POETTS
Perioperative Exercise Testing & Training Society

Cardiopulmonary Exercise Testing for Pre-Operative Assessment Course

Delegate Workbook

V12_2020_DZHL

POETTS was established in July 2016 to provide laboratory guidelines, recommend training standards for clinicians performing CPET and co-ordinate multicentre research studies.

A society website listing active CPET centres and identifying centres who are happy to mentor newly established services and clinicians is now live at www.poetts.co.uk and provides an educational resource and lists a number of active centres with contacts.

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An Introduction to Cardiopulmonary Exercise Testing

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Background: The perioperative medicine challenge

It is estimated that more than 300 million surgical procedures are performed globally annually and this number is increasing. Surgery is associated with a substantial burden of perioperative morbidity and mortality that represents a significant public health challenge. As life expectancy continues to rise, an increasing proportion of patients are likely to be elderly with multiple comorbidities. This will present challenges to both anaesthetists and surgeons. The optimum perioperative management of high-risk patients involves multidisciplinary collaborative decision-making. Accurate pre-operative risk stratification is essential to ensure this process is based on reliable data.

Reduced exercise capacity is associated with worse health outcomes in general and specifically with worse outcomes following surgery. Cardiopulmonary exercise testing (CPET) is an assessment modality for exercise intolerance and its functional correlates.

CPET can play a central role in the perioperative medicine pathway by providing an objective evaluation of functional capacity. It has a number of possible roles:

1. To contribute to pre-operative risk assessment and estimate the likelihood of perioperative morbidity and mortality.
2. To inform the processes of multidisciplinary shared decision-making and consent.
3. To guide clinical decisions about the most appropriate level of perioperative care (ward vs critical care).
4. To direct pre-operative referrals/interventions to optimise comorbidities.
5. To identify previously unsuspected pathology.
6. To evaluate the effects of neoadjuvant cancer therapies including chemotherapy and radiotherapy.
7. To guide prehabilitation and rehabilitation training programmes.
8. To guide intra-operative anaesthetic practice.

What does cardiopulmonary exercise testing involve?

Exercise intolerance ensues when the increased demands for ATP re-synthesis in exercising muscles can longer be supported by appropriate increases in tissue oxygen delivery consequent to impairments in ventilation, cardiac output and/or skeletal muscle blood flow. In the peri-operative context, the increased ATP demand for metabolic work requires increased tissue oxygen delivery which must be matched by increased ventilation and cardiac output, if failure of tissue perfusion and oxygenation are to be avoided.

The principle underlying CPET is that system failure typically occurs while the system is under stress, e.g. during exertion. The goal of CPET is, therefore to stress the involved organ systems with progressive exercise to a level at which response abnormality becomes discernible, from the magnitude or profile of the response. The interpretation of the results is then based on two inter-related perspectives:
(a) discriminating an abnormal magnitude or pattern of response (compared with the age-, gender- and activity-matched standard subject) of appropriately selected variables, and
(b) matching the magnitude or pattern of abnormality with that characteristic of particular impairments of physiological system function.

What does CPET offer that other pre-operative tests lack?

Cardiopulmonary exercise testing (CPET) has several advantages:
It is Integrative: CPET provides a global assessment of the integrated responses of the pulmonary, cardiovascular and metabolic systems that are not adequately reflected through measurement of individual organ system function. This is in contrast to tests assessing the function of a single organ in isolation, e.g. echocardiography or lung function tests.
It is Dynamic: Resting pulmonary and cardiac function testing cannot reliably predict exercise performance and functional capacity. Overall health status correlates better with exercise tolerance rather than with resting measures. CPET is a dynamic test that assesses organ function at rest and during exertional stress. Thus CPET gives information about physiological reserve.
It is Objective: Patients self-reported exercise capacity is often inaccurate. Furthermore, functional capacity scores including the Duke Activity Survey have not been validated in the surgical population.

CPET detects and evaluates cardiac and pulmonary dysfunction by identifying the consequences of oxygen uptake being challenged to keep pace with the increasing oxygen demands of progressive exercise. In the event of oxygen demand exceeding supply, there is a transition to increasing anaerobic metabolism and a consequent progressive metabolic acidosis. Such anaerobic metabolism is unsustainable and results in organ dysfunction if oxygen supply is not restored.

Surgical patients are often relatively sedentary because of their comorbidities or their lifestyle. Consequently physical deconditioning, as distinct from clinical disease, may contribute to or cause their reduced functional capacity. The degree of functional impairment predicts the postoperative outcome. The aetiology of this functional impairment is probably less important. The perioperative literature does not differentiate between the different causes of functional impairment when predicting perioperative risks although this requires further clarification.

Why is CPET useful?

By assessing the integrative functioning of physiological systems in response to the stress of progressive exercise, CPET provides a means of individually:

- Establishing the exercise capacity and the limits of physiological system function during exercise.
- Evaluating the normalcy of exercise responses with regard to a reference population, or with regard to other physiological functions
- Identifying the cause(s) of exercise intolerance
- "Triggering" an abnormality (e.g. exercise-induced asthma)
- Stratifying surgical risk, with the potential utility to guide decisions relating to surgery and peri-operative care
- Providing a frame of reference for change with respect to therapeutic interventions (e.g. pharmacological, O_2 supplementation, surgical) or training (e.g. pulmonary rehabilitation, cardiac rehabilitation, surgical pre-habilitation), and
- Establishing prognostic outcomes

What does CPET involve? (see later sections for more detail)

CPET is an exercise stress test with concomitant gas exchange analysis. Expired tidal volumes, oxygen and carbon dioxide concentrations, heart rate and respiratory rate are measured and a number of ventilatory, gas exchange and cardiovascular variables are derived from these. 12 Lead ECG and oxygen saturations are also continuously monitored.

The Exercise Protocol

The rapid incremental ramp to the limit of tolerance that is used for many other indications is the standard protocol for perioperative CPET (see guidelines(Levett et al. 2018)). This is a short protocol, with a low initial work rate and a brief duration of high intensity exercise. Cycle ergometry is used in preference to treadmill as the exercise mode. It allows accurate determination of the external work-load and requires less skill. Early pre-operative CPET studies employed submaximal incremental tests because of safety concerns. These concerns have been allayed, such that maximal tests to the limit of tolerance are now routinely used and are preferred.

CPET equipment: What do we measure?

Cardiopulmonary exercise testing equipment varies in detail, but the principles of all 'metabolic carts' are the same. They have an oxygen analyser (paramagnetic/fuel cell/zirconia fuel cell/mass spectrometer), a carbon dioxide analyser (infrared in the majority of cases) and a flowmeter (turbine/pneumotachograph/us etc). Computerised systems integrate the continuously-measured flow and gas concentration signals into real-time, breath-by-breath calculation of variables such as oxygen uptake (VO_2), CO_2 output (VCO_2), ventilation (VE) and end-tidal PO_2 and PCO_2 ($P_{ET}CO_2$, $P_{ET}O_2$). The accurate alignment of flow with gas concentration signals is a key element, and can be a significant source of error. Most systems also provide 12 lead ECG, pulse oximetry (for arterial O_2 saturation) and non-invasive arterial blood pressure monitoring. The heart rate signal can either be derived from the ECG or a heart rate monitor.

Equipment Calibration and Validation

Valid data is a pre-requisite for making valid clinical recommendations about perioperative care. Thus equipment calibration and validation are an important aspect of running a CPET laboratory. The manufacturer bears the initial responsibility for demonstrating that a CPET system is accurate and precise (and this should include a description of the methods used in their validation). However, the user bears the responsibility for ensuring that the measurements remain accurate.

Unfortunately, there are currently no universally accepted guidelines for equipment calibration procedures and laboratory quality control for clinical exercise testing in the UK. The British Association of Sport and Exercise Sciences (BASES) provides laboratory accreditation for non-clinical physiological laboratories (www.bases.org.uk). The statement on CPET by the American Thoracic Society provides the most comprehensive guidance for clinical laboratories (Physicians, 2003). The POETTS CPET guidelines make recommendations for the calibration and maintenance of CPET equipment.

CPET equipment, especially when it uses breath-by-breath gas exchange analysis, requires meticulous attention to calibration procedures to assure accurate and reproducible measurements. It is good practice to calibrate the system before every test and to maintain a calibration log book so that long-term trends can be monitored.

Daily Calibration Procedures

The details of the calibration procedures will vary from system to system depending on the nature of the pressure/flow/gas sensors. The principles however pertain to all systems. The following require calibration before each test

- Barometric pressure
- Carbon dioxide sensor
- Oxygen sensor
- Flowmeter
- Phase Delay – i.e. integrated function: so that the airflow and gas concentration signals can be properly aligned

Tolerances are detailed in "Principles of Exercise Testing and Interpretation" (Wasserman et al 2011) and the American Thoracic Society/American College of Chest Physicians 2003 Statement on CPET(ATS/ARCP 2003).

Gas Analysers

Two point calibration with two precision gas mixtures which are typically:
5-6% CO2, 15% oxygen (i.e. approximates expired gas)

0% CO2, 21% oxygen (i.e. approximates atmospheric air)

Flowmeter

Verification of calibration of the flow or volume transducer can be performed with a calibrated 3L syringe. A range of flow rates should be performed to simulate the wide range of flow rates that occur in proceeding from rest to heavy exercise. Agreement in calculated volumes to within +/- 3% signifies adequate performance.

Intermittent Equipment Quality Control

Other calibration procedures need to be performed but on a less frequent basis.

These include:

1. Metabolic Simulators/Calibrators *(Huszczuk et al., 1990)*

These devices were developed to permit the quality control of the gas exchange measurements made by automated systems. A reciprocating piston is used to inject a precision gas mixture at a precisely measured rate thereby accurately simulating a known VE, VCO_2 and VO_2. Day to day variation of these should be in the region of +/- 3%. These devices use dry gas only and so do not assess the CPET system's ability to dry exhaled air or their humidity corrections. Furthermore, they are unable

to simulate the normal variation of breathing pattern waveforms and as such are most useful for detecting variations in the performance of the system (precision) rather than accuracy.

2. Physiological Validation

A healthy member of the laboratory staff, consuming a stable diet, performs a constant work rate test at sub AT workloads (e.g. 50,100,150W) at regular intervals (approximately monthly). Subsequent steady state values for VE, VO_2 and VCO_2 are then compared with the database and values outside the 95% CI for that individual should engender a thorough system-wide reassessment. The oxygen-consumption:work rate relationship does NOT change with training at sub AT work rates. Thus these values are independent of changes in physical activity or physical fitness.

3. Ergometer Calibration

These require dynamic calibration with the use of a dynanometer (torque meter) yearly or whenever the ergometer is moved. The calibration should be linear in the range of 0 to 400W. This can be performed by ergometer manufacturers or independent commercial vendors.

4. Timed expired Gas calibration

Time expired gas collections (Douglas Bag) made during steady state exercise can be used as a gold standard to validate ventilation and gas exchange measurements.

Data Averaging

Data averaging is applied to reduce the effect of aberrant breaths caused by coughing, for example, which are not reflective of the underlying physiological response. A variety of types of data averaging may be employed including time based averaging and breath based averaging. Each represents a compromise between avoiding excessive non-physiological noise without blunting the underlying physiological signal. It is important to select a method and use it consistently as the data averaging interval can effect the test results significantly (Matthews et al., 1987). Popular averaging methods for clinical testing include a 20 or 30 second time interval average, or the 'middle 5 of 7 breaths' average.

Data Presentation: Nine-Panel Plots

Interpretation of the exercise response is facilitated by using a graphical representation of the data. The data is usually transformed into a graphical

display of 9 panels on a single page containing 15 graphs (see below). Different panels provide information relevant to different physiological systems permitting diagnosis of the abnormal exercise response. The data can be displayed in a variety of formats and unfortunately there is not a consistent standard used in all cardiopulmonary exercise testing. It is important to use the plot which facilitates interpretation for your particular clinical application.

ERS eight- or nine-panel plot – Preferred for Perioperative CPET

The modified European Respiratory Society (ERS) format, which simplifies identification of the anaerobic threshold (Roca et al 1997) has been proposed as the preferred plot for perioperative CPET. It was originally presented as eight panels, but we have found it useful to include a ninth 'undesignated' panel that the user can format for local purposes. In particular it may be useful to plot the ventilatory equivalents and end tidal response against time, particularly in patients with noisy breathing for whom sequential points in the VO_2 response may not be sequential in time.

An example from the perioperative CPET Guidelines is outlined below.

Starting from top-left and proceeding to the right:

Panel 1: $\dot{V}CO_2$ vs $\dot{V}O_2$ - modified V Slope for AT interpretation

Panel 2: $\dot{V}O_2$ and VCO_2 vs work rate – VO_2/WR response and peak exercise, also allow identification of mask leak

Panel 3: HR and $\dot{V}O_2$/HR vs $\dot{V}O_2$ - Cardiac response to exercise and oxygen pulse

Panel 4: $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ vs $\dot{V}O_2$ - gas exchange efficiency and AT determination

Panel 5: $\dot{V}_E$ vs $\dot{V}CO_2$ - Ventilatory response to exercise

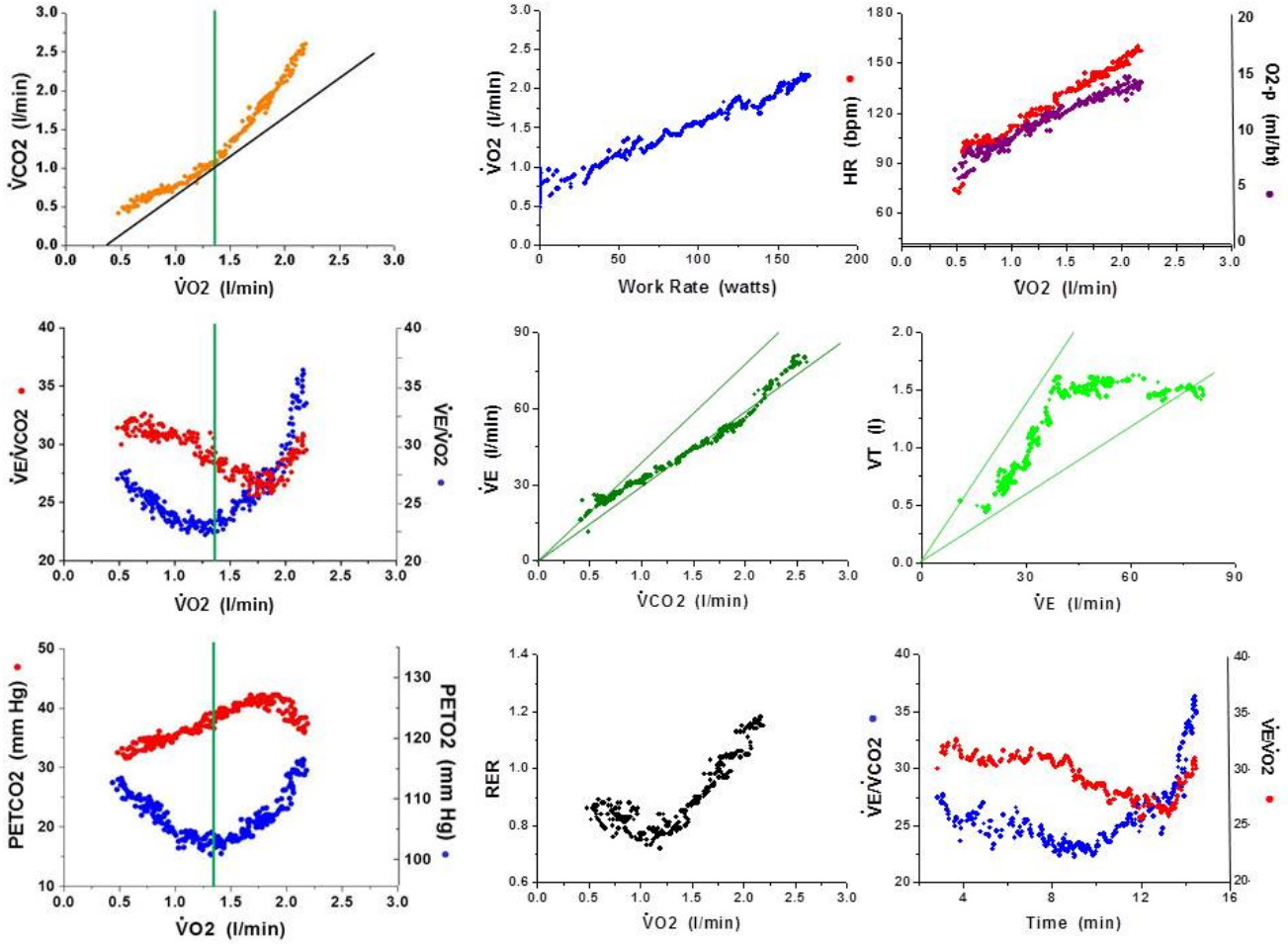
Panel 6: V_T vs $\dot{V}_E$ - Breathing reserve and ventilatory limitation

Panel 7: $P_{ET}CO_2$, $P_{ET}O_2$ vs VO_2 **–** useful for AT determination

Panel 8: RER vs $\dot{V}O_2$ (or time or work rate) – Identify hyperventilation, evaluate calibration and determine maximal effort.

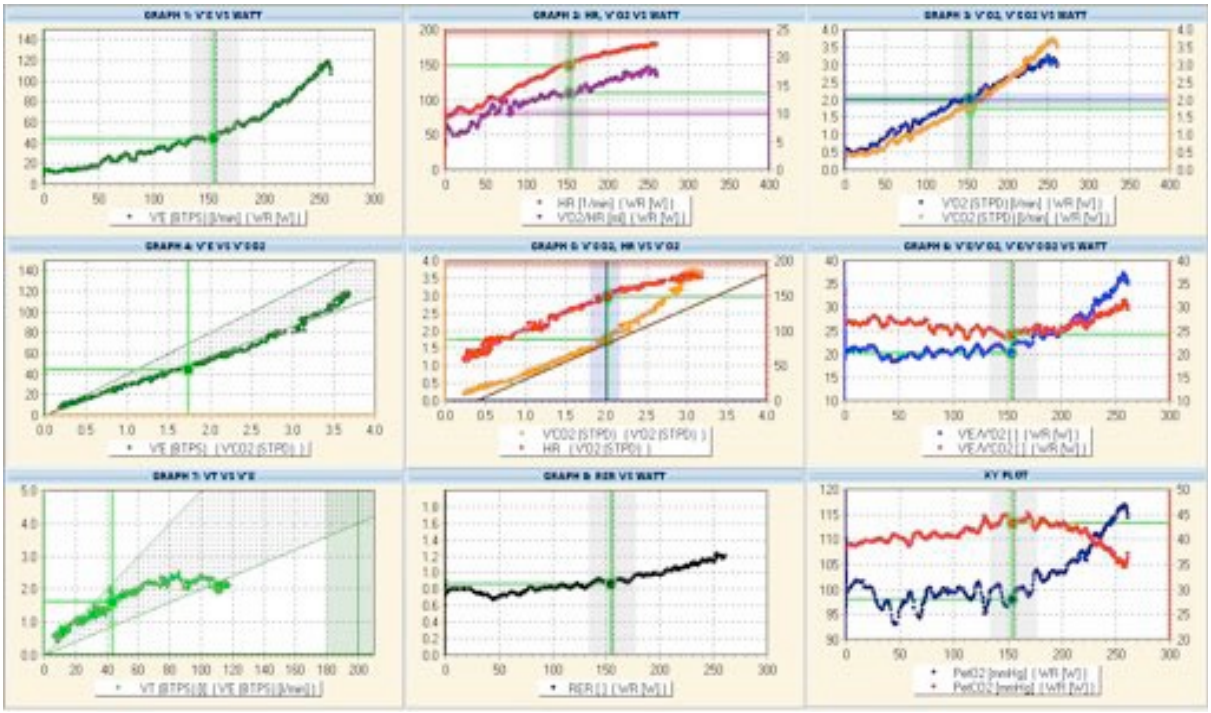
Panel 9: undesignated – e.g. $\dot{V}_E$ vs time or work rate or $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ and $P_{ET}CO_2$, $P_{ET}O_2$ against time.

The left-hand column of panels (i.e. Panels 1, 4 and 7) provide the information required for anaerobic threshold estimation. Panels 1-4 provide information on cardiovascular responses and limitations, Panels 4-7 provide information on ventilatory responses and limitations.



Harbor-UCLA nine-panel plot

This is the plot originally proposed by Karl Wasserman and his colleagues at UCLA-Harbour and is widely-used in diagnostic CPET. Recently the UCLA-Harbour plot has been modified. data display in diagnostic CPET although the original has recently been modified (e.g. Wasserman et al., 2011).



Starting from top-left and proceeding to the right:

Panel 1: $\dot{V}_E$ vs work rate (or time)

Panel 2: Heart rate (HR) and $\dot{V}O_2$/HR (oxygen pulse) vs work rate (or time)

Panel 3: $\dot{V}O_2$ and $\dot{V}CO_2$ vs work rate (or time)

Panel 4: $\dot{V}_E$ vs $\dot{V}CO_2$

Panel 5: $\dot{V}CO_2$ and HR vs $\dot{V}O_2$

Panel 6: $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ vs work rate (or time)

Panel 7: Tidal volume (V_T) vs $\dot{V}_E$

Panel 8: Respiratory exchange ratio (RER) vs work rate (or time)

Panel 9: $P_{ET}CO_2$, $P_{ET}O_2$ vs work rate (or time)

Thus:
Panel 3 provides information on exercise capacity
Panels 3, 6 and 9 provide information required for anaerobic threshold estimation
Panels 2, 3 and 5 provide information on cardiovascular responses and limitations
Panels 1, 4 and 7 provide information on ventilatory and breathing pattern responses and limitations
Panels 3 and 8 provide information on metabolic abnormalities

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Normal Values and Estimated Risk Thresholds

***Remember* Risk Thresholds are *estimates* & will vary for different procedures and will evolve as perioperative care evolves eg change in surgical technique and so are NOT fixed**

Variable and Units	Normal Value							Abnormal/Associated with risk (approximates for risk)
VO_2peak (ml/kg/min) Cycle ergometry Nb treadmill approx. 10% higher than cycle ergometer	Age	20-29 yrs	30-39 yrs	40-49 yrs	50-59 yrs	60-69 yrs	>70 yrs	• < 15ml/kg/min associated with increased perioperative risk • < 10 ml/kg/min very high risk
	M	42.0	30.8	28.0	26.1	22.9	21	
	F	30.8	22.2	20.1	18	16.6	16	
AT (ml/kg/min)	• 15-25ml/kg/min • Patients normal range 40-60% • Normal range 40-80% of VO_2peak							• < 9-10 associated with increased perioperative risk
VO_2/WR (ml/min/watt)	• 10 ml/min/watt • Normal range 9-12							• <9 abnormal (only linear portion of slope) • ↓ Gradient suggests impaired dynamic ventricular function • Abrupt change in gdnt suggests sudden impaired CO – ischaemia/arrhythmia/aortic stenosis/HOCUM
Peak HR (bpm)	• 220-age • Normal is 90% of predicted +/- 15bpm							• Note standard deviation 20-30

Peak Oxygen Pulse (ml/bt)	• VO_2= (SVxHR)(AV O_2 extraction ratio)
	• O_2 pulse = VO_2/HR= SV(O_2extraction ratio)
	• Normal > 80% of predicted approx:
	  ○ Males: 15-20
	  ○ Females: 10-15
								• Peak O_2 pulse reduced in heart failure and deconditioning
								• < 80% predicted value is abnormal
								• Early flattening of O_2 Pulse with ↑HR suggests acute SV limitation – ischaemia, arrhythmia, heart failure

Breathing Reserve (ml/L or % of MVV)	• 25-30% of MVV • estimate MVV from FEV1X40							• < 15% of MVV = ventilatory limitation – limiting resp disease
VE/VCO_2 at AT *or* Minimum VE/VCO_2	• 23-34 • Increases with age to max 32							• > 34 abnormal & associated with ↑ perioperative risk (heart failure/respiratory disease)
VE/VCO_2 slope	• 25 in young • Increases with age to max 32 • Gradient – exc kinetic phase & above RCP							• > 35 associated with V/Q mismatch – heart failure, pulmonary hypertenstion, respiratory disease • ↑perioperative risk in thoracics > 35
Resp Rate (bpm)	• 8-12 rest							
Rest ETO_2 (mmHg)	• 90-110 mmHg, Increases above AT							
Rest $ETCO_2$ (mmHg)	• 35-42 mmHg, • Decreases above the AT, but should not be falling at the AT							• Low resting values in acute hyperventilation, heart failure and LV
Rest RER	• 0.7-1.0							• < 0.7 ? calibration. > 1.0 ? hyperventilation
Peak RER	• > 1.15							• > 1.15 suggests physiologically maximal effort

Normal Values for CPET

Normal reference values provide the comparative basis for assessing the normalcy of exercise responses in patients and can significantly impact the clinical decision- making process.

Standardisation of normal reference values is necessary to facilitate interpretation and optimize clinical application. There is currently no published set of normal values directly relevant to an adult surgical population in the UK.

Requirements for an optimal set of normal values:

Population Characteristics: The subjects studied should possess characteristics similar to those of the patient population to which the reference values will be applied. Minimally, this should include age, sex and anthropomorphic considerations. Other important factors include: level of physical activity, racial composition and co-existing medical conditions.

- **Sample Size:** Sufficiently large to permit an appropriately powered sample size with a uniform distribution of subjects for sex and age groups – especially women and older individuals
- **Randomization**: avoid the potential bias seen when more physically active subjects volunteer for the study
- **Quality assurance of equipment and methodologies**
- **CPET protocol**: standardised and appropriate ramp protocol
- **Data averaging**: appropriate and standardised
- **Validation**: Reference equations must be validated in populations other than those used to generate the existing data

The currently available sets of reference values do not fulfil all these requirements. Among the most commonly used sets of reference values, there are significant differences in population characteristics, sample size, equipment, methodology and measurements. The issues with the currently available normal values are discussed in a recent systematic review (Takken et al. 2019). Several series of reference values for incremental exercise test indices including $\dot{V}O_2$peak have been published (Puente-Maestu 2007; Wasserman K 2011). The most widely used in clinical practice are those produced by Hansen and Jones (Hansen, Sue, and Wasserman 1984; Jones et al. 1985)(details below). These values were obtained from North American populations and have not

been specifically validated in a UK surgical population.

Jones et al 1985 (Jones et al, 1985)
- Small number: 50M, 50F (university workers/general population)
- Not randomized selection
- Smokers included
- Lack of definition of the confidence limits for individual or specified characteristics

Hansen et al 1984 (Hansen et al, 1984)
- Small number: 77M (American, asbestos exposed)
- Male only
- Retrospective
- Not randomized
- Smokers included
- Different racial groups included
- Lack of definition of the confidence limits for individual or specified characteristics

With these limitations in mind, reference values are useful to identify an abnormal response and the reference values used should be standardised within a CPET laboratory. A common convention used to relate measured $\dot{V}O_2$peak to reference values is: > 80% not abnormal or within the 95% confidence interval; 71-80% mildly reduced; 51-70% moderately reduced; and < 50% severely reduced (Puente-Maestu 2007). It should be appreciated however that the majority of clinical cohorts in surgical patients have reported $\dot{V}O_2$peak as an absolute value indexed to body weight rather than as a percentage of predicted value. As a consequence the published risk thresholds for surgical patients pre-operatively are absolute values of AT and $\dot{V}O_2$peak indexed to body weight. Indexing to body weight may have implications for patients at extremes of bodyweight, potentially over-estimating risk in the morbidly obese patient and under-estimating risk in cachectic patients. Despite this consideration, in morbidly obese bariatric patients AT indexed absolute body weight was more predictive of outcome than AT indexed to body surface area or to ideal body weight (Hennis et al. 2012). Caution should be used when interpreting exercise capacity values indexed to body weight in patients with a low BMI. Alternatives to indexing to absolute body weight include ideal body weight and body surface area.

Introductory Exercise Physiology for Cardiopulmonary Exercise Testing

Susan A Ward

Exercise intolerance results when an individual is unable to sustain a required work rate (WR) sufficiently long for the successful completion of the task. In the context of incremental exercise, exercise intolerance is reflected in a lower than predicted peak WR and peak oxygen uptake ($\dot{V}O_2$peak). It is task specific, with appreciably higher values of peak $\dot{V}O_2$ being attained for large muscle-mass exercise (e.g. cycling) than for smaller muscle-mass (e.g. arm cranking). Exercise intolerance is what restricts the patient with cardiorespiratory disease to a mild domiciliary regime. Its cause, typically, reflects failure in one or more of the components of systemic oxygen transport and muscle mitochondrial electron transport (which are linked at cytochrome oxidase). The consequences, typically, are perceptions of breathlessness and limb fatigue. However, the transition from simply recognizing a response abnormality to discerning its cause, and its consequences for physical activity, requires a clear understanding of the normal bioenergetic and associated physiological determinants of the individual systemic responses. These are typically characterised by means of incremental exercise challenges. Here, the responses of muscle metabolism are considered.

1. MUSCLE FORCE GENERATION

Skeletal muscle may be regarded as an ensemble of non-interacting, force-generating units or muscle fibres, which can be classified according to their contractile and histochemical properties. A motor neuron projecting to skeletal muscle innervates numerous muscle fibres (a motor unit). Each individual muscle fibre in a motor unit is of the same fibre type, with its motor neuron exerting an important trophic influence. However, the individual fibres of a motor unit are not spatially contiguous, but are distributed throughout the muscle.

The type 1 (or slow-twitch) muscle fibre has a relatively slow time to peak tension (determined in large part by the ability of its myosin-adenosine triphosphatase, ATPase), a high mitochondrial content, high concentrations of oxidative enzymes, a high capillary density, and the presence of myoglobin (thought to facilitate O_2 diffusion within the muscle). The type 1 fibre is thus fatigue-resistant, with high oxidative capacity and low glycolytic capacity. The type 2 (or fast-twitch) muscle fibre has a relatively fast time to peak tension as a result of its different myosin-ATPase activity, high glycolytic enzyme activity, high concentrations of glycogen and creatine phosphate, low mitochondrial

density and low levels of mitochondrial enzymes. It therefore has poor fatigue-resistance and oxidative capacity, but high glycolytic capacity. There are two sub-types: type 2a having some oxidative capacity, and type 2b (2x, in humans) with little or no oxidative capacity.

The physiological consequences of generating a given work rate during exercise are, in part, dependent on the fibre-type recruitment pattern for the force generation. For incremental exercise, the smaller type 1 motor units are recruited first, with the larger type 2 units only being recruited later in the test when progressively greater power generation is required (i.e. the 'size principle' of recruitment). The recruitment of type 2 fibres, while beneficial for force generation, introduces challenges for acid-base balance because of their reliance on anaerobic metabolism with its associated proton generation and metabolic (largely lactic) acidosis.

Respiratory and cardiac diseases may evidence skeletal muscle dysfunction. COPD, for example, is characterised by muscle wasting, which may involve factors such as disuse consequent to inactivity, inflammation, oxidative stress, hypoxemia and possibly apoptosis. Also, in some lower-limb muscles, selective loss of type 1 fibres in favour of type 2x has been reported in COPD, PAH and cardiac disease.

2. METABOLISM

Normally, a mixture of fat and carbohydrate is catabolised by muscle during exercise. Both are essentially equally efficient at providing ATP at the required rate for the task. In terms of weight, fat has a significant advantage over glycogen with respect to energy yield: 9.1 kcal/g compared with 3.8 kcal/g for glycogen. However, carbohydrate is the more efficient fuel for oxidative ATP yield, providing ~15% more energy per litre of O_2 utilized than fatty acids. However, carbohydrate oxidation results in ~25% more CO_2 production per unit of energy yield than free fatty acid oxidation. As WR increases, there is a preferential shift towards aerobic carbohydrate metabolism away from fatty acid oxidation, evident as an increasing respiratory quotient (RQ, tissue CO_2 production/tissue O_2 consumption) and respiratory exchange ratio (RER, pulmonary CO_2 output/pulmonary O_2 uptake). However, with further increases in WR, a point is reached where aerobic metabolism can no longer generate ATP at the required rate for the WR, the shortfall having to be met by anaerobic metabolism (i.e. above the anaerobic or lactate threshold) through recruitment of type 2 muscle fibres.

Under anaerobic conditions, carbohydrate is the obligatory metabolic substrate, with an ATP yield substantially lower than for the complete oxidation of carbohydrate (~12-fold less, from glycogen). Lactic acid results, which is almost completely dissociated (into lactate anions and

H^+) at normal pH. Buffering of a proportion of these H^+ ions by the carbonic acid–bicarbonate buffer system yields additional CO_2 (i.e. in excess of that produced by aerobic metabolism), with a consequent fall in muscle and blood [bicarbonate].

In COPD, for example, locomotor muscle oxidative capacity is compromised, reflective in part by the greater reliance on type 2 fibres. This is reflected in reductions of mitochondrial density, levels of mitochondrial transcriptional factors and coactivators (e.g. peroxisome proliferatoractivated receptors, peroxisome proliferator-activated *γ* coactivator-1) and enzyme activities (e.g. citrate synthase, succinate dehydrogenase, 3-hydroxyacyl-coenzyme A dehydrogenase, cytochrome oxidase). Whether these effects translate to reduced efficiency of oxidative phosphorylation and whole-body work efficiency, and whether they reflect disease-specific myopathic processes rather than simply the consequence of disuse is presently unclear, however. Importantly, the compromised oxidative capacity predisposes to premature anaerobiosis, expressed as a lower than predicted lactate threshold and peak $\dot{V}O_2$.

3. CARDIOVASCULAR SYSTEM

Cardiac output (CO, L/min) normally increases linearly with respect to O_2 uptake (, $\dot{V}O_2$L/min), with a slope of ~5 and an intercept of ~5 L/min (for cycle ergometry); the relationship appearing to be largely independent of gender or fitness. Thus, the arterio-mixed venous O_2 content difference ((a - $\bar{v}$)O_2) increases hyperbolically (or the mixed venous O_2 content decreases hyperbolically, as arterial O_2 content not normally falling during exercise at sea level). The linear CO increase in as a function of $\dot{V}O_2$ reflects increases in: (a) heart rate (HR) via a combination of initial parasympathetic withdrawal and later sympathetic activation at the sino-atrial node; and (b) stroke volume (SV) (during upright exercise, although not supine exercise for which SV is already at near-maximal levels at rest) resulting largely from the increase in pre-load consequent to central translocation of blood from the periphery at exercise onset (muscle pump).

The oxygen pulse (O_2-P) is useful for providing further inferences for cardiovascular function. That is:

$$\dot{V}O_2/HR = SV.\ (CaO_2 - C\bar{v}O_2) = O_2\text{-}P$$

O_2-P is higher in fit individuals at a given $\dot{V}_{O_2}$ as a result of the higher SV. As SV typically becomes constant early on in exercise, the subsequent time course of O_2-P will reflect that of the proportional change in tissue O_2 extraction.

As SV is higher the fitter the individual but CO at a given $\dot{V}O_2$ is largely independent of fitness, HR at a given $\dot{V}O_2$ is lower. Consequently, as maximum HR does not change with fitness (at a given age), then a higher range of WRs (and hence $\dot{V}O_2$) can be attained prior to the maximum HR being achieved. Conversely, in sedentary individuals and respiratory patients, HR at a given submaximal $\dot{V}O_2$ will be higher. It is often the case that the peak HR achieved by respiratory patients is less than predicted, consequent to exacerbated dyspnoeic sensations and premature cessation of exercise; the 'heart rate reserve' (HR max,pred – HR peak) can therefore be appreciable.

The increased CO is preferentially redistributed to the contracting muscle units, largely via local vasodilatation in the contractile units resulting from the influence of local metabolites on arteriolar smooth muscle cells. Although the precise details of this process are remain controversial, increases in intramuscular [K^+], [H^+], PO_2, osmolarity, temperature, catecholamine levels, [nitric oxide] and shear stress have all been implicated. The reason that blood flow does not increase in most other vascular beds, despite the increased driving pressure for flow (i.e. mean systemic blood pressure increases progressively as WR increases) is that vascular resistance increases as a result of the increased sympathetic drive. On the basis of the contracting muscles apparently having a greater potential to accommodate blood flow than is actually achieved at maximum exercise, CO is considered to provide the more important cardiovascular limitation to exercise in normal individuals.

4. VENTILATORY SYSTEM

Ventilation during incremental exercise responds in close proportion to pulmonary CO_2 output ($\dot{V}CO_2$), to regulate arterial PCO_2 ($PaCO_2$) and pH (pHa).

For alveolar ventilation ($\dot{V}_A$), the mass-balance relationship (*Fick principle*) is given by:

$$\dot{V}_A = 863 \times \dot{V}CO_2/PaCO_2$$

Consequently, to regulate $PaCO_2$, $\dot{V}_A$ must change as an appropriate linear function of $\dot{V}CO_2$. However, with respect to total ventilation (i.e. $\dot{V}_E$), the relationship is complicated by the ventilation of the physiological dead space which is conventionally accounted for by the dead-space fraction of the breath (V_D/V_T), such that:

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

Considerations of what constitutes an "appropriate" ventilatory response to exercise thus have to take account of three determining variables:

(a) $\dot{V}CO_2$ – the "metabolic" component,
(b) $PaCO_2$ – the ventilatory control "set-point", and
(c) V_D/V_T – reflecting the "efficiency" or, more properly, the "inefficiency" of pulmonary gas exchange.

The ventilatory requirement at a given work rare (WR) is increased when carbohydrate oxidation is the preferred route of ATP resynthesis, reflecting a ~25% higher CO_2 production per unit of energy yield than for free fatty acid oxidation. This has the potential to be problematic in respiratory disease, where ventilatory limitation is often a major contributor to exercise intolerance.

A far greater challenge is presented by elevations in V_D/V_T, however, consequent to ventilation-perfusion ($\dot{V}_A/\dot{Q}$) maldistribution and/or tachypnoeic patterns of breathing. Also, the arterial hypoxemia that results from $\dot{V}_A/\dot{Q}$ maldistribution, increased shunt fraction and/or diffusion impairments can result in hypoxic-mediated hyperventilation with consequent hypocapnia (i.e. a reduced $PaCO_2$ set-point). The ability to achieve the 'required' ventilation can be further compromised by abnormalities in lung and chest-wall mechanics and respiratory muscle function. This will exacerbate the associated degree of dyspnoeic sensation, often to limiting levels.

$\dot{V}_E$ has been widely demonstrated to change as linear function of $\dot{V}CO_2$ over a wide range of WRs during incremental exercise:

$$\dot{V}_E = m\,\dot{V}CO_2 + c$$

where the slope (m) equals $\Delta\,\dot{V}_E/\Delta\,\dot{V}CO_2$, and *c* is the $\dot{V}_E$- intercept.

$\dot{V}_E$ can also usefully be normalised with respect to $\dot{V}CO_2$ to yield the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$):

$$\dot{V}_E/\dot{V}CO_2 = m + c/\dot{V}CO_2$$

Re-arranging the previous equation in terms of the slope yields:

$$m = \dot{V}_E/\dot{V}CO_2 - c/\dot{V}CO_2$$

That is, $\dot{V}_E/\dot{V}CO_2$ will decline with increasing WR and $\dot{V}CO_2$ in a curvilinear or hyperbolic fashion, with $\dot{V}_E/\dot{V}CO_2$ asymptoting to a minimum value equal to *m* at very high WRs (for convenience, this is

often approximated by the $\dot{V}_E/\dot{V}CO_2$ value at the lactate threshold). This behaviour is the consequence of the small, positive $\dot{V}_E$-intercept on the $\dot{V}_E$- $\dot{V}CO_2$ relationship.

Both *m* and the minimum $\dot{V}_E/\dot{V}CO_2$ are influenced only by V_D/V_T and $PaCO_2$, and are often referred to as indices of "ventilatory efficiency": Indeed, when $PaCO_2$ is constant, $\dot{V}_E/\dot{V}CO_2$ will fall in exact proportion to V_D/V_T.

An important feature of the $\dot{V}_E$ response for rapid-incremental tests is that the linearity of the $\dot{V}_E$- $\dot{V}CO_2$ relationship is maintained beyond the lactate threshold; i.e. $\dot{V}_E$ changes in proportion to the *total* CO_2 load, which at these WRs represents the aerobic metabolic component supplemented by additional CO_2 released by the bicarbonate buffering of the lactic acidosis. That is, ***there is no evidence of $PaCO_2$ being reduced to provide respiratory compensation for the lactic acidosis;*** Rather, the respiratory compensation begins at higher WRs, when both $\dot{V}_E/\dot{V}CO_2$ and *m* begin to increase. The phase between the lactate threshold at the respiratory compensation point (RCP) is sometimes termed the phase of "isocapnic buffering". The cause of the delayed respiratory compensation with rapid WR incrementation is unclear, but has been argued by some to reflect sluggish $\dot{V}_E$ response kinetics to the falling arterial pH. This may reflect the existence of a time- or amplitude-related threshold for $[H^+]$ detection by carotid body chemoreceptors, possibly involving slow intracellular expression of the metabolic acidosis and/or slow signal transduction at the level of an H^+-sensitive type I voltage-sensitive tandem-P-domain K^+ channel.

As $\dot{V}_E$ is so closely linked to $\dot{V}CO_2$ and as $\dot{V}CO_2$ varies markedly with the WR incrementation rate (CO_2 being released by bicarbonate-buffering faster when WR is incremented more rapidly), $\dot{V}_E$ does not change in a usefully-constant relationship to $\dot{V}O_2$, and hence is rarely used in this context. The ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}O_2$), however, is used as an index of the additional ventilatory drive that attends the accelerated CO_2 output at work rates above the lactate threshold. Having declined throughout the moderate work-rate range in a similar fashion to $\dot{V}_E/\dot{V}CO_2$, $\dot{V}_E/\dot{V}O_2$ begins to increase *at* the lactate threshold reflective of the ventilatory consequences of the increased $\dot{V}CO_2$.

The normal stereotypical pattern of ventilatory response to incremental exercise is often not followed in disease conditions, because the determining variables - V_D/V_T and $PaCO_2$ - can change in complex and unpredictable ways. High values of the minimum $\dot{V}_E/\dot{V}CO_2$ are typical in respiratory and cardiac disease, and may reflect either a ***low* $PaCO_2$, *high* V_D/V_T or *both*.** Naturally, if one is known or may be plausibly assumed, then the high $\dot{V}_E/\dot{V}CO_2$ may be interpreted in terms of the other. It should be noted, however, that a high V_D/V_T does not necessarily reflect abnormal pulmonary function, as it is highly dependent on the pattern of breathing: rapid, shallow breathing, for example, yields a high V_D/V_T even in individuals with normal pulmonary function.

Breathing reserve and volume reserve

When a patient has ostensibly exercised to the limit of tolerance, it is useful to discern whether certain features of the systems that contribute to the energy exchange have reached their limit. Naturally, to make this judgement, it is necessary to have an index of what that limit is. For example, if the maximum voluntary ventilation (MVV) determined at rest is considered to be the maximum ventilation attainable, then the difference between this and the value actually attained at the end of exercise can be considered to represent the patient's "breathing reserve" (BR). The breathing reserve can be zero (or even less than zero, for example, in a patient who bronchodilates during exercise) either as a result of the MVV being low, as in patients with lung disease, or in normal but highly fit individuals who have a normal MVV but can achieve high rates of metabolic rate and hence of ventilation. Likewise, if the maximum expiratory airflow produced with a maximum expiratory effort is considered to reflect the greatest possible flow at a particular lung volume (this, of course, is not necessarily the case in patients with COPD), then failure to achieve these flows on a breath during exercise is reflective of a *lack of flow reserve*.

Similarly, a tidal volume that encroaches upon the inspiratory capacity is reflective of *lack of volume reserve.*

End-tidal PCO_2 and PO_2

End-tidal gas tensions ($P_{ET}CO_2$, $P_{ET}O_2$) during exercise, i.e. the values determined at the end of an exhalation, are easy to measure and extremely difficult to interpret. During exhalation, the instantaneous alveolar PCO_2 (P_ACO_2) continues to increase at a rate that is dependent on the mixed venous PCO_2 value (by diffusion) and to a level that depends on the duration of the exhalation. Thus, at the end of the

exhalation $P_{ET}CO_2$ will be higher than the mean P_ACO_2 (and the mean $PaCO_2$). During the subsequent inspiration, the instantaneous P_ACO_2 will decline back consequent to the diluting effects of the inspired air. This creates an intra-breath P_ACO_2 'oscillation' whose magnitude in the moderate-intensity domain (i.e. below the lactate threshold) becomes more marked as WR increases, because of the demands of increasing $\dot{V}CO_2$. The scenario for $P_{ET}O_2$ is essentially similar, but the mirror-image of PCO_2; i.e. with $P_{ET}O_2$ declining with increasing WR despite a reasonably stable arterial PO_2.

Thus, the profile of $P_{ET}CO_2$ during incremental exercise is normally such that it increases progressively up to the lactate threshold, with a subsequent period of stability (isocapnic buffering) above the lactate threshold before falling at the respiratory compensation point. In contrast, $P_{ET}O_2$ progressively decreases up to the lactate threshold, at which it starts to increase systematically (i.e. hyperventilation relative to O_2), accelerating further with the onset of respiratory compensatory.

These intra-breath oscillations in the alveolar gas tensions will also be reflected in arterial blood. However, the latter are not normally measured, as blood is sampled over several respiratory cycles yielding the *mean* of the $PaCO_2$ and $PaCO_2$ oscillations. Importantly, it should be recognised that the mean $PaCO_2$ will differ from the mean P_ACO_2 when pulmonary gas exchange is disturbed, e.g. a result of ventilation-to-perfusion inhomogeneities and/or right-to-left shunt. This leads to $P_{ET}CO_2$ being commonly less than $PaCO_2$ in patients with COPD for example. Consequently, $P_{ET}CO_2$ being *equal to or less th*an mean $PaCO_2$ during exercise is reflective of abnormal gas exchange.

End-tidal PCO_2 should *not* therefore be used to represent arterial PCO_2 in computing V_D/V_T. Doing so overestimates V_D/V_T in normal individuals (*tending to make abnormal what is normal*) and underestimates it in patients with lung disease (*tending to make normal what is abnormal*). Algorithms for estimating $PaCO_2$ from $P_{ET}CO_2$ are poor in normal individuals and do not work in patients with lung disease.

Thus, the profile of $P_{ET}CO_2$ with increasing WR is normally such that it increases progressively up to the AT, with a subsequent period of stability (isocapnic buffering) above AT before falling at the point of respiratory compensation. In contrast, $P_{ET}O_2$ progressively decreases up to the AT, at which it starts to increase systematically, accelerating further with the onset of compensatory hyperventilation.

5. EXERCISE INTENSITY

While the tolerable duration of a given WR is known to depend upon the intensity of the exercise being performed, there is to date no generally-agreed scheme for characterizing work intensity. Two widely-used procedures fail to meet the demands of critical scrutiny in this regard: the "met" increment ("mets" or "metabolic equivalents" are multiples of the resting metabolic rate, expressed in terms of $\dot{V}O_2$ in units of ml/min/kg) and the percentage of the maximal O_2 uptake (% $\dot{V}O_2$max). This is because the anaerobic threshold (AT), an important parameter characterizing the patient's ability to sustain exercise, *does not* occur at a common "met" increment or a % $\dot{V}O_2$max in different individuals. Consequently, different patients at the same "met" level can have markedly different degrees of metabolic acidaemia. Similarly, in normal individuals, while the lactate threshold occurs at approximately 50% of $\dot{V}O_2$max, the distribution is very large, with the normal range extending from 35% to at least 80%. Consequently, if the exercise intensity is assigned to a particular percentage of $\dot{V}O_2$max (e.g. 70%), then one patient could be exercising at a sub-AT WR and be "comfortable" whereas for another the WR could be greater than AT causing that patient to quickly exhaust.

Anaerobic or Lactate Threshold

The causes of the arterial blood [lactate] increase during incremental exercise that underlie the lactate threshold remain highly contentious. Three potential causes warrant consideration:

Limitation of O_2 availability: if O_2 is not utilized as the terminal oxidant in the mitochondrial electron transport chain, then lactate will be produced anaerobically to sustain the ATP production rate.

Enzymatic rate limitation: via factors involved in oxidative energy transfer - e.g. the number of mitochondria, the levels of certain Krebs cycle enzymes (e.g. succinate dehydrogenase), mitochondrial respiratory chain enzymes (e.g. cytochrome oxidase), and also of myoglobin (which facilitates O_2 diffusion).

Fibre-type composition of muscle: lactate production is more likely if an increment of WR is produced by a Type II fibre than by a Type I fibre; and Type I fibres tend to be recruited initially at low WRs, and as WR increases the Type II fibres are recruited proportionally more.

Often, patients may not be able to attain a $\dot{V}_{O_2}$max in the conventional sense (or the investigator may not wish to stress them to these levels) because of limitation by some system-related perception (e.g. dyspnoea, limb fatigue). However, as lactate threshold estimation does not require such efforts, it therefore provides, for example:

(a) an index of the functional status of the respiratory-circulatory-metabolic integration that allows exercise to be sustained aerobically;
(b) an index of sustainability for a particular task;
(c) a frame of reference for optimizing training protocols;
(d) an index of the efficacy of physical training, rehabilitation and drug interventions; and
(e) an essential component of decision-making strategies for elucidating the dominant system(s) responsible for exertional dyspnoea and exercise intolerance.

Therefore, the lactate threshold has proven to be a useful index of the onset of an exercise-induced metabolic acidaemia. One can forego the necessity for serial arterial blood sampling and even, in many cases, enhance the discriminability of the lactate threshold by utilizing a particular cluster of ventilatory and pulmonary gas-exchange variables, which provides noninvasive estimation of the lactate threshold. Lactate threshold discriminability, however, under "complicating" conditions such as progressive exercise-induced hypoxemia or impaired peripheral chemosensitivity with an associated high airway resistance, for example, remain to be established.

6. FATIGUE

The most widely accepted view of fatigue is that it reflects a decrement in a relevant index of muscle function, such as force or power generation, for a given degree of stimulation. However, as the pathway linking the central component of the muscular command and the actual intra-muscular mechanism of force generation is complex, the fatigue could arise at any one (or more) of the sites in the pathway: from the nerves which transmit the motor information, the neuromuscular junction, and the fibre itself, with the perception of the effort itself or some metabolite-related consequence of the contraction (involving the sensory cortex) also playing a role. The muscle itself, however, is considered to be a major locus for fatigue during exercise, with depletion of energy resources and/or increase in fatigue metabolites being contributory.

Intramuscular ATP concentration remains relatively high even with fatiguing exercise (except for high-intensity, short-duration activities such as sprinting). Also, limitations of substrate supply in the form of glycogen and fatty acids do not seem to play an appreciable role in the fatigue process. During prolonged exercise, however, substrate stores, especially glycogen, can play a decisive role in limiting exercise tolerance.

The decrease in intracellular pH during exercise is predominantly a result of the increased proton production associated with anaerobic glycolysis and lactate formation, i.e. it is not the result of lactic acid production *per se* with subsequent dissociation into its ionic constituents. The consequently low intramuscular pH has the potential to inhibit glycolysis through its influence on the regulatory enzyme phosphofructokinase, thus reducing the ATP production rate. However, as intramuscular ATP levels are maintained during most fatiguing exercise, this is thought to be unlikely to play an important role in decreasing force generation by the muscle. Intramuscular acidosis is unlikely to be the sole mediator of fatigue, as fatigue develops even more rapidly when glycolysis is prevented either experimentally or in conditions such as McArdle's Syndrome (myophosphorylase B deficiency). Under these conditions, the intramuscular pH is actually increased as the fatigue develops, as a result of the consequently high rate of creatine phosphate breakdown.

Increased levels of inorganic phosphate can also markedly reduce force generation in skinned skeletal muscle preparations, with the increase in monobasic phosphate thought by some to be more influential than the total inorganic phosphate. But intramuscular pH is also important in determining the proportion of the total inorganic phosphate in the mono- and dibasic forms. That is, as pH falls more of the inorganic phosphate will be in the monobasic form. The exercise-induced increase in free radicals and their related redox-active derivatives may also influence the fatigue process. It is known, for example, that exercise can induce oxidative stress as a result of high rates of reactive oxidant production at high WRs. Furthermore, the rate of production of reactive oxygen intermediates has been shown to correlate well with decrements of endurance performance in normal individuals. Beneficial effects of anti-oxidant supplementation, however, have proved difficult to demonstrate during whole-body endurance exercise, both in normal individuals and in respiratory patients. An alternative focus is the central nervous system. For example, increased circulating levels of the amino acid tryptophan have been proposed to lead to increased rate of cerebral serotonin formation and consequently induce ‘central’ fatigue.

7. VALUES ATTAINED AT THE LIMIT OF TOLERANCE

When a patient has ostensibly exercised to the limit of tolerance, it is useful to discern whether certain features of the systems that contribute to the energy exchange have reached their limit. Naturally, to make this judgement, it is necessary to have an index of what that limit is. For example, if the maximum voluntary ventilation (MVV) determined at rest is considered to be the maximum ventilation attainable, then the difference between this and the value actually attained at the end of exercise can be considered to represent the patient's “breathing reserve”

(BR). The breathing reserve can be zero (or even less than zero, for example, in a patient who bronchodilates during exercise) either as a result of the MVV being low, as in patients with lung disease, or in normal but highly fit individuals who have a normal MVV but can achieve high rates of metabolic rate and hence of ventilation. Similarly, if the maximum expiratory airflow produced with a maximum expiratory effort is considered to reflect the greatest possible flow at a particular lung volume (this, of course, is not necessarily the case in patients with obstructive lung disease), then failure to achieve these flows on a breath during exercise is reflective of a *lack of flow reserve*. Similarly, a tidal volume that encroaches upon the inspiratory capacity is reflective of *lack of volume reserve.* Whether a patient has significant "heart rate reserve" at maximum exercise is usually judged in the light of the expected maximum value for an individual of that age - unfortunately the variability of this expected age-dependent maximum heart rate is very wide.

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Exercise Capacity: VO_2max and VO_2peak

Denny Levett

Maximum exercise capacity is expressed as the VO2peak and VO2max. Although these terms are sometimes used interchangeably, this is incorrect and they have different definitions and physiological implications.

$\dot{V}O_2$**peak** is defined as the highest oxygen uptake ($\dot{V}O_2$) attained on a rapid incremental test at end-exercise. As such, it is reflective of the patient's 'best effort' on the CPET test but it may not reflect what was potentially *achievable* for that patient, i.e. it is not necessarily a physiologically maximal end-point. $\dot{V}O_2$**peak** may be influenced by patient volition.

The highest $\dot{V}O_2$ that **could** be attained by a patient is defined as the **maximum** $\dot{V}O_2$ ($\dot{V}O_2$**max):** 'the oxygen uptake during an exercise intensity at which actual oxygen uptake reaches a maximum beyond which no increase in effort can raise it' ie it is a physiological end point (Hill AV 1924). The physiological endpoint at $\dot{V}O_2$max is shown by demonstrating a plateau in $\dot{V}O_2$ in the face of increasing work rate, e.g. $\dot{V}O_2$ increasing by less than 2 ml/kg/min (Shephard et al. 1968) or less than 50% of the expected increase in $\dot{V}O_2$. $\dot{V}O_2$max reflects the attainment of a physiological limitation at one or more points in the O_2 transport pathway between the lungs and the site of the mitochondrial O_2 consumption at the cytochrome oxidase terminus of the electron transport chain. (Wagner 2000) Thus, dysfunction in the responses of the convective pulmonary or vascular O_2 fluxes, or in the diffusive pulmonary or muscle-tissue O_2 fluxes will result in an abnormally low $\dot{V}O_2$max.

$\dot{V}O_2$peak may reflect the patient's physiological limits but this can only be assumed if there is a plateauing of the $\dot{V}O_2$–WR relationship as the limit of tolerance is approached (Hawkins et al. 2007). Unfortunately not all individuals will exhibit a plateau during rapid incremental exercise even when they have attained a physiological maximum (Myers et al. 1989) (Day et al. 2003). In the absence of a plateau in the $\dot{V}O_2$ response, additional criteria may be used to help support $\dot{V}O_2$peak representing a physiologically maximal effort. These include:

- A peak HR within 10 bpm of the age-predicted maximum and
- A peak respiratory exchange ratio (RER) of more than 1.15 (Howley, Bassett, and Welch 1995).

It should be noted, however, that pathology or medication may affect either or both of these criteria in a patient population eg chronotropic incompetence

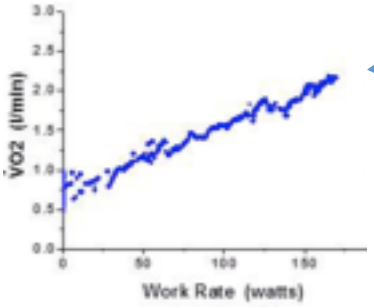
or beta blockade reducing the maximum heart rate response or respiratory-mechanical flow limitation limiting exercise before the generation of a metabolic acidosis in severe chronic obstructive pulmonary disease resulting in a peak RER < 1. ***Thus an effort may be physiologically maximal without these criteria being attained and consequently they should be interpreted with caution in the light of the entire exercise response.*** Furthermore, $\dot{V}O_2$peak may be affected by the patient's volitional exercise effort (Malhotra et al. 2016).

Despite the uncertainty regarding the presence of physiological limitation at $\dot{V}O_2$peak, importantly $\dot{V}O_2$peak has been shown to predict both postoperative morbidity and mortality in surgical populations and so has predictive clinical utility. In addition, it is both easy to identify and reproducible. A good patient effort is aided by familiarisation prior to the test as well as encouragement by the investigator during the later stages of the test.

$\dot{V}O_2$peak should be calculated as an averaged value over a short period extending from the end-exercise point back into the incremental phase to minimise the influence of breath-to-breath noise, i.e. capturing the true end-point without weighting it unduly towards submaximal breath values (Myers et al. 1990; Ward 2007). A reasonable choice is a period of ~20 seconds or ~3-5 breaths, with the value being reported, as an absolute value (ml/min or L/min) or indexed to bodyweight (ml/kg/min or L/min/kg).

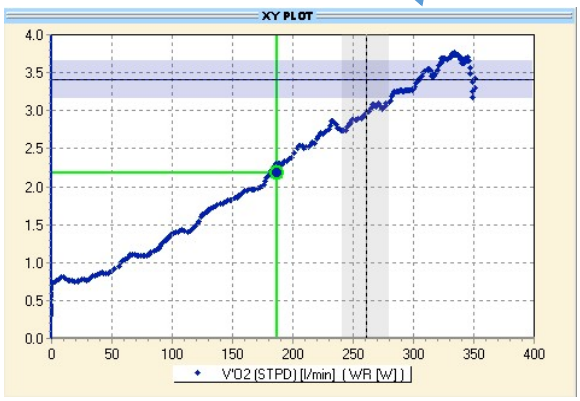
With good subject effort, $\dot{V}O_2$peak is independent of the work rate incrementation rate (Whipp 1994). However, peak work rate (WRpeak) is progressively greater the faster the rate of work rate increase (i.e. the greater the incremental ramp gradient) because of the underlying $\dot{V}O_2$ response kinetics (Whipp 1994). As a consequence, WRpeak varies with the ramp gradient and consequently is not as reproducible as $\dot{V}O_2$peak.

In summary $\dot{V}O_2$peak is a measure of maximal exercise capacity but may be affected by volition. Practically, $\dot{V}O_2$peak is easy to identify and reproducible. Importantly it predicts postoperative outcome in major surgical patients.



VO_2peak

VO_2max



VO_2 (l/min)

Work Rate (Watts)

$\dot{V}O_2$peak: **Definition, Measurement and Key Characteristics**
$\dot{V}O_2$peak is a metabolic rate defined as the highest $\dot{V}O_2$ attained on a rapid incremental test at end-exercise
$\dot{V}O_2$peak should be calculated as an averaged value over ~20 seconds or ~3-5 breaths
$\dot{V}O_2$peak should be reported as an absolute value (ml/min or L/min) and indexed to bodyweight (ml/kg/min or L/min/kg)
$\dot{V}O_2$peak is reproducible and is independent of the ramp gradient
$\dot{V}O_2$peak may be affected by patient volition
$\dot{V}O_2$peak is associated with post-operative morbidity and mortality in the majority of clinical cohorts

Identifying the Anaerobic Threshold

Susan Ward and Denny Levett (from Levett et al 2018)

The 'anaerobic' (or 'lactate') threshold (AT) is the highest oxygen uptake ($\dot{V}O_2$) at which arterial [lactate] does not show a systematic and sustained rise above resting levels. It provides an index of submaximal, sustainable exercise capacity and, if present, cannot be volitionally influenced by the patient. Importantly, it predicts post-operative complications and mortality in a wide range of surgical populations with more precision than other CPET variables.

The low AT values typical of chronic sedentary and cardiac and pulmonary diseases are typically ascribed to compromised O_2-dependent processes, although intramuscular enzymatic rate limitation and fibre-type recruitment may also be putative candidates.

The preferred approach in the clinical setting is to estimate AT non-invasively using a symptom-limited rapid incremental or preferably ramp exercise test. Not only are the demands on patients and technical support minimised, but better AT discrimination typically also results.

Anaerobic Threshold

The AT is a metabolic rate defined as the $\dot{V}O_2$ above which arterial [lactate] first begins to increase systematically during incremental exercise (Wasserman and McIlroy 1964). The lactate accumulates as a consequence of anaerobic glycolysis and its associated metabolic acidosis. However, the causes of this remain controversial (Brooks 1986; Connett 1996; Myers and Ashley 1997; Gladden 2004; Wasserman K 2011; Clanton, Hogan, and Gladden 2013; Lindinger 2008). The AT may also be termed the lactate threshold, lactic acidosis threshold, ventilatory threshold, first ventilatory threshold or gas exchange threshold, (Wasserman K 2011). **In the perioperative CPET literature, the term anaerobic threshold has been used consistently and is consequently preferred.**

The AT is conventionally estimated non-invasively from respired gas measurements using an incremental ramp exercise test (Whipp, Ward, and Wasserman 1986; ATS/ARCP 2003; Wasserman K 2011). The AT should be identified using a three point discrimination technique as described by Whipp and colleagues (Whipp, Ward, and Wasserman 1986). The modified V-slope or V-slope method can be used to identify the inflection point in the CO_2 output ($\dot{V}CO_2$) response and this should be supported by evaluating changes in the ventilatory equivalents and end-tidal partial pressures of oxygen and carbon dioxide to confirm hyperventilation with respect to oxygen but not to carbon dioxide (figure 3)(Beaver, Wasserman, and Whipp 1986; Whipp,

Ward, and Wasserman 1986; Sue et al. 1988). The methods used to identify the AT are summarised in the table below.

Criterion 1: 'Excess' $\dot{V}CO_2$ above the AT identified by the V-slope methods

The increasing anaerobic glycolysis above the AT results in a progressive metabolic acidosis. This is buffered to an extent by intra- and extra-cellular bicarbonate [HCO_3^-] in the exercising muscle. Consequently, arterial [HCO_3^-] starts to decrease as work rate increases above the AT, essentially mirroring the developing [lactate] increase. These buffering reactions generate CO_2 that is additional to the CO_2 produced during aerobic metabolism (i.e. 'excess' $\dot{V}CO_2$). Thus $\dot{V}CO_2$ is supplemented and the $\dot{V}CO_2$-$\dot{V}O_2$ relationship steepens at the AT causing an inflection in the $\dot{V}CO_2$-$\dot{V}O_2$response. The AT is identified by this inflection point in the $\dot{V}CO_2$-$\dot{V}O_2$ response and can be detected by the V-slope method (figure 1) or by the modified V-slope method (figure 2) (Beaver, Wasserman, and Whipp 1986), (Sue et al. 1988). This inflection point has been demonstrated to coincide with the first point of systematic increase in arterial [lactate] and decrease in arterial [HCO_3^-] and thus does not originate in either an acceleration of aerobic metabolism or in acute hyperventilation relative to CO_2. (Beaver, Wasserman, and Whipp 1986).

V-slope method (figure 1). At the start of the incremental phase of the test, the $\dot{V}CO_2$ response initially lags behind that of $\dot{V}O_2$ reflecting its slower response kinetics. The $\dot{V}CO_2$ then increases linearly with respect to $\dot{V}O_2$. The slope of the $\dot{V}CO_2$-$\dot{V}O_2$ relationship ($\Delta\dot{V}CO_2/\Delta\dot{V}O_2$) in this linear region has been termed S_1 and has a value typically slightly less than one in patients on a typical Western diet (i.e. reflecting the influence of the respiratory quotient (RQ)). Immediately above the AT, the gradient of the $\dot{V}CO_2$-$\dot{V}O_2$ relationship becomes steeper as excess $\dot{V}CO_2$ develops, with a slope termed S_2. **The AT is the point at which the linear regression lines of the S1 and S2 components intersect (the S_1-S_2 inflection point). The initial portion of the $\dot{V}CO_2$-$\dot{V}O_2$ relationship that is distorted by changes in body CO_2 stores – the 'kinetic' phase (approximately the first 60 seconds exercise) and the portion of the curve above the respiratory compensation point (RCP) (defined as > 15% change in gradient in $\dot{V}E$ - $\dot{V}CO_2$ relationship) are excluded from the analysis** (Beaver, Wasserman, and Whipp 1986). In those cases in which there is not a sufficiently linear S_2 region, the first detectable point of $\dot{V}CO_2$ acceleration relative to $\dot{V}O_2$ can be used as an alternative AT estimator.

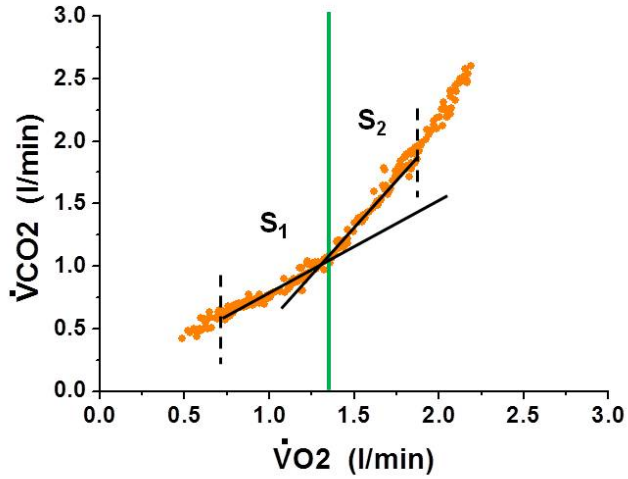


Fig 1 (From Levett et al, BJA 2018)

Example of a V-slope estimation in a normal individual. The $\dot{V}CO_2$-$\dot{V}O_2$ relationship is partitioned into linear S_1 and S_2 regions within the region of interest demarcated by the two vertical lines (left: to exclude the initial kinetic phase of response – approximately 60 seconds; right: to exclude respiratory compensation- > 15% change in gradient of the $\dot{V}E$-$\dot{V}CO_2$ relationship) (Beaver, Wasserman, and Whipp 1986). Their point of intersection (vertical green line) represents the point at which 'excess' $\dot{V}CO_2$ first becomes evident, and is taken to represent the AT.

Modified V-slope method (figure 2). The modified V-slope method is an alternative to the V-slope method which has particular utility when the $\dot{V}CO_2$-$\dot{V}O_2$ relationship cannot be partitioned into two linear segments (i.e a curvilinear response), which is common. This is based on the assumption that the S_1 slope should have a value of 1.0 or less (the highest RQ, for carbohydrate, being 1.0) and that the S_2 slope should have a value greater than 1.0 (because of excess $\dot{V}CO_2$). Ensuring that the $\dot{V}O_2$ and $\dot{V}CO_2$ axes are scaled identically, the effective S_1-S_2 inflection point can be estimated by 'running in' a unitary tangent or 'line of one' (i.e. line with gradient $\Delta\dot{V}CO_2/\Delta\dot{V}O_2$ = 1.0) from the right until it first impacts on the $\dot{V}CO_2$-$\dot{V}O_2$ relationship. The $\dot{V}O_2$ at which this occurs is taken as the AT, as all higher data points manifest excess $\dot{V}CO_2$ (i.e. with $\Delta\dot{V}CO_2/\Delta\dot{V}O_2$ > 1.0.)

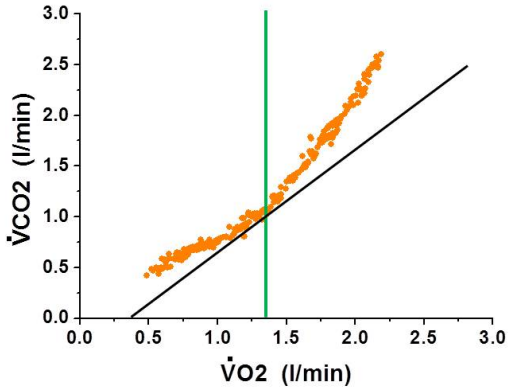


Fig 2 (From Levett et al, BJA 2018)

Example of a modified V-slope estimation for the normal individual depicted in Figure 2. A unitary tangent or 'line of one' (black line, with a slope, $\Delta\dot{V}CO_2/\Delta\dot{V}O_2$, = 1.0) has been 'run in' to the $\dot{V}CO_2$-$\dot{V}O_2$ relationship from the right. Its first point of impact (vertical green line) represents the point at which excess $\dot{V}CO_2$ first becomes evident, and is taken to represent the AT.

The V-slope and modified V-slope methods depend solely on the physicochemical reaction of metabolically-produced hydrogen ions with bicarbonate and as such the occurrence of the breakpoint is independent of chemoreceptor sensitivity and the ventilatory response to exercise. The V-slope methods are therefore particularly useful for AT estimation in conditions characterised by poor respiratory chemosensitivity or premature respiratory-mechanical limitation that prevent the development of a discernible $\dot{V}E$ response to excess $\dot{V}CO_2$ (e.g. chronic obstructive pulmonary disease) (Beaver, Wasserman, and Whipp 1986).

Criterion 2: Hyperventilation relative to O_2: the ventilatory equivalent for O_2 and end tidal PO_2 at the AT (figure 3)

At the AT the excess $\dot{V}CO_2$ generated from anaerobic glycolysis results in a proportional increase in $\dot{V}E$. There is no equivalent increase in $\dot{V}O_2$ at this point. Consequently $\dot{V}E$ driven by $\dot{V}CO_2$ and starts to increase at a greater rate with respect to $\dot{V}O_2$; i.e. hyperventilation relative to O_2. This is reflected in $\dot{V}E/\dot{V}O_2$ and alveolar end-tidal PO_2 ($P_{ET}O_2$) both starting to increase at the AT. Thus at the AT the following occur:

- **The $\dot{V}E/\dot{V}O_2 - \dot{V}O_2$ relationship having been flat or decreasing to a nadir begins to increase systematically.**

- **The $P_{ET}O_2$-$\dot{V}O_2$ relationship having been declining or flat begins to increase systematically.**

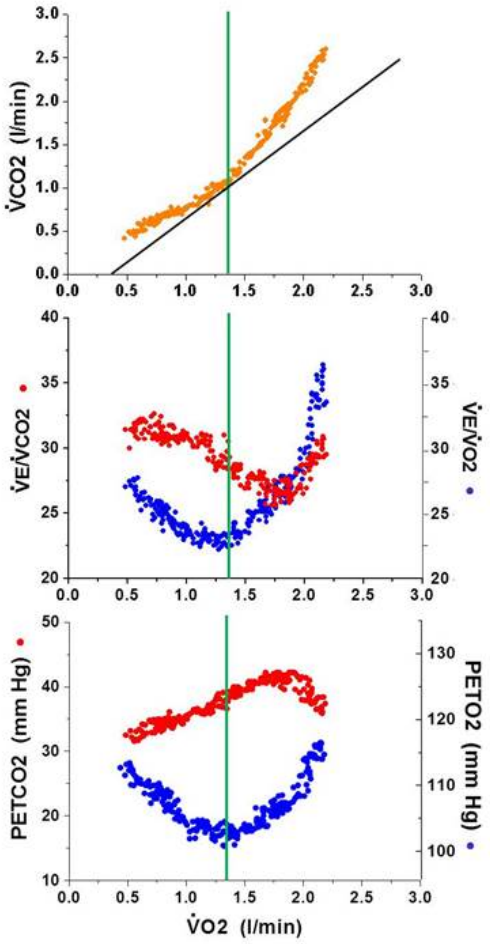


Figure 3 (From Levett et al, BJA 2018)

Example of comprehensive AT estimation for the normal individual depicted in Figures 2 and 3. The top panel presents the $\dot{V}CO_2$-$\dot{V}O_2$ relationship, with the modified V-slope index of AT estimation. The middle panel presents the responses of the ventilatory equivalents for CO_2 and O_2 ($\dot{V}E/\dot{V}CO_2$, $\dot{V}E/\dot{V}O_2$) expressed as a function of $\dot{V}O_2$. The $\dot{V}E/\dot{V}O_2$ relationship having been flat begins to increase systematically while the $\dot{V}E/\dot{V}CO_2$, continues to decrease. The bottom panel presents the responses of the end-tidal PCO_2 and PO_2 ($P_{ET}CO_2$. $P_{ET}O_2$) expressed as a function of $\dot{V}O_2$. $PETO_2$ increases without a reciprocal decrease in $PETCO_2$ because respiratory compensation for metabolic acidosis causing a reduction in $PaCO_2$ does not occur until several minutes later for rapid incremental exercise tests. The estimated anaerobic threshold is marked with the vertical green line on all three plots.

Criterion 3: No hyperventilation relative to CO_2: the ventilatory equivalent for CO_2 and end-tidal PCO_2 at the AT (figure 4)

The $\dot{V}CO_2$-$\dot{V}O_2$ (V-slope) relationship and hyperventilation relative to oxygen do not alone provide a sufficiently rigorous criterion for AT estimation. It is important that non-specific hyperventilation (with an attendant fall in arterial PCO_2 ($PaCO_2$)) due to factors such as anxiety, pain or arterial hypoxaemia is first excluded as a cause of the excess $\dot{V}CO_2$ identified by the V-slope method. This requires examination of the ventilatory consequences of the excess $\dot{V}CO_2$. Below the AT, $\dot{V}E$ is proportional to $\dot{V}CO_2$ such that alveolar end-tidal PCO_2 ($P_{ET}CO_2$) and arterial PCO_2 remain stable. This proportionality is initially maintained above the AT because the normal compensatory hyperventilation expected with an exercise-induced metabolic acidosis (which lowers the $PaCO_2$ and thereby compensates for the falling pH) does not occur immediately at the AT for rapid incremental exercise (Whipp 1991; Whipp 2008; Ward 2013). Rather, respiratory compensation is delayed to a somewhat higher work rate – defined as the respiratory compensation point (RCP). The exact location of the RCP depends on factors such as the work rate incrementation rate and peripheral (carotid body) chemoreflex responsiveness (Wasserman et al. 1973; Whipp, Davis, and Wasserman 1989). This delay, which is possibly consequent to slow carotid chemosensory response kinetics generates a phase of 'isocapnic buffering' between the AT and RCP within which neither $P_{ET}CO_2$ nor $PaCO_2$ decline i.e. there is no immediate hyperventilation relative to CO_2 at the AT (Whipp, Davis, and Wasserman 1989). To ensure that the inflection point identified as the AT is not as a result of non-specific hyperventilation that could be from pain, hypoxaemia or primary hyperventilation syndrome, hyperventilation relative to CO_2 at the AT must be excluded by confirming the following:

1. **$\dot{V}E/\dot{V}CO_2$ remains constant or continues to decrease at the AT as the $\dot{V}E/\dot{V}O_2$ starts to rise systematically.**
2. **The absence of a fall in $P_{ET}CO_2$ at the AT. This is because ventilatory compensation for the metabolic acidosis above the AT which causes a reduction in $PaCO_2$ does not occur until several minutes later during rapid incremental exercise tests (i.e.at RCP).**

Above the RCP towards the end of the exercise test, the $\dot{V}CO_2$-$\dot{V}O_2$ and $\dot{V}E$-$\dot{V}CO_2$ relationships steepen, as respiratory compensation develops in response to the metabolic acidosis of exercise; i.e. reflecting the loss of CO_2 from arterial stores as $PaCO_2$ is driven down by hyperventilation.

Summary (See Table Below)

In summary, rigorous AT estimation requires that support be sought not only from excess $\dot{V}CO_2$ but also from the profiles of the ventilatory equivalents and end-tidal partial pressures for O_2 and CO_2 to establish the development of hyperventilation relative to O_2 but not with respect to CO_2. This requires the demonstration that, coincident with the modified V-slope break point, $\dot{V}E/\dot{V}O_2$ and $P_{ET}O_2$ start to increase (i.e. hyperventilation relative to O_2), but with no coincident increase in $\dot{V}E$ / $\dot{V}CO_2$ and decrease in $P_{ET}CO_2$ (i.e. no hyperventilation relative to CO_2). In practice, it can be the case that noisiness in the data set may preclude reliable discrimination of all three break points simultaneously, in which case greater weight should be placed on V-slope indices.

Anaerobic Threshold (AT) – Definition, Identification and Key Characteristics
The AT is a metabolic rate, and is defined as the $\dot{V}O_2$ above which arterial [lactate] first begins to increase systematically during incremental exercise reflecting increased glycolysis. It is expressed in ml/kg/min or ml/min.
The AT should be identified using a three-criterion discrimination approach
AT Criterion 1 - Identifying excess $\dot{V}CO_2$ relative to $\dot{V}O_2$ above the AT by: • **Modified V-slope** (figure 2): The tangential breakpoint in the $\dot{V}CO_2$ - $\dot{V}O_2$ relationship from a line with a gradient of one ('line of one;' $\Delta\dot{V}CO_2/\Delta\dot{V}O_2$ = 1.0). The breakpoint is identified by moving the 'line of one' from the right until it first impacts on the $\dot{V}CO_2$-$\dot{V}O_2$ relationship. The $\dot{V}O_2$ at which this occurs is taken as the AT. **OR** • **V-slope** (figure 1): The inflection point in the $\dot{V}CO_2$-$\dot{V}O_2$ relationship identified as the intersection point of the linear regression lines of the S1 (below AT) and S2 (above AT) components. The initial kinetic portion of the relationship and the portion above the respiratory compensation point are excluded from the linear regression.
AT Criterion 2: Identify hyperventilation relative to oxygen The $\dot{V}E/\dot{V}O_2$-$\dot{V}O_2$relationship, having been flat or decreasing, begins to increase and does not return to baseline. • The $P_{ET}O_2$-$\dot{V}O_2$relationship, having been declining or flat, begins to increase and does not return to baseline.
AT Criterion 3: Exclude hyperventilation relative to CO_2 At the AT inflection point identified by criteria 1 and 2: • The $\dot{V}E/\dot{V}CO_2$-$\dot{V}O_2$ relationship remains constant or continues to decrease at the point where $\dot{V}E/\dot{V}O_2$ starts to increase systematically. • There is no reciprocal decrease in $P_{ET}CO_2$ at the point where $P_{ET}O_2$ begins to increase systematically.

What is the optimal criterion for AT discrimination?

It is most appropriate that the V-slope approach is used in conjunction with the ventilatory equivalent and end-tidal gas tensions to establish a cluster of variables which cohere with each other to provide the best possible confidence in the estimation. That is, it is important to emphasise that the demonstration of a break-point in the $\dot{V}CO_2$-$\dot{V}O_2$ relationship cannot, on its own, be confidently ascribed to the onset of a metabolic (lactic) acidosis, as non-specific hyperventilation due to factors such as anxiety, pain or hypoxaemia cannot be ruled out. This requires additional ventilatory-based criteria to demonstrate the onset of hyperventilation relative to O_2 at AT, but not to CO_2 - despite a falling arterial pH.

What is the optimal work-rate incrementation rate for AT discrimination?

It is conventional practice that the incremental phase duration of a ramp test should be of the order of 10-12 minutes; i.e. ~15-20 Watts/min in normal individuals, but less in unfit individuals and most patients ~10-15 watts/min. Importantly, while AT is largely independent of the WR incrementation rate (being measured as a $\dot{V}O_2$), the corresponding WR at which AT is achieved becomes progressively greater the more rapid the WR incrementation rate (as is also the case for $\dot{V}O_2$ peak).

Slow WR incrementation rates are not recommended as they not only induce boredom and seat discomfort because of the prolonged test duration, but may also compromise the ability to convincingly discriminate AT. This is the consequence of a slower rate of arterial [lactate] increase above AT, a slower rate of arterial [HCO_3^-] decrease and a smaller contribution to $\dot{V}CO_2$ (the increase in $\dot{V}CO_2$ from these buffering reactions being a function of the rate at which arterial [HCO_3^-] is falling), R and therefore $\dot{V}_E$. The change of slope between the S_1 and S_2 segments of the V-slope plot will therefore be smaller and harder to discern with confidence ('false negative'). Also, the onset of respiratory compensation will be far less delayed relative to AT, constraining the range of isocapnic buffering and impairing the ability to conclusively rule out non-specific hyperventilation as the cause of threshold behaviour $\dot{V}_E$.

Automated AT

The V-slope method is utilised in the majority of commercial metabolic carts to identify an automated AT. These automated ATs should only ever be used as a guide and should be interpreted with caution. In the presence of a curvilinear $\dot{V}CO_2$-$\dot{V}O_2$ relationship linear regression may not accurately identify the AT. In addition, care should be taken to ensure that the kinetic phase at

the start of the incremental ramp and the portion of the data above the respiratory compensation point are excluded from the regression analysis which requires manual interrogation of the data. Finally, automated V-slope methods do not utilise confirmation of the AT by the ventilatory criteria discussed above and thus particularly in the presence of noisy data may not accurately identify the AT.

False positives or pseudo-thresholds: Hyperventilation

Transient volitional hyperventilation occurring just prior to the start of a ramp exercise test or in its early stages can compromise AT estimation and cause a pseudothreshold, where the criteria for an AT can be identified but before the onset of the exercise-induced metabolic acidosis. (Whipp 2007) In such circumstances, acute hyperventilation causes acute wash-out of CO_2 from rapidly-exchanging body stores. Consequently, at the start of the test, a greater-than-normal proportion of the metabolic CO_2 production will initially be diverted into the depleted body stores to recharge them back to normal levels, with less therefore reaching the lungs and less being cleared at the mouth. Over this period, the $\dot{V}CO_2$-$\dot{V}O_2$ slope and RER are thus abnormally low. When the CO_2 stores have subsequently been repleted, $\dot{V}CO_2$ and RER will be restored towards normal levels, resulting in a relative steepening of the $\dot{V}CO_2$ - $\dot{V}O_2$ relationship and an apparent threshold. This relative acceleration of $\dot{V}CO_2$ relative to $\dot{V}O_2$ will, in turn, elicit proportional increases in $\dot{V}E$ and therefore $\dot{V}E/\dot{V}O_2$, but no change in $\dot{V}E/\dot{V}CO_2$. This creates threshold-like behaviour (i.e. the standard non-invasive criteria for AT discrimination are met) but at a time when arterial [lactate] has not yet started to increase. The clue to pseudo-threshold behaviour is a concurrent systematic fall in RER to abnormally low values (consequent to the transiently high CO_2 storage rate) immediately prior to the supposed threshold. Thus the presence of prolonged volitional hyperventilation immediately prior to or at the start of a ramp test requires the AT estimate to be interpreted with caution.

Diagnostic CPET: Common Respiratory Pathology

Marshall Riley

Several abnormalities occur in patients with respiratory disease on cardiopulmonary exercise testing:

Exercise capacity is often reduced shown by a reduced maximum VO_2. The anaerobic threshold may not be reached in patients with severe respiratory impairment as respiratory mechanics limit exercise before there is sufficient cardiovascular stress to result in significant lactic acidosis. In patients with less severe impairment, the anaerobic threshold is likely to be low in absolute terms, reflecting deconditioning. The respiratory exchange ratio (VCO_2/VO_2) at peak exercise tends to be low, often failing to rise above 1.0. The low respiratory exchange ratio reflects a low rate of anaerobic metabolism.

The ventilatory reserve, i.e. the difference between maximum voluntary ventilation and the maximum ventilation used during the exercise test, is typically low. Ventilation is the product of tidal volume and respiratory rate, and patients with different lung diseases augment their ventilation in different patterns. Patients with fibrosis tend to reach a maximum tidal volume early during exercise, further increases in ventilation being achieved by increasing respiratory rate. Patients with obstructive lung disease tend to augment both tidal volume and respiratory frequency throughout exercise. Ventilatory efficiency is low in many respiratory disorders and this is reflected in elevated ventilatory equivalents for CO_2 and O_2 (VE/VCO_2 and VE/VO_2). There may also be oxyhaemoglobin desaturation with exercise, particularly in patients with lung fibrosis.

Exercise flow-volume loops may be compared with the maximum resting loop to study ventilation further. Patients with lung fibrosis exhibit volume limitation, consistent with their inability to augment tidal volume. Patients with obstructive lung disease often show expiratory flow limitation. However, obstructive lung disease may also result in volume limitation as well as flow limitation. Due to expiratory flow limitation, the volume exhaled during each breath may fail to match the volume inhaled. A progressive increase in functional residual capacity during exercise, known as dynamic hyperinflation may result. Dynamic hyperinflation may be severe enough to lead to volume limitation in obstructive lung disease.

Diagnostic CPET: Common Cardiac Pathology

Marshall Riley

Like respiratory disease, cardiac diseases exhibit certain abnormal patterns on cardiopulmonary exercise testing:

Patients with cardiac disease often have reduced exercise capacity, evidenced by a reduction in maximum VO_2. Anaerobic threshold is typically low in absolute terms, although in patients with moderate or severe heart failure often occurs at quite a high percentage of the reduced maximum VO_2. The pattern of increase in VO_2 with work rate may be helpful. Normally, during exercise, VO_2 increases at a rate of approximately 10 ml min^{-1} W^{-1}. In cardiac failure, but especially in pulmonary hypertension, there is often a reduction in the rate of increase of VO_2 at work rates above the anaerobic threshold. This reduction in the rate of increase of VO_2 is likely to be due to increasing anaerobic metabolism. In addition, in ischaemic heart disease, an abrupt decline in ventricular function at the onset of ischaemia may be shown by a sudden marked decline in the rate of VO_2 increase with work rate. This decline in VO_2 – work rate slope may precede the appearance of ST segment abnormalities. The respiratory exchange ratio (VCO_2/VO_2) at peak exercise tends to be above 1.0, reflecting significant anaerobic metabolism.

The ratio of VO_2 to heart rate, the oxygen-pulse, reflects both stroke volume and systemic O_2 extraction. Where stroke volume is decreased in cardiac disease, the oxygen-pulse is usually also low. In coronary artery disease, the oxygen-pulse may decline abruptly at the onset of ischaemia, reflecting an ischaemia-induced fall in stroke volume. The corollary of a low oxygen-pulse is an abnormally high rate of increase in heart rate with respect to VO_2. In many patients with cardiac disease, not only those taking heart rate limiting drugs, there is a reduced maximum exercise heart rate, known as chronotropic incompetence.

There is typically a normal or elevated ventilatory reserve in patients who have cardiac disease and normal pulmonary function. Nonetheless, ventilatory efficiency is low in cardiac failure due to an elevated dead-space tidal volume ratio. The elevated dead-space tidal volume ratio is reflected in elevated ventilatory equivalents for CO_2 and O_2, and low end-tidal CO_2. However, unlike patients with lung disease, patients with cardiac failure do not generally exhibit oxyhaemoglobin desaturation. Patients with pulmonary hypertension exhibit many of the features of patients with cardiac disease, but are notable for dramatic elevations in ventilatory equivalents, and some degree of oxyhaemoglobin desaturation. The latter is thought to be due to very low mixed venous pO_2 in association with the normal anatomical right

to left shunt. In addition, some patients with pulmonary hypertension may open up a patent foramen ovale during exercise, and this opening is reflected in sudden oxyhaemoglobin desaturation and further elevation in ventilatory equivalents.

Indications and Contraindications for Perioperative CPET (PCPET)
POETTS Guidelines

INDICATIONS

PCPET is indicated to provide an objective assessment of exercise capacity preoperatively and to identify the causes of exercise limitation**.** This information may be used to assist clinicians and patients in decisions about the most appropriate surgical and non-surgical management during the perioperative period. Studies support the use of PCPET for risk prediction in major abdominal surgery (Snowden et al. 2010; Wilson et al. 2010b; Older 1999), colorectal surgery (West, Parry, et al. 2014; West, Lythgoe, et al. 2014), urological surgery (Prentis et al. 2013; Wilson et al. 2010b), hepatobiliary surgery (Snowden et al. 2010; Ausania et al. 2012), liver transplantation (Prentis et al. 2012), bariatric surgery (Hennis et al. 2012; McCullough et al. 2006), vascular surgery (Carlisle and Swart 2007; Ausania et al. 2012), thoracic surgery (Brutsche et al. 2000; Benzo et al. 2007; Brunelli et al. 2009) and oesophageal-gastric surgery (Forshaw et al. 2008; Older, Hall, and Hader 1999; Jack et al. 2014) and also for guiding exercise-training interventions prior to and/or immediately after surgery (West et al. 2015; Barakat et al. 2016) The evidence supporting PCPET is continuously evolving and consequently the indications for PCPET require regular reassessment.

INDICATIONS FOR CPET INCLUDE

- To estimate the likelihood of perioperative morbidity and mortality and contribute to preoperative risk assessment.
- To inform the processes of multidisciplinary shared decision-making and consent.
- To guide clinical decisions about the most appropriate level of perioperative care (ward vs. critical care).
- To direct pre-operative referrals/interventions to optimise comorbidities
- To identify previously unsuspected pathology.
- To evaluate the effects of neoadjuvant cancer therapies including chemotherapy and radiotherapy.
- To guide prehabilitation and rehabilitation training programmes.
- To guide intra-operative anaesthetic practice.

CONTRAINDICATIONS

Published contraindications to CPET have addressed its use as a diagnostic and prognostic tool for patients with cardiac or respiratory disease, to monitor disease progression in chronic cardiorespiratory disease, to quantify exercise capacity and to evaluate likely causes of exercise intolerance. (ATS/ARCP 2003; Wasserman K 2011) These are largely based on the expert opinion of respected authorities.

Contraindications and relative contraindications to exercise testing in the perioperative setting are summarised in the table below. These are based on recommendations in other areas of CPET modified for the perioperative context to take into account the specific patient population. Patients with relative contraindications should be directly supervised by a physician. For relative contraindications to exercise testing, the risks and potential benefits of undertaking PCPET should be considered on a patient-by-patient basis both before and during the test. If the risk-benefit relationship changes as the test progresses, the test can be terminated early – a submaximal test. For example, in a colorectal cancer patient with newly identified asymptomatic severe aortic stenosis, PCPET may be considered to delineate the functional impairment caused by the valve stenosis. The test may help determine the relative priority of valve replacement and tumour resection. However, if the patient developed chest pain or hypotension during the test, this would indicate critical stenosis and an increased risk of syncope and should lead to test termination.

Table 1: Absolute and relative contraindications for PCPET

Absolute Contraindications	Relative Contraindications
Acute myocardial infarction (3-5 days)	Untreated left main stem coronary stenosis
Unstable angina	Asymptomatic severe aortic stenosis
Uncontrolled arrhythmia causing symptoms or haemodynamic compromise	Severe untreated arterial hypertension at rest (>200 mmHg systolic, > 120 mmHg diastolic)
Syncope	Tachyarrhythmias or bradyarrhythmias
Active endocarditis	Hypertrophic cardiomyopathy
Acute myocarditis or pericarditis	Significant pulmonary hypertension
Symptomatic severe aortic stenosis	Thrombosis of the lower extremity until treated for a minimum of 2 weeks.
Uncontrolled heart failure	Within 2 weeks of acute symptomatic pulmonary embolus
Suspected dissecting or leaking aortic aneurysm	Abdominal aortic aneurysm > 8.0 cm
Uncontrolled asthma	Electrolyte abnormalities
Arterial desaturation at rest on room air < 85 %	Advanced or complicated pregnancy

*Adapted from (ATS/ARCP 2003)

Legend: patients with relative contraindications should be discussed with an appropriate clinician and the risks and benefits of testing evaluated. Patients with relative contraindications should be directly supervised by a physician.

Perioperative CPET Service Structure and Supervision and Training in CPET

Perioperative Exercise Testing and Training Society Guidelines

(Levett et al. 2018)

A PCPET service should be managed and led by an individual expert in PCPET. PCPET expertise incorporates an understanding of the equipment and exercise protocols, expertise in exercise physiology and pathophysiology and an understanding of perioperative risk.

PCPET testing and interpretation can be divided into three distinct stages:
Stage One: **CPET Practitioner**: The practicalities of test performance, including the exercise protocol, equipment operation and maintenance and quality control.
Stage Two: **Advanced CPET Practitioner**: Integration of the physiological data to provide a comprehensive interpretation of the patient's exercise capacity and the main causes of exercise limitation, including the identification of undiagnosed pathology.
Stage Three: **CPET Competent Perioperative Physician:** Interpretation of the implications of the patient's exercise limitation for his/her perioperative risk and formulating recommendations for pre-operative interventions and perioperative care.

The competencies required for each of these stages are different. Within a PCPET service different individuals may perform each of the three stages of the testing and interpretation process. Alternatively, a single individual may be able to perform all three stages. Stages one and two may be performed by non-clinicians, but clinical expertise in perioperative medicine is required for stage three. Competence and expertise in each stage of the PCPET process should be defined by specific training and documented experience, rather than defined medical roles (e.g. doctor, nurse, clinical physiologist).

All competent PCPET practitioners and advanced practitioners must be able to identify and manage adverse events in relation to PCPET by discriminating between normal and abnormal responses to exercise including abnormal symptoms, hypertension, hypotension, abnormal arterial O_2 saturation (measured by pulse oximetry (SpO_2)) and electrocardiographic (ECG) evidence of arrhythmia and ischaemia(Myers et al. 2009). PCPET practitioners and advanced practitioners must have appropriate knowledge and experience in first aid and resuscitation (Myers et al. 2009).

A minimum of two members of staff should be directly available for every test, one of whom should be a competent CPET advanced practitioner. At least one member of staff should have current Intermediate Life Support competence and the other a minimum of current Basic Life Support with Automated External Defibrillator (AED) competence (defined by Resuscitation Council UK criteria (www.resus.org.uk)) (Myers et al. 2009). A resuscitation team with advanced life support skills (cardiac arrest team or paramedic team) must be immediately available (Myers et al. 2009). A physician should be available to review any patient who develops complications during a test (Myers et al. 2009). High-risk CPET tests, including tests where relative contraindications are present, should be directly supervised by a physician (Myers et al. 2009).

When a new service is being set up without established local expertise, formal mentoring from a suitably accredited trainer is recommended (e.g. Perioperative Exercise Testing and Training Society accreditation, POETTS). CPET practitioners who will be performing and reporting PCPET tests should have completed an accredited course, performed 25 tests under supervision and reported at least 50 tests under supervision before gaining accreditation and reporting independently (Myers et al. 2009). CPET practitioners should review or report 25 tests per year to maintain their competence (Myers et al. 2009). CPET practitioners who will be performing CPET tests but not interpreting tests should complete an accredited course and perform a minimum of 25 tests under supervision before testing independently.

PCPET Testing Protocol

Perioperative Exercise Testing and Training Society Guidelines (Levett et al. 2018)

Good practice recommendations for the conduct of perioperative CPET are summarised below.

PREPARATION FOR THE TEST

Patient Information and Consent

Patients should be provided with information on the process, risks and benefits of PCPET. The process of informed decision-making and consent should be documented and may involve formal written consent. Patients should take their regular medication but avoid caffeine, alcohol, cigarettes and strenuous exercise on the day of testing. For two hours prior to the test, patients should not eat and drink only water.

Risk of Adverse Events

CPET is a relatively safe investigation, especially in individuals with no comorbidity. A review of the exercise testing literature (primarily in patients with cardiac disease), suggests an incidence of a complication requiring hospitalisation of $\leq$ 2 in 1000 (Myers et al. 2009), of a major cardiac event of 1.2 per 10,000 tests (Myers and Bellin 2000; Balady et al. 2010) and of mortality of 2 to 5 per 100,000 clinical exercise tests (ATS/ARCP 2003; Myers et al. 2009). To date, no deaths have been reported during PCPET in the UK.

Baseline Data Collection

Baseline data collection should include patient demographic information, the reason for referral and the proposed surgery (Myers et al. 2009). The patient's medical history should be reviewed with particular attention to cardiac and respiratory disease to identify potential contraindications to exercise testing (Myers et al. 2009). A full drug history should also be taken to identify medication that may interfere with the exercise response (Myers et al. 2009). A recent haemoglobin level should be reviewed, since anaemia may impair exercise capacity (Plumb, Otto, and Grocott 2016; Wright et al. 2014).

The Cardiopulmonary Exercise Testing Protocol

The exercise protocol, equipment and quality control of perioperative CPET are discussed below. The recommendations within this section are based on key position statements and policy documents from national and international specialist bodies which use CPET in other clinical contexts and represent good practice standards.(Palange et al. 2007; ATS/ARCP 2003; Balady et al. 2010; Myers et al. 2009; ERS 1997)

Exercise protocol

Cardiopulmonary exercise testing provides a global assessment of the integrated response of the pulmonary, cardiovascular, metabolic and haematological systems. Key is the integration of respired gas analysis (O_2 and CO_2 concentrations) with ventilatory flow measurements, thereby enabling calculation of O_2 uptake ($\dot{V}O_2$) and CO_2 output ($\dot{V}CO_2$), typically on a breath-by-breath basis, under conditions of progressively increasing physiological stress imposed by a defined profile of external work rate (WR).

Heart rate (HR), SpO_2, blood pressure and 12-lead ECG (for rate, rhythm and S-T segment morphology evaluation) should be monitored throughout the test (Palange et al. 2007; ATS/ARCP 2003; Balady et al. 2010; Myers et al. 2009; ERS 1997). Resuscitation equipment including supplemental O_2 must be immediately accessible (Palange et al. 2007; ATS/ARCP 2003; Balady et al. 2010; Myers et al. 2009; ERS 1997).

For PCPET the rapid ramp (or incremental) exercise test performed to the limit of tolerance should be used (Whipp et al. 1981). The advantages of this protocol are as follows:

1. It evaluates the exercise response across the entire range of functional capacity.
2. The initial work rate is low and there is a relatively short duration of high intensity exercise.
3. The entire protocol is of short duration, with 8 to 12 minutes of exercise during the incremental phase.
4. It permits assessment of the normality or otherwise of the exercise response.
5. It permits identification of the cause of functional exercise limitation.
6. It gives an appropriate frame of reference for training or rehabilitation targets.

Submaximal tests, (stopping the incremental ramp above the anaerobic threshold but before peak exercise) were initially widely used in the perioperative setting, primarily because of safety concerns and may still be considered in some clinical contexts for example in patients with angina or moderate to severe aortic stenosis. However, maximal tests to the limit of tolerance provide additional information which may have prognostic and diagnostic utility and are preferred, unless safety concerns preclude continuing to maximal exercise.

Cycle ergometry has been used in all bar one of the published perioperative CPET cohorts. Cycle ergometry permits accurate determination of the external work rate and thus, for example, evaluation of the $\dot{V}O_2$-WR relationship which is difficult with a treadmill (Porszasz 2007). Consequently, cycle ergometry (using an electromagnetically braked ergometer) is the preferred mode of exercise for PCPET. For patients who are unable to perform cycle ergometry, arm cranking may be considered although the risk thresholds for this modality of exercise in the perioperative setting have not been identified (Loughney et al. 2014).

A period of approximately three minutes of resting data collection (rest phase) should be followed by three minutes of resistance-free pedalling (unloaded cycling phase) and then a continuous gradual, uniform increase in work rate until the limit of tolerance is attained (incremental phase). The ramp slope (watts/minute) is selected to produce 8 to 12 minutes of exercise during the ramp phase (ATS/ARCP 2003). For healthy active individuals, ramp slopes of 15, 20 or 25 watts per minute are common, while lower values in the range of 5 to 15 watts per minute are more appropriate for most patients**.** Higher ramp slopes in frail patients are likely to lead to premature test termination and consequently a truncated period of data acquisition, which precludes reliable test interpretation.

Algorithms based on individual patient characteristics (age, height, weight) are available to estimate the ramp slope required to produce a test duration of approximately 10 minutes (i.e. within the recommended 8-12 min range). For example: (Wasserman K 2011).

ramp slope (watts/min) = (peak $\dot{V}O_2$ – unloaded $\dot{V}O_2$)/100

where

unloaded $\dot{V}O_2$ (ml/min) = 150 + (6 x weight (kg))

peak $\dot{V}O_2$ (ml/min) = [height (cm) – age (years)] x 20 for males

or

peak $\dot{V}O_2$ (ml/min)= [height (cm) – age (years)] x 14 for females

The validity of such predictive algorithms in a general surgical population has not been established. (Ahmadian et al. 2013) Anecdotal evidence suggests that exercise capacity of the surgical patient population tends to be overestimated by these equations; a reduction in the calculated value should therefore be considered.

PCPET Equipment

Test equipment should include an electronically-braked cycle ergometer and a metabolic cart capable of analysing respired flow, [O_2] and [CO_2] with a response time less than 90ms to provide breath-by-breath measurements of ventilatory and gas exchange variables, together with ancillary equipment for serial monitoring of SpO_2, blood pressure, ECG and perceptual responses (perceived exertion, dyspnoea) (ERS 1997; ATS/ARCP 2003; Porszasz 2007; Wasserman K 2011). Perceptual responses such as perceived exertion and breathlessness may be assessed by the Borg scale or a visual analogue scale (Borg 1982), (Stark, Gambles, and Lewis 1981).

Calibration and Quality Control

The accuracy and reproducibility of the values obtained during testing is dependent on meticulous quality control (ERS 1997; ATS/ARCP 2003; Porszasz 2007; Wasserman K 2011). Calibration of primary sensors for flow and O_2 and CO_2 gas measurement should be performed **immediately before each exercise test**. The calibration should take into account barometric pressure, ambient humidity and temperature. While the precise calibration procedures will vary with the model and manufacturer of the metabolic cart, there are certain underlying principles that should be adhered to.

Flow calibration

The flow sensor should be calibrated as directed by the manufacturer over a physiological range of flow rates. This typically involves the use of a precision syringe (typically 3 litres) over a physiological range of flow rates.

Gas analyser calibration

Calibration gas mixtures for the O_2 and CO_2 sensors should be prepared by gravimetric weighing to ensure a concentration accuracy of ±1 %. Sensor calibration should be performed at two points, within the range for inhaled (21% O_2 and 0% CO_2 in N_2) and exhaled gas compositions (e.g. 15% O_2 and 5% CO_2 in N_2).

Phase Delay Calibration

Because of the transport delay associated with the gas concentration sensors (a phase delay typically in the region of 250ms), the flow and gas concentration signals have to be time-aligned prior to further processing.

This phase delay should be measured prior to each test rather than assumed, as small deviations from the correct value can have significant impact on the gas exchange computations (Lamarra 1995; ERS 1997; Brunelli et al. 2009; Porszasz 2007; Wasserman K 2011). It is measured as the delay between the imposition of a step change in gas concentration at the distal end of the sample line and the resulting gas concentration response at the respective sensor (phase delay), and values should lie within the manufacturer's stated range.

Validation of the equipment overall performance

The performance of the gas exchange algorithms cannot be assessed in the routine pre-test calibration phase. This requires simultaneous comparison of the metabolic cart responses with those obtained with an accepted independent standard.

Metabolic Simulator

The contemporary (and expensive) 'gold standard' method uses an automated gas exchange simulator. This comprises a reciprocating piston system that generates 'expired' gas to simulate metabolic rates by injecting a precision gas mixture into a chamber at precisely metered rates to mix with inspired air, thus allowing comparison of 'measured' breath-by-breath values of $\dot{V}O_2$, $\dot{V}CO_2$ and ventilation ($\dot{V}E$) with predicted values.(Huszczuk, Whipp, and Wasserman 1990) It has been proposed that the measured outputs and their variation with changes in pump frequency should lie within ~ $\pm$3 %. Values falling outside this range should prompt a comprehensive reassessment of the entire monitoring system (ATS/ARCP 2003). Small, progressive deteriorations in sensor performance and sample line transit delay over time may have a significant effect on gas exchange computation. Validation against a gas exchange simulator may be performed annually as part of the metabolic cart service.

Biological or Physiological Quality Control

A practical (and inexpensive) alternative is provided by regular 'biological quality control' (conducted monthly or more frequently), utilizing responses of a 'standard' subject (typically a member of the laboratory staff familiar with testing procedures) (Porszasz 2007) (Atkinson, Davison, and Nevill 2005; Macfarlane 2001; Balady et al. 2010).

It is recommended that the subject performs two **sub-anaerobic threshold (AT)** constant work rate tests, each of at least 6 minutes' duration, with the steady-state $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ responses at each work rate being obtained by averaging data over the final 2 minutes of the test (i.e. when a steady state has been achieved) (figure 1). It is essential that the work rates

chosen are BELOW the anaerobic threshold. The relationship between VO2 and work rate in this range is constant for cycle ergometry and will not change if the subject exercise trains. This allows the development of a serial quality control data base comprising absolute $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ responses at standardized work rates, as well as derived indices such as the respiratory exchange ratio (RER, $\dot{V}CO_2/\dot{V}O_2$) and the slope of the $\dot{V}O_2$-WR relationship ($\Delta\dot{V}O_2/\Delta$WR) (which is relatively independent of age, gender and fitness). Differences in 'expected' response can then be identified, both in terms of previous subject performance and also relative to normal population values. While there are no formal recommendations for assigning a 'significant' change relative to a quality control database, decisions could be based on:

1. Responses falling outside the data base 95% confidence interval (CI) (ATS/ARCP 2003) or
2. $\dot{V}O_2$ at a given work rate deviating by more than 5-10% of database values (Wasserman K 2011) or more than ±10 % of the predicted value (Porszasz et al. 2016), where $\dot{V}O_2$pred = (5.8 x weight (kg)) + 151 + (10.1 x watts) (Wasserman and Whipp 1975); or
3. $\Delta\dot{V}O_2/\Delta$WR between the two work rates deviating (above or below) from data base values or from a normal of ~10-11 ml·min^{-1}·watt^{-1}, with 95% CI ~8.5–12.5 ml·min^{-1}·watt^{-1}. (Neder et al. 2001; Hansen et al. 1987; Hansen et al. 1988)

Ideally the cycle ergometer should be calibrated at least annually and whenever it is moved (which can disturb the calibration), using a device such as a dynamic torque meter. The calibration should be linear from 0 to ~ 400 watts, and independent of pedalling cadence over a physiologically reasonable range(Russell and Dale 1986; Van Praagh et al. 1992; Clark and Greenleaf 1971). Sudden deviations in the normal slope value of the $\dot{V}O_2$-WR relationship warrant investigation, both of cycle ergometer and metabolic cart performance.

Practicalities of test conduct

Spirometry

Resting spirometry should be performed to measure forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1). Maximum voluntary ventilation (MVV) can be estimated from FEV1 as (FEV_1 x 35) or (FEV_1 x 40) (Gandevia and Hugh-Jones 1957), (Campbell 1982).

The patient should be familiarised with the cycle ergometer and the breathing assembly (facemask or breathing valve and mouthpiece), and should be instructed to give his/her 'best effort' but counselled to stop if symptoms such as chest pain develop. The patient should be discouraged

from talking during the test, as this will compromise data quality; an alternative method of communication should be established before commencing the test (thumb up = yes, thumb down = no). The patient should understand that he or she can stop at any time, whilst recognising that the aim is to pedal for as long as possible. During testing, data should be displayed in both tabular and graphical formats to monitor for abnormalities; core variables are presented in the table below.

The exercise test consists of four main phases: rest, unloaded cycling, ramp exercise and recovery.

Rest (3 minutes). A minimum of three minutes of resting data should be recorded, with the ECG being monitored for ischaemia or arrhythmia. If hyperventilation is present (RER > 1.0) this should be allowed to settle before commencing the next phase of the test. It is important to note that sustained hyperventilation can precipitate a premature 'false positive' or 'pseudothreshold' for AT estimation, which can obscure events triggered by the actual threshold (see False positives below) (Whipp 2007). Also, if the RER is persistently less than 0.7, the test should be halted as this is suggestive of inaccurate calibration and the calibration procedure should be repeated.

Unloaded Cycling (~3 minutes). Unloaded cycling allows functionally limited patients to acclimate to pedalling. Three minutes is sufficient in healthy individuals for HR, $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ to attain new steady states prior to the ramp phase commencing. The patient is encouraged to adopt a comfortable pedalling cadence, between 55 and 75 rpm throughout the test (ERS 1997; ATS/ARCP 2003; Porszasz 2007; Wasserman K 2011).

Ramp Phase (8-12 minutes). It is recommended that this phase is started without providing any cues to the patient, who should be instructed to continue pedalling for as long as possible. The limit of tolerance is defined as the point at which the patient is unable to maintain the pedalling cadence despite encouragement. The Borg score may be recorded at the end of the exercise to evaluate subjective effort.

Recovery (~5 minutes). Once the load is removed, the patient should be encouraged to pedal for a further period to prevent venous pooling in the legs and consequent syncope. Monitoring should continue until any dysrhythmia or ST changes have reverted to baseline, HR has fallen to within 10 bpm of resting values and blood pressure has returned to baseline.

Indications for Stopping the Test

An exercise test may be terminated as a result of ostensive 'good effort' (i.e. with symptom limitation) or because of the development of clinically-inappropriate symptoms. The reasons for stopping the test should be recorded, both from the subject's and the operator's perspectives. For

example, 'The patient stopped pedalling due to fatigue,' 'The patient failed to maintain a cadence greater than 40 rpm for more than one minute despite encouragement' or 'The patient felt light headed'. Commonly accepted criteria for the operator terminating an exercise test prematurely are listed in the table below. These are not absolute criteria and should be interpreted within the context of individualised risk of continuing the test and benefit from gaining more information.

Indications for the premature termination of an exercise test (adapted from(ATS/ARCP 2003))

Angina
> 2 mm ST depression if symptomatic or 4 mm if asymptomatic or > 1 mm ST elevation
Significant arrhythmias causing symptoms or haemodynamic compromise
Fall in systolic blood pressure > 20 mmHg from the highest value during the test
Hypertension > 250 mm Hg systolic; > 120 mm Hg diastolic
Severe desaturation: SpO_2 < 80% (lower may be accepted in patients with known underlying lung disease)
Loss of coordination
Mental confusion
Dizziness or faintness

Interpreting the CPET Test
Perioperative Exercise Testing and Training Society Guidelines (Levett et al. 2018)

Interpretation of the Exercise Test

Interpretation of a PCPET includes two main elements:

1. Integration and interpretation of the physiological data to provide a comprehensive description of the patient's exercise capacity and the main causes of exercise limitation. (Table below)
2. Interpretation of the implications of the patient's exercise limitation for his/her perioperative risk and recommendations regarding pre-operative interventions (out-with the scope of this guideline, to be addressed in a subsequent document).

While the former can be standardised, the latter is based on incorporation of functional capacity into the overall patient pre-operative assessment. The latter is an evolving field with a requirement for frequent (re-) evaluation of the clinical literature. A summary of the relevant literature can be found on the POETTS website: www.poetts.co.uk and in the Evidence section of this course book.

The variables that have been most extensively associated with postoperative outcome are the AT, VO_2peak and the ventilatory equivalents for CO_2. (Wilson et al. 2010b; Carlisle and Swart 2007). It is likely that as the field develops other variables may be related to outcome and consequently ongoing re-evaluation of the evidence is important.

Detailed interpretation of underlying cardiac and respiratory pathology is covered elsewhere. (Palange et al. 2007; Balady et al. 2010; Myers et al. 2009; ATS/ARCP 2003; ERS 1997; Puente-Maestu et al. 2016; Wasserman K 2011). An integrated approach to PCPET interpretation and the key elements of a perioperative CPET report are also considered.

Key elements in PCPET interpretation

1. Determine the reason for CPET

2. Review pertinent medical history and laboratory information
3. Note overall test quality, assessment of patient effort and reasons for test termination
4. Use tabular and graphical presentation of the data
5. Report exercise capacity using anaerobic threshold and peak $\dot{V}O_2$ values
6. Report other indices related to perioperative risk eg $\dot{V}E/\dot{V}CO_2$at the anaerobic threshold
7. Evaluate exercise limitation and primary cause(s) for this, e.g. cardiovascular, respiratory, deconditioning
8. Comment on perioperative risk implications of the exercise test and suggestions for further investigation/referral/preoperative interventions

Data Averaging and Data Presentation

The breath-by-breath data should be averaged prior to graphical display and interpretation using, for example, a moving average (e.g. middle 5 of 7 breaths), a breath-based average (e.g. 3 to 5 breaths), or a time-based average (e.g. ~ 20 seconds), to reduce the influence of biological 'noise' (Lamarra et al. 1987; Whipp 2005).

The procedures for data editing and data averaging should be applied consistently within a CPET laboratory; otherwise, results may be adversely influenced. (Johnson et al. 1998; Myers et al. 1990) The quality of the test should also be commented upon in the report.

Key exercise response variables and their physiological basis

The key response variables typically recorded during the CPET test are summarised in the table below. A comprehensive description of these variables may also be found in key position statements and policy documents (Palange et al. 2007; ATS/ARCP 2003; Balady et al. 2010; Myers et al. 2009; ERS 1997).

Reporting Exercise Capacity or Functional Capacity

The terms functional capacity, exercise capacity and exercise tolerance are used synonymously to describe the patient's ability to perform exercise and thus provide insight into his/her physiological reserve. The AT and VO2peak

should be used to describe the patient's exercise capacity. These variables are both associated with postoperative morbidity and mortality.

Key response variables reported for perioperative CPET

Exercise Capacity Variables
• Anaerobic threshold (AT; ml/min and ml/kg/min)
• Peak O_2 uptake ($\dot{V}O_2$peak; ml/min and ml/kg/min)
• Peak work rate (WRpeak; watts) – peak exercise
Cardiorespiratory Variables
• $\dot{V}O_2$-work rate slope ($\Delta\dot{V}O_2/\Delta$WR; ml/min/watt)
• Heart rate (HR; bpm) – resting and peak exercise
• Heart rate reserve (HRR; bpm) - peak exercise = maximum predicted heart rate – measured maximum heart rate
• Oxygen pulse (ml/beat) - resting and peak exercise
• Blood pressure (BP; mm Hg) – resting and peak exercise
• Arterial O_2 saturation (S_pO_2; %) – resting and peak exercise
• Tidal volume (V_T; l or ml) - resting and peak exercise
• Respiratory rate (RR; breaths/min) - resting and peak exercise
• Ventilation ($\dot{V}E$; l/min) – resting and peak exercise
• Breathing reserve (BR; l/min and % of $\dot{V}E$) – peak exercise = maximum voluntary ventilation – ventilation at peak exercise
• Ventilatory equivalent for O_2 ($\dot{V}E/\dot{V}O_2$)* – at AT or minimum value
• Ventilatory equivalent for CO_2 ($\dot{V}E/\dot{V}CO_2$)* – at AT or minimum value
• $\dot{V}E$-$\dot{V}CO_2$ slope ($\Delta\dot{V}E/\Delta\dot{V}CO_2$)* (particularly if no definite AT identified)
• End-tidal partial pressure of O_2 ($P_{ET}O_2$; mmHg) - resting and peak exercise
• End-tidal partial pressure of CO_2 ($P_{ET}CO_2$; mmHg) - resting and peak exercise
Spirometry Variables (resting)
• Forced expiratory volume in 1 second (FEV_1) (l)
• Forced vital capacity (FVC) (l)
• MVV – directly measured or estimated as FEV_1 x 35-40 (l/min)
• Inspiratory capacity (IC) (l)

* dimensionless if primary variables are presented in same units

Normal Values and Indexing Exercise Capacity Variables

Several series of reference values for incremental exercise test indices including $\dot{V}O_2$peak have been published (Puente-Maestu 2007; Wasserman K

2011). The most widely used in clinical practice are those produced by Hansen and Jones (Hansen, Sue, and Wasserman 1984; Jones et al. 1985). These values were obtained from North American populations and have not been specifically validated in a UK surgical population. With these limitations in mind, reference values are useful to identify an abnormal response and the reference values used should be standardised within a CPET laboratory. A common convention used to relate measured $\dot{V}O_2$peak to reference values is: > 80% not abnormal or within the 95% confidence interval; 71-80% mildly reduced; 51-70% moderately reduced; and < 50% severely reduced (Puente-Maestu 2007). It should be appreciated however that the majority of clinical cohorts in surgical patients have reported $\dot{V}O_2$peak as an absolute value indexed to body weight rather than as a percentage of predicted value. As a consequence the published risk thresholds for surgical patients pre-operatively are absolute values of AT and $\dot{V}O_2$peak indexed to body weight. Indexing to body weight may have implications for patients at extremes of bodyweight, potentially over-estimating risk in the morbidly obese patient and under-estimating risk in cachectic patients. Despite this consideration, in morbidly obese bariatric patients AT indexed absolute body weight was more predictive of outcome than AT indexed to body surface area or to ideal body weight (Hennis et al. 2012). Caution should be used when interpreting exercise capacity values indexed to body weight in patients with a low BMI. Alternatives to indexing to absolute body weight include ideal body weight and body surface area.

Ventilatory Equivalents for Carbon Dioxide: $\dot{V}E/\dot{V}CO_2$

The ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) is the ratio of minute ventilation ($\dot{V}E$) to CO_2 output ($\dot{V}CO_2$) and as such is an index of 'ventilatory efficiency.' Greater-than-normal values indicate that either the physiological dead space fraction of the breath (dead space/tidal volume, reflective of pulmonary gas exchange efficiency) is abnormally increased and/or $PaCO_2$ is decreased (e.g. acute hyperventilation) (ATS/ARCP 2003; Wasserman K 2011). Thus $\dot{V}E/\dot{V}CO_2$ gives insight into the efficiency of ventilation-perfusion matching in the lung and the efficiency of gas exchange. The slope of the linear $\dot{V}E$-$\dot{V}CO_2$ relationship ($\Delta\dot{V}E/\Delta\dot{V}CO_2$), the ventilatory equivalent for CO_2 at the AT ($\dot{V}E/\dot{V}CO_{2AT}$) or, if the AT cannot reliably be estimated, the minimum value of $\dot{V}E$-$\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_{2MIN}$) are numerically similar (Wasserman K 2011). This allows the investigator to choose which of the three is most amenable to measurement in the test. The values are elevated in heart failure, respiratory disease and pulmonary hypertension.(Sun et al. 2001), (Wasserman K 2011; ATS/ARCP 2003) Furthermore elevated $\dot{V}E/\dot{V}CO_2$is predictive of mortality and disease progression in cardiac failure,(Arena et al. 2004; Sarullo et al. 2010; Guazzi

et al. 2012) and mortality and other outcomes in COPD and other respiratory diseases (Neder et al. 2017; Puente-Maestu et al. 2016; Dumitrescu et al. 2017). In the perioperative setting, $\dot{V}E/\dot{V}CO_2$ at the anaerobic threshold is associated with morbidity and mortality in hepatobiliary surgery,(Junejo et al. 2014; Junejo et al. 2012) abdominal aortic aneurysm surgery,(Carlisle and Swart 2007; Grant et al. 2015) urological surgery (Tolchard et al. 2015) and mixed surgical cohorts (Wilson et al. 2010b). Recent thoracic surgical cohorts suggest the $\dot{V}E/\dot{V}CO_2$ slope may be more predictive of post-operative mortality and pulmonary complications than VO_2peak although this requires further clarification (Brunelli et al. 2012; Shafiek et al. 2016; Torchio et al. 2010). However an association between $\dot{V}E/\dot{V}CO_2$ and surgical outcome has not been identified in all cohorts, with some studies reporting no predictive association (Snowden et al. 2010). Further studies are required to clarify the additional risk conferred by abnormal ventilatory efficiency in addition to impaired exercise capacity.

The Perioperative CPET Report

Perioperative Exercise Testing and Training Society Guidelines

(Levett et al. 2018)

It is recommended that the perioperative CPET report includes:

1. Reason for referral, relevant past medical history and drug history
2. CPET data, presented in tabular form and graphically
3. A description of the patient's exercise capacity and its normality or otherwise
4. A summary of the cause(s) of exercise limitation if exercise capacity is abnormal
5. A statement about the risk implications of the exercise limitation and other identified abnormalities.
6. Suggestions for possible referrals and interventions preoperatively

An example of a tabular report with a suggested minimum data set is presented below. It is conventional practice to present CPET data graphically in a multi-panel format, typically with 9 panels or 8 panels (Wasserman K 2011; ATS/ARCP 2003), (Rocca J 1997). It should be emphasised that the difference between the original 'Wasserman' and the 'European Respiratory Society' formats lies more in data presentation rather than in overall content. An advantage of the 'European Respiratory Society' format is that the panels required for AT estimation are conveniently placed in a single column to aid discrimination decisions across the three criterion indices (a practice that has been adopted in the updated 'Wasserman' 2011 format). For this reason, the European Respiratory Society format tends to be preferred for perioperative CPET, with the option for including a ninth panel as a non-assigned panel that can usefully be used for tailoring test results to allow, for example, tracking of temporal responses of interest. Interpretation with regard to normality is done against published normal-value databases and algorithms (ATS/ARCP 2003; Wasserman K 2011; Puente-Maestu 2007).

Risk Thresholds in Perioperative CPET

As surgical and perioperative practice evolves, risk thresholds are likely to change. Furthermore, it is likely that the variables used to predict risk are likely to evolve and expand. Practitioners should evaluate local data and published cohorts on a regular basis to guide these recommendations. Further research is required to accurately enumerate the absolute risk of

morbidity and mortality associated with different levels of functional capacity. National and possibly international data collection is planned by POETTS, to provide access to contemporaneous risk threshold data. A summary of current case cohorts is presented in the evidence section.

CARDIOPULMONARY EXERCISE TESTING REPORT

Patient Details: Name, DOB, hospital number
Reason for Referral: Pre-operative assessment for Whipple's for pancreatic cancer
Medical History:

Baseline Observations:

Weight		HR		Hb	
Predicted weight		Resting ECG	?ischaemia ?conduction defect ? arrhythmia	FEV1 (% predicted)	
BMI		Resting BP		FEV1/FVC	

Exercise protocol and test conduct:

Maximum incremental test with ramp	15 watts		
Test Quality	good/poor and reasons		
Subject effort (Borg scale 1(min)-10)	Borg Rest:	Borg at VO_2peak:	Description of effort
Reason Exercise Stopped	Patient reason Investigators Observations		

Exercise Capacity: Anaerobic Threshold and VO_2peak

VO_2peak	Absolute ml/min	ml/kg/min	% of predicted
Anaerobic threshold	Absolute ml/min	ml/kg/min	% of VO_2peak (40-80% normal range)
VO_2/WR	ml/min/watt (normal range 10ml/min/watt^ standard deviation 1)		

Cardiovascular Function:

ECG Changes	Ischaemia or arrhythmia or conduction defect – when this occurred during test
Predicted Maximum HR	(normal approximately 220 – age)
Maximum heart rate	Absolute and % of maximum predicted heart rate
Heart rate reserve	absolute and %
O_2 pulse	at VO_2peak percentage of predicted and comment on profile of the response

Ventilatory Limitation:

Breathing Reserve	absolute and percentage (normal > 15% or greater than 11l/min)	
VE/VCO_2 at Anaerobic threshold	(normal < 32)	
Oxygen Saturations	At Rest	AT VO_2peak
Spirometry		

Summary:

1. Explicit statement of normality or otherwise of exercise capacity.
2. Identify the cause of abnormal exercise capacity. Identify abnormalities in the exercise response. Important negatives and positives based on the patient's known comorbidities.

3. Risk Implications for the perioperative period.
4. Suggested pre-operative optimization/referrals and perioperative management.

Example summary

'Mr X's exercise capacity is severely impaired with a VO_2peak of 12 ml/kg/min and an AT of 8ml/kg/min. In keeping with his history of congestive cardiac failure, he had evidence of cardiovascular limitation to exercise with dynamic ventricular dysfunction and inefficient gas exchange (VE/VCO_2 38). He did not have any inducible ischaemia. In spite of his history of COPD, his spirometry showed a mild obstructive picture. He did not have ventilatory limitation to exercise and did not desaturate on exercise. His VO_2peak, AT and VE/VCO_2 put him in the group at very high risk of perioperative complications. We would recommend appropriate risk counselling, consideration of preoperative prehabilitation and perioperative management in a critical care environment.'

Informed Consent for CPET

An example of a written consent form for CPET is given below:

1. Purpose and Explanation of the Test

You will perform an exercise test on a cycle ergometer or a motor- driven treadmill. The exercise intensity will begin at a low level and will be advanced in stages depending on your fitness level. We may stop the test at any time because of signs of fatigue or changes in your heart rate, electrocardiogram (ECG), or blood pressure, or symptoms you may experience. It is important for you to realise that you may stop when you wish because of feelings of fatigue or any other discomfort.

2. Attendant Risks and Discomforts

There exists the possibility of certain changes occurring during the test. These include abnormal blood pressure, fainting, irregular, fast or slow heart rhythm, and in rare instances, heart attack, stroke, or death. Every effort will be made to minimise these risks by evaluation of preliminary information relating to your health and fitness and by careful observations during testing. Emergency equipment and trained personnel are available to deal with unusual situations that may arise.

3. Responsibilities of the Participant

Information you possess about your health status or previous experiences of heart-related symptoms (such as shortness of breath with low-level activity, pain, pressure, tightness, heaviness in the chest, neck, jaw, back and/or arms) with physical effort may affect the safety of your exercise test. Your prompt reporting of these and any other unusual feelings with effort during the exercise test itself is of great importance. You are responsible for fully disclosing your medical history, as well as symptoms that may occur during the test. You are also expected to report all medications (including non-prescription) taken recently and, in particular, those taken today, to the testing staff.

4. Benefits to be expected

The results obtained from the exercise test may assist in the diagnosis of your illness, in evaluating the effect of your medications, or in evaluating what type of physical activity you might do with low risk.

5. Enquiries

Any questions about the procedures used in the exercise test or the results of your test are encouraged. If you have any concerns or questions, please ask us for further explanations.

6. Use of Medical Records

The information that is obtained during exercise testing will be treated as privileged and confidential. It is not to be released or revealed to any person without your written consent. The information obtained, however, may be used for statistical analysis or scientific purposes with your right to privacy retained.

7. Freedom of Consent

I hereby consent to voluntarily engage in an exercise test to determine my exercise capacity and state of cardiovascular health. My permission to perform this exercise test is given voluntarily. I understand that I am free to stop the test at any point, if I so desire.

I have read this form, and I understand the test procedures that I will perform and the attendant risks and discomforts. Knowing these risks and discomforts, and having an opportunity to ask questions that have been answered to my satisfaction. I consent to participate in this test

Name of Participant

Signature of Participant

Date

Name of CPET practitioner

Signature of CPET practitioner

Date

Communicating Results and Shared Decision Making

Michael Swart/John Carlisle

Cardiopulmonary exercise data are turned into information by communication.

- Patients can then make informed decisions: to have an operation or not, to delay surgery or not, to prepare themselves and their family.
- Clinicians can then make informed decisions: to be involved in surgical treatment or not, to plan interventions before, during or after surgery to prepare a time, place and personnel to care for that patient.
- Managers can then make informed decisions: to organize personnel and other resources to meet the predicted weekly demand for different levels of care.

There are two types of people: those who believe in dichotomy and those who don't. Although decisions can be broken down into a series of dichotomies, just as waveforms can be broken down by Fourier analysis into a sequence of sine waves, the information that precedes such decisions is never dichotomous. Information is continuous. There is always doubt, about a test result, diagnosis, prognosis, treatment and so on.

We would strongly encourage delegates to particularly avoid using CPET results to dichotomize patients into 'should' and 'should not' have surgery. However, we do believe that a more general risk assessment – contributed to by CPET results – should be used to sequentially dichotomize patients to different levels of preoperative, operative and postoperative care. In doing so please keep the assumptions upon which you base such a decision tree explicit. In this way you will not lose sight of the fact that your decision tree is provisional, likely to be pruned and grafted as time passes. Your decision tree will and should evolve over time.

Assessment of benefits and risk for surgery

- The following influence post-operative mortality: Age (can be accurately assessed)
- Type of operation (predicted pre operatively but may change intra operatively)
- Past medical history: Heart Failure, Myocardial Infarction, Stroke, Renal Disease, Peripheral Arterial Disease
- Aerobic fitness (can be estimated or measured)

Morbidity risk is roughly double the mortality risk. It is more difficult to define and assess and hence less well reported or understood. It may be more

important than mortality to some patients. The benefits of surgery are increasing survival, increasing functional ability, reduced pain or a combination of all three.

Assessment of benefits and risks of observation or no surgical treatment There is a publication bias towards surgery in the disproportionate number of studies published on operation and outcome compared to the number of publications on no operation and outcome. Assumptions such as most patients benefit from surgical repair of a broken hip or removal of a colon cancer are probably correct. For other operations such as open prostatectomy for prostate cancer the observation of benefit are not so clear. Uncertainty needs to be acknowledged.

Communication of risk and benefit from the patient's perspective
This can be difficult.
The role of the clinician is to first estimate risk and benefit. The estimation of risk for operative or non-operative treatment based on age, sex, aerobic fitness, proposed surgery and medical co-morbidities may be certain or uncertain. The surgical options may be more than one choice and this choice may change over time. All or some of this now needs to be shared with the patient and their family. Shared decision making does not mean frightening patients with risk. You must first address the patient's perspective.
Start with explaining the problem in brief and then move on to finding out what the patient understands so far and what is their desired role in decision making. Be aware that a patient's first response to what they want to know may change as the consultation progresses. Go through the pros and cons of the available options including uncertainty. Now focus on the patients values and preferences. Surgical and anaesthetic training deals more with knowledge and application of technique to achieve a clinician determined outcome. At the same time we avoid uncertainty by either focusing on technical detail where there is certainty or collectively ignoring any difficult uncertainty. You have to understand why or how a patient is making a decision to help coach or guide them to make the best decision for them. Often something in the patients past experience or their family or social history will be the key to the patient's choice. Your role is not to judge their decision but to understand and ensure their decision is based on correct information and that they are not put under any undue pressure. Involving friends and family is useful. Sometimes decisions are reached quickly and sometimes they need deferring for more time or more information.

The future of shared decision making and high risk surgery

Barriers to shared decision making from clinicians include a perceived loss of autonomy, failure to recognise a patient's preference sensitive decision and our communication skills. We need better information about risk and benefit on long term survival, morbidity and patient related outcomes for open surgery and no surgery. This requires a database and the follow up of all patients considered for surgery. For clinicians the challenge is to learn more about risk assessment and risk communication. An even greater challenge is: communication by listening, ability to use open questioning, supporting patient's deliberation and non-directive guiding.
With the exception of general practice these are not taught in post graduate training. Other barriers are the lack of time or the lack of reimbursement for the time required for these consultations. There can be perverse incentives to operate if the reimbursement for a surgical procedure is disproportionate to the consultation. There are potential benefits in improved patient satisfaction and less litigation. There may also be a better allocation of health care resources in terms of the money going on good outcome for both patients and the health care system. In other surgical specialties shared decision making usually reduces patient's decisions to have surgery.
Decision aids have been developed for other surgical procedures. They can be in paper, audio or video format and can be put on the Internet. They provide information about treatment options, risks, benefits and uncertainty. The videos can be of clinicians or possibly of more relevance patients who have had to make decisions on surgery and can talk about the outcome of this decision. They can also be designed help find patients their preferred values. A Cochrane review on the use of decision aids found increased and improved patient knowledge, improved concordance between patients values and choices, an improve concordance between values and choices and reduced patient decisional conflict (patient regret).

Sources of Information on Risk and Shared Decision Making
Web site with a risk calculator: http://sites.google.com/site/informrisk
Kings Fund publication by Angela Coulter and Alf Collins:
http://www.kingsfund.org.uk/publications/nhs_decisionmaking.html
Website with a good background on medical consultations:
http://www.patient.co.uk/doctor/Consultation-Analysis.htm
RCGP Curriculum on Consultation: http://www.rcgp-curriculum.org.uk
Dartmouth Medical School (active over last 14 years on Shared Decision Making) web site with links to other sources of information:
http://www.dartmouth.edu/~cecs/decision_making.html
http://www.hitchcock.org/dept/csdm

Running a CPET service: business cases, staff requirements and support

Setting up a CPET service – a personal view Chris Snowden, Newcastle, UK. Before you do anything else….

- Use existing outcomes data to establish where the problem areas are for major surgical patients in your hospital.
- Ensure there are no other major holes in the standard of care which need to be sorted first. For example, does your hospital currently have monitoring to allow goal-directed haemodynamic optimisation of the high- risk patients which you will identify through CPET?
- Visit an established pre-operative assessment service – and use it to define the relevance of CPET to the types of surgical practice in your own hospital.
- Speak to your surgical and anaesthetic colleagues – your work will be tougher if there is a tidal wave of cynicism about CPET. Hopefully there won't be…
- Have a clear vision about how your data is going to be used to influence patient management. For instance, how will your surgeons react to the suggestion that an otherwise healthy-seeming patient may be a very high- risk candidate? It's all very well assessing the ropey ones who the surgeons are happy to see cancelled. Ensure anaesthetic colleagues will be able to hold firm when the high-risk punter has his or her HDU bed cancelled on the day…
- Get friendly with the pre-assessment nursing staff, as this is going to be the best resting place for your shiny new CPET kit.
- Establish benchmarks against which to audit your outcomes from a CPET service.
- Location, location…
- Pre-assessment clinics are here to stay, and I firmly believe this is the best area to locate a CPET service in because:
- CPET can be combined with the standard pre-op visit
- Nursing staff can act as your technician during the test, thus reducing costs
- Other tests can be completed before CPET
- It's the right environment in which to sit and talk to the patients after the test, to help put the results into context for them, and to discuss other aspects of their surgical or anaesthetic care at the same time. Pre-assessment clinics may come with their own administrative support staff

Staff requirements

- As stated above, a trained pre-assessment nurse can act as technical support before, during and after the test.

- Technician: useful, but relatively expensive, if not already in an established post. A lot of modern CPET kit is fairly user-friendly in terms of servicing and replacing vital bits.
- Often the data obtained from a test is not as textbook-like as we would like, and it's invaluable to have actually watched the test, and to interpret the data with all the other clinical factors in mind. Only an anaesthetist with a good amount of experience in looking after these patients can really deliver the whole package for the patient.
- Think about realistic treatment options for patients in your unit, especially in terms of post-operative location. There's no point in recommending something which is unlikely to happen for everyone. Different hospitals in different systems have different resources.

AUDIT all outcomes from patients undergoing CPET, irrespective of whether they have surgery or not.

FEEDBACK outcomes data to your surgical and anaesthetic on a regular basis, but bear in mind that it will take time to build up meaningful numbers.

The Evidence Base for Peri-operative CPET

Denny Levett

To date there is not a prospective, randomised trial assessing the efficacy of perioperative CPET. Prospective and retrospective case series data provide compelling evidence of an association between exercise capacity and surgical outcome. Patients identified as high risk by CPET are often triaged to ICU, which may subsequently confound outcome data – 'confounding by indication.' An up to date list of perioperative CPET studies can be found on the POETTS website www.poetts.co.uk.

Key perioperative outcome references are as follows:

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- Epstein 2004 (Epstein et al. 2004)
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- Carlisle 2007 (Carlisle and Swart 2007)
- Forshaw 2008 (Forshaw et al. 2008)
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- Snowden 2010 (Snowden et al. 2010)
- Prentis (2012) (Prentis et al. 2012)
- Swart 2012 (Swart and Carlisle 2012)
- Hennis 2012 (Hennis et al. 2012)
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- Hartley 2012 (Hartley et al. 2012)
- Junejo 2012 (Junejo et al. 2012)
- Ausania 2012 (Ausania et al. 2012)
- Snowden 2013 (Snowden et al. 2010)
- Otto 2012 (Otto et al. 2012)
- Lai 2013 (Lai et al. 2013)
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- West 2014 (West, Parry, et al. 2014)
- Jack 2014 (Jack et al. 2014)
- West 2014 (West, Loughney, et al. 2014)
- Grant 2015 (Grant et al. 2015)
- Carlisle 2015 (Carlisle et al. 2015)

- Swart 2017 (Swart, Carlisle, and Goddard 2017)
- Wijeysundera 2018 (Wijeysundera et al. 2018)

Systematic Reviews:

- Moran 2016 (Moran et al. 2016)
- *Hennis 2011* (Hennis, Meale, and Grocott 2011)
- Young 2012 (Young et al. 2012)
- Smith 2009 (Smith et al. 2009)

Reliability of the AT:

- Sinclair 2009 (Sinclair et al. 2009)
- Kothmann 2009 (Kothmann et al. 2009)

Narrative Reviews

- Older 2017 ***(Older and Levett 2017)***
- Levett 2015 ***(Levett and Grocott 2015a)***
- Levett 2015 ***(Levett and Grocott 2015b)***
- Harvie and Levett 2018 'perioperative CPET' in the surgical monograph below.

Up to date review of ALL clinical CPET including perioperative

European Society Mongraph 2018: Clinical Exercise Testing (Clinical Exercise Testing 2018)

Palange, Paolo Laveneziana Pierantonio Neder J. Alberto Ward Susan A. *https://books.ersjournals.com/content/clinical-exercise-testing*

Covers equipment, physiology, diagnostic and perioperative CPET

Prehabilitation – Exercise training before surgery

Denny Levett

The time between contemplation of surgery and the procedure offers a window of opportunity to optimise patients' nutritional, functional and psychological state prior to surgery. Traditionally pre-operative pathways have focused on the underlying disease process and 'fitness for surgery' with physical pre-assessment and risk counselling late in the pathway when there is little time available to intervene. With an increasingly elderly and comorbid surgical population, early physiological assessment and multidisciplinary collaborative decision making is increasingly important. Multimodal prehabilitation programmes may improve surgical outcome, facilitating rapid recovery from surgery and limiting postoperative functional dependence. Patient education and engagement is important if compliance with behavioural change is to be achieved and maintained. To date there is supportive evidence for pre-operative exercise training, smoking cessation, reduction in alcohol intake, anaemia management and psychosocial support. Further research is needed to identify the most effective elements of these complex preoperative interventions, as well as their optimum timing and duration.

Narrative Reviews

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Basics of Exercise Prescription – ExR_X

Karen Kerr, Sheffield

It's worth remembering that for most adults the benefits of exercise far outweigh the risks. And that the risk to the individual undertaking exercise to increase physical activity and improve fitness are also balanced against the risk to the individual associated with the surgery being considered at their present level of fitness.

Considerations regarding the individual and ExR_X

- Individual goals
- Physical ability
- Physical fitness
- Health status
- Schedule
- Physical and social environment
- Available equipment and facilities

Exercise Programme Considerations for ExR_X

Exercise is activity performed in addition to the activities of daily living. Any ExR_x can contain elements of activity familiar to the individual as an activity of daily living.

The exercises should address:

- Cardiorespiratory fitness (aerobic fitness)
- Resistance through muscular strength and endurance
- Flexibility considering body composition
- Neuromotor fitness (balance, coordination, gait, agility and proprioception training; sometimes call functional fitness training)
- Aiming to reduce the time spent in sedentary activities

Each of these ExR_X considerations can be approached by considering FITT-VP. This is described further below.

Exercise Prescription components

- **Warm up** (think reference phase)

Five to 10min of light to moderate intensity aerobic and muscular endurance activity, allowing the body to adjust to the changing physiologic, biomechanical and bioenergetic demands of what is to follow. It also has the potential to reduce injury by gently improving the individual's range of movement (ROM).

- **Conditioning** (think testing phase but think in intervals)

Twenty to 60min of aerobic, resistance, neuromotor and/or sports activities. The 'actual activities' are guided by the initial individual considerations. Conditioning can be undertaken in 10min blocks with the aim being that the individual accumulates at least 20 to 60min daily conditioning.

- **Cool down** (think recovery phase)

Five to 10min of light to moderate intensity cardiorespiratory and muscular endurance activity to facilitate the gradual recovery of heart rate and blood pressure and removal of metabolic end products.

- Stretching exercises

Either after the warm up or cool down, warm muscles stretch further and are less likely to suffer injury.

Exercise Prescription – FITT-VP

- **Frequency** (how often)

Consider aerobic conditioning 3 to 5 times a week. Balance the frequency with the intensity. If less intense then do more often.

- **Intensity** (how hard)

There is a positive dose response relationship with exercise, the greater the effort the greater the reward. It is believed that an upper limit to exercise benefit exists but presently no threshold has been identified for the very unfit.
Undertaking the activity in intervals as interval training has been shown to improve fitness quicker.

- **Time** (duration or how long)

The WHO guidance is 150min of moderate intensity exercise a week or 75min vigorous intensity exercise. HOWEVER benefits with less than 20min a day in previously sedentary individuals have been shown.

- **Type** (mode or what kind)

Rhythmic, aerobic type exercises involving large muscle groups are recommended for improving cardiorespiratory fitness; walking, leisurely cycling, aqua-aerobics, slow dancing. In common they require minimal skill or physical fitness.

- **Total Volume** (amount)

This volume is the product of the frequency, the intensity and the time.

- **Progression** (advancement)

Consider the individuals health status, physical fitness, likely training response and the exercise programme goals. Progression occurs by increasing the quantity or quality of any of the components of the FITT principle exercise prescription as tolerated by the individual. Increases can be small and initially just seconds.

Additional Information for ExR_X

- Resistance exercise examples:
  - **Multi-joint:** chest press, shoulder press, pull-down, dips, lower back extension, abdominal crunch/curl up, leg press, and squats.
  - **Single joint**: bicep curl, triceps extensions, quadriceps extensions, leg curls and calf raises.
- Resistance training for the large muscle groups necessary only 2 to 3 times a week
- 48hrs between same muscle group exercise sessions.
- Weights can be small used until the action produced fatigue then move on to another different muscle group.
- Choosing exercises the individual is familiar with can reduce injury and potential complications, Variety of exercise assists in injury prevention by avoiding overuse.
- Give consideration to the other potential benefits of the ExR_x; for those at risk due to low bone density then consider weight bearing and resistance exercise to maintain bone health.
- You are prescribing exercise not just for the potential reduction in surgical morbidity and mortality.

For more detail on Exercise Prescription please refer to:
ACSM's Guidelines for Exercise Testing and Prescription, ninth edition

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