Cardiopulmonary Exercise Testing: The ABC for the Clinical Cardiologist

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Abstract

Background: Cardiopulmonary exercise testing (CPET) is the most comprehensive technique which allows a holistic approach to cardiopulmonary diseases. **Summary:** This article provides basic information addressed to the Clinical Cardiologist regarding the utility and the indications of the CPET technique in the everyday clinical practice. Clinical application of CPET continues to evolve and protocols should be adapted to each specific patient to obtain the most reliable and useful information. **Key Messages:** Clinical Cardiologists with an interest over CPET may become familiar with this exercise method and its main measured variables, refresh their knowledge regarding the underlying pathophysiological mechanisms of oxygen transport chain, learn how to interpret the CPET results and promote appropriate patient referrals to experts.

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Introduction

Cardiopulmonary exercise testing (CPET) is the gold-standard approach in assessing CRF with an objective method and is probably the most comprehensive whole-body testing technique which allows the holistic evaluation of human body performance during exercise [1, 2]. Although test indications limited for a long time to a narrowed study of certain pathophysiological conditions, CPET now has transformed to a valuable tool to daily clinical practice as a result of a growing awareness of the considerable amount of valuable information provided. Subsequently, indications for ventilatory expired gas analysis during exercise have broadened to a wide array of confirmed or suspected cardiopulmonary diseases as well as musculoskeletal conditions and finally to individuals without a medical diagnosis [3–9]. The aim of this review is to help Clinical Cardiologists to become familiar with CPET technique and its key measured variables, to refresh their knowledge regarding the underlying pathophysiological mechanisms of oxygen transport chain, and to learn how to interpret the most important CPET results.

Which Patient's Populations Take Advantage from a Cardiopulmonary Exercise Test?

In cardiopulmonary disorders, the exercise intolerance is a major clinical feature from the early stages, becomes a source of symptoms and the predominant reason for referral to a physician. Its quantification may be approximated by several methods, but a thorough analysis of the organ systems and pathways involved in the impaired physiological response is obtained by exercise gas exchange analysis with CPET. The latter remains the gold-standard test for the selection of heart transplantation candidates with end-stage HF [7, 10]. Since exercise intolerance is one of the most disabling problems regarding patients with HF [7], the combined use of CPET-derived variables has led the physicians to the development of algorithms [11] and risk scores [12–14] covering the entire set of HF stages in patients with reduced or preserved left ventricular (LV) ejection fraction. Indeed, in patients with either HF or pulmonary arterial hypertension (PAH), the change in exercise capacity parallels with other clinical indicators of disease severity, such as survival, hemodynamic parameters, and time to clinical worsening [15].

Besides patients with HF, the role of routine CPET in Cardiology has been extended to other specific patient populations (unexplained dyspnoea [9], suspected ischemic heart disease [16], congenital heart or valvular diseases [17, 18], cardiomyopathies [19], suspected or confirmed PAH or even left-sided pulmonary hypertension [20–22]). Importantly, CPET has become a reproducible [23] and safe technique [24].

The Significance of Cardiopulmonary Exercise Test in Athletes

CPET is an important tool to optimize performance as part of a training program or for clinical purposes in athletes with established cardiovascular disease or in those with symptoms suggestive of cardiopulmonary pathology. Athletes demonstrate differences in exercise hemodynamic and gas exchange profiles as compared to nonathletes including higher cardiac output, faster heart rate recovery, higher peak VO_2 , higher prevalence of exercise-induced arterial hypoxemia, and lower breathing reserve (BR). 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 [25].

Using CPET for Diagnosis and Differentiation between Athletic Adaptation and Early Cardiomyopathy

LV enlargement not associated with systolic dysfunction and outside the context of a familial disease in trained individuals generally represents a benign physiological adaptation, especially if it is consistent with the type of sports participated (usually, endurance sports) and the body size of the athlete. On the contrary, a mildly reduced EF (45–50%) in an athlete with an enlarged LV cavity should not simply be considered as a normal adaptation. In these athletes, the presence of reduced peak oxygen consumption on CPET may provide supporting information for the differential diagnosis between athletic adaptation and early cardiomyopathy, especially in the context of an appropriate family history [26].

The Significance of Cardiopulmonary Exercise Test regarding Exercise Prescription

For medically stable individuals undergoing CPET, achieved volume of oxygen uptake (VO_2) at the level of the anaerobic threshold (AT) holds broad applicability in the context of assessing an individual's aerobic exercise capacity and determining the appropriate training intensity for a structured aerobic exercise program. Thus, the heart rate and workload that correspond to the level of an individual's VO_2 at AT should be used as targets for an aerobic exercise training program [6]. It is expected that an individual will improve VO_2 at AT (higher level) at the end of the training program.

Using the Changes in Peak VO_2 as a Clinical Trial Endpoint

It seems that monitoring the changes in peak VO_2 over time may be useful in HF patients. Indeed, a secondary analysis of the HF-ACTION study regarding the exercise training in HF patients indicated that a modest increase in peak VO_2 over 3 months was associated with a lower composite rate of all-cause mortality and all-cause hospitalization, even in the setting of optimal medical and device therapy for chronic systolic HF [27]. However, the results of a recent meta-analysis indicated that improvements in exercise capacity, estimated by CPET or 6MWT, after exercise-based cardiac rehabilitation, was a poor

surrogate endpoint for mortality and hospitalization in HF patients with a moderate validity for health-related quality of life [28].

The Chain of Oxygen Delivery during Exercise

Throughout CPET, the analysis of gas exchange during exercise is estimated. Modern systems measure breath by breath the VO_2 and the volumes of carbon dioxide production (VCO_2) and air expired (Ventilation [VE]) [29]. The human body behaves under physical stress as an integrated system which delivers oxygen (O_2) to mitochondria in order to perform aerobic exercise [30]. Optimal O_2 delivery depends on a set of biological interactions between the components of the O_2 transport chain (lung alveolar diffusion, blood oxygenation, cardiac output [CO], O_2 -carrying capacity of the blood, oxygen delivery, and adequate release to working muscles). Subsequently, CPET may reveal alterations in multiple body functions including the cardiovascular, respiratory, muscular, sympathetic, and neuro-hormonal systems [31, 32].

Estimation of O_2 Consumption by the Fick Principle

CPET enables the clinician to investigate potential causes of dyspnea and fatigue, precisely differentiate cardiac from pulmonary disorders, optimize the decision-making process and outcome prediction, and objectively determine targets for therapies [9]. These can be described by analyzing the framework of the Fick principle which estimates VO_2 by the following equation: $\text{VO}_2 = \text{stroke volume (SV)} \times \text{heart rate} \times (\text{CaO}_2 - \text{CvO}_2)$, where CaO_2 is arterial oxygen content, CvO_2 is venous oxygen content and $(\text{CaO}_2 - \text{CvO}_2)$ is the arteriovenous (a-v) difference in O_2 . Conclusively, O_2 delivery depends on SV and heart rate (CO) but also on the mechanisms involved in O_2 dissociation from hemoglobin (the ability of O_2 to diffuse from capillaries to cells and on mitochondria function). Gladly, tissue O_2 extraction remains preserved due to an “optimized” peripheral blood flow redistribution and high mitochondrial activity even in the presence of an inadequate increase in CO [33–35].

Normal, healthy adults can increase VO_2 up to 6-fold during exercise. The relative contribution of Fick’s equation determinants to VO_2 changes is approximately 1.2-, 2.5-, and 2.5-fold for SV, heart rate, and $\text{CaO}_2 - \text{CvO}_2$, respectively [10].

Choosing between Bike-Ergometer versus Treadmill for a Cardiopulmonary Exercise Test

During CPET, the patient either rides a stationary bicycle (bike-ergometer) or walks on a treadmill while breathing through a nonrebreathing mask and wearing electrocardiographic leads, a blood pressure cuff, and a pulse oximeter. When using a bike-ergometer, subjects are submitted to a ramp exercise protocol which permits a true estimation of workload. The most important point in favor of a bike-ergometer is the linearity in workload change. Using a treadmill, it is possible to change slope and speed, but not the workload itself, so that it is almost impossible to generate a linear increase in workload [36]. On the other hand, exercise in a treadmill may more accurately reflect the patient’s experience of exercise in day-to-day life compared to a bike-ergometer. A relevant issue in favor of the treadmill use is the potentially limited ability and habit of a number of the subjects to pedal. While biking is common in Europe and Eastern Asia, this is not the case in North and South America where, indeed, a treadmill is most frequently used. Finally, treadmill more readily highlights posture-dependent cardiac abnormalities like subaortic stenosis in LVOT obstruction and mitral insufficiency in mitral valve prolapse.

Protocol Description of a Cardiopulmonary Exercise Test

The test starts out easy and gets progressively harder until the patient fatigues, reaches $\geq 90\%$ of his/her predicted maximum heart rate (maximum heart rate [beats per min] = $220 - \text{age [years]}$) or, as in any stress test, experiences any other clinical indication for stopping, such as arrhythmias, hypotension, or severe symptoms (dyspnoea, angina, pre-syncope). Although CPET resembles exercise stress test, its purpose is not the ischemia or arrhythmia diagnostic evaluation. Instead, CPET estimates an individual’s fair or poor physical condition and is based on circulatory, metabolic, and ventilatory parameters. Patients are advised to wear comfortable workout clothes, and asked to try as hard as they can. The selected exercise ramp protocol, must allow exercise duration of ~ 10 min with an accepted interval ranging from 8 to 12 min [37, 38]. This means that the workload increase should be personalized for each patient, in order to achieve this test duration. Data must be recorded breath by breath. For interpretation, data are usually averaged by fixed time intervals (usually 20–30 s). Prediction equa-

Table 1. Key variables during a CPET session and their normal values at peak exercise

Parameter	Expected values at peak exercise
<i>Exercise</i>	
Duration, min	8–12
Work load, % predicted	>80
RER	>1.15
<i>Hemodynamic</i>	
Systolic blood pressure, mm Hg	<220
Heart rate, % predicted	>90
Heart rate reserve, % predicted	<10
Heart rate recovery (beats at 1° recovery)	>12
<i>Metabolic</i>	
Peak VO ₂ , % predicted	>84
AT, % predicted VO ₂	>40
O ₂ pulse, %	>80
VO ₂ /work, mL/min/W	9–11
<i>Ventilatory</i>	
BF, breaths/min	<60
BR, %	>20–40
PETCO ₂ at baseline, mm Hg	>33
PETCO ₂ at AT, mm Hg compared to baseline	>3–6
O ₂ desaturation, %	<4
<i>Prognostic</i>	
VE/VCO ₂ slope	<34
O ₂ recovery slope	>650
BF, breathing frequency.	

(3–4 min) of constant work rate exercise separated by resting periods and with loads progressively increased (rarely used clinically) [3, 40].

Key Variables Derived from a Cardiopulmonary Exercise Test

Overall, despite a wealth of persuasive evidence and numerous statements supporting the utility of CPET in prevention and in early stages of several cardiopulmonary diseases, practitioners have not generally adopted a portfolio of variables that provides a 3-dimensional view of cardiorespiratory fitness with diagnostic and prognostic applicability, and an effective means to evaluate therapeutic benefits [10]. CPET variables (independently and combined) offer useful prognostic information. The Wassermann's 9-plot uses several CPET variables as they interact to each other. Many of them reflect the ventilator,

cardiac and metabolic inefficiencies that result from the extensive central and peripheral pathophysiological mechanisms seen in patients with cardiopulmonary diseases (shown in Fig. 1) [41–43]. Besides the metabolic variables, the ventilatory ones are important even in patients with HF who usually present a lung restrictive syndrome due to congestion and physical interaction between the heart and lung [44–46] with impaired exercise-induced tidal volume increase [47–50] and an expiratory flow limitation [46, 51]. The following main parameters are examined and interpreted at the end of the test, usually by the order they appear below, in order to evaluate the adequacy of the examinee's effort (Table 1).

Respiratory Exchange Ratio

It is calculated as the ratio between peak VCO₂ production and peak VO₂ consumption, is important as an indicator whether a maximal or near maximal exercise test has been performed. Exceeding a RER value of 1.05 and even better 1.15 indicates a good effort [52].

Workload

It represents the maximum load to which the examinee is subjected during CPET session in order to produce work. It is referred as an absolute value (in watts) as well as in relation to its predicted value (%). Maximum workload >90% predicted is necessary in order to indicate a good effort [53].

Max Heart Rate

The examinee has to reach ≥90% of his/her predicted maximum heart rate in order to complete a maximal exercise. Although patients under chronotropic medications are not sometimes capable to meet this criterion, a maximal exercise maybe completed as it is indicated by the interpretation of RER and Workload [36].

VO₂ at Peak Exercise (Peak VO₂)

It is the most important parameter derived from a CPET and at the same time is the gold standard to objectively assess functional limitations in cardiac patients [7]. It can be reported as VO₂ max or peak VO₂. Peak VO₂ describes the highest achieved VO₂ value during an exercise test (averaged over a complete 20–30 s period). Peak VO₂ can be reported as an absolute value (mL/min) or indexed by body weight (mL/min/kg) or as a percentage of predicted value (%) normalized to sex, age, height, and weight measurement. Weber's classification characterizes the individual's response to exercise as normal when VO₂ >20 mL/min/kg (stage A), mildly to moderately im-

paired when $\text{VO}_2 \leq 20$ mL/min/kg (stage B), moderately to severely impaired when $\text{VO}_2 \leq 16$ mL/min/kg (stage C) and severely impaired when $\text{VO}_2 \leq 10$ mL/min/kg (stage D). It is important to consider that the absolute peak VO_2 value is $\sim 10\%$ higher on a treadmill, compared to a cycle ergometer [54].

To this day, a peak VO_2 equal or above 14 mL/kg/min remains a positive prognostic threshold with lower values carrying a poor CV prognosis [3]. Moreover, heart transplant guidelines report that HF patients with peak VO_2 threshold values ≥ 12 mL/min/kg or ≥ 14 mL/min/kg (in those treated or not treated by β -blockers, respectively) may be safely removed from the transplantation list [55, 56]. However, both the absolute and the % of predicted peak VO_2 value must be reported and combined since the latter seems more reliable than absolute values in patients with HF [7, 57, 58]. In the recent ESC position paper regarding the role of CPET in clinical stratification in heart failure, the achievement of a peak $\text{VO}_2 \geq 18$ mL/min/kg from patients with HFrEF confers a favorable outcome [53]. However, this might not be fit for “specific” individual patients as the very young patients with HFrEF. In this group, a peak VO_2 equal to 18 mL/kg/min might already be significantly reduced, and the integration of peak VO_2 percentage might be useful [53].

VE/VCO₂ Slope

VE/VCO₂ responses to exercise typically evaluate ventilatory efficiency providing information about the effectiveness of the minute VE for a given metabolic rate. When VE/VCO₂ is elevated, it is important to understand the underlying physiological mechanism for the increased VE relative to metabolic rate (increase in dead space and/or alveolar VE) [59]. VE/VCO₂ is undoubtedly, the most relevant ventilatory parameter, which has a key prognostic role in HF, pulmonary artery hypertension, congenital heart disease, and lung diseases (normal values < 34) either as a single value or in combination with other parameters [60]. Therapeutic intervention in cardiovascular and lung diseases aims to improve prognosis, limit morbidity, and increase the quality of life, all of which are markers associated with higher peak VO_2 values and lower VE/VCO₂ slopes [10].

AT or Otherwise Ventilatory Threshold

Achieved either earlier than expected or on time, AT is important in order to evaluate an individual's aerobic capacity to exercise. It is defined as the VO_2 at the time point of the anaerobic metabolism initiation (submaximal exercise) which can be determined using the expired

concentrations of oxygen and carbon dioxide during a CPET session. Researchers have also used the terms “1st and 2nd AT” (also termed the “AT” and “point of respiratory compensation,” respectively) to establish the exercise intensity. Given that metabolic acidosis drives pulmonary VE, an inflection in blood lactate concentration above baseline levels is coincident to the 1st AT while at 2nd AT, a higher marker of exercise intensity compared to 1st AT, lactate has quickly accumulated in the blood [61].

There are 3 CPET-derived methods for detecting VO_2 at AT: (i) the V-slope, the point at which the incremental volume of VCO₂ becomes higher, as compared with VO_2 , due to the additional CO₂ produced by lactic acid buffering; (ii) the end-tidal CO₂ (PETCO₂) versus the end-tidal O₂ (PETO₂) method (when an opposite kinetic point of these variables occurs with PETO₂ progressively increasing and the PETCO₂ slightly decreasing); and (iii) the oxygen minute VE equivalent (VE/VO₂) versus carbon dioxide minute VE equivalent (VE/VCO₂) change in pattern (the point of continuous increase in VE/VO₂ and stable VE/VCO₂ kinetics) [10]. Ventilatory equivalents (VE/VO₂, VE/VCO₂) and end-tidal partial pressures (PETO₂, PETCO₂) represent the ventilatory response of anaerobic metabolism generated at the muscular level [62]. Inability to determine the AT with any of these methods occurs approximately in 10% of patients with HF and carries a strong independent prognostic role [10].

Oxygen Pulse

It is the ratio of VO_2 to heart rate and reflects the amount of O₂ extracted per heartbeat. The O₂ pulse provides an estimate of LV SV changes during exercise, assuming that (a-v) O₂ is maximal and no anemia or hypoxia is present [10]. A low, unchanging flat O₂ pulse with increasing work rate be interpreted as resulting from a reduced SV and/or as a failure for further skeletal muscle O₂ extraction [3]. In a recent study, abnormal O₂ pulse curve pattern had low sensitivity and negative predictive value for the diagnosis of obstructive CAD since it was not associated with the myocardial ischemia defined by scintigraphy. Instead, a flat O₂ pulse curve was associated with the extent of global perfusion defect, probably reflecting myocardial dysfunction [63].

VO₂/Work Load Ratio

Observed during the entire exercise, it attracts pathophysiological interest since it shows oxygen delivery to the working muscles. It increases throughout the entire

Fig. 2. How to interpret a CPET and fill the report form.

incremental exercise period in parallel with the aerobic ATP augmentation reaching normal values (9–11 mL/min/W). Reduced values of the VO_2 versus work relationship imply an impaired O_2 delivery [3]. Moreover, this slope can be suddenly decreased during exercise, due to cardiac ischemia or mitral insufficiency [64].

PETCO₂ Kinetics

When estimated at baseline, AT and peak exercise it will help discrimination between a normal performed exercise or an exercise under the patterns of HF or chronic obstructive pulmonary disease (COPD) or PAH [65]. Normally, $PETCO_2$ is >33 mm Hg at baseline, increases by $>3-6$ mm Hg at the AT point and then decreases at peak exercise just above the baseline values. In HF and COPD, $PETCO_2$ is <33 mm Hg at baseline and increases less than 3 mm Hg at the AT point. However, $PETCO_2$ decreases at peak exercise in HF while it forms a plateau in COPD. Finally, in PAH $PETCO_2$ starts well <33 mm Hg at baseline and continuously decreases at the AT point and the peak exercise [59].

Breathing Reserve

It describes the relationship between exercise VE and maximal breathing capacity, as estimated by resting maximal voluntary VE [3]. Values $<15\%$ suggest a ventilatory limitation and may help to discriminate between patients with HF and those with comorbid COPD [66].

Differential Diagnosis between the Circulatory or Respiratory System Insufficiency and Poor Physical Condition

When a subject/patient achieves a lower than expected peak VO_2 after a CPET session, we need to differentiate between the circulatory/respiratory system insufficiency and poor physical condition. Circulatory system insufficiency is characterized by exhaustion, max HR $\sim$ max HR predicted, $RER \geq 1.1$, O_2 saturation $>88\%$, no ventilatory limitation. On the other hand, respiratory system insufficiency is characterized by exhaustion, max HR $<$ max HR predicted, AT $>40\%$ max VO_2 predicted,

O₂ saturation <88%, and ventilatory limitation (BR <15%, expiratory flow limitation, and hyperinflation). Finally, in poor physical condition, VO₂ at AT is moderately decreased (<40% max VO₂ predicted), max HR ~ max HR predicted, BR >15% and % O₂ saturation >88% [59].

How to Interpret a Cardiopulmonary Exercise Test and Fill the Report Form

A 8-step approach consisted of 8 questions and their corresponding answers will be valuable in order for the clinician to fill the CPET report form. The latter including data from all exercise phases (baseline, AT, peak exercise, and recovery) will give answers to the following questions regarding the evaluation of a subject's/patient's ability for exercise. A clear interpretation of the findings should be provided in order to facilitate the appropriate diagnostic or/and therapeutic decisions (shown in Fig. 2).

1st Question: Why CPET Was Performed?

The reason(s) for the examinee's (or patient's) referral to a CPET laboratory regarding his cardiorespiratory evaluation (dyspnea, easy fatigue, evaluation of cardiopulmonary disease severity, and/or treatment plan sufficiency) along with his demographics (gender, age, height, and weight) and a short description of past medical history/medications need to be included in the CPET report form.

2nd Question: What Protocol Was Used?

The mode of exercise (bike-ergometer or treadmill), the selected exercise protocol (ramp or incremental) and the duration of exercise answer that question.

3rd Question: May We Characterize the Current CPET as Complete?

If the examinee/patient achieved a maximal exercise effort (RER >1.05–1.15) while exercised for 8–12 min until physical exhaustion reaching peak work load >80% predicted and regardless of the maximum heart rate, then the current CPET session should be characterized as complete.

4th Question: Did the Patient Have an Impaired Exercise Capacity?

The evaluation of the metabolic parameters VO₂, AT, O₂ pulse (presented as absolute and % predicted values)

and VO₂/work at peak exercise after a complete exercise effort characterize the examinee's (or patient's) exercise capacity as adequate or abnormal.

5th Question: Did the Patient Have Any Hemodynamic Instability During Exercise?

The estimation of hemodynamic parameters at baseline and peak exercise (blood pressure, heart rate, heart rate reserve, and heart rate recovery) evaluates any hemodynamic instability during exercise.

6th Question: Did the Patient Have an Ischemic or Arrhythmic Event or a Reason to Prematurely End the Exercise?

An ECG review during the whole exercise along with a short description should be provided in order to reveal any ischemic or arrhythmic events. Simultaneously, the presence of any cardiorespiratory symptoms or BP drop ≥20 mm Hg compared to baseline levels (main reasons for exercise interruption) should be mentioned in CPET report form.

7th Question: Did the Ventilatory System Participate in Patients' Impaired Exercise Capacity?

The study of ventilatory parameters at peak exercise (VE, BR, PETCO₂, O₂ desaturation) will give the appropriate answers. CPET may distinguish between circulatory and respiratory failure as well as poor physical condition responsible for impaired exercise capacity.

8th Question: Did the Test Provide Any Prognostic Information?

Significant prognostic parameters (VE/VCO₂ ratio, O₂ recovery slope) should be revised and mentioned in CPET report form.

Conclusions

CPET is the most comprehensive technique which allows an holistic approach to cardiopulmonary diseases. Clinical application of CPET continues to evolve and protocols should be adapted to each specific patient to obtain the most reliable and useful information. Interested Clinical Cardiologists should increase personal familiarity with test interpretation and promote appropriate patient referrals.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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