

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 no 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, O₂ 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_{ETCO_2} , P_{ETO_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, VCO₂ and VO₂. 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, VO₂ and VCO₂ 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 dynamometer (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 'undesigned' 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 $\dot{V}O_2$ 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 – $\dot{V}O_2$ /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

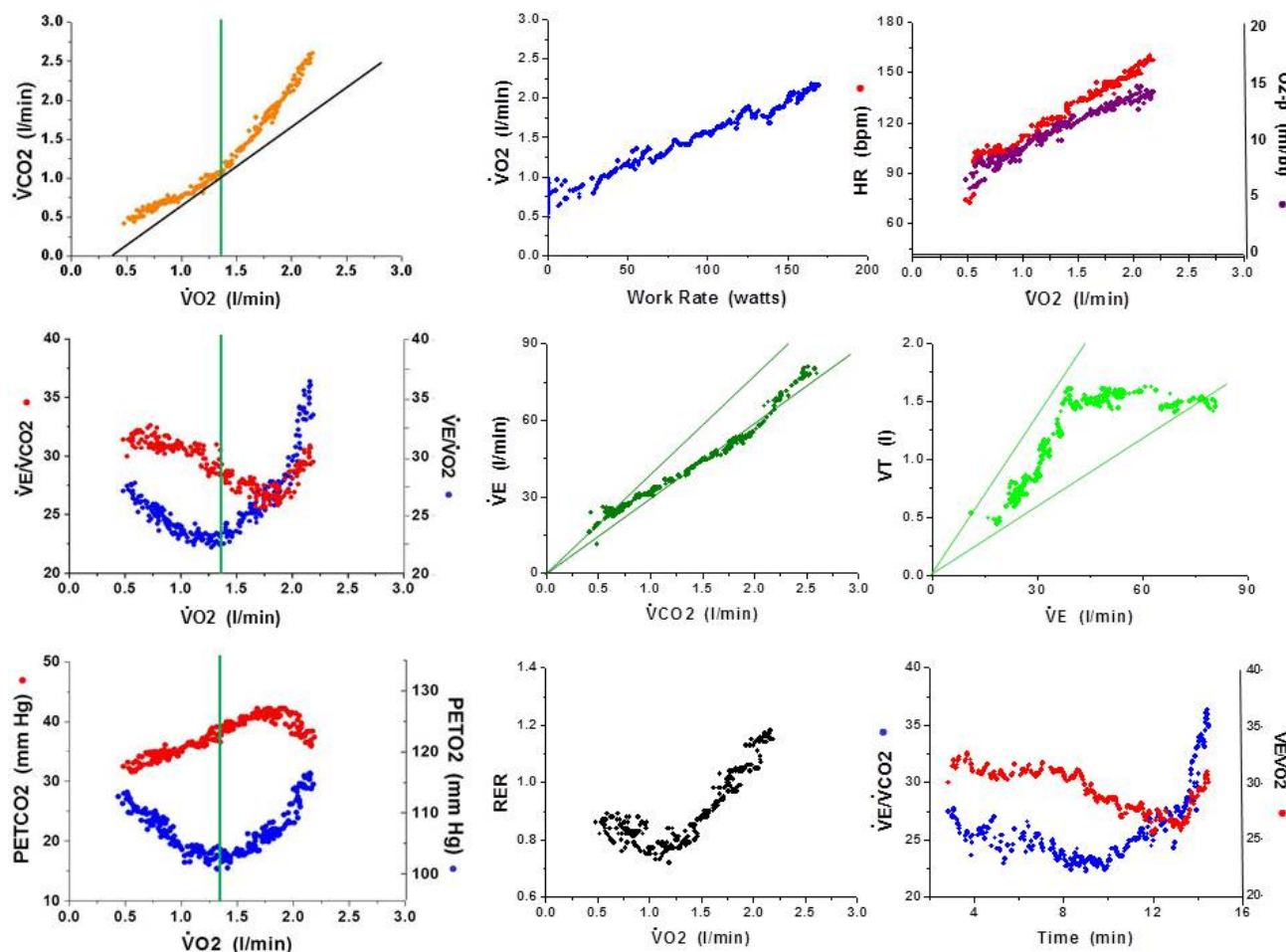
Panel 6: V_T vs $\dot{V}_E$ - Breathing reserve and ventilatory limitation

Panel 7: $P_{ET}CO_2$, $P_{ET}O_2$ vs $\dot{V}O_2$ – 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.

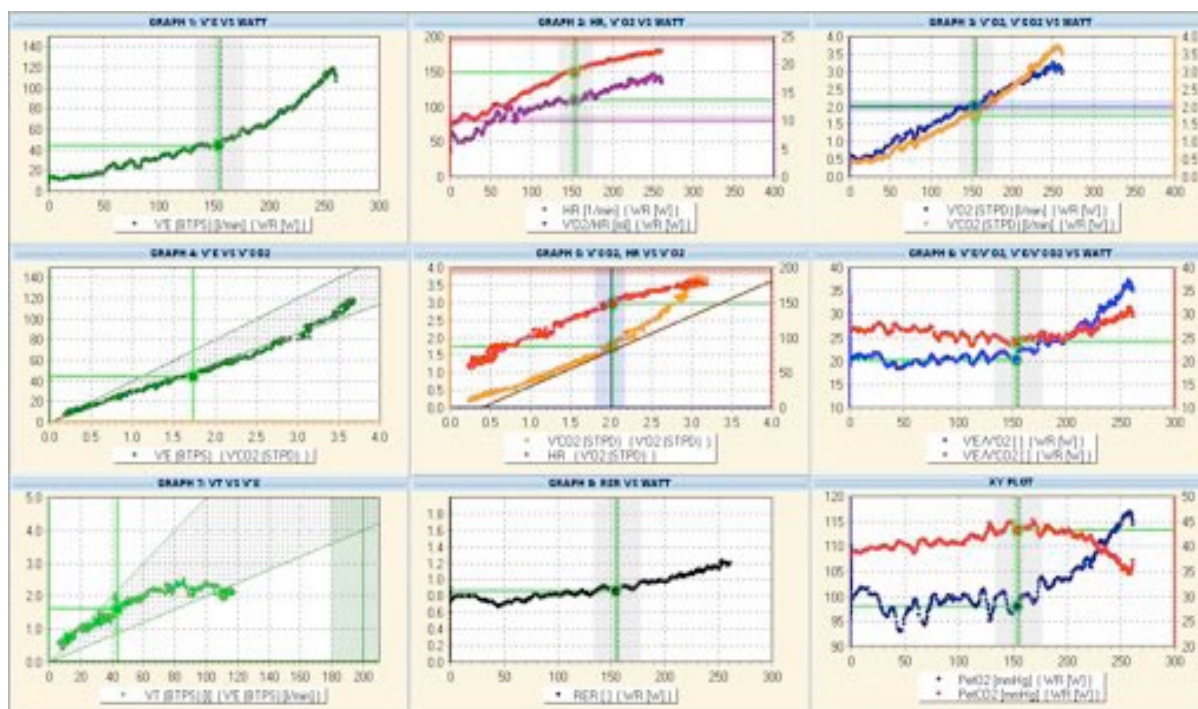
Panel 9: undesigned – e.g. $\dot{V}_E$ vs time or work rate or $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ and $P_{ET}CO_2$, $P_{ET}O_2$ against time.

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)
VO₂peak (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 VO₂peak							< 9-10 associated with increased perioperative risk
VO₂/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)	- VO₂ = (SVxHR)(AV O₂ extraction ratio) - O₂ pulse = VO₂/HR = SV(O₂extraction ratio) - Normal > 80% of predicted approx: - Males: 15-20 - Females: 10-15							- Peak O₂ pulse reduced in heart failure and deconditioning < 80% predicted value is abnormal - Early flattening of O₂ 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/VCO₂ at AT or Minimum VE/VCO₂	23-34 - Increases with age to max 32							> 34 abnormal & associated with ↑ perioperative risk (heart failure/respiratory disease)
VE/VCO₂ 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 hypertension, respiratory disease ↑ perioperative risk in thoracics > 35
Resp Rate (bpm)	8-12 rest							
Rest ETO₂ (mmHg)	90-110 mmHg, Increases above AT							
Rest ETCO₂ (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.