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Preoperative Cardiopulmonary Exercise Testing (PCPET): consensus clinical guidelines on indications, organisation, conduct and physiological interpretation

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Abstract

The use of preoperative cardiopulmonary exercise testing (PCPET) to evaluate the risk of adverse perioperative events and inform the perioperative management of patients undergoing surgery has increased over the last decade. PCPET provides an objective assessment of exercise capacity preoperatively and identifies 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. Information gained from the PCPET can be used to estimate the likelihood of perioperative morbidity and mortality, to inform the processes of multidisciplinary collaborative decision making and consent, to triage patients for perioperative care (ward vs critical care), to direct preoperative interventions and optimisation, to identify new comorbidities, to evaluate the effects of neoadjuvant cancer therapies, to guide prehabilitation and rehabilitation and to guide intra-operative anaesthetic practice. With the rapid uptake of PCPET, standardisation is key to ensure valid, reproducible results that can inform clinical decision making. Recently, an international Perioperative Exercise Testing and Training Society (POETTS) has been established (www.poetts.co.uk) promoting the highest standards of care for patients undergoing exercise testing and/or training in the perioperative setting. These clinical cardiopulmonary exercise testing (CPET) guidelines have been developed by consensus by the Perioperative Exercise Testing and Training Society after systematic literature review. The guidelines have been endorsed by the Association of Respiratory Technology and Physiology (ARTP).

Keywords: Anaerobic threshold, Cardiopulmonary exercise testing, Perioperative Medicine

The use of preoperative cardiopulmonary exercise testing (PCPET) to evaluate the risk of adverse perioperative events and inform the perioperative management of patients undergoing surgery has increased over the last decade, particularly in the UK. [1, 2] With the rapid uptake of PCPET, standardisation is key to ensure valid, reproducible results that can inform clinical decision making. Recently, an international Perioperative Exercise Testing and Training Society (POETTS) has been established (www.poetts.co.uk). This body developed from the UK National Perioperative PCPET forum and has the specific aims of: (i) promoting the highest standards of care for patients undergoing exercise testing and/or training in the perioperative setting and to promote the professional practice of exercise testing and/or exercise training in the perioperative setting; (ii) promoting and delivering training and education in exercise testing and/or exercise training in the perioperative setting including advising on education and training curricula for medical and healthcare practitioners; (iii) promoting the development, conduct and dissemination of audit, quality improvement, research and innovation to further the development of perioperative exercise testing and/or training.

These clinical cardiopulmonary exercise testing (CPET) guidelines have been developed by consensus by the Perioperative Exercise Testing and Training Society after systematic literature review. The guidelines have been endorsed by the Association of Respiratory Technology and Physiology (ARTP). The guidelines represent what is considered to be best practice by expert consensus and by setting a standard the intention is help all who do PCPET to reach this standard. They will be used to benchmark practice and subsequently will be revised in the light of new information or evidence.

METHODS

Guideline development

An early set of UK CPET guidelines (unpublished) were produced by Helen Luery (UCLH), Jonathan Wilson (York), John Carlisle and Michael Swart (Torbay) in 2001 based on the work of Paul Older. The concept of consensus national guidelines was first formally raised

at the first National Perioperative CPET Meeting at the Evidence Based Perioperative Medicine conference in July 2008 and formally discussed at the second meeting in 2009. Following initial open forum discussion at the 3rd National CPET meeting in 2010, the authors produced the first draft of this manuscript based on systematic review of the literature (see below), guidelines from other applications of clinical CPET [3-5] established practice standards, and input from experts in the field (BJ Whipp). The recommendations were reviewed by the authorship group until consensus was achieved by email. The guidelines were then peer reviewed by the delegates at the National Perioperative CPET meetings. Firstly, an item-by-item chaired open discussion took place in 2011 and the document was revised and updated. Further point-by-point iterative discussion took place in chaired open discussion at the National CPET Meetings in 2012, 2013, 2014, and 2016. Consensus was achieved for elements without a firm evidence base. In this case the recommendations are based on what is considered to be good practice standards by experts in the field. This final version was then refined and edited by the authors over late 2016 until all authors were satisfied with the final document which was then submitted for publication.

Systematic Review

The writing process was informed by multiple published systematic reviews of the relevant literature including Smith (2009)[6], Hennis (2011)[7] and Moran (2016)[8]. In addition, to identify recently published studies, we performed repeated updated PubMed systematic searches during the development of this manuscript (until submission) based on the search strategy of Stone and Hennis and using the follow search terms: 'CPET/surgery', 'CPEX/surgery', 'cardiopulmonary/exercise testing/surgery', 'VO_2peak/surgery' and 'VO_2max/surgery.'

Strength of Recommendations and Levels of Evidence

To indicate the basis on which recommendations were made, all evidence was classified according to an accepted hierarchy of evidence that was originally adapted from the US Agency for Healthcare Policy and Research Classification.[9] Each recommendation is graded A to D based on the level of associated evidence using a scheme formulated by the Clinical Outcomes Group of the NHS Executive that has been used in NICE guidelines.[10] (see Appendix 2).

In contrast to questions of clinical efficacy and effectiveness, the practice recommendations within these guidelines relate to the indications, organisation, conduct and physiological interpretation of PCPET. Such questions are rarely, if ever, amenable to direct evaluation through randomised controlled trials (RCTs), therefore all recommendations are graded B (well-conducted clinical studies but no RCTs on the topic of recommendation; or extrapolated from RCT or systematic review), C (expert committee reports or opinions and/or clinical experiences of respected authorities OR extrapolated from well-conducted clinical studies - this grading indicates that directly applicable clinical studies of good quality are absent or not readily available) or D (recommended good practice standard based on the clinical experience of the guidelines development group).

Guidelines Scope

CPET evaluates the integrated physiological response to exercise and provides an objective measure of exercise capacity (functional capacity or physical fitness). It also permits interrogation of the aetiology of exercise intolerance when exercise capacity is abnormal. Exercise capacity is predictive of post-operative outcome[11], reflecting the physiological reserve available to respond to the stress of surgery and postoperative recovery. This guideline is intended to provide guidance on the use of CPET perioperatively. The use of CPET for other applications has been comprehensively covered elsewhere[3-5, 12-15].

INDICATIONS AND CONTRAINDICATIONS FOR CPET

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 [16-18], colorectal surgery [19, 20], urological surgery [17, 21], hepatobiliary surgery [16, 22], liver transplantation [23], bariatric surgery [24, 25], vascular surgery [22, 26], thoracic surgery [27-29] and oesophageal-gastric surgery [30-32] and also for guiding exercise-training interventions prior to and/or immediately after surgery [33, 34] The evidence supporting PCPET is continuously evolving and consequently the indications for PCPET require regular reassessment.

Recommendations

Indications for PCPET include:

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

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.[3, 15] These are largely based on the expert opinion of respected authorities.

Recommendations

Contraindications and relative contraindications to exercise testing in the perioperative setting are summarised in table 1. These are based on recommendations in other areas of CPET modified for the perioperative context to take into account the specific patient population **(Grade C).** Patients with relative contraindications should be directly supervised by a physician **(Grade C).** 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 **(Grade D)**. If the risk-benefit relationship changes as the test progresses, the test can be terminated early – a submaximal test **(Grade D)**. 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.

PCPET SERVICE STRUCTURE AND SUPERVISION

A PCPET service should be managed and led by an individual expert in PCPET **(Grade C).** 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) **(Grade C).** [5]

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 **(Grade C).** [5] PCPET practitioners and advanced practitioners must have appropriate knowledge and experience in first aid and resuscitation **(Grade C).** [5]

A minimum of two members of staff should be directly available for every test, one of whom should be a competent CPET advanced practitioner **(Grade D).** 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)) **(Grade C).** [5] A resuscitation team with advanced life support skills (cardiac arrest team or paramedic team) must be immediately available **(Grade C).** [5] A physician should be available to review any patient who develops complications during a test **(Grade C).** [5] High-risk CPET tests, including tests where relative contraindications are present (table 1), should be directly supervised by a physician **(Grade C).** [5]

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) **(Grade D)**. 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 **(Grade C).**[5] CPET practitioners should review or report 25 tests per year to maintain their competence **(Grade C).** [5] 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 **(Grade D)**.

Preparation for the Exercise Test

(Grade C, Good Practice Recommendations, unless otherwise stated)

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 should 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 [5], of a major cardiac event of 1.2 per 10,000 tests [13, 35] and of mortality of 2 to 5 per 100,000 clinical exercise tests. [3, 5] 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**.** [5] The patient's medical history should be reviewed with particular attention to cardiac and respiratory disease to identify potential contraindications to exercise testing. [5] A full drug history should also be taken to identify

medication that may interfere with the exercise response.[5] A recent haemoglobin level should be reviewed, since anaemia may impair exercise capacity (Grade D). [36, 37]

CONDUCT OF THE EXERCISE TEST

(Grade C, Good Practice Recommendations, unless otherwise stated)

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.[3-5, 12, 13]

Exercise protocol (Grade C)

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, arterial blood pressure and 12-lead ECG (for rate, rhythm and S-T segment morphology evaluation) should be monitored throughout the test**.** [3-5, 12, 13] Resuscitation equipment including supplemental O_2 must be immediately accessible. [3-5, 12, 13]

For PCPET the rapid ramp (or incremental) exercise test performed to the limit of tolerance should be used. [38] 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 min 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.

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. [39] 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. [40]

A period of approximately 3 min of resting data collection (rest phase) should be followed by 3 min 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 min of exercise during the ramp phase. [3] For healthy active individuals, ramp slopes of 15, 20 or 25 watts per min are common, while lower values in the range of 5 to 15 watts per min 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: [41]

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

where

unloaded $\dot{V}O_2$ (ml min^{-1}) = 150 + (6 x weight (kg))

peak $\dot{V}O_2$ (ml min^{-1}) = [height (cm) – age (yr)] x 20 for males

or

peak $\dot{V}O_2$ (ml min^{-1})= [height (cm) – age (yr)] x 14 for females

The validity of such predictive algorithms in a general surgical population has not been established. [42] 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 **(Grade D)**.

PCPET Equipment (Grade C)

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). [3, 4, 15, 39] Perceptual responses such as perceived exertion and breathlessness can be assessed by the Borg scale or a visual analogue scale. [43, 44]

Calibration and Quality Control (Grade C)

The accuracy and reproducibility of the values obtained during testing is dependent on meticulous quality control.[3, 4, 15, 39] 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.

The flow sensor should be calibrated for volume with a precision syringe (typically 3 litres) over a physiological range of flow rates. 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).

Because of the transport delay associated with the gas concentration sensors (a phase delay typically in the region of 250 ms), 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 gas exchange computations.[4, 15, 29, 39, 45] 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.

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. 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.[46] 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.[3] 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.

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).[39 13, 47, 48] It is recommended that the subject performs two sub-anaerobic threshold (AT) constant work rate tests, each of at least 6 min 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 min of the test (i.e. when a steady state has been achieved) (figure 1). 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 (a) responses falling outside the data base 95% confidence interval (CI) [3] (b) $\dot{V}O_2$ at a given work rate deviating by more than 5-10% of database values [15] or more than ±10 % of the predicted value [49], where $\dot{V}O_2$pred = (5.8 x weight (kg)) + 151 + (10.1 x watts) [50]; or (c) $\Delta\dot{V}O_2/\Delta$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}. [51-53]

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. [54-56] 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 (Grade C)

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). [57, 58] 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 table 2.

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

Rest (3 min). 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). [59] 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 min). 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. [3, 4, 15, 39]

Ramp Phase (8-12 min). 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 min). 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 (Grade C)

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 table 3. 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.

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 4)
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 and will be the subject of a later guideline. In this guideline we focus on the interpretation of exercise capacity, which is a fundamental consideration in perioperative risk evaluation. We will also discuss the ventilatory equivalents for CO_2 as this is associated with surgical outcome in several surgical cohorts. [17, 26] It is likely that as the field develops other variables may be related to outcome and these guidelines will be reviewed and revised as appropriate. Detailed interpretation of underlying cardiac and respiratory pathology is covered elsewhere. [3-5, 12-15] An integrated approach to PCPET interpretation and the key elements of a perioperative CPET report are also considered.

Data Averaging and Data Presentation (Grade C)

(Grade C, Good Practice Recommendations, unless otherwise stated)

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 sec), to reduce the influence of biological 'noise'. [60, 61]

The procedures for data editing and data averaging should be applied consistently within a CPET laboratory; otherwise, results may be adversely influenced. [62, 63] 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 table 4. A comprehensive description of these variables may also be found in key position statements and policy documents. [3-5, 12, 13]

Reporting Exercise Capacity or Functional Capacity

(Grade C, Good Practice Recommendations, unless otherwise stated)

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. Two variables are widely used to describe exercise capacity in perioperative CPET: $\dot{V}O_2$peak and the AT. These variables are both associated with postoperative morbidity and mortality. [8]

Peak $\dot{V}O_2$ (see table 5 for summary)

$\dot{V}O_2$peak is a metabolic rate 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' but it may not reflect what was potentially *achievable* for that patient, i.e. it is not necessarily a physiologically maximal end-point.

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' (a physiological end point). [64] Rigorous determination of $\dot{V}O_2$max relies on demonstration of a plateau in $\dot{V}O_2$ in the face of increasing work rate, e.g. $\dot{V}O_2$ increasing by < 2 ml kg^{-1} min^{-}

[1 65] although the classical approach for determining for $\dot{V}O_2$max is demanding as it requires the completion of several discrete exhausting constant work rate tests. [66, 67] $\dot{V}O_2$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. [68] 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. [69] Unfortunately not all individuals will exhibit a plateau during rapid incremental exercise even when they have attained a physiological maximum. [70 71] 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, including a peak HR within 10 bpm of the age-predicted maximum and a peak respiratory exchange ratio (RER) of more than 1.10. [72] It should be noted, however, that pathology or medication may affect either or both of these criteria in a patient population for example 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. [73]

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. [11] 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. [63, 74] A reasonable choice is a period of ~20 sec or ~3-5 breaths, with the value being reported, as an absolute value (ml min^{-1} or L min^{-1}) or indexed to bodyweight (ml kg^{-1} min^{-1} or L min^{-1} kg^{-1}). With good subject effort, $\dot{V}O_2$peak is independent of the work rate incrementation rate. [75] However, this is not the case for peak work rate (WRpeak) which 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. [75] 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.

Anaerobic Threshold (see table 6 for summary)

The AT 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. [11]

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. [76] The lactate accumulates as a consequence of anaerobic glycolysis and its associated metabolic acidosis. However, the causes of this remain controversial. [15, 77-82] The AT may also be termed the lactate threshold, lactic acidosis threshold, ventilatory threshold or gas exchange threshold. [15] In the perioperative CPET literature, the term anaerobic threshold has been used consistently and is consequently preferred **(Grade D).**

The AT is conventionally estimated non-invasively from respired gas measurements using an incremental ramp exercise test. [3, 15, 83] The AT should be identified using a three point discrimination technique as described by Whipp and colleagues. [83] The modified 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 O_2 and CO_2 to confirm hyperventilation with respect to oxygen but not to carbon dioxide (figure 4). [83-85] The methods used to identify the AT are summarised in table 6.

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 2) or by the modified V-slope method (figure 3). [84, 85] 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. [84]

V-slope method (figure 2). 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. [84] 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.

Modified V-slope method (figure 3). 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.)

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). [84]

Criterion 2: Hyperventilation relative to O_2: the ventilatory equivalent for O_2 and end tidal PO_2 at the AT (figure 4)

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.

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. [86-88] 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. [89, 90] 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. [90] 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 (Table 6)

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.

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

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. [59] 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.

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. [15, 91] The most widely used in clinical practice are those produced by Hansen and Jones. [92, 93] 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. [91] 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.[11] 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. [24] Caution should be used when interpreting exercise capacity values indexed to body weight in patients with a low BMI.

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).[3, 15] 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. [15] 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.[94, 3, 15] Furthermore elevated $\dot{V}E/\dot{V}CO_2$is predictive of mortality and disease progression in cardiac failure,[95-97] and mortality and other outcomes in COPD and other respiratory diseases.[14, 98, 99] In the perioperative setting, $\dot{V}E/\dot{V}CO_2$ at the anaerobic threshold is associated with morbidity and mortality in hepatobiliary surgery,[100, 101] abdominal aortic aneurysm surgery,[26, 102] urological surgery [103] and mixed surgical cohorts.[17] 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.[104-106] 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.[16] Further studies are required to clarify the

additional risk conferred by abnormal ventilatory efficiency in addition to impaired exercise capacity.

The Perioperative CPET Report

(Grade C, Good Practice Recommendations, unless otherwise stated)

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. **(Grade D)**
6. Suggestions for possible referrals and interventions preoperatively **(Grade D)**

An example of a tabular report with a suggested minimum data set is presented in Appendix 3. It is conventional practice to present CPET data graphically in a multi-panel format, typically with 9 panels or 8 panels (figure 5). [3, 15, 107] 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 (figure 5). Interpretation with regard to normality is done against published normal-value databases and algorithms. [3, 15, 91]

Risk Thresholds in Perioperative CPET

Specific recommendations about risk thresholds and recommendations for perioperative care are outside the remit of these guidelines. 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 data collection is planned by POETTS, to provide access to contemporaneous risk threshold data. A summary of current case cohorts is presented in Appendix 1.

Summary

The dynamic metabolic challenge imposed by perioperative CPET provides an objective means of evaluating exercise capacity. It can be used to evaluate chronic comorbidities and may enable identification of new pathology that requires treatment and/or optimisation pre-operatively. The data derived from CPET may be used to inform collaborative (shared) decision-making and the process of consent, to triage patients to high dependency care and to direct individualised exercise training programmes pre- and postoperatively. If CPET data are to help determine surgical patients perioperative care, it is essential that CPET procedures are reproducible and of high quality. This requires laboratory equipment to be maintained, calibrated and validated regularly. Standardised exercise protocols with standardised graphical display of key variables to describe exercise capacity and to investigate possible causes of exercise intolerance should be employed. These guidelines provide direction in these several regards for clinicians performing and interpreting CPET on perioperative patients.

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Author contributions

DZHL, SJ, MPWG, MS, JC, CS, GD, JW, MR, PO, SW: Developed concept and reviewed literature to establish standards

DZHL, SJ, MPWG, MS, JC: Wrote first draft of the paper

DZHL, SJ, MPWG, MS, JC, CS, GD, JW, MR, PO, SW: Critical revision and review of the paper

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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 [3]

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.

Table 2: Key response variables reported for perioperative CPET

Exercise Capacity Variables
• Anaerobic threshold (AT; ml min^{-1} and ml kg^{-1} min^{-1})
• Peak O_2 uptake ($\dot{V}O_2$peak; ml min^{-1} and ml kg^{-1} min^{-1})
• 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^{-1} $watt^{-1}$)
• 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 $beat^{-1}$) - resting and peak exercise
• Arterial 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^{-1}) - resting and peak exercise
• Ventilation ($\dot{V}E$; L min^{-1}) – 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

Table 3: Indications for the premature termination of an exercise test (adapted from[3])

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

Table 4: 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

Table 5: $\dot{V}O_2$peak Definition, Measurement and Key Characteristics

$\dot{V}O_2$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^{-1} or L min^{-1}) and indexed to bodyweight (ml kg^{-1} min^{-1} or L min^{-1} kg^{-1})
$\dot{V}O_2$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

Table 6: AT Definition, Measurement and Key Characteristics

Anaerobic Threshold – Definition, identification and key characteristics
The AT is a metabolic rate expressed in ml kg^{-1} min^{-1} or ml min^{-1}. It is defined as the $\dot{V}O_2$ above which arterial [lactate] first begins to increase systematically during incremental exercise reflecting increased glycolysis.
The AT should be identified using a three criterion discrimination technique (figure 4)
AT Criterion 1 - Identifying excess $\dot{V}CO_2$ relative to $\dot{V}O_2$ above the AT by: • **Modified V-slope:** (figure 3) 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 2) 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 (figure 4) • 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 the baseline.
AT Criterion 3: Exclude hyperventilation relative to CO_2 (figure 4) 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 rise systematically. • There is no reciprocal decrease in $PETCO_2$ at the point where $P_{ET}O_2$ starts to rise systematically.

FIGURES

Figure 1: Biological calibration: steady-state $\dot{V}O_2$at 20 watts and 60 watts in a representative laboratory subject. The relationship between $\dot{V}O_2$ and work rate is 10 ml min^{-1} $watt^{-1}$ – thus a 40 watt increment in work rate is associated with a 400 ml increment in $\dot{V}O_2$.

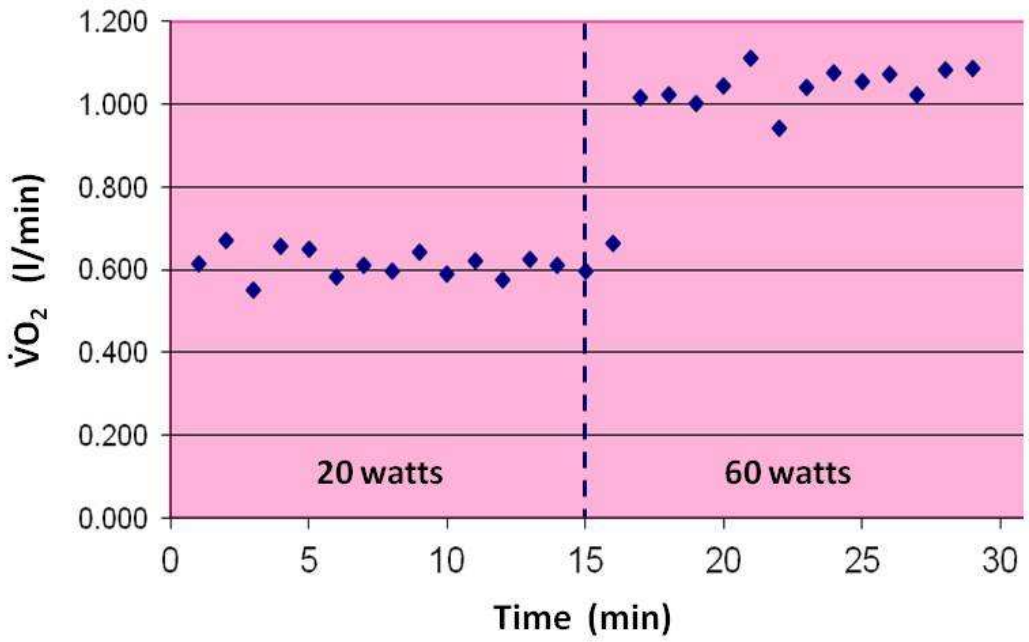


Figure 2: Example of a V-slope estimation in a normal individual. The $\dot{V}CO_2$-$\dot{V}O_2$ relationship is partitioned into linear S_1 and S_2 regions within the region of interest demarcated by the two vertical lines (left: to exclude the initial kinetic phase of response – approximately 60 seconds; right: to exclude respiratory compensation- > 15% change in gradient of the $\dot{V}E$-$\dot{V}CO_2$ relationship) [84]. 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. See text for further details.

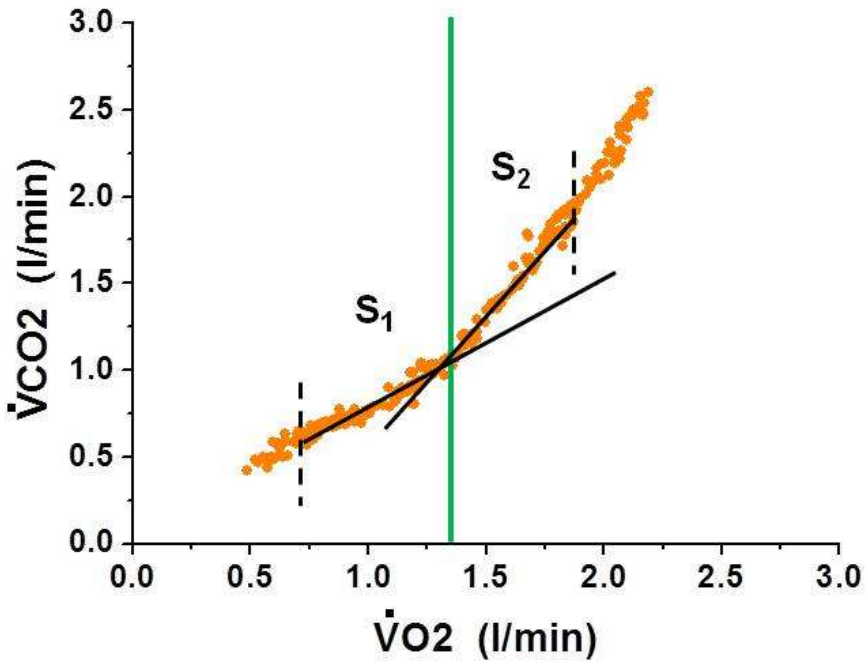


***Figure 3*:** Example of a modified V-slope estimation for the normal individual depicted in Figure 2. A unitary tangent or 'line of one' (black line, with a slope, $\Delta\dot{V}CO_2/\Delta\dot{V}O_2$, = 1.0) has been 'run in' to the $\dot{V}CO_2$-$\dot{V}O_2$ relationship from the right. Its first 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. See text for further details.

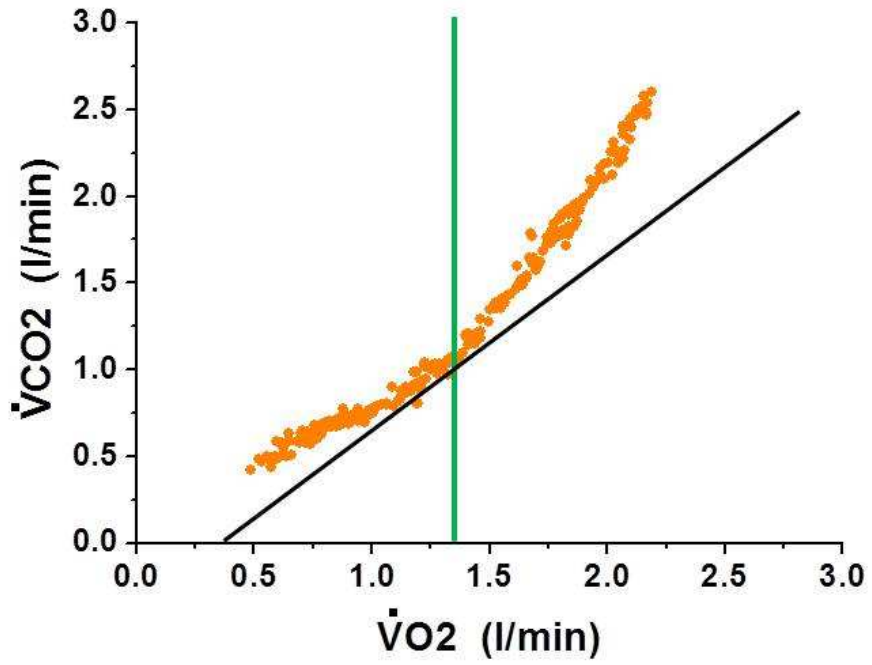


***Figure 4**:* Example of comprehensive AT estimation for the normal individual depicted in Figures 2 and 3. The top panel presents the $\dot{V}CO_2$-$\dot{V}O_2$ relationship, with the modified V-slope index of AT estimation. The middle panel presents the responses of the ventilatory equivalents for 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. See text for further details.

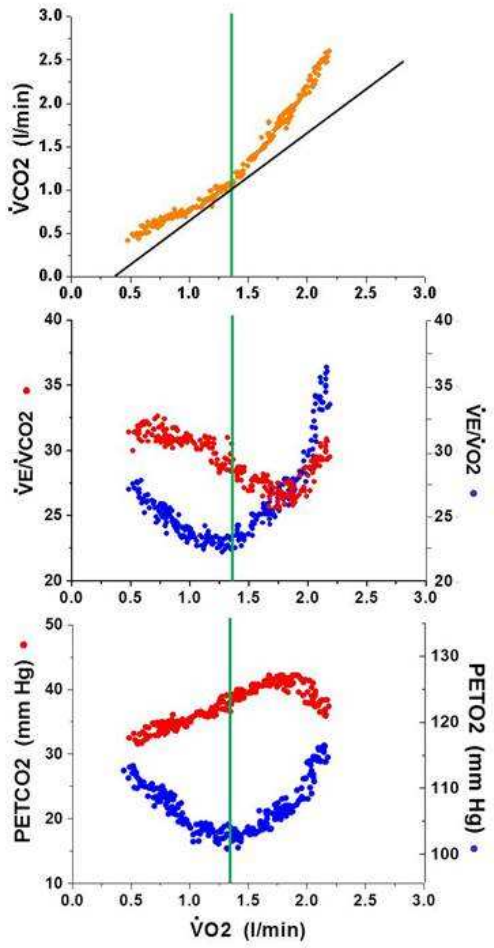
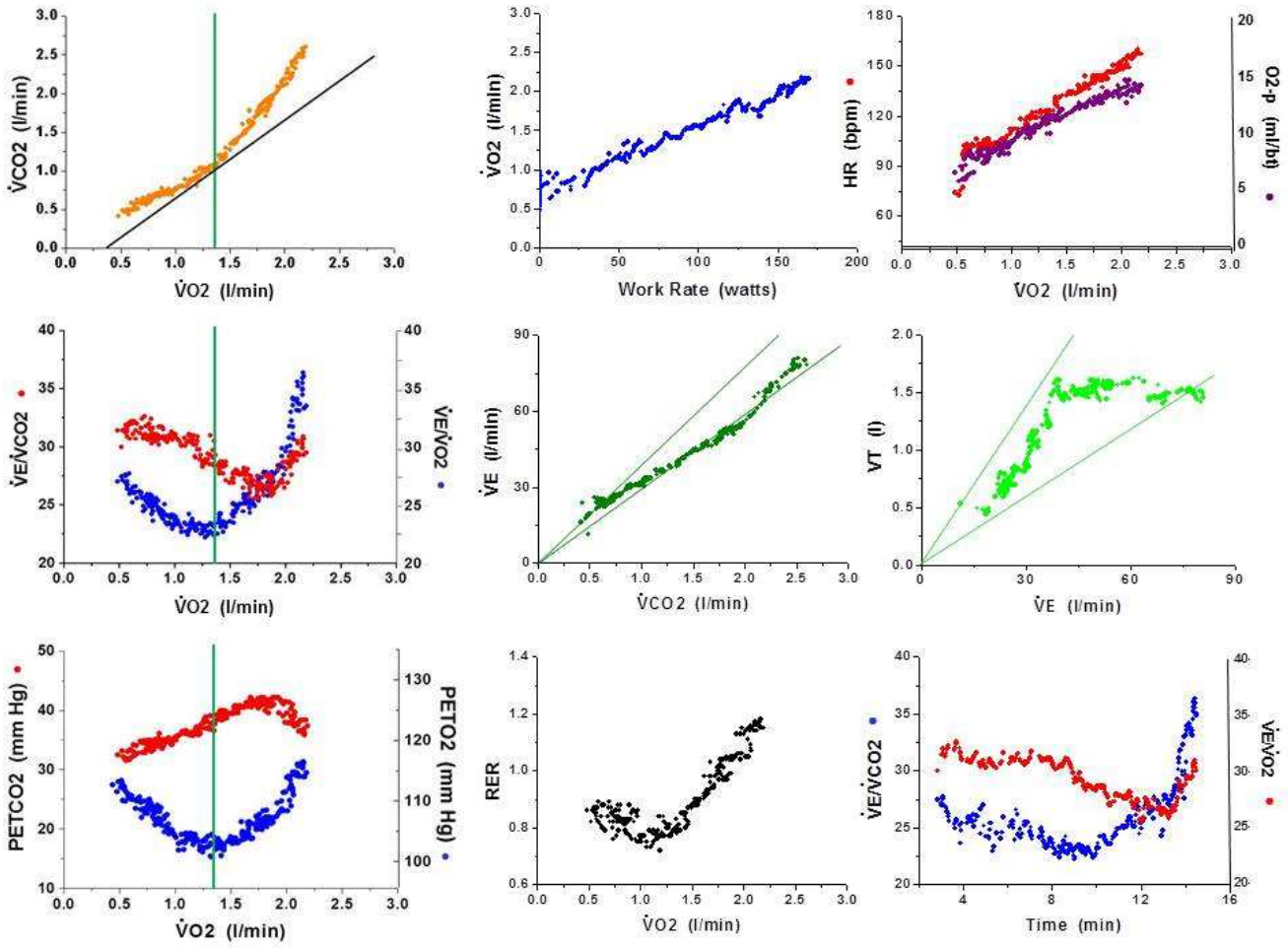


Figure 5: Example of a nine-panel CPET display for the normal individual depicted in Figures 2, 3 and 4 (modified European Respiratory Society format). Top row, Panel 1: $\dot{V}CO_2$ vs. $\dot{V}O_2$; Panel 2: $\dot{V}O_2$ vs. work rate; and Panel 3: HR and O_2 pulse ($\dot{V}O_2$/HR) vs. $\dot{V}O_2$. Middle row, Panel 4: $\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}O_2$ vs. $\dot{V}O_2$; Panel 5: $\dot{V}E$ vs. $\dot{V}CO_2$; and Panel 6: V_T vs. $\dot{V}E$. Bottom row, Panel 7: $P_{ET}O_2$ and $P_{ET}CO_2$ vs. $\dot{V}O_2$; Panel 8: RER vs. $\dot{V}O_2$; and Panel 9: unassigned, but here showing $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ vs. time. Suggested clusters for interpretation: AT estimation (green vertical line), Panels 1, 4, 7 (and 8); cardiovascular limitation, Panels 2 and 3; respiratory limitation, Panels 4, 5, 6 and 7. See text for further details.



Appendix 1: A table of cohort studies reporting a relationship between CPET variables and surgical outcome. AT – anaerobic threshold, $\dot{V}O_2$peak – peak oxygen uptake; $\dot{V}E/\dot{V}CO_2$– ventilatory equivalents for carbon dioxide; POMS [1]– post operative morbidity survey – a survey of postoperative complications in 8 domains; Clavien-Dindo[2] – a postoperative morbidity index covering all domains of morbidity. Adapted from [3]

Author, Year, Journal	Patients	n	AT Association & Risk Threshold (mls/kg/min)	$\dot{V}O_2$ peak Association & Risk Threshold (mls/kg/min)	$\dot{V}E/\dot{V}CO_{22}$	Outcome
MAJOR INTRA ABDOMINAL SURGERY						
Older 1993 *Chest* [4]	Major Intra Abdominal	187	Y <11	Submaximal tests not measured	Y	CVS Mortality
Older 1999 *Chest* [5]	Major Intra Abdominal	548	Y <11	Submaximal tests not measured	Y	Mortality
Wilson 2010 *BJA* [6]	Major Intra Abdominal	847	Y <10.9	Submaximal tests not measured	>34	Mortality
Snowden 2010 *Ann Surg* [7]	Major Intra Abdominal	116	Y <10.1	Y	N	Morbidity - D7 POMS
Hightower 2010 *BJA* [8]	Major Intra Abdominal	32	Y	N	N	Morbidity – self defined
James et al. 2014[9]	Major Intra Abdominal	83	Y	-	-	Morbidity - Major adverse cardiac events
Colson 2012 *BJA* [10]	Major thoraco-abdominal surgery	1,725	N	N	-	Mortality 5 year
COLORECTAL SURGERY						
Lai 2013 BJA [11]	Colorectal surgery	269	Y<11 no CPET or no AT			Mortality 2 year LOS
West 2014 *BJA* [12]	Colon Resections	136	Y <10.1	Y <16.7	Y	Morbidity - D5 POMS; Clavien-Dindo
West 2014 *BJS* [13]	Rectal Resections	105	Y <10.6	Y <18.6	-	Morbidity - D5 POMS; Clavien-Dindo
ABDOMINAL AORTIC ANEURYSM SURGERY						
Nugent 1998 *Iri. Med* [14]	AAA	30	N	N <20 increased morbidity	-	Mortality
Hartley 2012 *BJS* [15]	AAA	415	Y <10.2	Y <15	Y	Mortality
Prentis 2012 *J Vas Surg* [16]	AAA (84 open 101 EVAR)	185	Y <10	Y	-	Morbidity – self defined ICU LOS, LOS
Goodyear 2013 *Periop M* [17]	AAA	188	Y <11	-	-	Mortality LOS, Cost

Author, Year, Journal	Patients	n	AT Association & Risk Threshold (mls/kg/min)	$\dot{V}O_2$ peak Association & Risk Threshold (mls/kg/min)	$\dot{V}E/\dot{V}CO_{22}$	Outcome
Carlisle 2007 *BJS* [18]	AAA	130	Y	Y	Y>42	Mortality midterm
Grant 2015 BJA [19]	AAA	506	Y<10.2	Y<15	Y	Mortality 3 years
Hartley 2012 Br J Surg [15]	AAA	415	Y<10.2	Y<15	Y	Mortality 30 & 90 day
Nugent 1998 Ir J Med Sci. [14]	AAA	30		Y<20		Morbidity
Carlisle JB 2015 [20] Anaesthesia	AAA	1096		Y in multivariable model		Mortality up to 5 years
HEPATOBILIARY SURGERY						
Snowden 2013 *Ann of Surg* [21]	Major Hepatobiliary	389	Y	Y	Y	Mortality LOS
Junejo 2012 *BJS* [22]	Hepatic resection	108	Y <9.9	Y	Y>35	Mortality Morbidity – POMS, Clavien Dindo
Kaibori 2013 BMC Gastroenterol. [23]	Hepatectomy	61	Y<11.5			Mortality Morbidity – Clavien Dindo
Dunne 2014 J. Surg. Oncol. [24]	Liver surgery	197	N	N	N	Morbidity – Clavien Dindo
Ausania 2012 BJS [25]	Whipples	124	Y<10.1	Y	Y	Morbidity – POMS Pancreatic Leak
Ausania, 2012 *Ann R Coll Surg Engl.*[25]	Pancreatic (Palliative Double Bypass)	50	N			Morbidity- POMS
Chandrabalan 2013 *HPB (Oxford).*[26]	Pancreatic surgery	100	Y<10			Morbidity – Clavien-Dindo, pancreatic leak LOS
Junejo 2014 Ann surg Oncol[27]	Pancreatico-duodenectomy	64	N	N	Y>41	Mortality Self defined
Prentis 2012 Liver Transpl.[28]	Liver transplant	60	Y<9			Mortality 90 day
Epstein 2004 Liver Transpl.[29]	Liver transplant	59	Y	Y		Mortality

Author, Year, Journal	Patients	n	AT Association & Risk Threshold (mls/kg/min)	$\dot{V}O_2$ peak Association & Risk Threshold (mls/kg/min)	$\dot{V}E/\dot{V}CO_{22}$	Outcome
Bernal *2014* *Liver Transpl.*[30]	Liver transplant	223	Y	Y		Mortality
Neviere 2014 Am J Transplant[31]	Liver transplant	263	N	Y		Morbidity
UPPER GASTROINTESTINAL SURGERY						
Nagamatsu 1994 [32]*Nihon Kyobu Geka Gakkai Zasshi.*	Oesophagectomy	52	Y	Y	-	Cardiopulmonary Morbidity – self defined
Nagamatsu 2001 *J Thor & CV Surg* [33]	Oesophagectomy	91	Y	Y <800ml	-	Cardiopulmonary Morbidity – self defined

Author, Year, Journal	Patients	n	AT Association & Risk Threshold (mls/kg/min)	$\dot{V}O_2$ peak Association & Risk Threshold (mls/kg/min)	$\dot{V}E/\dot{V}CO_{22}$	Outcome
Moyes 2013 Ann R Coll Surg [34]	Upper GI	108	Y < 9 42%complication vs 29%	Y		Cardiopulmonary Morbidity Common terminology criteria/self defined
McCullough 2006 *Chest* [35]	Bariatric	109	Y	Y <15.6	N	Morbidity – self defined Mortality composite
Hennis 2012 *BJA* [36]	Bariatric	106	Y <11	Y	Y	Morbidity POMS D5
UROLOGICAL SURGERY						
Prentis 2013 BJU Int [37]	Radical Cystectomy	82	Y <12	Y	-	Morbidity - Clavien-Dindo LOS
Ting 2013 J Am Soc Nephrol. [38]	Kidney transplant	70	Y<40% predicted			Mortality
Tolchard 2015 BJU Int. [39]	Radical cystectomy	105	Y<11		Y>33	Clavien-Dindo LOS
Ulubay 2010 Ann Transplant [40]	Renal and cardiac transplant	16	Y		Y	Heart transplant had lower AT and raised $\dot{V}E/\dot{V}CO_2$
THORACIC SURGERY						
Brunelli et al 2012 Ann Thorac Surg[41]	Pulmonary resection	225		Y	Y > 35	Pulmonary complications Mortality
Brutsche et al 2000 Eur Respir J[42]	Non-small cell lung cancer resection	125		Y	Y	Morbidity
Benzo et al 2007 Respir Med[43]	Meta-analysis of lung resection cancer patients	955		Y		Morbidity
Bolliger et al 1995 Am J Respir Crit Care Med[44]	Lung resection (not all carcinoma)	80		Y		Morbidity
Win et al 2005 Chest[45]	Non-small cell lung cancer resection	101		Y		Morbidity
Shafiek et al 2016 Eur Jour Cardiothoracic surgery	Lung resection	83		Y	Y>35	Morbidity

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Appendix 2: Levels of Evidence and Grade of Recommendations used, adapted from evidence levels used in NICE guidance [9 10]

Level of Evidence	Type of Evidence	Recommendation Grade	Evidence
I	Evidence obtained from a single randomised controlled trial or a meta-analysis of randomised controlled trials	A	At least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence level I) without extrapolation
IIa	Evidence obtained from at least one well-designed controlled study without randomisation	B	Well-conducted clinical studies but no randomised clinical trials on the topic of recommendation (evidence levels II or III); or extrapolated from level I evidence
IIb	Evidence obtained from at least one other well-designed quasi-experimental study		
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies		
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities	C	Expert committee reports or opinions and/or clinical experiences of respected authorities (evidence level IV) or extrapolated from level I or II evidence. This grading indicates that directly applicable clinical studies of good quality are absent or not readily available
		D	Recommended good practice based on the clinical experience of the Guideline Development Group

Adapted from [9] Eccles M, Mason J (2001) How to develop cost-conscious guidelines. *Health Technology Assessment* 5:16 and Mann T (1996) *Clinical*

Guidelines: Using Clinical Guidelines to Improve Patient Care Within the NHS. London: Department of Health.

Appendix 3: An example of a perioperative cardiopulmonary exercise testing report

Patient Details:

Indication for Referral and specific questions:

Medical History:

Medications:

Baseline Observations:

Weight		Ideal Weight		BMI		Hb	

Exercise protocol and test conduct:

Incremental test gradient	Watts/min		Incremental phase duration: minutes
Test quality	good/poor and reasons		
Perceived exertion (Borg scale, range: 1-10)	Borg, rest:	Borg, peak exercise:	Observer description of effort
Reason exercise stopped	Patient reason and Investigators' observations		

Exercise Capacity: Anaerobic Threshold and $\dot{V}O_2peak$

$\dot{V}O_2peak$	Absolute ml/min	ml/kg/min	% of predicted	
Anaerobic threshold	Absolute ml/min	ml/kg/min	% of $\dot{V}O_2peak$	
WR	At AT	Watts	At $\dot{V}O_2peak$	Watts
RER at peak exercise				

Cardiovascular Function:

Resting ECG		
Exercise ECG	Ischaemia or arrhythmia or conduction defect – when this occurred during test	
Predicted maximum HR	(normal approximately 220 – age bpm)	
BP	Rest: mm Hg	Peak exercise: mm Hg
Peak HR	Absolute and % of maximum predicted value	
Heart rate reserve	Absolute and %	
O_2 pulse	Absolute and % of predicted peak exercise value; **comment on profile of response**	
$\dot{V}O_2$/WR	ml/min/watt (normal range 10 ml/min/watt; standard deviation +/- 1)	

Respiratory Function:

Breathing Reserve	Absolute and percentage (normal > 15% or greater than 11 l/min)	
$\dot{V}E/\dot{V}CO_2$ at Anaerobic threshold	(normal < 32)	
$\dot{V}E/\dot{V}CO_2$ gradient	(normal < 32)	
Oxygen saturation	Rest %	Peak exercise %
Spirometry	FEV_1 absolute and % predicted, FEV_1/FVC, MVV calculated (e.g. FEV_1 x 40)	

Summary: (a summary containing the following information)
1. Exercise capacity 2. Cause(s) of limitation of exercise capacity & abnormalities in the exercise response 3. Risk implications for the perioperative period 4. Suggested pre-operative optimization/referrals and perioperative management.