A Clinician's Guide to Cardiopulmonary Exercise Testing: Part 1 – An Introduction

Claire Taylor , Simon Nichols , Lee Ingle * PhD

Department of Sport, Health and Exercise Science, University of Hull, Kingston-upon-Hull, HU6 7RX

*Address for correspondence

[1]003 Don Building

Department of Sport, Health & Exercise Science

University of Hull

Cottingham Road

Kingston-upon-Hull

HU7 6RX

United Kingdom

Tel: 01482 463141

Fax: 01482 463855

Email: .Ingle@hull.ac.uk

Conflicts of Interest: None

Compared to standard exercise tolerance testing, cardiopulmonary exercise testing is a reliable and powerful tool that can be used for risk stratification, exercise prescription and clinical diagnosis.

Introduction

Cardiopulmonary exercise testing (CPX or CPET) is a physiological investigation that offers the clinician a wealth of information, beyond that obtainable from standard exercise tolerance testing (ETT). It provides a 'global' assessment of the cardiovascular, ventilatory, and metabolic responses to exercise, and when used correctly, is a powerful diagnostic and prognostic tool.

Multiple factors contribute to exercise intolerance across a wide spectrum of patients with cardiovascular disease and establishing the aetiology and prognostic importance of this intolerance is a significant challenge for clinicians. The purpose of this 2-part guide is to review the rationale for CPET; define and interpret key CPET variables; and provide clinicians with practical guidelines to aid clinical decision-making and patient management. The present article is intended to provide an introduction and orientation to CPET, its key principles and test preparation considerations.

Cardiopulmonary exercise testing combines maximal or symptom-limited progressive intensity exercise with ventilatory expired gas analysis. It is the breath-by-breath monitoring of oxygen () and carbon dioxide () during exercise that enables accurate assessment of a patient's functional capacity and the underlying aetiology of exercise limitation. Since the direct measurement of ventilatory expired gas is both reliable and reproducible it overcomes the many inaccuracies associated with estimating a patient's aerobic capacity from submaximal exercise testing, via for example, a 6-minute walk or incremental shuttle walk test.

It should be emphasised that the interpretive power of CPET in clinical decision-making lies in the *integrated* analysis of cardiorespiratory variables. Exercise capacity is not likely to be

limited by any single component of the transport/utilisation process, but rather, the co-existence of cardiovascular and respiratory abnormalities and their interactions. Cardiopulmonary exercise testing can meaningfully quantify these interactions and in conjunction with other features of importance during exercise, such as electrocardiographic (ECG) changes and perceptual responses (symptoms), can optimise clinical interpretation of exercise intolerance.

In contrast to traditional ETT, which has been shown to have poor sensitivity and specificity for myocardial ischaemia detection (Belardinelli et al., 2003), CPET is not reliant upon ischaemic ECG changes. Gas exchange is able to identify abnormal haemodynamic responses to exercise through changes in key cardiopulmonary exercise test variables (e.g. the attenuation of stroke volume [SV] and cardiac output) during exercise by observing changes in key CPET variables, such as pulse (/heart rate), a surrogate marker of SV. An observed abnormality in pulse is likely to become evident earlier than the appearance of ST segment depression on ECG or symptoms of angina (Chaudhry et al., 2009).

The contribution of CPET can be appreciated across a wide spectrum of clinical settings however its most common indications include those depicted in Box 1.

Box 1: Indications for CPET

a) Pre-operative assessment
b) Evaluation for heart-lung transplantation
c) Prognostic assessment and risk stratification
d) Evaluation of exercise intolerance and functional exercise capacity
e) Evaluation of disease severity and/or progression
f) Exercise prescription for rehabilitation
g) Determining effectiveness of pharmacological agents/exercise intervention

Data Capture

The integrative response of the cardiorespiratory system to increasing work rate during CPET is recorded in real time by computer-linked analysers and displayed graphically in a Wasserman nine-panel plot. These plots and their underlying principles have been

developed by Wasserman and colleagues over the past 30-40 years. They remain the pre-eminent tool for CPET interpretation, however it should be noted that the configuration of the 9 panels has been recently revised in the fifth edition of the textbook (Wasserman et al., 2011). Detailed description of the exercise physiology underpinning these plots is beyond the scope of this guide, with explanation and interpretation limited to only that of key CPET variables. The interested reader is directed to Wasserman et al. (2011) and other published guidelines (Balady et al., 2010; Mezzani et al., 2009) for more detailed elucidation.

The key variables obtained during CPET include; oxygen uptake ($\dot{V}$), minute ventilation (VE), carbon dioxide production ($\dot{V}$), and heart rate (HR). However from these central variables, a number of other prognostically important markers of cardiorespiratory function can also be derived (Table 1).

Table 1. CPET v Standard exercise tolerance test (ETT) variables

Clinical Standard CPET	Standard ETT
Standard ETT markers plus: Peak Oxygen Uptake ($\dot{V}$) Maximal Oxygen Uptake ($\dot{V}$) Respiratory Exchange Ratio (RER) Ventilatory Anaerobic Threshold (VAT) Ventilatory Efficiency (VE/$\dot{V}$ slope) Oxygen Uptake Efficiency Slope (OUES) Oxygen Pulse ($\dot{V}$/HR)	HR Recovery Estimated METs ECG morphology

Maximal exercise testing with integrated gas exchange is a safe procedure, even in populations with higher underlying risk diagnoses; including heart failure, hypertrophic cardiomyopathy, pulmonary hypertension, aortic stenosis, and chronic obstructive pulmonary disease (Skalski, Allison, & Miller, 2012). Reported rates of death for patients during maximal exercise testing are approximately 2 to 5 per 100,000 clinical exercise tests (Balady et al., 2010). Although event rates are low regardless of patient population, complications resulting from maximal exercise testing can occur, therefore absolute and relative contraindications for CPET should be observed (Table 2).

Table 2. Absolute and relative contraindications for CPET

Absolute	Relative
Acute Myocardial Infarction (3–5 Days)	Left main coronary stenosis or its equivalent
Unstable Angina	Moderate stenotic valvular heart disease
Uncontrolled arrhythmias causing symptoms or Haemodynamic compromise	Severe untreated arterial hypertension at rest (>200 mm Hg systolic, >120 mm Hg diastolic)
Syncope	Tachyarrhythmias or bradyarrhythmias
Active endocarditis	High-degree atrioventricular block
Acute myocarditis or pericarditis	Hypertrophic cardiomyopathy
Symptomatic severe aortic stenosis	Significant pulmonary hypertension
Uncontrolled Heart Failure	Advanced or complicated pregnancy
Acute pulmonary embolus or pulmonary Infarction	Electrolyte abnormalities
Thrombosis of lower extremities	Orthopaedic impairment that compromises exercise performance
Suspected dissecting aneurysm	
Uncontrolled asthma	
Pulmonary oedema	
Ambient desaturation at rest $\leq$ 85%	
Respiratory failure	
Acute non-cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise	
Mental impairment leading to inability to cooperate	

Conducting a CPET

General methodological guidelines for CPET are available (American Thoracic Society/American College of Chest Physicians, 2003; Myers et al., 2009) however the following pre-test practices are recommended (Box 2):

Box 2: Pre-Test Considerations

- Patient consent
- Protocol selection and full explanation of test protocol
- History and clinical examination
- Compliance with pharmacological treatments
- Assessment of co-morbidities e.g. orthopaedic limitations
- Anthropometric measurements: height, weight, waist-hip ratio, body mass index, body composition (% lean mass and fat mass)
- Resting ECG: resting heart rate, sinus rhythm or atrial fibrillation
- Pre-test spirometry

The goal of CPET is to interrogate the cardiorespiratory system under increasing physical stress. The selection of an appropriate exercise test protocol therefore is an important consideration. Several protocols can be used with either a cycle ergometer or motorised treadmill, but both should employ a progressively increasing workload.

Since the responses of key variables of interest ($\dot{V}$, $\dot{V}$ and VE) lag behind changes in work rate, incremental protocols that involve small to modest work rate increments per stage are preferred e.g. Naughton (Naughton, Sevelius, & Balke, 1963) or Balke (Balke & Ware, 1959) (Balke and Ware, 1959). Alternatively, continuous ramp (where work increments are negligible) or pseudo-ramp protocols (where typically work rate will increase at 10-60 sec intervals, often in 5W-20W increments) help to maintain a more constant rate of work increase and therefore better preserve the relationship between $\dot{V}$ and work rate (Myers et al., 1991). Protocols with large work-rate increments e.g. Bruce and Modified Bruce (American College of Sport Medicine, 2014) may lead to rapid lactate accumulation and therefore premature cessation of effort during exercise. Indeed, Ingle and colleagues (2008) showed that 42% of patients with suspected chronic heart failure were unable to complete a maximal CPET (defined as a peak RER>1.0) when undertaking a Modified Bruce protocol.

Initial exercise workloads should be individualised according to a patient's perceived exercise capacity and clinical circumstances, in order to elicit volitional exhaustion after 8 - 12 minutes (regardless of baseline fitness level). Avoiding unnecessarily prolonged or prematurely terminated exercise is important if a "true" $\dot{V}$ and the source of exercise limitation is to be accurately established (Box 3).

Within the clinical setting treadmill exercise is still common, since for most patients walking is a more familiar activity than cycling. However, cycle ergometry has become increasingly popular, particularly for those patients who are obese or have severe orthopaedic limitations, gait or balance instability. Though it should be noted that $\dot{V}$ during cycling is systematically 10-20% lower than that achieved during treadmill exercise (Myers et al., 1991) Cycling performance is often limited by localised leg fatigue and because it is non-weight bearing, metabolic demand is lower.

Equipment Calibration

Irrespective of the metabolic cart used for CPET data capture, adherence to calibration and quality assurance procedures is crucial for accurate measurement of metabolic gas exchange and valid test interpretation. Although individual calibrations and manufacturers recommendations will differ, all systems should be calibrated immediately before each test for known gas volumes and concentrations. The reader is referred to the Scientific Statement from the American Heart Association published in 2010, where a comprehensive overview of the procedures for calibration of gas exchange systems is presented (Balady et al., 2010).

Pre-CPET Spirometry

Spirometry is an effective tool in establishing whether ventilatory limitation is a primary cause or contributor to exercise intolerance. Forced spirometry manoeuvres including forced expiratory volume in one second ( ); forced vital capacity (FVC); and peak expiratory flow (PEF) are therefore also required to substantiate the extent of any respiratory limitation during CPET. All these variables can be obtained from a resting flow volume loop, conducted in accordance with the standards published by the American Thoracic Society/European Respiratory Society (2005).

The ratio of to FVC (/FVC) is a widely accepted index of resting pulmonary function; with a value less than 0.70 indicating obstructive (flow-related) respiratory disease (National Insitute for Health and Care Excellence, 2010; Wasserman et al., 2011). However, resting lung function alone will not sufficiently predict the extent to which respiratory disease limits exercise capacity. Maximum voluntary ventilation (the maximum volume of air ventilated in 60 seconds) and breathing reserve (BR), derived from CPET, can aid in the determination of normal respiratory function.

Maximum voluntary ventilation (MVV) is a parameter calculated at rest and is commonly estimated (eMVV) by the formula x 40 (Blackie et al., 1991). Breathing reserve is the difference between eMVV and the maximum exercise ventilation ( ) recorded during CPET.

In healthy individuals, exercise capacity will be rarely affected by respiratory limitation since respiratory capacity far exceeds the demands of peak exercise. In such cases, a normal BR at

peak exercise (≥20% of MVV) will be observed (Balady et al., 2010). In contrast, patients whose exercise is limited by respiratory disease will have a BR close to zero at peak exercise, since cardiovascular efficiency surpasses respiratory efficiency.

It should be noted that in the presence of certain respiratory diseases, such as dynamic hyperinflation, BR cannot be reliably determined by the formula x 40, and therefore precludes the determination of ventilatory limitation via standard pre-CPET spirometry.

Determination of maximal effort and test termination

The verification of a maximal effort is crucial for accurate CPET interpretation, particularly where a patient's $\dot{V}_E$ is reduced and clear physiologic limitation is not elicited during exercise. Patients should be encouraged to exercise until a "true" symptom-limited maximal effort is achieved. Whilst there is currently no gold standard evaluation of maximal effort, one may be confirmed if the patient attains two of the following criteria* (Box 3):

Box 3: Maximal Effort Criteria

- Failure of HR to increase with further increases in exercise intensity (achieving ≥85% of age-predicted maximal HR is a well-recognised indicator of patient effort)
- A plateau in $\dot{V}O_2$ (or failure to increase by 150 $mL \cdot min^{-1}$) with an increased workload
- A respiratory exchange ratio (RER = $\dot{V}CO_2 / \dot{V}O_2$) at peak exercise ≥ 1.10
- A rating of perceived exertion (RPE) > 17 on the 6-20 Borg scale or >9 on the 0-10

Footnote: *It should be noted that despite maximal effort, patients often fail to achieve a plateau in oxygen uptake during peak exercise. We suggest that peak RPE and peak RER are used, which may be substantiated by examining additional variables such as blood lactate, if routinely collected (ACSM, 2014).

Achieving a clear plateau in $\dot{V}$ has traditionally been considered the best evidence of $\dot{V}_{max}$ (the highest achievable level of oxidative metabolism involving large muscle groups) and thus the gold standard index of cardiorespiratory fitness. Yet as indicated, patients may

often fail to achieve a plateau in $\dot{V}$, despite maximal effort. The term $\dot{V}$ (an accepted estimate of $\dot{V}_{max}$) is therefore preferred when defining the limits of the cardiorespiratory system.

Conclusion

This article has sought to provide an introduction to CPET, summarise the basic and essential parameters that can be derived from it and illustrate its clinical value when evaluating patients with, or suspected of having, cardiovascular or respiratory disease. Part two of this guide will focus specifically on CPET data interpretation and the application of CPET findings for the purposes of patient diagnosis and risk stratification.

Key Points

1. Multiple factors contribute to exercise intolerance across a wide spectrum of patients; establishing the aetiology and prognostic importance of these limitations is a significant challenge for clinicians.

2. When combined with the standard tools of clinical investigation, the cardiopulmonary exercise test is the “gold standard” method for objectively assessing cardiorespiratory physiology

3. Cardiopulmonary exercise testing offers a more comprehensive assessment of cardiorespiratory function than standard exercise tolerance tests

References

American College of Sport Medicine. (2014). *ACSM's Guidelines for exercise testing and prescription*. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health.

American Thoracic Society/American College of Chest Physicians. (2003). ATS/ACCP Statement on cardiopulmonary exercise testing. *American Journal of Respiratory and Critical Care Medicine, 167*(2), 211. doi: 10.1164/rccm.167.2.211

American Thoracic Society/European Respiratory Society. (2005). Standardisation of spirometry. *Eur Respir J, 26*(2), 319-338. doi: 10.1183/09031936.05.00034805

Balady, G. J., Arena, R., Sietsema, K., Myers, J., Coke, L., Fletcher, G. F., . . . Research, O. (2010). Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association. *Circulation, 122*(2), 191-225. doi: 10.1161/CIR.0b013e3181e52e69

Balke, B., & Ware, R. W. (1959). An experimental study of physical fitness of Air Force personnel. *US Armed Forces Medical Journal, 10*, 675-688.

Belardinelli, R., Lacalaprice, F., Carle, F., Minnucci, A., Cianci, G., Perna, G., & D'Eusanio, G. (2003). Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J, 24*(14), 1304-1313. doi: 10.1016/S0195-668X(03)00210-0

Blackie, S. P., Fairbarn, M. S., McElvaney, N. G., Wilcox, P. G., Morrison, N. J., & Pardy, R. L. (1991). Normal values and ranges for ventilation and breathing pattern at maximal exercise. *Chest, 100*(1), 136-142. doi: 10.1378/chest.100.1.136

Chaudhry, S., Arena, R., Wasserman, K., Hansen, J. E., Lewis, G. D., Myers, J., . . . Boden, W. E. (2009). Exercise-Induced Myocardial Ischemia Detected by Cardiopulmonary Exercise Testing. *The American Journal of Cardiology, 103*(5), 615-619. doi: 10.1016/j.amjcard.2008.10.034

Ingle, L., Witte, K. K., Cleland, J. G. J. F., & Clark, A. L. (2008). The prognostic value of cardiopulmonary exercise testing with a peak respiratory exchange ratio of <1.0 in patients with chronic heart failure. *International Journal of Cardiology, 127*(1), 88-92. doi: 10.1016/j.ijcard.2007.04.075

Mezzani, A., Agostoni, P., Cohen-Solal, A., Corrà, U., Jegier, A., Kouidi, E., . . . Vanhees, L. (2009). Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. *European Journal of Cardiovascular Prevention & Rehabilitation, 16*(3), 249-267. doi: 10.1097/HJR.0b013e32832914c8

Myers, J., Arena, R., Franklin, B., Pina, I., Kraus, W. E., McInnis, K., . . . Nursing, t. C. o. C. (2009). Recommendations for Clinical Exercise Laboratories: A Scientific Statement From the American Heart Association. *Circulation, 119*(24), 3144-3161. doi: 10.1161/circulationaha.109.192520

Myers, J., Buchanan, N., Walsh, D., Kraemer, M., McAuley, P., Hamilton-Wessler, M., & Froelicher, V. F. (1991). Comparison of the ramp versus standard exercise protocols. *Journal of the American College of Cardiology, 17*(6), 1334-1342. doi: 10.1016/S0735-1097(10)80144-5

National Insitute for Health and Care Excellence. (2010). *Chronic obstructive pulmonary disease. Management of chronic obstructive pulmonary disease in adults in primary and secondary care (update)*. (CG101.). Retrieved from ://guidance.nice.org.uk/CG101

Naughton, J., Sevelius, G., & Balke, B. (1963). PHYSIOLOGICAL RESPONSES OF NORMAL AND PATHOLOGICAL SUBJECTS TO A MODIFIED WORK CAPACITY TEST. *The Journal of sports medicine and physical fitness, 3*, 201.

Skalski, J., Allison, T. G., & Miller, T. D. (2012). The Safety of Cardiopulmonary Exercise Testing in a Population With High-Risk Cardiovascular Diseases. *Circulation, 126*(21), 2465-2472. doi: 10.1161/circulationaha.112.110460

Wasserman, K., Hansen, J., Sue, D., Stringer, W., Sietsema, K., Sun, X.-G., & Whipp, B. (2011). *Principles of exercise testing and interpretation: Including pathophysiology and clinical applications* (Fifth ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.