A clinician's guide to cardiopulmonary exercise testing 2: test interpretation

Data obtained from cardiopulmonary exercise testing offer additional interpretive power over conventional exercise tolerance testing. When used correctly, these data allow improved clinical decision making in patients with cardiometabolic and respiratory disease.

The following article concludes the authors' recent article (Taylor et al, 2015) summarizing the preparatory requirements for cardiopulmonary exercise testing. This article focuses on the interpretation of a cardiopulmonary exercise test and how to accurately apply findings for the purposes of patient diagnosis and risk stratification. Readers are reminded that cardiopulmonary exercise testing 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 cardiopulmonary exercise testing data

Peak oxygen uptake

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

$VO_2 = Q \times (a\text{-}vO_2 \text{ diff})$

Where Q is cardiac output and $a\text{-}vO_2$ diff is the difference between arterial and venous oxygen content. VO_2 is normally reported in absolute terms (litres/min) or relativised to body mass (ml/kg/min), 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 et al (1991) was among the first to identify a threshold based on VO_{2peak} data (<14 ml/kg/min) which could be used to guide clinical decision making for cardiac transplantation in patients with left ventricular systolic dysfunction. Indeed, VO_{2peak} is an integral component of the Heart Failure Survival Score (Aaronson et al, 1997) and is listed in the current UK guidelines (*Table 1*) as criteria for referral and assessment of adults for cardiac transplantation (Banner et al, 2011).

Furthermore, Weber and colleagues (1982) developed a classification system for grading the severity of chronic heart failure, suggesting <10 ml/kg/min and >18 ml/kg/min 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, 2012). The first decision is to determine whether VO_{2peak} is abnormally low (<75% of predicted VO_{2max}) as defined by Wasserman et al (2012). However, a low VO_{2peak} may be the result of poor patient effort, therefore criteria for evaluating maximal effort should always be considered (*Table 2*). Alternatively, abnormally low VO_{2peak} may suggest a cardiovascular limitation as a result of a reduction in cardiac output, arterial O_2 content, muscle oxygen extraction and/or ineffective vascular shunt. Although VO_{2peak}

Table 1. Conventional criteria for heart transplantation

Impaired left ventricular systolic function	
New York Heart Association class 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, angiotensin-converting enzyme inhibitors and aldosterone antagonists)	
Cardiac resynchronization treatment, implantable cardioverter defibrillator or both implanted (if indicated)	
Evidence of a poor prognosis	Cardiorespiratory exercise testing (maximal oxygen uptake ($VO_{2\,max}$) <12 ml/kg/min if on β-blockade, <14 ml/kg/min if not on β-blockade, ensuring respiratory quotient >1.05)
	Markedly elevated B-type natriuretic peptide (or N-terminal pro-B-type natriuretic peptide) serum levels despite full medical treatment
	Established composite prognostic scoring system, e.g. Heart Failure Survival Score or Seattle Heart Failure Model

Table 2. 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

Mr Simon Nichols *is Exercise Physiologist,* **Ms Claire Taylor** *is Exercise Physiologist and* **Dr Lee Ingle** *is Reader in Exercise Science for Health in the Department of Sport, Health and Exercise Science, University of Hull, Kingston-upon-Hull HU6 7RX*

Correspondence to: Dr L Ingle (L.Ingle@hull.ac.uk)

quantifies cardiorespiratory fitness, it does not indicate the cause of an exercise limitation and further assessment is needed to determine any underlying pathophysiology.

Cardiopulmonary exercise tests are often conducted in patients with a known clinical diagnosis. In these circumstances a lower VO_{2peak} may be expected, so it may be useful to compare test results with 'normative' values for a specific patient group. *Table 3* illustrates how cardiopulmonary exercise testing can distinguish between different pathologies by comparing a healthy individual with a patient with chronic heart failure and a patient with chronic obstructive pulmonary disease. While VO_{2peak} is considered by many to be the primary cardiopulmonary exercise testing-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 can be used to improve prognostic power and assist in the quantification of cardiorespiratory fitness.

Ventilatory anaerobic threshold

During cardiopulmonary exercise testing, VO_2 and expired carbon dioxide (VCO_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 VO_2 and VCO_2 as shown in plot 3 of the 9-panel plot. This point marks the ventilatory anaerobic threshold (also known as VT1).

The V-slope method is perhaps the most widely used technique for determining the ventilatory anaerobic threshold (Beaver et al, 1986; Wasserman et al, 2012) and is achieved by plotting VO_2 as a function of VCO_2. A trend line is drawn through the plots from the initiation of exercise to the point at which the linear relationship between VCO_2 and VO_2 is lost (slope slightly less than 1). A second trend line is then drawn from the end of the test through to the deflection point. The point at which these two lines bisect indicates the ventilatory anaerobic threshold; a value in ml/kg/min should be reported which can then be calculated as a percentage of VO_{2peak}.

The ventilatory anaerobic threshold a reliable marker of aerobic capacity as a low ventilatory anaerobic threshold indicates decreased O_2 transport chain efficiency. Patients with superior cardiorespiratory fitness will have a ventilatory anaerobic threshold closer to their VO_{2peak}, but for most patients the ventilatory anaerobic threshold will lie between 40 and 60% of their peak aerobic capacity.

A ventilatory anaerobic threshold <40% of peak VO_2 (or predicted VO_{2max}) is indicative of disease pathology or significant physical deconditioning (Mezzani et al, 2009). A ventilatory anaerobic threshold <11 ml/kg/min is commonly used to identify patients at higher perioperative risk and is associated with a 5.3-fold increase in mortality (Gitt et al, 2002). However, many patients with chronic heart failure have heterogeneous muscle fibre types, abnormal metabolism and compromised exercise haemodynamics. These abnormalities preclude the detection of ventilatory anaerobic threshold with non-detection indicative of poor prognosis (Agostoni et al, 2013).

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

Plot	Health	Chronic heart failure	Chronic obstructive pulmonary disease
1	Peak VO_2 within normal predicted range $\Delta VO_2/\Delta WR$ slope normal (9.8 ml/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)
2	Normal O_2/heart rate (97% of predicted) Normal peak heart rate (107% of predicted)	O_2/heart rate flattens after 2 minutes of exercise Peak heart rate low (56% of predicted)	Normal O_2/heart rate (84% of predicted) Heart rate reserve high
3	Ventilatory anaerobic threshold normal (49% of predicted VO_{2peak})	Ventilatory anaerobic threshold low (38% of predicted VO_{2peak})	Ventilatory anaerobic threshold low (41% of predicted VO_{2peak})
4	Normal ventilatory equivalents	VE/VCO_2 at ventilatory anaerobic threshold high (44) suggesting elevated V_D/V_T	Ventilatory equivalents high (increased V_D)
5	Not relevant	Not relevant	Not relevant
6	Normal (<34)	Elevated	Elevated
7	Normal partial pressures	Normal arterial oxygen saturation	Arterial oxygen saturation low at peak (88%)
8	Normal respiratory exchange ratio	Normal respiratory exchange ratio	Normal respiratory exchange ratio
9	Normal breathing reserve (93)	Normal breathing reserve (39)	Low breathing reserve (2)

ΔVO_2 = change in oxygen uptake; ΔWR = change in work rate; VD = ventilatory dead space; VE = minute ventilation; VO_2 = oxygen uptake; VT = ventilatory tidal volume

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With increasing exercise intensity above the ventilatory anaerobic threshold, intracellular bicarbonate is no longer able to adequately offset metabolic acidosis. At this point an increase in minute ventilation 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 is a marker of the upper limit of sustainable aerobic exercise effort and so, like ventilatory anaerobic threshold and VO_{2peak}, is an important parameter describing O_2 transport and use. It is usually reached at about 70–80% VO_{2peak} and 80–90% heart rate peak (Mezzani et al, 2013). The ventilatory compensation point correlates well with '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 ventilatory compensation point is identifiable in plot 6 of the 9-panel plot as an inflection in minute ventilation (VE) *vs* VO_2 or inflection in VE/VO_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 ventilatory compensation point may not be seen in patients who have failed to achieve a near-maximal effort during cardiopulmonary exercise testing.

VE/VCO_2 slope

The slope of the relationship between VE and VCO_2 (VE/VCO_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/VCO_2 slope will steepen. Muscle ergoflex activation is also a proposed mechanism of increased VE/VCO_2 slope in patients with chronic heart failure. The VE/VCO_2 slope is determined by three 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:

$$VE = 863 \times VCO_2/PaCO_2 \ (1\text{-}V_D/V_T)$$

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/VCO_2 slope elevation is frequently observed in patients with chronic heart failure (Sullivan et al, 1988) and determining whether this anomaly has 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 can effectively lower VE/VCO_2 slope including exercise training (Guazzi et al, 2004), angiotensin-converting enzyme inhibitors (Guazzi et al, 1999), cardiac resynchronization therapy (Malfatto et al, 2005) and heart transplantation (Carter et al, 2006). Serial cardiopulmonary exercise testing may be advantageous in assessing the efficacy of such therapeutic interventions. Most contemporary metabolic carts provide automated analysis of VE/VCO_2 slope, but the slope can be calculated by linear regression when plotting VE as a function of VCO_2. The mathematical method used to calculate this variable may make it more reproducible (Bensimhon et al, 2008) than VO_{2peak} although adequate reproducibility data remain elusive. *Table 3* illustrates the differences in VE/VCO_2 slope observed in a healthy male, a patient with chronic heart failure and a patient with chronic obstructive pulmonary disease. A VE/VCO_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/VCO_2 slope may also have a predictive role in the risk assessment of patients with coronary heart disease (Van de Veire et al, 2006).

Measurement of circulatory function during cardiopulmonary exercise testing

Oxygen pulse, heart rate and VO_2 *vs* work rate

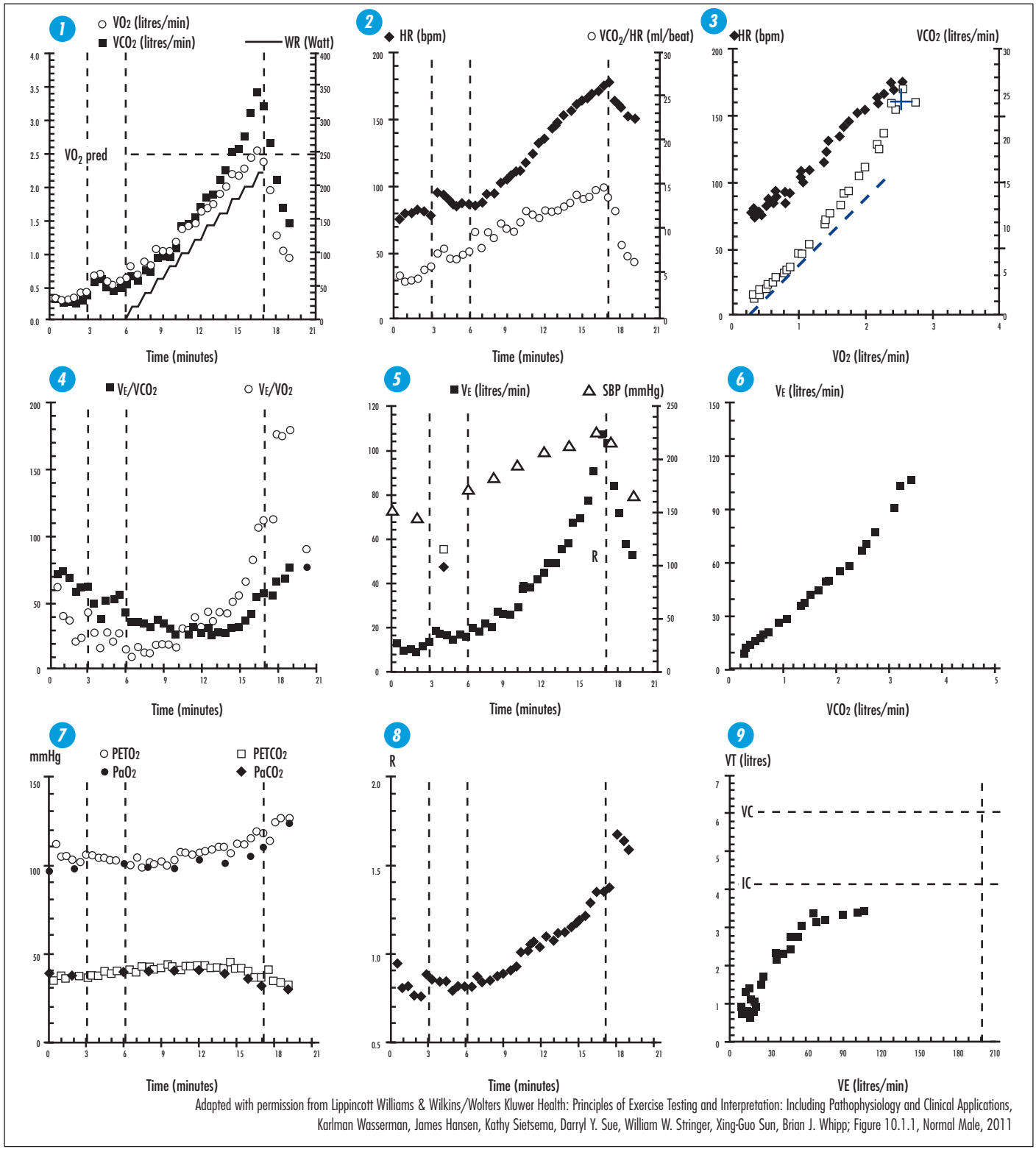
Exercise-induced myocardial ischaemia diagnosed through electrocardiographic changes has poor sensitivity and specificity (Belardinelli et al, 2003). However, ischaemia-induced left ventricular dysfunction occurs earlier in the 'ischaemic cascade' and may be detectable before electrocardiographic changes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

Stroke volume can be estimated during cardiopulmonary exercise testing through the calculation of an exercise 'oxygen pulse' (O_2/heart rate; dividing VO_2 by heart rate (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/heart rate, early plateau or inflection (*Figure 2*, plot 2) suggests decreasing stroke volume with Q being partially sustained through heart rate 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/heart rate with the VO_2 *vs* work rate slope ($\Delta VO_2/\Delta WR$ slope). In healthy individuals, a linear $\Delta VO_2/\Delta WR$ slope of 10 ml/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 VO_2 plateau. A uniform flattening of this relationship throughout cardiopulmonary exercise testing suggests a general

reduction in cardiovascular efficiency (*Figure 2*, plot 1) and may be attributed to conditions such as chronic heart failure. Cardiopulmonary exercise testing has good sensitivity and specificity in detecting exercise-induced myocardial ischaemia (87% and 74% respectively). Belardinelli et al (2003) established the criteria of $\Delta VO_2/\Delta WR$ slope

Figure 1. Normal male. From Wasserman et al (2011). HR = heart rate; IC = inspiratory capacity; MVV = maximum voluntary ventilation; $PaCO_2$ = partial pressure of arterial carbon dioxide; PaO_2 = partial pressure of arterial oxygen; $PETCO_2$ = partial pressure of end tidal carbon dioxide; $PETO_2$ = partial pressure of end tidal oxygen; R = respiratory exchange ratio; SBP = systolic blood pressure; VC = vital capacity; VCO_2 = expired carbon dioxide; VE = minute ventilation; VO_2 = oxygen uptake; VT = ventilatory tidal volume; WR = work rate.



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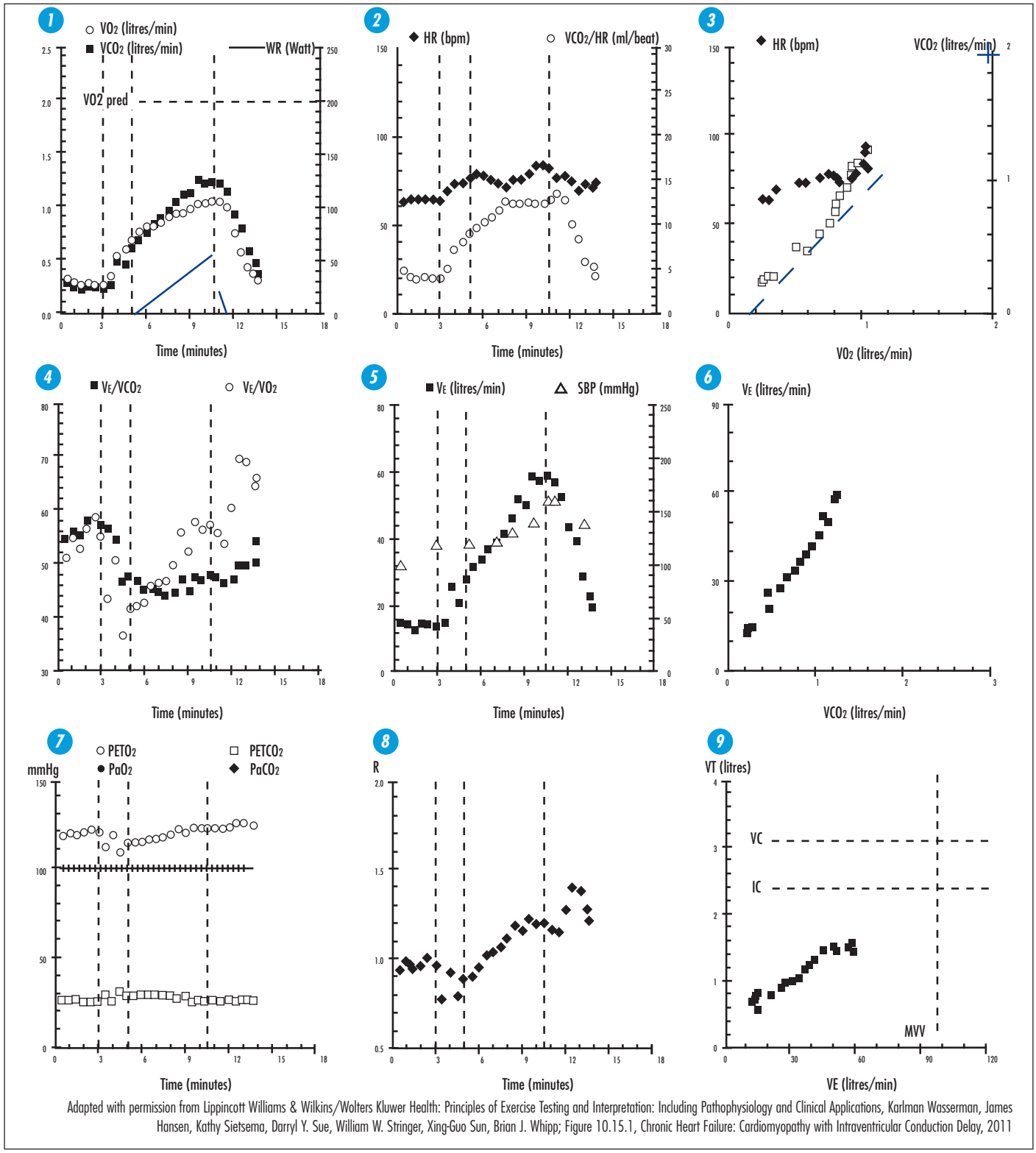
inflection and concurrent O_2/heart rate inflection duration for the positive identification of exercise-induced myocardial ischaemia as compared to myocardial scintigraphy (area under the curve 0.83). A value of 3.9 ml/min/watt was selected as the strongest independent predictor of myocardial ischaemia using a hierarchical model.

Figure 2. Chronic heart failure: cardiomyopathy with intraventricular conduction delay. From Wasserman et al (2011). HR = heart rate; IC = inspiratory capacity; MVV = maximum voluntary ventilation; $PaCO_2$ = partial pressure of arterial carbon dioxide; PaO_2 = partial pressure of arterial oxygen; $PETCO_2$ = partial pressure of end tidal carbon dioxide; $PETO_2$ = partial pressure of end tidal oxygen; R = respiratory exchange ratio; SBP = systolic blood pressure; VC = vital capacity; VCO_2 = expired carbon dioxide; VE = minute ventilation; VO_2 = oxygen uptake; VT = ventilatory tidal volume; WR = work rate.



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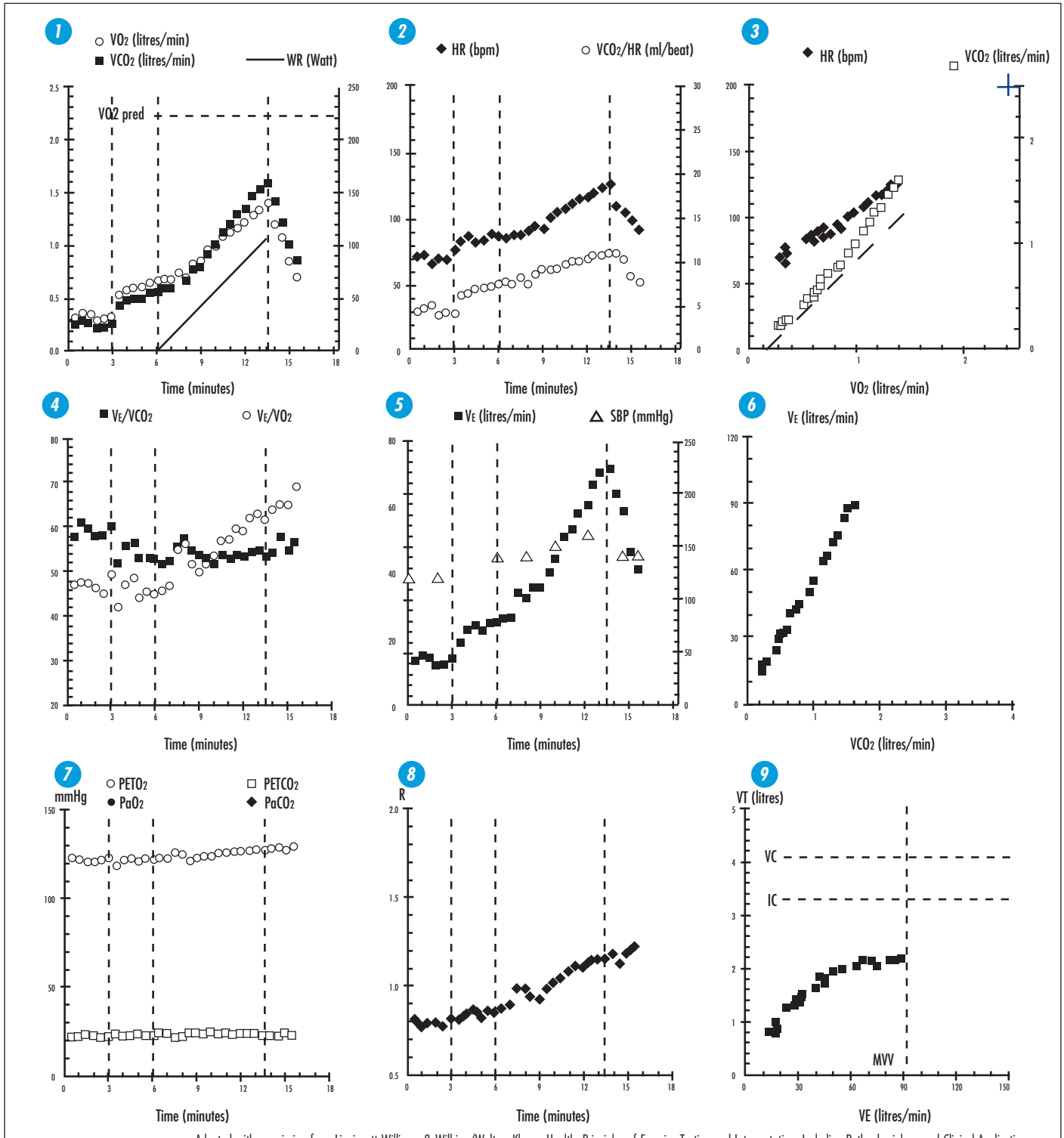
The absence of $\Delta VO_2/\Delta WR$ slope and O_2/heart rate inflection can be considered negative criteria for myocardial ischaemia. It should be noted, however, that the application of this technique may be best suited to ramp protocols or protocols with small work increments for the reasons previously explained.

Figure 3. Emphysema with mild airway obstruction. From Wasserman et al (2011). HR = heart rate; IC = inspiratory capacity; MVV = maximum voluntary ventilation; $PaCO_2$ = partial pressure of arterial carbon dioxide; PaO_2 = partial pressure of arterial oxygen; $PETCO_2$ = partial pressure of end tidal carbon dioxide; $PETO_2$ = partial pressure of end tidal oxygen; R = respiratory exchange ratio; SBP = systolic blood pressure; VC = vital capacity; VCO_2 = expired carbon dioxide; VE = minute ventilation; VO_2 = oxygen uptake; VT = ventilatory tidal volume; WR = work rate.



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Measurements of ventilatory function during cardiopulmonary exercise testing

Oxygen uptake efficiency slope and $VEqCO_2$ nadir

Often during clinical exercise testing, true maximal criteria are not met and therefore the term VO_{2peak} is used. However, VO_{2peak} can underestimate the true cardiorespiratory reserve and other key variables such as VE/VCO_2 slope lose predictive power when exercise is not conducted beyond the ventilatory anaerobic threshold (Arena et al, 2007b; Ingle et al, 2007). Cardiopulmonary exercise testing results that fail to elicit satisfactory patient effort may require an alternative assessment technique.

The oxygen uptake efficiency slope is calculated by plotting VO_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 minute ventilation and reflects both the efficiency of oxygen delivery to the muscle and mitochondrial oxygen use. The oxygen uptake efficiency slope 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 cardiorespiratory fitness to be calculated. Furthermore the reproducibility of the oxygen uptake efficiency slope is superior to that of the ventilatory anaerobic threshold and VO_{2peak} (Van Laethem et al, 2009). An oxygen uptake efficiency slope of <1.4 is indicative of poor survival (hazard ratio 4.3, 95% confidence interval 2.4–7.9, $P<0.001$) regardless of whether or not the ventilatory anaerobic threshold is reached (Arena et al, 2007b).

The $VEqCO_2$ nadir is the lowest point in the minute ventilation and CO_2 relationship when plotted over the course of a cardiopulmonary exercise test and normally occurs around the ventilatory anaerobic threshold in most patients (plot 4). Work from the authors' laboratory (Ingle et al, 2011) has shown that this variable calculated from submaximal data has greater prognostic value than other variables collected from maximal cardiopulmonary exercise testing. Therefore, in patient cohorts where a maximal cardiopulmonary exercise test cannot be conducted (e.g. low functional capacity groups), the oxygen uptake efficiency slope and $VEqCO_2$ nadir should be calculated to enhance risk stratification.

Exercise oscillatory ventilation

Exercise oscillatory ventilation, sometimes referred to as exercise periodic breathing, is characterized by a sinusoidal pattern of minute ventilation during incremental exercise to volitional exhaustion. It occurs in up to one third of patients with chronic heart failure and is associated with very poor outcome (Ingle et al, 2009). While the genesis of exercise oscillatory ventilation 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.

Cardiopulmonary exercise testing-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 use more data derived from cardiopulmonary exercise testing. For example, the Hull cardiopulmonary exercise testing risk score was developed by the authors' laboratory. They found that individual predictors of mortality ranged from 0.60 to 0.71 (Harrell's C statistic), but the optimal combination of exercise oscillatory ventilation + VE/VCO_2 slope + oxygen uptake efficiency slope + $VEqCO_2$ nadir reached 0.75 in patients with mild-to-moderate chronic heart failure. The Hull cardiopulmonary exercise testing risk score had a significantly higher area under the curve (0.78) when compared to the Heart Failure Survival Score (area under the curve=0.70; $P<0.001$) (Ingle et al, 2014). These findings indicate that data derived solely from cardiopulmonary exercise testing out-perform traditional prognostic risk markers which are collected from a range of different investigations. Cardiopulmonary exercise testing appears to be a time-efficient and cost-effective modality for stratifying risk in patients with chronic heart failure.

Patient case study

Table 4 summarizes the results of a cardiopulmonary exercise test performed by a patient who attended the authors' exercise laboratory for risk stratification and cardiorespiratory fitness assessment. The patient was a 62 year-old man (body mass index 32 kg/m^2) in normal sinus rhythm with an unremarkable electrocardiogram. The patient complained of dyspnoea on light exertion and had recently been diagnosed with coronary heart disease and undergone elective percutaneous coronary intervention. Incremental cardiopulmonary exercise testing 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 *Table 2*.

The patient's failure to achieve at least 75% of his predicted VO_{2max} (Wasserman et al, 2012) was consistent with reduced cardiorespiratory fitness (Guazzi et al, 2012). Using standard exercise tolerance test criteria, his 12-minute test duration would have been considered 'normal'. The reduction in cardiorespiratory fitness may have been the result of severe deconditioning, but this was excluded as his ventilatory anaerobic threshold was within the normal range (>40% actual/predicted VO_{2peak}). Data therefore suggested respiratory or cardiac limitation. Pre-test spiro-

metry values from three reproducible attempts were within normal range and peak exercise breathing reserve (VE_{max}/estimated maximum voluntary ventilation) was also >20%, suggesting adequate ventilation for the exercise intensity (Balady et al, 2010). It was thus deemed unlikely that respiratory disease was underlying exercise limitation.

The rise in O_2/heart rate was blunted coinciding with a significantly steepened VO_2/heart rate relationship suggesting stroke volume limitation. This pattern of left ventricular dysfunction during exercise is consistent with myocardial ischaemia. Both the oxygen uptake efficiency slope and ventilatory anaerobic threshold were pseudonormal, but suggested a reduction in O_2 transport/use. However, the VE/VCO_2 slope was significantly elevated (>34), indicating inefficient ventilation and importantly, poor prognosis (30% likelihood of suffering a cardiac event within 3 years) (Arena et al, 2007b). The most likely cause of the VE/VCO_2 slope elevation was circulatory limitation, given the attenuation of O_2/heart rate and compensatory response of heart rate in relation to VO_2 needed to sustain Q. The absence of any overt respiratory abnormality during spirometry, normal breathing reserve at peak exercise, history of percutaneous coronary intervention and moderately reduced ejection fraction at rest support the conclusion that the patient's exercise limitation was caused by an underlying circulatory limitation.

Table 4. Cardiopulmonary exercise test report showing key variables for the patient case study

Patient information	Gender: male	Age: 61 years	Height: 174.7 cm
	Weight: 97 kg	Body mass index: 31.67 kg/m^2	Waist–hip ratio: 1.06
	Blood pressure: 100/78 mmHg	Pulse: 61 bpm – sinus rhythm	
	Past medical history: percutaneous coronary intervention, obesity, gout		
	Smoker: yes – 20 per day		
	Current medications: aspirin, clopidogrel, bisoprolol, simvastatin, glyceryl trinitrate spray		
	Reported symptoms: shortness of breath on exertion		
Spirometry results	Peak expiratory flow	7.6 ‡	
	FVC	4.39 ‡	
	FEV1	3.4 ‡	
	FEV1/FVC ratio	0.77 ‡	
	eMVV	136	
	Breathing reserve	44 ‡	
Cardiopulmonary exercise test results	Test duration	Minutes: 12 ‡	Seconds: 1
	Test termination criteria	Leg fatigue and inability to maintain required work rate	
	VO_{2peak}	20.6 ml/kg (79.8% predicted maximum) ●	
	Peak heart rate	130 bpm (83% of predicted maximum) ◊	
	Ventilatory anaerobic threshold	13.5 ml/kg (66% VO_{2peak}, 52% predicted VO_{2peak})	
	Oxygen uptake efficiency slope	1.9 ◊	
	Minute ventilation/VCO_2 slope	42.19 ●	
	O_2/heart rate	Blunted rise at 1 minute 57 seconds ●	
	VO_2/heart rate relationship	Elevated at 4 minutes and 28 seconds ●	
	ST segment depression	1.8 mm ◊	
	Chest pain	Nil ‡	
	Breathing reserve at peak exercise	22% ‡	

‡ = within normal range; ◊ = pseudo normal; ● = abnormal. FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; eMVV = estimated maximal voluntary ventilation; VCO_2 = expired carbon dioxide; VO_{2peak} = peak oxygen uptake

Conclusions

This article provides a concise, uncomplicated evidence-based summary of cardiopulmonary exercise testing and presents an approach to data interpretation for clinical decision-making. For this reason, detailed description of patient preparation procedures and technical aspects of equipment calibration and test conduction is beyond the scope of this guide. The authors recommend that readers review key publications giving guidance for cardiopulmonary exercise testing (American Thoracic Society/American College of Chest Physicians, 2003; Balady et al, 2010).

Cardiopulmonary exercise testing 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 can discriminate cardiovascular, ventilatory and peripheral limitations during exercise by monitoring disturbances in key variable responses (VO_2, minute ventilation, VCO_2 and heart rate). Cardiopulmonary exercise testing offers additional interpretive power over conventional stress testing, so can improve clinical decision making and risk stratification in patients with cardiometabolic and respiratory disease. **BJHM**

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Aaronson KD, Schwartz JS, Chen T-M, Wong K-L, Goin JE, Mancini DM (1997) Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* **95**: 2660–7 (doi: 10.1161/01.cir.95.12.2660)

Agostoni P, Corra U, Cattadori G et al (2013) Prognostic value of indeterminable anaerobic threshold in heart failure. *Circ Heart Fail* **6**: 977–87 (doi: 10.1161/circheartfailure.113.000471)

American Thoracic Society/American College of Chest Physicians (2003) ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* **167**(2): 211 (doi: 10.1164/rccm.167.2.211)

Arena R, Myers J, Abella J, Peberdy MA (2005) Influence of heart failure etiology on the prognostic value of peak oxygen consumption and minute ventilation/carbon dioxide production slope. *Chest* **128**: 2812–17 (doi: 10.1378/chest.128.4.2812)

Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, Guazzi M (2007a) Development of a ventilatory classification system in patients with heart failure. *Circulation* **115**: 2410–17

Arena R, Myers J, Hsu L et al (2007b) The minute ventilation/carbon dioxide production slope is prognostically superior to the oxygen uptake efficiency slope. *J Cardiac Fail* **13**: 462–9 (doi: 10.1161/

CIRCULATIONAHA.107.686576)
Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, Nishibata K (1996) Oxygen uptake efficiency slope: A new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol* **28**: 1567–72 (doi: 10.1016/S0735-1097(96)00412-3)
Balady GJ, Arena R, Sietsema K et al, American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research (2010) Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* **122**: 191–225 (doi: 10.1161/CIR.0b013e3181e52e69)
Banner NR, Bonser RS, Clark AL et al (2011) UK guidelines for referral and assessment of adults for heart transplantation. *Heart* **97**: 1520–7 (doi: 10.1136/heartjnl-2011-300048)
Beaver WL, Wasserman K, Whipp BJ (1986) A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* **60**: 2020–7
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**: 1304–13 (doi: 10.1016/S0195-668X(03)00210-0)
Bensimhon DR, Leifer ES, Ellis SJ et al (2008) Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing). *Am J Cardiol* **102**: 712–17 (doi: 10.1016/j.amjcard.2008.04.047)
Carter R, Al-Rawas O, Stevenson A, Mcdonagh T, Stevenson R (2006) Exercise responses following heart transplantation: 5 year follow-up. *Scott Med J* **51**: 6–14 (doi: 10.1258/rsmsmj.51.3.6)
Chaudhry S, Arena R, Wasserman K et al (2009) Exercise-induced myocardial ischemia detected by cardiopulmonary exercise testing. *Am J Cardiol* **103**: 615–19 (doi: 10.1016/j.amjcard.2008.10.034)
Davies LC, Wensel R, Georgiadou P, Cicoira M, Coats AJS, Piepoli MF, Francis DP (2006) Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J* **27**: 684–90 (doi: 10.1093/eurheartj/ehi672)
Dekerle J, Baron B, Dupont L, Vanvelcenaher J, Pelayo P (2003) Maximal lactate steady state, respiratory compensation threshold and critical power. *Eur J Appl Physiol* **89**: 281–8 (doi: 10.1007/s00421-002-0786-y)
Gitt AK, Wasserman K, Kilkowski C et al (2002) Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation* **106**: 3079–84 (doi: 10.1161/01.cir.0000041428.99427.06)
Guazzi M, Palermo P, Pontone G, Susini F, Agostoni P (1999) Synergistic efficacy of enalapril and losartan on exercise performance and oxygen consumption at peak exercise in congestive heart failure. *Am J Cardiol* **84**: 1038–43 (doi: 10.1016/S0002-9149(99)00495-6)
Guazzi M, Reina G, Tumminello G, Guazzi MD (2004) Improvement of alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure. *J Appl Physiol* **97:** 1866–73 (doi: 10.1152/japplphysiol.00365.2004)
Guazzi M, Adams V, Conraads V et al (2012) Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J* **33**: 2917–27 (doi: 10.1093/eurheartj/ehs221)
Hollenberg M, Tager IB (2000) Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol* **36**: 194–201 (doi: 10.1016/S0735-1097(00)00691-4)
Ingle L (2007) Theoretical rationale and practical recommendations for cardiopulmonary exercise testing in patients with chronic heart failure. *Heart Fail Rev* **12**: 12–22 (doi: 10.1007/s10741-007-9000-y)
Ingle L, Goode K, Carroll S, Sloan R, Boyes C, Cleland JGF, Clark AL (2007) Prognostic value of the VE/VCO2 slope calculated from different time intervals in patients with suspected heart failure. *Int J Cardiol* **118**: 350–5 (doi: 10.1016/j.ijcard.2006.07.105)
Ingle L, Isted A, Witte KK, Cleland JG, Clark AL (2009) Impact of different diagnostic criteria on the prevalence and prognostic significance of exertional oscillatory ventilation in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil* **16**: 451–6 (doi: 10.1097/HJR.0b013e32832a4f54)
Ingle L, Sloan R, Carroll S, Goode K, Cleland JG, Clark AL (2011) Prognostic significance of different measures of the ventilation-carbon dioxide relation in patients with suspected heart failure. *Eur J Heart Fail* **13**: 537–42 (doi: 10.1093/eurjhf/hfq238)
Ingle L, Rigby AS, Sloan R, Carroll S, Goode KM, Cleland JG, Clark AL (2014) Development of a composite model derived from cardiopulmonary exercise tests to predict mortality risk in patients with mild-to-moderate heart failure. *Heart* **100**: 781–6 (doi: 10.1136/heartjnl-2013-304614)
Malfatto G, Facchini M, Branzi G et al (2005) Reverse ventricular remodeling and improved functional capacity after ventricular resynchronization in advanced heart failure. *Ital Heart J* **6**: 578–83
Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Wilson JR (1991) Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* **83**: 778–86 (doi: 10.1161/01.cir.83.3.778)
Mezzani A, Agostoni P, Cohen-Solal A et al (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. *Eur J Prev Cardiol* **16**: 249–67 (doi: 10.1097/HJR.0b013e32832914c8)
Mezzani A, Hamm LF, Jones AM et al (2013) Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. *Eur J Prev Cardiol* **20**: 442–67 (doi: 10.1177/2047487312460484)
Sullivan MJ, Higginbotham MB, Cobb FR (1988) Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. *Circulation* **77**: 552–9 (doi: 10.1161/01.cir.77.3.552)
Taylor C, Nichols S, Ingle L (2015) A clinician's guide to cardiopulmonary exercise testing 1: an introduction. *Br J Hosp Med* **76**(4): 192–5 (doi: 10.12968/hmed.2015.76.4.192)
Van de Veire NR, Van Laethem C, Philippé J, De Winter O, De Backer G, Vanderheyden M, De Sutter J (2006) VE/VCO2 slope and oxygen uptake efficiency slope in patients with coronary artery disease and intermediate peakVO2. *Eur J Cardiovasc Prev Rehabil* **13**: 916–23 (doi: 10.1097/01.hjr.0000238400.35094.72)
Van Laethem C, De Sutter J, Peersman W, Calders P (2009) Intratest reliability and test–retest reproducibility of the oxygen uptake efficiency slope in healthy participants. *Eur J Cardiovasc Prev Rehabil* **16**: 493–8 (doi: 10.1097/HJR.0b013e32832c88a8)
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.* Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia
Weber KT, Kinasewitz GT, Janicki JS, Fishman AP (1982) Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation* **65**: 1213–23 (doi: 10.1161/01.CIR.65.6.1213)
Whipp BJ, Higgenbotham MB, Cobb FC (1996) Estimating exercise stroke volume from asymptotic oxygen pulse in humans. *J Appl Physiol* **81**(6): 2674–9

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 as 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 good sensitivity and specificity in the detection of exercise-induced myocardial ischaemia.