

Preoperative cardiopulmonary exercise testing: physiological basis and investigation

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Abstract

The number of cardiopulmonary exercise testing (CPET) centres has doubled in the UK since 2011. Approximately 30,000 tests are performed every year in the UK now. It is a useful tool helping preoperative risk stratification. Patients with poor exercise tolerance are more likely to suffer perioperative complications and death. Interpretation of a large amount of data generated during the test requires a good understanding of basic exercise physiology and its clinical application. Incorporation of CPET data in a global preoperative assessment provides a personalized risk estimate for a patient. This risk estimate discussed with the multidisciplinary team and the patient is an opportunity to make a decision which is in the patient's best interest. Such decisions also help in the best use of healthcare resources. Newer studies in this field are addressing the ongoing debate about the future use of CPET-derived parameters.

Keywords Anaerobic threshold; cardiopulmonary exercise testing; peak oxygen consumption; physiology; postoperative outcomes; preoperative investigation; ventilatory efficiency for carbon dioxide

Introduction

Subjective assessment of patients' physical functional capacity is a poor predictor of major postoperative cardiac complications.¹ Cardiopulmonary exercise testing (CPET) is an objective and comprehensive preoperative assessment of patient's cardiovascular, respiratory and metabolic response to the physiological stress of exercise. It simulates the increase in baseline oxygen consumption produced by the stress of major surgery in the perioperative period, which is usually sustained for days afterwards. CPET is a dynamic and non-invasive test.

CPET-dependent variables can help predict major postoperative cardiovascular events such as myocardial injury, myocardial infarction and death. Submaximal parameters (anaerobic threshold and V_E/VCO_2 , i.e. ventilatory equivalent for CO_2) have been reported to have an association with non-cardiac perioperative complications such as pulmonary, renal, gastrointestinal, infective, neurological, haematological and wound complications.² Low anaerobic threshold has been linked with pancreatic leak after pancreaticoduodenectomy. CPET-recorded parameters also bear a relationship with hospital length of stay or the need for a critical care bed postoperatively.

Current research data related to the use of CPET comes from major vascular and coelomic surgeries (oesophagogastric, major abdominal, bariatric surgery, hepatobiliary, liver transplantation, colorectal, urological and thoracic surgery).³

Indications and contraindications of CPET³

The following are the listed indications for preoperative CPET testing in consensus clinical guidelines by Perioperative Exercise Testing and Training Society (POETTS).³

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

Absolute and relative contraindications of CPET are comprehensively explained in [Table 1](#) and [Box 1](#).

Physiology of exercise testing

Increased demand for oxygen and muscle fuels, and the need to remove the waste products of a higher metabolic rate, trigger various physiological systems in the body using various mechanical and chemical stimuli.

Cardiovascular response to exercise

Cardiac output increases linearly with exercise intensity, especially at submaximal exercise. This is due to an increase in heart rate (HR) and stroke volume (SV). The systolic blood pressure

Absolute contraindications for CPET (POETTS guidelines 2018)

Cardiovascular	Respiratory
Acute M.I. (3–5 days)	Uncontrolled asthma
Unstable angina	Arterial saturation <85% (at rest on room air)
Uncontrolled and symptomatic arrhythmia	
Syncope	
Active pericarditis, myocarditis or endocarditis	
Symptomatic severe aortic stenosis	
Uncontrolled cardiac failure	
Suspected dissecting or leaking aortic aneurysm	

Table 1

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Relative contraindications of CPET (POETTS guidelines 2018)

Cardiovascular

- Untreated left main stem coronary stenosis
- Asymptomatic severe aortic stenosis
- Severe untreated arterial hypertension at rest (systolic BP > 200 mmHg, diastolic BP > 120 mmHg)
- Tachyarrhythmias or bradyarrhythmias
- Significant pulmonary hypertension
- Thrombosis of the lower extremity until treated for a minimum of 2 weeks
- Acute symptomatic pulmonary embolus (within 2 weeks)
- Hypertrophic cardiomyopathy
- Abdominal aortic aneurysm >8.0 cm

Other reasons

- Electrolyte abnormalities
- Advanced or complicated pregnancy

Box 1

rises along with a fall in systemic vascular resistance secondary to vasodilatation in the muscles, improving blood flow. The calf pump improves venous return to the heart contributing to increased stroke volume. The increase in oxygen uptake is due to increased cardiac output and fall in oxygen content of central venous blood as explained by Fick's equation:

$$VO_2 = Q \times (CaO_2 - CvO_2)$$

Where VO_2 = oxygen uptake in ml/min; Q (cardiac output) = $HR \times SV$; CaO_2 = oxygen content of arterial blood; CvO_2 = oxygen content of central venous blood. (Oxygen content of blood is dependent on the amount of haemoglobin (Hb) in grams/dL, the partial pressure of oxygen and oxygen saturation of haemoglobin in per cent. This relationship applies to both arterial and central venous blood.)

VO_{2max} refers to the maximum VO_2 value a patient could achieve physiologically. VO_{2peak} refers to the peak VO_2 value a patient has been able to achieve during the test and it can be limited to due to many factors such as physiological deconditioning and comorbidities.

Exercise tolerance could be reduced due to many pathologies such as cardiac failure, impaired diastolic filling and myocardial ischaemia.

Ventilatory response to exercise⁴

Increased work leading to higher CO_2 production stimulates a rise in tidal volume and respiratory rate (RR), leading to a proportionate rise in minute ventilation (V_E). This increase in minute ventilation is linear until the patient reaches a high VO_2 .

$$V_E = V_T \times RR$$

where V_E = minute ventilation; V_T = tidal volume; RR = respiratory rate.

Exercise-induced increase in ventilation is much more than an increase in cardiac output. The formula below, which could be used for non-invasive determination of VO_2 by analysing respiratory gases, explains why:

$$VO_2 = V_E(FIO_2 - FEO_2)$$

VO_2 = oxygen uptake; V_E = minute ventilation; FIO_2 = fraction of inspired oxygen; FEO_2 = fraction of expired oxygen.

In normal circumstances, FIO_2 and FEO_2 remain stable and the difference between them does not change. Hence the best way to increase VO_2 is by increasing minute ventilation (V_E).

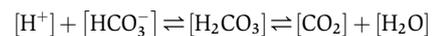
Diffusing capacity of lungs may increase up to threefold during exercise. This is due to the increased diffusion capacity of the membrane and increased volume of blood in pulmonary capillaries.

Pathologies related to any of these factors contribute to poor exercise capacity in patients with pulmonary diseases.

Metabolic response to exercise⁵

ATP (adenosine triphosphate) is the common source of energy for the muscles to contract. However, the body is able to store only enough ATP for 1 to 2 seconds of activity. Therefore, physiological mechanisms in the body are designed for rapid regeneration of ATP. There are three main mechanisms for ATP generation in the muscles. Each one has a different role but all are important for exercise.

1. *Phosphorylcreatine linked pathway (anaerobic)*: During early exercise, phosphorylcreatine, a high-energy compound, is hydrolysed at myofibrils to release ATP quickly but its contribution lasts a few seconds. It also provides ATP during a high level of sustained exercise by cycling between creatine and its phosphorylated molecule (Figure 1).
2. *Aerobic oxidation of free fatty acids and carbohydrates*: During rest and light exercise, free fatty acids are used as the main source of energy, but their metabolism is a slow process. As the intensity of exercise increases, carbohydrates (glucose/glycogen) are metabolized preferentially to keep up with the energy demands. It is an aerobic process which is more efficient, producing 38 ATP per molecule of glucose metabolized via the Krebs cycle and electron transport chain (Figure 2). A patient's CO_2 elimination at this stage matches O_2 consumption (respiratory exchange ratio, i.e. $VCO_2/VO_2=1$).
3. *Anaerobic glycolysis* occurs if the energy needs of the muscles cannot be met by aerobic glycolysis and phosphorylcreatine-linked ATP generation and/or myocytes are hypoxic. It is an inefficient process releasing 2 ATP per molecule of glucose metabolized, but does not require the presence of oxygen. It also produces more H^+ ions than aerobic process due to excess lactic acid, which when buffered by bicarbonate produces H_2O and CO_2 .



The excess CO_2 produced, in addition to aerobic metabolism, will change the balance of oxygen utilization and CO_2 production. VO_2 measured at this point is called the anaerobic threshold (AT).

Anaerobic glycolysis occurs at high intensity exercise in fit patients but could be triggered early in patients with low exercise capacity. Sustained anaerobic environment leads to cellular dysfunction.

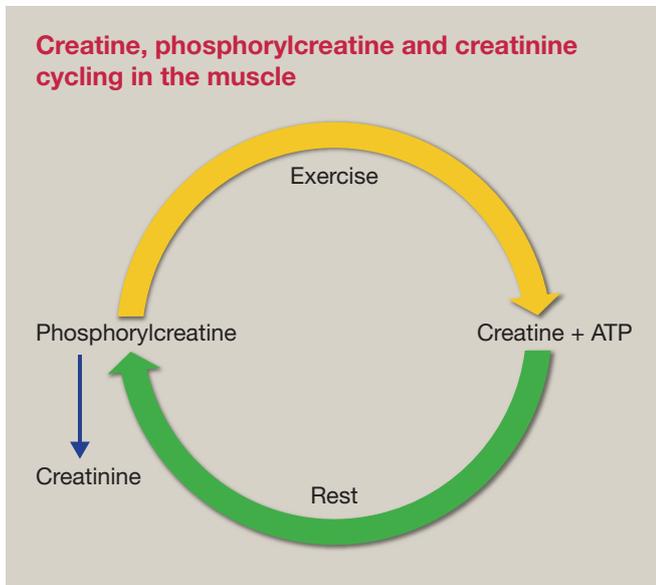


Figure 1

Conduct of the test⁶

Full resuscitation equipment should be immediately available at the time of the test. It is preferable to have two members of staff present during the test.

Meticulous quality control of equipment being used is paramount to ensure high quality data. The flow, O₂ and CO₂ sensors should be calibrated before each test. The cycle ergometer should be calibrated each time it is moved and annually.

Before the start of the exercise a patient's height, weight and resting spirometry data (vital capacity and forced expiratory volume in 1 second, i.e. FEV₁) is collected. The patient is familiarized with the equipment such as cycle ergometer (with

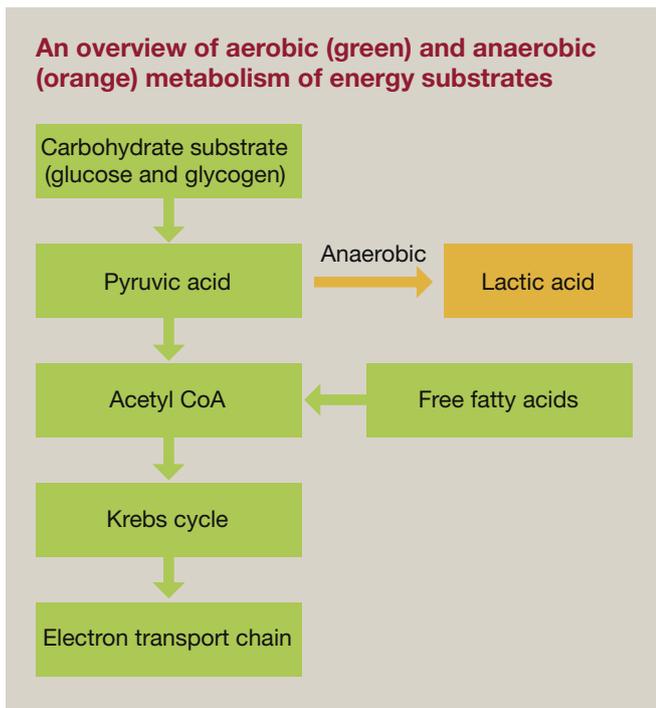


Figure 2

electronically variable load) and the face mask. The height of the cycle's saddle is adjusted, and the patient is trained to maintain a pedalling speed of 55–75 rpm. The patient's work on the cycle can be changed in a controlled fashion by a computer and recorded along with other variables once the test is commenced.

Other equipment required for the test are a metabolic cart containing a rapid gas analyser (response time <90 millisecond) for breath-by-breath analysis of respiratory gases, a flow-volume measurement tachograph attached to the facemask, patient monitors to continuously record 12-lead ECG with ST-segment analysis, heart rate, non-invasive blood pressure, SpO₂, and a graphic display of information recorded during the test. Patient exertion, breathlessness or severity of musculoskeletal pain can be measured by the Borg scale or visual analogue scale.

Patients are verbally encouraged to achieve their best effort during the exercise, aiming to record true peak values, but the test can be stopped at any time by the patient, e.g. fatigue/breathless, chest pain or by the staff due to adverse signs such as ST segment changes or arrhythmias. Patients are discouraged to talk during the exercise but could communicate using pre-agreed signs.

Full monitoring is continued for up to 10 minutes after completion of the exercise to record any adverse signs or their recovery, if developed during the test.

The test is conducted in four phases.

Rest phase (3 minutes)

A minimum of 3 minutes of data is recorded allowing the patient to get comfortable with the cycle ergometer, face mask and other equipment. The ECG is monitored for any adverse changes and any hyperventilation is allowed to settle. Patients are on the cycle but not pedalling during this phase.

Unloaded cycling (3 minutes)

To allow for the HR and ventilatory parameters to attain a steady state prior to the ramp phase. This phase also allows the patient to get used to a pedalling pace between 55 and 75 rpm for the duration of the test but there is no additional resistance added to the cycling.

Ramp phase (8–12 minutes)

The work of pedalling is gradually and uniformly increased based on preselected criteria until the limit of tolerance is achieved for the patient. The limit of tolerance is defined as the point at which the patient is unable to maintain the pedalling pace despite encouragement. Algorithms are available which can estimate the ramp slope based on age, height and weight.

Recovery (5 minutes)

The load on the cycle is removed and the patient is encouraged to keep pedalling to prevent any venous pooling. Monitoring is continued until the heart rate has fallen to within 10 bpm of resting value, BP has returned to the baseline, and any adverse changes to the ECG have reverted.

The reason for stopping the test is noted, e.g. breathlessness, musculoskeletal fatigue, pain or ST-depression.

A vast amount of data is collected during a CPET session, which usually presented as a nine-panel plot of graphical display for interpretation of results.

Analysis of CPET results

Analysis of data generated by CPET testing could be considered as a two-stage process:

Interpretation of physiological data collected during the test

This stage consists of evaluating patient's functional capacity and identifying the reasons for its limitations.

Most of the research around CPET and postoperative outcomes have identified three main variables which predict perioperative risks for a patient undergoing major surgery: anaerobic threshold (AT), peak oxygen consumption (VO_{2peak}), and ventilatory equivalent for CO_2 (V_E/VCO_2).

Anaerobic threshold (AT): The anaerobic threshold is the most commonly reported variable in the literature as a predictor of perioperative outcomes. Out of all variable recorded by CPET, AT is considered most precise in predicting postoperative complications and mortality in the surgical population. It is an indicator of capacity for sustained but submaximal exercise. AT is not subjective to a patient's motivation to exercise during CPET.³

During sustained high intensity exercise metabolism in muscles changes predominantly to an anaerobic state, leading to increased lactic acid levels in the blood. The circulating bicarbonate buffers this excess lactic acid resulting in excretion of more CO_2 via lungs than in aerobic state (see above). This appears as a disproportionate rise in VCO_2 in the VO_2/VCO_2 plot.

AT could be measured using three different criteria, one of them being the V-slope method. The intersection point of two linear regression lines through VCO_2 data points indicate an estimate of AT in L/min. This value is indexed to the body weight providing VO_2 in ml/kg/min which is expressed as AT for a patient (Figure 3). AT linked to the body weight was a better predictor of outcomes than body surface area or ideal weight in morbidly obese patients in a study.⁷ However, caution should be exercised in analysing observed CPET variable values in patients with low BMI.

The value of AT which is associated with poor outcomes has been reported variably in the literature. Patients with AT <11 ml/kg/min have been categorized as high-risk for a wide range of intra-abdominal major surgeries. More recently, studies have suggested a threshold of AT <9 ml/kg/min for liver transplant patients and AT <9.9 ml/kg/min for pancreatic resection patients.⁸ A systemic review by Moran et al.⁹ provides recommendations for different cohorts based on high quality data available in the literature and discusses current issues around the use of CPET variables for risk prediction. A summary of their main findings is presented in Table 2.

AT can vary depending on the muscle group and the equipment used, e.g. a treadmill may have a different threshold from a cycle. There are no approved protocols for arm-crank test and the data generated using an arm-crank has not been benchmarked for risk prediction.

Peak oxygen consumption (VO_{2peak}): As seen in Figure 4, the VO_2 increases linearly in proportion to the workload. At the end of the rapid incremental work test, a maximum oxygen uptake

achieved by the patient is recorded. It is called VO_{2peak} . It is indicative of a patient's best effort and may be affected by the patient's motivation. It is easier to estimate and the results are reproducible. A fit and healthy patient may achieve the physiologically possible maximum oxygen uptake called VO_{2max} which is different from VO_{2peak} .

The VO_{2peak} has been shown to be predictive of postoperative morbidity and mortality in major surgical patients for abdominal and thoracic surgery. Patients with VO_{2peak} <15 ml/kg/min are categorized as a high-risk group in the majority of surgical cohorts. VO_{2peak} is considered superior to AT for risk prediction in AAA repair.

CPET has been recommended in international guidelines for risk stratification of patients undergoing lung cancer surgery. Patients with VO_{2peak} <10 ml/kg/min are considered at a high risk; patients with VO_{2peak} 10–15 ml/kg/min at intermediate risk; and VO_{2peak} >20 ml/kg/min is associated with low risk for postoperative death and complications.¹⁰

The ventilatory equivalent for CO_2 (V_E/VCO_2) is a ratio of minute ventilation (V_E) and carbon dioxide production (V_{CO_2}) used as a measure of gas exchange. It also indicates the ventilation–perfusion relationship for a patient's lungs. Higher than normal values suggest abnormal physiological dead space but could be due to abnormal hyperventilation or both. The value of V_E/VCO_2 quoted at AT point is similar to the slope of linear V_E/VCO_2 on a plot. Patients with chronic cardiac failure, COPD and pulmonary hypertension have a raised V_E/VCO_2 slope.

The V_E/VCO_2 slope is less than 32–34 in normal individuals and it increases gradually with age.^{11,12} The threshold levels associated with poor outcomes range from 34 to 43^{13–15} in peer-reviewed publications. The V_E/VCO_2 has been reported to be predictive of adverse outcomes in some but not all patient groups studied. Recent studies suggest the V_E/VCO_2 slope might be a better predictor of postoperative mortality and pulmonary complications than VO_{2peak} after thoracic surgery, but this needs further consideration.¹⁶

Patients who are unable to complete the CPET due to physical or cognitive limitations are known to have poor outcomes even though the test has not been able to record any objective parameters.

Implications of findings of CPET results

The detailed analysis of physiological data is combined with the rest of the preoperative assessment. This provides a complete picture of implications of the patient's exercise limitation for the perioperative period and an individualized risk assessment is made. Recommendation for preoperative optimization, intra-operative and postoperative care are made on this basis.

Preoperative optimization: CPET complements the concept of general preoperative assessment for optimization of identified limitations/poorly controlled condition. It can identify the main domain limiting the exercise tolerance of a patient, i.e. pulmonary, cardiac or musculoskeletal, and the patient could be referred back to the GP or specialist to further improve control of conditions such as cardiac failure and COPD.

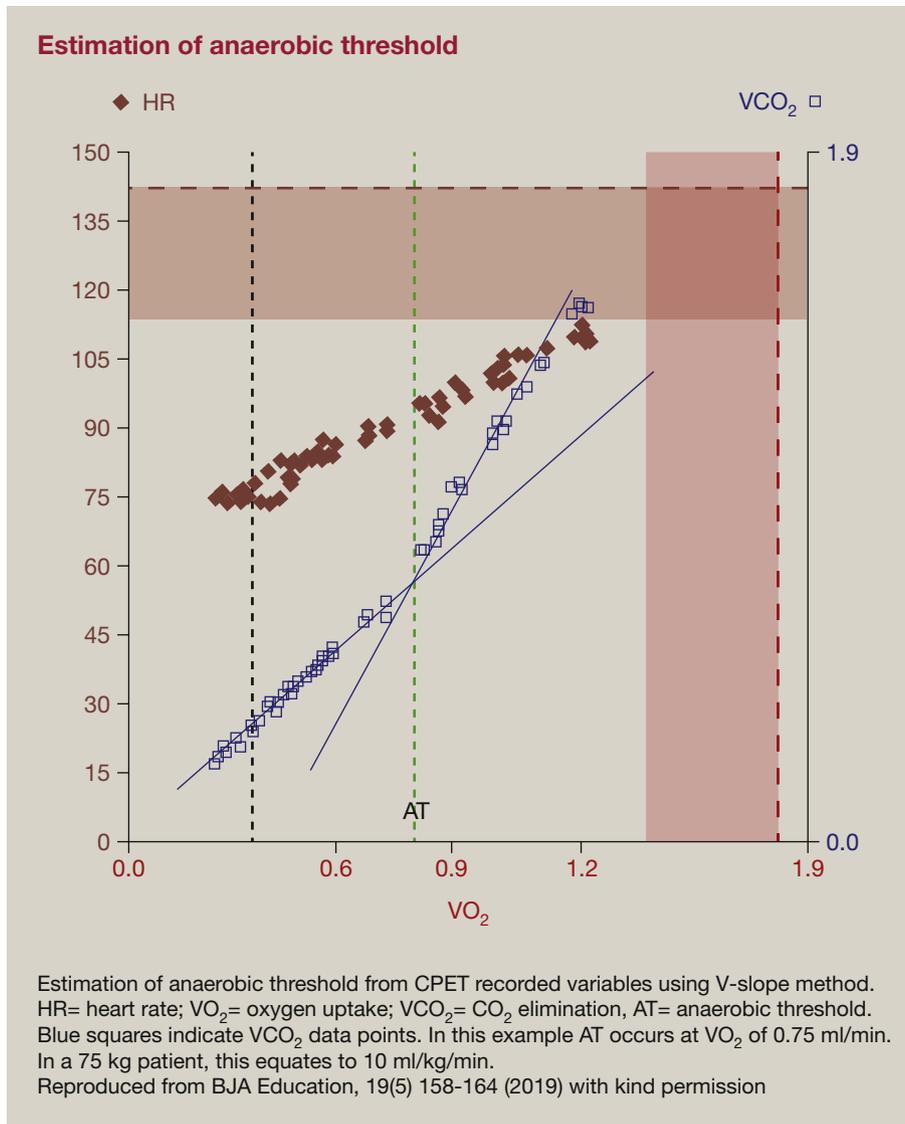


Figure 3

A summary of recommendations by Moran et al. (2016) from their systematic review

Patient cohort	Postoperative outcome	CPET variable	Cut-off point (All values in ml/kg/min)
Hepatic transplant and resection	90-day survival	AT	9
	3-year survival	AT	11.5
	ICU/HDU admission	AT	<9.9
Intra-abdominal surgery	Mortality	AT	10.9
	Morbidity	AT	10.1
	"treat with caution"	AT	10.1–12
	Length of stay and morbidity	AT	10–10.1
Abdominal aortic aneurysm repair	90-day survival	VO_{2peak}	15

AT: anaerobic threshold, VO_{2peak} : peak oxygen consumption

Table 2

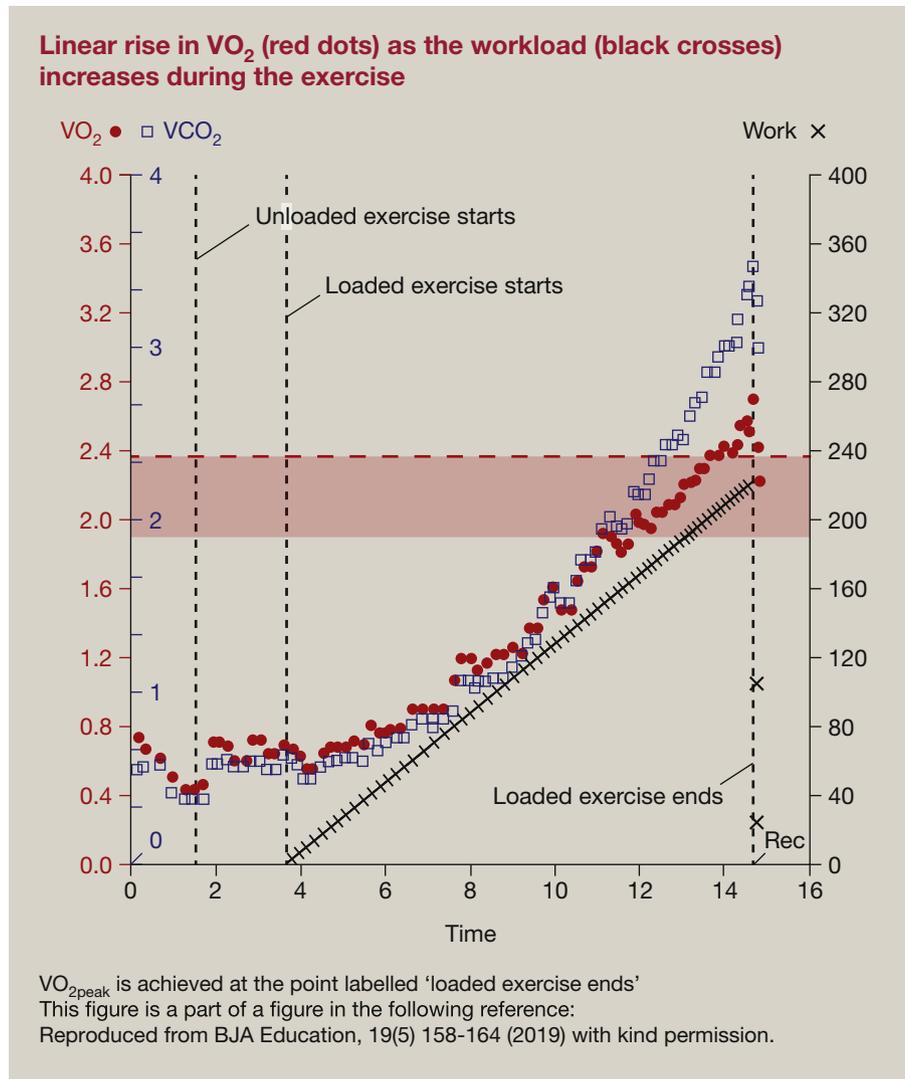


Figure 4

Multidisciplinary decision approach: The data collected from CPET along with general preoperative assessment provides a reliable best estimate of the likelihood of benefit or harm from a planned surgical intervention. This should be shared with different team members such as surgeons, anaesthetists, geriatricians and intensivists, and most importantly with the patient to arrive at a decision which is truly in the patient's best interest and respecting their wishes, e.g. downgrading surgery.

Prehabilitation refers to a range of interventions aiming to increase the preoperative capacity of a patient to deal with the stress of major surgery. It consists of medical optimization of comorbidities such as diabetes, preoperative physical exercise training regime, nutritional support and psychological support to reduce stress/anxiety.¹⁷ CPET forms a part of a baseline assessment of exercise tolerance and assesses the effect of training after it is completed. Many studies have reported improvement in the cardiovascular markers of fitness after a few weeks of exercise preoperatively but there is still a relative lack of research studying its translation into the reduction of adverse postoperative outcome.

Chemotherapy/chemoradiotherapy: The downsizing of locally advanced tumours using neoadjuvant chemotherapy and chemoradiotherapy is a standard of care for many cancers. Such interventions reduce the patient's physical fitness, which on a background of poor exercise tolerance could change the benefit/harm ratio of a planned procedure. Exercise training regimes after neoadjuvant therapy improve the CPET recorded variables of exercise capacity but data is needed to assess its impact on patient outcomes (see Further reading).

Intraoperative and postoperative care: CPET analysis has been guiding other decisions for intraoperative care such as the use of intraoperative invasive monitoring and goal-directed fluid therapy. A previous case-control study of patients undergoing open colorectal surgery demonstrated AT <11 ml/kg/min is associated with fewer cardiac events if managed in a critical environment postoperatively when compared with standard ward care.¹⁸ The knowledge of such thresholds provides useful information for preoperative planning of care and has the potential to reduce adverse outcomes.

Much work has been done in the area of CPET, but there are still unanswered questions. Most of the previous studies have

been unblinded, single-centre and retrospective. In some studies, VO_{2peak} has not been recorded due to concerns around maximal exercise or confounding factors influencing the results which were identified. These shortcomings have been recognized and newer studies are attempting to overcome these limitations. A latest multicentre, prospective, blinded study suggests CPET variables are predictive of postoperative pulmonary and surgical site infections, critical care admission and repeat surgical interventions. However, the Duke Activity Status Index and increased preoperative NT pro-BNP could be better indicators of adverse cardiovascular events as compared to CPET.¹

Summary

A thorough preoperative assessment allows clinicians and patients to make the best decisions about their care. CPET provides an objective preoperative assessment of a patient's functional capacity and an opportunity to tailor strategies for preoperative optimization, intraoperative and postoperative care, minimizing chances of poor outcomes. Good understanding of basic physiology forms a solid foundation for the interpretation of CPET findings providing reliable data for such decisions. CPET is a risk assessment tool to be used along with clinical knowledge and judgment. The risk threshold and parameters identified has helped in improving patient care. CPET is an evolving field, and with ever changing surgical techniques and new research information coming in light is likely to change how and which data variables we could use in the future to support our clinical decisions. ♦

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