Review article

Cardiopulmonary Exercise Test

Koutra M, Curtis R, Rao Baikady R*

Email: rbaikady@yahoo.co.uk

Abstract

Cardiopulmonary exercise testing (CPET) allows the objective measurement of patients' exercise capacity. In contrast to traditional and static investigations for limited exercise tolerance, CPET can provide a global and dynamic evaluation of both cardiovascular and respiratory systems and their functional interactions. There is increasing literature to support the use of CPET in various clinical settings. Its role has been established for the evaluation of chronic heart failure especially for prognosis, measurement of response to treatment and assessment of suitability for heart transplantation. CPET has also been used for assessment of patient's suitability for lung resection. There is currently a lot of interest in the use of CPET as a tool for the preoperative evaluation of patients for noncardiac surgery. Poor fitness levels as measured by CPET variables are shown to be associated with perioperative morbidity and mortality. It can therefore be very useful in risk stratification, preoperative optimisation, patient informed consent process for surgery and allocation of healthcare resources. In this article we review the basic physiological principles behind its use and the conduct of testing. We also summarise the latest evidence relevant to its current clinical applications, with emphasis on management of chronic heart failure, assessment of patient's suitability for lung resection and preoperative stratification of surgical risk.

Keywords: Anaerobic threshold, cardiopulmonary testing, oxygen pulse

Introduction

Cardiopulmonary exercise testing (CPET) allows the comprehensive, dynamic evaluation of a patient's cardiovascular and respiratory systems. From its beginnings in the world of sports medicine, it has evolved into having an increasing role in the assessment of risk for patients undergoing major surgery. Within this article we review the physiological principles behind its use, the conduct of testing and its relevance to major surgery.

Physiology of exercise

During exercise, actin and myosin interaction within the filaments of myofibrils cause contraction to occur, shortening skeletal muscle. This contraction leads to the generation of a force, which in turn allows work to be done. The interaction of actin and myosin requires a supply of adenosine triphosphate (ATP) to provide the energy for the contraction. ATP is rapidly depleted during muscle contraction; initial replenishment occurs when stored creatinine phosphate is used to reform ATP. Once the creatinine phosphate is exhausted it therefore needs to be continually generated within muscle cells by the process of oxidative phosphorylation, which occurs within the mitochondria of the cells. This requires the supply of a substrate (glucose, glycogen or fatty acids) and oxygen. Upon exercise, the body increases blood flow to exercising muscles to allow the additional delivery of substrate and oxygen. Aerobic metabolism occurs when the supply of oxygen to the muscles is sufficient to allow the continuation of the Kreb's cycle and the generation of the maximal amount of ATP from the substrate molecules. From the Kreb's cycle, carbon dioxide (CO_2) is produced. Anaerobic metabolism occurs

R Curtis, MBBS, FRCA
Perioperative fellow in Anaesthesia

M Koutra, MBBS, FRCA
Perioperative fellow in Anaesthesia

R Rao Baikady, MBBS, DA, DNB, FRCA
Consultant in Anaesthesia

The Royal Marsden NHS Foundation Trust, Fulham Road, London, UK, SW3 6JJ

How to cite this article: Koutra M, Curtis R, Rao Baikady R. Cardiopulmonary exercise test. Ind J Resp Care 2014; 3(2): 460-8.

when the supply of oxygen is not sufficient to maintain aerobic metabolism alone. Under these circumstances, the hydrogen ions produced from the breakdown of carbohydrates and fatty acids are transferred to pyruvate to form lactate, which allows further generation of small amounts of ATP. The lactate generated leaves the cell, entering the capillaries and causing blood lactate level to rise. Here it dissociates to form free hydrogen ions, which are buffered by bicarbonate to produce CO_2 which can then be exhaled.

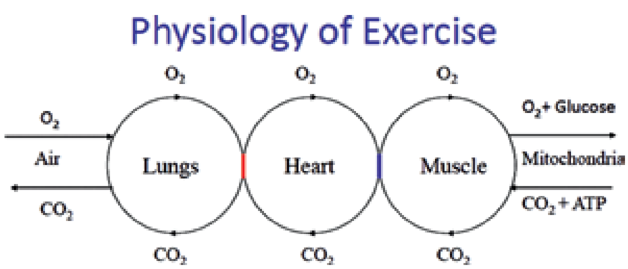

Figure 1: Gas transport system - Oxygen uptake and CO_2 excretion.

Stress response to surgery

After a surgical insult, the body goes into a catabolic state. There is an increase in glucose levels. Predominantly skeletal muscle protein is catabolised to provide amino acids and lipolysis of triglycerides occurs. The increase in catabolism is associated with an increase in oxygen demand of the tissues. As in the exercising state, the body is required to increase supply of oxygen to tissues. If this is not possible, then an oxygen debt is incurred, leading to the generation of lactate and resultant acidosis.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) is a measure of the ability of the cardiopulmonary system to respond to an increase in the metabolic demands of the body. In sports science, it has been used to test the fitness of athletes in order to optimise performance. Given that both exercise and surgery require the body to increase oxygen supply to metabolically active tissue, Older and colleagues first described the use of exercise testing to determine the fitness of patients for surgery.[1] As with testing for sports science, the use of CPET in medicine requires the measurement of key variables.

Oxygen consumption

Oxygen consumption ($\dot{V}O_2$) is the amount of oxygen taken up by the body per minute for metabolism. Its value can be obtained by the Fick equation;

$$\dot{Q} \times (CaO_2 - CvO_2)$$

Where $\dot{Q}$ is a given cardiac output (cardiac output = stroke volume multiplied by heart rate), CaO_2 is the arterial oxygen content and CvO_2 is the venous oxygen content of blood. It is expressed in millilitres per minute, or by millilitres per kilogram per minute if adjusted for weight. During CPET, it is calculated by analysing the oxygen content of inhaled and exhaled gases.

$\dot{V}O_2$ max is the maximum rate of oxygen consumption during exercise. One method of determining this is to demonstrate that there is a plateau in oxygen consumption during increasing levels of exercise. $\dot{V}O_2$ peak is the maximum oxygen consumption that is achieved by a person during the course of a CPET, regardless of whether a plateau has been reached. $\dot{V}O_2$ peak is therefore dependent on the amount of effort that a subject makes. In practical terms during clinical testing of patients, non-athletes will not reach their $\dot{V}O_2$ max during CPET. Hence, the $\dot{V}O_2$ peak is more accurately reported during CPET (as a surrogate for $\dot{V}O_2$ max).

Carbon dioxide production

During exercise, CO_2 is produced from the metabolism of substrate during the generation of energy. CO_2 production ($\dot{V}CO_2$) is a measure of the amount of CO_2 in millitres produced per minute. During CPET, it is measured by gas analysis of the expired air.

Anaerobic threshold

Anaerobic threshold (AT), also known as the lactate threshold, is the oxygen consumption point at which lactate starts to accumulate in the blood due to aerobic metabolism being supplemented by anaerobic metabolism. The AT is most accurately determined by taking blood samples during exercise. During CPET tests, it is determined noninvasively *via* either the inflection point on a graph of $\dot{V}O_2$ *versus* $\dot{V}CO_2$ or the lowest inflection point on a graph plotting the ventilatory equivalents $(\dot{V}E)/\dot{V}O_2$ ratio against $\dot{V}O_2$. These inflection points occur as the body increases ventilation in an attempt to maintain normal pH in the face of an increasing lactate (*i.e.* acidic) load.

Respiratory exchange ratio

Respiratory exchange ratio (RER) is the ratio of the amount of carbon dioxide eliminated to oxygen consumed ($\dot{V}CO_2/\dot{V}O_2$). RER value depends in part on the recent diet that an individual has consumed, and its value is typically 0.8 at rest. If an individual is hyperventilating, for example at the beginning of a CPET, then the RER may be artificially high. As $\dot{V}CO_2$ increases past the AT, there is a rise in RER reflecting the increase in $\dot{V}CO_2$ as the body increases ventilation in an attempt to maintain normal pH.[1]

Ventilatory equivalents

Ventilatory equivalents ($\dot{V}E$) to either oxygen or carbon dioxide are the ratio of ventilation in the form of minute volume to either $\dot{V}O_2$ or $\dot{V}CO_2$. It is an indication of the efficiency of ventilation of the lungs. A high resting $\dot{V}E/\dot{V}CO_2$ ratio indicates a degree of respiratory dysfunction in the form of increased dead space. During the course of exercise both $\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}O_2$ decrease to the AT point before rising afterwards.

FVC, FEV_1 and MVV

Forced vital capacity (FVC) and the forced expiratory volume in one second (FEV_1) are the basic respiratory spirometry tests that are performed prior to commencing a CPET. The FEV_1/FVC ratio can be indicative of respiratory disease. The product of 40 multiplied by the FEV_1 gives the maximum voluntary ventilation (MVV), which can be used in the interpretation of CPET results to determine if there was any respiratory limitation during the course of the test.

Oxygen Pulse

The oxygen pulse is the amount of oxygen consumed by the tissues from each stroke volume (SV). It is calculated by modifying the Fick's equation.

VO_2 (Oxygen consumption) = (HR x SV) X (CaO_2 - CvO_2)

VO_2/HR (Oxygen pulse) = SV x (CaO_2 - CvO_2)

Oxygen extraction is a sensitive indicator of stroke volume deficiency and thus is a good predictor of left ventricular dysfunction or valvular heart disease. The resting oxygen pulse is around 5 ml/beat increasing steadily to 13 - 15 ml/beat at peak exercise in normal individuals.[1]

Practical Aspects of Cardiopulmonary Exercise Testing

The test is carried out as an outpatient procedure. The patient is advised to have a light meal approximately two hours before the test. The test is done in a well aerated room with easy access to all resuscitation facility. Excessive carbohydrate meal must be avoided to keep the respiratory quotient (RER) with in normal range. The subject is asked to sit on a bicycle ergometer or walk on a treadmill and is connected to 12 lead electrocardiogram (ECG), blood pressure cuff and pulse oximeter. The inspired and expired gases are sampled by a metabolic cart *via* a mouthpiece or facemask, allowing measurement of oxygen consumption and carbon dioxide excretion. The computer screen will display the various graphs which can be printed as 9 pane plots at the end of exercise. The patient is asked to pedal the cycle or walk on the treadmill at a steady pace (at 50 to 60 rpm). The resistance is set depending on the patient's general exercise capability. A pre-test spirometry is done before commencing the exercise. The patient is requested to breathe through the mouth during the test. The test lasts for about 10 - 15 minutes. If patient has any acute symptoms of chest pain or ischaemic ECG changes, the test is stopped immediately.

The rate of increment of work is determined by the following formulae depending on the age, sex, height and weight of the patient.

Work increment (W/min) =

Peak $\dot{V}O_2$ (ml/min) men = height (cm) - age (years) x 20

Peak $\dot{V}O_2$ (ml/min) women = height (cm) - age (years) x 14

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

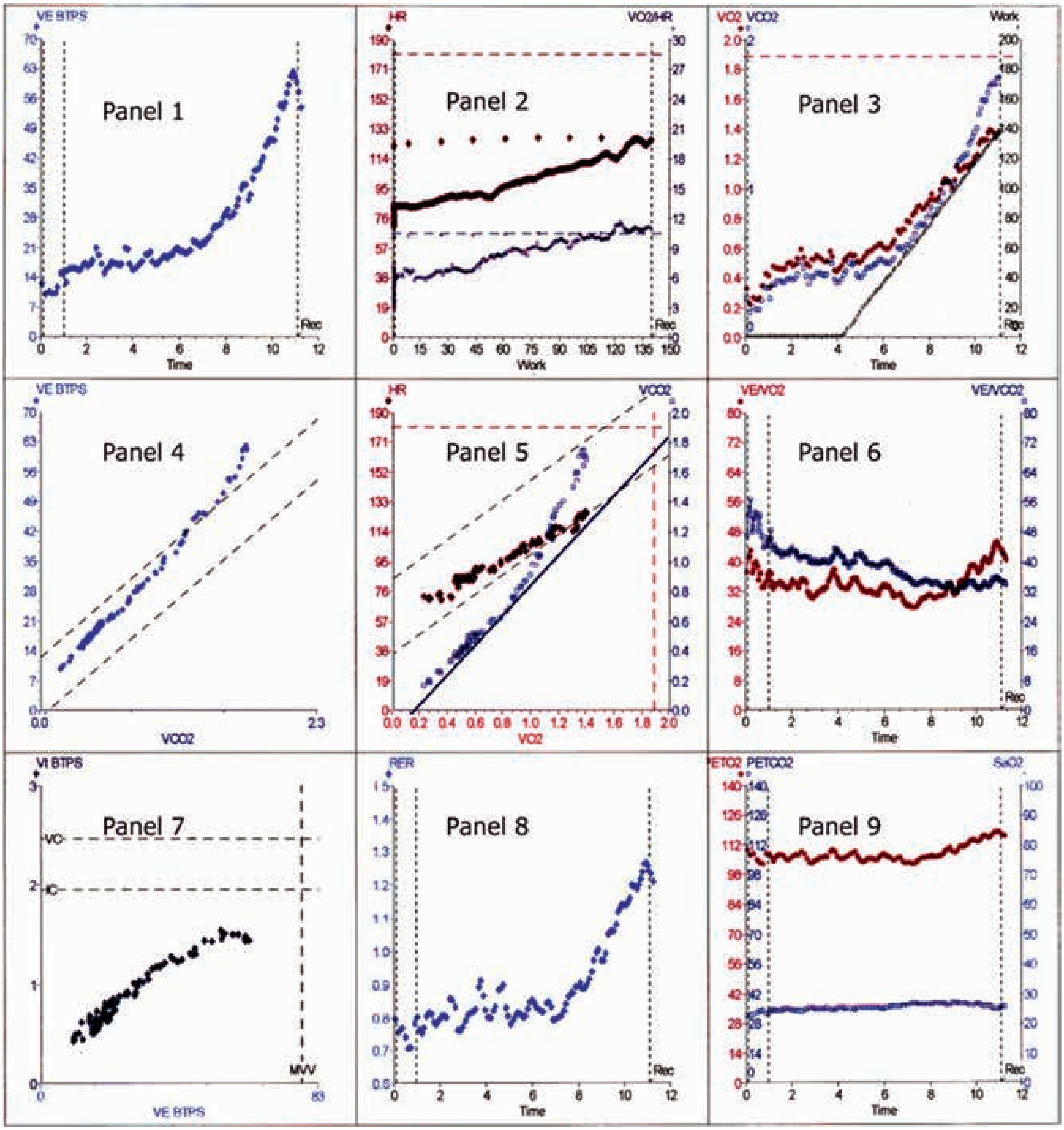

Figure 2: Nine panel plot of normal cardiopulmonary exercise test. Panels 2, 3, and 5 relate to the cardiovascular system, panels 1, 4, and 7 examine ventilation, and panels 6, 8, and 9 look at the ventilation perfusion relationships. Vertical dashed line in panel 1,6, 8 and 9 indicate beginning and end of exercise test. Unloaded cycling is before the left vertical line. In panel 3 slope of work is represented as a line as increase in VO_2 at a slope of 10 ml/min/W. In panel 5 the line with change in VO_2 slope is used to determine the AT.

The resting baseline values are recorded during the first three minutes of the test. Then the patient is requested to start cycling at a steady pace (50 to 60 rpm). Initial few minutes of unloaded cycling is followed by continuously increasing resistance to the cycle ergometer at a predetermined ramp rate.

During exercise, the patient is encouraged to maintain steady pace and complete the test. Predetermined hand signs are used to communicate to avoid speaking during the test. The test lasts for 10 -15 minutes including a 3-minute recovery period. The test can be terminated at any time if patient cannot cycle or any acute ECG changes are present. The most common reasons for termination of the test are exhaustion and leg cramps.[2,3]

Clinical applications of CPET

Preoperative assessment

The indications and contraindications for CPET are summarised in *Table 1* and *2*. The CPET is widely used by cardiologists and respiratory physicians in the management of exertional dyspnoea, cardiac failure and optimisation of various cardiac pathologies. In the last 20 years, there has been an increasing use of CPET to evaluate functional status of a patient prior to major surgery.

Major cavity surgery results in systemic inflammatory response and increased oxygen consumption. The increased oxygen demand continues postoperatively for several days. The increase in oxygen demand is from 110 $ml/min/m^2$ at rest to 170 $ml/min/m^2$ in postoperative recovery period. The cardiorespiratory reserve is crucial in good postoperative outcome.

Older *et al* are one of the pioneers of application of exercise test for risk stratification in major surgery. Nearly twenty years ago they published data from 548 elderly patients undergoing major abdominal surgery. The patients were risk stratified based on their anaerobic threshold (AT) and maximal VO_2. Patients with AT more than 11 ml/kg/min had good postoperative outcome even with ward care, whereas patients with AT less than 11 ml/kg/min required high dependency unit (HDU)/Intensive care (ICU) admission postoperatively with higher mortality and morbidity. They concluded that AT is an excellent predictor of mortality from cardiopulmonary causes in the postoperative period.[4] Preoperative screening with CPET allowed the identification of high risk patients and appropriate perioperative management.[5] In the last decade, various centres around the world have adapted these strategies with similar results. However, most of these studies are single centre trial or observational analysis. The studies have been published for oesophagogastric surgery[6], hepatic transplantation[7], Whipple's procedure[8], pulmonary resection surgery[9,10], major intra-abdominal surgery,[11] vascular surgery,[12] and other intracavitary surgical specialities.[13,14] The results are used for preoperative optimisation of the patients, discuss appropriate surgical techniques and triage of patients for postoperative care in ICU, HDU or surgical ward.

In the last few years, some centres have adapted presurgery exercise programme to improve cardiorespiratory fitness.[15] These regimens can improve fitness by twenty to thirty per cent. The CPET has also been used to quantify chemotherapy induced deconditioning of cancer patients and commence appropriate treatment strategies.[16] Multicentre randomised trials are required to widen the use of this simple practical test in optimisation of major surgery patients. CPET will enhance clinician's understanding of basics in gas exchange and aid in application of test results in appropriate clinical settings.

CPET in the clinical evaluation of patients with heart failure

Limitation of exercise ability is the hallmark symptom of chronic heart failure (CHF) as the impaired heart is unable to meet the increased demands of skeletal musculature. CPET is a well-

Table 1: Indications for CPET

1.	Heart failure - risk stratification and optimisation of treatment
2.	To optimise arrhythmia and BP therapy - Atrial fibrillation, biventricular pacemaker
3.	Exercise regimen - athletes, obesity, functional incapacity (disability determination)
4.	Preoperative assessment for major surgery - risk stratification, optimisation of cardio-respiratory function, improve general fitness before major surgery
5.	Evaluation of exertional dyspnoea, respiratory symptoms.

Table 2: Contraindications for CPET

1.	Symptomatic ischaemic heart disease - angina, acute ischaemic changes on ECG.
2.	Unable to pedal the ergometer cycle or walk on treadmill - severe peripheral vascular disease, severe arthritis.
3.	Any acute illness with inability to exercise - infection, trauma
4.	Recent symptomatic pulmonary embolism, DVT, stroke (less than 3 months)

established technique for risk stratification and transplant selection in patients with heart failure.[17] Although it can provide very useful information for the differential diagnosis of exercise intolerance and dyspnoea, its diagnostic accuracy for heart failure is still not validated.[18]

The impaired systolic function of the left ventricle could explain some of the symptoms and signs associated with heart failure but the pathophysiological mechanism of limited functional capacity in these patients is very complex and not fully understood yet.

The most significant CPET findings in patients with chronic heart failure (CHF) and the possible underlying pathophysiology are as follows:

Low $\dot{V}O_2$max and AT: As described earlier $\dot{V}O_2 = \dot{Q}$ x (CaO_2 - CvO_2). The variable $\dot{Q}$ represents cardiac output. Patients with heart failure have an impaired ability to increase the contractility in order to meet the increased demands of skeletal muscle, which means that for given workload, the cardiac output is lower than in healthy individuals. There is also a decreased ability to increase heart rate, which might be due to β-blockade or chronotropic incompetence. The reduced supply of oxygen to the tissues results in a reduced AT and $\dot{V}O_2$max. The characteristic plateau in oxygen uptake when $\dot{V}O_2$max is achieved is often not seen in patients with CHF, as they are unable to exercise at high intensity level. For these patients the term $\dot{V}O_2$ peak is therefore used instead.

Reduced oxygen pulse: As exercise intensity increases, patients with CHF develop an increased heart rate response relative to oxygen uptake. The ratio $\dot{V}O_2$/HR is termed 'oxygen pulse' and represents the amount of oxygen extracted per beat. The oxygen pulse can represent an estimator of stroke volume. In healthy individuals, the oxygen pulse increases linearly with exercise intensity. In patients with CHF, the oxygen pulse remains low or shallow and reflects low oxygen extraction from the muscles. Sometimes the oxygen pulse may increase immediately post-exercise as a result of the sudden decrease of left ventricular afterload.

Reduced $\dot{V}E/\dot{V}CO_2$ slope: This is a result of increased ventilation relative to CO_2 production. There are two possible explanations for this finding: Firstly, there is a higher proportion of fatiguable Type II skeletal muscle fibres in patients with CHF. These fibres produce more metabolic products during exercise, which stimulate the respiratory chemoreceptors. Secondly, there is augmented response ergoreceptor activation in patients with CHF, resulting in a sympathetic response and hyperventilation during exercise.

Exercise oscillatory ventilation is a characteristic periodic breathing pattern that produces oscillations in minute ventilation during incremental exercise in patients with CHF. It is most commonly seen in patients with advanced disease and is most likely due to derangement of the respiratory homeostasis.[19]

Respiratory disease often co-exists in patients with CHF and restrictive pulmonary impairment is often observed in these patients. This could be possibly due to interstitial or alveolar pulmonary oedema. This abnormality becomes more apparent during exercise as the tidal volume (V_T) increases less in proportion to the respiratory rate (RR), and there is higher dead space to tidal volume ratio (V_D/V_T) for given exercise intensity.

Spirometry manoeuvres before the initiation of exercise can be very useful in differentiating respiratory causes of exercise limitation. The Ventilatory Reserve (VR) reflects the patient's maximum ability to breathe during maximum effort. The VR can be calculated as the difference between MVV and peak minute ventilation during exercise. An abnormally high reserve indicates respiratory disease.[20] Another sign of concurrent respiratory disease is an observed RR>50 breaths per minute during CPET.

The most common application of CPET in patients with CHF is for prognosis and assessment of transplant candidates. The $\dot{V}O_2$peak is the most reliable parameter used for risk stratification. $\dot{V}O_2$peak > 18 ml/kg/min indicates low risk. The CPET thresholds for cardiac transplantation are subject to debate. It should also be noted that peak $\dot{V}O_2$ figures should be adjusted to age, gender and body mass index (BMI). Currently a cut-off of $\dot{V}O_2$peak < 10 ml/kg/min is being used by some centres for the selection of heart transplant recipients.[21]

CPET in the preoperative assessment for lung resection surgery

Spirometry values have traditionally been used in the preoperative risk stratification and decision making for patients considered for lung resection. Although these values reflect the degree of existing airway obstruction, they do not provide direct information about the efficacy of gas exchange and the cardiovascular system. CPET parameters are based on the interactions amongst the respiratory function, the cardiovascular system and the oxygen uptake from the peripheral tissues. Multiple cardiovascular and respiratory comorbidities are often present in candidates for lung resection. CPET can therefore provide a more global and dynamic assessment of their functional status and there is increasing evidence to support its use as an independent risk prediction tool in this patient group.

FEV_1 is useful in predicting the risk of postoperative complications, including death. Absolute FEV_1 values are expressed in litres but may be inappropriate in the elderly, female and patients of short stature. For these patient groups, it is more accurate to use the percentage of the predicted normal value. Large restrospective studies have indicated that a pre-operative value of FEV_1 > 2 L or FEV_1 > 80% of predicted for pneumonectomy and FEV_1 > 1.5 L or FEV_1 > 40% of predicted for lobectomy are associated with low mortality rates. It is therefore commonly accepted to use the above values as criteria, which if met by patients would allow surgery without a need for additional investigations.

Carbon monoxide diffusion capacity (DLCO), expressed as a percentage of predicted, is another useful tool for assessment of patient's suitability for lung resection and risk stratification. Preoperative values of DLCO < 80% of predicted are associated with increased morbidity and preoperative values of < 60% of predicted are associated with increased mortality. DLCO has higher sensitivity in predicting postoperative deaths than spirometry values.

The predicted postoperative values (ppo) of FEV_1 and DLCO can be estimated either by calculating the fraction of lung segments that will remain after resection by using radionuclide scanning and quantitative computed tomography techniques. The ppoFEV_1 has been used to identify patients who may benefit from surgery, but were assessed as unfit based on their preop FEV_1 and DLCO value. A ppo FEV_1 and ppoDLCO less than 40% of predicted normal is associated with high postoperative complication and mortality rates.

Preoperative CPET values and especially $\dot{V}O_2$max have been shown to correlate well with postoperative outcomes.[10] A $\dot{V}O_2$max greater 20 ml/kg/min is associated with good outcomes. If $\dot{V}O_2$max is less than 15 ml/kg/min, it indicates an increased risk of complications and if it less than 10 ml/kg/min, a mortality risk may be up to 50%. There are several studies that describe exercise testing as a useful tool in determining those patients with poor conventional lung function tests, who might be able to tolerate resection. Cohorts of patients with poor respiratory function (FEV_1 < 40%, ppo-FEV_1 < 33% or $PaCO_2$ > 6 kPa) but $\dot{V}O_2$max greater than 15 ml/kg/min survived lobectomy.

The British Thoracic Society (BTS) and the American College of Chest Physicians (ACCP) have published guidelines for the assessment of lung resection candidates, which are similar.[22,23] The guidelines incorporate CPET as a last step in the algorithm. CPET is recommended in order to identify possible surgical candidates amongst patients with ppo FEV_1 <40% and ppo DLCO < 40% of predicted *(Figure 3)*.

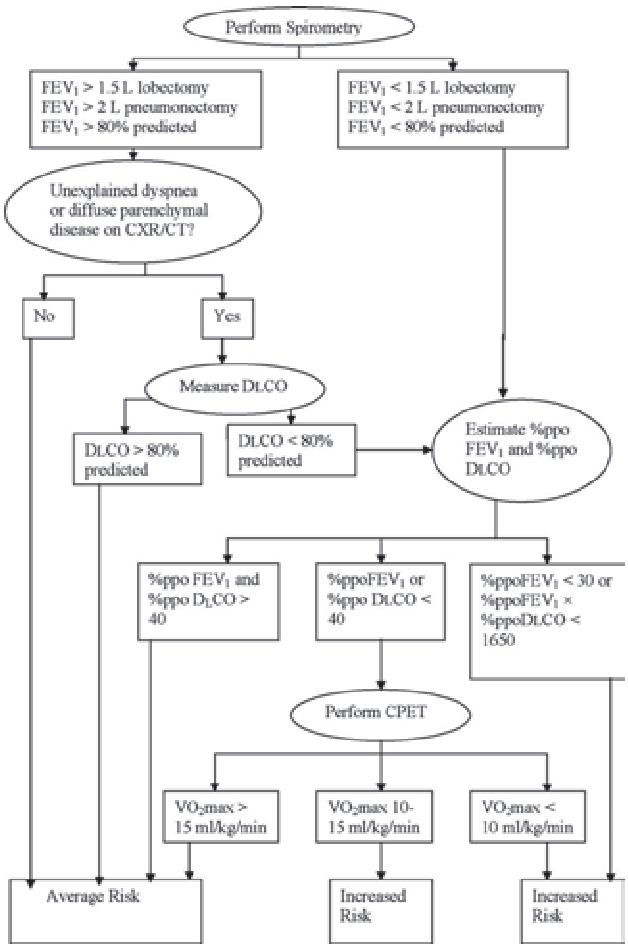

Figure 3: Physiologic Evaluation of the Patient With Lung Cancer Being Considered for Resectional Surgery*: ACCP Evidenced-Based Clinical Practice Guidelines (2nd Edition)

ACCP Evidenced-Based Clinical Practice Guidelines (2nd Edition)

Abbreviations -
O_2 - Oxygen
CO_2 - Carbon dioxide
CPET - Cardiopulmonary exercise testing
AT - Anaerobic threshold
$\dot{V}O_2$ - Oxygen uptake
$\dot{V}CO_2$ - Carbon dioxide output
$\dot{V}E$ - Minute ventilation
$\dot{V}E/\dot{V}O_2$ - Ventilatory equivalence for oxygen
$\dot{V}E/\dot{V}CO_2$ - Ventilatory equivalence for carbon dioxide
MET - Metabolic equivalent
RER - Respiratory Exchange Ratio
MVV - Maximum Voluntary Ventilation
FEV_1 - Forced Expiratory Volume in one second
FVC - Forced Vital Capacity
P_ETCO_2 - Partial Pressure of end tidal carbon dioxide
P_ETO_2 - Partial pressure of end tidal oxygen
CaO_2 - Arterial Oxygen Content
CvO_2 - Venous Oxygen Content
VT - tidal volume
RR - respiratory rate
VR - Ventilatory Reserve
CHF- Chronic heart failure
BMI - body mass index
DLCO - Carbon dioxide diffusion capacity
PPO - Postoperative predicted value
BTS - British Thoracic Society
ACCP - American College of Chest Physicians

References

1. Milani RV, Lavie CJ, Mehra MR, Ventura HO. Understanding the basics of cardiopulmonary exercise testing. *Mayo Clinic proceedings* 2006; **81**:1603-11.
2. Wasserman K, Hansen J, Sietsema K. Exercise testing and Interpretation including pathophysiology and clinical applications. 5th ed. Philadelphia, USA: Lippincott Williams & Wilkins; 2012.
3. Cooper C, Storer T. Exercise testing and Interpretation. UK: Cambridge University Press; 2001.
4. Older P, Smith R, Courtney P, Hone R. Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. *Chest* 1993; **104**:701-4.
5. Older P, Hall A, Hader R. Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. *Chest* 1999; **116**:355-62.
6. Hall A, Older P. Cardiopulmonary exercise testing accurately predicts risk of major surgery including esophageal resection: letter 1. *Ann Thorac Surg* 2009; **87**:670-1; author reply 1-2.
7. Ow MM, Erasmus P, Minto G, *et al.* Impaired functional capacity in potential liver transplant candidates predicts short-term mortality before transplantation. Liver transplantation : official publication of the American Association for the

Study of Liver Diseases and the International Liver Transplantation Society 2014.

8. Chandrabalan VV, McMillan DC, Carter R, *et al.* Pre-operative cardiopulmonary exercise testing predicts adverse post-operative events and non-progression to adjuvant therapy after major pancreatic surgery. HPB : the official journal of the International Hepato Pancreato Biliary Association 2013.
9. Win T, Jackson A, Sharples L, *et al.* Cardiopulmonary exercise tests and lung cancer surgical outcome. *Chest* 2005; **127**:1159-65.
10. Bolliger CT, Jordan P, Soler M, *et al.* Exercise capacity as a predictor of postoperative complications in lung resection candidates. *Am J Resp Crit Care Med* 1995; **151**:1472-80.
11. Wilson RJ, Davies S, Yates D, Redman J, Stone M. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *Br J Anaesth* 2010; **105**:297-303.
12. Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg* 2007; **94**:966-9.
13. Colson M, Baglin J, Bolsin S, Grocott MP. Cardiopulmonary exercise testing predicts 5 yr survival after major surgery. *Br J Anaesth* 2012; **109**:735-41.
14. Hightower CE, Riedel BJ, Feig BW, *et al.* A pilot study evaluating predictors of postoperative outcomes after major abdominal surgery: Physiological capacity compared with the ASA physical status classification system. *Br J Anaesth* 2010; **104**:465-71.
15. O'Doherty AF, West M, Jack S, Grocott MP. Preoperative aerobic exercise training in elective intra-cavity surgery: a systematic review. *Br J Anaesth* 2013; **110**:679-89.
16. Adamsen L, Quist M, Andersen C, *et al.* Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. *BMJ* 2009; **339**:b3410.
17. Ingle L. Prognostic value and diagnostic potential of cardiopulmonary exercise testing in patients with chronic heart failure. *Eur J Heart Failure* 2008; **10**:112-8.
18. Balady GJ, Arena R, Sietsema K, *et al.* Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010; **122**:191-225.
19. Guazzi M, Arena R, Ascione A, Piepoli M, Guazzi MD, Gruppo di Studio Fisiologia dell'Esercizio CdSeRCotISoC. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. *Am Heart J* 2007; **153**:859-67
20. Arena R, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. *Circulation* 2011; **123**:668-80.
21. Fleg JL, Pina IL, Balady GJ, *et al.* Assessment of functional capacity in clinical and research applications: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association. *Circulation* 2000; **102**:1591-7.
22. British Thoracic S, Society of Cardiothoracic Surgeons of Great B, Ireland Working P. BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. *Thorax* 2001; **56**:89-108.
23. Colice GL, Shafazand S, Griffin JP, Keenan R, Bolliger CT, American College of Chest P. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest* 2007; **132**:161S-77S.