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) Ila fibre with intermediate levels of myoglobin as well as oxidative and glycolytic enzymes, ii) Ilb fibres with low oxidative and high glycolytic enzymes and iii) Ilc fibres which can differentiate into Ila or Ilb fibre types. Marathon runners have a greater predominance 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 up to approximately 50% of vital capacity (VC) after which 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

\[ \text{VA} = \text{VE} - \text{VD} \]

or \[ \text{VA} = \text{VE} \times (1 - \frac{\text{VD}}{\text{VT}}) \]

Where \(\frac{\text{VD}}{\text{VT}}\) is the ratio of physiologic dead space to tidal volume.
In order to maintain alveolar PCO$_2$ and PO$_2$ at a
constant level during exercise, VA changes in precise
proportion to carbon dioxide output (VCO$_2$) and oxygen
intake (VO$_2$) (2).

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

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 ex-
change ratio: $R = \frac{VCO_2}{VO_2}$

2.1 Breathing reserve

Breathing reserve is the difference between the
maximal ventilatory capacity and the maximal ventilati-
ion achieved (VE max) during exercise. For practical
purposes, maximal voluntary ventilation (MVV) is con-
sidered 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
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 equa-
tion results in:

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

where HR is heart rate and SV is stoke volume.

Oxygen pulse (VO$_2$/HR) is therefore oxygen con-
sumption per heart beat. A plateau in O$_2$ pulse during an
exercise test is achieved when the maximum oxygen ex-
traction 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 pre-
dicted and attained maximal heart rate is defined as the
estimated heart rate reserve (7).

Systemic arterial blood pressure rises during ex-
ercise 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 vascu-
lar resistance due to marked vasodilation in working
muscles. Pulmonary vascular resistance also falls con-
siderably during exercise with the rise in mean pulmo-
nary artery pressure of 15 mm Hg or less in young adults
(8).

4. Pulmonary gas exchange

Pulmonary gas exchange during exercise is evalu-
atated by measuring the alveolar - arterial oxygen pres-
sure 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 fol-
loows (9,10):

$$P_A \, O_2 = PIO_2 - (PaCO_2 \times (FIO_2 + 1 - FIO_2) - PaO_2)$$
$$VT$$

where PIO$_2$ is the partial pressure of O$_2$ in the in-
spired gas and FIO$_2$ is the fractional concentration of
oxygen in the inspired gas (dry).

$$VD = \frac{(PaCO_2 - PECO_2) \times PaO_2 \times VT - valve \, VT}{VT}$$

where PECO$_2$ is the partial pressure of CO$_2$, in the
expired gas.

5. Cardio-Pulmonary exercise testing

The equipments required for cardio-pulmonary ex-
ercise testing include treadmill or cycle ergometer, flow
meters, gas analyzers and electrocardiographs(11). Four
primary signals (flow, oxygen, carbon dioxide and elec-
trocardiogram) 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 spec-
trometer which can measure simultaneously all respiratory gases (O₂, CO₂ and nitrogen(N₂)). 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 O₂. It is inexpensive, reliable and accurate, but is slow responding. Paramagnetic analyzer determines O₂ on the basis of its property to distort a magnetic field. Since CO₂ has the property of absorbing infrared radiation, infrared analyzers are used for the analysis of CO₂.

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 (PETO₂ and PETCO₂) 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, O₂ and CO₂ of each sample are then integrated to obtain ventilation, oxygen consumption and CO₂ 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>
<thead>
<tr>
<th>Table 1</th>
<th>Measurements during cardiopulmonary exercise testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>1. Oxygen uptake (VO₂)</td>
<td></td>
</tr>
<tr>
<td>2. Carbon dioxide output (VCO₂)</td>
<td></td>
</tr>
<tr>
<td>3. AnaerobicThreshold (AT)</td>
<td></td>
</tr>
<tr>
<td>4. Respiratory exchange ratio (R)</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
</tr>
<tr>
<td>1. Minute ventilation (VE)</td>
<td></td>
</tr>
<tr>
<td>2. Tidal volume (VT)</td>
<td></td>
</tr>
<tr>
<td>3. Respiratory Frequency (f)</td>
<td></td>
</tr>
<tr>
<td>4. Ratio of tidal volume to vital capacity (VT/VC)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>1. Electrocardiogram</td>
<td></td>
</tr>
<tr>
<td>2. Oxygen pulse (VO₂/HR)</td>
<td></td>
</tr>
<tr>
<td>3. Blood pressure</td>
<td></td>
</tr>
<tr>
<td>4. VO₂/Work rate</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary gas exchange</strong></td>
<td></td>
</tr>
<tr>
<td>1. Arterial oxygen saturation (SaO₂)</td>
<td></td>
</tr>
<tr>
<td>2. Arterial partial pressure oxygen (PaO₂)</td>
<td></td>
</tr>
<tr>
<td>3. Alveolar to arterial oxygen tension difference [P(A-a)O₂]</td>
<td></td>
</tr>
<tr>
<td>4. Ratio of physiologic dead space to tidal volume (VD/VT)</td>
<td></td>
</tr>
<tr>
<td>5. Arterial to end tidal CO₂ tension difference [P(a-ET)CO₂]</td>
<td></td>
</tr>
<tr>
<td>6. Ventilatory equivalent for oxygen (VE/VO₂)</td>
<td></td>
</tr>
<tr>
<td>7. Ventilatory equivalent for CO₂ (VE/VCO₂)</td>
<td></td>
</tr>
<tr>
<td><strong>Acid-base balance</strong></td>
<td></td>
</tr>
<tr>
<td>1. pH</td>
<td></td>
</tr>
<tr>
<td>2. PaCO₂</td>
<td></td>
</tr>
<tr>
<td>3. HCO₃⁻</td>
<td></td>
</tr>
<tr>
<td>4. Lactate</td>
<td></td>
</tr>
</tbody>
</table>

(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 l/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/m$^2$/mm). VO$_2$ should be expressed both in absolute units (l/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.

<table>
<thead>
<tr>
<th>VO$_2$ Responses</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_2$ max</td>
<td>&gt; 84% predicted</td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td>&gt; 40% VO$_2$ max predicted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart Response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>O$_2$ pulse</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>Heart rate reserve (beats/min)</td>
<td>&lt; 15 bpm</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt; 220/90</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Breathing Responses</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathing reserve</td>
<td>VEmax/MVV&gt;75%; MVV-VEmax&gt;11L</td>
</tr>
<tr>
<td>VT/VC</td>
<td>&lt; 55</td>
</tr>
<tr>
<td>Frequency (breaths/min)</td>
<td>&lt; 60 brpm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary Gas Exchange (peak values)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>VE/VO$_2$ at anaerobic threshold</td>
<td>&lt; 34</td>
</tr>
<tr>
<td>VD/VT</td>
<td>&lt; 0.28</td>
</tr>
<tr>
<td>P(a-ET)/CO$_2$</td>
<td>&lt; 0</td>
</tr>
<tr>
<td>PaO$_2$</td>
<td>&gt; 80 mm Hg</td>
</tr>
<tr>
<td>P(A-a)O$_2$</td>
<td>&lt; 35 mm Hg</td>
</tr>
</tbody>
</table>

(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\(_2\) 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 increase in 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.

**5.2.2. 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 V-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 in patients 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 transplantsations (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.

REFERENCES


