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Cardiopulmonary Exercise Test: Background, Applicability and Interpretation

Artur Haddad Herdy,^{1,2,3} Luiz Eduardo Fonteles Ritt,^{4,5} Ricardo Stein,^{6,7,8} Claudio Gil Soares de Araújo,^{9,10} Mauricio Milani,¹¹ Romeu Sérgio Meneghelo,^{12,13} Almir Sérgio Ferraz,¹² Carlos Hossri,¹⁴ Antonio Eduardo Monteiro de Almeida,^{15,16} Miguel Morita Fernandes-Silva,¹⁷ Salvador Manoel Serra¹⁸

Instituto de Cardiologia de Santa Catarina,¹ São José, SC; Universidade do Sul de Santa Catarina (UNISUL),² Florianópolis, SC; Sociedade Brasileira de Cardiologia (SBC),³ Rio de Janeiro, RJ; Hospital Cardio Pulmonar da Bahia,⁴ Salvador, BA; Hospital Santa Izabel da Santa Casa de Misericórdia da Bahia,⁵ Salvador, BA; Serviço de Cardiologia – Universidade Federal do Rio Grande do Sul,⁶ Porto Alegre, RS; Grupo de Pesquisa em Cardiologia do Exercício do Hospital de Clínicas de Porto Alegre,⁷ Porto Alegre, RS; Vitta Centro de Bem Estar Físico,⁸ Porto Alegre, RS; Instituto do Coração Edson Saad Universidade Federal do Rio de Janeiro,⁹ Rio de Janeiro, RJ; Clínica de Medicina do Exercício, CLINIMEX,¹⁰ Rio de Janeiro, RJ; Clínica Fitcordis Medicina do Exercício,¹¹ Brasília, DF; Instituto Dante Pazzanese de Cardiologia,¹² São Paulo, SP; Hospital Israelita Albert Einstein,¹³ São Paulo, SP; Hospital do Coração (HCOR),¹⁴ São Paulo, SP; Hospital Universitário Lauro Wanderley e Departamento de Educação Física (UFPB),¹⁵ João Pessoa, PB; Cardio Lógica Métodos Diagnósticos,¹⁶ João Pessoa, PB; Brigham and Women's Hospital, Harvard Medical School,¹⁷ Boston, MA – USA; Instituto Estadual de Cardiologia Aloysio de Castro (IECAC),¹⁸ Rio de Janeiro, RJ – Brazil

Abstract

Cardiopulmonary exercise test (CPET) has been gaining importance as a method of functional assessment in Brazil and worldwide. In its most frequent applications, CPET consists in applying a gradually increasing intensity exercise until exhaustion or until the appearance of limiting symptoms and/or signs. The following parameters are measured: ventilation; oxygen consumption (VO_2); carbon dioxide production (VCO_2); and the other variables of conventional exercise testing. In addition, in specific situations, pulse oximetry and flow-volume loops during and after exertion are measured. The CPET provides joint data analysis that allows complete assessment of the cardiovascular, respiratory, muscular and metabolic systems during exertion, being considered gold standard for cardiorespiratory functional assessment.¹⁻⁶

The CPET allows defining mechanisms related to low functional capacity that can cause symptoms, such as dyspnea, and correlate them with changes in the cardiovascular, pulmonary and skeletal muscle systems. Furthermore, it can be used to provide the prognostic assessment of patients with heart or lung diseases, and in the preoperative period, in addition to aiding in a more careful exercise prescription to healthy subjects, athletes and patients with heart or lung diseases.

Similarly to CPET clinical use, its research also increases, with the publication of several scientific contributions from Brazilian researchers in high-impact journals.

Keywords

Exercise Test; Exercise; Evaluation; Lung Volume Measurements; Oxygen Consumption.

Mailing Address: Artur Haddad Herdy •

Instituto de Cardiologia de Santa Catarina – Rua Newton Ramos 91- 601-A.

CEP: 88015-395, Centro, Florianópolis, SC - Brazil

E-mail: aherdy@cardiol.br, arherdy@cardiosport.com.br

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Therefore, this study aimed at providing a comprehensive review on the applicability of CPET to different clinical situations, in addition to serving as a practical guide for the interpretation of that test.

Major variables and their meanings

Oxygen consumption (VO_2): is the volume of O_2 extracted from the air inhaled during pulmonary ventilation in a period of time. It is usually expressed in $\text{mL}\cdot\text{min}^{-1}$ or $\text{L}\cdot\text{min}^{-1}$ (STPD). In practice, maximum VO_2 ($\text{VO}_2 \text{ max}$) is defined as the highest value reached, despite progressive increase of the load applied, with the development of a plateau in the VO_2 curve during an incremental exercise test. When no plateau can be identified, the highest value obtained at the end of an exhausting exercise is characterized as peak VO_2 , which, in practice, is used as $\text{VO}_2 \text{ max}$. Mean values at intervals of 10 to 60 seconds should be measured depending on the protocol (short-interval means for protocols with short stages and longer-interval means for protocols with longer stages). The response is influenced by a central mechanism (cardiovascular and/or pulmonary) and peripheral function (skeletal muscle).¹⁻⁶ The normal values depend on several factors, such as: age, sex, weight, height, physical activity level, genetic variability and ethnicity. Different equations to predict the normal values of $\text{VO}_2 \text{ max}$ or peak VO_2 have been determined from different populations. Although the equation proposed by Wasserman and Whipp⁶ is the most frequently used, a national equation⁷ seems to be more suitable for Brazilians.

The term 'peak VO_2 ' is used as a synonym for $\text{VO}_2 \text{ max}$ throughout this text. Peak VO_2 is considered abnormal when below 85% of the predicted value.⁶ It has been used as a universal marker^{1-3,5} that can broadly reflect disease severity in patients with heart failure (HF), pulmonary hypertension, hypertrophic cardiomyopathy (HCM), chronic obstructive pulmonary disease (COPD) and restrictive pulmonary disease, in addition to physical fitness level.^{1-5,8} The VO_2 value measured in the first ventilatory threshold (VT1) or anaerobic threshold (AT) is determined by the nonlinear increase of pulmonary ventilation (VE) in relation to VO_2 . From the physiological viewpoint, AT represents the upper limit of workloads during exercise, which can be sustained over a prolonged period

of time without progressively increasing blood lactate and consequent pulmonary hyperventilation.⁶ Peak $\dot{V}O_2$ and AT values are influenced by genetic predisposition, diseases, exercise and aerobic training types. The normal mean AT values expected for adults are around 40% to 65% of peak $\dot{V}O_2$.⁶ The AT values are important for the individualized prescription of exercise, as well as for the diagnosis of anemia, physical unfitnes, myopathies and cardiopathies in the presence of values lower than the predicted ones.²⁻⁶

Pulmonary ventilation (VE): expressed as liters per minute, is the volume of air moved in and out of the lungs. It is determined as the product of respiratory rate by the volume of air exhaled at every cycle (tidal volume). At rest, 7 to 9 L/min are ventilated, but in athletes that value can reach 200 L/min at maximal exertion.⁶ Ventilation increases continuously during progressive effort on CPET and undergoes additional increases influenced by the anaerobic metabolism resulting from the accumulation of lactic acid, well defined as the first and second ventilatory thresholds. Periodic (or oscillatory) ventilation is defined as the resting oscillatory pattern that persists in $\geq 60\%$ of the effort with an amplitude $\geq 15\%$ as compared to mean resting values.⁹ It reflects disease severity and relates to worse prognosis in patients with HF.³⁻⁵

Respiratory coefficient or respiratory exchange ratio (R): expresses the ratio between CO_2 production and O_2 consumption ($\dot{V}CO_2/\dot{V}O_2$). It is currently the best non-invasive indicator of maximal or quasi-maximal exercise intensity. Values above 1.0 can reflect intense exercise, but those ≥ 1.10 are those searched on CPET, and have been accepted as a parameter of exhaustion or quasi-exhaustion.^{3,7}

Ventilatory equivalents for oxygen ($VE/\dot{V}O_2$) and for carbon dioxide ($VE/\dot{V}CO_2$): are the ratios between pulmonary ventilation and O_2 consumption ($VE/\dot{V}O_2$) or CO_2 production ($VE/\dot{V}CO_2$). Both decline from rest to submaximal exercise intensities, with $VE/\dot{V}O_2$ reaching minimum values before AT, when its progressive increase occurs, caused by the increase in ventilation to eliminate extra CO_2 production. That results in lactate buffering by blood bicarbonate.⁶ Later, $VE/\dot{V}CO_2$ increases (respiratory compensation point - RCP, or second ventilatory threshold - VT2), resulting from ventilatory increase (compensatory respiratory alkalosis) in response to blood pH reduction due to the progressive accumulation of lactic acid at muscle level.⁶ The $VE/\dot{V}O_2$ reflects the ventilatory need for a certain O_2 consumption level, being, thus, an index of ventilatory efficiency. Patients with inadequate ratio between pulmonary ventilation and pulmonary perfusion (increased physiological dead space) ventilate inefficiently and have high $VE/\dot{V}O_2$ values (pulmonary disease and HF).⁶ Peak values above 50 have been useful to diagnose patients suspected of having mitochondrial myopathy.¹⁰ On the other hand, $VE/\dot{V}CO_2$ represents the ventilatory need to eliminate a certain amount of CO_2 produced by active tissues, being influenced by partial pressure of carbon dioxide ($PaCO_2$). In addition, $VE/\dot{V}CO_2$ slope is the relationship between VE, plotted in the Y axis, and $\dot{V}CO_2$, in the X axis, both measured as L/min. The $VE/\dot{V}CO_2$ slope can be determined in submaximal tests.¹¹ It relates to changes in the ventilation-perfusion relationship or hyperventilation. The $VE/\dot{V}CO_2$ slope reflects the severity and prognosis of patients with

HF, pulmonary hypertension, HCM, COPD and restrictive pulmonary disease.^{1,3-5,8,11,12}

End-tidal CO_2 partial pressure (PET CO_2): reflects ventilation-perfusion within the pulmonary system, and, indirectly, cardiac function.⁶ Its value ranges from 36 to 42 mmHg, with 3- to 8-mmHg elevations during moderate intensity exercise, reaching a maximal value with subsequent drop, due to VE increase, characterizing RCP.¹ Abnormal values can represent disease severity in patients with HF, HCM, pulmonary hypertension, COPD and restrictive pulmonary disease.^{3-6,8,12}

Oxygen pulse (O_2 pulse): is the ratio between $\dot{V}O_2$ (mLO_2/min) and heart rate (HR - bpm). Its meaning is better understood by observing the Fick equation: $\dot{V}O_2 = HR \times \text{systolic volume (SV)} \times \text{arteriovenous oxygen difference [(A-V) O_2 diff]}$. Considering that, in many clinical situations, (A-V) O_2 diff does not substantially change in incremental exercise, O_2 pulse represents SV, and, in a way, left ventricular performance. Thus, $\dot{V}O_2 \cong HR \times SV$ or $\dot{V}O_2/HR \cong SV$. Under certain circumstances, the morphological analysis of its curve aids in the diagnosis of ventricular dysfunction and important effort-induced myocardial ischemia.^{1,3-6}

Breathing reserve (VE/MVV): represents the ratio between maximal ventilation during exercise (VE) and maximum voluntary ventilation (MVV) at rest, both variables in L/min. Equations to predict MVV can be used (forced expiratory volume in the first second - FEV₁ $\times 40$), although it can be measured directly on pre-test spirometry. Normal values are greater than 0.20. However, in both athletes and those performing strenuous exercises, a higher fraction of breathing reserve can be physiologically used. It is useful in the differential diagnosis of dyspnea related to pulmonary mechanism.⁶

$\Delta\dot{V}O_2/\Delta W$ Relationship: relationship between $\dot{V}O_2$ (Y axis in $mL \cdot min^{-1}$) and workload (X axis in Watts), measured only during exercise on a cycle ergometer with ramp protocol, whose value is progressively and linearly incremented until maximal effort. It is useful in the diagnosis of patients suspected of having myocardial ischemia with left ventricular dysfunction on exertion. Its normal value for adults is $9 mL \cdot min^{-1} \cdot W^{-1}$ (the lowest limit being $8.6 mL \cdot min^{-1} \cdot W^{-1}$).

Other variables: the minimum $VE/\dot{V}O_2$ value is the cardiorespiratory optimal point (COP).¹³ It is a submaximal variable that reflects the best integration between the respiratory and cardiovascular systems. Although it is easy to obtain, further studies are required to determine its clinical applicability and prognostic meaning. Oxygen uptake efficiency slope (OUES) was widely studied, being measured by the relationship between $\dot{V}O_2$ and the logarithmic transformation (base 10) of VE. The OUES provides information on the severity of HF.¹⁴ Similarly to $VE/\dot{V}CO_2$ slope, it does not require a maximal test. $T_{1/2} \dot{V}O_2$ is the time necessary for a 50% drop in $\dot{V}O_2$ measured at peak exercise (from the beginning of recovery) until the third minute of recovery. It decreases with physical training and its increase is negatively associated with the prognosis of HF patients.¹⁵ Circulatory power is the product of peak systolic blood pressure (SBP) by peak $\dot{V}O_2$, while ventilatory power is peak SBP divided by $VE/\dot{V}CO_2$ slope. Both have prognostic value in HF.¹⁶ Finally, the association of CPET with measurements of

cardiac output and SV, by use of non-invasive hemodynamic analysis (impedance cardiography - ICG), can provide variables, such as $\Delta Q/\Delta VO_2$ slope to assess coronary artery disease (CAD), HF and some myopathies.¹⁰

Functional assessment and CPET-based aerobic exercise prescription

The CPET is considered the best method to assess aerobic performance, and, mainly, to support aerobic exercise prescription.^{17,18} Considered class IIa indication - optimized prescription of exercise to healthy individuals, individuals with heart or lung diseases entering a program of regular exercise - and class IIb indication - athletes -, it is still rarely used with such purposes by clinical cardiologists.

By use of the joint analysis of exhaled gases, work and/or exertion performed and the behavior of hemodynamic variables, mainly HR, a more comprehensive functional assessment can be obtained. Thus, a more precise and individualized program of aerobic exercise can be outlined. Apparently healthy individuals who engage in moderate- to high-intensity aerobic practice can benefit from CPET regarding exercise prescription and performance assessment.¹⁸ For individuals with heart diseases and high-performance athletes, such benefits have been widely established. Prescription errors, both insufficiency and excess, in such individuals can have a negative impact on the results expected from a training program.

Briefly, for the prescription of aerobic exercises, the most relevant data obtained from CPET are HR and exercise intensity at which the ventilatory thresholds occur, especially, AT or VT1.¹⁹ The exercise intensity at which VT1 occurs characterizes the highest submaximal level tolerated by a certain individual for long time periods. Because that exercise intensity varies even between two individuals with identical maximal functional capacity (and even with similar maximal VO_2 values measured), its precise determination via CPET enhances and refines the quality of aerobic exercise prescription. In practical terms, HR values in different points of maximal CPET are used to establish the bases for a more objective prescription. More often, the following values are considered: HR at rest with the individual lying down (resting HR), maximal HR (HRmax), HR at AT, HR at RCP, and HR at the 'R = 1' point. Traditionally, exercises have been prescribed based on the intensity related to HR, but the workload related to thresholds and maximal effort can also be used.^{1,20} When the objective is to train up to a moderate subjective intensity that can be sustained for long periods, we set the limit at the AT. Between the AT and RCP, the exercise intensity is higher, but usually still tolerated for prolonged periods, with wide individual variations. Finally, the training can be performed above the RCP, with very intense and much more difficult to sustain exercises, which can be of the interval type (alternating resting periods with some type of mild-to-moderate intensity exercise).²⁰

There are numerous protocols that can be used for both healthy individuals and those with diverse pathologies.²¹ These protocols are used to prescribe steady-state aerobic exercise (walking or running) or interval exercise, with an important

component of "anaerobic" exercise, alternating rhythms and intensities (alternate walking and running, up and down walking and cycling, ball sports and spinning classes).

However, the quality of that prescription, based on HR derived from CPET, depends on some factors. It is convenient that CPET be performed with a ramp protocol, minimum duration of eight minutes, on an ergometer more similar to the aerobic exercise that will be prescribed (cycle ergometer for cyclers, treadmill for runners). Longer protocols tend to allow greater differentiation and precision in identifying the exercise intensity that corresponds to the thresholds. It is worth noting that data collected during a CPET performed in an air-conditioned room can differ from those obtained during a walk or cycling or even a long running (more than 45 minutes) at open air locations and under more adverse climate conditions, in which there may be a cardiovascular drift²² phenomenon, characterized by a progressive increase of HR, instead of remaining in steady-state, despite of a constant intensity of exercise. However, for patients using HR-controlling devices or on regular use of medications with negative chronotropic action, specific care should be taken so that the HR-based prescription obtained on CPET can remain valid. The most obvious case is that of patients on beta-blockers on a single daily dose, which make HR during exercise vary according to the time interval between medication administration and exercise performance.²³ To minimize that chronopharmacological effect, such patients should undergo CPET at the time closest to that of regular exercise. In patients with pacemakers, resynchronization devices and atrial fibrillation, the HR measured by these HR sensors is inaccurate. For those individuals and some athletes whose training intensity is based on load or velocity, exercise can be prescribed based on velocities or loads relative to thresholds. Some studies have suggested that the load relative to 'R = 1' bears the best correlation with maximal exertion in metabolic balance.²⁴

Finally, other potentially relevant variables can be obtained via exhaled breath analysis, including some that do not require maximal exertion, such as mechanical efficiency analysis and COP,¹³ which widens the CPET value for prescription of primarily aerobic exercises.

CPET in heart failure

Chronic heart failure (CHF) is a systemic syndrome, and reduced functional capacity is one of its main features. The cardiovascular deficit has a direct influence on other organs and systems, such as the pulmonary, renal and skeletal muscular ones. CPET is considered "gold standard" for the functional assessment of patients with CHF, propitiating diagnostic and prognostic data derived from direct measurement of VO_2 , VCO_2 and VE. In addition, the variables VE/VO_2 , VE/CO_2 , VCO_2/VO_2 and R, as well as the metabolic points AT and RCT, are useful parameters to indicate accurately the maximal aerobic capacity, to quantify functional restriction, to measure the response to drug therapy and to guide physical training prescription.

The Brazilian Society of Cardiology guidelines for the management of patients with CHF present CPET as class I

indication in the assessment of both heart transplantation candidates and dyspnea mechanisms. The use of CPET is class II indication for exercise prescription, and to assess the severity, prognosis and responses to therapeutic interventions in CHF.^{25,26}

The response to CPET of a patient with CHF is characterized by: reduced $\dot{V}O_2$, AT < 40% of the predicted $\dot{V}O_2$ max, O_2 pulse < 85% and as a plateau, increased VE/VCO_2 , reduced OUES, wide breathing reserve and usually normal O_2 saturation.² Peak $\dot{V}O_2$ is the specific and direct measure of functional capacity. Several studies have shown its independent prognostic capacity in CHF. According to the Brazilian guidelines for heart transplantation, a peak $\dot{V}O_2$ lower than 10 mL.kg⁻¹.min⁻¹ is class I indication for that procedure, while a peak $\dot{V}O_2$ below 12 mL.kg⁻¹.min⁻¹ (patients on beta-blocker) or below 14 mL.kg⁻¹.min⁻¹, is class IIa indication, particularly for those with other criteria of worse prognosis (VE/VCO_2 slope > 35).²⁷ Weber et al.²⁸ have proposed a classification for peak $\dot{V}O_2$ results: class A = $\dot{V}O_2$ > 20 mL.kg⁻¹.min⁻¹; class B = $\dot{V}O_2$ 16-20 mL.kg⁻¹.min⁻¹; class C = $\dot{V}O_2$ 10-15 mL.kg⁻¹.min⁻¹; and class D = $\dot{V}O_2$ < 10 mL.kg⁻¹.min⁻¹. It is worth noting that, for peak $\dot{V}O_2$ value to have prognostic accuracy, the test has to meet the requirements of a maximal test (proposed for HF: R > 1.05, at least).

Other important variables measured via CPET that add independent prognostic value for patients with CHF are: VE/VCO_2 slope, OUES, $T_{1/2}\dot{V}O_2$, HR recovery in the first post-exertion minute, presence of periodic ventilation, and $PETCO_2$ and O_2 pulse behaviors.

Chua et al.,²⁹ assessing patients with CHF using CPET, have observed those with VE/VCO_2 slope > 34 were at higher risk for hospitalization due to decompensation, and for death. Other authors,³⁰⁻³² assessing the prognostic value of VE/VCO_2 slope in CHF, have shown it to be a variable with excellent independent value, even higher than that of peak $\dot{V}O_2$, and important to patients who reach only submaximal exertion. In a population with CHF due to Chagas disease, Ritt et al.³³ have reported that the best cutoff point for worse prognosis was VE/VCO_2 slope > 32.5, thus earlier than those reported by studies on other etiologies. Arena et al.³⁴ have published the following ventilatory classes based on VE/VCO_2 slope values: class I, $VE/VCO_2 \leq 29.9$; class II, 30-35.9; class III, 36-44.9; class IV, ≥ 45 . In 2 years, event-free survivals (death, transplantation or implantation of ventricular assistance device) for classes I-IV were 97.2%, 85.2%, 72.3% and 44.2%, respectively (P < 0.0001). Assessing a population of patients via CPET for heart transplantation, Ferreira et al.³⁵ have found a VE/CO_2 slope cutoff point of ≥ 43 as ideal to determine the indication for heart transplantation. The use of VE/VCO_2 slope as a criterion for selection of candidates for transplantation could reclassify correctly 18.3% more patients than the classic peak- $\dot{V}O_2$ -based criteria (p < 0.001).³⁵

In addition, OUES has an independent prognostic value. Initially, Baba et al.³⁶ have described that variable behavior, whose cutoff point and independent prognostic value were subsequently assessed by other authors. A cutoff point < 1.47 L/min determines a group with more severe CHF.^{37,14}

$T_{1/2}\dot{V}O_2$ is identified in patients with CHF. Studying patients with $\dot{V}O_2 \geq 15$, between 10.1 and 14.9, and ≤ 10 mL.kg⁻¹.min⁻¹, Groote et al.³⁸ have reported $T_{1/2}\dot{V}O_2$ values of 108 ± 44.6 , 137 ± 58.7 , and 176 ± 75 seconds, respectively.³⁸ In patients with no heart disease, $T_{1/2}\dot{V}O_2$ is usually < 90 seconds.³⁹

The kinetics of HR recovery (HRR) is a well-established prognostic marker in patients with CAD,⁴⁰ related to changes in post-exertion autonomic balance. In CHF, it is also an independent factor of mortality, even in patients on beta-blockers.⁴¹ The cutoff point established for that population was ≤ 16 bpm in an active recovery protocol (hazard ratio: 4.6; 95%CI: 2.8-7.5; p < 0.001). Its clinical usefulness has been assessed for heart transplantation indication in patients in the intermediary zone of peak $\dot{V}O_2$ ($\dot{V}O_2$ 10.1-13.9 mL.kg⁻¹.min⁻¹), in whom, the HRR analysis aggregated value to peak $\dot{V}O_2$ and VE/VCO_2 slope. The prognosis of patients with altered HRR and VE/VCO_2 slope was comparable to that of those with $\dot{V}O_2 < 10$ mL.kg⁻¹.min⁻¹.⁴²

Wide oscillations in ventilation during exertion relates to cardiovascular events and death in patients with CHF. That pattern, analogous to the Cheyne-Stokes respiration, was named periodic ventilation. The occurrence of periodic ventilation during exertion (characterized by an amplitude variation > 5 L/min for at least three cycles) was related to an up to three-fold higher mortality in patients with CHF (hazard ratio: 2.97; 95%CI: 1.34 - 6.54; p < 0.007).^{9,43,44} The presence of periodic ventilation increased the risk of patients with reduced peak $\dot{V}O_2$ and elevated VE/VCO_2 slope.⁴⁵

Another index that reflects the dynamics of pulmonary changes and CO_2 diffusion at alveolar level is $PETCO_2$ at rest. Mean values < 33 mmHg after 2 minutes at rest were independently correlated with worse prognosis and greater mortality in CHF (hazard ratio: 2.17; 95%CI: 1.48-3.19; p < 0.001).⁴⁶

O_2 pulse can be assessed regarding its absolute value and its behavior during exertion. A plateau is usually related to an insufficient increase in SV on exertion. An O_2 pulse < 85% of the predicted value correlates independently with major cardiovascular events in CHF. Among patients with peak $\dot{V}O_2 < 14.3$ mL.kg⁻¹.min⁻¹ and O_2 pulse < 85% of the predicted values, mortality was greater than among those with only one of those parameters altered (hazard ratio: 4.76 versus 2.31, respectively). O_2 pulse could also reclassify the risk of patients into intermediate zone of peak $\dot{V}O_2$ for transplantation (10-14 mL.kg⁻¹.min⁻¹). Patients in the O_2 pulse < 85% zone had mortality similar to those with $\dot{V}O_2 < 10$ mL.kg⁻¹.min⁻¹.⁴⁷

Each CPET variable correlates with the interaction of HF with another organ or system. Thus, the joint analysis of those variables can better stratify the risk of those patients. The CPET variables can be combined into risk scores in CHF. Levy et al. have shown that the addition of VE/VCO_2 slope data to Seattle Heart Failure Model could improve the prognostic ability of that score, reclassifying 40% of the patients into a more appropriate risk category (p = 0.002).⁴⁸

To determine the prognostic significance of CPET in CHF, Cahalin et al. have conducted a meta-analysis of studies

published until 2013 and calculated the odds ratios (OR) of each prognostic variable. The OR of the main prognostic variables assessed (peak VO_2 , VE/VCO_2 slope, OUES and periodic ventilation) were 4.10 (CI: 3.16-5.33), 5.40 (CI: 4.17-6.99), 8.08 (CI: 4.19-15.58) and 5.48 (CI: 3.82-7.86), respectively.⁴⁹

For those not dealing with CPET on a daily basis, the assessment of each variable can be unpractical. Myers et al.⁵⁰ have developed a score that combines the information of the main CPET variables into a number. The points are attributed as follows: VE/VCO_2 slope ≥ 34 - 7 points; HRR ≤ 16 bpm - 5 points; OUES ≤ 1.4 - 3 points; $PETCO_2 < 33$ mmHg - 3 points; peak $VO_2 \leq 14$ mL.kg⁻¹.min⁻¹ - 2 points. The score ranges from 0 to 20, 0-5 being the reference. The others correlated in an increasing manner with the risk of death/transplantation or implantation of ventricular assistance device: 6-10 (hazard ratio: 2.74, 95%CI: 2.16-3.48; $p < 0.001$), 11-15 (hazard ratio: 4.6, 95%CI: 3.55-5.98; $p < 0.001$) and > 15 (hazard ratio: 9.25, 95%CI: 5.75-14.88; $p < 0.001$). In three years, the mortality of patients with score > 15 was 12.2%, in comparison to 1.2% in those with score < 5 . A recent analysis⁵¹ applied that score to class B patients according to Weber heart failure classification (analogous to NYHA class II). In the three-year follow-up, patients with score ≥ 10 had an event-free survival equivalent to that of Weber class C patients, and those with score < 10 had a prognosis equivalent to that of Weber class A patients.

The CPET plays a preponderant role in the assessment of patients with CHF, not only regarding the selection of candidates for transplantation, but also to determine the prognosis and help with the therapeutic decision. Figure 1 shows a stratification strategy that combines those variables.

CPET to assess myocardial ischemia

CPET can help to assess myocardial ischemia in patients with suspected CAD, a clinical condition where a significant ischemic load, during exercise, is expected to negatively influence systolic myocardial performance.¹ During incremental exercise, the myocardial unbalance between O_2 offer and demand triggers a sequence of metabolic changes that can ultimately lead to the insufficient physiological elevation of SV. On CPET, this is observed as a depressed, in plateau or declining shape curve of O_2 pulse.

Three CPET variables are indicated to assess the presence and severity of myocardial ischemia: 1) O_2 pulse; 2) VO_2 curve and elevation; and 3) relationship between VO_2 variation and load variation, in watts, in this case, exclusively, on cycle ergometer.⁵²

Oxygen pulse and oxygen consumption curve

Usually, (A-V) O_2 diff tends to remain constant during incremental exertion, except for rare cases of anemias,

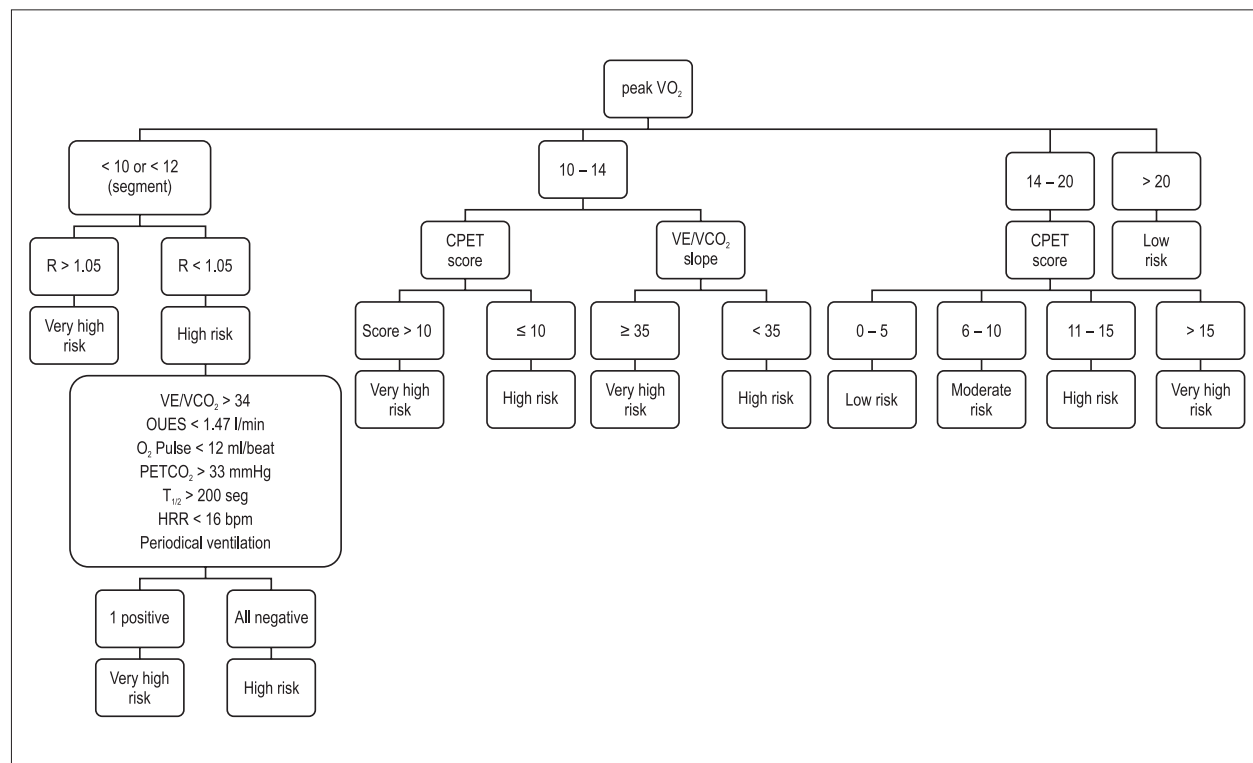


Figure 1 – Risk stratification based on CPET results from patients with CHF (Modified from Ribeiro JP, Stein R, Chiappa GR. *J Cardiopulm Rehabil.* 2006 Mar-Apr;26(2):63-71). CPET: cardiopulmonary exercise test; VO_2 : oxygen consumption; R: respiratory exchange ratio; VE/VCO_2 slope: ratio between pulmonary ventilation and carbon dioxide production; $PETCO_2$: extrapolated end-tidal carbon dioxide tension; $T_{1/2}$: time necessary for a post-exertion 50% drop in VO_2 measured; OUES: oxygen uptake efficiency slope; HRR: heart rate recovery.

hemoglobinopathies, some congenital heart diseases and COPD, in which there is a significant drop in peripheral oxygen saturation. Except for those clinical conditions, one can infer that SV behavior during incremental exercise is reflected by the equation: $VO_2/HR = SV$. The VO_2/HR ratio, called “oxygen pulse” and measured in milliliters per beat, reflects the O_2 volume ejected into the aorta at every systole. Likewise, SV, also measured in milliliters per beat, reveals the blood volume ejected into the aorta at every systole. Thus, those two variables, despite being numerically different, reflect left ventricular hemodynamic behavior during CPET.

The analysis of the VO_2/HR curve as a function of time, which should have the increasing morphology of a parabola, is as important as the numerical O_2 pulse value during the incremental phase of CPET. The identification of a curve with a plateau or decline indicates a reduction in O_2 pulse and SV during exercise, and can indicate myocardial ischemia⁵³ (Figure 2). It is worth noting that other clinical conditions can cause similar changes, such as ventricular dysfunctions due to non-ischemic cardiomyopathies, providing prognostic information on HF with reduced ejection fraction,³ and obstructive valve heart diseases. In the presence of severe chronotropic changes, artificial electric stimulation and arrhythmias, such as atrial fibrillation, O_2 pulse analysis becomes compromised and inaccurate.

$\Delta VO_2/\Delta WR$ Ratio (Watts)

To every increase in load imposed during CPET, a similar increase in VO_2 is expected. Normally, a 1-Watt increment

in workload should correspond to a $10 \text{ mL}\cdot\text{min}^{-1}$ -increase in absolute VO_2 . The loss of this linear relationship, with a reduction of slope often to less than $5 \text{ mL}\cdot\text{min}^{-1}\cdot\text{Watt}^{-1}$, despite the increase in exercise intensity during CPET, contributes to the diagnosis of myocardial ischemia⁵² (Figure 3).

It is worth noting that the changes suggestive of ischemia on CPET become more evident as ischemia severity increases. The CPET variables should be analyzed in light of the pre-test clinical suspicion. CPET can be indicated for functional assessment of patients with established CAD, as well as for the investigation of myocardial ischemia diagnosis, mainly in the following conditions:

1. When there is moderate to high pre-test likelihood of myocardial ischemia;
2. To increase diagnostic accuracy of myocardial ischemia, when, on CPET, there is clinical, hemodynamic or electrocardiographic change, hindering the diagnosis via conventional exercise test;
3. In the presence of a large ischemic myocardial area, hindering left ventricular function due to SV reduction during exercise;
4. For follow-up assessment after percutaneous or surgical revascularization;
5. Similarly to other clinical conditions, CPET can be recommended to assess the prognosis of patients with CAD, with or without evidence of ischemia, by using other variables usually used for that purpose, such as VE/VCO_2 slope, peak VO_2 , OUES, periodic ventilation and $T_{1/2}VO_2$,

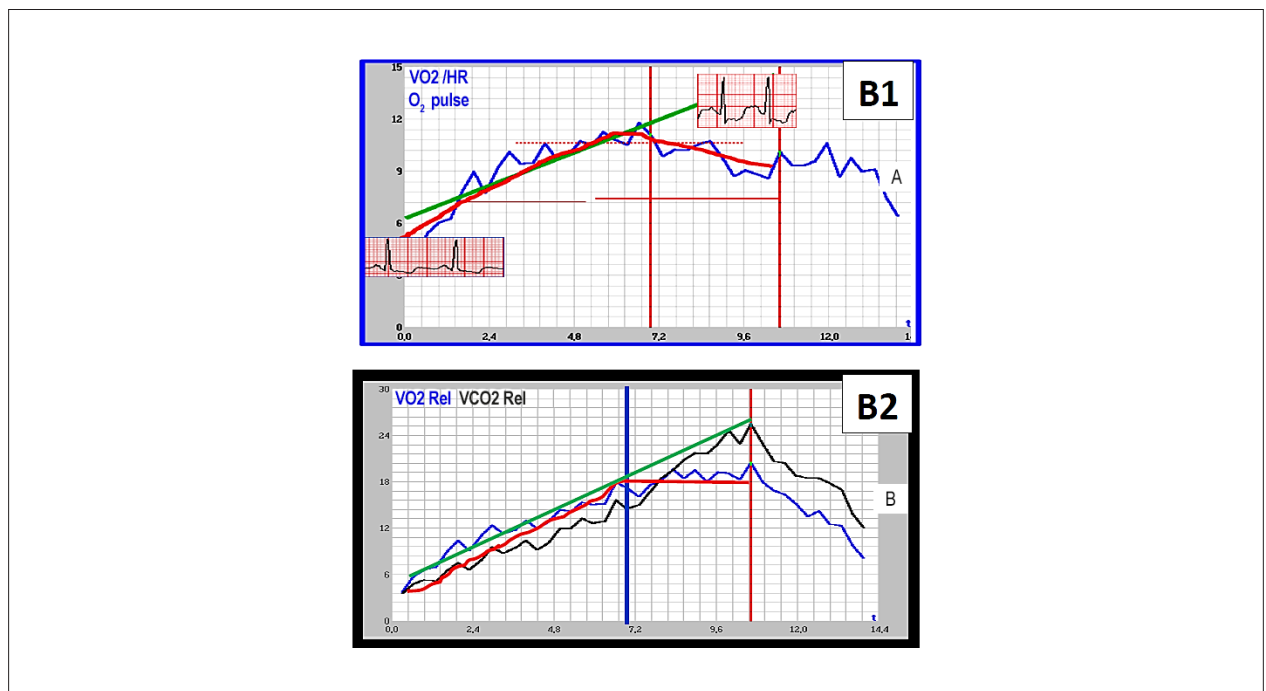


Figure 2 – Cardiopulmonary exercise test in the pre-rehabilitation assessment of a 57-year-old hypertensive, diabetic, overweight male patient with three-vessel coronary disease, who refused to undergo myocardial revascularization surgery eight years earlier. A) evident drop in oxygen pulse. B) early plateau of oxygen consumption. Both changes (A and B) were due to ischemic depression of the ST segment (evident in A), followed by progressive chest pain.

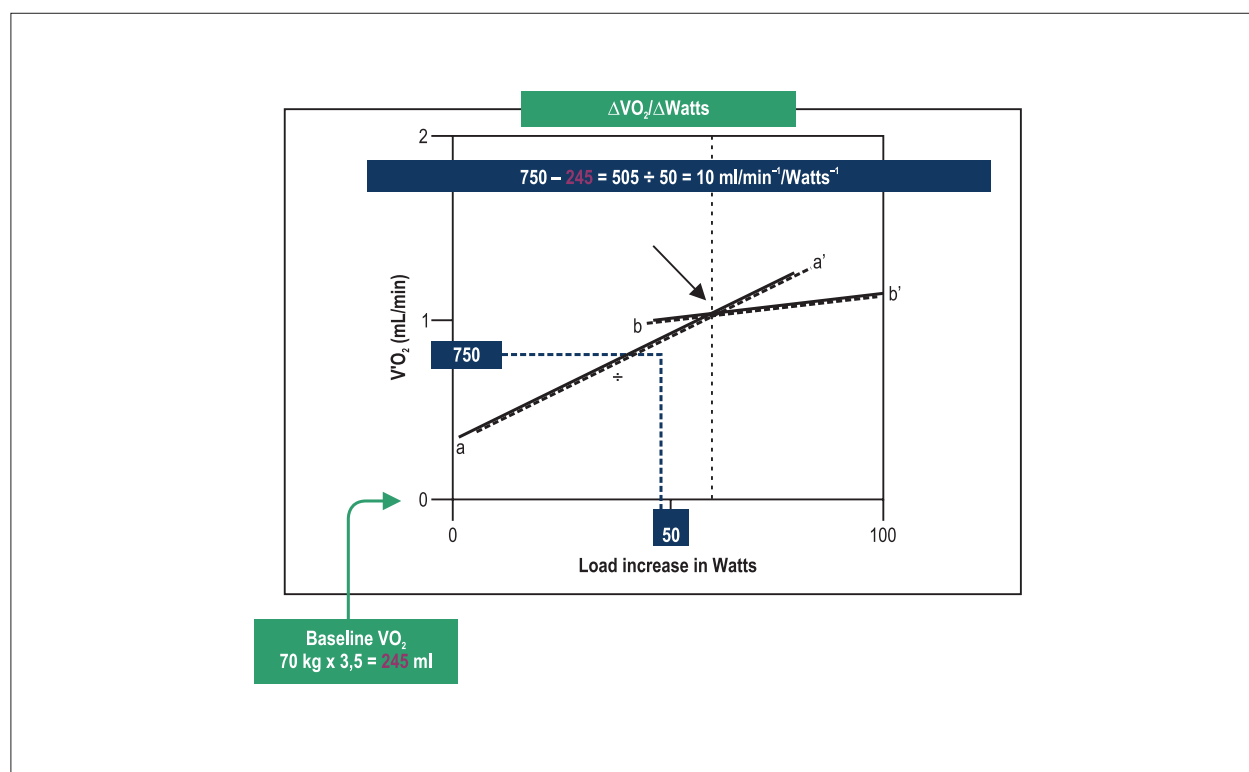


Figure 3 – The $\Delta\text{VO}_2/\Delta\text{Watts}$ relationship around $10\text{mL}\cdot\text{min}\cdot\text{Watts}^{-1}$ suddenly reduces, despite the exercise intensity increase. This loss of linear relationship could indicate the presence of myocardial ischemia by use of CPET performed on a cycle ergometer (modified from reference 52).

in addition to other CPET variables that wait for more solid studies.^{6,54-57}

CPET in the differential diagnosis of dyspnea

Dyspnea is a common symptom in several clinical situations, characterized by the perception of respiratory difficulty or discomfort. Its pathophysiology is complex, involving neuro-humoral and mechanical mechanisms. From the practical viewpoint, the differential diagnosis can be classified into four categories: cardiac, pulmonary, mixed cardiopulmonary, and non-cardiopulmonary.^{58,59}

The use of CPET for dyspnea assessment can be divided into two settings - patients with dyspnea without an established diagnosis and patients with multiple possible causes - in whom the test is useful to determine which mechanism prevails and causes symptoms. The dyspnea, whose cause cannot be elucidated via history, physical examination and complementary tests at rest, should be better assessed by using CPET. By use of joint analysis, from rest to maximal exertion, the cardiovascular, respiratory and peripheral metabolism responses can provide information on the dyspnea mechanism. Because of its low cost, CPET can be indicated early in the investigative hierarchy of dyspnea assessment, serving to guide other complementary tests, when required, for therapeutic management and prognostic assessment (Table 1).

Studies on the clinical value of CPET in patients with chronic dyspnea (more than 1 month) of undetermined origin

or dyspnea of multiple causes have evidenced practical use: to differentiate dyspnea of cardiocirculatory primary origin from dyspnea of pulmonary ventilatory etiology or that related to problems in the ventilation-perfusion binomial; to quantify the different mechanisms of multiple-cause dyspnea; to identify an unsuspected or underestimated circulatory component; and to identify a psychogenic or simulation component.^{60,61}

The differential diagnosis of those pathologies requires pragmatic interpretation of CPET data.⁶² The first step is to assess peak VO_2 and to determine the percentage of the predicted value achieved. Pulmonary, cardiovascular and metabolic diseases or physical unfitness can account for VO_2 reduction. Then, breathing reserve should be assessed, and, when low, it can identify underlying pulmonary disease. Breathing reserve lower than 20% is found in pulmonary diseases; however, as already described, highly-trained individuals or those in situations of extreme exertion can also consume their ventilatory reserve on maximal exertion as a compensatory mechanism, but, in such cases, peak VO_2 will not be significantly reduced.

The following step is the analysis of O_2 saturation. A drop greater than 4% on peak exertion as compared to resting is characteristic of pulmonary limitation. High VE/VCO_2 slope and $\text{PETCO}_2 < 33$ mmHg at rest and/or elevation greater than 8 mmHg during exertion suggest respiratory mechanisms as the cause of dyspnea.^{3,63}

Observation of O_2 pulse and $\Delta\text{VO}_2/\Delta\text{Watts}$ ratio can identify heart disease, if the curves show plateau or decline, reflecting

Table 1 – Behavior of major CPET variables in several causes of dyspnea

Dyspnea origin Variables	Cardiovascular	Pulmonary	Vascular-pulmonary	Hyperventilation	Fake
VO ₂	reduced	reduced	reduced	normal	reduced
AT	early	normal	early	normal	normal
R	normal	reduced	normal/reduced	normal/reduced	reduced
VE/VCO ₂ slope	high	high	high	high	normal
PETCO ₂	low	low	low at AT	low at AT	normal
VE/MVV	normal	reduced	normal	normal	normal
O ₂ pulse	reduced/plateau	normal/plateau	reduced/plateau	normal	normal
O ₂ Sat	normal	drop	drop	normal	normal
ΔVO ₂ /ΔWR	reduced/plateau	normal/plateau	reduced/plateau	normal	normal

VO₂: oxygen consumption; AT: anaerobic threshold; R: respiratory exchange ratio; VE/VCO₂ slope: ratio between pulmonary ventilation and carbon dioxide production; PETCO₂: extrapolated end-tidal carbon dioxide tension; VE/MVV: ventilatory reserve; O₂ Sat: oxyhemoglobin saturation; ΔVO₂/ΔWR: relationship between oxygen consumption and workload.

an inadequate SV to the load imposed.⁶⁴ However, individuals with lung disease and some degree of pulmonary hypertension can also develop a plateau of O₂ pulse. The combination of plateau of O₂ pulse with a decrease in O₂ saturation, VE/VCO₂ slope > 40 and reduced PETCO₂ (< 33 mmHg at rest or < 36 mmHg at AT) strongly suggests pulmonary hypertension or a pathology with pulmonary vascular impairment.^{3,63,65}

Patients with dyspnea due to cardiovascular limitation have reduced VO₂, early AT, ventilatory inefficiency (high VE/VCO₂ slope), inefficient O₂ uptake (reduced OUES), plateau of O₂ pulse or of ΔVO₂/ΔWR ratio, with normal ventilatory reserve, PETCO₂ < 33 mmHg at rest and/or increase < 3 mmHg during exertion, in addition to lack of drop in O₂ saturation.^{3,63}

Patients with physical unfitness and anemia have reduced VO₂ and increased ΔVO₂/ΔWR (cycle ergometer), but they do not meet the criteria for pulmonary or cardiovascular limitation. Extremely physically unfit patients can have reduced AT and increased HR/VO₂ ratio. On the other hand, a low R, despite the sensation of extreme fatigue on BORG scale, points to a peripheral mechanism as the cause of limitation to exertion.

Patients with hyperventilation have reduced ventilatory efficiency (high VE/VCO₂ slope), reduced PETCO₂ at AT, sudden changes in the ventilatory pattern with phases of tachypnea and hypopnea, and extremely increased respiratory rate on exertion. Usually, the ventilatory reserve is normal and O₂ saturation has a physiological behavior.

Studying 39 patients with asthma of difficult control, McNicholl et al. have reported that, in 14 of them, the persistent complaint of dyspnea was explained by hyperventilation, preventing the undue increase of the dose of bronchodilators in those patients.⁶⁶ In legal situations, facing a complaint of dyspnea, the medical expert can have difficulty to determine if the symptom is true or to establish an effective symptom graduation, and CPET can be used to clarify the scenario. To diagnose fake dyspnea by using CPET: the patient reports extreme fatigue, asks for exertion interruption

and shows normal ventilatory reserve, normal O₂ saturation behavior, AT within the expected range for the maximal VO₂ predicted (40%-60%), but an R compatible with submaximal exertion (<1), in addition to apparent chronotropic deficit.

CPET in pulmonary diseases

Chronic obstructive pulmonary disease

The severity of COPD is determined based on symptoms and spirometry results. Pulmonary function tests at rest, however, do not accurately predict the grade of intolerance to exertion.⁶⁴ The inability to increase ventilation to levels that allow high gas exchange is one of the mechanisms that explain dyspnea on exertion. That phenomenon can be observed on CPET and is usually interpreted as ventilatory limitation. Although characteristic of obstructive scenarios, it can occur in restrictive diseases, such as interstitial pulmonary diseases, and in abnormalities of the thoracic cage. The criterion that defines ventilatory limitation is arguable, but, when the breathing reserve at peak exertion is lower than 15%, limitation is considered to occur, especially when R is lower than 1.0.⁶⁷

In patients with COPD, peak VO₂ continues to be the best index of aerobic capacity, as long as patients exercise to their limit. However, other aspects should be considered when interpreting the CPET of patients with COPD. There is a combination of low ventilatory capacity and high ventilatory demand, increasing the sensation of dyspnea. The perception of lower limb exertion is often exaggerated in such patients and can be a limiting factor, especially in tests performed on a cycle ergometer. Another factor that can significantly contribute to the development of unbearable dyspnea during exercise is dynamic hyperinflation. With the increase of respiratory flow during exercise, the air is held in the lungs, causing a progressive increase in residual volume, thus reducing the inspiratory capacity (Figure 4). That frequently occurs together with a

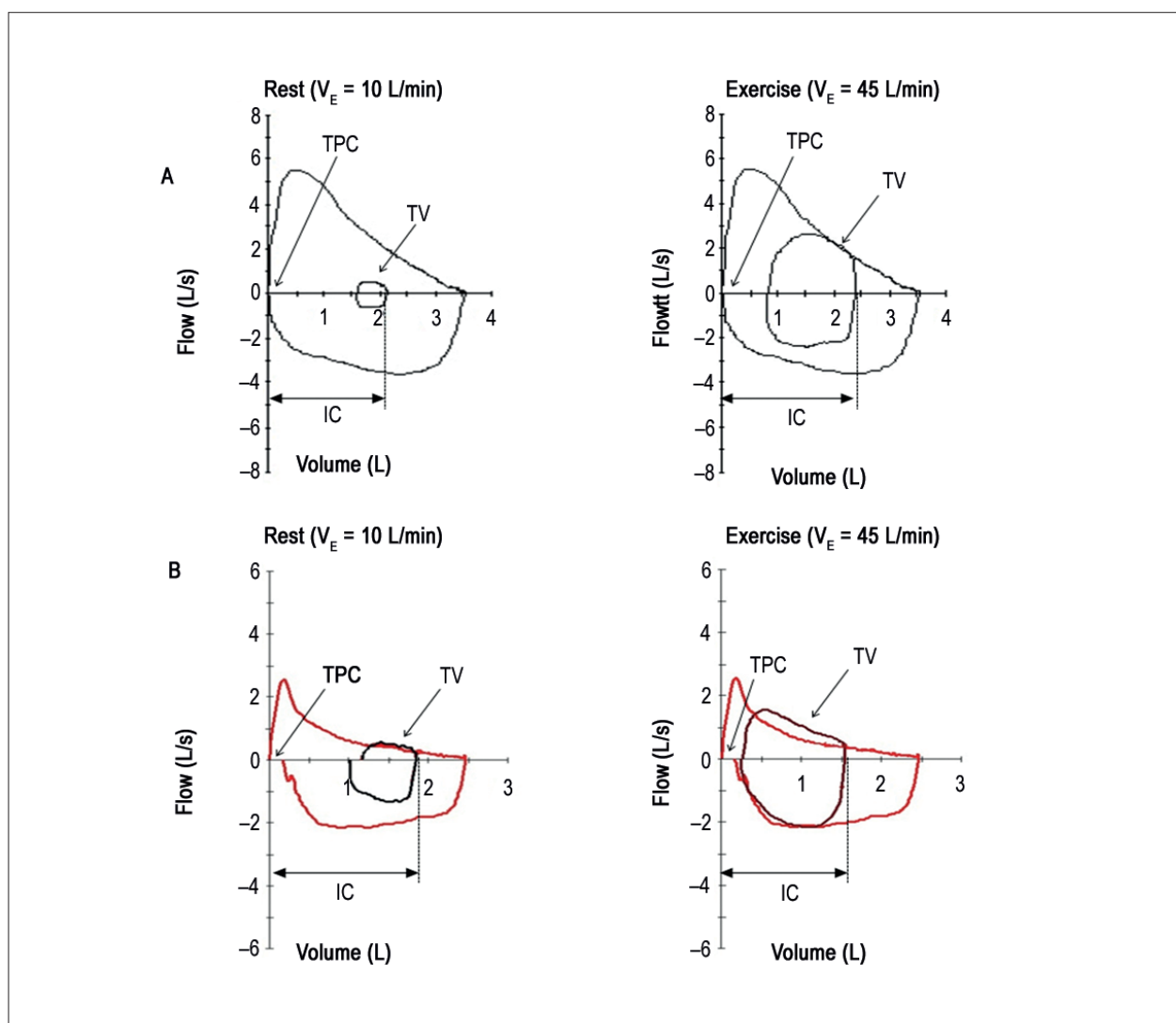


Figure 4 – Flow-volume curves: A) patient without pulmonary disease; B) patient with chronic obstructive pulmonary disease. Note loop displacement to the left with overlapping. IC: inspiratory capacity; TPC: total pulmonary capacity, TV: tidal volume.

reduction in tidal volume, indicating that the respiratory mechanics has reached its functional limit. Dynamic hyperinflation can be observed on CPET when periodic analyses of the flow-volume curve occurs with inspiratory capacity measured during exercise. That is especially useful when symptom intensity and the grade of airway obstruction is disproportional.⁶²

Exertion-induced bronchospasm

Exertion-induced bronchospasm (EIB) is the acute narrowing of airways resulting from exercise. Its clinical manifestations include “chest wheezing”, cough, dyspnea or chest pressure usually 5 to 10 minutes after exercise, and, less commonly, during exercise. Its diagnosis requires a specific protocol with repeated post-exertion spirometry, typically at 5, 10 and 15 minutes. A drop in FEV1 equal to or greater than 10% as compared

to that of pre-exertion is diagnosed as EIB.⁶⁷ For the diagnosis of bronchial hyperreactivity, that test is less sensitive than bronchoprovocation challenge tests with bronchoconstrictors (methacholine, histamine), being, however, more specific for the diagnosis of EIB.

Early detection of pulmonary vascular disease

In addition, CPET has been used to the early detection of pulmonary vascular disease. However, the pathophysiological aspects of pulmonary hypertension are worth considering to understand and interpret the findings in the clinical context.

Pulmonary hypertension is defined as mean pulmonary artery pressure (mPAP) equal to or greater than 25 mmHg,^{68,69} and dyspnea on exertion is usually its earliest symptom. The pulmonary circulation has high capacitance, and normal mPAP values are frequently observed at the early

stages of pulmonary vascular disease. For an increase in mPAP levels at rest to occur, more than 50% of the pulmonary circulation needs to be obstructed, resulting in a relatively late diagnosis of pulmonary vascular disease.^{69,70}

The identification of pulmonary hypertension during exertion requires the use of a pulmonary artery catheter for direct measurement during exercise. This is part of the invasive (or advanced) CPET, available only at a few centers. One limitation is that the definition of pulmonary hypertension on exertion, mPAP greater than 30 mmHg, is arbitrary,^{69,71} and healthy individuals can reach much higher values. In addition, there are not enough data to conclude that patients with that “abnormal hemodynamics” will progress to true pulmonary hypertension at rest.

CPET can provide information to help the clinician suspect pulmonary hypertension when assessing a patient with dyspnea of undefined etiology. The VE/VCO₂ ratio at AT and peak exertion are extremely elevated in patients with pulmonary hypertension, higher than that of patients with HF and same functional class.⁷³ In addition, low PETCO₂ values at the end of expiration, both at rest and exercise, were associated with pulmonary hypertension.

It has been suggested that, in the absence of acute hyperventilation (normal R), VE/VCO₂ ratio greater than 37 and PETCO₂ below 30 mmHg at AT could indicate pulmonary vascular disease. Exceptionally low PETCO₂ values (below 20 mmHg) are uncommon in other diseases and increase the suspicion of pulmonary hypertension in patients assessed for dyspnea on exertion.⁷⁴

Prognostic assessment in pulmonary hypertension

CPET can be used to assess both the severity of pulmonary hypertension in patients with established disease and the response to therapy. Studying idiopathic pulmonary arterial hypertension, Wensel et al. showed that individuals with peak VO₂ lower than 10.4 mL.kg⁻¹.min⁻¹ and peak SBP lower than 120 mmHg had worse prognosis.⁷⁵ The guidelines of the European Society of Cardiology^{69,70} recommend that peak VO₂ values greater than 15.0 and lower than 12.0 mL.kg⁻¹.min⁻¹ indicate good and bad prognosis, respectively. However, that parameter should not be assessed isolated, but be part of a comprehensive assessment to determine pulmonary hypertension severity.

In addition, VE/VCO₂ ratio at AT and VE/VCO₂ slope have been associated with pulmonary hypertension prognosis, with values equal to or greater than 54 and 62, respectively, indicating shorter survival.⁷³ However, that relationship seems not to apply to all forms of pulmonary hypertension. A more elevated VE/VCO₂ slope was observed in pulmonary hypertension due to chronic pulmonary thromboembolism as compared to pulmonary arterial hypertension. It is worth noting that, in pulmonary hypertension due to chronic pulmonary thromboembolism, VE/VCO₂ slope did not associate with functional class, suggesting no relationship with severity and high values at early phases.⁷⁶ Another parameter associated with the worse survival of patients with

pulmonary arterial hypertension is the presence, on CPET, of signs of right-to-left shunt during exercise.⁷⁷

Figure 4: Flow-volume curves: A) patient without pulmonary disease; B) patient with chronic obstructive pulmonary disease. Note loop displacement to the left with overlapping.

CPET in children and adolescents

In the pediatric population, the use of CPET is similar to that of the adult population, but with specific particularities related to the childhood universe. Environmental conditions should allow children to adapt to the test, therefore enabling good performance assessment.⁷⁸

CPET has been very useful to assess healthy individuals and those with complex congenital heart diseases,⁷⁹ allowing the determination of pathophysiological causes that limit functional capacity.⁸⁰ Protocols and ergometers (treadmill and cycle ergometer) are selected according to the objectives and experience of the laboratories conducting the tests. Ramp protocols, however, are currently the most often applied.

Comparing the cardiorespiratory responses of healthy children with those of healthy young adults, Prado et al.⁸¹ have evidenced lower cardiovascular (evidenced by lower O₂ pulse) and respiratory (lower PETCO₂) efficiencies, higher respiratory rate and VE/VO₂ at peak exercise and at AT level. However, healthy children have higher metabolic efficiency (lower R and peak VO₂, similar to those of healthy young adults).

The literature indicates possible reasons for the immaturity of the anaerobic metabolism of children during physical exercise, such as lower muscular glycogen levels,⁸² reduced activity of phosphofrutokinase-1⁸³ and of lactate dehydrogenase,⁸⁴ and higher proportion of muscle fibers of slow contraction.⁸⁵

In addition, children with heart diseases usually have lower aerobic potency than young adults and children without heart diseases.⁸⁶ Other variables derived from CPET are extremely useful to measure the response to exercise. OUES indicates systemic and pulmonary perfusion, and correlates strongly with peak VO₂. In children without heart diseases, OUES increases with their development.⁸⁰ However, according to the study by Dias et al.,⁸⁶ in congenital heart disease, an association was identified between OUES and functional impairment severity in 59 children in the late postoperative period of congenital heart disease correction. Those authors have reported that reduced OUES was associated with low peak VO₂ (below 80% of the predicted value) in 90% of the cases, confirming the presence of a cardiovascular disorder during exertion.

In addition, ergospirometric assessment has been extremely useful in the follow-up of partially or completely treated complex congenital heart diseases, as an aid to indicate the ideal time for new therapeutic interventions. Table 1 shows the performance of children in the late postoperative period of several cyanogenic congenital heart diseases, such as Fallot tetralogy, transposition of the great arteries and single ventricle heart.

Table 2 – * Comparison of the ergospirometric performance of children with complex congenital heart disease and healthy ones undergoing maximal incremental test

	Heart disease (n = 30)	Normal (n = 30)	p
Age	11.8 ± 6.2	11.9 ± 6.7	NS
Incremental test performance			
Max. velocity (km.h ⁻¹)	9.8 ± 3.1	10.9 ± 4.9	0.001
AT velocity (km.h ⁻¹)	5.7 ± 1.7	6.9 ± 1.5	0.001
Max. inclination (%)	5.2 ± 4.8	6.1 ± 4.7	0.049
Distance (m)	1091.2 ± 384.1	1262.9 ± 307.1	0.001
Time (min)	8.6 ± 1.5	11.5 ± 2.1	0.001
Cardiovascular			
Resting HR (bpm)	71.47 ± 11.3	79.0 ± 12.0	0.042
Peak HR (bpm)	175.9 ± 23.0	185.8 ± 19.7	0.031
Resting SBP (mmHg)	106.8 ± 21.4	106.2 ± 19.0	NS
Delta SBP (mmHg)	36.1 ± 1.1	39.2 ± 0.9	0.001
_{PEAK} O ₂ Pulse mL.beat ⁻¹	10.4 ± 5.5	13.5 ± 3.6	0.001
_{AT} O ₂ Pulse mL.beat ⁻¹	8.3 ± 5.1	12.5 ± 3.2	0.001
OUES	1693.5 ± 761.9	1876.6 ± 564.5	0.0001
OUES/kg	34.1 ± 11.1	46.1 ± 9.2	0.0001
Circul. pow. (mmHg/mL/kg)	1924.0 ± 550	3937.5 ± 1220	0.0001
Metabolic			
_{PEAK} VO ₂ mL.min ⁻¹	1021 ± 474.2	1637.40 ± 834.0	0.0001
_{PEAK} VO ₂ mL.kg.min ⁻¹	31.5 ± 7.2	42.3 ± 7.0	0.0001
VO _{2AT} mL.min ⁻¹	19.5 ± 4.5	25.9 ± 5.3	0.0001
VO _{2AT} mL.kg.min ⁻¹	643.4 ± 301.8	1004.2 ± 567.5	0.0001
R (VCO ₂ /VO ₂)	1.02 ± 0.1	1.04 ± 0.1	NS
PETCO ₂ mmHg	30.83 ± 4.5	34.2 ± 4.0	0.0001
Ventilatory and gas exchanges			
Peak VE L.min ⁻¹	50.4 ± 22.0	55.2 ± 22.2	0.38
RR (rpm)	61.0 ± 15.2	58.6 ± 10.9	NS
PETCO ₂ mmHg	32.83 ± 3.90	34.41 ± 3.29	0.0005
VE/VCO ₂ slope	41.2 ± 6.40	35.5 ± 4.3	0.0001
O ₂ Sat (%)	90.9 ± 8.2	97.6 ± 1.2	0.0001

AT: anaerobic threshold; HR: heart rate; peak HR: maximal HR reached; delta SBP: difference between peak and resting systolic blood pressure; OUES: oxygen uptake efficiency slope; Circul. pow.: circulatory power; _{PEAK}VO₂: oxygen consumption at peak exertion; VO_{2AT}: oxygen consumption at anaerobic threshold; VE: pulmonary ventilation; RR: respiratory rate; O₂ Sat (%): oxyhemoglobin saturation (modified from reference 86); NS: non-significant.

Kempny et al.⁸⁷ have reported the reference values of the major ergospirometric variables of adults with congenital heart disease, and have correlated their data with those in the literature to guide the recreational, sports and professional activities of those individuals.

Thus, the association of cardiovascular variables, such as O₂ pulse and peak VO₂, and ventilatory variables (VE/VCO₂ slope) provides more comprehensive and objective data about the true functional capacity of children and adolescents with

congenital heart disease. We provide major examples: after late correction of Fallot tetralogy, evolution with pulmonary insufficiency and possible right ventricular dilation and dysfunction can indicate exchange or, currently, implantation of new prostheses, such as Melody's.^{88,89} CPET can indicate the best time for intervention, when the morphology of the O₂ pulse curve shows a depression or early plateau, in addition to ventilatory inefficiency characterized by high VE/VCO₂ slope values. After late correction of transposition of the great arteries according to Mustard's or Senning's technique, an

older method, many children show worsening of their metabolic efficiency (more reduced peak VO_2 and excessive ventilation – greater VE/VCO_2 slope), which does not occur when submitted to Jatene's surgery, considered the ideal technique. Additionally, CPET allows the analysis of gas exchange in other more complex congenital heart diseases with pulmonary hypertension, such as Eisenmenger's syndrome.^{88,89}

CPET has been a valuable complementary resource in the follow-up of patients with congenital heart diseases to both assess the exercise capacity and indicate the ideal time for new therapeutic approaches, providing objective, diagnostic and prognostic information on the patient's true cardiopulmonary functional status.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical

analysis, Obtaining financing, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Herdy AH, Ritt LEF, Stein R, Araújo CGS, Milani M, Meneghelo RS, Ferraz AS, Hossri CAC, Almeida AEM, Fernandes-Silva MM, Serra SM.

Potential Conflict of Interest

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