

# Cardiopulmonary Exercise Testing: A Review of Techniques and Applications

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## Introduction

Patients who have an inducible myocardial ischemia or a limited cardiac reserve are often at an increased risk of perioperative complications [1]. Preoperative identification of this patient group is important for risk stratification, future intervention studies, and for the efficient use of healthcare resources [2]. Although exercise physiologists and pulmonary physicians have used exercise testing with respiratory gas analysis for many years, its application to cardiovascular medicine is relatively new.

The Duke Activity Status Index is frequently used to assess the level of physical activity the patient in metabolic equivalents (MET) [3]. One MET represents the oxygen consumption of adult at rest ( $3.5 \text{ ml.kg}^{-1} \cdot \text{min}^{-1}$  in a 70 kg man in sitting position). Patients should be able to perform more than 4 METs (climbing at least one flight of stairs) if they are to undergo the stress of major surgery. However, patients often overestimate their exercise capabilities making false assumptions about their own their exercise tolerance level. Echocardiography or spirometry are often used to measure cardiac and pulmonary functions but are limited in usefulness as they are performed at rest, and of doubtful value in predicting postoperative complications [4,5]. Treadmill testing, nuclear cardiology stress studies and debutamine stress echocardiography have been used to ascertain perioperative risk in patients undergoing major noncardiac surgery [6]. However these studies focus on a single organ in contrast to the Cardiopulmonary Exercise Testing (CPET) which provides a global assessment of the integrated response to incremental exercise involving the cardiovascular, respiratory, neurophysiological and skeletal muscle systems, all of which are activated during the neurohumoral stress response to surgery [7].

CPET is a low risk, non-invasive investigation that allows accurate, dynamic assessment of cardiac and pulmonary performance during exercise in a variety of surgical settings [8,9]. By measuring dynamic gas exchange during graded exercise, CPET can identify potential deficiencies within these systems. These are often not adequately reflected in the indices of resting lung and cardiac function. The purpose of this review is to discuss the physiologic basis for functional exercise testing, methodological considerations, and its clinical applications.

## Physiology of CPET

When performing graded exercise, the expired minute volume (VE), oxygen consumption ( $\text{VO}_2$ ) and  $\text{CO}_2$  production ( $\text{VCO}_2$ ) per minute increase linearly with respect to variables like work rate and time [10]. With increasing exercise lactate begins to accumulate in the muscles which are buffered by circulating bicarbonates. However at one point of time  $\text{VCO}_2$  increases out of proportion as the  $\text{HCO}_3^-$ -buffering the lactate produced generates an excess of  $\text{CO}_2$  which is then expired.

The Anaerobic Threshold (AT) is an estimate of the onset of anaerobic metabolism induced lactic acidosis due to an oxygen supply: demand imbalance in the muscles during exercise. This is seldom measured invasively but is usually taken as the time at which the patient starts to exhale increasing amounts of carbon dioxide ( $\text{VCO}_2$ ) and expired minute volume (VE) to compensate for a build-up of lactic acid. However the increase in both  $\text{VCO}_2$  and VE is out of proportion to the increase in  $\text{VO}_2$  at this time.  $\text{VO}_{2\text{max}}$  is an important determinant in CPET as it indicates the maximum possible oxygen consumption. A plateau in oxygen consumption between the final two work rate increments identify that maximum oxygen output has been reached.  $\text{VO}_{2\text{max}}$  is limited by cardiovascular reserve (heart rate and stroke volume) rather than respiratory reserve.  $\text{VO}_{2\text{max}}$  is also dependent on mode of exercise, age, sex, body weight and training.

If we plot  $\text{VCO}_2$  against  $\text{VO}_2$  (the V-slope method) during an incremental exercise regimen the slope is initially similar, however at some time  $\text{VCO}_2$  increase more in respect to  $\text{VO}_2$ . This point of deflection identifies the AT (Figure 1). Another method is by plotting the point of increase in ventilatory equivalent for oxygen ( $\text{VE}/\text{VO}_2$ ) to a relative constant ventilatory equivalent for carbon dioxide ( $\text{VE}/\text{VCO}_2$ ) to identify the anaerobic threshold point (Figure 2). The normal pattern of change in  $\text{VE}/\text{VO}_2$  is a decrease in early exercise to a nadir at

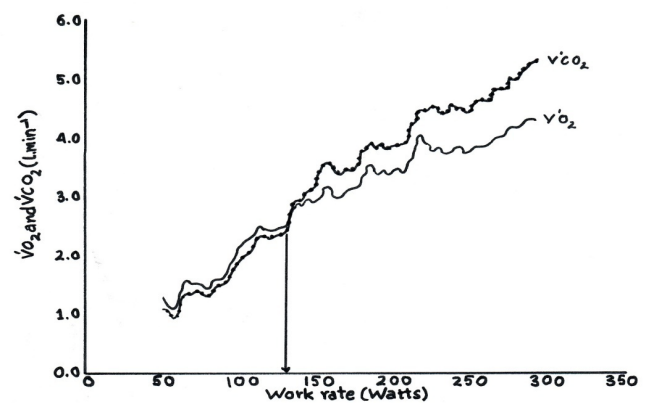


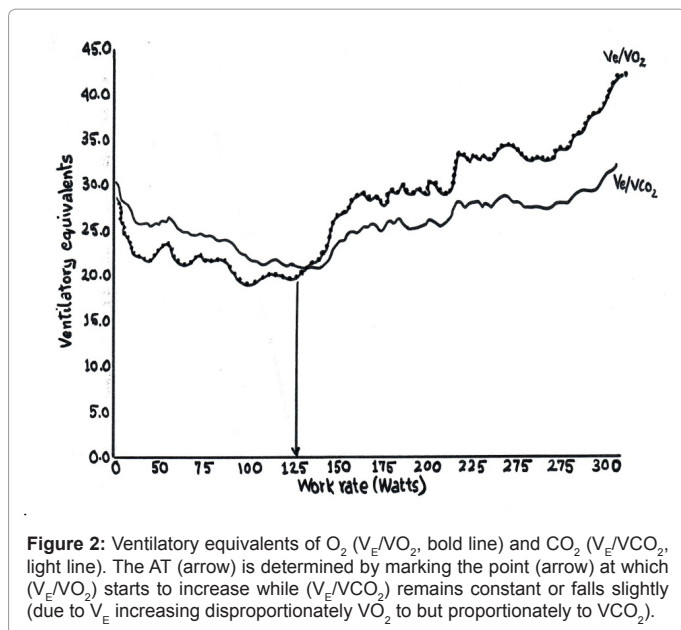
Figure 1: During exercise  $\text{VO}_2$  and  $\text{VCO}_2$  increase linearly till  $\text{VCO}_2$  (light line) outstrips  $\text{VO}_2$  rise (bold line). Arrow denotes the AT.

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or close to the anaerobic threshold and then an increase as maximum exercise capacity is approached. The increase in ventilation that causes this increase in  $VE/VO_2$  is caused by the increased carbon dioxide evolution due to the buffering of lactate [7]. The recommendation from the Joint Guideline of the American Thoracic Society and the American College of Chest Physicians is to use both the V-slope method and ventilatory equivalents method (dual criteria) to minimize errors [11].

AT should always be expressed as a percentage of the maximum oxygen max uptake ( $VO_{2max}$ ). The AT occurs at about 50–60% of  $VO_{2max}$  in normal individuals and a value of below 40% of  $VO_{2max}$  is indicative of severe exercise limitation [11]. It is a marker of maximum work that can be sustained for a prolonged period [12].  $VO_{2max}$  decrease with age. Thus an AT of 11 ml.kg<sup>-1</sup>.min<sup>-1</sup> in a 20 years-old male would be far significant than the same result in an 80 years-old. Failure to perform sufficient exercise till AT is reached however suggests less motivation or a non-cardiac problem [12,13]. The AT if reached will not vary with patient motivation and therefore provides a reliable, repeatable, patient-specific measurement of dynamic functional capacity.

### Indications and Contraindications of CPET

The American Thoracic Society and the American College of Chest Physicians have enlisted the following indications of cardiopulmonary exercise testing [11].

1. Evaluation of exercise tolerance, where the diagnosis is known, in order to objectively evaluate functional capacity, disability or response to treatment.
2. Evaluation of undiagnosed exercise intolerance where cardiac and respiratory aetiologies may coexist, the symptoms are disproportionate to the results of resting investigations or the investigations are non diagnostic.
3. Evaluation of patients with cardiovascular diseases.
4. Evaluation of patients with respiratory diseases/symptoms.
5. Pre-operative evaluation.

Absolute	
• Acute myocardial infarction (3-5 days)	
• Unstable angina	
• Uncontrolled arrhythmias causing symptoms or haemodynamic compromise	
• Syncope	
• Active endocarditis	
• Acute myocarditis or pericarditis	
• Symptomatic severe aortic stenosis	
• Uncontrolled heart failure	
• Acute pulmonary embolus or pulmonary infarction	
• Thrombosis of lower extremities	
• Suspected dissecting aneurysm	
• Uncontrolled asthma	
• Pulmonary oedema	
• Room air desaturation at rest <85%	
• Respiratory failure	
• Acute noncardiopulmonary disorder that may affect exercise performance or beaggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)	
• Mental impairment leading to inability to cooperate	
Relative	
▪ Left main coronary stenosis or its equivalent	
▪ Moderate stenoticvalvular heart disease	
▪ Severe untreated arterial hypertension at rest (>200 systolic and >120 mm Hg diastolic)	
▪ Tachyarrhythmias or bradyarrhythmias	
▪ High-degree atrioventricular block	
▪ Hypertrophic cardiomyopathy	
▪ Significant pulmonary hypertension	
▪ Advanced or complicated pregnancy	
▪ Electrolyte abnormalities	
▪ Orthopaedic impairment that compromises performance	

**Table 1:** Absolute and relative contraindications of CPET.

6. Exercise evaluation and prescription for pulmonary rehabilitation.
7. Evaluation for lung, heart and heart-lung transplantation.

Table 1 shows the absolute and relative contraindication of cardiopulmonary exercise testing [11].

### Performing the CPET

Incremental exercise for the purpose of CPET is by using either the treadmill or the stationary cycle ergometer. Maximal oxygen uptake on the treadmill has been reported to be 5-20% greater than equivalent cycle ergometer work due to involvement of more muscle groups [7]. In the clinical setting, however, in which testing involves nonathletic individuals, it is often possible to achieve maximal oxygen uptake within the more modest metabolic demands of the bicycle [7,14]. With the treadmill, patients may have difficulty in maintaining a continuous forward momentum.

The equipment consists of a metabolic cart and a static cycle/treadmill. The metabolic cart contains gas analyser, a computer and screens which display continuously 12-lead ECG ST segment analysis, and graphical displays of the physiological changes as they occur during exercise. The gas analysers are capable of breath-by-breath measurement of oxygen consumption ( $VO_2$ ) and carbon dioxide production ( $VCO_2$ ) and flow calibration is done before each test [3].

The test is performed in an adequately ventilated room with all resuscitation facilities. After a period of rest to allow the patient to

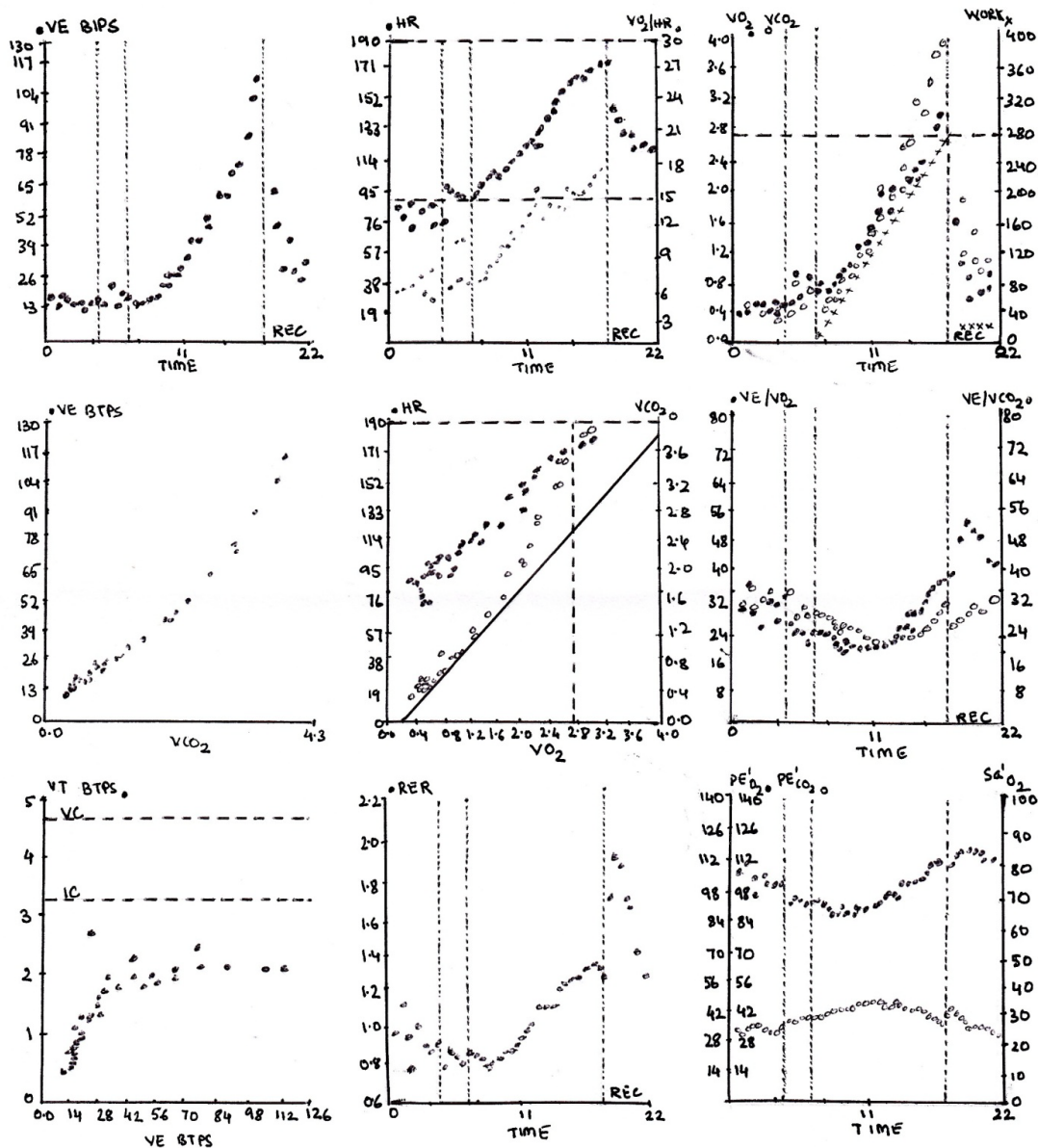


Figure 3: The 'nine-panel plot' numbered 1 to 9 from top left to bottom right of CPET with Anaerobic threshold (AT) at plot 5.

become familiar with the equipment and the bicycle/treadmill, the resting Heart Rate (HR), Blood Pressure (BP), SpO<sub>2</sub>, ECG and gas exchange values are recorded. In a cycle ergometer the saddle height is adjusted and patients advised to pedal at constant speed of 50 to 60 rpm with monitors attached and the tight-fitting facemask/mouthpiece in place with no resistance for a short period of 2 to 3 minutes. Thereafter work rate is increased by 10 to 20 W · min<sup>-1</sup> by the computer, increasing both the gradient and speed (treadmill) or increasing the resistance of the pedals (bicycle) while the subject maintains a constant pedaling rate (bicycle). The optimal duration of the test is around ten minutes for proper assumption of the VO<sub>2max</sub> [15]. The maximum aerobic capacity i.e. VO<sub>2max</sub> is the highest VO<sub>2</sub> recorded when a patient's VO<sub>2</sub> value reaches a plateau with work rate increments and are based on predetermined formulae using the patients age, height, gender and weight [16] (Table 2).

The gas analysers should have a fast response (less than 90 milliseconds) to enable breath by breath measurement of respiratory variables which are averaged every 15 to 45 seconds [17]. Gas flows and volume are quantified by a pressure differential pneumotachograph attached to the patient's mouth piece or a tight fitting mask. There should be minimal static work, as this is not measured. Exercise finishes with a cool down stage in which the patient pedals the bicycle for a brief period against zero resistance or the treadmill is slowed to a walking pace.

The test can be terminated at any stage because of significant chest pain, light headedness, breathlessness or exhaustion of the patient, or by the technician if complications arise such as significant ST changes (>2 mm ST depression with pain or >3 mm ST-depression without pain), severe arrhythmias (frequent and multifocal ectopy, rapid atrial

Work rate increment ( $W \text{ min}^{-1}$ )= $VO_{2\text{max}} - VO_2 \text{ unloaded}/100$
$VO_{2\text{max}}$ ( $\text{ml min}^{-1}$ ) men= $\text{height (cm)} - \text{age (yr)} \times 20$
$VO_{2\text{max}}$ ( $\text{ml min}^{-1}$ ) women= $\text{height (cm)} - \text{age (yr)} \times 14$
$VO_2 \text{ unloaded}$ ( $\text{ml min}^{-1}$ )= $150 + [6 \times \text{weight (kg)}]$

**Table 2:** Formula for determining  $VO_{2\text{max}}$  and work rate increment.

fibrillation, second or third degree heart block), significant decrease or increase in blood pressure, severe desaturations ( $SpO_2 < 80\%$ ), severe pallor or failure to maintain 40 rpm for more than 30 seconds despite constant encouragement. As patients cannot speak they are taught to communicate in predetermined signs regarding significant problems during performance of the test. All patients are followed up for ten minutes with full monitoring in the recovery period. The risk of death is between two and five per 100,000 tests [11].

The AT needs to be reported in the context of the other results so that a more accurate assessment can be made of not only prognosis but possible therapeutic interventions. The things to be noted during a CPET testing are the patient's cooperation and effort; the anaerobic threshold (absolute number and as a percentage of  $VO_{2\text{max}}$ ); the peak and predicted maximum  $VO_2$  ( $VO_{2\text{max}}$ ); cardiac ischaemia, if detected, how it was measured and when it occurred; and lastly a summary of what the team feel the cardiorespiratory risk for the patient is and if they feel any intervention or change in medication would help.

### Interpretation of Data from CPET

A large amount of data is obtained from CPET testing which are displayed in a nine panel plot (Figure 3). These include work rate in watts and metabolic gas exchange parameters such as oxygen consumption ( $VO_2$ ), carbon dioxide production ( $VCO_2$ ), Respiratory Exchange Ratio (RER) and Anaerobic Threshold (AT). Cardiovascular parameters include heart rate, 12 lead ECG with ST analysis, NIBP, and oxygen pulse ( $VO_2/HR$ ) which approximates stroke volume. Ventilatory measurements include minute Ventilation (VE), Tidal Volume (VT) and respiratory rate. Pulmonary gas exchange can be assessed by measuring  $SpO_2$ , ventilator equivalents for oxygen ( $VE/VO_2$ ) and carbon dioxide ( $VE/VCO_2$ ).

As the work rate increases, exercising muscle requires more oxygen to that has to be met by increasing cardiac output.  $VO_2$  is equal to cardiac output multiplied by arterial-mixed venous oxygen difference. Cardiac output increases linearly with  $VO_2$ .

When  $VO_2$  is plotted against  $VCO_2$ , the relationship is composed of two linear components; the first with a slope slightly less than 1.0 (aerobic metabolism) and the second with a slope more than 1.0 (aerobic plus anaerobic metabolism) [18]. The AT is found at the break point between these two components. Though there is inter-observer variability in determining AT, this is acceptable [18].

The oxygen pulse ( $VO_2/HR$ ) is a non-invasive estimate of the stroke volume. It is a ratio of the  $VO_2$  to Heart Rate (HR) and a reflection of the amount of oxygen extracted per heart beat. If the HR is fixed and the  $VO_2$  remains low during exercise then the heart is not able to increase stroke volume and is rate dependent to meet any increase in oxygen demand. Failure of oxygen pulse to increase can be an indicator of poor left ventricular function [7].

### CPET as a Preoperative Assessment Tool

Preoperative risk depends upon the type, site and duration of surgery, apart from associated co-morbid diseases in the patients. A  $VO_{2\text{max}}$  value of less than  $15 \text{ ml.kg}^{-1}.\text{min}^{-1}$  and an AT of less than 11

$\text{ml.kg}^{-1}.\text{min}^{-1}$  is associated with increased perioperative complications and have been shown to discriminate between higher and lower risk patients in noncardiac surgery [9,10,19].

Peak  $VO_2$  of at least  $800 \text{ ml. min}^{-1}.\text{m}^2$  correlates best with postoperative cardiopulmonary outcome after oesophagectomy [20]. Similarly  $VO_{2\text{max}}$  values of less than  $20 \text{ ml.kg}^{-1}.\text{min}^{-1}$  are associated with postoperative complications and 30 day mortality after abdominal aortic aneurysm surgery [9]. Evaluation of CPET before thoracotomy again demonstrates that low AT and peak  $VO_2$  are associated with poor outcome [21].

Patients having AT of more than  $11 \text{ ml.kg}^{-1}.\text{min}^{-1}$  have lesser cardiovascular mortality and length of stay after major surgery [19,22]. Pre-surgical exercise training improve patients' cardiorespiratory fitness (increase in average peak  $VO_2$  by  $3.3 \text{ ml.kg}^{-1}.\text{min}^{-1}$  (20-30%) and reduce postoperative mortality [23]. Anaerobic threshold (AT) of  $< 11$  and  $< 8 \text{ ml O}_2.\text{kg}^{-1}.\text{min}^{-1}$  represent high and very high peri-operative risk, respectively [24-26]. On multivariable analysis, greater values of the ventilator equivalent for  $CO_2$  ( $VE/VCO_2$ ) at anaerobic threshold were found to be associated with worse 30-day mortality and mid-term survival [26].

In thoracic surgery, a  $VO_2 < 15 \text{ ml O}_2.\text{kg}^{-1}.\text{min}^{-1}$  identifies high-risk cases [27]. Preoperative CPET testing is not necessary for all patients, but is considered to have value in patients who after lung resection are expected to have a forced expiratory volume in one second ( $FEV_1$ ) or transfer factor (DLCO) of less than 40% predicted for their age, height and sex. Patients who prove to have a  $VO_{2\text{max}}$  of less than  $15 \text{ ml}^{-1}.\text{kg}^{-1}.\text{min}^{-1}$  on preoperative testing are considered to be at high risk of complications following lung resection [28]. CPET with AT value of less than  $10 \text{ ml. kg}^{-1}.\text{min}^{-1}$  objectively predicted the cardiovascular reserve in operative patients more accurately compared with morbidity indices like POSSUM or the Revised Cardiac Risk Index (RCRI) [25]. However, CPET needs to be validated for each surgical procedure.

### Limitations of CPET

The foremost limiting factor of universal CPET application is the associated cost (about 20,000 pounds for the machine and 3,000 pounds for yearly maintenance). Several factors could introduce error in AT measurement during the CPET. These include genuine alterations in level of fitness; the reliability of the CPET equipment regarding gas leak, miscalibration and malfunction; along with the possibility of inter and intra observer variations in interpretation of CPET results [18]. Variation in protocols and changes in performance caused by a learning effect (an increased skill or improved performance caused by previous exposure to the exercise) with repeated testing can also affect results.

Many patients with impaired left ventricular function are heart rate dependent to increase oxygen delivery. This poses a difficult question for patients who have a low AT who are on beta blockers. In patients on beta blockers with a low AT, CPET allows a safe assessment of their cardiac response during stress when beta blockers are stopped. If the AT improves and little or no ischaemia is found, then this would seem a safer way forward. On the other hand if ischaemia is detected and the AT remains low, either the stress of the operation and recovery need to be modified or coronary perfusion will have to be improved.

Hyperventilation before the start of exercise leads to depletion of body stores of carbon dioxide and may lead to inaccurate estimation of anaerobic threshold with a 'pseudo-threshold' being seen before the onset of metabolic acidosis [7]. Those severely limited by

musculoskeletal or neuromuscular diseases will find any sort of exercise difficult. In patients with lower limb weakness, it can be possible to gain an estimate of functional capacity using a hand cycle ergometer. However,  $VO_{2max}$  values obtained from arm ergometry are only about 70% of those obtained from leg exercise and increase in lactate is often seen early in exercise [7].

## The Functional Walk Tests

Functional walk tests utilize an activity that patients are familiar with, are inexpensive, require little equipment and when the more comprehensive gold standard CPET is not available [24]. The most widely employed and investigated of these are the 6-Minutes Walk Test (6MWT) and the Incremental Shuttle Walk Test (ISWT). Both these tests are highly reproducible. However, these tests are of limited value in patients having lower limb arthritis or ischemia.

In 6MWT a subject can walk for 6 minutes in their own maximum pace along a flat level corridor, turning around cones placed at 30 meters/100 feet distances at each end. Median distances covered are 500-600 meters in healthy subjects. Other measurements include  $SpO_2$ , maximum heart rate and the Borg scale assessment of dyspnoea and leg fatigue [29]. The ISWT involves patients walking around cones set at a distance of 9 meters (going around them is covering 10 meters) at speeds that increase every minute by 0.17 meter per sec in time to audio signals. As the test progresses, the time allowed for walking the shuttle between beeps decreases. Failure to reach the cone before the next tone or exhaustion will stop the test and total distance walked will then be recorded. Distance walked in both tests correlates well with peak  $VO_2$  as measured by CPET, although the ISWT is less familiar to patients and more difficult to administer than the 6MWT and requires more motivation. Incremental shuttle walk test testing in the assessment of preoperative fitness of general surgical patients found that many patients with poor scores or shuttle distances had acceptable levels of oxygen consumption with reasonable anaerobic thresholds (anaerobic threshold greater than 11  $ml \cdot kg^{-1} \cdot min^{-1}$ ) [30].

Preoperative studies show that a 6MWT distance of less than 350 meters has been used as a trigger to consider Lung Volume Reduction Surgery (LVRS) for management of significant COPD and distances less than 200 meters predict high 6-months mortality following LVRS [31]. A threshold distance of 350 m on ISWT predicts low mortality after oesophagectomy. A distance of 400 m on the shuttle test has been shown to correlate with a peak oxygen consumption of at least 15  $ml \cdot kg^{-1} \cdot min^{-1}$  on formal exercise testing [32].

Using the regression method, a patient with a positive test (6MWT < 427 meters;  $AT < 11 \text{ ml } O_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) is likely to be at high perioperative risk, and a patient with a negative test (6MWT > 563 meters) would be considered low risk, with the zone of 'clinical uncertainty' in between taking into consideration the clinical risk factor [24].

## Conclusion

Cardiopulmonary exercise testing is a blend of conventional exercise testing procedures (e.g. ECG, blood pressure) along with ventilatory expired gas analysis (e.g. oxygen consumption, carbon dioxide production and minute ventilation). This combination of variables provides the ability to assess an individual's response to physical exertion and stress in a refined manner. Therefore, CPEX is highly valuable when unexplained exertional limitations are present as this assessment technique can help to isolate physiologic abnormalities in the cardiovascular, pulmonary and/or skeletal muscle systems.

Moreover, a number of CPET variables have proven to be highly prognostic in a number of patient populations [33].

The question that needs to be resolved over the coming years is the utility of CPET in the preoperative assessment and testing of patients. Presently, CPET is a showing encouraging results in patients with unexplained exertional dyspnea as well as those diagnosed with heart failure. To be noted as well is the emerging evidence suggesting CPET has clinical utility in patients with suspected and or confirmed pulmonary arterial hypertension or secondary pulmonary hypertension, pulmonary disease, hypertrophic cardiomyopathy, suspected myocardial ischemia, and suspected mitochondrial myopathy. It appears very likely that the clinical application of CPET will expand in the coming years.

In conclusion, based on the body of research in this area, CPET clearly provides highly valuable clinical information in a number of patient populations. It is being hoped that clinicians would have a more objective data in patient assessment other than just functional status, which would benefit these subset of patient population and be of value in clinical practice.

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