Healthcare professional's guide to Cardio-Pulmonary Exercise Testing

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Abstract

Cardiopulmonary exercise testing (CPEX) is a valuable clinical tool that has proven indications within the fields of cardiovascular, respiratory and pre-operative medical care. Validated uses include investigation of the underlying mechanism in patients with breathlessness, monitoring functional status in patients with known cardiovascular disease and pre-operative functional state assessment. An understanding of the underlying physiology of exercise, and the perturbations associated with pathological states, is essential for healthcare professionals to provide optimal patient care. Healthcare professionals may find performing CPEX to be daunting, yet this is often due to a lack of local expertise and guidance with testing. We outline the indications for CPEX within the clinical setting, present a typical protocol that is easy to implement, explain the key underlying physiological changes assessed by CPEX, and review the evidence behind its use in routine clinical practice. There is mounting evidence for the use of CPEX clinically, and an ever-growing utilisation of the test within research fields; a sound knowledge of CPEX is essential for healthcare professionals involved in routine patient care.

Keywords: cardio-pulmonary exercise testing; CPEX; exercise testing; CPEX evidence; guide to CPEX; guide to exercise testing; understanding CPEX; CPEX supervision; CPEX training; basic CPEX; CPEX indications.

Key messages:

1. CPEX provides valuable insight into pathophysiology of a breathless patient.
2. CPEX is a safe test and increasingly performed on high risk patients.
3. There is strong evidence for CPEX data in monitoring heart failure patients and predicting peri-operative risk in lung and abdominal surgery.
4. Knowledge of CPEX is essential for the healthcare professional, with mounting evidence in the field.

Introduction

Cardio-pulmonary exercise (CPEX) testing is used to establish the degree of exercise limitation, to identify the underlying mechanisms responsible in patients with breathlessness, and to monitor functional status in cardiovascular disease (1). It is an important prognostic tool and decision-aid in the assessment of perioperative risk (2). In addition to the routine parameters measured during the exercise electrocardiogram (ECG) stress test, CPEX can provide measurements of oxygen (O_2) consumption, carbon dioxide (CO_2) production, and lung ventilation to provide valuable information about respiratory, cardiovascular and muscle metabolic function as well as the subject's effort during the test. Despite its useful diagnostic and prognostic functions, and established role in several guidelines for management of cardiovascular diseases, CPEX has remained largely a research or sport sciences tool, and is grossly under-utilized in clinical practice. This is commonly due to a lack of local expertise or awareness about the utility of CPEX among physicians. We review the indications and contraindications for CPEX and describe a standard protocol for cardiopulmonary stress testing. Additionally, we propose a practical reporting and data interpretation guide for the junior cardiology/respiratory trainee.

Indications and contraindications of CPEX

The diagnostic and prognostic indications, along with the contraindications for CPEX testing are listed in Table 1. The ATS/ACCP guidelines (2003) include these absolute contraindications to CPEX (3), however recently the test has been performed safely in conditions like severe aortic stenosis (4). Indications to perform the test are also increasing, as in the diagnosis of heart failure with normal ejection fraction (5) and in exercise prescription for heart failure patients (6).

Table 1: Indications and contraindications of cardio-pulmonary exercise testing

Indications
Diagnostic
Breathlessness of unknown cause
Cardiac ischemia detection
Prognostic
Heart failure (prioritization for heart transplantation)
Perioperative risk in patients undergoing major surgery
Chronic obstructive pulmonary disease (COPD)
Pulmonary hypertension
Risk of lung resection
Congenital heart disease
Absolute Contraindications
Acute myocardial infarction (3-5 days)
Acute myocarditis
Severe symptomatic aortic stenosis
Uncontrolled heart failure
Uncontrolled arrhythmia
Dissecting aneurysm
Resting Oxygen saturation of <86%

Preparation for CPEX Assessment

Patients are advised to avoid caffeine, nicotine and food for two hours prior to CPEX (7). Enquiry into the patient's past medical history, medications, any limitations and any special requirements for participation in CPEX should be made. If the patient has a pacemaker, defibrillator or a cardiac resynchronisation device, guidance of the cardiac physiologist or rhythm management specialist should be sought. Additional assessments which should be completed in advance of CPEX include: clinical examination of the cardiovascular, respiratory and peripheral vascular systems, ECG, resting oxygen saturation, blood pressure (BP), spirometry, including vital capacity and forced expiratory volume in the first second (FEV1).Commonly used abbreviations in CPEX are given in table 2.

Table 2: Commonly used abbreviations in CPEX (8)

VO_2 (oxygen uptake)	Amount of oxygen extracted from inspired gas per unit time (may be expressed as an absolute value (ml/min) or corrected for weight (ml/kg/min))
VCO_2	Amount of carbon dioxide exhaled from the body per unit time (usually, per minute)
VO_2 max	Maximum oxygen uptake achievable (confirmed by repeated tests), despite further work rate increases
Peak VO_2	Highest VO_2 achieved during presumed maximal effort (as indicated by RER>1.15), for that test
R (or Respiratory Exchange Ratio)	Ratio of carbon dioxide output to oxygen uptake (VCO_2/VO_2)
VE	Volume of air inhaled or exhaled by the body in 1 minute
MVV (Maximum Voluntary Ventilation)	The maximum potential ventilation achievable (estimated as FEV1X40)
Anaerobic threshold (AT)	Exercise limit above which the subject's anaerobic high energy phosphate production supplements aerobic metabolism
Breathing Reserve	The difference between maximum voluntary ventilation and the achieved maximum exercise minute ventilation

Checklist before the test

- Clinical history
- Drug history
- Device history (pacemakers/defibrillators)
- Clinical examination
- Electrocardiogram
- Blood pressure
- Oxygen saturation
- Recent haemoglobin

Protocol

The patient is prepared by connecting them to an ECG monitor and facemask. The facemask is tested for any air-leak and connected to the gas analyser. An alternative to facemask is mouthpiece with a nose-clip. Saliva dribbling from the mouthpiece is however a problem especially at peak exercise. A pulse oximeter and sphygmomanometer are attached. Oxygen saturation could be measured either through a finger or earlobe probe (3). New forehead sensors are another alternative.

Incremental exercise testing can either be performed on a treadmill or an electronically-braked cycle. Treadmills are widely used in USA and UK (9), and are a popular method allowing most patients to exercise to their maximal physical limit, achieving satisfactory end-points. Cycle ergometers are advantageous for quantifying work-rate accurately and additionally enable clinicians to gain arterial blood gas (ABG) samples if necessary. People with musculoskeletal limitations or imbalance that might limit weight-bearing may prefer the cycle ergometer, however hamstring fatigue could stop cycle exercise before true peak VO_2 is reached (9). The peak VO_2 achieved on cycle is usually 10-20% lower than that on a treadmill (9). Figure 1 shows a patient performing CPEX on a cycle ergometer.

Figure 1: CPEX test performed on a cycle ergometer

1. **ECG monitor**
2. **Gas exchange monitor**
3. **Saturations probe**
4. **Oxygen and carbon dioxide sampler**

Current software calculates the maximum watts achievable automatically, based on the patient's sex, age, height, and weight. Then a protocol is selected to reach the maximum exercise in 10-minutes, usually by dividing likely maximum watts by 10. The patient should be encouraged to exercise to his/her maximum physical limit, so that O_2 consumption at peak exercise can be measured.

Several protocols with different increments in workload exist; a typical example is presented in Table 3. Following a 2-minute warm-up period, the exercise starts with speed and gradient increased by 1 km/hour and 1% respectively every minute. Less fit patients can use a protocol with half a kilometre speed increase every minute. The operator records the reason for stopping the test at the end.

Table 3: Example of a typical treadmill CPEX protocol

	Warm-up 2 mins	Stage 1 1 min	Stage 2 1 min	Stage 3 1 min	Stage 4 1 min	Stage 5 1 min	Stage 6 1 min	Stage 7 1 min	Stage 8 1 min	Stage 9 1 min
Speed Kilometre/hour	2	1	2	3	4	5	6	7	8	3
Gradient	0%	1%	2%	3%	4%	5%	6%	7%	8%	0%

Patients should be monitored closely for complications. Table 4 lists the indications for terminating the test early.

Table 4 : Indications for terminating a CPEX test (3)

<u>Symptoms and signs</u> Limiting chest pain Dizziness Poor co-ordination Sudden pallor Confusion
<u>Measurements</u> Significant ECG changes suggesting ischemia (ST depression >3 mm, ST elevation, LBBB) Second or third degree heart block Ventricular tachycardia Supraventricular tachycardia, new onset atrial fibrillation Fall in systolic blood pressure of >20 mmHg Severe desaturation to <80%

Physiological parameters

Anaerobic threshold

Oxygen (O_2) consumption and carbon dioxide (CO_2) production increase with incremental workload on exercise. CO_2 production is linearly related to the amount of O_2 consumed during exercise, until the onset of anaerobic metabolism (3). The lactate produced by anaerobic metabolism contributes to additional CO_2 production, measured in the expired air from this time point, resulting in a disproportionate increase in CO_2. This inflection point between the linear component and the progressively greater increase in CO_2 production relative to the O_2 consumption is called the anaerobic threshold (10). An example is shown in figure 3.

Peak and Max VO_2

O_2 consumption obtained at peak exercise (averaged over 60 seconds) is called peak VO_2 (PVO_2). A peak VO_2 <85% of that predicted for age and gender, indicates significant exercise limitation (3). Normal age and sex specific values for Peak VO_2 have been defined in various studies (11, 12). At maximal exercise, the VO_2 consumption plateaus despite incremental increases in workload. This state is achievable in healthy adults (13). Max VO_2 is a term used to denote the maximum O_2 consumption possible for that subject, and is measured by several constant-work-rate exercise tests, each at varying workloads. Peak VO_2 achieved in incremental testing is usually very close to the Max VO_2. Max VO_2 is not routinely used in the clinical setting.

Maximum Voluntary Ventilation (MVV)

Maximum Voluntary Ventilation (MVV) is estimated from pre-test FEV1 obtained by spirometry and multiplied by maximum respiratory rate (MVV = FEV1X40). Breathing reserve is then calculated by subtracting the ventilatory equivalent, (VE, expressed in litres/minute) measured at peak exercise from the MVV (BR= MVV-peak VE [normal >11 litres]). Breathing reserve is preserved in patients with cardiac limitation and in those with deconditioning, but is usually reduced to <11L in patients with respiratory disease (14).

Lung Dead Space

The ratio of the lung dead space (VD) to the tidal volume (VT) is another important measurement. The VD/VT is increased in patients with obstructive or restrictive lung diseases and in pulmonary vascular disease (15-17). VD/VT can be calculated by the formula:

$$VD/VT = (PaCO_2 - PECO_2)/PaCO_2$$

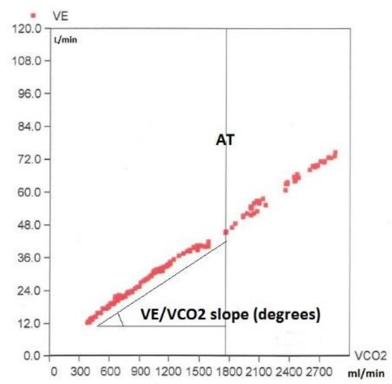
[$PaCO_2$-partial pressure of arterial CO_2 (blood gas measurement); $PECO_2$-patial pressure of CO_2 in expired air (CPEX measurement) (18)]

Ventilation-Perfusion mismatch

Arterial Blood Gas measurements can provide valuable additional information. The difference between alveolar and arterial O_2 levels [$P(A\text{-}a)O_2$] is usually between 20-30 mm Hg and this does not increase during exercise in normal subjects. In patients with lung disease or pulmonary vascular disease the difference is exaggerated during exercise due to ventilation-perfusion (V/Q) mismatch. Additionally, the difference between arterial and end-tidal CO_2 levels [$P(a\text{-}ET)CO_2$] remains positive throughout exercise in patients with lung disease, again due to V/Q mismatch (18).

When ventilation (VE on Y axis) is plotted against carbon dioxide (VCO_2 on the X axis), the relationship is linear until the anaerobic threshold is reached, with a slope of 23-28 degrees. The relationship is steeper in conditions associated with increased VD/VT ratio such as heart failure, pulmonary vascular disease, interstitial lung disease and COPD, while it is normal in patients with exercise limitation due to deconditioning (3,19). The slope is measured from the beginning of exercise to just after the anaerobic threshold, as shown in figure 2. The VE/VCO_2 slope increases with age in normal subjects. A value of <30 degrees is considered normal.

Figure 2: VE/VCO_2 slope measurement-The slope is measured from the beginning to just after the anaerobic threshold. (AT-anaerobic Threshold, VE-ventilation per minute, VCO2- CO2 produced per minute)



Analysis and interpretation

A peak VO_2 of <85% predicted (for age and gender) indicates significant exercise limitation (3).

Respiratory Exchange ratio

Respiratory Exchange Ratio (RER or simply R) is the ratio of the CO_2 production to O_2 consumption ($RER=VCO_2/VO_2$). Once anaerobic metabolism begins, RER progressively increases. A RER of >1.15 at peak exercise indicates an adequate exercise test (3). Current software measures RER automatically and is displayed throughout the test.

Anaerobic threshold measurement

Anaerobic threshold can be identified from several scatter graphs obtained by automatic software by plotting gas exchange markers against each other. The V-slope method, where the VCO_2 is plotted against VO_2 is the preferred method (see Figure 3). Other graphs used for determining the anaerobic threshold are VO_2, VCO_2 against time (see Figure 4), VE/VCO_2, VE/VO_2 against time, and $PETCO_2$, $PETO_2$ against time.

Figure 3: V-slope method for detecting anaerobic threshold – NB: this is independent of the subject's ventilatory response. (AT-Anaerobic Threshold)

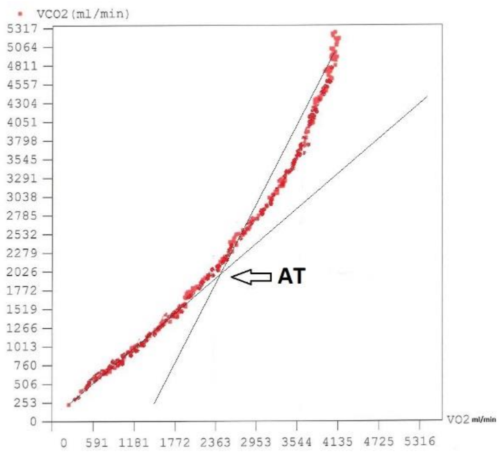
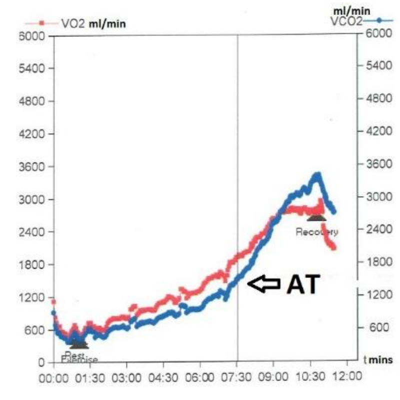


Figure 4: Another method for detecting anaerobic threshold. VO_2 and VCO_2 plotted against time

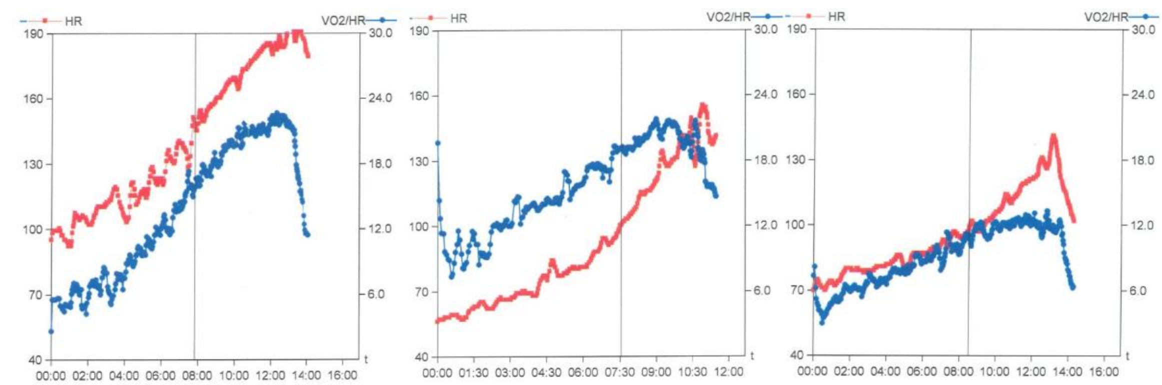


Heart disease

Oxygen consumption per heart rate (HR) (termed "oxygen pulse") can be calculated by dividing the Oxygen consumption by HR, and this rises steadily throughout exercise. A fall of oxygen pulse with increasing workload indicates a fall in cardiac output (Figure 5). A normal breathing reserve, low VO_2 at anaerobic threshold (VO_2 at anaerobic threshold (AT) of <40% of predicted Peak VO_2)), flattening oxygen pulse, and high VE/VCO_2 slope indicate to a cardiac pathology (3). Flattening of the O_2 pulse in a person with normal left ventricular function and spirometry could suggest myocardial ischemia, and this precedes ECG changes (20).

Figure 5: Oxygen pulse in different subjects

A- Healthy volunteer. VO_2 pulse increases steadily with work rate
B- Myocardial ischemia. Late flattening at high workload caused by myocardial dyskinesia
C- Dilated cardiomyopathy. Early flattening of VO_2 pulse



Patients with a patent foramen ovale (PFO) may develop a right-to-left cardiac shunt during exercise, when the right atrial pressure exceeds that of the left atrium due to functional pulmonary hypertension (21). This may cause an abrupt decrease in the partial pressure of the exhaled CO_2 ($PETCO_2$), with simultaneous abrupt increases in VE/VCO_2, VE/VO_2 (due to increase in minute ventilation, VE) and a drop in arterial O_2 saturation (21).

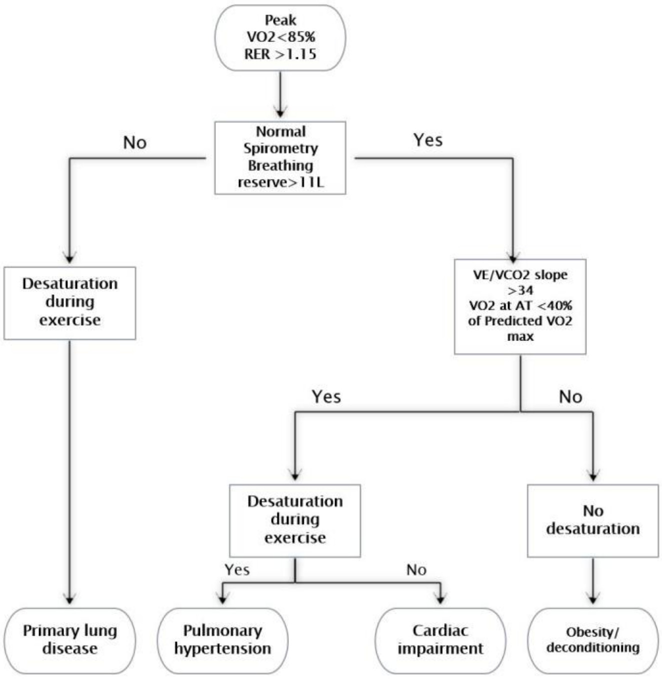
Lung disease

An abnormal spirometry, high VD/VT, desaturation during exercise, low breathing reserve, and increase in alveolar-arterial O_2 gradient [$(A\text{-}a)O_2$] indicate respiratory pathology (3). Normal individuals exhaust their cardiovascular potential at peak exercise. Their breathing reserve is preserved (>11L) at peak exercise, indicating that the limitation to further exercise is the cardiovascular system (3). One exception to this are athletes who have excellent cardiovascular fitness; they can deplete their breathing reserve at peak exercise to <11 L, but achieve a supra-normal peak VO_2 (22).

Deconditioning

A low peak VO_2, normal VE/VCO_2 slope, normal VO_2 at anaerobic threshold, and preserved breathing reserve indicate deconditioning (3). A simplified diagnostic approach is shown in Figure 6.

Figure 6: Simplified diagnostic flowchart



Evidence base

Heart Failure

CPEX is a cornerstone test in identifying heart failure patients for heart transplantation; a peak VO_2<14 mL/kg/min in patients not on beta-blockers and peak VO_2<12 mL/kg/min in patients on beta-blockers is the current recommendation for consideration for heart transplantation (23-25).

VE/VCO_2 slope is another predictor of mortality in heart failure patients. Gitt et al showed a low VO_2 at anaerobic threshold (AT) of <11 mL/kg/min and a high VE/VCO_2 slope of >34 degrees at AT were strong predictors of 6 month prognosis in heart failure patients (26). However, the VE/VCO_2 slope is yet to find a place in cardiac transplant guidelines.

Lung resection

In the case of lung tumour resection surgery, Beckles' et al review of the literature (27) showed lung cancer patients with:

1. Peak VO_2 of >20 were not at increased risk of complications

2. Peak VO_2 of <15 were at increased risk of post-operative complications

3. Peak VO_2 of <10 were at very high risk of peri-operative complications

CPEX is not necessary in all patients undergoing lung resection, but to risk-stratify patients with an FEV1 or diffusion capacity <80% of predicted on pre-operative testing (28).

Abdominal surgery

CPEX is increasingly used for risk stratification in patients with known cardiovascular and respiratory disease being considered for major non-cardiac surgery. Current evidence is:

1. VO_2 at AT of >11 mL/kg/min combined with a VE/VCO_2 slope of <35 are predictors for low cardio-vascular risk after major abdominal surgery (29, 30).

2. A VO_2 at AT of >11 mL/kg/min is correlated with improved post-operative survival in open and endo-vascular aortic surgery (31). Nagamatsu et al showed that in patients undergoing oesophagectomy, a low peak VO_2 was associated with increased cardiovascular complications (32). They concluded that a peak VO_2 of <800 ml/m2 is associated with a higher risk.

Reporting

A standard reporting format includes pre-test observations, test findings and interpretation. An example is given below. In our department, an experienced cardiologist reports all CPEX's. An accurate interpretation of the test should be made available within 72 hours; this ought to be earlier if the findings are significantly abnormal (33). A sample reporting tool is shown in table 5.

Table 5: Sample reporting tool for cardio-pulmonary exercise test

Name Age DOB Hospital ID	
Height Weight BMI	Ideal body weight Haemoglobin Smoking status
Spirometry: FEV1 FVC	FEV1/FVC KCO MVV
Exercise test details: Protocol Duration of exercise Reason for stopping the test	
Resting heart rate Resting blood pressure Resting Oxygen saturation	Peak Heart Rate Peak blood pressure Peak Oxygen Saturation
Exercise test findings: Peak Respiratory Exchange Ratio (RER) Predicted Peak VO_2 Peak VO_2 Peak VO_2/ Predicted peak VO_2 % VO_2 at Anaerobic Threshold Peak Ventilation (VE) Breathing reserve	VE/VCO_2 slope Oxygen Pulse (VO_2/heart rate) at peak exercise ΔVO_2/Work rate VD/VT (if blood gas measured) $PETCO_2$ at Rest Peak Exercise Peak $PETCO_2$ ECG changes
Interpretation	

Supervision and monitoring

The risk of acute myocardial infarction (AMI) during an exercise test is 1 in 2500 and risk of death is 1 in 10000 cases (34). The physician in-charge of the exercise laboratory decides on the appropriateness of the request for testing, and the degree of supervision needed depending on the specific clinical situation. In patients who have had a recent AMI (7-10 days), severe valvular stenosis, or complex arrhythmias, direct physician supervision is indicated (35). In most other cases appropriately trained physiologists and specialist nurses can conduct the test safely, with the physician in the immediate vicinity. Two people are required to conduct the test, both qualified in cardio-pulmonary resuscitation (36). Blood pressure should be measured every 2-3 minutes and more frequently in high risk patients (13). Continuous ECG monitoring is mandatory during the test and should be continued 6 minutes into recovery (13).Manual measurement of blood pressure is still the preferred method during stress test (34). Staff performing the test should be aware of the indications for exercise test and be able to recognise adverse events (13).

The AHA guidelines (2000) recommend that a physician in-charge should have participated in 50 procedures over a dedicated 4 week period to achieve competence in supervision and reporting of exercise tests, and should continue to perform 25 cases per year to preserve competence (35). The physician is responsible for data interpretation and suggesting further evaluation and testing (33). The physician should also maintain advanced cardiovascular life support competence. The AHA guidelines detail the cognitive skills required for performing and interpreting the test (35).

The exercise laboratory should be a spacious room and have the necessary equipment for advanced cardiac life support. Each laboratory should have a written emergency plan and all personnel should rehearse it on a regular basis (36). Written informed consent is required prior to the exercise test (9).

Conclusion

CPEX testing is a relatively safe non-invasive tool which provides excellent diagnostic and prognostic information in patients with heart or lung disease. It should be utilized as a complementary diagnostic tool in the investigation of breathless patients, along with chest X-ray, echocardiography, pulmonary angiography, right heart catheterisation, and coronary angiography.

It is increasingly used in pre-operative risk assessment, cardiac and pulmonary rehabilitation, and adult congenital heart disease. With increasing applications and understanding, a sound grasp of the nuances of CPEX testing is mandatory for the cardiac, pulmonary and general physician.

References

(1) Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. Am J Cardiol 1985;55(2):22A-31A.

(2) Bolliger CT, Jordan P, Soler M, Stulz P, Gradel E, Skarvan K, et al. Exercise capacity as a predictor of postoperative complications in lung resection candidates. American Journal of Respiratory and Critical Care Medicine 1995;151(5):1472-1480.

(3) ATS/ACCP Statement on Cardiopulmonary Exercise Testing. American Journal of Respiratory and Critical Care Medicine 2003;Vol. 167(No. 2):211-277.

(4) Levy F, Fayad N, Jeu A, Choquet D, Szymanski C, Malaquin D, et al. The value of cardiopulmonary exercise testing in individuals with apparently asymptomatic severe aortic stenosis: A pilot study. Archives of Cardiovascular Diseases 2014 10;107(10):519-528.

(5) Mahadevan G, Dwivedi G, Williams L, Steeds RP, Frenneaux M. Epidemiology and diagnosis of heart failure with preserved left ventricular ejection fraction: Rationale and design of the study. European Journal of Heart Failure 2012;14(1):106-112.

(6) Mezzani A, Agostoni P, Cohen-Solal A, Corrà U, Jegier A, Kouidi E, et al. Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: A report from the exercise physiology section of the European association for cardiovascular prevention and rehabilitation. European Journal of Cardiovascular Prevention and Rehabilitation 2009;16(3):249-267.

(7) Chapter3:Pre-Exercise evaluation. In: Pescatello L, Arena R, Riebe D, Thompson P, editors. ACSM's Guidelines for Exercise Testing and Prescription 9th Ed. 2014. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2014. p. 39-58.

(8) Wasserman K, Hansen J, Darryl Y. Sue, William Stringer, Kathy E. Sietsema, Xing-Guo Sun, et al. Symbols and Abrreviations. ; 2012. p. 542-544.

(9) Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: A scientific statement from the American heart association. Circulation 2013;128(8):873-934.

(10) Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986 American Physiological Society;60(6):2020-2027.

(11) Wasserman K, Hansen J, Sue D, Stringer W, Sietsema K, Sun X, et al. NORMAL VALUES. . 5th ed. PHILADELPHIA: LIPPINCOTT WILLIAMS & WILKINS; 2012. p. 155.

(12) Gargiulo P, Olla S, Boiti C, Contini M, Perrone-Filardi P, Agostoni P. Predicted values of exercise capacity in heart failure: Where we are, where to go. Heart Fail Rev 2014;19(5):645-653.

(13) Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's guide to cardiopulmonary exercise testing in adults: A scientific statement from the American heart association. Circulation 2010;122(2):191-225.

(14) Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. Am Rev Respir Dis 1984;129(2 SUPPL.):S49-S55.

(15) Martinez FJ, Stanopoulos I, Acero R, Becker FS, Pickering R, Beamis JF. GRaded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. Chest 1994 January 1;105(1):168-174.

(16) Elbehairy AF, Ciavaglia CE, Webb KA, Guenette JA, Jensen D, Mourad SM, et al. Pulmonary Gas Exchange Abnormalities in Mild Chronic Obstructive Pulmonary Disease. Implications for Dyspnea and Exercise Intolerance. Am J Respir Crit Care Med 2015 Jun 15;191(12):1384-1394.

(17) Miller A. Pulmonary Function in Asbestosis and Asbestos-Related Pleural Disease. Environ Res 1993 4;61(1):1-18.

(18) Wasserman K, Hansen J, Sue D, Stringer W, Sietsema K, Sun X, et al. Chapter 4; Measurements during integrative cardiopulmonary exercise testing. Principles of Exercise testing and interpretation; 5th edition. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 91-94.

(19) Myers J, Arena R, Cahalin LP, Labate V, Guazzi M. Cardiopulmonary Exercise Testing in Heart Failure. Curr Probl Cardiol 2015 8;40(8):322-372.

(20) Belardinelli R, Lacalaprice F, Carle F, Minnucci A, Cianci G, Perna GP, et al. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. Eur Heart J 2003;24(14):1304-1313.

(21) Sun X, Hansen JE, Oudiz RJ, Wasserman K. Gas Exchange Detection of Exercise-Induced Right-to-Left Shunt in Patients With Primary Pulmonary Hypertension. Circulation 2002 January 01;105(1):54-60.

(22) Folinsbee LJ, Wallace ES, Bedi JF, Horvath SM. Exercise respiratory pattern in elite cyclists and sedentary subjects. Med Sci Sports Exerc 1983;15(6):503-509.

(23) Peterson LR, Schechtman KB, Ewald GA, Geltman EM, De Las Fuentes L, Meyer T, et al. Timing of cardiac transplantation in patients with heart failure receiving ß-adrenergic blockers. Journal of Heart and Lung Transplantation 2003;22(10):1141-1148.

(24) Mancini DM, Eisen H, Kussmaul W, Mull R, Edmonds Jr. LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83(3):778-786.

(25) Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing Criteria for Heart Transplantation: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates-2006. Journal of Heart and Lung Transplantation 2006;25(9):1024-1042.

(26) Gitt AK, Wasserman K, Kilkowski C, Kleemann T, Kilkowski A, Bangert M, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. Circulation 2002;106(24):3079-3084.

(27) Beckles MA, Spiro SG, Colice GL, Rudd RM. The physiologic evaluation of patients with lung cancer being considered for resectional surgery. Chest 2003;123(1 SUPPL.):105S-114S.

(28) Voduc N. Physiology and clinical applications of cardiopulmonary exercise testing in lung cancer surgery. Thoracic Surgery Clinics 2013;23(2):233-245.

(29) 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(2):355-362.

(30) Wilson RJT, 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(3):297-303.

(31) Goodyear S, Yow H, Saedon M, Shakespeare J, Hill C, Watson D, et al. Risk stratification by pre-operative cardiopulmonary exercise testing improves outcomes following elective abdominal aortic aneurysm surgery: a cohort study. Perioperative Medicine 2013;2(1):10.

(32) Nagamatsu Y, Shima I, Yamana H, Fujita H, Shirouzu K, Ishitake T. Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with squamous cell carcinoma of the thoracic esophagus. J Thorac Cardiovasc Surg 2001 6;121(6):1064-1068.

(33) Pina HL, Balady GJ, Hanson P, Labovitz AJ, Madonna DW, Myers J. Guidelines for clinical exercise testing laboratories: A statement for healthcare professionals from the committee on exercise and cardiac rehabilitation, American Heart Association. Circulation 1995;91(3):912-921.

(34) Myers J, Arena R, Franklin B, Pina I, Kraus WE, McInnis K, et al. Recommendations for clinical exercise laboratories: A scientific statement from the american heart association. Circulation 2009;119(24):3144-3161.

(35) Rodgers GP, Ayanian JZ, Balady G, Beasley JW, Brown KA, Gervino EV, et al. American College of Cardiology/American Heart Association Clinical Competence Statement on Stress Testing: A report of the American College of Cardiology/American Heart Association/American College of Physicians - American Society of Internal Medicine Task Force on Clinical Competence. J Am Coll Cardiol 2000;36(4):1441-1453.

(36) Colquhoun D, Freedman B, Cross D, Fitzgerald B, Forge B, Hare DL, et al. Clinical Exercise Stress Testing in Adults (2014). Heart, Lung and Circulation (0).