Editorial

CARDIO-PULMONARY EXERCISE TESTING

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Introduction

The observation by Lavoisier and LaPlace in 18th century that muscular contraction consumes oxygen (0,) and produces carbon dioxide (CO,) had made it possible to study the mechanisms of exercise performance in human beings (1). An individual's capacity to perform increasing levels of dynamic work depends upon the amount of oxygen that can be delivered to working muscles and on the capacity of muscles to oxidize substrates. The structural and physiological integrity of the respiratory, cardiovascular and muscular systems is essential for delivery of oxygen to the tissues and removal of carbon dioxide from the body. Cardio-Pulmonary exercise testing (CPX) is one of the important investigative tools to evaluate patients with dyspnoea or exercise intolerance who have pulmonary or cardiac dysfunctions or both and in the assessment of work impairment. Exercise testing provides clinically useful information that is not available at rest. In addition, CPX is recognized as an useful non-invasive method to evaluate healthy individuals in competitive sports. In order to detect and interpret abnormalities during exercise, it is essential that one should have a knowledge of normal cardio-pulmonary and metabolic responses to exercise.

1. Muscular system

Human skeletal muscle produces high energy phosphate compounds that are essential to initiate and sustain forceful contraction. This is achieved by metabolism of nutrients (carbohydrates, fats and proteins) and the energy thus produced is stored in the form of high-energy phosphate compounds. Carbohydrates are generally preferred over fats as a muscle fuel and protein is used only in severe catabolic states.. Carbohydrate (glycogen or glucose) undergoes glycolysis to form pyruvate. Pyruvate is then metabolized in the Krebs cycle to generate substantial adenosine triphosphate (ATP). Subsequent reaction in the electron transport chain produces additional ATP This is achieved by adequate supply of oxygen to the mitochondria. When oxygen demand exceeds supply, anaerobic metabolism sets in. Accumulation of lactic acid during anaerobic metabolism along with hypoxia limits exercise tolerance (2).

Skeletal muscles are composed of two major varieties of contractile cells (2,3). Type I (oxidative or slow twitch) fibres have prolonged repetitive contraction and are more resistant to the development of fatigue. Type II (glycolytic or fast twitch) fibres have faster contractile characteristics and fewer oxidative enzymes and are more easily fatigable. Fibre type distribution in a given muscle group is fixed by heredity and cannot be modified by training. Type II fibres are subdivided into three types: i) IIa fibre with intermediate levels of myoglobin as well as oxidative and glycolytic enzymes, ii) IIb fibres with low oxidative and high glycolytic enzymes and iii) IIc fibres which can differentiate into IIa or IIb fibre types. Marathon runners have a greater predominanace of slow type (Type I) fibres while sprinters have a marked increase in fast twitch (Type II) fibres.

2. Respiratory system

Respiratory system consists of two major components: a gas exchanging organ (the lungs) and the pump that ventilates the lung. The pump consists of chest wall (rib cage and abdominal compartments), the ventilatory muscles, the centres in the nervous system and the intervening neural connections. There is a progressive increase in minute ventilation (VE) during incremental exercise. In younger subjects, tidal volume (VT) increases during progressive exercise upto approximately 50% of vital capacity (VC) afterwhich increase in VE are achieved mainly by increases in the breathing frequency(f) (4). In older subjects, a greater proportion of VC is used (average 60%) before VE response becomes predominantly a frequency response (5). Pulmonary ventilation increases during exercise in proportion to metabolic rate in order to achieve alveolar and hence arterial blood gas partial pressures at or close to resting levels. Minute ventilation (VE) consists of alveolar ventilation (VA) and dead space ventilation (VD). Alveolar ventilation, therefore, is the difference between the total ventilation of the lung (VE) and the ventilation of the dead space (VD). Hence

$$VA = VE - VD$$

$$\text{or } VA = VE\ (1 - VD/VT)$$

Where VD/VT is the ratio of physiologic dead space to tidal volume.

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In order to maintain alveolar PCO_2 and PO, at a constant level during exercise, VA changes in precise proportion to carbon dioxide output (VCO_2) and oxygen intake (VO_2) (2).

$$VA = \frac{863 \times VCO_2}{PACO_2} = \frac{863 \times VO_2}{(PIO_2 - PAO_2)}$$

$$\text{Thus } VE = \frac{863 \times VCO_2}{(PACO_2\ (1 - VD/VT)}$$

where $PACO_2$ and PAO_2 are partial pressures of CO_2 and O_2 in the alveolar gas respectively and PIO_2 is the partial pressure of O_2 in the inspired gas.

Ventilation during muscular exercise is therefore determined by three variables: $PACO_2$, VD/VT and VCO_2. The ratio of VCO_2 to VO_2 is defined as respiratory exchange ratio: $R = \frac{VCO_2}{VO_2}$

2.1 Breathing reserve

Breathing reserve is the difference between the maximal ventilatory capacity and the maximal ventilation achieved (VE max) during exercise. For practical purposes, maximal voluntary ventilation (MVV) is considered equivalent to maximal ventilatory capacity. MVV can be either measured (12-second MVV) or calculated (FEV1 x 35). The breathing reserve can be calculated in the following ways (6) :

1. difference between the MVV and the maximal minute ventilation achieved during exercise, MVV-VE max.
2. percentage of the maximal ventilatory capacity used during exercise, VE max/MVV and
3. percentage of the maximal ventilatory capacity that remains available after a maximal exercise test, MVV - VE max/MVV.

3. Cardiovascular system

The cardiac output is defined by Fick's principle as:

$$Q = \frac{VO_2}{CaO_2 - CvO_2}$$

Where Q is the cardiac output and CaO_2 and CvO_2 are the concentrations of oxygen in arterial and mixed venous blood respectively. A rearrangement of this equation results in :

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

$$= HR \times SV \times (CaO_2 - CvO_2)$$

$$VO_2/HR = SV \times (CaO_2 - CvO_2)$$

where HR is heart rate and SV is stoke volume,

Oxygen pulse (VO_2/HR) is therefore oxygen consumption per heart beat. A plateau in O_2 pulse during an exercise test is achieved when the maximum oxygen extraction and maximum stroke volume have been achieved. If oxygen extraction is assumed to be normal, O_2 pulse represents an estimate of stroke volume (2) Normally heart rate and VO_2 are linearly related during incremental exercise testing. The difference between predicted and attained maximal heart rate is defined as the estimated heart rate reserve (7).

Systemic arterial blood pressure rises during exercise to levels around 200 mm Hg in maximal exercise. The rise in diastolic pressure is much less (to around 90 mm Hg) and mean arterial pressure increases from 90 mm Hg at rest to 140 mm Hg in maximal exercise (8). There is considerable fall in systemic peripheral vascular resistance due to marked vasodilation in working muscles. Pulmonary vascular resistance alsofalls considerably during exercise with the rise in mean pulmonary artery pressure of 15 mm Hg or less in young adults (8).

4. Pulmonary gas exchange

Pulmonary gas exchange during exercise is evaluated by measuring the alveolar - arterial oxygen pressure difference ($P(A-a)O_2$) and the physiological dead space to tidal volume ratio (VD/VT). The equation for the measurements of $P(A-a)O_2$ and VD/VT ratio are as follows (9,10):

$$P\ (A-a)O_2 = PIO_2 - (PaCO_2 \times (FIO_2 + \frac{1 - FIO_2)}{R}) - PaO_2$$

where PIO_2 is the partial pressure of O_2 in the inspired gas and FIO_2 is the fractional concentration of oxygen in the inspired gas (dry).

$$\frac{VD}{VT} = \frac{(PaCO_2 - PECO_2) / PaCO_2 \times VT - \text{valve } VD}{VT}$$

where $PECO_2$ is the partial pressure of CO, in the expired gas.

5. Cardio-Pulmonary exercise testing

The equipments required for cardio-pulmonary exercise testing include treadmill or cycle ergometer, flow meters, gas analyzers and electrocardiographs(11). Four primary signals (flow, oxygen, carbon dioxide and electrocardiogram) are obtained by these equipments. Flow meter that is commonly used is pneumotachometer and other flow devices are anemometer and turbine flow meters. The most accurate gas analyzer is a mass spectrometer which can measure simultaneously all respiratory gases (O_2, CO_2 and nitrogen(N_2)). However, it is the most expensive equipment. Oxygen can also be determined either by fuel cell analyzer (zirconium electrochemical cell) or paramagnetic analyzer. Fuel cell analyzer measures the difference in electrical potential across the membrane induced by the presence of O_2. It is inexpensive, reliable and accurate, but is slow responding. Paramagnetic analyzer determines O_2 on the basis of its property to distort a magnetic field. Since CO, has the property of absorbing infrared radiation, infrared analyzers are used for the analysis of CO,.

Expired respiratory gases are analyzed either by a mixing chamber (12) or breath-by-breath analysis (13). In a mixing chamber, the exhaled gas which consists of dead space and alveolar air is mixed with baffles to obtain actual expired gas. A representative sample of the 20 seconds of expired gas is analyzed and used with flow to make the calculations. In this system, end-tidal measurements ($PETO_2$ and $PETCO_2$) cannot be made. In the breath-by-breath analysis system, the four signals are aligned and each expiration is sampled at a rate of 100 to 120 times per second,. The flow, O_2 and CO_2 of each sample are then integrated to obtain ventilation, oxygen consumption and CO_2 production for each breath.

The exercise testing can be done using either a treadmill or a cycle ergometer. Even though several treadmill protocols are available, the most widely used protocols are the Bruce (14) and the Balke (15). The measurements that are made during cardio-pulmonary exercise testing are listed in Table 1 and the suggested normal maximum cardio-pulmonary variables for cycle exercise testing in adults (16) are described in Table 2.

Table 1
Measurements during cardiopulmonary exercise testing

Metabolic
1. Oxygen uptake (VO_2)
2. Carbon dioxide output (VCO_2)
3. AnaerobicThreshold (AT)
4. Respiratory exchange ratio (R)

Respiratory
1. Minute ventilation (VE)
2. Tidal volume (VT)
3. Respiratory Frequency (f)
4. Ratio of tidal volume to vital capacity (VT/VC)

Cardiovascular
1. Electrocardiogram
2. Oxygen pulse (VO_2/HR)
3. Blood pressure
4. VO_2/Work rate

Pulmonary gas exchange
1. Arterial oxygen saturation (SaO_2)
2. Arterial partial pressure oxygen (PaO_2)
3. Alveolar to arterial oxygen tension difference [$P(A\text{-}a)O_2$]
4. Ratio of physiologic dead space to tidal volume (VD/VT)
5. Arterial to end tidal CO, tension difference [$P(a\text{-}ET)CO_2$]
6. Ventilatory equivalent for oxygen (VE/VO_2)
7. Ventilatory equivalent for CO_2 (VE/VCO_2)

Acid-base balance
1. pH
2. $PaCO_2$
3. HCO_3
4. Lactate

(Source: Reference 6)

5.1. Maximal Oxygen consumption

The maximal oxygen consumption (VO_2 max) or aerobic capacity is the highest oxygen uptake during exhaustive exercise of large muscle mass. Maximal oxygen consumption is reached when O_2 uptake-does not increase, but plateaus or decreases despite further increase in power (17). The VO_2 max is achieved during exercise testing when there is increase of less than 0.15 I/min or 2.1 ml/kg/min with a further increase in treadmill elevation of 2.5%(6). The VO_2 measured at maximal exercise without reaching a plateau is called VO_2 peak (6). In order to assume that the individual has reached the VO_2 peak, one of the following requirements must occur (6,18): i) patient must look exhausted, ii) heart rate or VE must be close to the maximal predicted values, iii) lactate is greater than 8m Eq/l or iv) respiratory exchange ratio is greater than 1.15. In clinical practice VO_2 peak and VO_2 max are used interchangeably. VO_2 max measured during running on a treadmill is normally 10% higher than that determined on a cycle ergometer. VO_2 is expressed in liters per minute. It can also be expressed by normalizing VO_2 for body weight (as ml/kg/min) and for square meter of body surface area (ml/m2/mm). VO_2 should be expressed both in absolute units (I/mm) and in the normalized fashion.

5.2. Anaerobic threshold

Anaerobic threshold is defined as the level of exercise VO_2 above which aerobic energy production is supplemented by anaerobic mechanisms and is associated with a significant increase in the lactic acid production (19). The different methods of determining anaerobic threshold is listed in Table 3.

Table 2

Guidelines for normal maximum cardiopulmonary exercise variables in adults.

VO_2 Responses		
VO_2 max	>	84% predicted
Anaerobic threshold	>	40% VO_2 max predicted
Heart Response		
O_2 pulse	>	80%
Heart rate reserve (beats/min)	<	15 bpm
Blood pressure	<	220/90
Breathing Responses		
Breathing reserve	VEmax/MVV>75%; MVV-VEmax>11L	
VT/VC	<	55
Frequency (breaths/min)	<	60 brpm
Pulmonary Gas Exchange (peak values)		
VE/VCO_2 at anaerobic threshold	<	34
VD/VT	<	0.28
$P(a\text{-}ET)CO_2$	<	0
PaO_2	>	80 mm Hg
$P(A\text{-}a)O_2$	<	35 mm Hg

(Source: Reference 16).

Table 3

Methods for the determination of anaerobic threshold

1. Noninvasive determination		
a) Conventional (Ventilatory threshold), VE/VO_2, VE/VCO_2, $PETO_2$, $PETCO_2$, R.		
b) Ventilatory equivalents threshold VE/VO_2 and VE/VCO_2		
c) V-slope (gas exchange threshold) VCO_2 vs VO_2 (computerized)		
d) Modified V-slope (gas exchange threshold) VCO_2 vs VCO_2 (Manual)		
2. Invasive determination		
a) Lactate threshold		
	Ordinary plot:	Lactate vs VO_2 or power or time. Logarithm of lactate vs logarithm of VO_2.
b) Bicarbonate threshold		
	Ordinary plot:	Standard HCO_3 vs VO_2 or power or time. Logarithm of standard HCO_3 vs logarithm of VO_2.

(Source: Reference 6)

5.2.1. Conventional methods

Simultaneous analysis of ventilatory equivalent for O_2 (VE/VO_2), ventilatory equivalent for CO_2 (VE/VCO_2), end tidal O_2 tension ($PETO_2$), end tidal CO, tension ($PETCO_2$) and respiratory exchange ratio(R) is used in the conventional method to determine AT (20). At anaerobic threshold, excess production of CO_2 stimulates ventilation (VE) leading to an increase in VE/VO_2 and $PETO_2$ without a change in VE/VCO_2 and $PETCO_2$. This is due to the fact that VE increases proportionally to VCO_2 and metabolic acidosis has not yet developed. This lasts for 2 minutes and is called isocapnic buffering. As exercise proceeds, there is further increasein lactic acid production. This results in metabolic acidosis which is an additional stimulus to increase ventilation out of proportion to VCO_2. This leads to an increase in VE/VCO_2 and a decrease in $PETCO_2$. At the point at which VCO_2 is produced in excess of VO_2, the respiratory exchange ratio(R) is around 1. AT is thus determined by looking for the lowest point (nadir) of VE/VO_2 and $PETO_2$ before they begin to rise consistently coinciding with an unchanged VE/CO_2 and $PETCO_2$ with a R of around 1. VO_2 corresponding to this point is AT. This is also called ventilatory threshold. If AT is determined using only VE/VO_2 and VE/VCO_2, it is called ventilatory equivalent threshold.

52.2. V slope method

Conventional method may not be accurate in situations where there is abnormal control of breathing or of mechanical derangements of the lungs (as in COPD) as the lungs are not able to increase the ventilation. In these situations, V slope method based on the direct measurement of VCO_2 and its relation to the VO_2 is used (21). Before AT, there is a linear relationship between CO_2 production and O_2 uptake and at anaerobic threshold, the excess production of CO_2 is related to lactic acid production and not to O_2. As a result, the slope of the VCO_2 versus VO_2 relationship changes and becomes steeper. The VO_2 at which the change in slope occurs is AT. Mathematical calculations can be done by a computer and this method is also called gas exchange threshold. When AT is measured manually for VCO_2 and VO_2 measurements, it is known as modified\/-slope method. In this method, the VCO_2 is plotted against VO_2 and a line parallel to the line of identity is drawn through VCO_2 vs VO_2 points during the incremental plan of the exercise test. The point at which the VCO_2 departs from the line (begins to increase more rapidly than O_2) is taken as the V slope AT and the VO_2 corresponding to this point is the AT.

Cardiopulmonary exercise testing is emerging as an important investigative modality to evaluate patients with dyspnoea on exertion because it is found to be useful to differentiate cardiac from ventilatory causes of exertional dyspnoea (22). It also helps to identify psychogenic dyspnoea. By determining anaerobic threshold and VO_2 max during CPX, it is possible to detect impaired cardiac function and to assess severity of chronic heart failure (23). CPX can also be used to evaluate the efficacy of long-term treatment of heart failure. CPX provides useful information inpatients with pulmonary hypertension secondary to pulmonary vascular disease (24). Early diagnosis and monitoring of treatment are also possible with CPX in patients with interstitial lung disease (25). In COPD, it is possible to assess exercise limitation and physiological factors that contribute to exercise limitation (26). Pulmonary rehabilitation is another important area where the cardiopulmonary exercise testing enables us to measure exercise tolerance, assess causes of exercise limitation and screen for exercise-induced asthma (27). Clinical exercise testing is also increasingly used in the evaluation of impairment and disability (28) and of preoperative evaluation of patients for lung resection (29,30). It also provides objective guidelines for cardiac transplantation (31) and assessment of functional outcome in recipients of lung and heart and lung transplantations (32).

Establishment of normative prediction equations is essential for interpretation of CPX (33). There are not many publications from our country on CPX (34-37). Therefore, studies from normal subjects, in addition to data from various cardio-pulmonary diseases are required urgently from India.

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