O<sub>2</sub>, oxygen; P, pressure;  $\dot{V}E/\dot{V}CO_2$ , ventilatory equivalent for carbon dioxide;  $\dot{V}O_2$ , oxygen uptake; V/Q, ventilation perfusion. <sup>1</sup>Refers to endurance athletes with a high aerobic/oxidative metabolism. <sup>2</sup>Athletes reach their AT at a later stage, meaning that aerobic metabolism can be maintained over an extended period of time. <sup>3</sup>Indirect estimate of stroke volume. <sup>4</sup>Maximal HR in athletes is significantly lower than in the normal population emphasizing the role of an increased stroke volume. <sup>5</sup>Physiologically,  $\dot{V}E$  increases until V<sub>T</sub> is fully utilised (60% of vital capacity [VC]), then  $\dot{V}E$  increases with a rise in BF. <sup>6</sup>BR indicates the actual percentage of the maximum ventilatory capacity (not shown in this article). A low BR indicates reduced ventilatory capacity due to impaired lung mechanics or increased ventilatory demands during exercise. Exercise is normally not limited by breathing and athletes may have breathing reserves (MVV- $\dot{V}E$  divided by MVV x 100) close to zero. The maximum voluntary ventilation (MVV) is usually calculated indirectly as forced expiratory volume in 1 second (FEV<sub>1</sub>) x 40 before the exercise test. <sup>7</sup>Elite athletes demonstrate (highly efficient) low values for  $\dot{V}E/\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  (relative hypoventilation) with consecutive P<sub>ET</sub>CO<sub>2</sub> increases during exercise.

## Conclusion

The benefit of performing CPET is that it provides a thorough assessment of the integrative global physiological response to exercise. CPET requires a sound understanding and knowledge of exercise physiology and pulmonary gas exchange. Assessments of pulmonary gas exchange, in particular, are fundamental to the understanding of the pathophysiology of exercise limitation and go far beyond simple measurements of  $\dot{V}O_2$  peak or  $\dot{V}O_2$  max. This is because they also provide a physiological link with ventilation-perfusion matching (e.g. ventilatory efficiency as determined by  $\dot{V}E/\dot{V}CO_2$ ). Considering that the first gas exchange threshold ( $=AT$ ) and the prognostic  $\dot{V}E/\dot{V}CO_2$  relationship are determined at submaximal levels of exercise increases, CPET can also be applied in elderly or unfit individuals who may be unable to provide maximal effort. It is important to ensure that CPET findings are not interpreted in isolation and instead take the individual clinical and (patho)physiological context into account.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

TG was responsible for the conception of the manuscript including figure and tables and wrote the initial draft manuscript. CT contributed to write and review the draft manuscript. Both authors were responsible for the decision to publish the manuscript.

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