

REVIEW ARTICLE

Cardiopulmonary Exercise Testing in Pulmonary Hypertension

Carlos Alberto Cordeiro Hossri^{1,2}, Romulo Leal Almeida², Felipe Rodrigues da Costa Teixeira², Glauber Luasse Osima², Luiz Eduardo Mastrocola^{1,2}

Hospital do Coração – HCor¹ e Instituto Dante Pazzanese de Cardiologia² – São Paulo, SP – Brazil

Abstract

The cardiopulmonary exercise test (CPET) is a complementary test that provides important data about the patient's actual functional capacity, metabolic and ventilatory responses, and gas exchange. Thus, it enables a classification of the cardiorespiratory fitness of an individual and identification of disorders that limit exercise continuity by analyzing several variables drawn from this diagnostic and prognostic propaedeutic method. In this regard, situations that are relatively common in clinical practice but are not often identified, such as pulmonary hypertension (PH), can be better addressed, assessed, and measured. Thus, the analysis of exhaled gases using CPET may provide better PH management by enabling a classification of the aerobic capacity, ventilatory response and gas exchange in patients with this pulmonary vascular disorder.

Introduction

Cardiopulmonary exercise testing (CPET) is a complementary test increasingly used in clinical practice as an important tool to investigate cardiovascular diseases. CPET has several well-established indications, including the assessment of cardiorespiratory fitness, support in the investigation and follow-up of patients with myocardial ischemia, objective prescription of training zones (in healthy individuals and patients with

cardiac diseases) and differential diagnosis of dyspnea,¹⁻³ among others. The foundations of the CPET are based on a ventilatory analysis of the exhaled gases, with the purpose of quantifying the consumption of oxygen (VO_2), the production of carbon dioxide (VCO_2), and minute ventilation (VE) at rest and during exercise and recovery. Valuable information provided about pathophysiologic responses in the rest-exercise transition and the identification of the functional capacity include: (1) a precise assessment of the aerobic power, (2) evaluation of cardiometabolic variables at levels of submaximal and maximal effort (e.g.: ventilatory threshold), and (3) evaluation of ventilatory efficiency.⁴ Although its initial use was geared toward a more precise identification of the functional capacity, especially in heart failure (HF) and in the differential diagnosis of dyspnea, CPET has also demonstrated to be a fundamental tool in the evaluation of central cardiovascular disorders affecting the pulmonary vasculature, as observed in the presence of pulmonary hypertension (PH), which leads to increased morbidity and mortality.⁵⁻⁷ PH can be associated with several other pathologies, such as those affecting the left cardiac chambers, the arterial circulation, and the interstitium and pulmonary parenchyma. Rarely, this pathology may be primary and not associated with any other causal factor.⁸ Patients with PH have a reduced functional capacity, caused by a decreased ventilatory efficiency, cardiac output (CaO), and oxygen supply to peripheral tissues. Many of these aspects can be assessed and measured by CPET, making it a graphical method displaying ventilation and cardiac and peripheral metabolism with excellent application in such circumstances.⁹ Despite the limited number of studies of CPET in PH, Wensel et al. demonstrated in 2002 its value in the prognostic evaluation of patients with PH.¹⁰

Keywords

Hypertension, Pulmonary / physiopathology; Respiratory, Function Tests; Breathing Exercises; Exercise Test.

Mailing Address: Carlos Alberto Cordeiro Hossri

Afonso de Freitas, 550. Postal Code: 04006-052. Paraíso, São Paulo, SP – Brazil
E-mail: reabhcor@hcor.com.br, cahossri@gmail.com

DOI: 10.5935/2359-4802.20160062

Manuscript received May 20, 2016; revised manuscript June 26, 2016; accepted August 22, 2016.

The aim of this article is to highlight the important aspects of CPET in patients with increased pulmonary systolic arterial pressure (PSAP), defining the most frequent standards and characteristic findings of this test.

Pathophysiology

The pathological changes found in PH are multifactorial and complex. Variables such as genetic predisposition, risk factors (use of anorexigenic agents, HIV), and cardiovascular and pulmonary diseases increase the venous and/or arterial pulmonary pressure and cause vascular dysfunction that results in vasoconstriction and remodeling of the pulmonary circulation.⁸

In the primary pathophysiological process leading to an inadequate increase in pulmonary arterial pressure, there is disproportion between pulmonary ventilation and perfusion (normal ventilation / decreased perfusion), which results in an increased physiological dead space and a decreased ventilatory efficiency. This process translated into a greater ratio between increased VE

and VCO_2 production, as well as a change in this ratio's slope (VE/VCO_2 slope). In addition, there is a reduction in the end-tidal carbon dioxide pressure ($PETCO_2$), which characterizes a pattern of hyperventilation.

Patients with PH may also have decreased CaO due to a reduction in the left ventricular preload, causing the interventricular septum to bulge, affecting the function of this ventricle. Such effects lead to a decreased peak VO_2 and VO_2 at the anaerobic (AT) or ventilatory threshold (LV1), which are variables extracted and measured during the CPET. In addition to these described metabolic changes, a decrease in oxyhemoglobin saturation may occur, induced by stress, as a consequence of difficulties in gas diffusion in the pulmonary circulation, contributing to exercise intolerance in these patients. In short, the decrease in oxygen supply to the skeletal muscle has a negative impact on the aerobic metabolism (reduced VO_2 in LV1 and early lactic acidosis) and on the ventilatory efficiency, with an elevation of the VE/VCO_2 slope⁹ (Figure 1).

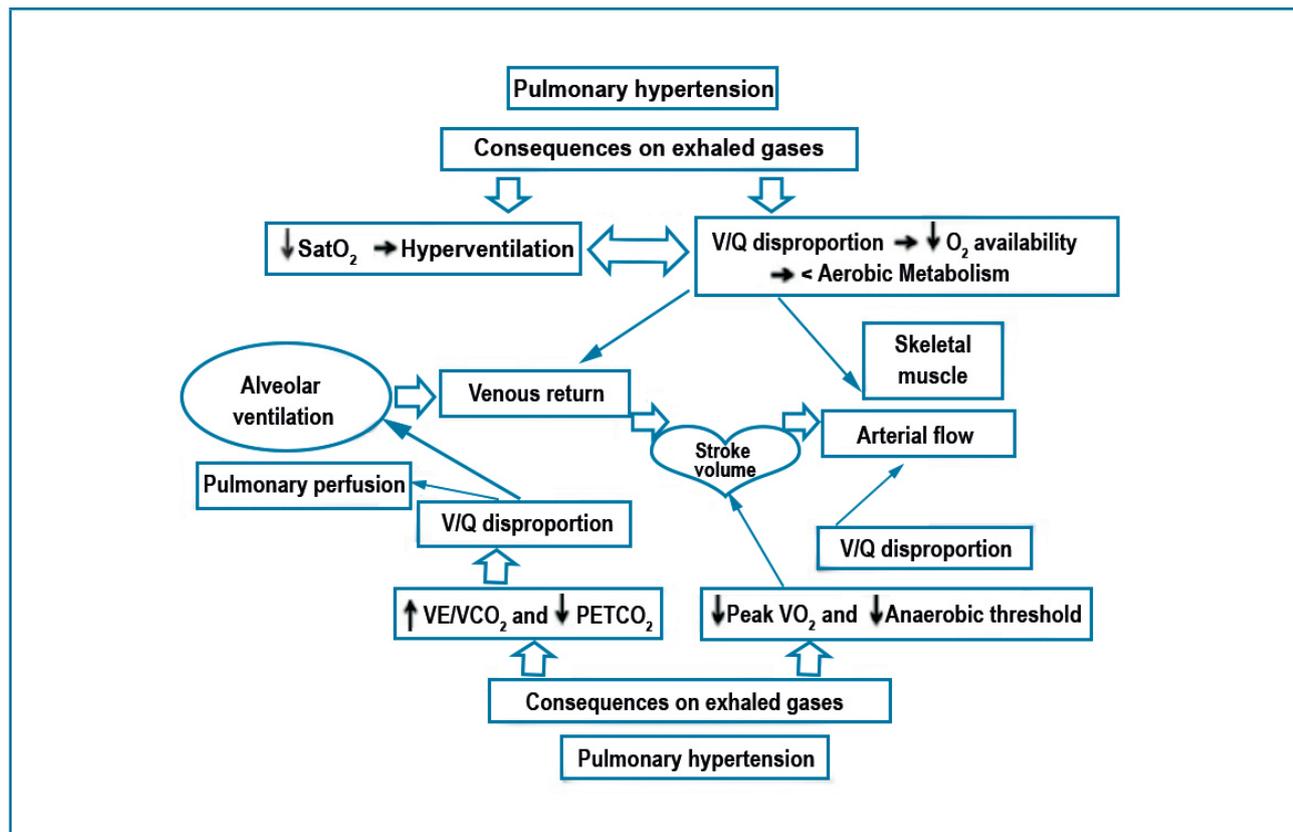


Figure 1

Adapted from Arena, R. et al.; J Heart Lung Transplant 2010; 2: 159-73.

CPET findings

Changes in the ratio or relation between pulmonary ventilation and perfusion increase the dead space and reduce the ventilatory efficiency, which can be easily observed by increased $\dot{V}E/\dot{V}CO_2$ values and a steeper slope in the relation $\dot{V}E \times \dot{V}CO_2$ (Figure 2b). Monitoring of the changes in $\dot{V}E/\dot{V}CO_2$ at rest and during the entire exercise should be the focus of special attention in PH since it helps to identify objectively the development of right-left shunt during exercise. The changes in the analysis of the $\dot{V}E/\dot{V}CO_2$ slope are comparable to changes found in patients with HF.⁹ However, individuals with advanced PH tend to show proportionately higher values (Figure 2).

The ventilatory inefficiency is also evidenced in the $PETCO_2$ at rest, its curve during effort, and its values obtained at the peak, characteristics of patients with PH, who require greater ventilation to release the same amount of CO_2 when compared with normal patients. Therefore, a reduction in $PETCO_2$ values is observed in such condition.^{9,11}

The ratio between the dead space (V_d) and the tidal volume (V_t) decreases at the beginning of the exercise due to a more evident and expressive increase in V_t than

V_d . Due to a greater increase in dead space, patients with PH do not display the expected behavior for this ratio (V_d/V_t), which then shows much higher values during exercise.¹¹

The $\dot{V}O_2$ is directly proportional to the CaO , demonstrated by Fick's equation: $\dot{V}O_2 = CaO \times C(a-v)_2$; therefore, the CaO reduction in patients with PH is evidenced by a reduction in the peak $\dot{V}O_2$ and in the ratio between $\dot{V}O_2$ and heart rate, named O_2 pulse (the latter represents a behavior of the stroke volume during effort). The $\dot{V}O_2$ at the AT is also decreased, and the hypoxemia caused by PH associated with a reduction in the CaO causes lower availability of O_2 for aerobic metabolism, resulting in earlier lactic acidosis and first threshold. To better analyze the aerobic power measurement, the peak $\dot{V}O_2$ must be correlated with the body weight and predicted value for the patient's age.¹¹

In addition to the ventilation, gas diffusion also seems to be impaired in patients with PH, since recent studies have shown a reduction in the oxygen uptake efficiency slope (OUES) associated with an elevation in PSAP, in addition to a correlation between the O_2 uptake efficiency with the $\dot{V}E/\dot{V}CO_2$ and the $PETCO_2$.^{9,11}

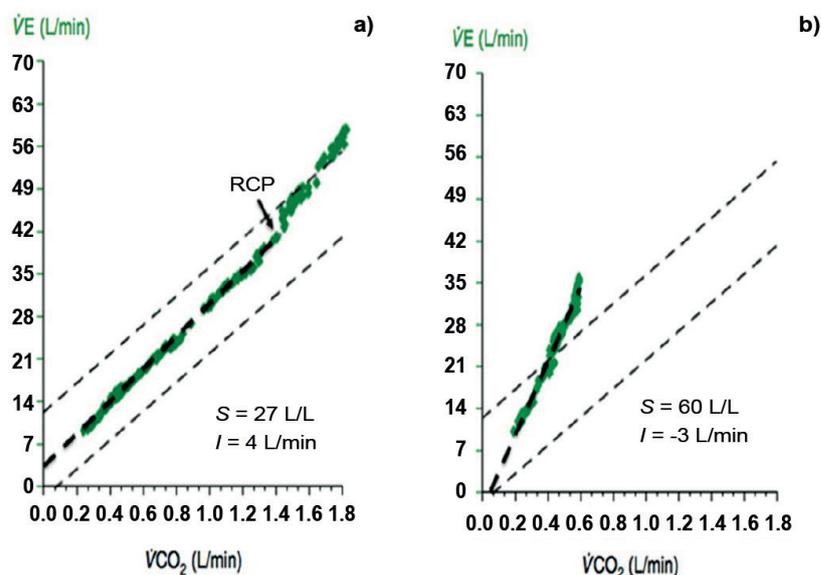


Figure 2

To the left (2a), a $\dot{V}E/\dot{V}CO_2$ curve in a patient without comorbidities and to the right (2b), in a patient with PH with a clear tendency toward verticalization of the line, in which the slope (S) corresponds to 60, i.e., to eliminate 1 liter of CO_2 , the patient had to ventilate 60 liters of air. Adapted from J Alberto Neder et al.¹¹ *Annals ATS* Volume 12 Number 4 / April-2015.

It is important to emphasize that PH must be regarded as the main pathophysiological mechanism in patients with unexplained dyspnea and with (1) no echocardiographic left ventricular abnormalities, (2) a normal pulmonary function test, (3) changes in CPET, including low aerobic capacity, elevation in the VE/VCO₂ slope, and decrease in PETCO₂, and (4) a possible desaturation during exercise.

It should also be noted that patients with HF, hypertrophic cardiomyopathy, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis may also develop PH as a result of the primary pathophysiological condition. If PH coexists with these primary cardiac or pulmonary conditions, the ventilatory changes in the exhaled gases (peak VO₂, VE/VCO₂ slope, and PETCO₂) will be typically more severe and reflect the degree of the PSAP elevation.^{9,11}

Thus, as in HF, the peak VO₂ and the VE/VCO₂ are prognostic variables and some articles have demonstrated a superiority of the latter, since it does not rely on maximum exercise and has better discrimination in identifying patients with worse prognosis. These CPET variables (peak VO₂, respiratory exchange ratio [RER], VE/VCO₂ slope, and PETCO₂) have high reliability in the diagnostic and prognostic evaluation of patients with PH and should, therefore, be included in the assessment of these patients.^{9,11}

The improvements in peak VO₂, VE/VCO₂ slope, RER, and PETCO₂ may be evident in assessments conducted before and after treatment (both medical and intervention treatments), in particular in treatments improving pulmonary hemodynamics (*e.g.*, correction of congenital heart diseases).^{9,11}

With regard to safety, data in the literature indicate that CPET is a safe test to be carried out in patients with PH. Episodes of syncope, complex cardiac arrhythmias, and/or acute right ventricular failure are some examples of adverse events and are considered contraindications for a maximal exercise test. An analysis of the VE/VCO₂ slope and the PETCO₂ at rest and at submaximal exercise may provide valuable clinical information when the performance at maximal exercise test raises safety concerns.

Use of CPET in the prescription of exercise

The reduction in the peak VO₂ and VO₂ at the AT in patients with PH represents a decreased ability to

perform daily activities. CPET may be used to assess the degree of deficiency and guide the patient or caregiver about the activities that may be performed safely and those that should be avoided due to the occurrence of associated symptoms.¹²⁻¹⁴

The CPET analysis, particularly VO₂ in the LV1, if detectable, serves to recommend aerobic activities that the patient can perform safely.¹⁵

Guided physical training improves symptoms and functional capacity in patients with PH.^{9,16} The current evidence indicates that CPET also provides a precise and objective description of the PH severity and may offer prognostic information related to the ventilatory efficiency,¹⁷ (Figure 3) including after therapeutic interventions. In addition, the exercise protocols used in the tests and the key variables analyzed in the exhaled gases (peak VO₂, VE/VCO₂, and PETCO₂) are very similar among patients diagnosed with HF and PH.⁹

Final comments

CPET has an important role in evaluating patients with PH, evidencing the pathophysiological mechanisms of exercise intolerance and contributing to therapeutic assessment, monitoring, and prognosis in this group of patients. However, additional studies are needed for a better understanding of these mechanisms during the diagnostic and prognostic evaluation of patients with clinical suspicion of this disease entity.

Author contributions

Conception and design of the research: Hossri CAC, Almeida RL. Acquisition of data: Hossri CAC, Almeida RL, Teixeira FRC, Osima GL, Mastrocola LE. Analysis and interpretation of the data: Hossri CAC, Mastrocola LE. Writing of the manuscript: Hossri CAC, Teixeira FRC, Osima GL. Critical revision of the manuscript for intellectual content: Hossri CAC, Almeida RL, Mastrocola LE.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

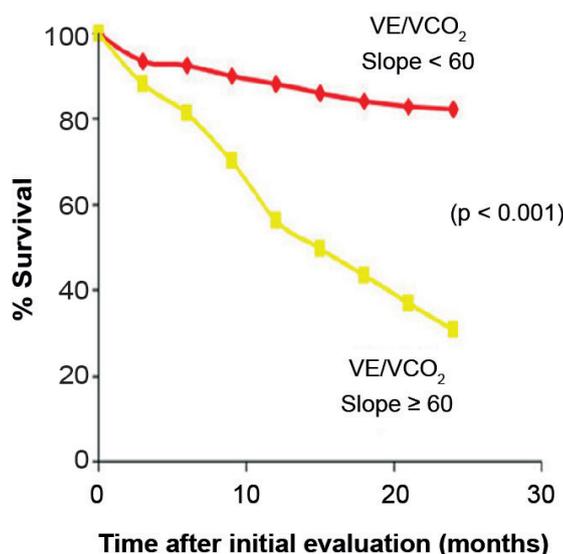


Figure 3

Percentage of survival according to the inclination cutoff of the relation VE/VCO_2 (VE/VCO_2 slope) up to 30 months after an initial CPET evaluation.

References

- Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al; American College of Cardiology.; American Heart Association Task Force on Practice Guidelines.; American College of Chest Physicians.; International Society for Heart and Lung Transplantation.; Heart Rhythm Society. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005;112(12):e154-235.
- Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, et al. ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol*. 1997;30(1):260-311.
- Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol*. 2002;40(8):1531-40. Erratum in: *J Am Coll Cardiol*. 2006;48(8):1731.
- Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, et al; American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Nursing. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation*. 2007;116(3):329-43.
- Yasunobu Y, Oudiz RJ, Sun XG, Hansen JE, Wasserman K. End-tidal PCO_2 abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest*. 2005;127(5):1637-46.
- Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation*. 2001;104(4):429-35.
- Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. *Circulation*. 2002;105(1):54-60.
- Sociedade Brasileira de Cardiologia. Diagnóstico, avaliação e terapêutica da hipertensão pulmonar. Diretrizes da SBC [internet]. [Acesso em 2016 jan 10]. Disponível em: <http://publicacoes.cardiol.br/consenso/2005/039.pdf>
- Arena R, Lavie CJ, Milani RV, Myers J, Guazzi M. Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review. *J Heart Lung Transplant*. 2010;29(2):159-73.
- Wensel R, Opitz CF, Anker SD, Winkler J, Höffken G, Kleber FX, et al. Assessment of survival in patients with primary pulmonary hypertension. *Circulation*. 2002;106(3):319-24.
- Neder JA, Ramos RP, Ota-Arakaki JS, Hirai DM, D'Ársigny CL, O'Donnell D. Exercise intolerance in pulmonary arterial hypertension: the role of cardiopulmonary exercise testing. *Ann Am Thorac Soc*. 2015;12(4):604-12.
- Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, et al; American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Nursing. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation*. 2007;116(3):329-43.
- American Thoracic Society; American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167(2):211-77. Erratum in: *Am J Respir Crit Care Med*. 2003;145:1-2.

-
14. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2001;104(14):1694-740.
 15. Myers J. Information from ventilatory gas exchange data. In: Washburn R. (editor). *Essentials of cardiopulmonary exercise testing*. Champaign (IL): Human Kinetics; 1996. p. 83-108.
 16. Uchi M, Saji T, Harada T. [Feasibility of cardiopulmonary rehabilitation in patients with idiopathic pulmonary arterial hypertension treated with intravenous prostacyclin infusion therapy]. *J Cardiol*. 2005;46(5):183-93.
 17. Schwaiblmair M, Faul C, von Scheidt W, Berghaus TM. Ventilatory efficiency testing as prognostic value in patients with pulmonary hypertension. *BMC Pulm Med*. 2012;12:23.