CHAPTER 8

Clinical exercise testing

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Impairment of exercise tolerance in chronic respiratory disorders, in particular chronic obstructive pulmonary disease (COPD), has important implications on health-related quality of life [1–3], hospitalisation rate [4, 5] and survival [6, 7]. Consequently, exercise testing is progressively being considered an essential component in the routine clinical assessment of these patients’ functional status.

Exercise intolerance results when a subject is unable to sustain a required work rate sufficiently long for the successful completion of the task. The physiological cause, most commonly, is an oxygen demand that exceeds the O_2 conductance capability of the oxygen transport chain. This is usually seen in physically fit individuals [8]. However, a limited potential for oxygen utilisation at mitochondrial level must also be considered as a factor of exercise limitation in healthy sedentary subjects [9–12]. The consequence of exercise intolerance is a perception of limb fatigue, breathlessness or even, in some conditions, frank pain. Exercise intolerance is the hallmark of a range of cardiovascular, respiratory and other systemic diseases, of which congestive heart failure (CHF) and COPD are the most prominent.

Cardiopulmonary exercise testing (CPET) is a unique tool to assess the limits and mechanisms of exercise tolerance. It also provides indices of the functional reserve of the organ systems involved in the exercise response, with inferences for system limitation at peak exercise. Moreover, CPET is useful for establishing the profiles and adequacy of the system responses at submaximal exercise. Several studies [13, 14] have shown that the functional reserve (i.e. aerobic capacity) of patients with COPD and interstitial lung disease is not accurately predicted from resting lung function indexes.

The appropriateness of the integrated systemic responses are best studied utilising incremental exercise testing, either as a ramp or small work-rate increments each of short duration. CPET has been classically built around the rapid ramp-incremental exercise test (performed on a cycle-ergometer or motorised treadmill), breath-by-breath monitoring of cardiopulmonary variables (e.g. O_2 uptake, CO_2 output, ventilation, heart rate) and formulation of graphical clusters of response profiles that optimise estimation of key parameters, such as peak O_2 uptake (V′O_2) and the lactate threshold and the characterisation of pertinent response profiles (e.g. V′O_2–oxygen pulse, minute ventilation–carbon dioxide production (V′E–V′CO_2)).

This provides a convenient means of: 1) determining whether the magnitude and pattern of response of particular variables is normal with respect to other variables or to work rate; 2) establishing a subject’s limiting or maximum attainable value for physiological variables of interest; and 3) establishing exercise intensity domains, such as the transition between moderate and heavy intensity exercise. It is important to recognise, in this context, the difference between submaximal and maximal exercise
levels. In submaximal exercise, the components of the O$_2$ transport pathway can provide adequate O$_2$ flux between the air and the mitochondria. Mitochondrial oxidative capacity has not been reached, symptoms are usually tolerable and muscle fatigue has not occurred, or at least may be insufficient to impair performance appreciably. Figures 1 and 2 indicate the characteristics of different types of exercise protocols described in the

Fig. 1. – Response of oxygen uptake ($V^{\text{O}_2}$) to: a) a series of constant-work rate exercise tests, from moderate to heavy exercise; and b) a ramp-incremental test. Note that peak oxygen uptake (-----) is not different between the protocols (a and b). There was no evidence of plateau in oxygen uptake response (maximum O$_2$ uptake). Steady-state oxygen uptake was observed at moderate intensity constant-work rate exercise (a). Reproduced with permission from [113].

Fig. 2. – Mean oxygen uptake ($V^{\text{O}_2}$) profiles of the eight chronic obstructive pulmonary disease patients during four different clinical exercise protocols (mean±SEM): incremental cycling (○); incremental shuttle (●); six-minute walk test (▲); and stairs climbing (□).
At maximal exercise, symptoms have caused the patient to stop exercising. At this stage, one or more of the following possibilities exist:

1) Limits to oxygen transport have been reached and maximal $V'O_2$ ($V'O_{2,max}$) attained; under such conditions, breathing 100% $O_2$, for example, could increase $V'O_{2,max}$ [15].

2) Mitochondrial oxidative capacity has been reached and again the subject would be considered to be at $V'O_{2,max}$, but adding $O_2$ would not raise $V'O_2$.

3) Maximal exercise has occurred at a level that does not require maximal $O_2$ transport or maximal oxidative capacity and here exercise has been limited by unusually severe symptoms. Under these conditions a plateau in $O_2$ ($V'O_{2,max}$) has not been reached and the appropriate term is peak, rather than $V'O_{2,max}$.

Subjects with lung disease often experience exercise intolerance at extremely low work rates. There are many kinds of lung disease, however, and in any one patient the structural and functional severity of the disease may range from the barely discernible to the very severe. As a result, responses to exercise in patients with lung disease do not show the tight stereotypical pattern of normal subjects. However, despite the widespread clinical use of CPET, it does not typically provide a substantial improvement in primary diagnostic power over the more classical clinical tools/assessments (e.g. spirometry). What CPET can do, however, is: 1) reveal specific abnormalities that occur only when support systems are stressed by exercise (e.g. dynamic hyperinflation in COPD); and 2) provide a functional frame of reference for assessing the efficacy of interventions targeted to ameliorate such abnormalities (e.g. bronchodilators for dynamic hyperinflation).

More recently, test paradigms designed to quantify endurance performance have evolved and other exercise protocols, described below, have also become popular. It is of note, however, that CPET is now highly developed in this regard and it is the accepted "gold standard".

**Responses to exercise in health and disease**

There is nothing intrinsically different in the direction of the overall system response to exercise comparing normal subjects and patients with lung diseases. Thus, as a patient exercises harder, $O_2$ consumption, $CO_2$ production, ventilation and cardiac output all increase to fulfill increased muscle bioenergetic requirements, as they do in the normal subject [16], but peak levels attained are less, more so with increasing severity of the disease. What may be different from normal in lung diseases regarding exercise responses include: 1) resting function; 2) physical deconditioning; 3) the intensity and duration of exercise that can be performed, and the relationship between intensity/duration and symptom development; 4) the specific responses of the heart and lungs/chest wall to a given exercise load in terms of rate, magnitude and performance limits; 5) the relative importance of each part of the $O_2$ and $CO_2$ transport pathway in contributing to any limitation of exercise that is found; 6) the relative importance of peripheral and respiratory muscle fatigue; and 7) metabolic accompaniments of exercise, in particular lactate release and accumulation, and high energy phosphate levels.

**Pulmonary response to exercise in healthy subjects**

It is well known that ventilation and cardiac output markedly increase during exercise to match $O_2$ transport with augmented cellular $O_2$ requirements [17] (fig. 3). Since ventilation increases to a higher relative extent than pulmonary blood flow, the ratio of total alveolar ventilation to blood flow (overall $V'/Q'$ ratio) rises rather substantially. At moderate levels of exercise, the dispersion of the $V'/Q'$ distributions does not change
Pulmonary function
(ventilation and gas exchange)

Blood O₂ carrying capacity

Cardiovascular system
(cardiac output and regional distribution of blood flow)

Muscle capillary O₂ transfer capacity

Mitochondrial oxidative capacity
(cellular O₂ utilisation)

Fig. 3. – Major elements of the O₂ transport/O₂ utilisation pathway. Integrated effects of all steps involved to move oxygen from air to mitochondria are essential to determine the maximum capacity of the system. In disease, nonuniformity of ventilation/perfusion ratios in the lung and/or metabolism/perfusion ratios in the peripheral tissues may be of considerable importance.

[18–20] but the $V'_{A}/Q'$ ratios at the mean of both ventilation and perfusion distributions markedly increase due to the higher overall $V'_{A}/Q'$ ratio. Consequently, the efficiency of the lung as an O₂ and CO₂ exchanger improves at these exercise levels. Mixed venous oxygen partial pressure falls dramatically during exercise because the relative increase in $V'_{O₂}$ is considerably greater than that of cardiac output, and mixed venous carbon dioxide partial pressure levels rise equally remarkably. Arterial $P_{O₂}$ levels generally remain unchanged until extremely high levels of exercise are undertaken. Arterial $P_{CO₂}$ levels are also relatively stable until the appearance of high blood lactate levels generates acidosis, even more ventilation, and thus a fall in $P_{a,CO₂}$ levels. The alveolar–arterial O₂ gradient ($AaPO₂$), however, progressively increases with the level of exercise, reaching values of 20–30 mmHg close to maximal exercise ($V_{O₂}$ peak) in average subjects, and even greater (up to 40 mmHg or more) in some elite athletes [21]. Such an increase in $AaPO₂$ indicates inefficiency of pulmonary gas exchange during heavy exercise that is even more apparent in other animal species, such as the horse [22]. It has been shown that the increase in the $AaPO₂$ during exercise is due, in part, to $V'_{A}/Q'$ mismatching [18–20] but it is mostly explained by alveolar-capillary O₂ diffusion limitation [19, 23]. Experimental studies suggest that development of subclinical pulmonary oedema [19, 24] may explain the deterioration of pulmonary gas exchange during heavy exercise in elite athletes.

Pulmonary response in lung diseases

In COPD patients, resting levels of $V'E$ are abnormally high but, during exercise, the slope between $V'E$ and work rate is normal. For a given level of $V'E$ during exercise, tidal volume ($V'T$) tends to be lower and respiratory rate ($f$) higher in patients than in healthy subjects [25, 26]. Moreover, the O₂ cost of breathing per unit ventilation is higher in COPD patients than in healthy subjects. Impaired respiratory mechanics requires more effort to move a given volume of air. Peak exercise $V'T$ is strongly related to vital capacity in these patients [27]. They adopt two strategies during exercise to increase $V'E$ [25]:

1. **Increased tidal volume**: Patients with COPD are able to increase their tidal volume ($V'T$) significantly during exercise. This increase is thought to be due to a reduction in respiratory muscle strength and endurance, as well as to an increase in ventilatory drive.
2. **Increased respiratory rate**: Patients with COPD are also able to increase their respiratory rate ($f$) during exercise. This increase is thought to be due to an increased drive to breathe and to a decreased efficiency of the respiratory muscles.

These strategies allow patients with COPD to maintain their oxygen delivery to the tissues, but they also increase the work of breathing and may lead to respiratory failure if not managed properly.
1) end-expiratory lung volume (EELV) increases, allowing higher maximum expiratory flow rates (fig. 4). This dynamic hyperinflation does not occur in normal humans, who show a fall in EELV during exercise [25]; and 2) inspiratory flow rate increases, so that inspiratory time decreases and more time is available for expiration [25].

Impaired respiratory mechanics (dynamic hyperinflation) seems to play a major role limiting exercise tolerance in these patients. During exercise in COPD, a balance is struck between the need for ventilation and the high cost of breathing. The most common end-result is a small raise in arterial $P_{CO_2}$ and similar fall in $P_{a,O_2}$. However, unless pulmonary carbon monoxide transfer capacity ($DL_{CO}$) is severely impaired (<50% predicted value), $P_{a,O_2}$ does not fall during exercise, and may even increase in some subjects. Studies using the multiple inert gas elimination technique in COPD show that $V_{A}/Q$ mismatch is usually unaltered from that at rest, that shunts do not develop, and that diffusion limitation also does not occur [28]. This is even the case when COPD is severe [28]. In milder disease, there is evidence that small improvements in $V_{A}/Q$ relationships may occur on exercise [29, 30], providing a partial reason for improvement in arterial $P_{O_2}$. However, it is not infrequently observed that when the patient with COPD is encouraged to maximal effort, sudden hypoxaemia and hypercapnia can develop just before the patient quits exercising [28].

In a variety of chronic respiratory disorders, such as interstitial lung diseases (ILD) and pulmonary vascular diseases (PVD), abnormally high resting levels of $V^E$ and normal slope between $V^E$ and work rate during exercise are commonly observed, but not dynamic hyperinflation, as seen in COPD patients. They do not change EELV significantly during exercise [31]. Oxygen cost of breathing per unit ventilation is increased in patients with ILD because the increased elastic recoil requires more inspiratory muscle activity. They show a strong linear relationship between peak exercise $V_T$ and vital capacity [31], suggesting that differences in peak $V_T$ are mainly due to abnormal respiratory mechanics. During exercise, patients with ILD generally show typical and substantial blood-gas changes, even at moderate effort. While arterial $P_{CO_2}$ is

![Fig. 4. – The resting maximal flow–volume curve from a chronic obstructive pulmonary disease patient is represented by the solid line. The solid smallest loop corresponds to tidal volume at rest and the dashed curve indicates tidal volume at maximal exercise. During exercise, end-inspiratory and end-expiratory lung volumes are increased (dynamic hyperinflation) and expiratory flow limitation is seen over most of expiration. Reproduced with permission from [113].](image-url)
generally unaffected [31], P_{a,O2} falls in almost all patients [32–34], sometimes severely, as does mixed venous P{O2}. It is this profound degree of arterial hypoxaemia (and not respiratory mechanics) that mostly limits exercise tolerance in ILD [35–38]. Worsening of V'A/Q' mismatching and shunt does not play a relevant role in exercise-induced hypoxaemia seen in these patients [32]. Therefore, the blood gas changes on exercise are mostly the consequence of: 1) insufficient increase of alveolar ventilation relative to the rise in P_{a,CO2}; and 2) secondary effects from the fall in mixed venous P{O2} causing a fall in arterial P{O2} [39]. Also, O{2} diffusion limitation is seen in most ILD patients during exercise, further adding to the hypoxaemia [32]. The presence of O{2} diffusion limitation in these patients despite the relatively low cardiac output at peak exercise (<10 L.min^{-1}) is likely related to the combination of: 1) an abnormally low mixed venous P{O2}; 2) a short capillary transit time; and 3) some increased interstitial resistance for the diffusion of O{2} from the alveolar gas to the capillary blood caused by the large collagen deposits there.

Exercise-induced hypoxaemia in patients with PVD has been found to be largely due to the fall in mixed venous P{O2}, because there is no systematic change in V'A/Q' relationships nor does diffusion limitation develop [32].

Haemodynamic responses to exercise in health and disease

In healthy subjects, cardiac output (Q'T) shows a linear increase in relation to O{2} uptake during exercise. Likewise, both stroke volume and heart rate (HR) also increase as V'O_{2} increases. In well-trained subjects, up to five-fold increase (~25 L.min^{-1}) in Q'T at peak exercise can often be seen. Systolic pulmonary pressure increases during exercise, but pulmonary vascular resistance falls because of vascular recruitment. At systemic levels, systolic pressure increases, but not diastolic pressure. It is of note, however, that elite athletes at peak exercise show a potent sympathetic vasoconstriction at systemic level inducing massive redistribution of cardiac output, which ensures preferential perfusion to active skeletal muscle (due to local exercise-induced vasodilator effects) while preserving blood flow and O{2} delivery to essential organs such as the brain [40]. It has been reported that in well-trained cyclists during maximal exercise, respiratory muscles subvert blood flow that otherwise would have been directed to limb muscles. In these subjects, unloading the respiratory system with proportional assist ventilation resulted in an increase in both leg blood flow and leg vascular conductance [41, 42]. This phenomenon is not seen in chronic respiratory patients because they are unable to reach such extreme levels of O{2} uptake during exercise but despite this they may show increased O{2} cost of breathing per unit ventilation [43].

In chronic respiratory diseases, pulmonary vascular abnormalities are present well before frank heart failure occurs. There is pulmonary hypertension often even evident at rest, and usually during exercise. The increase in pressure per unit increase in cardiac output is some three times greater in these patients than in the normal subjects.

Contrary to the normal subjects in whom pulmonary vascular resistance normally falls during exercise due to a combination of vascular recruitment and distension in the lungs, in COPD, vascular resistance remains constant or may even rise. The vascular destruction or obstruction that is well-known to occur in these diseases, together with some distortion and also hypoxic vasoconstriction are the reasons underlying these physiological abnormalities. Eventually, as the diseases progress, the right heart will hypertrophy and ultimately fail, and clinically significant cor pulmonale will be present. Despite the 2–3-fold increase in vascular resistance and high pulmonary artery pressures, it is remarkable that even in advanced lung disease the heart can pump essentially normally as a function of filling pressure, as shown from the limited data available.

At peak exercise, systemic O{2} delivery is clearly below normal level [25]. While the
obvious culprit is impaired pulmonary function, it is not always through a reduction in oxygen saturation in arterial blood that systemic O2 delivery is primarily reduced, since despite $V'$A/Q' inequality and reduced effective alveolar ventilation, hypoxaemia may not necessarily provoke a marked fall in arterial O2 content [25]. It is well accepted that cardiac output at peak exercise is always well below normal levels. However, in COPD patients as in normal subjects, cardiac output increases linearly in relation to oxygen uptake as work rate increases during incremental exercise, such that cardiac output at a given submaximal O2 uptake [44] is close to the expected normal value. It should be noted, however, that the rise in cardiac output during exercise is usually achieved through a higher heart rate and lower stroke volume than in healthy subjects.

Since total ventilation, cardiac output and exercise intensity remain closely coupled in COPD as in health, the inability to raise ventilation appears as the principal governor of the O2 transport process: a low ceiling on ventilation means a low ceiling on cardiac output and thus on systemic O2 delivery. It should be mentioned that the mechanisms that couple ventilation to cardiac output during exercise are still not well understood. Montes de Oca et al. [45] proposed that the large pleural pressure swings observed during exercise can be paramount to constrain left ventricular function, thus limiting both peak cardiac output and exercise tolerance in very severe COPD patients. The coupling between whole-body O2 uptake and cardiac output during exercise implies that the O2 difference between arterial and mixed venous blood and the fractional O2 extraction are normal or near normal [11, 46]. The cardiac response to exercise in patients with ILD is similar to the description for COPD patients. In contrast, patients with PVD show different cardiac response to exercise. Certainly, at peak exercise cardiac output is lower. More importantly, however, the slope of the relationship between $V'$O2 and cardiac output appears different. This suggests that for any given degree of exercise (i.e. $V'$O2), cardiac output in patients with PVD does not increase as much as in controls or patients with COPD or ILD. This abnormal behaviour is likely related to the increased after-load of the right ventricle [47–49]. As expected, patients with PVD have, at rest, pulmonary artery hypertension and increased pulmonary vascular resistance. Compared with patients with COPD and ILD, patients with PVD show, by far, the worse haemodynamic situation. During exercise, pulmonary artery pressure increases in direct proportion to the increase in cardiac output and reaches extremely high values. This indicates the lack of pulmonary vascular reserve. In fact, the pathologically elevated pulmonary vascular resistance seen at rest does not change substantially during exercise.

Muscle oxygen utilisation in health and disease

It has been reported that well-trained males show O2 supply dependency of maximum O2 uptake [8], indicating that mitochondrial capacity does not constitute the rate limiting factor for maximum exercise performance. In contrast, data from healthy sedentary subjects [9, 10] strongly suggest that muscle mitochondrial function is a limiting step for maximum O2 uptake (fig. 5). Studies including direct measurements of cell PO2 saturation during exercise, breathing different inspiratory oxygen fraction (FiO2), further indicates that sedentary subjects do not show O2 supply dependency of $V'$O2,max [12]. The plasticity of skeletal muscle during a high-intensity physical training programme [50] fully accounts for the differences alluded to between athletes and sedentary subjects. The scenario is far more complex in patients with COPD. Femoral blood flow ($Q_{leg}$) measurements in patients with moderate-to-severe airflow limitation [11, 51] have shown, as for cardiac output, a marked reduction in leg blood flow at peak exercise. However, leg blood flow (and leg O2 delivery) [11, 52] at a given submaximal whole-body O2 uptake (and leg $V'$O2) is above normal, which may indicate increased
peripheral muscle O2 demand. Moreover, poor muscle capillary network in these patients
seem to suggest that low peripheral O2 diffusion capacity may also contribute to
exercise-induced cell hypoxia, even in the absence of arterial hypoxaemia. Increased
lactate production [11, 54–56] is responsible for the fall in muscle pH, which, in turn, may
play a role in determining exercise intolerance in these patients [56]. Premature lactic
acidosis during exercise in COPD patients has been associated with reduced oxidative
enzyme concentrations in the lower limb muscles [54, 55] that can be, at least partly,
reversed by physical training.

Several studies [11, 57, 58] exercising different muscle groups in heterogeneous groups
of COPD patients have consistently shown lower cellular bioenergetic status (31P-
Nuclear magnetic resonance spectroscopy) and lower pHi than those seen in healthy
sedentary controls at equivalent levels of exercise. There is evidence [11] suggesting that
muscle deconditioning plays a major role to explain the disturbances of skeletal muscle
bioenergetics in COPD patients. Recent lines of evidence indicate that intrinsic skeletal
muscle dysfunction may be present in patients with COPD, as well as in other chronic
disorders, such as CHF [59–61]. Abnormal redox status [59–62] plays a central role
prompting muscle mass wasting particularly in susceptible subsets of COPD patients.

Factors determining exercise performance: integrated response

It is presently well accepted that the level of exercise tolerance is set by the integrity of
each of the functions involved in the O2 transport/O2 utilisation system, as well as by
proper interactions among all of the physiological responses alluded to above [63].
Complex integrative pathways both at whole body level and at cellular level have been
identified. Since not only intracellular pH [64], but also cell PO2 [65] has been shown to
modulate mitochondrial function, O2 transport (cell PO2) and O2 utilisation
(mitochondrial capacity) cannot be analysed as separate systems.
Also of major interest are the events surrounding peak or maximal $V'\text{O}_2$ and the physiological basis of why peak or maximal $V'\text{O}_2$ is reduced as it almost always is in disease. In this regard, it must be noted that the amount of $V'\text{O}_2$ achieved by a given patient is not only set by the intrinsic characteristics of the system, it also depends on several other factors that modulate the physiological response of the whole body, such as: 1) environmental conditions (altitude above sea level, $F_1,\text{O}_2$); 2) amount of exercising muscle mass (cycling, walking, localised quadriceps exercise); and 3) type of exercise protocol (incremental, endurance test, 6-min walking distance test (6MWT), shuttle test, etc.) (fig. 2). Since the catabolic capacity of the myosin ATPase is such that it outstrips by far the capacity of the respiratory system to deliver energy aerobically, exercise tolerance ($V'\text{O}_2,\text{max}$) is determined by the capacity of the $\text{O}_2$ transport/O2 utilisation system rather than by the muscle’s contractile machinery. Two physiological muscle properties (muscle strength and muscle fatigability) may modulate functional performance of the patient in daily life activities, as well as during clinical exercise testing. Muscle strength is defined as the force generated by a muscle. It is determined by the number and type of motor units recruited; whereas muscle fatigue has been defined as a loss of contractile functions (force, velocity, power or work) that is caused by prolonged exercise and is reversible by rest. Factors involved in muscle fatigue are complex, mainly: 1) contractile machinery; 2) muscle respiratory capacity; and 3) redox status of the muscle. In practical terms, it may be useful to consider two different scenarios ($V'\text{O}_2,\text{peak}$ and $V'\text{O}_2,\text{max}$) (fig. 1). These are the following:

1. A peak $V'\text{O}_2$ has been reached without evidence of $V'\text{O}_2$ plateauing. This is perhaps the commonest outcome in the clinical setting. Taken as it is, one cannot say whether this peak $V'\text{O}_2$ is limited by $\text{O}_2$ supply, mitochondrial oxidative capacity, or perhaps neither (i.e. symptoms are so severe that neither $\text{O}_2$ supply nor mitochondrial function have been fully exploited). In these circumstances, it will be useful to identify the $V'\text{O}_2$ at which the transition from moderate to heavy exercise took place (lactate threshold) and evaluate the organ system responses (ventilation, gas exchange, heart rate, etc.) during submaximal exercise and at peak $V'\text{O}_2$. Despite not having information about the capacity of the system (a plateau of $\text{O}_2$ uptake was not identified), we will know about: 1) the physiological burden imposed by exercise; and 2) the reserve of the system depending upon the location of the transition from moderate to heavy exercise.

2. A plateau in $V'\text{O}_2$ at maximal exercise is clearly identified such that the subject achieved his/her maximum exercise (maximum $\text{O}_2$ uptake) capacity in that particular setting or there is physiological evidence that they are very close to maximum. In this circumstance, two situations may be faced:

2.1. $V'\text{O}_2,\text{max}$ is the result of having reached mitochondrial oxidative capacity. In this scenario, the key concept is that acute increases in $\text{O}_2$ supply to the mitochondria would not lead to any further increase in $V'\text{O}_2,\text{max}$. In other words, no $\text{O}_2$ supply dependency is observed by giving 100% $\text{O}_2$ to breath or by blood transfusion.

2.2. $V'\text{O}_2,\text{max}$ is the result of having reached limits to the supply of $\text{O}_2$. In this circumstance, one or more components of the integrated $\text{O}_2$ transport system (the lungs, heart and blood vessels, blood and muscles) has reached maximal capacity for the given conditions and it can be tested experimentally by augmenting any one of the components alluded to above.

Clinical indications and exercise protocols

There is a range of indications for CPET. It is useful, for example, in the diagnosis of a range of disease conditions, namely: exercise-induced asthma, cardiac ischaemia,
foramen ovale patency with development of right-to-left shunt during exercise, and McArdle's syndrome [66]. In addition, CPET provides information on dysfunction, monitoring or prognostic value in a wide range of conditions. However, an adequate identification of the clinical problem requiring study should be considered a necessary prelude to CPET, as should an appropriate assessment of the patient by: 1) medical history; 2) physical examination; 3) chest radiograph; 4) pulmonary function testing; and 5) electrocardiogram (ECG). The clinical problem that prompts the CPET and the specific aims of the test (i.e. assessment of exercise tolerance, analysis of pulmonary gas exchange during exercise, etc.) determine both the type of exercise protocol to be used and the variables to be considered in the interpretation of the test. Assessment of exercise tolerance and potential limiting factors constitutes the most important indication of CPET. This is particularly important to evaluate dyspnoea, but also to assess the degree of impairment in several chronic diseases. Appropriate use of CPET allows the investigator: 1) to quantify the degree of abnormal limitation and to discriminate among causes of exercise intolerance; 2) to differentiate between dyspnoea of cardiac or pulmonary origin when respiratory and cardiac diseases co-exist; and 3) to analyse unexplained dyspnoea when initial pulmonary function impairment does not provide conclusive results.

A second area of indication of CPET is pre-operative assessment in different conditions, namely, major abdominal surgery in elderly patients [67, 68]. Also, CPET are indicated in lung cancer resectional surgery and lung volume reduction surgery. Information on predicted post-operative lung function: 1) helps to modulate the amount of lung parenchyma to be resected; and 2) determines the type of peri-operative strategy needed to prevent post-surgical complications. Resting pulmonary function tests are considered adequate to evaluate patients with low risk (forced expiratory volume in one second \( \text{FEV}_1 \) >2 L and \( D_{\text{L},\text{CO}} \) within the reference limits) of post-surgical complications [69–74]. However, CPET play a pivotal role in the evaluation of patients with moderate-to-high risk [72, 73, 75, 76]. Assessment of patients included in transplantation programmes (lung, heart) also constitutes an indication for CPET.

CPET should always play a central role assessing candidates before the rehabilitation programme and in the subsequent modulation of the exercise prescription, whereas simpler tests (i.e. 6MWT) are useful for monitoring during the rehabilitation programme. Finally, assessment of impairment-disability also constitutes a central indication of CPET. It is now well accepted that CPET provides different and relevant information in impairment-disability evaluation [77–79], compared to resting cardiopulmonary measurements [80]. Consequently, CPET constitutes a key tool in this area.

**Exercise protocols**

The goal of CPET protocols is to stress the organ systems involved in the exercise response in a controlled manner. For this reason the testing generally involves exercising large muscle groups, usually the lower extremity muscles. A key requirement is that exercise stimulus must be quantifiable in terms of the external work and power performed. The appropriateness of the integrated systemic responses to the tolerable range of work rates is best studied utilising incremental exercise testing. This provides a smooth incremental stress to the subjects so that the entire range of exercise intensities can be spanned in a short period of time. The recommended incremental exercise testing protocol, usually electronically-braked cycle ergometry with constant pedalling frequency, of 60 rpm is recommended. Equivalent results are obtained when work rate is either increased continuously (ramp test) or by a uniform amount each minute (1-min incremental test) until the patient is limited by symptoms (he/she cannot cycle >40 rpm) or is not able to continue safely. The increment size should be set according to
the characteristics of the patient in order to obtain ~10 min duration of the incremental part of the protocol. This may represent incremental rates of 10–20 W per minute in a healthy sedentary subject or less in a patient. Sufficient density of data to be acquired in a test lasting <20 min from start to finish, including: 1) measurements at rest; 2) 3 min of unloaded exercise; 3) incremental exercise (~10 min); and 4) 2 min recovery, at least. Standard noninvasive CPET carried out whilst breathing room air (F I,O2=0.21) involves acquisition of breath-by-breath expired O2 and CO2 concentrations (expiratory oxygen fraction and expiratory carbon dioxide fraction, respectively), work rate, expired airflow, HR and systemic arterial pressure as primary variables. ECG and pulse oximetry should be continuously monitored during the test. It is useful to establish a sense of the patient’s exercise-related perceptions during the exercise test and at the point when the subject discontinues exercise. This includes exertion, dyspnoea, chest-pain and skeletal muscle effort. Quantifying these perceptions should be done using standardised rating procedures (Borg scale, visual analogue scale (VAS) etc.).

Proper evaluation of pulmonary gas exchange in patients with lung disease requires assessment of arterial respiratory blood gases [81]. In these cases, arterial cannulation (preferentially radial, or brachial) is needed (P a,O2 and P a,CO2 measurements and calculation of AaPO2) [81, 82]. This also provides information on acid-base status (pH, P a,CO2 and base excess) and allows continuous monitoring of systemic arterial blood pressure during the test. However, while "arterialised venous blood" (e.g. from the dorsum of the heated hand) gives good values for P CO2 and pH it is not appropriate for P O2. Furthermore, estimation of arterial respiratory blood gases through expired O2 and CO2 profiles or "transcutaneous" electrodes and pulse oximetry should not be used as indices of arterial P O2 and P CO2 during exercise [83–85]. It is important to recognise that arterial blood sampling immediately after exercise does not provide an adequate assessment of blood gases at peak exercise. However, while pulse oximetry does not indicate arterial P O2, it does provide valuable information on oxyhaemoglobin saturation during exercise.

If the ergometer used in the CPET is a motor driven treadmill, then the Balke’s protocol [81, 86] is considered the most appropriate for its simplicity. The speed of the treadmill is kept constant (3–3.5 mph) during the protocol while the slope is progressively increased (1–2% min −1). It is of note, however, that the assessment of the relationships between oxygen uptake and external work rate is more accurately carried out using a cyclo ergometer than using a treadmill.

Alternative protocols can be considered for specific purposes [87]. Simpler tests, such as step tests or timed distance walks (i.e. 6MWT or 12 min-walk) are widely used and they can provide measures of exercise tolerance but are not as useful in diagnosis as incremental tests [88–90]. The timed walking tests have been extensively used in the clinical evaluation of patients with chronic cardiopulmonary disorders mainly because of their simplicity. A present, these tests are recognised to add prognostic information useful to the staging of patients with COPD [4, 7], primary pulmonary hypertension [91] and congestive heart failure [92]. Timed walking tests have shown to be sensitive to changes after interventions such as inhaled bronchodilators [93], volume reduction surgery [94] and pulmonary rehabilitation [95, 96]. The 6MWT, for example, is currently performed in a large number of rehabilitation programmes. Recent studies [97] suggest that encouraged 6MWT is a strenuous protocol that evaluates sustainable exercise performance; that is critical power. The 6MWT and the incremental cycling protocols should be considered complementary tests.

Constant-work rate protocols can result in steady-state responses when work rate is of moderate intensity. In contrast, constant work rate of high intensity for the individual typically results in continually changing values in most variables of interest. Consequently, attainment of, or failure to attain, a steady-state V'O2 during a constant-load test can be used to determine if a particular task is sustainable by the individual. During a constant-work
rate protocol, the period of dynamic adjustment to a constant-work rate test provides information regarding the dynamic behaviour of lung function, haemodynamics and tissue \( \text{O}_2 \) utilisation. However, there is to date virtually no information on the confidence limits, reproducibility and predictive value of the derived parameters in patient populations. Consequently, the utility of quantifying dynamic responses to constant-work rate exercise in clinical exercise testing remains to be established. The constant-work rate protocols are, however, useful to assess the impact of a given intervention on the system responses to exercise (\textit{i.e.} bronchodilator therapy) [98]. Alternatively, the use of high intensity constant-work rate to assess exercise-induced asthma has been traditionally used in the clinical setting, but it might be progressively substituted [99].

**Testing procedures**

Cardiopulmonary exercise testing should be conducted only by adequately trained personnel with a basic knowledge of exercise physiology. Technicians familiar with normal and abnormal responses during exercise and trained in cardiopulmonary resuscitation (CPR) should be present throughout the test. CPET should be performed under the supervision of a physician who is appropriately trained to conduct exercise tests and in advanced CPR. The degree of subject supervision needed during the test can be determined by the clinical status of the subject being tested and the type of exercise protocol. While it is preferable for the physician to be present during the test, if not he/she must be readily available to respond as needed. Additional roles for the physician are the evaluation of the patient immediately before the test and the interpretation of the results.

**Patient preparation**

At the time of scheduling, the subject should be instructed to adhere to his/her usual medical regimen; he/she should not to eat for at least 2 h before the test, avoid cigarette smoking and caffeine, and dress appropriately for the exercise test. A brief history (with detailed inquiries about the medications) and physical examination should be done to rule out contraindications to testing. Results of recent resting pulmonary function tests, as a minimum forced spirometry, should be available for patients in whom pulmonary disease is suspected.

On arrival at the CPET laboratory, a detailed explanation of the testing procedure and equipment should be given to the patient outlining risks and potential complications as described below. The subject should be told how to perform the exercise test and the testing procedure should be demonstrated if needed. The patient should be encouraged to ask questions to reduce any anxiety. The patient needs to become familiar with the equipment. If the treadmill is used, time is provided for several practice trials of starting and stopping until the patient feels confident. If the cycle ergometer is used, the seat height is adjusted so that the subject’s legs are almost completely extended when the pedals are at the lowest point and the cycling rhythm practiced. \textit{Before the test}, the ECG electrodes are carefully placed and secured after preparing the skin to ensure good recordings (if necessary, the area of the electrodes placement should be shaved). A sphygmomanometer cuff is placed on the upper arm. The mouthpiece and noseclip are then tried and the position adjusted until adopting a comfortable position. The patient is informed that it is acceptable to swallow with the mouthpiece in place and that he/she must signal any unexpected difficulty by the signal “thumbs down”. The patient is advised to point to the site of discomfort if chest or leg pain is experienced.
During the test, the patient is encouraged to carry on with a regular pedalling cadence. Symptoms and degree of discomfort are periodically checked (see below safety precautions). Good communication with the patient throughout the whole procedure increases the subject’s confidence and predisposes to good effort. During recovery, the patient is told to continue to pedal, without external work load (or walk at a slow pace on the treadmill), for at least 2 min during recovery in order to prevent fainting and to accelerate lactate removal. At the point when the subject discontinues exercise, after removal of the mouthpiece, the physician should ask for symptoms (type and intensity) that prompted the patient to stop exercise. If blood gas analysis is done, a last blood sample is taken at 2 min of recovery. If the test does not provide adequate diagnostic information because of premature termination or inadequate cooperation of the patient, it should be repeated after a resting period of 30–45 min.

Although CPET may be considered to be a safe procedure, risks and complications have been reported. Good clinical judgment should be paramount in defining indications and contraindications for exercise testing [100]. Cardiac (bradyarrhythmias, ventricular tachycardia, myocardial infarction, heart failure, hypotension and shock) and noncardiac (musculoskeletal trauma, severe fatigue, dizziness, fainting, body aches) complications of CPET have been reported. Consequently, during the test, the personnel should be alert to any abnormal event. The indications to stop the test must be clearly established and known by all the personnel involved in testing. These indications include symptoms such as: 1) acute chest pain, 2) sudden pallor, 3) loss of coordination, 4) mental confusion, and 5) extreme dyspnoea; and signs such as: 1) depression of ST segment >0.1 mV (less specific in females), 2) T-wave inversion, 3) sustained ventricular tachycardia, and 4) fall in systolic pressure either below the resting value or ~20 mmHg below its highest value during exercise testing. Relative indications to stop the test are: 1) polymorphic and/or frequent premature ventricular beats; and, 2) hypertension (>250 mmHg systolic, >130 mmHg diastolic). If the exercise test has been stopped for one of the above-listed reasons, the patient should be monitored in the CPET laboratory until symptoms or ECG modifications have completely cleared. Admission to hospital for longer observation or more often for complementary investigation will be necessary in very rare cases. If necessary, intensive care can be administered on site. Full cardiopulmonary resuscitation equipment should be available in the CPET laboratory.

Interpretation strategies

The greatest diagnostic potential and impact on the clinical decision making process of exercise testing should rely not on the utility of any one individual measurement, although some are obviously more important than others, but rather on their integrated use. Identification of a cluster of responses characteristic of different diseases is often useful. The major portion of the interpretation strategy is focused on CPET results generated during maximal, symptom-limited, incremental exercise testing. This is currently the most popular, albeit not the exclusive protocol. Often, insufficient attention is paid to trending phenomena as the work rate progresses from submaximal to peak levels. To facilitate this type of analysis, the results should be formatted in an appropriate manner. Figure 6 displays data obtained in a normal subject performing cycle ergometry, using an ergometer that utilises an "assist" to provide an actual zero-watt work rate at "unloaded" pedalling. Figures 6a–d provide, in addition to the peak $V'\text{O}_2$, the variables commonly used to provide an indirect estimation of the lactate threshold. That is, identification of the $\text{O}_2$ uptake at which the transition between moderate to heavy-intensity exercise occurs. Figure 6e ($\text{O}_2$ uptake versus work rate) reflects the exercise
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Fig. 6. – Exercise performance in a healthy sedentary male subject. The basic plots for the interpretation of cardiopulmonary exercise testing are reported. In plots a–d, in addition to peak oxygen uptake ($\dot{V}O_2$), the variables commonly used to indirectly estimate lactic threshold (LT) are given. That is, the $\dot{V}O_2$ at which the transition from moderate to high intensity exercise occurs is identified (vertical dashed line). The expected LT for a healthy subject (55% of predicted $\dot{V}O_2$,peak) is indicated in plots a) to d) by a small arrow (continuous line). Predicted $\dot{V}O_2$,peak is indicated in a) by an arrow (dashed line). In plot e), $\dot{V}O_2$ versus work rate reflects the exercise efficiency and limits of exercise tolerance of the subject; with the expected peak exercise performance represented by the asterisk. Plots f) and h) indicate minute ventilation ($\dot{V}E$) versus carbon dioxide uptake ($\dot{V}CO_2$) and tidal volume ($\dot{V}T$) versus $\dot{V}E$, respectively; these two plots describe the characteristics of the ventilatory response during submaximal and peak exercise. Finally, plot g) presents characteristics of the haemodynamic response to exercise with estimated peak heart rate represented by the asterisk and predicted peak $O_2$ pulse by the arrow. $PET.O_2$: end-tidal pressure of oxygen; $PET.CO_2$: end-tidal pressure of carbon dioxide; RER: respiratory exchange ratio. Reproduced with permission from [113].
efficiency and the limits of exercise tolerance of the subject. Figure 6f (ventilation versus CO₂ output) and figure 6h (tidal volume versus ventilation) characterise aspects of the ventilatory response during submaximal and maximal exercise. However, some investigators find the relationship between $V^E$ and $V^O_2$ during such tests to be useful. Finally, figure 6g, which plots heart rate (and O₂ pulse) versus O₂ uptake, is informative with respect to the characteristics of the haemodynamic response to exercise. The next step is to choose adequate reference values to establish patterns of normal or abnormal response. Available reference values and present limitations in this particular issue are discussed below. Relatively few studies have evaluated the sensitivity, specificity and predictive value of patterns of measurements in distinguishing among different clinical entities. Even more importantly, the precise role of clusters of variables commonly used in the decision making process in well identified diseases (i.e. evaluation of ILD, pre-operative evaluation for resection lung cancer surgery, etc.) is insufficiently known. For the future, studies addressing the use of likelihood ratios might be even more useful to clinicians than sensitivity/specificity, since likelihood ratios refer to actual test results before disease status is known. This shift to an evidence-based approach for CPET interpretation will hopefully provide important answers to clinically relevant questions that are not immediately available.

Selection of appropriate reference values is an important step to establish patterns of normal or abnormal response to exercise stress. An initial analysis of available data on healthy subjects [88, 89, 101–111] clearly indicated that only some of these studies [89, 103, 105–107] fulfil minimum requirements to be considered as candidates to be used in the clinical setting. Blackie et al. [105] cover a limited age span (from 55–80 yrs) and Bruce et al. [107] provide data obtained with treadmill in a population of rather physically fit people. Hence, the analysis of potential studies in healthy sedentary people, providing prediction equations for $V^O_2,peak$ obtained with cycling incremental exercise testing, is then even more reduced to three sets [102, 106, 112]. Reference values estimated by Fairbarn et al. [106] are consistently higher than those provided by Jones et al. [102], both in males and females. Predicted values by Wasserman et al. [89] and Hansen et al. [112] are closer either to Jones et al. [102] or to Fairbarn et al. [106], depending upon the values of height-weight of the subject in whom the equations are used. The characteristics of the presently available prediction equations for peak O₂ uptake (and peak work rate) clearly impose limitations to the interpretative strategy. Moreover, except for HR in the study of Fairbarn et al. [106] the profile of response in healthy sedentary subjects (i.e. from submaximal to peak exercise results) are not available. Further, adequate prediction equations for the most important variables obtained from the same group of reference subjects are not currently available.

**Summary**

The role of the O₂ transport/O₂ utilisation system determining maximum O₂ uptake has been analysed in an integrative manner. The system responses to exercise in healthy subjects (athletes and sedentary) and in common pulmonary diseases have been examined. Finally, basic principles of exercise testing and interpretation of the results have been reviewed.

**Keywords:** Aerobic capacity, cardiopulmonary exercise testing, endurance, lactic threshold, oxygen uptake, work rate.
References


