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REVIEW ARTICLE
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Cardiopulmonary exercise tests in rare cardiovascular diseases

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Abstract

Cardiopulmonary exercise testing (CPET) is commonly used in clinical practice for both functional and diagnostic assessments of patients with cardiovascular and pulmonary disease. It provides assessment of the integrative exercise responses involving the pulmonary, cardiovascular and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function. In a group of patients with a congenital heart disease or pulmonary hypertension assessment of exercise capacity and exercise tolerance can be a long term evaluation of treatment efficacy. It is also an objective diagnostic and prognostic tool of exercise capacity that allows to evaluate full actual physical condition of this population. JRCD 2015; 2 (5): 139–143

Key words: orphan diseases, exercise capacity, oxygen uptake, congenital heart diseases

Introduction

Cardiopulmonary exercise testing (CPET) is commonly used in clinical practice for both functional and diagnostic assessments of patients with cardiovascular and pulmonary diseases. It provides integrative assessment of exercise responses involving the pulmonary, cardiovascular and skeletomuscular systems, which are not adequately reflected through individual measurements of systems' functions. In a group of patients with congenital heart disease or pulmonary hypertension assessment of exercise capacity and exercise tolerance can be a long term evaluation of treatment efficacy. It is also an objective diagnostic and prognostic tool of exercise capacity that allows to fully evaluate actual physical condition of this population [1–6].

CPET measures a broad range of variables related to cardiorespiratory function including expiratory ventilation (VE) and pulmonary gas exchange (oxygen uptake [VO_2] and carbon dioxide output [VCO_2]), along with the ECG and blood pressure, with the goal of quantitatively linking metabolic, cardiovascular, and pulmonary responses to exercise [3–6].

Most widely used CPET protocols involve incremental exercise on either a treadmill or a cycle ergometer continued to symptom limitation.

The standard expression of capacity for endurance, or aerobic, exercise is the maximum VO_2 reflecting the highest attainable rate of transport and use of oxygen. Peak VO2 reached during a symptom-limited incremental CPET protocol usually approximates maximal VO_2 and is commonly expressed either as indexed to body weight or as percentage of an appropriate reference value. Maximal VO_2 (VO_2 max) is an important measurement because it is considered to be the metric that defines the limits of the cardiopulmonary system [1,3,4].

Because most daily activities do not require maximal effort, a widely used submaximal index of exercise capacity is the anaerobic or ventilatory threshold (VT). The term VT indicates that this physiological event is assessed by ventilatory expired gas, defined by the exercise level at which VE begins to increase exponentially relative to the increase in VO_2. Although VT usually occurs at approximately 45% to 65% of measured peak or maximal VO_2 in healthy untrained subjects, it generally occurs at a higher percentage of exercise capacity in endurance-trained individuals. Moreover, high re-test reliability has been demonstrated for VT in both apparently healthy and chronic disease cohorts. However, the ability to detect VT may be lower in patients with heart failure (HF), perhaps secondary to a greater likelihood of submaximal effort during CPET [3–7].

Achievement of at least 85% of age-predicted maximal heart rate (HR) is a well-recognized indicator of sufficient subject effort dur-

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Table 1. Indications for cardiopulmonary exercise testing [3,7]

Evaluation of exercise tolerance
Determination of functional impairment or capacity (peak VO_2)
Determination of exercise-limiting factors and pathophysiologic mechanisms
Evaluation of undiagnosed exercise intolerance
Assessing contribution of cardiac and pulmonary etiology in coexisting disease
Symptoms disproportionate to resting pulmonary and cardiac tests
Unexplained dyspnoea when initial cardiopulmonary testing is nondiagnostic
Evaluation of patients with cardiovascular disease
Functional evaluation and prognosis in patients with heart failure
Selection for cardiac transplantation
Exercise prescription and monitoring response to exercise training for cardiac rehabilitation (special circumstances; i.e. pacemakers)
Evaluation of patients with respiratory disease
Functional impairment assessment (see specific clinical applications)
Chronic obstructive pulmonary disease
Establishing exercise limitation(s) and assessing other potential contributing factors, especially occult heart disease (ischemia)
Determination of magnitude of hypoxemia and for O_2 prescription
When objective determination of therapeutic intervention is necessary and not adequately addressed by standard pulmonary function testing
Interstitial lung diseases
Detection of early (occult) gas exchange abnormalities
Overall assessment/monitoring of pulmonary gas exchange
Determination of magnitude of hypoxemia and for O_2 prescription
Determination of potential exercise-limiting factors
Documentation of therapeutic response to potentially toxic therapy
Pulmonary vascular disease (careful risk–benefit analysis required)
Cystic fibrosis
Exercise-induced bronchospasm
Specific clinical applications
Preoperative evaluation
Lung resectional surgery
Elderly patients undergoing major abdominal surgery
Lung volume resectional surgery for emphysema (currently investigational)
Exercise evaluation and prescription for pulmonary rehabilitation
Evaluation for impairment–disability
Evaluation for lung, heart–lung transplantation

VO_2 – oxygen consumption

ing a CPET. However, beta-blockers usage by the HF population complicates the maximal HR response to exercise by significantly blunting it [1, 3–6].

The respiratory exchange ratio (RER), defined as the ratio between VCO_2 and VO_2, obtained exclusively from ventilatory expired gas analysis, obviates the need to asses HR in determining such effort. With progression to higher exercise intensities, lactic acid buffering contributes to VCO_2 and VO_2 which increase the numerator at a faster rate than the dominator. This physiological response to exercise is consistent in healthy subjects which makes peak RER the most accurate parameter of a subject's effort. The peak RER of >1.10 is generally considered an indication of an excellent subject's effort during CPET [1, 3–6].

Ventilatory efficiency can be assessed by evaluation of the rise in minute ventilation (VE) relative to work rate, VO_2 or VCO_2. The relationship between VE and VCO_2 during exercise is tightly coupled because the former is modulated by the metabolic and anaerobic production of the latter.

Indications and contraindications for cardiopulmonary exercise testing

Comprehensive CPET is useful in wide spectrum of clinical settings (Table 1) Its impact can be appreciated in all phases of clinical decision making including diagnosis, assessment of severity, disease progression, prognosis, and response to treatment. In practice, CPET is performed when specific questions persist after analysis of basic clinical data including history, physical examination, chest X-ray, pulmonary function tests (PFTs), and resting electrocardiogram (ECG).

Contraindications for CPET are listed in Table 2. It should be emphasized that as the test requires maximal physical activity any factors limiting exercise (such as angina pectoris or intermittent claudication) will make the test non-diagnostic and thus should be regarded as relative contraindications for CPET.

Cardiopulmonary exercise testing in patients with congenital heart disease

Many analysis confirmed that patient after surgical correction of congenital heart disease have worse exercise capacity parameters as measured by CPET than observed in healthy adults, and the health status does not fulfill the definition of complete recovery. These studies demonstrate that exercise capacity is limited even among asymptomatic patients and that self-estimated physical functioning is a poor predictor of measured exercise capacity. Fredriksen et al [8] reported a significantly lower peak VO_2 in patients with a wide range of conditions, including atrial septal defect [9, 10], transposition of the great arteries corrected with the Mustard procedure, congenitally corrected transposition of the great arteries, tetralogy of Fallot, Ebstein anomaly, and modified Fontan procedure [11]. Compared with healthy control subjects across the adult lifespan and peak VE/VCO_2 is an important predictor of those at risk of hospitalization or death. Among patients with noncyanotic congenital heart disease the VE/VCO_2 slope ≥38 is associated with a 10-fold increased risk of mortality [5, 12, 13].

The VE/VCO_2 slope is also significantly higher in subjects with congenital heart defects (≈30 to >70, depending on congenital defect) compared with healthy control subjects (≈25). Surgical procedures to close atrial septal defects or Fontan fenestrations are reported to reduce the VE/VCO_2 slope significantly, whereas only the former procedure significantly increased peak VO_2 [5, 14–18].

Table 2. Absolute and relative contraindications for cardiopulmonary exercise testing [3,7]

Absolute	Relative
Acute myocardial infarction (3–5 days) Unstable angina Uncontrolled arrhythmias causing symptoms or haemodynamic compromise Syncope Active endocarditis Acute myocarditis or pericarditis Symptomatic severe aortic stenosis Uncontrolled heart failure Acute pulmonary embolus or pulmonary infarction Thrombosis of lower extremities Suspected dissecting aneurysm Uncontrolled asthma Pulmonary oedema Respiratory failure Acute non-cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (infection, renal failure, thyrotoxicosis) Mental impairment leading to inability to cooperate	Left main coronary stenosis or its equivalent Moderate stenotic valvular heart disease Severe untreated arterial hypertension at rest or haemodynamic compromise (>200 mm Hg systolic, >120 mm Hg diastolic) Tachyarrhythmias or bradyarrhythmias High-degree atrioventricular block Hypertrophic cardiomyopathy Significant pulmonary hypertension Advanced or complicated pregnancy Electrolyte abnormalities Orthopaedic impairment that compromises exercise performance

Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension

CPET has been used safely in patients with pulmonary arterial hypertension (PAH) for the following indications: prognostic assessment, evaluation of impairment and disability, evaluation and monitoring of responses to various treatment modalities, evaluation for the presence of a patent foramen ovale and right-to-left shunting, development of an exercise prescription for pulmonary rehabilitation and evaluation of patients for lung or heart-lung transplantation [19,21]. One of the leading causes of PAH are chronic lung diseases, and CPET has been used to differentiate lung disease patients with and without PAH; in those with PAH, a significantly reduced ventilatory efficiency is noted, along with a lower rest and exercise arterial oxygen saturation [22].

In chronic PAH a significantly reduced ventilatory efficiency is noted. The VO_2 max provides an index of disease severity; it is lower in patients with a high total pulmonary vascular resistance (PVR) and lower cardiac index and is highly correlated with mean pulmonary artery pressure (mPAP). In patients with severe primary PAH, the VE/VCO_2 ratio correlates significantly with PVR but not with mPAP or cardiac index [19, 21, 23].

Cardiopulmonary exercise testing in patients with heart failure due to systolic dysfunction

Reduced exercise capacity is the cardinal symptom of chronic HF. Determination of peak VO_2 during a maximal symptom-limited treadmill or bicycle CPET is the most objective method to assess exercise capacity in HF patients. Thus, CPET has gained widespread application in the functional assessment of patients with HF. It is a useful test to determine the severity of the disease and to help to determine whether HF is the cause of exercise limitation, provide important prognostic information and identify candidates for cardiac transplantation or other advanced treatments, facilitate the exercise prescription and assess the efficacy of new drugs and devices.

Peak VO_2 is undoubtedly the single most important parameter. It reflects physical capacity of the individual and closely correlates with disease progression. In HF peak VO_2 is decreased i.e. it is below 80% of the reference value adjusted for sex, age, height and body mass. Apart from peak VO_2, its rate of increase is also decreased. On the basis of the available literature peak VO_2 > 18 ml/min/kg is considered to correlate with a good yearly prognosis whereas peak VO_2 < 10 ml/min/kg with particularly poor prognosis [6, 25, 26].

Due to difficulty in estimating prognosis for those with peak VO_2 < 18 ml/min/kg and > 10 ml/min/kg, another prognostic CPET parameter has been searched for. Current data demonstrate prognostic significance of the ventilatory response to exercise (most frequently measured by the VE/VCO_2 slope). It has been estimated that VE/VCO_2 slope > 34 (even if peak VO_2 > 18 ml/min/kg) is a risk factor for mortality in a long-term observation. It has also been demonstrated that the time required for a credible and reproducible assessment of the ventilatory response to exercise is first 3 minutes of exercise on the treadmill, which enables assessment of this parameter in patients with advanced HF, who are unable to achieve maximal effort and thus a fully diagnostic CPET [6, 24–26].

In the last couple of years exertional oscillatory ventilation (EOV) and partial pressure of end-tidal carbon dioxide (PET CO_2) has also been shown to be strong prognostic parameters in this population of patients. The diagnostic and prognostic algorithm for patients with HF includes both these 4 parameters and the four parameters of a classic exercise stress test (ECG, hemodynamic response, post-exercise HR recovery, the reason for stopping the test).

Recently much attention has been paid to chronotropic response during exercise and recovery. Patients with HF demonstrate impaired chronotropic response as compared to healthy volunteers measured

Table 3. Weber and Ventilatory Classification Systems Used in Chronic Heart Failure [36,37]

Disease Severity	Weber Class		Ventilatory Class	
	Peak VO_2 [ml/min/kg]		VE/VCO_2 slope	
Mild to none	A	>20	I	≤29.9
Mild to moderate	B	16–20	II	30.0–35.9
Moderate to severe	C	10–16	III	36.0–44.9
Severe	D	<10	IV	≥45.0

peak VO_2 – maximal oxygen consumption, VE/VCO_2 – minute ventilation/carbon dioxide production relationship

by exercise HR changes and percentage of predicted maximum HR achieved at maximal exercise. It is related to increased all-cause mortality in this group. The imbalance in autonomic function is reflected by the rate of post-exercise HR recovery (HRR). The HRR parameter is lower in patients with HF as compared to healthy volunteers. It has also been demonstrated that lower than normal HRR after 1 minute is a poor prognostic factor in patients with HF [6, 27, 28].

Cardiopulmonary exercise testing in patients with heart failure and preserved left ventricle ejection fraction

Most literature on the use of CPET in patients with HF is based on patients with systolic dysfunction. Its use in patients with HF with normal ejection fraction (diastolic dysfunction) is still a matter uncertainty but initial investigations are promising. It seems that patients with HF (either systolic or diastolic) have the same degree of impaired aerobic capacity and comparably reduced oxygen-uptake efficiency slope [29, 30]. On the other hand ventilatory efficiency (VE/VCO_2 slope) appears to be higher in patient with HF with systolic dysfunction compared to those with diastolic dysfunction [6, 31, 33].

Initial investigations also demonstrate that the VE/VCO_2 slope, exercise oscillatory breathing (EOB), and peak VO_2 may be strong prognostic parameters of poor outcome in patients with diastolic dysfunction, with the first two parameters providing superior prognostic value to the last one. Despite promising findings, more research is needed before any definite conclusions as to the clinical value of CPET in patients with HF with normal ejection fraction can be drawn [6, 32–34].

Prognostic assessment of candidates for transplantation or other major interventions

The ability of CPET parameters to predict adverse events in patients with systolic HF is one if its greatest clinical utilities, especially with respect to consideration of major interventions when accurate estimation of prognosis without the intervention is needed. Since the demonstration that peak VO_2 could be used to identify patients for whom heart transplantation could be delayed without excess mortality, CPET has been incorporated into recommendations for the pretransplantation assessment of HF patients [35, 40].

Much research shows that parameters such as VE/VCO_2 slope and peak VO_2 improve when pharmacological (beta-blockers, renin-angiotensin-aldosteron axis inhibitors, sildenafil), device (cardiac resynchronization therapy), and lifestyle (exercise training) interventions are initiated [38–40].

Subsequently additional variables from CPET have been identified as prognostic in this population, including the VE/VCO_2 slope, which appears to have superior prognostic power compared with peak VO_2 A multivariate approach further improves the ability to identify individuals at greatest risk [41]. Four-level classification systems have been developed for both peak VO_2 and, more recently, the VE/VCO_2 slope (Table 3) [5, 36, 37].

Currently the borderline values for peak VO_2 in patients with HF are 14 ml/min/kg and 12 ml/min/kg for those with or without intolerance to beta-blockers respectively [5, 6, 40].

In case of patients younger than 50 years of age and women it has been suggested to use the so called percent achieved of predicted peak oxygen uptake, which if ≤50% of the norm can be used as an indication for heart transplantation. Another criterion with weaker class of recommendation is based on the value of VE/VCO_2 slope > 35 in patients with HF who achieved submaximal effort (RER < 1,05) and also in obese patients whose peak VO_2 should be normalized to body muscle mass and then the threshold of 19 ml/min/kg is optimal to qualify for heart transplantation [5, 6, 40].

Summary

In summary, these data provide strong evidence that CPET can provide useful objective information regarding exercise tolerance and prognosis among patients after correction of congenital heart disease and pulmonary hypertension. Potential additional applications of CPET among these patients include assessment of exercise tolerance before and after therapeutic surgical and medical interventions, including exercise training programs.

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