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

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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

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A Clinician's Guide to Cardiopulmonary Exercise Testing: Part 2 – Test Interpretation

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Data obtained from cardiopulmonary exercise testing offers additional interpretive power over conventional exercise tolerance testing. When used correctly, it allows improved clinical decision-making in patients with cardiometabolic and respiratory disease.

Introduction

The following article is the conclusion to our recently published '...Clinician's Guide to Cardiopulmonary Exercise Testing: Part 1 – An Introduction' (Taylor et al., 2015) summarising the preparatory requirements for cardiopulmonary exercise testing (CPET). This article will focus on the interpretation of a CPET and how to accurately apply findings for the purposes of patient diagnosis and risk stratification. Readers are reminded that CPET should be treated as any other medical investigation and every care should be taken to ensure rigorous calibration and test preparation. Failure to do so will compromise data accuracy resulting in reduced test sensitivity and specificity.

Interpretation of CPET data

Peak oxygen uptake

Peak oxygen uptake ($\dot{V}O_{2peak}$) reflects the body's maximal capacity to generate energy through aerobic metabolism. It can be defined using the Fick equation:

$$\dot{V}O_2 = Q \times (a\text{-}vO_2\ diff)$$

Where Q is cardiac output and $a\text{-}vO_2\ diff$ is the difference between arterial and venous oxygen content. $\dot{V}O_2$ is normally reported in absolute terms ($L \cdot min^{-1}$) or relativised to body mass ($ml \cdot kg^{-1} \cdot min^{-1}$), and plotted as a function of time or workload (plot 1 of the 9-panel plot). Peak oxygen uptake is an independent predictor of mortality and has wide clinical application. The seminal paper by Mancini and colleagues (1991) was amongst the first to identify a threshold based on $\dot{V}O_{2\text{-}peak}$ data ($<14 ml \cdot kg^{-1} \cdot min^{-1}$) which could be used to guide clinical decision making for cardiac transplantation in patients with left ventricular systolic dysfunction. Indeed, $\dot{V}O_{2peak}$ is an integral component of the Heart Failure Survival Score

[HFSS] (Aaronson et al., 1997) and is listed in the current UK guidelines (Box 1) as criteria for referral and assessment of adults for cardiac transplantation (Banner et al., 2011).

Box 1: Conventional Criteria for Heart Transplantation

- Impaired LV systolic function
- NYHA III (e.g. patient cannot climb one flight of stairs without symptoms) or IV symptoms
- Receiving optimal medical treatment (including target or maximum tolerated doses of β-adrenergic antagonists, ACE inhibitors and aldosterone antagonists)
- CRT, ICD or CRTD device implanted (if indicated)
- Evidence of a poor prognosis, for example,
    i. Cardiorespiratory exercise testing (VO_{2max} <12 ml/kg/min if on β-blockade, <14ml/kg/min if not on β-blockade, ensuring respiratory quotient $\geq$ 1.05)
    ii. Markedly elevated BNP (or NT-proBNP) serum levels despite full medical treatment
    iii. Established composite prognostic scoring system, such as the HFSS or SHFM

BNP, B-type natriuretic peptide; CRT, cardiac resynchronisation treatment; CRTD, CRT and ICD treatment; VO_{2max}, maximal oxygen uptake HFSS, Heart Failure Survival Score; ICD, implantable cardioverter defibrillator; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA class IV, New York Heart Association; SHFM, Seattle Heart Failure Model.

Furthermore, Weber and colleagues (1982) developed a classification system for grading the severity of chronic heart failure (CHF), suggesting <10 $ml \cdot kg^{-1} \cdot min^{-1}$and >18 $ml \cdot kg^{-1} \cdot min^{-1}$ to be indicative of high and low risk groups.

Integrated into most contemporary metabolic carts are decision tree algorithms designed to assist with diagnosing the cause of any exercise limitation (Wasserman et al., 2011). The first decision is to determine whether $\dot{V}O_{2peak}$ is abnormally low (<75% of predicted $\dot{V}O_{2max}$) as defined by Wasserman and colleagues (2011). However, a low $\dot{V}O_{2peak}$ may be due to poor patient effort, therefore criteria for evaluating maximal effort should always be

considered (Box 2). Alternatively, abnormally low $\dot{V}O_{2\ peak}$ may suggest a cardiovascular limitation due to reduction in cardiac output, arterial O_2 content, muscle oxygen extraction, and/or ineffective vascular shunt. Although $\dot{V}O_{2peak}$ quantifies cardiorespiratory fitness (CRF), it does not indicate the cause of an exercise limitation and it is necessary to conduct further assessment to determine any underlying pathophysiology.

Cardiopulmonary exercise tests are often conducted in patients with a known clinical diagnosis. In these circumstances a lower $\dot{V}O_{2\ peak}$ may be expected, therefore it may be useful to compare test results with "normative" values for a specific patient group. Table 1 illustrates how CPET can distinguish between different pathologies by comparing a healthy individual with a CHF and chronic obstructive pulmonary disease patient. Whilst $\dot{V}O_{2\ peak}$ is considered by many to be the primary CPET-derived outcome variable, its reproducibility and prognostic power are affected by a number of factors including patient effort, test protocol design, familiarity, and disease severity. Alternative markers of aerobic capacity such as the ventilatory anaerobic threshold (VAT) can be used to improve prognostic power and assist in the quantification of CRF.

Box 2: Maximal Effort Criteria

- Failure of HR to increase with further increases in exercise intensity (achieving $\geq$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 $\geq$ 1.10
- A rating of perceived exertion (RPE) > 17 on the 6-20 Borg scale or >9 on the 0-10

Table 1. Interpretation of CPET data for a healthy male (Figure 1); a patient with chronic heart failure (Figure 2); a patient with emphysema and mild-moderate obstructive lung disease (Figure 3).

PLOT	HEALTHY (FIG 1)	CHF (FIG 2)	COPD (FIG 3)
PLOT 1	Peak VO_2 within normal predicted range (102% of predicted) $\Delta VO_2/\Delta WR$ slope normal (9.8ml/min/W)	Peak VO_2 low (52% of predicted) $\Delta VO_2/\Delta WR$ slope low (5.7ml/min/W)	Peak VO_2 low (63% of predicted) $\Delta VO_2/\Delta WR$ slope low (7.3 ml/min/W)
PLOT 2	Normal O_2/HR (97% of predicted) Normal peak HR (107% of predicted)	O_2/HR flattens after 2 minutes of exercise Peak HR low (56% of predicted)	Normal O_2/HR (84% of predicted) HRR High
PLOT 3	VAT normal (49% of predicted VO_{2peak})	VAT low (38% of predicted VO_{2peak})	VAT low (41% of predicted VO_{2peak})
PLOT 4	Normal ventilatory equivalents	VE/VCO_2 at VAT high (44) Suggesting elevated V_D/V_T	Ventilatory equivalents high (increased V_D)
PLOT 5	N/A	N/A	N/A
PLOT 6	Normal (<34)	Elevated	Elevated
PLOT 7	Normal partial pressures	Normal SPO_2	SPO_2 Low at peak (88%)
PLOT 8	Normal RER	Normal RER	Normal RER
PLOT 9	Normal BR (93)	Normal BR (39)	Low BR (2)

CPET, Cardiopulmonary exercise test; CHF, Chronic heart failure; VO_2, Oxygen uptake; ΔVO_2, Delta oxygen uptake; ΔWR, Delta work rate; COPD, Chronic obstructive pulmonary disease; HR, Heart rate; HRR, Heart rate reserve; VAT, Ventilatory anaerobic threshold; VE, Minute ventilation; VD, Ventilatory dead space; VT, Ventilatory tidal volume; SPO_2, Arterial oxygen saturation; RER, Respiratory exchange ratio; BR, Breathing reserve

Ventilatory Anaerobic Threshold (VAT)

During CPET, $\dot{V}O_2$ and expired carbon dioxide ($\dot{V}CO_2$) increase linearly until the point where oxidative metabolism can no longer sustain the required workload. Anaerobic glycolysis is increasingly required for energy synthesis to maintain higher work rates leading to increased blood lactate accumulation. Bicarbonate buffering of associated H^+ ions results in increased CO_2 production that is ventilated to maintain pH balance. This causes a breakpoint in the linear relationship between $\dot{V}O_2$ and $\dot{V}C\ O_2$ as shown in plot 3 the 9-panel plot. This point marks the VAT (also known as VT_1).

The V-slope method is perhaps the most widely used technique for VAT determination (Beaver et al., 1986, Wasserman et al., 2011) and is achieved by plotting $\dot{V}C\ O_2$ as a function of $\dot{V}O_2$. A trend line is drawn through the plots from the initiation of exercise to the point at which the linear relationship between $\dot{V}C\ O_2$ and $\dot{V}O_2$ is lost (Slope slightly less than 1). A second trend line can then be drawn from the end of the test through to the deflection point. The point at which these two lines bisect indicates the VAT; a value in $ml \cdot kg^{-1} \cdot min^{-1}$ should be reported which can then be calculated as a percentage of $\dot{V}O_{2\ peak}$.

The ventilatory anaerobic threshold is considered a reliable marker of aerobic capacity since a low VAT indicates decreased O_2 transport chain efficiency. Patients with superior CRF will have a VAT closer to their VO_{2peak}, however for most patients VAT will lie between 40-60% of their peak aerobic capacity.

A VAT <40% of peak $\dot{V}O_2$ (or predicted $\dot{V}O_{2\ max)}$ is indicative of disease pathology or significant physical deconditioning (Mezzani et al., 2009). A VAT <11 $ml \cdot kg^{-1} \cdot min^{-1}$ is commonly used to identify patients at higher peri-operative risk and is associated with a 5.3 fold increase in mortality (Gitt et al., 2002). However, many CHF patients have heterogeneous muscle fibre types, abnormal metabolism and compromised exercise haemodynamics. These abnormalities preclude the detection of VAT with non-detection indicative of poor prognosis (Agostoni et al., 2013).

With increasing exercise intensity above the VAT, intracellular bicarbonate is no longer able to adequately offset metabolic acidosis. At this point an increase in VE in excess of VCO_2 can be observed and marks the ventilatory compensation point (also referred to as VT_2).

Ventilatory Compensation Point

The ventilatory compensation point (VCP) is a marker of the upper limit of sustainable aerobic exercise effort and therefore like VAT and $\dot{V}O_2$ peak, is an important parameter describing O_2 transport and utilisation. It is usually attained at approximately 70–80% VO_2peak and 80–90% HR peak (Mezzani et al., 2013). The VCP is well-correlated to 'critical power' (Dekerle et al., 2003) representing the highest power sustainable in conditions of both VO_2 and lactate steady state (i.e. at the limit between high and very-high exercise intensity domains). The VCP is identifiable in plot 6 of the 9-panel plot as an inflection in VE vs $\dot{V}CO_2$ or inflection in VE/$\dot{V}CO_2$ (plot 4) with a concurrently occurring deflection point in end-tidal CO_2 ($PETCO_2$; plot 7). It is important to note that a VCP may not be identifiable in patients who have failed to achieve a near-maximal effort during CPET.

VE/VCO_2 slope

The slope of the relationship between VE and $\dot{V}CO_2$ (VE/$\dot{V}CO_2$ slope) during incremental exercise describes ventilatory efficiency and quantifies the ventilatory rate required to eliminate 1 litre of CO_2 (plot 6 of the 9 panel plot). If an inappropriately high ventilatory response, caused by hyperactive peripheral chemoreceptors or increased V_D/V_T is present, $PaCO_2$ will drop and the VE/$\dot{V}CO_2$ slope will steepen. Muscle ergoflex activation is also a proposed mechanism of increased VE/$\dot{V}CO_2$ slope in patients with CHF. Mathematically, the VE/$\dot{V}CO_2$ slope is determined by 3 factors: the amount of CO_2 produced; the physiological

dead space/tidal volume ratio (V_D/V_T); and $PaCO_2$. The relationship can be explained by the equation:

$$VE = 863 \times \dot{V}CO_2 / PaCO_2 \ (1-V_D/V_T)$$

Where, 863 is a constant (corrects for different environmental conditions, and assumes core temperature of 37 °C), V_D/V_T is the physiological dead space/tidal volume ratio, and $PaCO_2$ is the arterial CO_2 partial pressure. A VE/$\dot{V}CO_2$ slope elevation is a phenomenon frequently observed in CHF patients (Sullivan et al., 1988) and discriminating whether this anomaly is a result of a respiratory or circulatory aetiology can be challenging. Clinical evaluation of past medical history and presenting diagnosis may help distinguish the likely cause.

A number of treatments have been shown to effectively lower VE/$\dot{V}CO_2$ slope including exercise training (Guazzi et al., 2004), angiotensin converting enzyme (ACE) inhibitors (Guazzi et al., 1999), cardiac resynchronisation therapy (Malfatto et al., 2005) and heart transplantation (Carter et al., 2006). Serial CPET may be advantageous in assessing the efficacy of such therapeutic interventions. Most contemporary metabolic carts provide automated analysis of VE/$\dot{V}CO_2$ slope however the slope can be calculated by linear regression when plotting VE as a function of $\dot{V}CO_2$. The mathematical method used to calculate this variable may make it more reproducible (Bensimhon et al., 2008) than $\dot{V}O_{2peak}$ although adequate reproducibility data remains elusive. Table 1 illustrates the differences in VE/$\dot{V}CO_2$ slope observed in a healthy male, a patient with CHF and a patient with chronic obstructive pulmonary disease (COPD). A VE/$\dot{V}CO_2$ slope >34 is commonly accepted as indicating poorer prognosis (Gitt et al., 2002, Arena et al., 2005, Ingle, 2007), although it is possible to further risk stratify patients according to a ventilatory classification system proposed by Arena et al (2007a). VE/$\dot{V}CO_2$ slope may also have a predictive role in the risk assessment of patients with coronary heart disease [CHD] (Van de Veire et al., 2006).

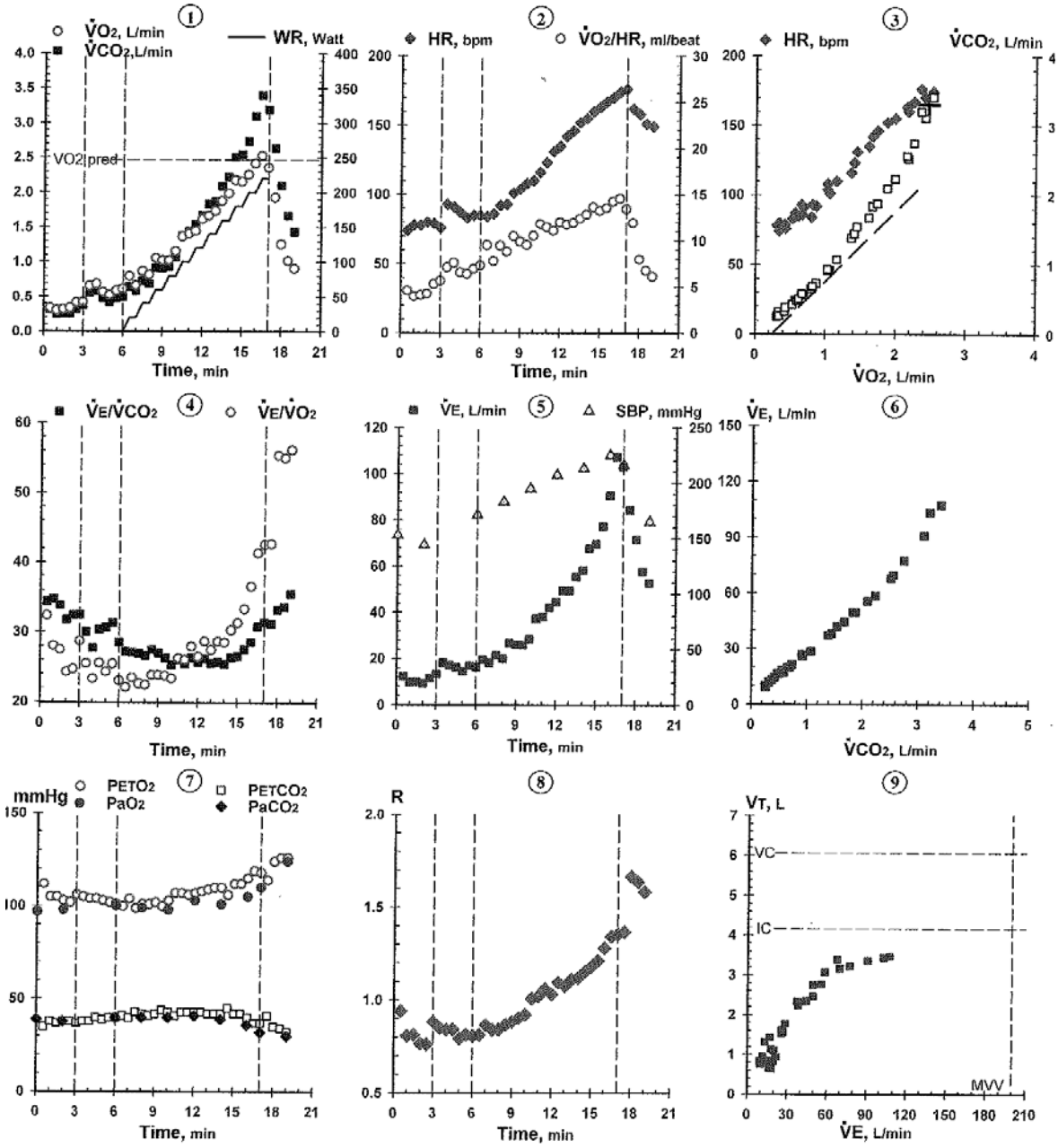

Figure 1. Adapted with permission from Lippincott Williams & Wilkins/Wolters Kluwer Health: Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications, Karlman Wasserman, James Hansen, Kathy Sietsema, Darryl Y. Sue, William W. Stringer, Xing-Guo Sun, Brian J. Whipp ; Figure 10.1.1, Normal Male, 2011
VO_2, Oxygen uptake; VCO_2, Expired carbon dioxide; WR, Work rate; HR, Heart rate; VE, Minute ventilation; SBP, Systolic blood pressure; VT, Ventilatory tidal volume; VC, Vital capacity; IC, Inspiratory capacity; MVV, Maximum voluntary ventilation; $PETCO_2$, Partial pressure of end tidal carbon dioxide; $PETCO_2$, Partial pressure of end tidal oxygen; PaO_2, Partial pressure of arterial oxygen; $PaCO_2$, Partial pressure of arterial carbon dioxide; R, Respiratory exchange ratio

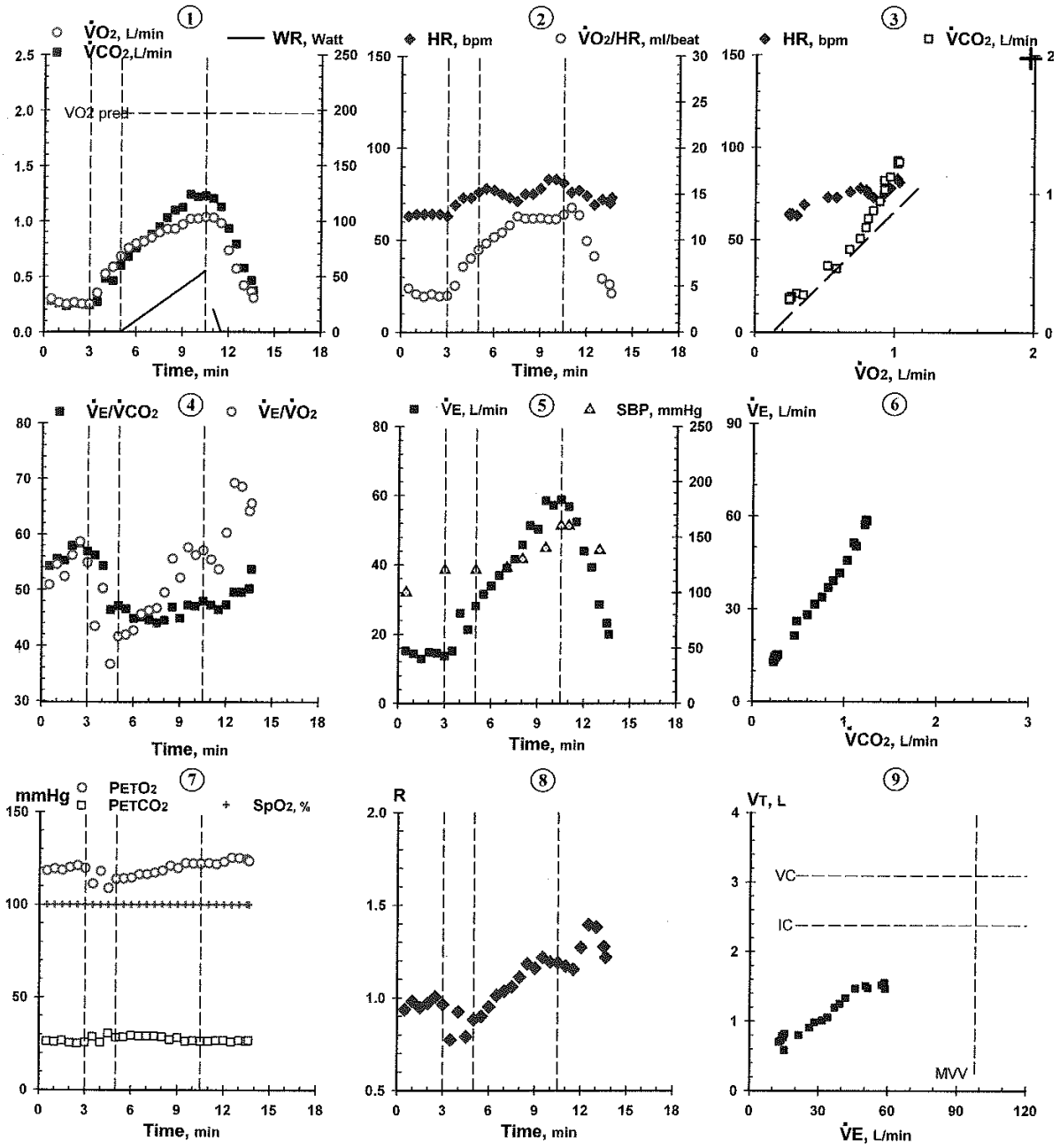

Figure 2. Adapted with permission from Lippincott Williams & Wilkins/Wolters Kluwer Health: Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications, Karlman Wasserman, James Hansen, Kathy Sietsema, Darryl Y. Sue, William W. Stringer, Xing-Guo Sun, Brian J. Whipp; Figure 10.15.1, Chronic Heart Failure: Cardiomyopathy with Intraventricular Conduction Delay, 2011

VO_2, Oxygen uptake; VCO_2, Expired carbon dioxide; WR, Work rate; HR, Heart rate; VE, Minute ventilation; SBP, Systolic blood pressure; VT, Ventilatory tidal volume; VC, Vital capacity; IC, Inspiratory capacity; MVV, Maximum voluntary ventilation; $PETCO_2$, Partial pressure of end tidal carbon dioxide; $PETCO_2$, Partial pressure of end tidal oxygen; PaO_2, Partial pressure of arterial oxygen; $PaCO_2$, Partial pressure of arterial carbon dioxide; R, Respiratory exchange ratio

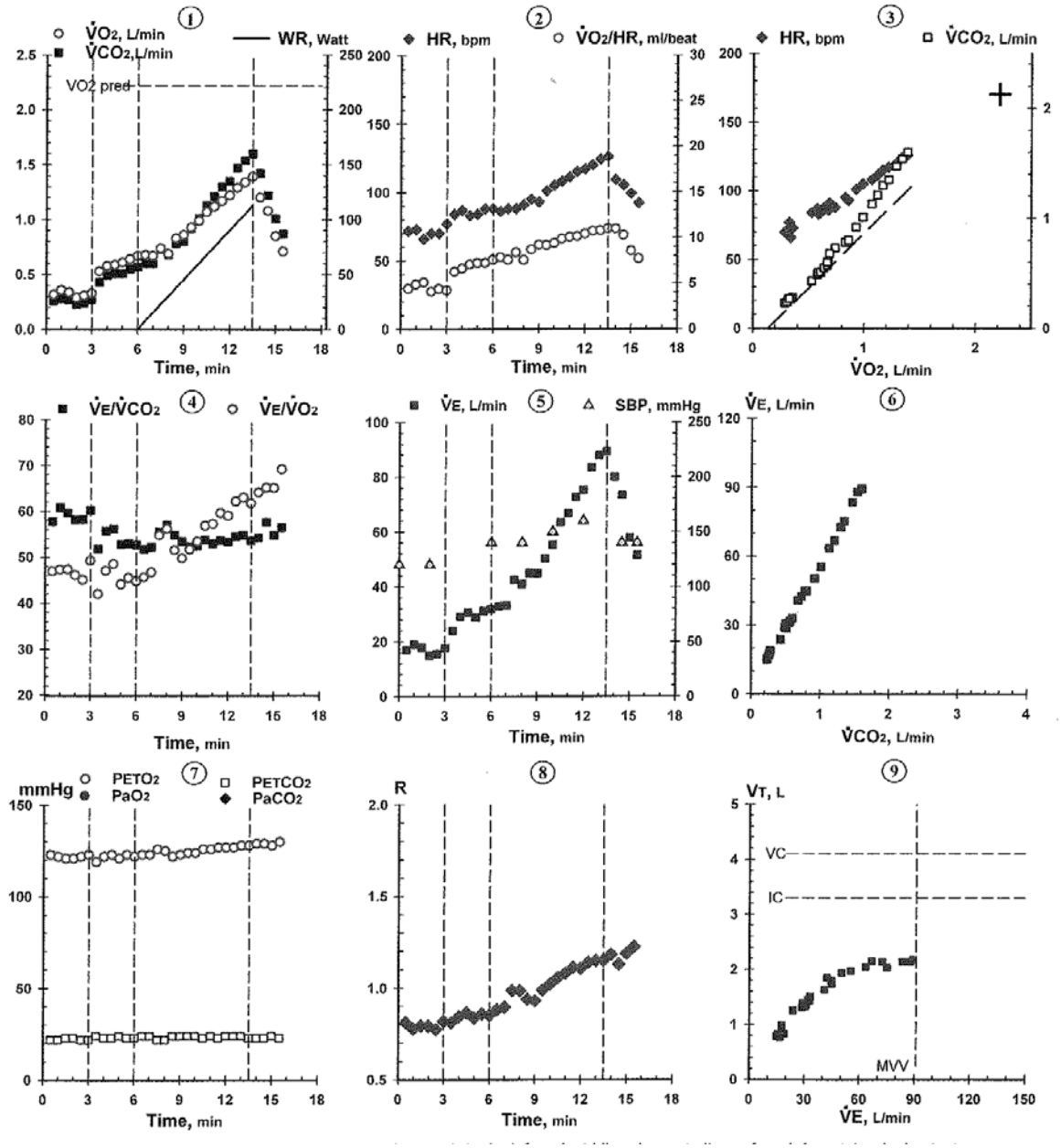

Figure 3. Adapted with permission from Lippincott Williams & Wilkins/Wolters Kluwer Health: Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications, Karlman Wasserman, James Hansen, Kathy Sietsema, Darryl Y. Sue, William W. Stringer, Xing-Guo Sun, Brian J. Whipp; Figure 10.46.1, Emphysema with Mild Airway Obstruction, 2011

VO_2, Oxygen uptake; VCO_2, Expired carbon dioxide; WR, Work rate; HR, Heart rate; VE, Minute ventilation; SBP, Systolic blood pressure; VT, Ventilatory tidal volume; VC, Vital capacity; IC, Inspiratory capacity; MVV, Maximum voluntary ventilation; $PETCO_2$, Partial pressure of end tidal carbon dioxide; $PETCO_2$, Partial pressure of end tidal oxygen; PaO_2, Partial pressure of arterial oxygen; $PaCO_2$, Partial pressure of arterial carbon dioxide; R, Respiratory exchange ratio

Measurement of circulatory function during CPET

Oxygen pulse, heart rate, and VO_2 versus work rate

Exercise-induced myocardial ischaemia diagnosed through electrocardiographic (ECG) changes has poor sensitivity and specificity (Belardinelli et al., 2003). Ischaemia-induced left ventricular (LV) dysfunction however, occurs earlier in the 'ischaemic cascade' and may be detectable before ECG changes or symptoms of angina due to its deleterious effect on Q. In normal (healthy) physiology (Figure 1), Q is increased via a synergistic rise in HR and stroke volume (SV). However, ischaemia-induced LV dysfunction during exercise can lead to abrupt reductions in SV and a concurrent attenuation of Q and VO_2 response during CPET.

Stroke volume can be estimated during CPET through the calculation of an exercise 'oxygen pulse' (O_2/HR; dividing $\dot{V}O_2$ by HR (units = ml O_2 per beat)) in a modification of the Fick equation (Whipp et al., 1996). Oxygen pulse normally rises progressively throughout exercise, however a shallow rise in O_2/HR, *early* plateau or inflection (figure 2, plot 2) suggests decreasing SV with Q being partially sustained through HR compensation at the onset of myocardial ischaemia (Chaudhry et al., 2009).

Early identification of an ischaemic threshold may also be observed with greater effect by combining O_2/HR with the $\dot{V}O_2$ versus work rate slope ($\Delta\dot{V}O_2/\Delta$WR slope). In healthy individuals, a linear $\Delta\dot{V}O_2/\Delta$WR slope of 10ml/min/watt is maintained until peak (Figure 1; plot 1), where at the upper limits of exercise, an inflection may occur, reflecting normal physiological limitation and $\dot{V}O_2$ plateau. A uniform flattening of this relationship throughout CPET suggests a general reduction in cardiovascular efficiency (figure 2, plot 1) and may be attributed to conditions such as CHF. Cardiopulmonary exercise testing has good sensitivity and specificity in detecting exercise-induced myocardial ischaemia (87% and 74% respectively). Belardinelli and colleagues (2003) established the criteria of $\Delta\dot{V}O_2/\Delta$WR slope inflection and concurrent O_2/HR inflection duration for the positive identification of exercise induced myocardial ischemia as compared to myocardial scintigraphy (area under the curve: 0.83). A value of 3.9ml/min/watt was selected as the strongest independent predictor of myocardial ischaemia using a hierarchical model.

The absence of $\Delta\dot{V}O_2/\Delta WR$ slope and O_2/HR inflection can be considered negative criteria for myocardial ischaemia. It should be noted however that the application of this technique may be best suited to ramp protocols or protocols with small work increments for the reasons previously explained.

Measurements of ventilatory function during CPET

Oxygen uptake efficiency slope and $VEqCO_2$ nadir

Often during clinical exercise testing, true maximal criteria are not met and we therefore use the term $\dot{V}O_{2peak}$. However, $\dot{V}O_{2\ peak}$ can underestimate the true cardiorespiratory reserve and other key variables such as $VE/\dot{V}CO_2$ slope lose predictive power when exercise is not conducted beyond VAT (Ingle et al., 2007, Arena et al., 2007b). Results obtained from CPET that fail to elicit satisfactory patient effort may require an alternative assessment technique.

The oxygen uptake efficiency slope (OUES) is calculated by plotting $\dot{V}O_2$ against the logarithmically transformed VE (Baba et al., 1996). The exponent of the linear relationship provides an index of oxygen uptake with respect to VE and reflects both the efficiency of oxygen delivery to the muscle and mitochondrial oxygen utilisation. OUES is only minimally altered when comparing submaximal to maximal test data (Hollenberg and Tager, 2000) with results differing by as little as 1% (Davies et al., 2006) and thus allowing an accurate index of CRF to be calculated. Furthermore the reproducibility of OUES has been shown to be superior to that of the VAT and $\dot{V}O_{2peak}$ (Van Laethem et al., 2009). An OUES of <1.4 is indicative of poor survival (hazard ratio: 4.3, 95% confidence interval: 2.4 to 7.9 p <0.001) regardless of whether VAT is reached (Arena et al., 2007b).

The $VEqCO_2$ nadir is the lowest point in the VE and CO_2 relationship when plotted over the course of a CPET and normally occurs around the VAT in most patients (plot 4). Recent work from our laboratory (Ingle et al., 2011) has shown that this variable calculated from

submaximal data has greater prognostic value than other variables collected from maximal CPET. Therefore, in patient cohorts where a maximal CPET cannot be conducted (e.g. low functional capacity groups), the OUES and $VEqCO_2$ nadir should be calculated to enhance risk stratification.

Exercise oscillatory ventilation

Exercise oscillatory ventilation (EOV) sometimes referred to as exercise periodic breathing (EPB) is characterised by a sino-soidal pattern of VE during incremental exercise to volitional exhaustion. It occurs in up to one third of patients with CHF and is associated with very poor outcome (Ingle et al., 2009). Whilst the genesis of EOV is unclear, two hypotheses have been postulated; the ventilatory hypothesis which is associated with abnormal chemoreceptor feedback, and the haemodynamic hypothesis which is concerned with fluctuations in cardiac output during incremental exercise.

CPET-derived prognostic scoring systems

With the advent of more powerful statistical analysis packages, there has been a move in recent years towards developing composite prognostic scoring systems and moving away from the traditional binary approach to risk stratification. The traditional approach focuses on the top performing variable(s) while discounting the additive or cumulative effect of a combination of different predictor variables. Composite risk scores, which combine the level of risk across a number of variables, have become more commonplace. The advantage of such an approach is that it allows the quantification of risk across the spectrum of abnormal responses. Increasingly, these models are beginning to utilise more data derived from CPET. For example, the Hull CPET risk score was recently developed by our laboratory. We found that individual predictors of mortality ranged from 0.60 to 0.71 (Harrell's C statistic), but the optimal combination of EOV + $VE/\dot{V}CO_2$ slope + OUES + $VEqCO_2$ nadir reached 0.75 in patients with mild-to-moderate CHF. The Hull CPET risk score had a significantly higher area under the curve (0.78) when compared to the Heart Failure Survival Score (AUC=0.70; $P<0.001$) (Ingle et al., 2014). Our findings indicate that data derived solely from CPET out-performs traditional prognostic risk markers which are collected from a range of different

investigations. CPET appears to be a time efficient and cost effective modality for stratifying risk in patients with CHF.

Patient case study

Table 4 summarises the results of a CPET performed by a patient who attended our exercise laboratory for risk stratification and CRF assessment. The patient was a 62 year-old male (body mass index of 32kg·m^{-2}) in normal sinus rhythm with an unremarkable ECG. The patient complained of dyspnoea on light exertion and had recently been diagnosed with coronary heart disease and undergone elective percutaneous coronary intervention. Incremental CPET on a treadmill was performed and breath-by-breath cardiorespiratory data collected (averaged over 15 seconds). A maximal effort was confirmed as the patient met two of the criteria in box 2.

The patient's failure to achieve at least 75% of his predicted $\dot{V}O_{2max}$ (Wasserman et al., 2011) was consistent with reduced CRF (Guazzi et al., 2012). Using standard exercise tolerance test criteria, his 12-minute test duration would have been considered 'normal'. The reduction in CRF may have been due to severe deconditioning, however this was excluded as his VAT was within the normal range (>40% actual/predicted $\dot{V}O_{2peak}$). Data were therefore suggestive of respiratory or cardiac limitation. Pre-test spirometry values from 3 reproducible attempts were within normal range and peak exercise breathing reserve (VE_{max}/estimated maximal voluntary ventilation) was also >20% suggesting adequate ventilation for the exercise intensity (Balady et al., 2010). The probability that respiratory disease was underlying exercise limitation was therefore deemed unlikely.

The rise in O_2/HR was blunted coinciding with a significantly steepened VO_2/HR relationship suggesting SV limitation. This pattern of LV dysfunction during exercise is consistent with myocardial ischaemia. Both the OUES and VAT were pseudo-normal, but were suggestive of a reduction in O_2 transport/utilisation. The VE/$\dot{V}CO_2$ slope however, was significantly elevated (>34) indicating inefficient ventilation and importantly, poor prognosis (30% likelihood of suffering a cardiac event within three years (Arena et al., 2007b). The most likely cause of the VE/$\dot{V}CO_2$ slope elevation was circulatory limitation, given the attenuation

of O_2/HR and compensatory response of HR in relation to $\dot{V}O_2$ needed to sustain Q. The absence of any overt respiratory abnormality during spirometry; normal breathing reserve at peak exercise; history of PCI; and moderately reduced ejection fraction at rest support the conclusion that the patient's exercise limitation was due to an underlying circulatory limitation.

Conclusion

The intention of this guide is to provide a concise, uncomplicated evidence based summary of CPET and present an approach to data interpretation for clinical decision-making. For this reason, detailed description of patient preparation procedures and technical aspects of equipment calibration/test conduction is beyond the scope of this guide. We recommend that readers review other key publications providing guidance for CPET (Balady et al., 2010, American Thoracic Society/American College of Chest Physicians, 2003).

CPET is a safe, non-invasive assessment of cardiorespiratory function. It allows the determination of key prognostic variables and can distinguish pathophysiology not apparent at rest. It is able to discriminate cardiovascular, ventilatory and peripheral limitations during exercise by monitoring disturbances in key variable responses ($\dot{V}O_2$, VE, $\dot{V}CO_2$ and HR). CPET offers additional interpretive power over conventional stress testing and thus can lead to improved clinical decision-making and risk stratification in patients with cardiometabolic and respiratory disease.

5 KEY POINTS

- Multiple factors (circulatory, ventilatory and metabolic) contribute to exercise intolerance across a wide spectrum of patients with cardiovascular disease. Establishing the aetiology and prognostic importance of exercise intolerance is a significant challenge for clinicians.

- Cardiopulmonary exercise testing allows the determination of a number of powerful prognostic markers widely accepted in clinical practice

- Protocols that involve small to modest work rate increments per stage are preferred since they better preserve the relationship between oxygen uptake and work rate.

- Multiple factors can affect exercise intolerance and a methodical approach to eliminating specific possible causes should be adopted.

- Cardiopulmonary exercise testing offers a more comprehensive assessment of cardiorespiratory function than exercise tolerance tests and has been shown to have good sensitivity and specificity in the detection of exercise-induced myocardial ischaemia.

Table 4: A cardiopulmonary exercise test report showing key variables for our patient case study

Patient Information			
Gender: Male		Age: 61	
Height: 174.7cm	Weight: 97Kg	BMI: 31.67kg/m^2	Waist-Hip Ratio: 1.06
Blood Pressure: 100/78mmHg		Pulse: 61bpm – Sinus Rhythm	
Past Medical History: PCI, Obesity, Gout		Smoker: Yes- 20 per day	
Current Medications: Aspirin, Clopidogrel, Bisoprolol, Simvastatin, GTN Spray		Reported Symptoms: Shortness of breath on exertion	
Spirometry Results			
PEF		7.6 ‡	
FVC		4.39 ‡	
FEV_1		3.4 ‡	
FEV_1/FVC Ratio		0.77 ‡	
eMVV		136	
Breathing Reserve		44 ‡	
CPET Results			
Test Duration		Minutes: 12 ‡	Seconds: 1
Criteria for Maximum Testing		HR ≥ 85% predicted HR max (age & β-Blocker adjusted) ‡	
Test Termination Criteria		Leg fatigue & inability to maintain required work rate	
VO_{2peak}		20.6ml/Kg^{-1} (79.8% predicted maximum) ●	
Peak HR		130bpm (83% of predicted maximum) ◊	
VAT		13.5ml/Kg^{-1} (66% $VO_{2peak,}$ 52% Predicted VO_{2peak})	
OUES		1.9 ◊	
VE/VCO_2 Slope		42.19 ●	
O_2/HR		Blunted rise at 1minute 57 seconds ●	
VO_2/HR Relationship		Elevated at 4 minutes and 28 seconds ●	
ST Segment Depression		1.8mm ◊	

Chest Pain	Nil ‡
Breathing Reserve at Peak Exercise	22% ‡

‡ = Within normal range; ◊ = Pseudo normal; ● = Abnormal
BMI = Body mass index; PCI = Percutaneous coronary intervention; GTN, Glyceryl triniatrate; PEF = Peak expiratory flow; FVC = Forced vital capacity; FEV_1 = Forced expiratory volume in 1 second; eMVV = estimated maximal voluntary ventilation; HR = Heart rate; VAT = Ventilatory anaerobic threshold; OUES = Oxygen uptake efficiency slope; VE = Minute ventilation; VCO_2, expired carbon dioxide; VO_{2peak} = peak oxygen uptake

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