A clinician's guide to cardiopulmonary exercise testing 1: an introduction

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.

Cardiopulmonary exercise testing is a physiological investigation that offers the clinician a wealth of information, beyond that obtainable from standard exercise tolerance testing. 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.

Many 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. This two-part guide reviews the rationale for cardiopulmonary exercise testing, defines and interprets key cardiopulmonary exercise testing variables, and provides clinicians with practical guidelines to aid clinical decision-making and patient management. This article provides an introduction and orientation to cardiopulmonary exercise testing, 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 (O_2) and carbon dioxide (CO_2) during exercise that enables accurate assessment of a patient's functional capacity and the underlying aetiology of exercise limitation. Since 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 emphasized that the interpretive power of cardiopulmonary exercise testing 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 O_2 transport and utilization 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 changes and perceptual responses (symptoms), can optimize clinical interpretation of exercise intolerance.

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In contrast to traditional exercise tolerance testing, which has poor sensitivity and specificity for myocardial ischaemia detection (Belardinelli et al, 2003), cardiopulmonary exercise testing is not reliant upon ischaemic electrocardiographic 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 and cardiac output) during exercise by observing changes in key cardiopulmonary exercise testing variables, such as O_2 pulse (O_2/heart rate), a surrogate marker of stroke volume. An observed abnormality in O_2 pulse is likely to become evident earlier than the appearance of ST segment depression on electrocardiography or symptoms of angina (Chaudhry et al, 2009).

Cardiopulmonary exercise testing can be used across a wide spectrum of clinical settings, but its most common indications are listed in *Table 1*.

Data capture

The integrative response of the cardiorespiratory system to increasing work rate during cardiopulmonary exercise testing is recorded in real time by computer-linked

Table 1. Indications for cardiopulmonary exercise testing

Preoperative assessment
Evaluation for heart–lung transplantation
Prognostic assessment and risk stratification
Evaluation of exercise intolerance and functional exercise capacity
Evaluation of disease severity and/or progression
Exercise prescription for rehabilitation
Determining effectiveness of pharmacological agents or exercise intervention

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 cardiopulmonary exercise testing interpretation; however, it should be noted that the configuration of the nine panels was revised in the fifth edition of the textbook (Wasserman et al, 2012). Detailed description of the exercise physiology underpinning these plots is beyond the scope of this article, with explanation and interpretation limited to only that of key cardiopulmonary exercise testing variables. The interested reader is directed to Wasserman et al (2012) and other published guidelines (Mezzani et al, 2009; Balady et al, 2010) for more detailed elucidation.

The key variables obtained during cardiopulmonary exercise testing include oxygen uptake (VO_2), minute ventilation, carbon dioxide production (VCO_2) and heart rate. However, from these central variables a number of other prognostically important markers of cardiorespiratory function can also be derived (*Table 2*).

Maximal exercise testing with integrated gas exchange is a safe procedure, even in populations with higher underlying risk diagnoses, including patients with heart failure, hypertrophic cardiomyopathy, pulmonary hypertension, aortic stenosis or chronic obstructive pulmonary disease (Skalski et al, 2012). Reported rates of death for patients during maximal exercise testing are approximately 2–5 per 100 000 clinical exercise tests (American Thoracic Society and American College of Chest Physicians, 2003). Although event rates are low regardless of patient population, complications resulting from maximal exercise testing can occur, therefore absolute and relative contraindications for cardiopulmonary exercise testing should be observed (*Table 3*).

Table 2. Cardiopulmonary exercise testing *vs* standard exercise tolerance test variables

Clinical standard cardiopulmonary exercise testing	Standard exercise tolerance testing markers plus:
	Peak oxygen uptake (VO_2 peak)
	Maximal oxygen uptake (VO_2 max)
	Respiratory exchange ratio
	Ventilatory anaerobic threshold
	CO_2 ventilatory efficiency (VE/VCO_2 slope)
	Oxygen uptake efficiency slope
	Oxygen pulse (VO_2/heart rate)
Standard exercise tolerance testing	Heart rate peak
	Heart rate recovery
	Blood pressure peak
	Estimated metabolic equivalents
	Electrocardiogram morphology

Conducting a cardiopulmonary exercise test

General methodological guidelines for cardiopulmonary exercise testing are available (American Thoracic Society and American College of Chest Physicians, 2003; Myers et al, 2009); however, the pre-test practices listed in *Table 4* are recommended.

Protocol selection

The goal of cardiopulmonary exercise testing is to interrogate the cardiorespiratory system under increasing physical stress. The selection of an appropriate exercise test protocol is therefore an important consideration. Several protocols can be used with either a cycle ergometer

Table 3. Absolute and relative contraindications for cardiopulmonary exercise testing

Absolute	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
	Ambient O_2 desaturation at rest < 85%
	Respiratory failure
	Acute non-cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise
	Mental impairment leading to inability to cooperate
Relative	Left main coronary stenosis or its equivalent
	Moderate stenotic valvular heart disease
	Severe untreated arterial hypertension at rest (>200 mmHg systolic, >120 mmHg 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

or motorised treadmill, but both should employ a progressively increasing workload.

Since the responses of key variables of interest (VO_2, VCO_2 and minute ventilation) lag behind changes in work rate, incremental protocols that involve small to modest work rate increments per stage are preferred, e.g. Naughton (Naughton et al, 1963) or Balke (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 second intervals, often in 5–20 W increments) help to maintain a more constant rate of work increase and therefore better preserve the relationship between VO_2 and work rate (Myers et al, 1991). Protocols with large work rate increments, e.g. Bruce and modified Bruce (American College of Sports 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 cardiopulmonary exercise testing (defined as a peak respiratory exchange ratio >1.0) when undertaking a modified Bruce protocol.

Initial exercise workloads should be individualized 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' VO_{2peak} and the source of exercise limitation is to be accurately established (*Table 5*).

Table 4. Pre-test considerations

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

Table 5. Maximal effort criteria

Failure of heart rate to increase with further increases in exercise intensity (achieving >85% of age-predicted maximal heart rate is a well-recognized indicator of patient effort)
A plateau in VO_2 (or failure to increase by 150 ml/min) with an increased workload
A respiratory exchange ratio (VCO_2/VO_2) at peak exercise >1.10
A rating of perceived exertion >17 on the 6–20 Borg scale or >9 on the 0–10 scale
Post exercise venous lactate concentrations >8–10 mmol/litre

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 patients who are obese or have severe orthopaedic limitations, gait or balance instability. However, VO_{2peak} during cycling is systematically 10–20% lower than that achieved during treadmill exercise (Myers et al, 1991). Cycling performance is often limited by localized leg fatigue and, because it is non-weight bearing, metabolic demand is lower.

Equipment calibration

Irrespective of the metabolic cart used for cardiopulmonary exercise testing 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-cardiopulmonary exercise testing spirometry

Spirometry is an effective tool in establishing whether ventilatory limitation is a primary cause of or contributor to exercise intolerance. Forced spirometry manoeuvres including forced expiratory volume in 1 second (FEV_1), forced vital capacity and peak expiratory flow are therefore also required to substantiate the extent of any respiratory limitation during cardiopulmonary exercise testing. All 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 Task Force (Miller et al, 2005).

The ratio of FEV_1 to forced vital capacity is a widely accepted index of resting pulmonary function, with a value less than 0.70 indicating obstructive (flow-related) respiratory disease (National Institute for Health and Care Excellence, 2010). 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, derived from cardiopulmonary exercise testing, can aid in the determination of normal respiratory function.

Maximum voluntary ventilation is a parameter calculated at rest and is commonly estimated by FEV_1 x 40 (Blackie et al, 1991). Breathing reserve is the difference between estimated maximum voluntary ventilation and the maximum exercise ventilation recorded during cardiopulmonary exercise testing.

In healthy individuals, exercise capacity will rarely be affected by respiratory limitation since respiratory capacity far exceeds the demands of peak exercise. In such cases, a normal breathing reserve at peak exercise (>20% of maximum voluntary ventilation) will be observed (Balady et al, 2010). In contrast, patients whose exercise is limited by respiratory disease will have a breathing reserve 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, breathing reserve cannot be reliably determined by the formula FEV_1 x 40, and therefore precludes the determination of ventilatory limitation via standard pre-cardiopulmonary exercise testing spirometry.

Determination of maximal effort and test termination

The verification of a maximal effort is crucial for accurate cardiopulmonary exercise testing interpretation, particularly where a patient's $VO2_{peak}$ is reduced and clear physiological limitation is not elicited during exercise. Patients should be encouraged to exercise until a 'true' symptom-limited maximal effort is achieved. While there is currently no gold standard evaluation of maximal effort, one may be confirmed if the patient attains two of the criteria in *Table 5**.

Achieving a clear plateau in VO_2 has traditionally been considered the best evidence of VO_{2max} (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 VO_2, despite maximal effort. The term VO_{2peak} (an accepted estimate of VO_{2max}) is therefore preferred when defining the limits of the cardiorespiratory system.

Conclusions

This article has provided an introduction to cardiopulmonary exercise testing, summarize 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. The second article will focus specifically on interpretation of cardiopulmonary exercise testing data and the application of cardiopulmonary exercise test findings for the purposes of patient diagnosis and risk stratification. **BJHM**

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*It should be noted that despite maximal effort, patients often fail to achieve a plateau in oxygen uptake during peak exercise. The authors suggest that peak rating of perceived exertion and peak respiratory exchange ratio are used, which may be substantiated by examining additional variables such as blood lactate, if routinely collected (American College of Sports Medicine, 2014).

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KEY POINTS

- 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.
- When combined with the standard tools of clinical investigation, the cardiopulmonary exercise test is the 'gold standard' method for objectively assessing cardiorespiratory physiology
- Cardiopulmonary exercise testing offers a more comprehensive assessment of cardiorespiratory function than standard exercise tolerance tests.